Review Article

AUTOIMMUNE DISEASES: IMMUNOPATHOLOGY AND ETIOPATHOGENESIS

CONTENTS

Autoimmune Diseases

Immunopathology and Etiopathogenesis

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RECENT ACCOMPLISHMENTS in cellular immunology, molecular biology, and genetics have influenced current thinking about autoimmunity. These accomplishments have led to an ever-increasing understanding of the basic aspects of antibody diversity, generation of cellular and humoral immune responses and their interdependence, mechanisms of tolerance induction, and the means by which reactivity develops against autoantigenic constituents.

Since the turn of the century, the central dogma of immunology has been that the body does not normally mount immune responses against itself. This phenomenon, described originally by Ehrlich,[1] is accepted today as immunologic tolerance to self-components, an obvious necessity for health. Conversely, autoimmunity defines a state in which the natural unresponsiveness or tolerance to self terminates.[2] As a result, antibodies and/or cells react with self-constituents, thereby causing disease ("*horror autotoxicus*" of Ehrlich). The above definition implies that responses against the self do not occur normally, and if they do occur, then the outcome, depending on their magnitude and duration, is harmful to the host. However, it has recently become apparent that autoimmune responses are not as rare as once thought and, importantly, that not all autoimmune responses are "forbidden" or harmful. Actually, certain forms of autoimmune responses, such as recognition of cell surface antigens encoded by the major histocompatibility complex (MHC) and of antiidiotypic responses against self-idiotypes, unlike the *horror autotoxicus* responses of Ehrlich, appear to be essential for the diversification and the normal functioning of the intact immune system. Therefore, *horror autotoxicus* must now be distinguished from normal or positive autoimmune responses.

It is now recognized that an abnormal autoimmune response is sometimes a primary cause and other times a secondary contributor to many human and animal diseases. Clinically, the wide spectrum of autoimmune diseases has been divided into systemic or "non-organ-specific" and "organ-specific" (Table 1). Types of autoimmune diseases frequently overlap, and more than one autoimmune disorder tends to occur in the same individual, especially those with autoimmune endocrinopathies.[3] For as yet unknown reasons, autoimmune syndromes may also be associated with lymphoid hyperplasia and malignant lymphocytic or plasma cell proliferation,[4,5] as well as immunodeficiency disorders such as hypogammaglobulinemia, selective IgA deficiency, and deficiencies in complement components.[6,7] Moreover, autoantibodies sometimes develop as part of the aging process.[8] Non-organ-specific autoimmune diseases, epitomized by systemic lupus erythematosus (SLE), are characterized by autoimmune responses directed against widely distributed self-antigenic determinants.[9,10] Although a given non-organ-specific disease usually involves many self-antigens, such diseases may also develop following abnormal immune responses against only one antigenic target that is, however, expressed in different organs, for example, antigens on basement membranes at diverse sites. In contrast to generalized autoimmune diseases, organ-specific diseases, such as certain forms of thyroiditis, result from abnormal responses directed against an

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antigen that is confined to a given organ. What determines the extent of autoimmune responses, the number of autoantigens that elicit them, or the target organ is unknown. Nor is it always clear whether autoimmune responses are directed against unmodified self-antigens or self-antigens that have been modified by any of numerous agents such as viruses and hapten groups.

Concerning the cause of these various autoimmune disorders, no single concept has achieved universal acceptance. To the contrary, studies in experimental animals tend to infer that autoimmune diseases result from a broad range of genetic and immunologic abnormalities that differ from one individual to another. Depending on the presence or absence, respectively, of many superimposed exogenous (viruses, bacteria) or endogenous (hormones, abnormal genes) accelerating factors, abnormalities of this type become apparent early in life or remain quiescent until later.

Immunopathologic Mechanisms in Autoimmune Diseases

Mediation of autoimmune diseases is divisible into three main routes, but in any given autoimmune disorder more than one may be involved at any given time. The *first* route involves autoantibody directed against unmodified or modified intracellular structures or cell surfaces. Destruction of cells or tissues ensues, usually in the presence of complement but also sometimes by antibody-mediated cellular cytotoxicity. In some instances, autoantibodies directed against functional cellular receptors stimulate or inhibit specialized cellular functions without associated cell destruction. The *second* is formation of autoantigen–autoantibody immune complexes in intercellular fluids or in the general circulation that ultimately mediate tissue damage.[11] Such complexes, depending on their size, which is primarily determined by the ratio of the two reactants, may circulate widely and deposit in tissues throughout the body, especially those with large filtering membranes (kidney, joint, choroid plexus). Complement factors, as well as granulocytic and monocytic cells, are then attracted to the sites of immune complex deposition, and their involvement leads to cell death. *Third*, the disease process may be caused by sensitized T lymphocytes, which produce tissue lesions by mechanisms that are still incompletely understood but presumably involve the release of lymphokines that are destructive themselves or that recruit other inflammatory cell types to the lesion.

The first group of autoimmune diseases is exemplified by autoimmune hemolytic anemias, neutropenias, lymphopenias, and thrombocytopenias as well as diseases caused by anti-basement membrane antibody, a variety of autoimmune endocrinopathies, and anti-receptor–mediated diseases (Table 1). The immunopathologic mechanisms of some of these diseases are summarized below. Hemolytic anemias can be idiopathic or secondary to such factors as viral infections and drugs, and the cause may be warm- or cold-reactive autoantibodies that are detectable bound to red cell surfaces or in serum examined by direct and indirect hemagglutination assay.[12] Lymphopenias, neutropenias, and thrombocytopenias are frequent secondary manifestations of autoimmune disorders such as SLE and rheumatism, in which anti-lymphocyte, anti-polymorphonuclear cell, and anti-platelet antibodies often develop.[9,10] Goodpasture's syndrome, characterized by glomerulonephritis and pulmonary hemorrhage, is caused by anti-basement membrane autoantibodies; by immunofluorescence, such antibodies can be found deposited uniformly along the membrane, resulting in a smooth, continuous, linear pattern.[13] A variety of endocrinopathies may result from autoantibodies directed against antigens on endocrine glands, hormones produced by them, or receptor sites for the hormones.[3,14-17] For example, Addison's disease may be the result of anti-adrenal autoantibodies; most patients with juvenile, insulin-dependent diabetes have islet cell antibodies in their serum; and patients with Hashimoto's thyroiditis and primary myxedema have antibodies to thyroglobulin, microsomal protein, and other thyroid constituents. Of interest, more than 30% of patients with autoimmune thyroid disease have concomitant gastric parietal cell antibodies in their serum, whereas thyroid antibodies have been demonstrated in up to 50% of patients with pernicious anemia. Parietal cells in many ways behave like endocrine cells, since they secrete intrinsic factor in response to stimulation by gastrin. The absence of intrinsic factor leads to malabsorption of vitamin B_{12}. Pernicious anemia may develop as a result not only of autoantibodies against parietal cells but also of autoantibodies specific for intrinsic factor.

A most interesting group of autoimmune endocrinopathies and of other autoimmune diseases is caused by autoantibodies against functional cell surface receptors.[17] Anti-receptor antibodies are known to underlie the pathogenesis of at least four diseases: 1) myasthenia gravis, with antibodies produced against the acetylcholine receptors (AChRs) of neuromuscular junctions; 2) Graves' disease, in which antibodies against the thyroid receptors for thyroid-stimulating hormone (TSH) develop; 3) the syndrome of acanthosis nigricans in which profound insulin resistance results from the production of anti-insulin receptor antibodies; and 4) ataxia telangiectasia,

Table 1—Autoimmune Diseases

	Autoantibody	Method of detection
Organ-specific		
Myasthenia gravis	Anti-acetylcholine	Immunoprecipitation of ^{125}I-α-bungarotoxin conjugated AChR
Graves' disease (diffuse toxic goiter)	Thyroid stimulating immunoglobulin (TSI) or anti-TSH receptor autoantibody	Bioassay, measurement of adenyl cyclase activity after incubation of thyroid tissue with Ig from patient's serum, radioreceptor assay for antibodies competing with TSH for the receptor on thyroid membranes
Hashimoto's thyroiditis	Antibodies to thyroglobulin and to microsomal antigens	RIA, tanned erythrocyte agglutination, complement fixation, IF
Insulin-resistant diabetes associated with acanthosis nigricans	Anti-insulin receptor	Inhibition of ^{125}I-insulin binding to receptors on monocytes or adipocytes
Insulin-resistant diabetes associated with ataxia telangiectasia	Anti-insulin receptor	Inhibition of ^{125}I-insulin binding to receptors on monocytes or adipocytes
Allergic rhinitis, asthma, functional autonomic abnormalities	Antibodies to β_2-adrenergic receptors	Binding of ^{125}I-protein A to lung membranes preincubated with sera; Ability of plasma to inhibit binding of ^{125}I-iodohydroxybenzylpindolol (IHYP) to calf-lung membranes; immunoprecipitation of soluble receptors complexed with I-IHYP in the presence of propanolol
Juvenile insulin-dependent diabetes	Antibodies to islet cells	Immunofluorescence (IF)
Pernicious anemia	Antibody to gastric parietal cells and to B_{12} binding site of intrinsic factor	IF, (RIA) Radioimmunoassay
Addison's disease	Antibodies to adrenal cells	IF
Idiopathic hypoparathyroidism	Antibodies to antigens of parathyroid cells	IF
Spontaneous infertility	Antibodies to sperm	Agglutination and immobilization of spermatozoa
Premature ovarian failure	Antibodies to interstitial cells and corpus luteum cells	IF
Pemphigus	Antibodies to intercellular substance of skin and mucosa	IF
Bullous pemphigoid	Antibodies against basement membrane zone of skin and mucosa	IF
Primary biliary cirrhosis	Antibodies to mitochondrial antigens	IF
Autoimmune hemolytic anemia	Anti-red blood cell antibodies	Direct and indirect Coombs' tests
Idiopathic thrombocytopenic purpura	Anti-platelet antibodies	IF
Idiopathic neutropenia	Anti-neutrophil antibodies	Agglutination, IF
Systemic		
Goodpasture's syndrome	Anti-basement membrane antibodies	IF, RIA
Rheumatoid arthritis and Sjogren's syndrome	Anti-γ-globulin antibodies Antibodies to EBV related antigens	Sensitized-SRBC agglutination, Latex-Ig agglutination, RIA, IF, Immunodiffusion
Systemic lupus erythematosus	Anti-nuclear antibodies (ANA)	IF
	Anti-ds and ss-DNA	Farr assay, solid phase enzyme and RIA, hemagglutination, counter-electrophoresis
	Anti-Sm antibodies	Hemagglutination, Immunodiffusion, RIA
	Anti-ribonucleoprotein (RNP) antibodies	Hemagglutination, RIA
	Anti-lymphocyte antibodies	IF, cytotoxicity
	Anti-red blood cell antibodies	Coombs' test
	Anti-platelet antibodies	IF
	Anti-neuronal cell antibodies	IF
	Anti-γ-globulins	RIA

another autoimmune disorder in which one finds antibodies against the insulin receptors. In each case, the antibody (usually IgG, but sometimes other immunoglobulins) competes with the neurotransmitter or hormone for binding sites on the cell surface. Attachment of antibody to the receptor can result in a variety of biologic effects such as 1) blocking of function by hastening degradation of the receptor, as, perhaps, in myasthenia gravis; 2) mimicking the action of a normally activated receptor, as in Graves'

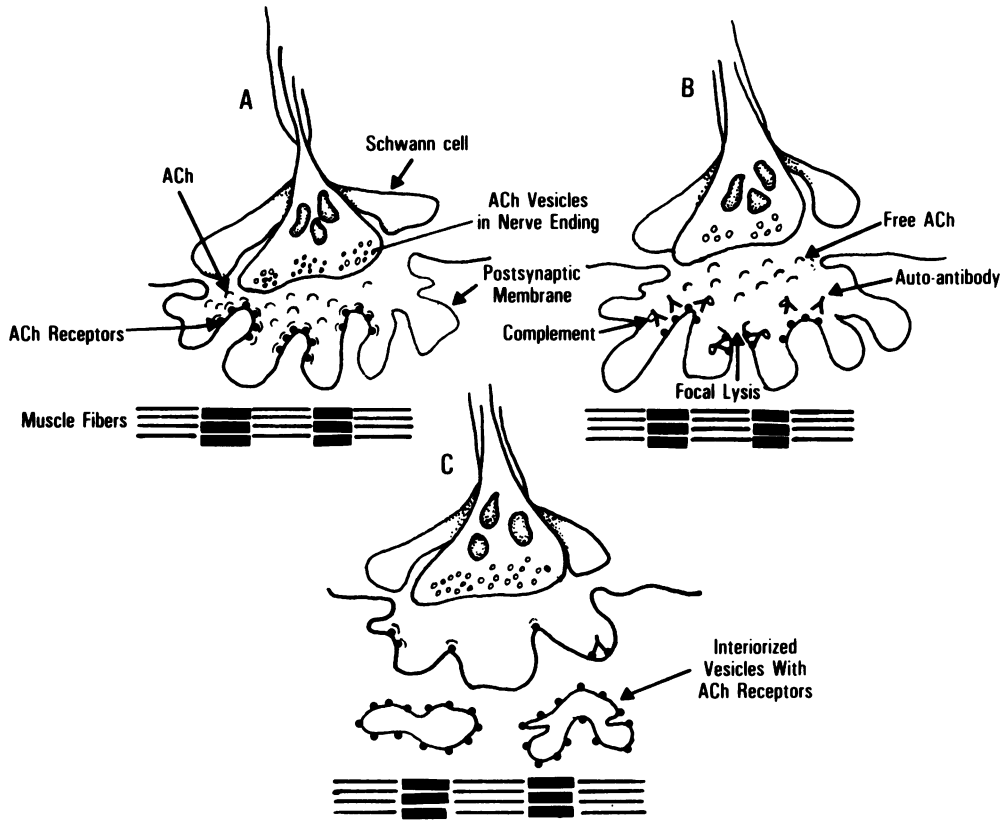

Figure 1—Immunopathologic features of myasthenia gravis. **A**—Normally, acetylcholine (ACh) synthesized and accumulated in vesicles at the motor nerve terminals is released by exocytosis. Thereafter, it interacts with AChR on the invaginated postsynaptic membrane of the muscle triggering the transient opening of cation-specific channels through which sodium and potassium flow according to their concentration gradient across the muscle cell membrane. If enough AChRs are activated, an action potential is triggered that is propagated along the muscle and activates the contractile machinery. Transmission is terminated, and the ion channels close following removal of ACh from the cleft by diffusion and destruction by acetylcholinesterase that is localized over the whole surface of the postsynaptic membrane. **B** and **C**—In myasthenia gravis, there is a reduction of AChRs due to focal lysis of the postsynaptic membrane by complement-fixing anti-AChR autoantibodies and/or antigenic modulation involving cross-linking of AChR, interiorization, and proteolysis. (Modified from Lindstrom J: Autoimmune response to acetylcholine receptors in myasthenia gravis and its animal model. Adv Immunol 1979, 27:1. Used with permission of the author and publishers)

disease and in certain cases of acanthosis nigricans with diabetes; or 3) blocking hormone binding, thereby inducing resistance to the hormone, as in ataxia telangiectasia.

Myasthenia gravis is a neuromuscular disorder manifested by weakness, fatigue of voluntary muscles, and often remarkable patient responsiveness to anticholinesterase drugs. The functional defect in neuromuscular transmission observed in this disease is localized in the postsynaptic surface of the neuromuscular junction. The structure of the neuromuscular junction is altered, and the number of functional AChRs decreases, all brought about by anti-AChR antibodies.[18] These autoantibodies interact with AChRs located on the postsynaptic membrane at or near the acetylcholine binding site, and this interaction leads to blockade, greatly increased receptor interiorization, and subsequent degradation as well as focal lysis in the presence of complement (Figure 1). The disease can be transmitted into experimental animals by serum IgG of myasthenic patients.

Graves' disease, characterized by overproduction of thyroxine and triiodothyronine, is probably caused by thyroid-stimulating immunoglobulins (TSIs), which stimulate the thyroid gland through a reaction with the cell receptor for TSH.[14,15,17,19] This reaction activates adenylate cyclase inside the cell membrane, initiating increased activity by protein kinases, which leads to increased secretion of thyroid hormones (Figure 2).

In a few nonobese patients with acanthosis nigricans, Type B, and diabetes, insulin is often present at normal or supranormal levels, but its binding to specific receptors is greatly diminished.[17,20,21] The insulin receptors, although normal in number, are almost completely inactivated by autoantibody directed against them. The antibodies attach themselves to the receptors, probably at some spot adjacent to the receptor, rather than at the actual insulin-binding site, changing the receptor's total structure in such a way that it can no longer bind insulin tightly (Figure 3). Sometimes such autoantibodies not only block and desensitize the receptors but, when bound, can also mimic insulin's action on target cells. Although this

insulin-mimicking effect lasts only a short while, it indicates that the information for turning on the cells is in the receptor, rather than in insulin itself. Insulin-resistant diabetes can also be found in approximately 60% of patients with ataxia telangiectasia, and this finding has been attributed to the presence in serum of blocking anti-insulin receptor antibodies.[17]

Recent findings suggest that anti-receptor autoantibodies may be responsible for many other syndromes. For example, autoantibodies to β_2-adrenergic receptors have been identified occasionally in the serum of patients with bronchial asthma or allergic rhinitis.[22] Receptor blockade by β_2-receptor antibodies could upset the balance between β-receptor–induced relaxation of airway smooth muscle and the opposing influence of other mediators such as α-receptor agonists, histamine, prostaglandins, and acetylcholine. The β-receptor antibodies might also reduce receptor density on smooth muscle cells by hastening receptor degradation, as with AChRs in myasthenia gravis. A very recent suggestion is that such autoantibodies may be more prevalent than originally thought and that they may play an important role in the pathogenesis of inherent functional autonomic abnormalities.[23]

The non–organ-specific autoimmune diseases are exemplified best by the prototype SLE, with its varied autoimmune responses and manifestations of immune complex disease, such as glomerulonephritis, vasculitis, and nonerosive polyarthritis. Among the various autoantibodies encountered, the most notable are those against nuclear components such as DNA, deoxyribonucleohistone, histone, RNA, nucleolar antigens, and components of the soluble nuclear extracts—the ribonucleoprotein antigen (RNP), the Sm antigen, and others.[24] High titers of antibody to double-stranded DNA and to Sm are found only in patients with SLE and can be considered diagnostic. Some antinuclear antibodies, especially antibodies to single-stranded DNA, occur with varying frequencies and titers in other rheumatic diseases as well. In SLE there also may be anti-red cell and anti-platelet antibodies that cause hemolytic anemia and thrombocytopenia as well as anti-lymphocyte antibodies directed against T and B cells[25-27] and anti-neuronal cell antibodies[28] that may play some role in the central nervous system manifestations of SLE. Recent studies of monoclonal anti-DNA antibodies derived from the MRL/1 strain of mice, which spontaneously develops SLE, have suggested to some investigators that the autoantibody spectrum of lupus may not be as broad as once thought, since individual monoclonal antibodies react with numerous substances (cardiolipin, phosphatidic acid, phosphatidyl glycerol, lupus anticoagulant factor, polynucleotides) whose molecules contain diester-linked phosphate groups.[29] It

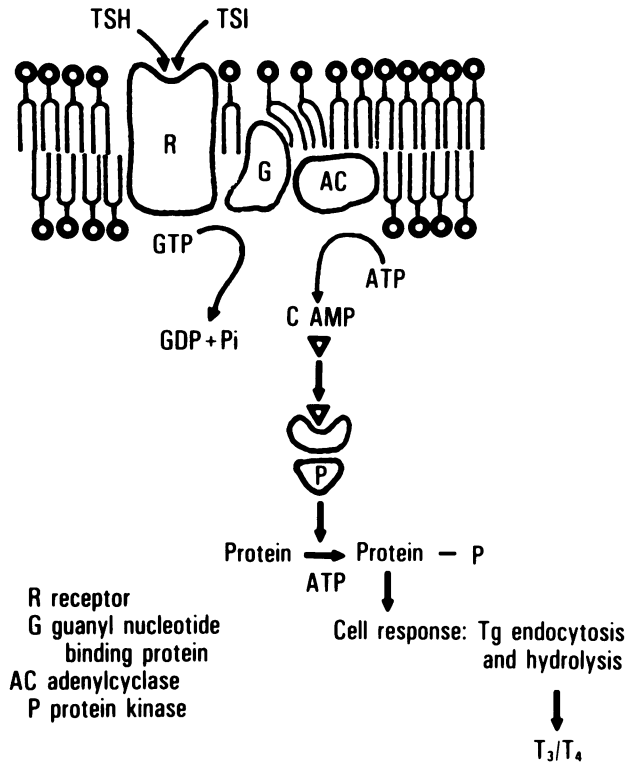

Figure 2—Pathogenesis of Grave's disease. TSI mimicks the action of TSH, thereby stimulating secretion of thyroid hormones. *GTP*, guanosine triphosphate; *GDP + Pi*, guanosine diphosphate + inorganic phosphorus. (From De Baets M, et al: Autoantibodies to the thyrotropin receptor and their significance in autoimmune thyroid disease, Recent Progress in Diagnostic Laboratory Immunology. New York, Masson, 1982, p 37. Used with permission of the authors and publishers)

was suggested that some of the diverse serologic abnormalities of SLE may result from the binding of certain autoantibodies to a phosphodiester-containing epitope that is present in diverse biologic molecules distributed widely throughout the body. More detailed experiments on specificity must be done before we can determine whether this is the case.

Antinuclear antibodies in the serum of humans and mice with SLE may have a much more fundamental effect than simply complexing with antigen in serum and being deposited in tissues. Experiments in SLE-prone strains of mice have indicated the presence in serum of autoantibodies directed not only against the classic right-hand helical DNA (B-DNA) but also against left-hand helical DNA, the so-called Z-DNA.[30] Z-DNA was proven to be strongly immunogenic in experimental animals, unlike the B-DNA for which such animals exhibit strong tolerance. Theoretically, Z-DNA is an inactive methylated form of DNA that, upon methylation and activation, becomes involved in gene regulation. Moreover, in recent research, autoantibodies to Sm and RNP interacted with a type of small RNA complexed with

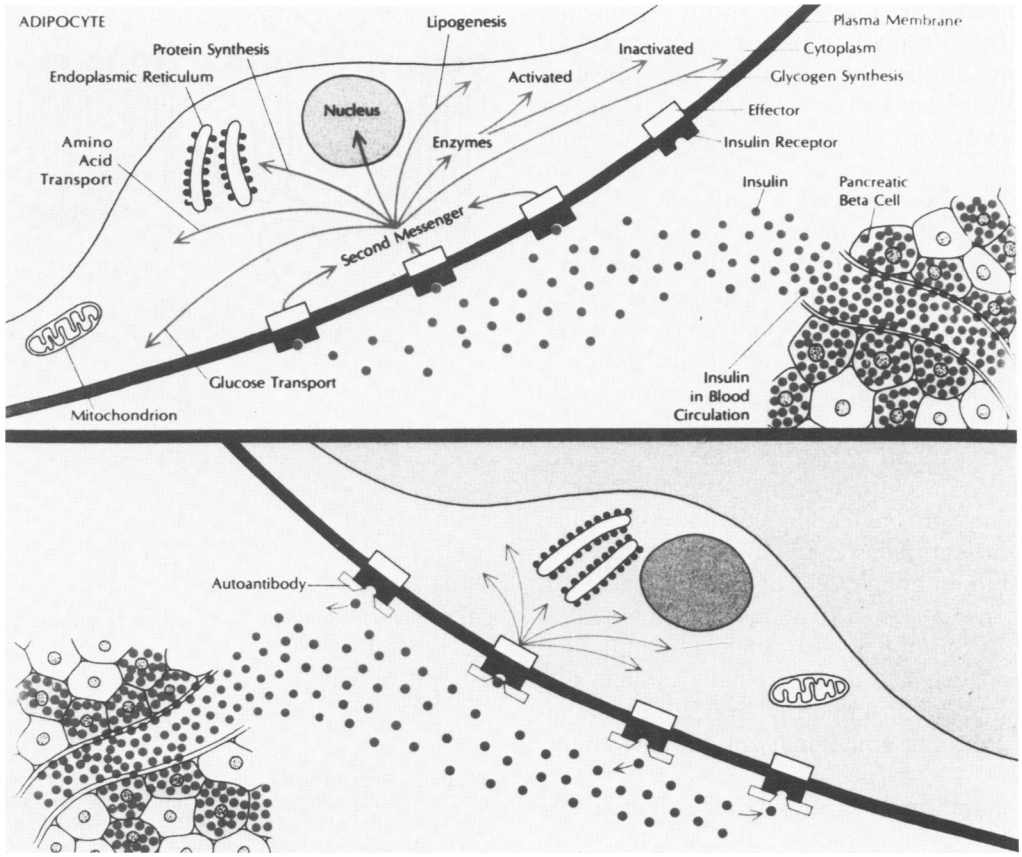

Figure 3—Pathogenesis of insulin-resistant diabetes associated with acanthosis nigricans. Insulin released from the pancreas normally binds to receptors on sensitive cells, and the hormone-receptor complex activates various intracellular processes (*top panel*). In a small number of diabetic patients, insulin secretion is normal, but receptor sites are partially blocked by autoantibody. Impaired hormone binding means that few sites are activated at any given time (*bottom panel*). (From Roth J: Insulin receptors in diabetes. Hospital Practice, May 1980:98. Illustrated by Albert Miller for Hospital Practice. Used with permission of the author and publishers)

protein.[31,32] This small RNA was highly conserved among the species tested. The anti-RNP antibodies recognized small nuclear ribonucleoprotein particles (snRNP) that contained U1 RNA, whereas the anti-Sm antibodies recognized, in addition to U1 RNA, particles containing the snRNP U2, U4, U5, and U6.[31] Experiments with an *in vitro* system containing HeLa cells infected with adenovirus revealed that both anti-RNP and anti-Sm antibodies could inhibit the appearance of spliced mRNAs by interfering with the function of the U1 snRNP, thus suggesting that these autoantibodies may inhibit nuclear editing by RNA transcripts.[32] The above findings, although provocative, may have limited importance in the pathologic process of SLE if the autoantibodies cannot penetrate living cells. Although certain investigators have obtained data suggesting penetration of cells by anti-RNP antibodies attached first via Fc surface receptors,[33] these findings remain controversial, and the bulk of evidence so far indicates that such autoantibodies do not internalize within living cells so as to interfere with specific metabolic processes.

Rheumatoid arthritis, another major autoimmune disease, is characterized by the presence in serum of autoantibodies directed against the Fc portion of IgG. Such autoantibodies, usually of IgM or IgG isotype, combine with IgG to form immune complexes that are considered to participate in the associated synovitis and vasculitis via activation of the complement cascade and attraction of polymorphonuclear cells to the sites of their deposition.[34,35]

In the course of these organ-specific and non-organ-specific autoimmune diseases, along with autoantibodies, certain cell types such as K cells and T cells also seem to participate as primary or accessory factors of the immunopathologic process. Of course, as discussed in subsequent sections of this review, abnormalities of regulatory T cells have been considered as one of the primary causes of autoantibody production by B cells.

As information has accumulated in the last few years concerning the immunopathologic mechanisms of autoimmune diseases, data have simultaneously accrued on such important topics as the diversity of

the immune system and the means of normal immunoregulation and tolerance induction. Thus, as reviewed below, one can now construct a reasonable framework on which future work concerning such disorders will be based.

The Diversity of Immune Responses

Humoral and cellular diversity in the immune system is intimately connected with the question of self–nonself discrimination. The first task of an immune system is to react against virtually any foreign substance. It is well established that an individual can produce specific antibodies to any antigenic determinant in the universe. In fact, the immune system is capable of producing specific antibodies even against all sorts of odd, artificially synthesized chemicals and molecules; ie, the immune system appears to be aware of all future possibilities. Simultaneously with acquisition of immune responsiveness, the immune system must fulfill a second requirement—that is, lack of or minimal reactivity against self-antigens. How such an enormous diversity of immune responses develops, accompanied by a very restricted self-responsiveness, is not as yet known, although several recent findings have greatly advanced our knowledge in these respects.

The great diversity of self-determinants seems to be the driving force that sets the necessary size of the immune repertoire.[36] If the repertoire is limited, then the possibility for self-reactivity via cross-reactions is high. If, on the other hand, the repertoire is large, then the possibility for cross-reactivity against self is greatly reduced. Two major theories offer genetic explanations for the enormous diversity of immunoglobulin (Ig)chain variable (V) regions, which determine the antigen-combining sites.[37,38] The *germ-line theory*, in its most extreme form, postulates that for every V region specificity there must exist a different gene in the germ line. In contrast, the *somatic mutation theory* proposes that a small number of germ-line genes diversify either by point mutations or by recombination events during the differentiation of lymphocytes to create the antibody repertoire *de novo* in each individual. Recent studies by DNA cloning of human and murine cells containing genes for Ig strongly indicate that both germ-line and somatically mutated genes contribute to antibody diversity. Thus, it has been clearly demonstrated that, although a large number of germ-line antibody genes exist (10^4–10^5), further expansion of antibody repertoire occurs via somatic recombinations and rearrangements of separate segments of DNA coding for particular portions of the antibody molecule (V, variable; J, joining; D, diversity; C, constant).[39,40] These multiple gene segments scattered along the chromosome of a germ-line genome assemble during the development of B lymphocytes and form a complete Ig gene (Figure 4). By further substitutions and mutations, especially occurring in V regions of IgG and IgA isotypes and far less, if at all, of the IgM isotype, a vast array of antibodies can be generated. Thereby, the germ-line diversity of 10^4–10^5 antibody specificities is expanded to a total diversity well over a million antibodies. Thus, through a large number of germ-line genes, somatic mutations, and selection of useful variant lymphocytes that react against foreign antigens, great diversity is generated. At present it is unclear at what stage of B-cell differentiation, from stem cell to mature B cell, commitment to an ultimate antibody specificity occurs.[41] However, central to understanding B-cell expression is the fact that most B cells are relatively short-lived (a few days),[42] and thus the repertoire is generated over and over again, presumably from stem cells within the marrow of mature individuals. Apparently lymphocytes are constantly "learning," in an evolutionary sense, throughout the life of their host, but this progress is lost when the animal or a particular clonotype dies, and the lymphocytes of the next generation of vertebrates must start again from the baseline "knowledge" of inherited V genes.

Concerning the second type of immunocyte, namely the T cell, little is proven about the mechanisms that drive its complex diversification. This, in large part, reflects the many unknowns surrounding the nature of T-cell receptors for antigen and such properties as affinity of antigen-binding by such cells, as well as the great technical difficulty, until recently, in obtaining relatively enriched or clonable antigen-specific T-cell populations for analysis. Experiments with murine hematopoietic radiation chimeras strongly suggest that the major organ in which T cells diversify is the thymus,[43–47] via contact or processing by epithelial and giant nursing cells, respectively. Jerne suggested in 1971 that the T-cell receptor repertoire is selected by these cells' reactivity with self-MHC antigens.[37] In Jerne's model, the starting point is an inherited set of T-cell receptor genes each specific for an allelic form of the MHC of the species. That species' total repertoire then reflects the extent of polymorphism for all its histocompatibility antigens. According to this theory and its later modifications by others[47–51] (Figure 5), in the first stage T cells initially specific for self-MHC gene products are selected in the thymus to differentiate and proliferate. The self-MHC antigens expressed in the thymic epithelial cells may be either Class I (K, D, L antigen of murine H-2 or -A, -B, and

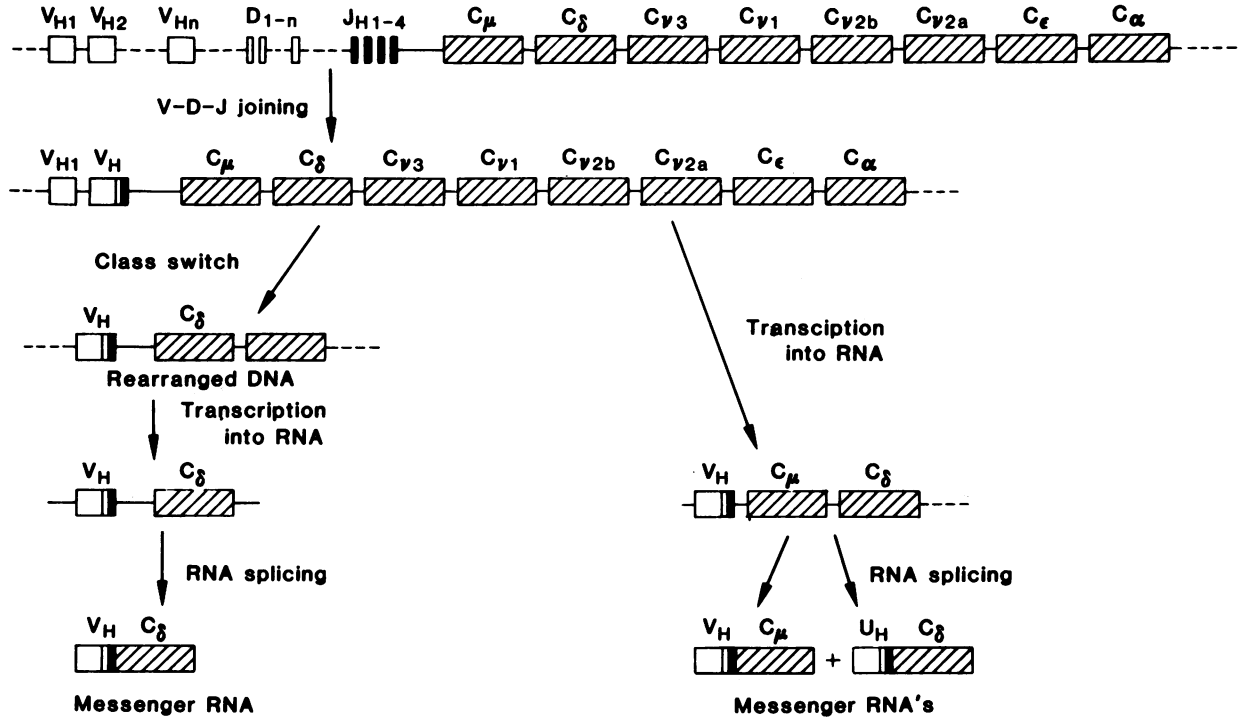

Figure 4—Heavy chain gene assembly. The upper diagram shows the arrangement in germ-line cells of the gene segments for antibody heavy chains. The assembly of a complete variable region gene (V_H) requires the joining of three gene segments, one of those designated V_{H_1} through V_{H_n}, one D, and one J. After V-D-J joining, transcription of the rearranged DNA into RNA, followed by differential splicing of the transcript, allows the simultaneous production of messenger RNAs for two different classes of heavy chain (shown in the right-hand branch of the diagram). The messengers direct the synthesis of either an IgM or IgD heavy chain. The shift to the final class of heavy chain that will be produced by the cell involves a further gene rearrangement (left-hand branch). In this case, the cell will make an IgD heavy chain, and the $C\mu$ gene segment has been deleted to bring the completed variable region gene nearer to the $C\delta$ gene segment. If the cell were going to make an IgA heavy chain, gene segments $C\mu$ through $C\varepsilon$ would have to be deleted. The rearranged DNA is transcribed and the RNA copy spliced to form the final messenger. (From Marx JL: Antibodies: Getting their genes together. Science 1981, 212:1015. Used with permission of the author and publishers)

-C antigens of the human HLA) or Class II (Ia antigens of mice, DR of humans). Stem cells that carry anti-Class I receptors are destined to become cytotoxic, whereas those carrying anti-Class II receptors eventually become helper T cells (see below). Then in a second stage, only those T cells that bear low affinity receptors for self-MHC antigens are allowed to mature and leave the thymus as functional T cells, while the high-affinity anti-self receptor-bearing T cells are eliminated by an unknown process. Such T cells with low reactivity for self-MHC antigens have concomitantly high affinity for allelic variants of self-MHC antigens. These clones of cells account for the high frequency of alloreactive T cells present in man and animals. Simultaneously and independently, the low-affinity anti-self cells modify their receptors, either in the thymus or in the periphery, by rapid mutational events, so as to recognize not only self-MHC antigens but also determinants on conventional thymus-dependent antigens. Recognition of either antigen (self-MHC and non-self-MHC antigen) separately is not enough to trigger T-cell differentiation to effector cells, whereas simultaneous recognition of both antigens delivers a sufficient signal to allow T-cell differentiation. Many modifications of this original postulate as well as new models have been proposed to explain T-cell diversification, alloreactivity, and the roles of the thymus and of self-MHC determinants in T-cell–dependent responses. At present it is a difficult task to prove or disprove any of these hypotheses as long as the T-cell receptor for antigens and the respective genes for such receptors are not identified. Nevertheless, one fact remains clear, as discussed further below: self-recognition is of extreme importance in diversification of repertoire and efficient T-dependent immune responsiveness.

Normal Autorecognition and Autoimmunity

Recognition of Self-MHC by T Cells

Numerous studies on colonial marine forms and flowering plants as well as on more sophisticated and diversified higher animals have demonstrated that

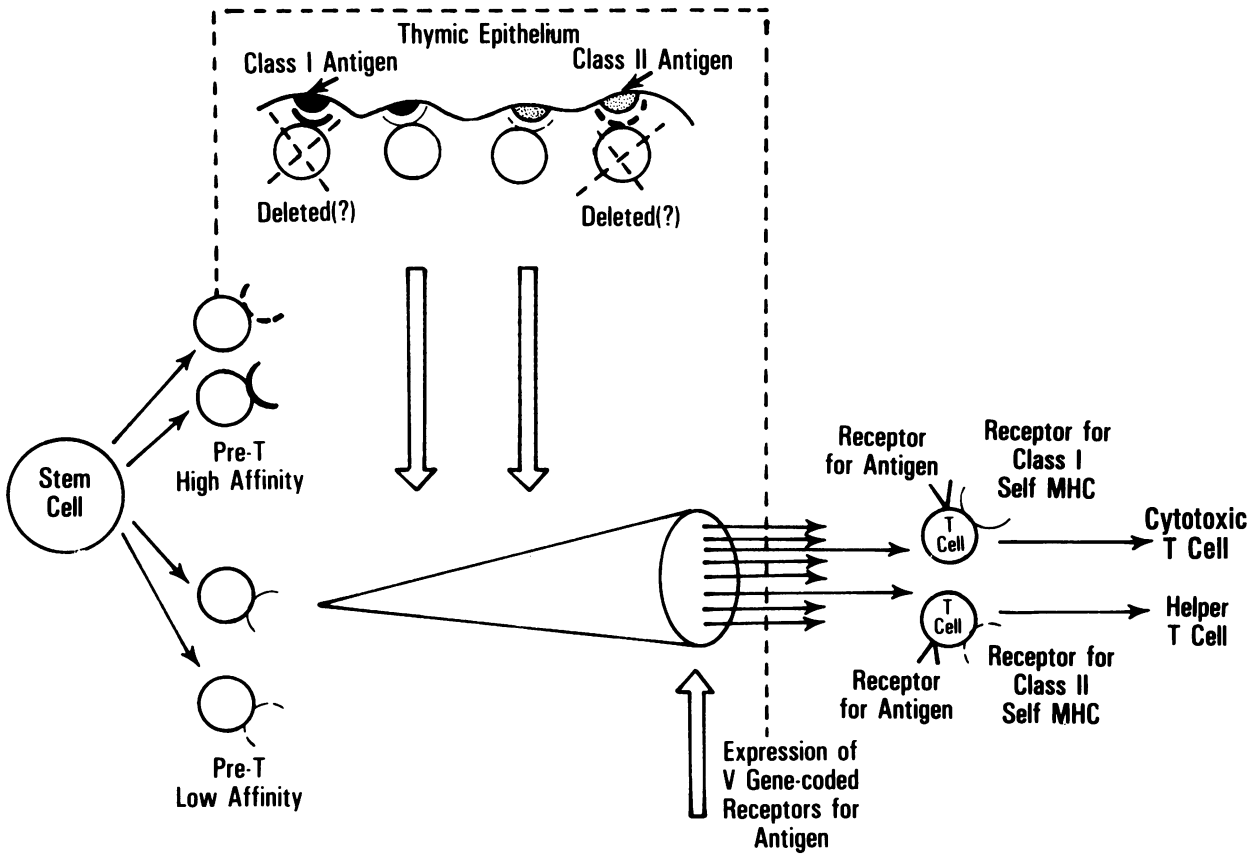

Figure 5—Stages in T-cell maturation and generation of T-cell repertoire (see text).

self-recognition mediated by cell-surface receptors is a fundamental biologic process concerned with many types of developmental and differentiation events.[52] Examples are the lectinlike cell-surface molecules of the cellular slime mold *Dictyostelium discoideum* that determine cellular cohesiveness, the specific cell-surface molecules of simple metazoa and of colonial tunicates that allow formation of colonies, and the cellular receptors on vertebrate embryonic cells that allow appropriate cells to aggregate into tissues and organs. Such self-recognition may occur between cells having identical receptors (like–like interactions), complementary receptors (lock and key interactions), or receptors interacting via a linker molecule.[53]

It has now been demonstrated beyond any doubt that certain elements of the vertebrate immune system preserve and express throughout life such a self-recognition capacity, and that it is an apparent requisite for the normal functioning and diversification of the immune system. This conclusion, now a fundamental tenet of immunologic theory and a radical departure from orthodox concepts of the near past, evolved during the last decade after discovery of the need for collaboration between the various cellular elements of the immune system for efficient responses.[54,55] The initial finding for most antigens was that collaboration between T-helper cells and precursors of effector cells (B cells, T-cytotoxic cells, T-suppressor cells) is required for antigen-driven differentiation to mature effector cells. In addition, T-helper cell differentiation begins only after association with antigen-presenting macrophages or antigen-expressing cells. In contrast, B cells and T-suppressor cells can proliferate after contact with free soluble antigen. Significantly, in murine humoral responses, T-cell help is initiated and delivered only if the T cells, B cells, and antigen-presenting macrophages are compatible at the MHC, more specifically at the I region (D/DR region for human HLA).[56,57] The complete uncovering of the MHC's role and self-recognition in immune responses came by virtue of the discovery that T-cell–mediated immunity and efficient killing of virus or hapten-modified cellular targets also required identity of the effector T-cytotoxic cells and target cells at the MHC, more specifically, at the K and/or D region of the murine H-2 (A and B for HLA).[47,58] This phenomenon, applicable to both T-helper and T-cytotoxic cells was termed the *MHC restriction phenomenon* and found to be operative in many species, including man, and in both *in vitro* and *in vivo* conditions. The

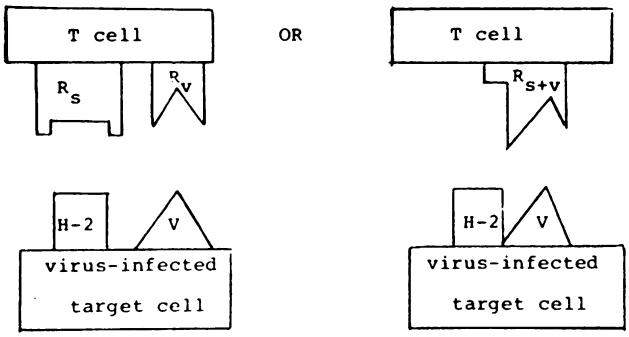

Figure 6—The one-receptor, two-receptor hypothesis for cytotoxic and helper T-cell recognition. It is still not clear whether the T cell expresses one receptor specific for self H-2 (Rs) and another that recognizes non-self-antigen (in the illustrated instance viral antigen, Rv), or a single receptor that recognizes a complex of self-H-2 and non-H-2 antigens (in the illustrated instance viral [V] antigens). (From Doherty PC, Bennink JR: Monitoring the integrity of self: Biology of MHC-restriction of virus-immune T-cells. Fed Proc 1981, 40:218. Used with permission of the authors and the publishers)

restriction and interaction of T cells with self-MHC-bearing stimulator cells results not from a like-like interaction between T cells and stimulator cells, but from a true T-cell anti-self receptor.[47,49]

A key question raised by MHC-restriction concerns the nature of the T-cell receptor. Two models have been proposed to explain the dual specificity of subsets of T cells for antigen and self-MHC products[47-49] (Figure 6): 1) The *two recognition sites model* states that T-helper and T-cytotoxic cells possess two separate recognition sites that are specific for two separate antigens on macrophages or target cells, respectively. One receptor site binds to the restricting self-MHC; the other receptor site binds to the cell surface associated non-MHC antigen. 2) The *single recognition site model* states that T cells express a single receptor site that is specific for a single neoantigenic determinant formed when the self-MHC complexes with the foreign antigen on macrophages or target cells. At present, no definite proof exists for either model, and convincing arguments for both models as well as additional models[59,60] have been presented. Nor has the nature of the T-cell receptor been clearly defined, although strong evidence implicates the V region of Ig heavy chain as responsible for both the specificity directed to MHC and the specificity for non-MHC antigenic determinants.[61-63]

Exactly why T cells are MHC-restricted and must recognize self together with foreign antigen for optimum participation in humoral and cellular responses is unknown. This dual recognition could quite well act as an efficient stimulus for T cells endowed with low-affinity receptors for foreign antigen only. Such dual recognition would appear to be advantageous for survival of the species.[64,65] For example, cytotoxic T cells seem to be essential for recovery from some acute primary viral infections. By recognizing and lysing virus-infected cells displaying viral antigens plus self-MHC antigens, before assembly of progeny virus particles, these T cells limit viral multiplication. If their antigen receptors bound avidly to free antigen (viral) molecules, these receptors would be inhibited in binding to foreign antigen on an infected cell's surface, thus reducing the cytotoxic T cell's antiviral function. Evolutionary pressure would therefore lead to retention of the self-recognition capability in cytotoxic T cells, which presumably evolved from a self-recognition system that existed before the appearance of adaptive immune responses. Regardless of the reason, generation of effector immune functions require that T cells recognize self-MHC along with an extraneous antigen.

Recognition of Self-Ig V Region Determinants and the Idiotype-Antiidiotype Network

As summarized above, responses of T cells to self-MHC antigens play an essential role in *initiating* both humoral and cellular immune responses. We shall see now that responses to self may also play a role in *regulating* these immune responses.

Clearly, the immune system interacts with antigenic determinants, also called *epitopes*, via antigen-combining sites present in the hypervariable regions of V domains within Ig molecules either on the surfaces of or secreted by lymphocytes. The B cells probably express the whole Ig molecule as their receptors but the T cells appear to express only the combining site derived from the V domains of heavy chains.[61-63] During the 1950s and thereafter important discoveries clearly demonstrated that an antibody molecule has a dual character, acting to recognize a given antigen and, in turn, itself becoming immunogenic, even in the animal that produces this antibody.[66,67] The hypervariable regions of a given Ig alone can act as antigenic determinants to generate another set of antibodies that recognize the uniqueness of that Ig as distinct from antibodies of different specificities. Sets of antigenic or epitopic determinants of Ig V domains were termed *idiotypes*, and the antibodies elicited against them were termed *anti-idiotypes*.[68-70] Each single idiotypic epitope located on different portions of the V region was called an *idiotope*. An anti-idiotope antibody does not react with the entire array of idiotypic determinants of an Ig molecule, but only with a single determinant, the *idiotope*. However, anti-idiotypic antibodies of a single specificity may be

represented in different Ig classes. Idiotypic determinants have been described that are on V_L alone, V_H alone, or both, involving either antigen-binding sites or noncombining sites (framework regions) of the V domains[68-71] (Figure 7). Idiotypes representing antigenic differences of Ig molecules at the V region differ from *allotypes*, which result from inherited variations (polymorphism) in the genes coding for certain amino acid sequences in the constant region (C region) of Ig molecules,[72,73] and from *isotypes*, which depict the different C regions found on Ig molecules ($C\mu$, $C\delta$, $C\gamma_3$, $C\gamma_1$, $C\gamma 2b$, $C\gamma 2a$, $C\varepsilon$, Ca). Both B cells and T cells, as well as their soluble products (antibodies, antigen-specific T-cell-derived helper and suppressor factors), express idiotypic determinants.[63,68] Moreover, in accord with the clonal selection theory of Burnet (see below), the idiotype of Ig secreted by an antibody-forming B cell is the same as that of the cell-surface Ig receptors for antigen.[74] The number of idiotypes that an individual possesses is apparently as large as one's range of antibody specificities or repertoire, actual and potential.

The responses of animals to most antigens involve several clones of reactive cells producing antibodies that have many idiotypic specificities or antigenic differences in the V region. However, after antigenic challenge, sometimes just a few clones of lymphocytes expand, resulting in the expression of a dominant idiotype. Idiotypic cross-reactions in inbred animals such as mice are not uncommon, especially among antibodies directed against relatively simple antigenic determinants. In most cases, cross-reactive idiotypes show linkage to allotypic markers present on the constant region of the Ig heavy chains.[75] In contrast, most outbred animals[76] and humans[77] infrequently express cross-reactive idiotypes consistent with the broadly heterogeneous regions that can combine with the different antigenic determinants present on a complex antigen. Nevertheless, even in outbred species, cross-reactive idiotypes are occasionally present[78-81] either as a result of inheritance of antibody genes among related individuals or preservation and sharing of certain germ-line genes by unrelated individuals within the species.

The dual characteristics of antibody molecules and the apparent presence within an individual's repertoire of V genes with specificities for other V region products stimulated Jerne to propose in 1974 that autoimmune responses to self-idiotypes might form the basis of immunoregulatory network systems in which homeostasis is preserved through a functional assembly of idiotype-anti-idiotype interactions.[69,70] According to this model, an antigen induces the production of an antibody (Ab_1) characterized by its idiotype (Id_1). In turn, the latter stimulates the synthesis of an anti-idiotypic antibody (a Id_1 or Ab_2) bearing the idiotype Id_2 that can trigger the production of anti-(anti-idiotypic) antibody (a Id_2 or Ab_3), and so on. Initial models of the network system suggested that the network was open-ended and of unlimited extent, whereas more recent studies tend to support a circular configuration of limited sets of idiotypes and anti-idiotypes.[82] According to network theories, for every *paratope* (antibody combining site of an antibody molecule) a complementary fitting idiotope on another antibody molecule can be found, and vice versa. Such an idiotope must be stereochemically (three-dimensional shape) similar to the epitope on the antigen against which the antibody was originally directed. Jerne calls the subset of Ig molecules that contain these idiotypes the "*internal image set*,"[69] and Lindenmann calls them "*homobodies*."[83]

Jerne assumes that such an idiotypic-anti-idiotypic

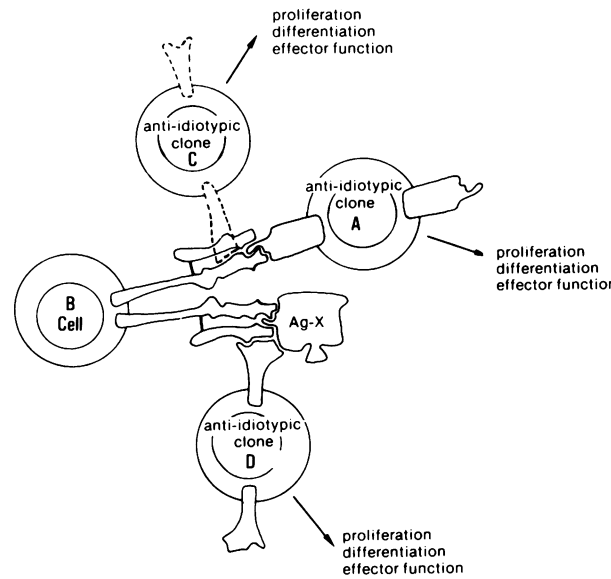

Figure 7—Specificity of anti-idiotypic antibodies. In this model a B-cell clone is the predominant clone reacting to an antigenic determinant on antigen X (Ag-X). Having expanded to the point that its antigen-binding receptors reach an immunogenic level, the B clone stimulates three separate lymphocyte clones, each of which possesses surface receptors that recognize idiotypic determinants on the immunoglobulins expressed by the B clone and its progeny cells. Anti-idiotype clone A recognizes idiotypic determinants within the antibody combining site, whereas clone C recognizes H-chain idiotypic determinants outside the combining site, and clone D recognizes L-chain idiotypic determinants in combination with determinants on antigen X. Each of these anti-idiotype clones could be in the T-cell or B-cell series, and the cells or their products could express helper or suppressor functions, leading respectively to idiotype-specific augmentation (positive feedback) or inhibition (negative feedback) of this immune response. In turn, since each anti-idiotype expands to the point that its antigen-specific receptors reach immunogenic levels, anti-(anti-idiotypic) responses of a positive and negative type could be induced. (Modified from Hood LE, Weissman, IL, Wood WB: Immunology. Menlo Park, Calif, Benjamin/Cummings Publishing Co., 1978. Used with permission of the authors and publishers)

network is functional, which means that its regulation should account for the various modes of the immune response (steady state, enhancement, suppression). One must infer that suppressive interactions dominate stimulatory ones in order to avoid the aberrant proliferation of clones. Moreover, before antigenic challenge, the system is in a virgin state that can be regarded as a stable reference state. Upon the introduction of antigens, macroscopic perturbation occurs and drives the system toward a new steady state characterized by immune memory or tolerance.

By now the idiotype network concept is widely accepted because of a rather impressive accumulation of data in support of its existence and functional importance. Thus, autoanti-idiotypic antibodies as well as operational suppressive and enhancing networks have been described. Autoanti-idiotypic antibodies have been detected in mice immunized with T-independent antigens such as phosphorylcholine, bacterial levan, trinitrophenyl (TNP)–Ficoll and others.[82,84-87] Apparently, antibody titers and numbers of specific antibody-secreting plaque-forming cells decrease, while the amount of autoanti-idiotypic antibodies increase, which seems to indicate that autoanti-idiotypic antibodies exert negative feedback on expression of the immune response. Moreover, in accord with predictions made by the network theory, when experimentally produced anti-idiotypic antibodies are administered passively to animals, suppression or enhancement of the relevant idiotype may ensue.[68,88-93] This is accomplished via the interaction of sets of B cells, T-helper and T-suppressor cells bearing complementary idiotypic and anti-idiotypic determinants, identical idiotypic determinants through an antigen bridge or an anti-idiotype bridge, or identical anti-idiotypic determinants through an idiotype bridge. For suppressive effects, the following hypothetical sequence of events could take place[89] (Figure 8A). First, antigens (in the illustrated instance, a T-independent antigen) induce proliferation of B lymphocytes whose receptors are characterized by Id_1. In a first step, precommitted precursor PB_1 cells differentiate into mature B_1 lymphocytes. The latter proliferate and differentiate into plasma cells (in the figure depicted as Z_1) secreting an antibody Ab_1 characterized by Id_1. Ab_1 recognizes and eliminates the antigen. Its idiotype, Id_1, stimulates the proliferation of anti-idiotypic (αId_1) B_2 cells, which differentiate from the precurosr PB_2. Presumably, this step is dependent on T cells that carry αId_1 receptors, since it has been established that an immune response to an Ig molecule requires helper T cells.[94] The B_2 cells differentiate into Z_2 plasma cells secreting αId_1 (Ab_2) antibodies, which act negatively on the Id_1-bearing B_1 cells. Anti-idiotypic antibodies, upon attaining concentrations above a critical threshold, can also exert negative influences on these idiotype-expressing cells by engaging subsets of suppressor T cells that express the relevant anti-idiotype. An intermediate T-helper cell whose receptor would express Id_1 idiotype may be necessary for interaction with anti-idiotypic antibodies and induction of anti-Id_1–bearing suppressor T cells (Figure 8B). By studying idiotype-induced suppression in mice, Nisonoff and Greene and Sunday et al have subdivided suppressor T cells into three populations.[95,96] The first population (Ts_1) is $Lyt1^+$, bears I-J and idiotypic determinants, and functions in a non-H-2(?) or V_H-restricted manner during the induction phase of the immune response. The Ts_1 population secretes a factor (TsF_1) that, together with antigen, induces a second complementary population of suppressor cells (Ts_2) that bear Lyt2 alloantigen, I-J determinants, and anti-idiotypic receptors. The latter population functions in an H-2 and V_H-restrictive manner during the effector phase of the immune response in previously primed animals. However, this second population does not contain the final suppressor T cells. The available data suggest that the Ts_2 cells, via a soluble factor (TsF_2), activate a third population of Lyt2, I-J, and idiotype-bearing T cells (Ts_3), the possible final suppressors in the immune recipient.

Anti-idiotypic antibodies can also induce enhancement of immune responses instead of suppression.[68,93] This can result either 1) from the stimulation of idiotype-bearing helper T cells that then induce idiotype-bearing B cells or 2) from the elimination of specific suppressor T cells. In this last instance, anti-idiotypic antibodies (αId_1, Ab_2) might induce the production of anti-anti-idiotypic antibody (αId_2, Ab_3), which is assumed to suppress the production of αId_1 antibody by B cells, on the one hand, and to eliminate αId_1-bearing suppressor cells, on the other.

Thus, various experimental models seem to indicate that idiotypic interactions, essentially autoimmune in nature, can play an important role in functional regulatory circuits of the immune system and in promoting communications between T and B cells. The system emerges as a self-contained, highly organized network of complementary T- and B-cell surface-bound and soluble idiotypes that is constantly engaged in self-recognition. If one agrees that idiotypes may sterically represent mirror images of antigens, then it would be reasonable for one to assume that the immune system accepts the structural diversity in the universe as nothing new or strange, since "it sees" these structures continuously in its complementary circuits. According to this extreme, yet provocative

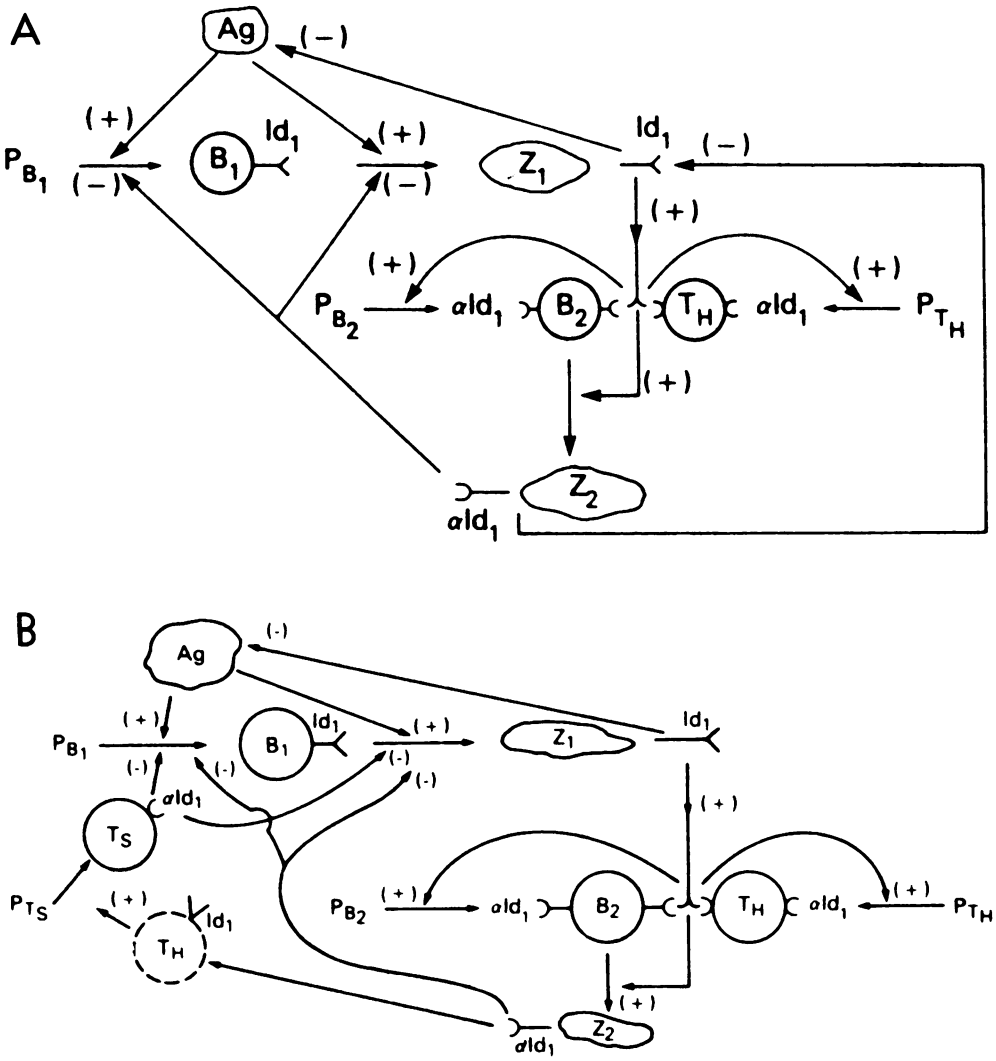

Figure 8A – Regulatory interactions leading to the production of autoantiidiotypic antibodies (αId_1), which suppress the proliferation and differentiation of Id^+_1 clones in the case of a T-independent response. P_{B_1} and P_{B_2}, respectively, are the precursors of B_1 and B_2 cells. Z_1 and Z_2 cells differentiate from the corresponding B cells. P_{T_H} are the precursors of the T helper (T_H) cells. Id_1 antibodies are specific for the antigen, whereas (αId_1) antibodies are specific for the idiotype Id_1. The sign + corresponds to activation and the sign – to inhibition. **B** – Regulatory circuit corresponding to a suppressive type of network where idiotype-specific T suppressor (T_S) cells are generated in the course of a T-independent response. P_{T_S} are the precursors of the T_S cells. The other elements of the circuit have been defined in the legend of Figure 8A. (From Hiernaux J: Antiidiotypic networks. Fed Proc 1981, 40:1484. Used with permission of the author and the publishers)

view, "foreign" determinants are in fact never foreign; and, consequently, challenge with non-self antigens is an epiphenomenon that does not set in motion any novel element in the system but only perturbs it until it reaches a new steady state.[91,97]

Theories of Tolerance Induction

Despite the foregoing conclusion that vertebrates have all the genetic information necessary to respond immunologically against self- and non-self-constituents and can induce and regulate their immunologic apparatus via self-recognition processes, the normal immune system is in general phenotypically tolerant to self.

There exist two types of tolerance, central and peripheral.[2] In central forms, no antibody is produced at all after antigenic challenge, since the responsible immunocytes are missing (clonal deletion) or are silenced (clonal anergy) directly. In peripheral forms, some antibody is initially produced; but then, due to the expression of suppressive mechanisms (suppressor T cells, antibodies, anti-idiotypes, and immune complexes), antibody production diminishes greatly or halts.

Early studies demonstrated that tolerance to self is acquired through an active process that involves a direct contact between self-components and specific antigen-reactive cells. For example, removal of the hypophysis from a tree frog during early life (tadpole), subsequently allowing the gland to differentiate in isolation from its donor, and, finally, transplanting the organ back into the mature donor result in rejection instead of acceptance.[98] Moreover, animals that are genetically deficient in certain proteins still make antibodies when given injections of the proteins.[99,100] After studying responsiveness to ex-

ogenous antigens in experimental animals, and assuming that responses against them are controlled by mechanisms similar to those for endogenous antigens, investigators have advanced several hypotheses to explain the apparent unresponsiveness to self by an individual that has the genetic information to do so.

The first serious attempt to explain how self-unresponsiveness might be acquired was undertaken by Burnet as a corollary to his clonal selection hypothesis.[101] He was the first to introduce the concept of the immunologic *clone*, a subset of immunocytes all having identical receptors for antigen. Burnet's clonal selection theory of acquired immunity proposed that virgin clones of immunocytes circulate in the body awaiting contact with their specific antigens, after which they undergo blast transformation and divide repeatedly to produce thousands of descendant cells of the same specificity. This concept followed Jerne's postulation that antibody molecules are not fashioned on a template formed by an invading antigen, but are preformed, waiting to be selected by their complementary antigen.[102] In other words, antibodies are made before the exposure to antigens, and their combining site specificity is solely determined by structural genes upon which antigens have no influence other than inducing proliferation of the clone that expresses the specific idiotype or V domain for that antigen.

In any event, Burnet[101] proposed that immune tolerance to self-antigens is subserved by a mechanism that causes fetal immunocytes to be deleted by contact with their specific autoantigen (*clonal deletion*, holes punched in the repertoire) (Figure 9). This proposition originated from the work of Owen,[103] who first demonstrated that contact with foreign antigenic substances during early life resulted in immunologic tolerance. He observed that mature dizygotic twin cows tolerated each other's body tissues in that they did not reject mutual grafts. Undoubtedly, the tolerance resulted from embryonic parabiosis in which blood was exchanged between the twins. Subsequently, Billingham, Brent, and Medawar[104] found that adult mice of an inbred strain tolerated skin grafts of a second inbred strain if, as newborns, animals of the first strain were injected with replicating cells of the second strain. For the development of autoimmune diseases, Burnet suggested that precursor lymphocytes committed to non-self but related to self-antigens mutate during their multiplication and accidentally make lymphocytes reactive to self.

The above theory was later redefined and expanded by Nossal and associates, who coined the terms *clonal abortion*, *clonal anergy*, *clonal silencing*, and *clonal purging*, all to describe the same event.[105] Nossal proposed that at some stage in their differentiation from stem cells to mature antibody-forming precursor cells, B lymphocytes go through a phase during which contact with antigen (whether endogenous or exogenous) induces only tolerance and not immunity (Figure 9). This phase is referred to as the *tolerance-sensitive* or *obligatory paralyzable phase*. The concept is based on work *in vivo* and *in vitro* showing that the amount of antigen required to produce an effective negative signal varies enormously with the B cell's degree of maturity. If a hapten, polyvalently substituted on essentially any carrier moiety, is allowed to act for several days on lymphocytes *in vivo* and then for a brief time *in vitro*, a typical situation producing tolerance might be one in which mature B cells need a high antigen concentration, for example, 2×10^{-7} M; immature B cells need 5×10^{-10} M, and cells "caught" in the pre-B to B transition need 5×10^{-13} M, for 50% of the cells to become tolerant. There is, then, a several-fold sensitivity difference between the extreme cases, and one should remember that the physiologic circumstance engendering acquisition of self-tolerance is that a B cell first encounters antigen during the pre-B to B transition. Further experiments showed that the early, tolerance-inducing encounter between antigen and immature B cells did not lead to death of the tolerant cells. In other words, the immature B cells received and stored some negative signal without having been eliminated. Given that an animal can have antigen-binding B cells incapable of reacting to antigen and present in a functionally silent state, the process whereby such tolerance is induced was more accurately redefined as "clonal anergy" than "clonal abortion" or "clonal deletion."

Additional studies clearly demonstrated the ease of inducing tolerance in neonatal spleen cells and bone marrow cells of neonates and adults with a concomitant resistance of tolerance induction in adult splenocytes.[41,106] Significantly, spleens of adult animals contain a minor subset of immature B-cells that can be tolerized as easily as neonatal B cells.[107] This finding suggests that the ease of tolerance induction is not a unique property of neonatal cells but of immature B-cells, in general, which are continuously produced throughout life. Subsequent experiments[108] showed that tolerance induction in immature or neonatal B-cells requires 1) protein and DNA synthesis, an active process that cannot be explained simply by a passive phenomenon such as receptor blockade, and 2) multivalency of the inducing antigen. This last finding suggests that receptor cross-linking is involved in negative signal generation and that many autolo-

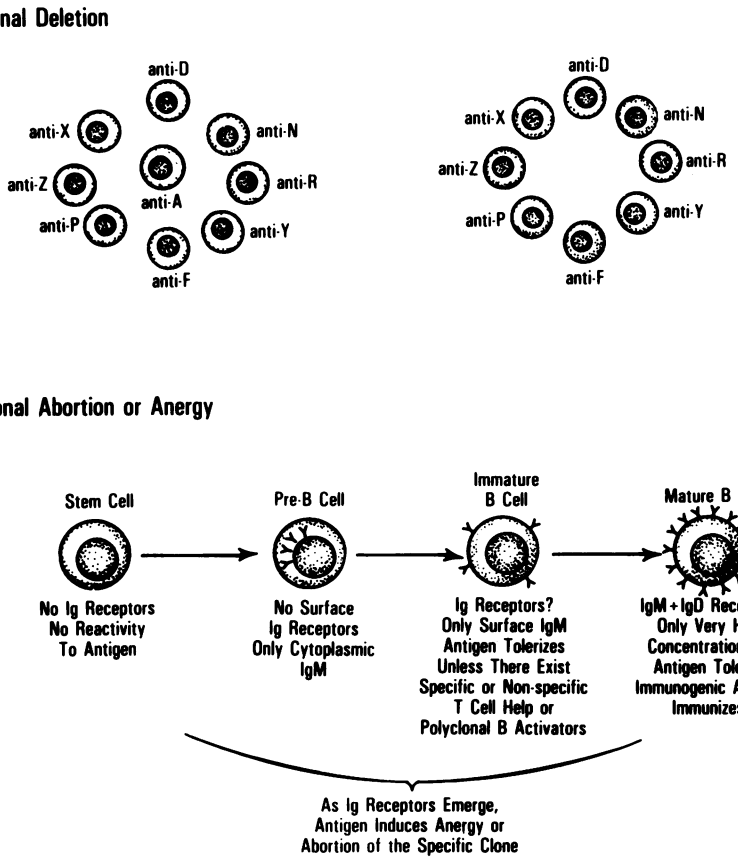

Figure 9—The clonal deletion and the clonal abortion theories of B-lymphocyte tolerance. (Modified from Nossal GJV, Pike BL: Antibody receptor diversity and diversity of signals, Immunology 80—Progress in Immunology. London, Academic Press, 1980, p 136. Used with permission of the authors and publishers)

gous proteins, present in serum and extracellular fluids in monovalent form, may not induce self-tolerance by this mechanism unless they become associated with certain cell membranes, thereby gaining operational multivalency. Of course, many key self-antigens are presented to the developing lymphoid system predominantly in multivalent form, such as the MHC determinants, which exist as cell membrane macromolecules.

The particular tolerance sensitivity of immature B cells was reinforced in experiments showing that fetal and neonatal spleen B lymphocytes, unlike adult splenocytes, were highly sensitive to suppression of cell surface Ig (antigen receptor) expression after exposure to heterologous anti-Ig antibodies.[109,110] Similar susceptibility can be observed in adult bone marrow B lymphocytes, clearly indicating that newly formed B-cells are susceptible to ligand-induced inactivation throughout life. These observations strongly suggest that interaction at the cell surface receptors of B lymphocytes at a particularly sensitive stage of the maturation cycle, regardless of this interaction's antigen specificity or nonspecificity, results in functional inactivation of such cells. At least in the case of anti-Ig modulation, this inactivation is expressed by the inability of such cells to replace receptors on their surface membranes. Whether or not this process involves inhibition of further intracellular Ig synthesis or, rather, reflects a cell's inability to transfer the intracellular Ig to the cell surface membrane has not been established. Nor has it been determined at the molecular level why immature B cells are so much more easily induced to become tolerant and inactive than their mature counterparts.

Until recently there was no clear indication that the T-lymphocyte class undergoes a central form of tolerance, in the sense of classic clonal deletion or anergy described above for B cells. However, the recent development of methods to produce clones of cytotoxic T lymphocytes from single precursor cells has enabled Nossal and Pike to address this question.[111] They find that a profound and long-lasting deficit in activated cytotoxic precursors, first demonstrated by the fifth day of life in the thymus and the eighth to tenth in the spleen, develops in mice rendered tolerant to semiallogeneic cells when newborn. Whether this represents their destruction through early contact with antigen (clonal deletion), their functional silencing through a mechanism akin to B-cell "clonal anergy" described above, the *in vivo* action of suppressor

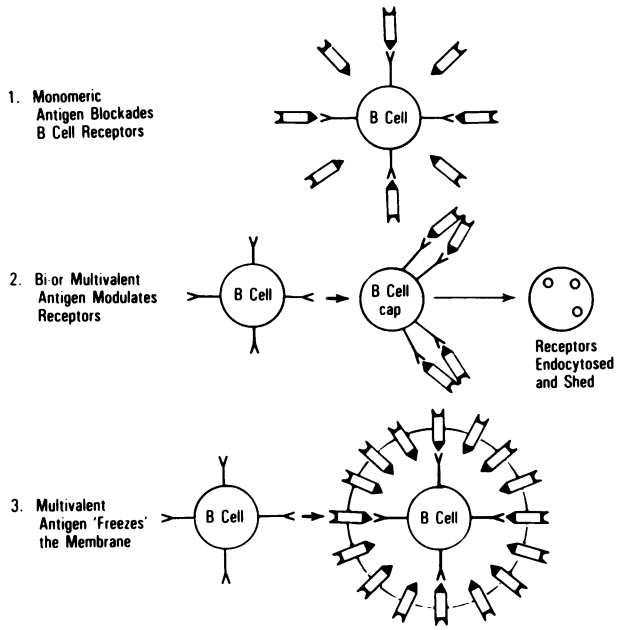

Figure 10—Antigen-blockade mechanisms of B-lymphocyte tolerance. (From Nossal GJV, Pike BL: Antibody receptor diversity and diversity of signals, Immunology 80—Progress in Immunology. London, Academic Press, 1980, p 136. Used with permission of the authors and publishers)

cells preventing their emergence, or some mixture of these phenomena remains to be determined. Experiments in murine lymphoid populations *in vitro* indicate that phenotypic deletion of inducer Lyt1$^+$ cells with specific helper activity and Lyt1$^+$ cells that induce suppressor cell activity by suppressor T cells may occur,[112] thereby suggesting that T-suppressor activity promotes clonal deletion of T-cell subsets such as helper and cytotoxic cells.

Centrally induced tolerance might otherwise result from antigen- or ligand-induced inactivation of immune responsiveness (Figure 10). The term *ligand-induced inactivation* is used in a broadly descriptive sense to indicate the loss of reactivity in a population of specific immunocompetent lymphocytes as a direct consequence of interaction between antigenic determinants and the cell surface receptors binding such determinants under circumstances or conditions that are either particularly unfavorable to triggering or are particularly favorable to inactivation of the cell.[2,54,105] Monomeric antigens could be incapable of signaling the immunocyte, in which case, at high molarity, they could occupy the B or T cells' antigen receptors sufficiently well to prevent macrophage-associated or other immunogenic forms of antigen from gaining access to these cells. Perhaps of relevance is that aggregate-free forms of antigens are much more tolerogenic than the aggregated forms.[2] Bivalent to multivalent antigens could, on the other hand, induce tolerance by depriving the cell of its antigen receptors through the patching-capping-endocytosis cycle, a process that has been called modulation. The example of anti-Ig-induced inactivation of immature B cells discussed above may be related. Finally, a third possibility is that high concentrations of certain multivalent antigens, especially those that are linear with repetitive units more or less equally spaced along the membrane, can immobilize antigen receptors, thus "freezing" the membrane and inhibiting transmission of stimulatory signals.

The absence of autoimmune reactions, in addition to resulting from clonal abortion or anergy as well as antigen blockade, may be partially caused by continuous and active suppression exerted peripherally by subsets of T cells, the so-called *suppressor T cells*[2,54,105,113,114] (Figure 11). In such instances, suppressor T cells may carry anti-idiotypic determinants for interacting with and silencing a B cell that carries the complementary idiotype, or they may antagonize the action of a helper T lymphocyte as outlined in the previous and subsequent sections.

Mice apparently develop three types of T cells:[114-116] Inducer cells, suppressor cells, and an intermediate cell type that acts on both inducer and suppressor cells. These cell types, apart from having separate and distinct physiologic functions, can be identified by characteristic surface markers associated with each. T cells containing the surface glycoprotein Lyt1$^+$ are known as inducer or initiator cells, since they induce or activate other effector cells sets

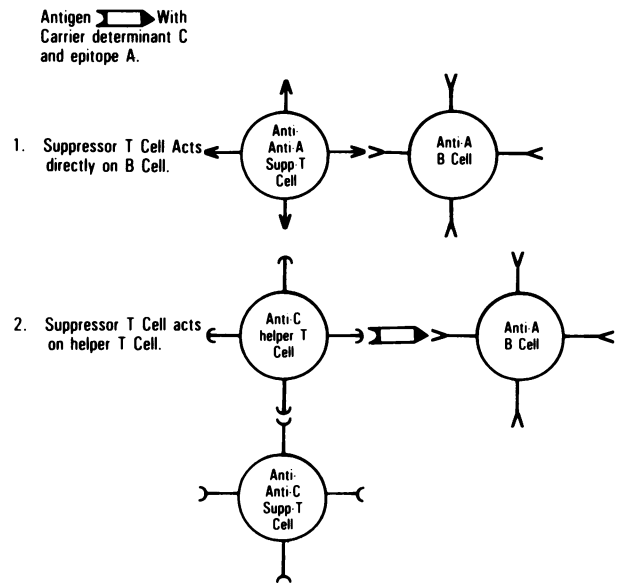

Figure 11—Suppressor mechanisms of B-lymphocyte tolerance. Suppressor T cells with complementary anti-idiotypic determinants may act either directly on B cells or on helper T cells. (From Nossal GJV, Pike BL: Antibody receptor diversity and diversity of signals, Immunology 80—Progress in Immunology. London, Academic Press, 1980, p 136. Used with permission of the authors and publishers)

to fulfill their respective genetic programs. These Lyt1$^+$ cells act to stimulate B cells to antibody production, induce macrophages and monocytes to participate in delayed type hypersensitivity reactions, and stimulate precursors of cytotoxic T cells to differentiate to killer-effector cells. Moreover, they induce a set of resting nonimmune T cells of the phenotype Lyt123$^+$, a precursor pool of cells that regulate supply and function of the more mature Lyt1$^+$ inducer and Lyt2$^+$ suppressors, to generate potent feedback inhibitory activity via the suppressor T-cell subset. Depending on the expression of surface alloantigens encoded by the J subregion of the I region of the murine MHC, the inducer Lyt1$^+$ cells, playing a pivotal role in the type of immune response produced, have been subdivided into two subsets: Lyt1$^+$:I-J$^+$ are inducers of suppressors, whereas Lyt1$^+$:I-J$^-$ are inducers of antibody secretion. The nature of these inducer T–B-cell interactions is not completely defined, but one possibility is that the T-inducer antigen-receptor structure related to the V region of Ig heavy chains may trigger only B cells that bind the same antigen and carry similar idiotypic determinants.

In contrast to Lyt1$^+$ inducer cells, cells of the Lyt2$^+$ set, representing approximately 10–20% of the T-cell pool (current studies with monoclonal antibodies suggest that all murine T cells carry varying densities of Lyt1$^+$ alloantigen[117]), are specifically equipped 1) to develop cytotoxic activity against alloantigens and hapten- or virus-modified target cells, 2) to suppress both humoral and cellular immune responses after immunization, 3) to amplify suppressor activity, and 4) to induce other cells to countermand suppressor signals (contrasuppression).[116] Suppressor and cytotoxic cells are probably two different subsets, and there probably is more than one type of suppressor T cell. Initial suppression of inducer Lyt1$^+$ T cells is brought about by suppressor T cells secreting antigen-binding protein that expresses MHC determinants (usually I-J) and idiotypic V region determinants. Such suppressor T cells then induce other idiotypically complementary subsets of suppressor T cells that, via complex interactions among themselves and with inducer T cells and B cells, finally diminish an immune response. A simplified version of these types of interactions is given in Figure 12. The induction of suppressor cells to many antigens is under the control of immune response (Ir) genes.

From the above description it becomes apparent that the immune system has evolved complex but sophisticated methods for preventing excessive responses to antigenic stimulation. In fact, the majority of immunologic cells do not seem to be effector cells ready to respond to foreign antigens, but regulatory

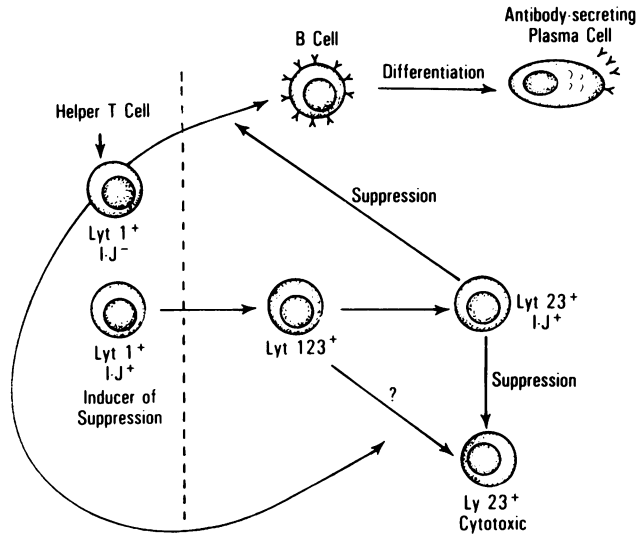

Figure 12—Regulatory circuits of murine T cells.

cells that respond to messages originating from within the immune system itself in the form of cell-surface-bound and soluble idiotypes and anti-idiotypes. Although the role of suppressor cells in tolerance induction and regulation of responses against conventional antigens, transplantation antigens, allotypes, and idiotypes is well-documented,[114] the importance of these cells in inducing tolerance to autoantigens and in preventing autoimmune responses remains unproven. Newborn animals appear to have an excessive number of suppressor T cells in the thymus and spleen; nevertheless, experimentally suppressor T cells are associated more with tolerance induction in adult life than in neonates. Certain antigens have been described that carry epitopic determinants endowed with the ability to interact specifically with suppressor but not helper T cells.[118]

Additional peripheral means of tolerance induction include circumstances in which the antibody alone or in the form of *immune complexes* in antibody excess may act suppressively relative to the ongoing response.[2,11] Suggested mechanisms[11] (Figure 13) of antibody and/or immune-complex-mediated suppression include 1) antigen shielding or masking by antibody, resulting in blockade of antigen recognition by antigen-receptor-bearing lymphocytes, 2) activation of IgG Fc-receptor-bearing suppressor T cells with subsequent release of soluble factors that suppress helper T cells, and 3) direct stimulation of B cells with Fc receptors to secrete soluble suppressor factors. Although some forms of antibody-induced suppression require the Fc portion of the molecule, others do not. Some suggest that suppressive effects exerted by high concentrations of antibody are independent of the Fc portion, whereas those exerted by

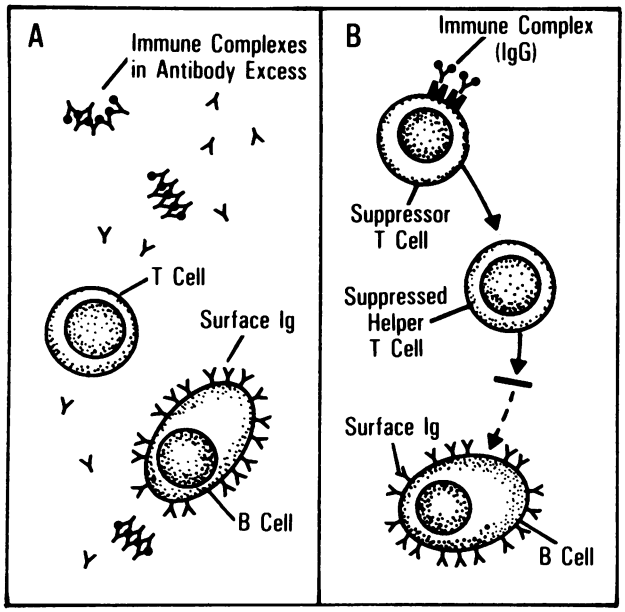

Figure 13—Suppression of immune responses by antigen-antibody complexes. **A**—Antigen shielding or masking by antibody (blockade of antigen recognition by antigen-receptor-bearing B and T cells). **B**—Activation of IgGFc-receptor-bearing suppressor T cells with release of factors that suppress helper T cells.

low concentrations are Fc-dependent. Antibody and/or immune complexes may also serve as "blocking factors" that impede an effective immune response to such cell-associated antigens as those on tumor cells. The premise is that such a response requires access of cytolytic T cells to antigenic determinants on the cell surface. However, stimulation of humoral immune responses and subsequent complexing of antibodies with antigen in the circulation may result either in masking of the antigenic determinants or occupation of the antigen receptors on the cytolytic cells, thus blocking these cells from access to and direct interaction with the target cell (Figure 14). Interestingly, autologous anti-idiotypic responses of mice to tumor-specific lymphocytes were found to suppress tumor regression, presumably via occupation of the antigen receptors on cytotoxic cells.[119]

Means for inducing tolerance or unresponsiveness varies, in that some inhibit immune responses centrally by paralyzing or silencing the responding cells, others by acting peripherally via suppressor cells or antibodies. Central forms of tolerance appear to be more compatible with the expected mechanisms for induction of tolerance to self.[2] However, the mechanisms described above should not be regarded as mutually exclusive. Indeed, it seems certain that different forms of the tolerant state result from separate mechanisms, and a diversity of mechanisms may operate simultaneously. Because self-antigens occur in diverse forms and concentrations, undoubtedly the same is true for physiologic self-tolerance.

Etiopathogenesis of Autoimmune Diseases

Many theories and mechanisms have been proposed for the generation of autoimmune responses (Table 2). Their theoretic bases, pertinent examples, and controversies concerning each are presented below, with findings in man and appropriate experimental animals, especially SLE-prone mice, summarized in parallel. Reviewing the available evidence, one must surmise that such spontaneous diseases have a multifactorial basis with immunologic, genetic, virologic, hormonal, and other factors playing essential roles, each acting alone or in variable combinations.

Immunologic Factors in Autoimmune Diseases

Release of Sequestered Antigens

As indicated above, for induction of self-unresponsiveness, contact between the autoantigen and the immune system is required. If an antigen is sequestered within an organ, thus precluding its contact with the lymphoreticular system, then no immunologic tolerance at the T- or B-cell level can be established. However, any tissue damage that exposes the antigen, especially later in life, would then provide an opportunity for autoantibody formation, since tolerance induction in adults with many mature B cells is much more difficult to achieve than in neonates, whose immature, easily tolerizable B cells predominate.[105-110] Autoantibody production following release of sequestered antigens has been repeatedly demonstrated: for example, autoantibody formation against sperm after vasectomy,[120] against lens crystalline after eye injury,[121] against heart muscle antigens after myocardial infarct,[122] and so forth. In most of these instances the autoimmune response is transient and probably disappears before clinical symptoms are generated. Progressive autoimmune disease appears to require persistent antigen that is presented in an immunogenic form. Conceivably, chronic autoimmune disease could also follow the liberation of antigen by nonspecific injury; the autoantibody thus induced might secondarily cause chronic release of antigen by participating with complement to mediate tissue injury.

Diminished Suppressor T-Cell Function

The down-regulation of immune response, by complex interactions between imune-response-helping and immune-response-suppressing cells and their sol-

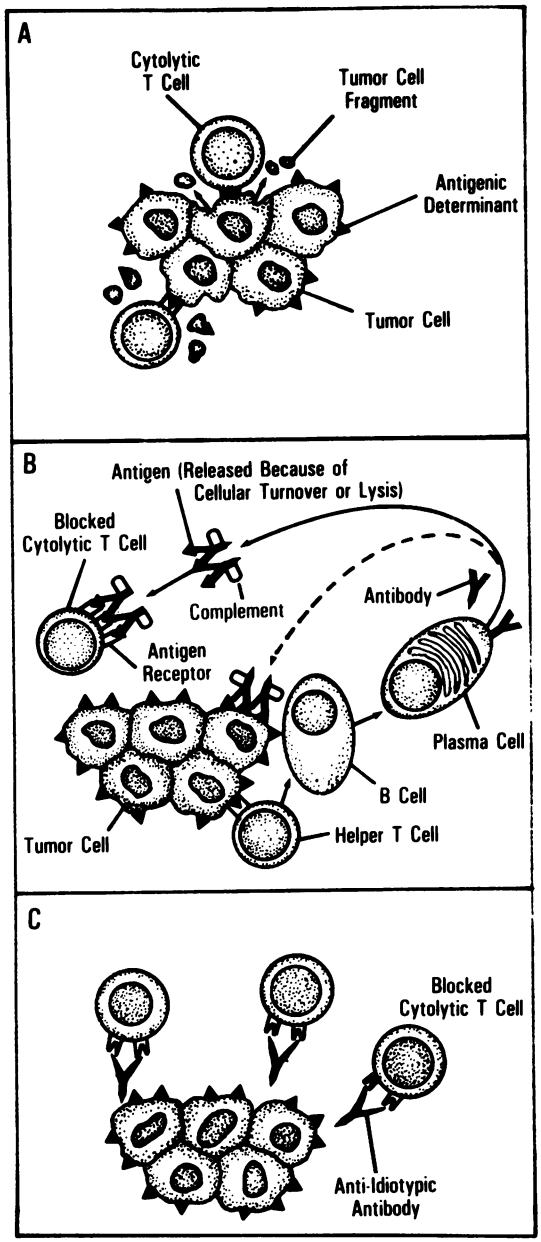

Figure 14—Blocking of anti-tumor-cell-mediated immunity by antibodies or antigen-antibody complexes. **A**—Cytolytic T cells with appropriate receptors and access to antigenic terminants on the tumor cell surface induce lysis of the target cells. **B**—Stimulation of humoral immune responses via antigen sensitization of antigen-receptor-bearing helper T and B cells will also result in antitumor antibodies. These antibodies, although usually beneficial to the host, may sometimes block anti-tumor cellular responses by combining directly with antigen on the tumor cell surface, thereby rendering it inaccessible to cytolytic T cells, or they may combine with tumor antigens (released or shed after tumor cell lysis) in the circulation, form complexes, and then bind to antigen-receptor-bearing cytotoxic T cells, thus blocking them from access to and direct interaction with tumor cell determinants. **C**—Anti-tumor antibodies may also induce anti-idiotypic antibodies directed against the antigen receptors (V-region) on cytolytic T cells, thereby inhibiting these cells from interacting with the target tumor cells.

Table 2—Theories of Autoimmunity

Release of sequestered antigens
Diminished suppressor T-cell function
Enhanced helper T-cell activity, T-cell bypass
Thymic defects
Presence of abnormal clones; defects in tolerance induction
Polyclonal B-cell activation; enhanced maturation
Refractoriness of B cells to suppressor messages
Defects in macrophages; antigen presentation
Stem cell defects
Defects in the idiotype-anti-idiotype network
Abnormal genes: Ir genes, Ig genes
Viral factors
Hormonal factors

uble products already described here, is logically followed by the conclusion that loss of a given autoantigen-specific suppressor T-cell subset or nonspecific loss of this class of cells could result in the spontaneous appearance of autoantibodies. Antigen-nonspecific suppressor T cells can be identified numerically by the expression of certain surface alloantigens detected by polyclonal or monoclonal antibodies (OKT-5, OKT-8) against them or by expression of surface Fc receptors for IgG.[123-126] Functionally these suppressors are marked by their ability to release soluble products after stimulation with concanavalin A (Con A), which suppresses B-mitogen-induced polyclonal activation and Ig secretion or allogeneic mitogenic responses.[127] With these methods, numerical and/or functional abnormalities of suppressor T cells have been noted in a variety of organ-specific and generalized autoimmune disorders.[128-137] However, the validity of ascribing reduced suppressor T-cell number or function assessed by the above procedures as causative in organ-specific autoimmune diseases must be questioned for the following reasons: 1) it is very difficult to imagine how a generalized suppressor T-cell defect could be expressed as an organ-specific autoimmune disease; and 2) it is equally difficult to imagine how elimination, reduction, or dysfunction of a very minor subset of suppressor T cells that reduces the activity of immunocyte clones responsive to a specific autoantigen could be expressed in the total compartment of suppressor T-cells that are enumerated with monoclonal antibodies or assessed functionally by Con A stimulation. Although more acceptable on theoretic grounds, the numeric or functional diminution of total suppressor T cells in generalized autoimmune diseases involving many autoimmune responses, such as SLE, also remains controversial. Usually, such subjects have significant lymphopenia and decreases in absolute and relative numbers of T cells.[137] T-cell functional studies in persons with SLE reveal, in most cases, impaired delayed hypersensitivity to various antigens in addition to decreased prolif-

erative responses to T-cell mitogens and to autologous (syngeneic mixed lymphocyte response) and allogeneic stimulator cells.[137,138] The severity of some of these impairments was thought to correlate with disease activity. Moreover, the subject of repeated claims is that T cells from patients with active SLE cannot generate antigen-nonspecific supressor signals.[131-136] This was considered to represent an inherent defect of T-suppressor cells, since B cells from such patients show normal responses to suppressor activity generated by normal T cells.[133] A related assertion is that anti-lymphocyte antibodies present in the serum of most patients with SLE have preferential reactivity with suppressor T-cell subsets.[139,140] The primary importance of these findings remains questionable, since most patients included in these studies are at an advanced stage of their disease and under treatment with a variety of anti-inflammatory drugs, such as corticosteroids, and of cytostatic agents that profoundly affect the immune system. Recent studies have failed to confirm some of the above findings, in that the polyclonal suppressor T-cell activity of the patients with SLE who were examined was within normal limits,[141] and anti-lymphocyte antibodies did not react preferentially with any particular type of immunocyte.[142]

Initial studies in the spontaneous SLE model of NZB and (NZB × NZW)F_1 (New Zealand strains, NZ) mice similarly suggested substantially lowered antigen-nonspecific suppressor T-cell function with age and the parallel appearance of disease[143]; the Lyt123$^+$ T-cell subset responsible for feedback suppression was reported to be absent or malfunctioning in NZ mice[144]; in BXSB mice the claim was made that Lyt1$^+$ cells were unable to induce Lyt123$^+$ cells, and in MRL/1 mice Lyt1$^+$ cells were insensitive to suppressor effects by Lyt123$^+$ cells.[115] However, subsequent studies showed no apparent defect in antigen-nonspecific (Con A-induced)[145] or exogenous antigen-specific suppressor T-cell function[146] in the susceptible NZ mice or the two newly described SLE murine strains, BXSB and MRL. Table 3 shows the origins, histologic, serologic and cellular characteristics of these SLE-prone strains of mice. Additional studies in these and other murine strains questioned the primary importance of natural thymocytotoxic antibodies (NTA), proposed by some investigators in the development of murine SLE,[147,148] since not all of the above three afflicted strains have NTAs in their serum.[149,150] Moreover, NTAs are found in some recombinant NZB inbred strains in the absence of other types of autoantibodies and vice versa,[151] and some strains with NTAs in their serum do not have detectable disease.[150] Therefore, the above studies cast doubt on the idea that a *generalized* defect of suppressor T cells or the presence of NTAs cause autoimmunity. Furthermore, as discussed in the section describing genetic aspects of autoimmunity, studies in murine models of SLE have excluded the presence in such animals of a unique gene predisposing to autoimmune responses, since the various autoantibodies found in these mice segregate independently in recombinant mice and in F_2 hybrid generations.[149,151,152] However, these findings still do not exclude abnormalities of specific subsets of suppressor T cells that control responses to autoantigens; nor do they exclude a secondary role of anti-T-cell autoantibodies in accelerating autoimmunity. In general, little current experimental data support the concept that suppressor T cells are important in controlling immune responsiveness to self. Undoubtedly, such new and sophisticated techniques as experimentally induced specific elimination *in vivo* of suppressor T cells, and the study of autoantigen-specific suppressor T-cell function as well as of idiotype-anti-idiotype regulation will eventually define the role of suppressor T cells in autoimmunity.

Enhanced Helper T-Cell Activity, Escape of Tolerance at the T-Cell Level and Other T-Cell Abnormalities

Helper T cells and B cells must collaborate for most immune responses—now a well-established principle. It has been proposed that unresponsiveness to self is maintained by self-tolerance at the helper T-cell level.[2] Where such tolerant helper T cells become activated via non-self-antigens that cross-react with self, or certain nonspecific factors replace helper T cells, existing non-self-tolerant B cells can be activated to produce autoantibodies. This concept derives from the work of Weigle, Chiller, and associates,[2] who found that T and B cells have different antigen concentration requirements for induction of tolerance and that escape from a tolerant state occurs much faster at the B-cell level than at the T-cell level. Thus, after injection of deaggregated human gamma globulin as a tolerogen, tolerance induction in the intact mouse takes 4–5 days for completion. Induction of tolerance in either thymus cells or peripheral T cells is rapid and parallels the kinetics of tolerance induced in the intact animal; peripheral B cells are only slightly slower to assume the tolerant state. Conversely, a latent period of 8–15 days follows injection of the tolerogen before tolerance is noticeable in bone marrow cells, and the tolerant state is not com-

Table 3—Characteristics of SLE-Prone Murine Strains

Derivation and genetic markers

Strain	Derivation	H-2	Lymphocyte surface alloantigens	Igh-1 (IgG2a) allotype	Accelerating gene(s)
NZB	Inbred for color from stock of undefined background	$H\text{-}2^d$	Thy1.2, Lyt1.2, Lyt2.2, Lyt3.2, $Qa\text{-}1^a$, Mls^a, Thy1.2	e	?
NZW	Inbred for color from stock of undefined background	$H\text{-}2^z$		e	
BXSB	Derived from (C57BL/6J × SB/Le)F_1	$H\text{-}2^b$	Thy1.2, TL^-, Lyt1.2, Lyt2.2, Lyt3.2, $Qa\text{-}1^b$	b	Y-linked
MRL	Genome = 75% LG, 13% AKR, 12% C3H and 0.3% C57BL/6	$H\text{-}2^k$	Thy1.2, TL^-, Lyt1.2, Lyt2.1, Lyt3.2, $Qa\text{-}1^b$	a	lpr only in MRL/1 (MRL/Mp-lpr/lpr) but not in MRL/n (MRL/Mp-+/+)

Mortality rates

Strain	50% Mortality (months)	90% Mortality (months)
NZB		
Female	16.0	21.0
Male	17.0	23.0
NZW		
Female	24.0	32.0
Male	25.5	33.5
(NZB × NZW)F_1		
Female	8.5	12.8
Male	15.0	19.0
MRL/l		
Female	5.0	7.3
Male	5.5	8.6
MRL/n		
Female	17.0	23.0
Male	23.0	27.0
BXSB		
Female	20.0	24.0
Male	5.5	8.0

Histoimmunopathologic characteristics

Strain	Glomerulonephritis	Thymic atrophy	Lymphoid hyperplasia	Arteritis	Myocardial infarct	Arthritis
NZB	+	+	+	0	+	0
(NZB × NZW)F_1	+ + +	+	+	0	+	0
MRL/l	+ + +	+	+ + +	+	+	+
BXSB	+ + +	+	+ +	0	+	0

Serologic characteristics

Common	Hyper-γ-globulinemia, anti-nuclear antibodies, anti-dsDNA, anti-ssDNA, anti-hapten antibodies, high levels of gp70, immune complexes, (DNA-anti-DNA, gp70-anti-gp70), reduced complement levels (NZB is C5-deficient)
Uncommon	Anti-Sm (MRL mice; with sensitive techniques such antibodies can also be found in the other SLE strains), IgG + IgM rheumatoid factors and intermediate complexes (MRL/1), anti-erythrocyte (NZB; NZB × NZW), NTA (NZB, NZB × NZW, BXSB)

Surface and functional characteristics of lymphoid cells

B cells	Hyperfunction and polyclonal activation in all strains, autoimmune clones in all strains, increased number in BXSB mice only, normal ontogeny of isotype diversity in all strains
T cells	Generalized suppressor function normal in all strains, T-cell number ($Lyt1^+$) and nonspecific T-helper function increased in MRL/l only, defects in interleukin-2 production and response in all strains, reduced syngeneic mixed lymphocyte response in all strains, cytotoxicity against H-2 compatible allogeneic cells in NZ mice only
Tolerance	Defective tolerance induction to some exogenous antigens in all strains
Thymus	Essential in MRL/l disease but not essential in NZ and BXSB disease
Nonlymphoid tissues	Noncontributory to disease development in any SLE-prone strain

plete in these cells until 21 days elapse. Of more importance to self-tolerance is the marked kinetic difference in the spontaneous termination of tolerance in peripheral T and B cells. Peripheral T cells, like intact mice, remain tolerant for 100–150 days, although peripheral B cells return to complete competency between 50 and 60 days after injection of tolerogen. The dose of antigen required to induce tolerance in adult thymus cells or peripheral T cells is 100–1000 times less than that required to induce tolerance in adult bone marrow cells or peripheral B cells. Therefore, when central unresponsiveness is induced with small doses of antigen, B cells remain competent or quickly escape from tolerance, whereas T cells become tolerant for a long time. On the basis of these findings, self-tolerance is apparently maintained despite the presence of self-responding B cells due to the lack of appropriate help from the tolerant T-cell partners. Accordingly, autoimmunity is then inducible 1) by direct stimulation of autoantigen-reactive B cells with polyclonal activators (see below), where T-cell help is not needed; 2) by circumvention of the T-cell unresponsive state to self-antigens through nonspecific T-cell–replacing helper factors; or 3) by induction of helper T cells via altered forms of the tolerated self-antigen or with antigen that cross-reacts with the tolerated self-antigen. Induction of autoreactivity by certain polyclonal B-cell activators will be discussed below. Factors have also been isolated from activated T cells that are capable of causing competent B cells to differentiate.[153–155] In theory, such factors that terminate tolerance to certain exogenous and endogenous antigens could be liberated from T cells during responses to allogeneic cells (allogeneic effector factor, AEF), presumably because of nonspecific activation of host T cells via a graft-versus-host (GVH) reaction.[156–158] A probable example of this mechanism is the appearance of autoantibodies, the development of immune-complex–mediated glomerulonephritis, and the deposition of immune complexes in the skin of some patients undergoing GVH reactions after bone marrow allotransplantation.[159] However, whether autoimmune responses are indeed induced by such T-replacing factors remains to be shown more directly. In fact, factors secreted from T cells activated by suboptimal concentrations of Con A failed to induce autoantibodies in recent experiments, despite enhancement of polyclonal Ig synthesis by B cells and induction of antibodies against heterologous serum proteins.[154] This inability of endogenous T-cell–replacing factors to collaborate with self-reactive B cells in the generation of autoantibody, if verified further, would suggest that the above proposed mechanism of autoimmunity, ie, the bypass of tolerant T cells by T cell–replacing factors secreted in response to nonspecific stimuli, is unlikely to be of significance *in vivo*.

Specific immunologic tolerance terminates after immunization either with altered preparations of the tolerated antigen or with antigens that cross-react with that tolerogen.[160,161] Thus, rabbits made tolerant to bovine serum albumin (BSA) after neonatal injection lose their tolerant state following injection of chemically altered BSA or heterologous albumins that cross-react with BSA.[162] In this situation the unrelated determinants on the cross-reacting albumins seem to activate T cells, permitting stimulation of B cells competent for both BSA and the unrelated determinants. Presumably, provision of a new carrier determinant for which no self-tolerance has been established bypasses the tolerant T cells and induces them to collaborate with non-self-tolerant B cells to produce autoantibodies. A new carrier determinant could arise through some modification of the self-molecule, for example, by defects in synthesis or abnormalities in lysosomal breakdown yielding a split product and exposing new groupings, by combination with a drug, by association with a new antigen that drugs or viruses have induced on cells, and finally by the presence of exogenous cross-reactive antigens that provide the new carrier with the ability to provoke autoantibody formation. Incorporation of autoantigens into Freund's complete adjuvant frequently endows them with the capacity to stimulate humoral and cellular immune responses in the species from which the antigen originated.[160,163] Drug-induced autoimmune responses are well documented; for example, autoimmune hemolytic anemia develops in association with the adminstration of α-methyl-dopa,[164] and production of antinuclear antibodies follows treatment with hydralazine, isoniazid, or procainamide.[165] Parenthetically, a genetically controlled polymorphism of the hepatic acetyltranferase enzymes is responsible for different rates of inactivation of drugs such as hydralazine, procainamide, isoniazid, sulfamethazine, and dapsone. Slow acetylators are more prone to develop antinuclear antibodies with hydralazine ingestion than high acetylators; but there is no predominance of slow acetylators among patients with SLE; nor are slow acetylators at greater risk of SLE development.[165] High titers of cold agglutinins to the I blood group arise as an occasional complication of *Mycoplasma pneumoniae* infections.[166] The autoantibody persists for only a few days but is associated with a short-lived and sometimes severe hemolytic episode. The cold agglutinin is thought to be a cross-reacting autoantibody arising from the response to I-like determinants of the *My-*

coplasma. Anti-I cold agglutinins also develop in rabbits given injected Group C streptococcal vaccine, due to cross-reactivity of the I blood group substance with the immunodominant sugar moiety of the Group C carbohydrate.[167] A similar situation probably occurs in human rheumatic fever, in which certain streptococci carry antigenic determinants that cross-react with heart muscle or neuronal tissues, resulting in Sydenham's chorea. The brain and nerve damage of some persons after a rabies vaccination may develop in much the same way if the rabies vaccine is prepared from heterologous brain tissue, as could autoantibodies evolve in patients receiving animal hormone replacement therapy, for example, with bovine insulin or adrenocorticotropic hormone (ACTH). There is also some evidence for the view that antigens common to *Trypanosoma cruzi* and cardiac muscle provide some of the immunopathologic lesions seen in Chagas' disease.[168,169]

Regarding possible increases in generalized or autoantigen-specific T-helper activity during autoimmune diseases, experiments in murine strains with SLE suggest that antigen-nonspecific T-helper activity is within normal limits in NZB, $(NZB \times NZW)F_1$, and BXSB mice but elevated in MRL/1 mice,[145] which are characterized by a profound proliferation of their $Lyt1^+$ T-cell subset.[170,171] Manipulations such as total lymphoid or whole body irradiation,[172] as well as neonatal thymectomy,[173] all of which suppress or completely inhibit the massive T-cell proliferation of this strain, result in markedly prolonged survival and reduced levels of autoantibodies.

Of these immunologically abnormal strains, MRL/1 mice exhibit, even at an early age, a profound progressive defect in Con A-induced proliferation as well as production of and response to exogenous interleukin-2 (IL-2).[174,175] A similar defect, but less severe, develops in the NZ and BXSB autoimmune mice. IL-2, previously called T-cell growth factor, is a lymphokine produced by mitogen- or antigen-stimulated T cells. IL-2 has significant T-cell regulatory function, since it stimulates thymocyte proliferation, provides helper activity for antibody production, facilitates the induction of cytotoxic T cells, and promotes the proliferation of helper and cytotoxic T lymphocytes in long-term culture.[176] The relationship, if any, of the defect in IL-2 production in SLE strains and their disease remains unclear at this time. It is of interest that, despite this defect *in vitro*, most SLE mice respond well to exogenous and of course to endogenous antigens, including T-dependent antigens, and exhibit normal cytotoxic responses against virus-infected targets as well as allogeneic cells when tested just preceding overt manifestations of their disease. These contrasting findings (reduced IL-2 production *in vitro* but normal or enhanced responsiveness *in vivo*) would suggest that the *in vitro* findings do not accurately reflect the *in vivo* situation, that IL-2 has little influence on the manifestations of immune function *in vivo*, or that one or more factors other than IL-2 stimulate T-cell proliferation.

Mixed lymphocyte responses in co-cultures of T lymphocytes with autologous or syngeneic non-T cells (SMLR), are also reported to decrease in both persons[138] and mice with SLE.[177] Normally in mice, this response results from the stimulation of $Lyt1^+$ T cells by antigens, presumably self-Ia antigens, expressed on B cells and macrophages.[178] The defect of older SLE mice found in the responder T-cell population remains undefined as to origin or pathogenic importance in generalized autoimmunity.

Thymic Defects

By virtue of its epithelial microenvironment, its giant nursing cells, and its hormonelike substances thymopoietin and thymosin, the thymus is essential for the differentiation of T cells and their helper, suppressor, and cytotoxic subsets. Whether generalized autoimmunity, such as that in SLE, can result from intrinsic thymic abnormalities is unclear, although a variety of related pathologic and hormonal thymic abnormalities have been described. Indeed, all SLE mice develop early thymic atrophy, particularly involving the cortex and, to a lesser extent, the medulla.[149] Such thymic atrophy associated with abnormal fine structure appears by the fourth month in $(NZB \times NZW)F_1$ mice, which at 6–7 months of age have lost 70–90% of their cortexes. In BXSB and MRL/1 mice, which die earlier than the $(NZB \times NZW)F_1$ mice, thymic atrophy and cystic necrosis appear by 2 months of age and progress to a complete loss of the cortical areas by 4½ and 3½ months of age, respectively. In addition, some have reported that adult NZB mice lack a serum activity, thought to be a thymic hormone,[179] and that administration of thymic hormone (ie, extract of thymic tissue) to NZB mice[180] or transplantation of thymuses or of thymocytes from young NZB mice to the older mice[181,182] may temporarily prevent some of the immunologic defects and delay the onset of autoimmunity. However, others have failed to inhibit the disease of autoimmune mice treated repeatedly with thymocytes from young counterparts[183,184] and attempts to confirm the therapeutic efficacy of thymosin in NZ mice have also failed.[185,186] Moreover, newborn thymectomy of $(NZB \times NZW)F_1$ and BXSB mice has little effect on the time of onset, mortality rate, or development of SLE in these strains of mice,[187,188] and congenitally

athymic (NZB × NZW)F_1 mice develop disease like their euthymic counterparts.[189] Furthermore, transplantation and exchange of thymuses between the congenic MRL/l and MLR/n mice—which exhibit markedly differential expression of SLE (the former dies by the fifth month of age with severe SLE, whereas the latter has a very late-developing SLE with death occurring at around the second year of life)—showed that the genotype of the thymus is not the determining factor in expression of this disease.[173] MRL/l mice neonatally thymectomized and then transplanted with either MLR/l or MRL/n thymus developed equally early disease, and MRL/n mice thymectomized and transplanted with MRL/n or MLR/l thymus developed late disease like their unmanipulated counterparts. However, in contrast to the situation in NZ and BXSB mice, MRL/l mice expressed the disease only in the presence of a thymus, irrespective of its genotype, and neonatally thymectomized animals did not develop SLE-like disease nor this strain's characteristic massive T-cell proliferation. Although these experiments strongly suggest that thymuses of autoimmune mice are not intrinsically abnormal or necessarily essential for autoimmunity, they do not exclude the possibility that secondary thymic defects or accelerated thymic involution occurring in such mice or man via a variety of means, including thymocytotoxic antibodies, may accelerate the autoimmune manifestations.

Polyclonal B-Cell Activation

Most, if not all, autoimmune diseases bear the characteristic mark of antibodies produced against numerous self-antigens by the host's B cells. Although such an abnormality may be secondary to T-cell defects (enhanced helper and/or reduced suppressor function), the alternative possibility that one or more defects at the B-cell level are the primary cause of autoimmunity must also be considered. Of course, such B-cell defects might secondarily induce T-cell abnormalities that could accelerate the disease process. The B-cell defect(s) might be intrinsic and genetically imposed—for example, certain clones of autoreactive B cells might have the ability to respond without T-cell help or express more receptors for T-cell-derived activating signals—or might be extrinsic—for example, B cells might be activated by endogenous or exogenous mitogens, the so-called polyclonal activators.

The belief that polyclonal B-cell activators can induce autoantibody production is based on the existence in the body of B cells that are not tolerant to self and the ability of B-cell mitogens to stimulate these cells directly or by substituting for helper T cells. Thus, when self-antigens are present in low concentrations, B cells with receptor reactivities ranging from low to high avidity are thought to escape tolerance induction and assume competence to interact with autologous antigens, while T cells are rendered tolerant.[2] Thereby, polyclonal B-cell activators could drive such B cells to autoantibody production.

Bacteria, viruses, and parasites as well as other substances act as polyclonal B-cell activators[190,191] (Table 4). Considering that such a large number of exogenous substances can act as polyclonal B-cell activators, many investigators have become interested in their ability to induce antibodies directed against the body's own components. Indications that this does occur are the development of such autoantibodies as rheumatoid factors and antinuclear, antilymphocyte, anti-erythrocyte and/or anti-smooth muscle antibodies after bacterial, parasitic, or viral infections.[167] Moreover, bacterial lipopolysaccharide (LPS) induces murine lymphocytes to form anti-DNA,[192,193] anti-γ-globulin,[194,195] anti-thymocyte,[196] and anti-erythrocyte autoantibodies,[197] primarily of the IgM class. Injection of mice with LPS induces IgM responses against self-IgG which account for between 25–85% of the total number of IgM-producing cells.[195] Many other bacterial products also provoke polyclonal B-cell activation, but their ability to induce autoantibodies remains unproven. Protozoan parasites, such as *Trypanosoma brucei*, *T cruzi*, and *Plasmodium malariae* are also polyclonal B-cell activators, and autoimmune responses to DNA, red blood cells, and thymocyte antigens have been observed in animals experimentally infected with *T brucei*.[198,199] Finally, some viruses act as polyclonal B-cell activators, the best known of which is Epstein–Barr virus (EBV).[200] Peripheral mononuclear cells from normal persons and patients with rheumatoid arthritis become activated to secrete polyclonal IgG and IgM anti-γ-globulin antibodies during incubation with EBV, but cells from the rheumatoid patients produce

Table 4—Polyclonal Activators of B-Lymphocytes*

Lipopolysaccharide (LPS)
Purified protein derivative of tuberculin (PPD)
Staphylococcus aureus protein A
Nocardia water-soluble mitogen
Lipid A-associated protein
2-Mercaptoethanol (2-ME)
α-Thioglycerol (α-TG)
Macrophage- and T-cell-derived lymphokines
Fc fragment of Ig
Proteolytic enzymes, eg, trypsin
Polyanions, eg, dextran sulfate, poly IC
Antibiotics, eg, nystatin, amphotericin B
Lanatoside C
Mycoplasma
Some viruses and viral components (EBV, gp70, measles)
Parasites (*Trypanosoma congolense*, *T cruzi*, *Plasmodium malariae*)

* From Goodman and Weigle.[190]

considerably greater quantities of antibody with higher affinity than cells from normals.[201] EBV activates the B cells directly, without requiring the participation of the helper T cells, although T cells can suppress this process. Thus, during EBV-induced infectious mononucleosis, suppressor T cells become activated, preventing B-cell activation *in vitro* by EBV as well as by other polyclonal B-cell activators such as pokeweed mitogen.[202] Cultured cells from patients with rheumatoid arthritis generate much less T-cell–mediated suppression for EBV-induced polyclonal B-cell activation than normal cells.[203] This defect in suppressor T-cell function is specific for EBV-induced polyclonal B-cell activation, although other T-cell suppressor functions such as Con A-induced suppression and even EBV-induced suppression of allogeneically induced polyclonal B-cell activation remain within normal limits. In addition, the defective T-suppressor function described in patients with rheumatoid arthritis is not a common feature of many other autoimmune diseases, including SLE.

Such other factors as macrophage- and T-cell–derived lymphokines, Fc fragments of Ig, proteolytic enzymes, polyanions, and certain antibiotics may express properties of polyclonal B-cell activators, but whether they can induce autoantibodies has not been tested. In general, autoantibodies induced by polyclonal activators are transient, of low affinity, and primarily of the IgM isotype, although induction of IgG type rheumatoid factors and anti-DNA by certain forms of lipopolysaccharides (LPS), especially those high in lipid A, has recently been demonstrated.[204] How often or whether such polyclonal activation occurs *in vivo* is unclear, but if so, it may be partly responsible for the low levels of autoreactive antibody found in the serum of normal individuals. Because these autoantibodies are usually of such low affinity, they probably have little significance.

Polyclonal activation of B cells may also contribute to the spontaneous SLE-like disease of susceptible murine strains. Indeed, B cells of all these strains are polyclonally activated very early in life.[145,149,205–207] This polyclonal activation is manifested by hypergammaglobulinemia, large numbers of Ig-containing and/or -secreting cells in their spleens, excessive production of Ig in splenocyte cultures, and production of anti-hapten antibodies *in vitro* and *in vivo*. Neither the role of this polyclonal activation nor its relationship to the specific autoantibody production has been totally clarified. Of note, introduction of the *xid* mutation of partially immunodeficient CBA/N mice into NZB mice,[208] but not into MRL/l mice,[209] prevents the development of high numbers of spontaneously activated B cells and other autoimmune phenomena. However, studies in recombinant strains of NZB mice[157] as well as their F_2 hybrids[210] showed that the polyclonal B-cell activation segregated independently of autoantibody production. Moreover, transfer of autoimmunity with bone marrows of SLE mice into histocompatible normal mice and the absence of autoimmunity after reciprocal transfers of normal bone marrow cells into SLE strains[211–216] further suggests the irrelevance of polyclonal nonlymphoid cell-associated activators as primary causative agents of murine SLE. This conclusion is reinforced by the findings that 1) known potent polyclonal B-cell activators induce primarily IgM autoantibodies, and yet the tissue damage that accompanies most autoimmune diseases is mediated by IgG autoantibodies; 2) induction of autoantibodies by polyclonal activators is transient and disappears with elimination of the activator; and 3) no endogenous polyclonal B-cell activator has been proven as an exclusive property of serum or tissue extracts of animals or humans with SLE. Nevertheless, in genetically predisposed individuals, polyclonal B-cell activators may serve secondarily as accelerators of autoimmunity.

Macrophage Defects

Essential in the cellular and molecular events that underlie immune competence is the mononuclear phagocyte, which processes and presents antigen to lymphocytes and generates humoral factors that influence the activities of lymphocytes.[217,218] Moreover, the phagocytic function is important in disposal of immunologically undesirable materials such as immune complexes. Surprisingly, little information is available on the functional state of mononuclear phagocytic cells in autoimmune disorders. Most experiments deal with the capacity of macrophages from mice and persons with generalized autoimmune diseases to process and degrade antigens and the ability of the reticuloendothelial system (RES) to remove immune complexes or other particles from the serum of such individuals.[219–225] Of reports on the phagocytic activity of NZB-derived macrophages, most have shown heightened phagocytosis of antigen,[221,222] although some data suggest that the NZB cells are relatively unable to degrade the ingested antigen.[222] Studies on the clearance of inert particles or immune complexes by macrophages of NZ mice are inconclusive; some have shown a reduction in clearance,[223] others portray clearance as increased or normal,[220,224] whereas still others claim normal clearance but weak affinity for binding to Fc receptors of Kupffer cells and therefore easy re-release into the circulation.[225] Decreased *in vivo* clearance of antibody-sensitized red blood cells has been described in humans with

autoimmune disorders.[219] We do not know whether this defect is primary due to a defect in the number or function of receptors for Fc or complement or secondary, due to occupation of the receptors by circulating immune complexes formed *in vivo*.

Phagocytes are essential for the development of various lymphocyte functions, in particular, those of the T lymphocytes.[217,218] As stated above, most T-lymphocyte activities require that the macrophage take up and present the antigen in a process modulated by the I region of the MHC. Macrophages from neonatal mice, tested at an age when immune responsiveness is low and tolerance is easily induced, present antigen poorly.[226] This defect has been correlated with the small number of macrophages that bear Ia antigens in spleens of neonatal mice, compared with adult mice.[227] Whether the ontogenic development of Ia antigens on macrophages of autoimmune and normal mice differ (earlier development in the former than the latter), accounting for the lack of tolerance to self, remains to be determined.

Defects in Tolerance Induction

All the murine SLE strains have proven to be defective in tolerance induction to deaggregated human gamma globulin, bovine gamma globulin, or hapten-substituted gamma globulin *in vitro* and *in vivo*.[149,228-231] Some studies have attributed this defect to T cells, others to B cells, and yet others to both types. Whether difficulty in tolerance induction applies to antigens other than deaggregated gamma globulins, both exogenous and endogenous, has not been investigated comprehensively. However, experiments with hapten-modified self-cells have shown that MRL/1 mice are as easily made tolerant as immunologically normal mice,[232] suggesting that the defect might not be universally applicable to all antigens.

Defects of Multipotential Stem Cells, Committed Progenitor Cells of Various Hemopoietic Lineages, and B-Cell Precursors

The humoral, cellular, microenvironmental, and viral factors from which autoimmunity develops are best defined by transferring autoimmune disease with specific tissues or tissue extracts taken from strains of animals having a genetic predisposition to autoimmunity and administered into recipients without this defect. Such transfer studies have been performed in SLE murine strains and their normal counterparts. Thus, NZB autoimmune disease has been transferred with this strain's fetal liver, bone marrow, or spleen cells into lethally irradiated, normal histocompatible strains of mice.[212-214] Lethally irradiated NZB mice transplanted with H-2-compatible allogeneic bone marrow or spleen cells from normal mice do not develop autoimmunity. In reverse transfers, NZB bone marrow cell suspensions were depleted of T cells; the H-2-compatible normal recipients were thymectomized, or anti-T-cell antibodies were given after transplantation. Still, disease developed.[213,216] These experiments have been cited as evidence that many of the NZB peculiarities may be intrinsic to hemopoietic cells and may develop independently of T-cell aberrations. However, incompatibilities between donor and recipient potentially complicate these interpretations. Similar experiments have been performed between BXSB male and female SLE mice.[211] Unmanipulated male BXSB mice develop severe early SLE with 50% mortality at 5-6 months of age, whereas the females develop late SLE with 50% mortality beyond 18 months. Reciprocal transfers of bone marrow or spleen cells between these mice show that male cells can transfer early disease in both lethally irradiated male and female recipients, but female cells cause late disease regardless of the recipient's sex. Further experiments indicate that transfer of spleen cells from older male BXSB mice with clearcut disease does not produce disease in recipients any faster than transfer of cells derived from premorbid mice. The conclusions are, therefore, that the active cells in these transfers are stem or precursor cells—not autoantibody-secreting B cells—and that the development of BXSB disease does not result from an accumulation of defects among stem cells, which are equally abnormal throughout the animal's life. Like the NZB mice, transfer of BXSB male disease by bone marrow cells can be accomplished in the absence of T cells in the inoculum and in thymectomized female recipients.[233] This finding implies that the defect of this strain of mice is associated with precursors of B-cell lineage.

Defects in Idiotype-Anti-Idiotype Network and Idiotype Mimicry of Autoantigen

As stated above, idiotypic or anti-idiotypic determinants on B cells, T cells, and their soluble products may regulate immune responses. Anti-idiotypic antibodies may suppress or enhance immune responses.[68,89,90] In most instances of autoanti-idiotypic responses to antibodies against exogenous antigens, the autoanti-idiotypic antibodies suppress the original immune response expressing the corresponding idiotype.[85,93] In addition to anti-idiotype-mediated suppression, stimulation of Ab_1 by anti-idiotypes representing the "mirror image" of antigens that Jerne postulated has been described in recent experiments. Initial studies provided evidence that expression of idiotypes specific for Ab_1 may reappear on Ab_3, since

Ab_4 bound to Ab_1, and Ab_1 inhibited the binding of radiolabeled Ab_3 or Ab_4.[82] These results suggest that the immune idiotypic network is not open-ended but is somehow circular. In additional experiments, animals immunized with Ab_2 (anti-idiotype) developed not only Ab_3 (anti-anti-idiotype) but also produced Ab_1 (idiotype), suggesting that Ab_2 contains antigenic determinants (epitopes) conformationally similar to those on the inciting antigen, therefore fulfilling the predicted concept of an "internal mirror image." Together, these observations suggest that a given antibody, as well as an autoantibody, could be viewed both as the product of original stimulation by the antigen and as the product of stimulation by Ab_2 (anti-idiotype) that can internally mimic the antigen. The induction of idiotypes in the absence of antigen has been demonstrated in several systems. For example, monoclonal IgM antibodies directed against sheep erythrocytes, when injected into normal mice, induced direct plaque-forming cells of the same specificity as the injected antibodies.[234] Moreover, induction of anti-tobacco mosaic virus (TMV) antibodies in mice given injected specific anti-idiotypic antibodies has been observed.[235] In this instance Ab_2 behaved like the antigen: it reacted with anti-TMV antibodies and also promoted the synthesis of anti-TMV antibodies in the total absence of TMV. Thus, these antibodies may be considered the internal images of TMV. Furthermore, injection of experimental mice with anti-idiotypic antibodies to the murine MHC ($H\text{-}2K^k$ specificity) induced anti-$H\text{-}2K^k$ antibodies in the absence of exposure to $H\text{-}2K^k$ antigen.[236] Anti-idiotypic antibodies have even been known to generate helper and killer T-cell subsets.[237,238]

In some instances anti-idiotypic antibodies not only induced the idiotype but also mimicked functional properties of the inciting antigen unrelated to the latter's capacity to stimulate the immune system. For example, anti-idiotypic antibodies prepared against bovine anti-insulin mimicked the action of insulin by interacting with insulin receptors on tissues and stimulating the physiologic action of insulin itself.[239] In this instance, a portion of the anti-idiotype, presumably part of its combining site, apparently resembled the insulin site reactive with insulin receptors. Similarly, anti-idiotypic antibodies against antibodies to retinol-binding protein[239] or to alprenolol (a β-adrenergic antagonist)[240] competed with retinol-binding protein or dihydroalprenolol binding to specific receptors on intestinal epithelial cells or red blood cells, respectively.

From the aforementioned, one can speculate that autoimmune responses may be the result of defects in immunoregulation that allow underproduction or overproduction of anti-idiotypic antibodies. Such defects would permit either unchecked production of autoantibodies or cyclic stimulation of Ab_1 (idiotype) in the absence of the inciting antigen, respectively. Ultimately, such defects must be connected to the B-cell, helper T-cell, suppressor T-cell circuit and their idiotypes and anti-idiotypes.

To summarize, quite clearly, any single or combination of T- and B-cell immunologic defects may lead to transient or permanent autoimmune manifestations. No one of these mechanisms excludes the others; and in fact, their concerted action is likely, since defects of the T-cell component are reflected by B cells and vice versa. Some of these abnormalities, such as in suppressor cells or helper cells, can be operative in either organ-specific or organ-nonspecific autoimmune diseases, whereas others, such as polyclonal B-cell activators and early thymic involution, whose effects are organ-nonspecific, would relate more closely to generalized diseases.

Genetic Factors in Autoimmune Disease

Autoimmune diseases of man and many laboratory animals clearly involve genetic factors that determine the incidence, onset, and nature of the autoimmune process.[241] However, for most of these conditions, it has not been possible to assign autoimmune predisposition to the action of a single genetic locus.

Primary candidates suspected of determining susceptibility or resistance to the development of autoimmune and, of course, to other types of diseases are those genes that code for the magnitude and nature of immune responses to antigens. These are the MHC genes and the Ig genes. The theoretical reasons for expecting MHC and Ig gene-linked associations with immune responses in general and autoimmune disease in particular are overwhelming, as discussed in the preceding sections of this chapter. As outlined, the murine MHC, designated *H-2*, is located on chromosome 17 and is subdivided into several subregions called K, I, S, D, and L, in order of increasing distance from the centromere. The human MHC, designated *HLA*, is located on chromosome 6 and contains regions comparable in character to those of murine MHC, but in slightly different order. The D or DR region, equivalent to the murine I region, is closest to the centromere, followed by the B and A regions, which are equivalent to murine D and K regions, respectively; the C region located between A and B is equivalent to the L region of H-2. These subregions code the different classes of cell-surface antigens that have such profound effects on both humoral and cellular immune responses (Table

Table 5—Involvement of H-2 Molecules in Various Immunologic Functions

Trait	Subregions of H-2 complex					
		I region				
	K	A ($A\alpha A\beta$)	E ($E\alpha E\beta$)	J	S	D
Serologically detectable antigens	+ + +	+ + +	+ + +	+	+ + +	+ + +
Rejection of allografts	+ + +	+ +	+ +	?	0	+ + +
Cell-mediated lympholysis	+ + +	+ +	+ +	?	0	+ + +
Mixed lymphocyte reactions	+	+ + +	+ +	+	0	+
Control of immune response	+	+ + +	+ + +	+	0	+
Control of T-B collaboration	0	+ + +	+ + +	?	0	0
Restriction of cytotoxic T cells	+ + +	0	0	0	0	+ + +
Restriction of helper T cells	0	+ + +	+ + +	?	0	0
Control of complement activity	0	0	0	0	+ + +	0

+ + +, strong involvement of molecules in expression of the trait; + +, +, intermediate and weak involvement, respectively; 0, no involvement.

5).[47,48,57,242,243] Thus, the K,D loci of murine MHC and A,B loci of human MHC code for the classic, serologically defined major transplantation antigens (Class I antigens) present on all cells except red blood cells and, pertinent to this text, for the target antigens with which cytotoxic T cells react. The I or D/DR regions for murine and human MHCs, respectively, contain the *immune response* (Ir) genes and encode the serologically defined Ia (murine) or DR (human) antigens (Class II antigens) present only on some cells, primarily macrophages and B cells as well as activated T cells. Ia (coded by the subregion I-A and I-E of the I region of the murine H-2) or DR antigens determine the magnitude of humoral responses to thymus-dependent antigens by virtue of their role in antigen presentation and helper T-cell–B-cell interaction. Genes of the I-J subregion of the I region of the murine H-2 complex code for alloantigens expressed on suppressor T cells and on antigen-specific suppressor factors which bear not only idiotypic determinants but also I-J determinants. In addition to containing genes for T- and B-lymphocyte functions (production of antibodies and of helper, suppressor, and cytotoxic T cells), the MHC includes in both man and mice genes (S region of the mouse H-2) that code for certain components (C2, C4, factor B) of the complement system, which is important in immunologic defense mechanisms (opsonization, lysis, chemotaxis) as well as the development of disease. Both the murine and human MHCs are extremely polymorphic, with large numbers of alleles for each locus. In addition to MHC genes, those coding for Ig are important at the effector arm of the immune system (genes for constant, C, region) as well as in immune regulation and antigen recognition (genes for variable, V, region) via the idiotype-anti-idiotypic determinants expressed on B- and T-cell surfaces and on their soluble products.

Susceptibility to disease in general and to autoantibody formation in particular could derive from allelic variants of the MHC or idiotypic and allotypic variants of Ig genes, judging from MHC and Ig genes' active status throughout the immune response from recognition to regulation. Assessing MHC function is difficult; consequently, its role in disease susceptibility is established by identifying its polymorphic allelic variants expressed in the form of alloantigens on surfaces of lymphocytes. Most studies seeking a correlation between HLA and disease susceptibility are analyses of population (association).[244] Individual diseases have been associated with certain alleles of the D, B, A, or C region, a particularly strong association linking the alloantigen B27 with ankylosing spondylitis.[245,246] The fact that even in this best of such examples a minority of persons carrying the B27 allele develop the disease suggests that additional genes and possibly environmental factors are required for disease expression. Moreover, if disease susceptibility genes exist, they are elsewhere or probably spread along the whole HL-A complex, since each locus or combination of loci is associated with some disease.

Autoimmune diseases have been linked with both MHC genes and Ig allotypic genes in many of the large number of studies available. From them, one must conclude that most autoimmune diseases, at least in Caucasian populations, are associated, albeit not to a very satisfactory degree, with the alleles DR2, DR3, DR4, and DR5 (Table 6).[247–250] Seropositive rheumatoid arthritis, which is independent of HLA-ABC, correlates primarily with DR4; whereas SLE, once assigned to HL-A-B8, is now generally associated with DR2 and DR3. This distinction could imply a very different pathogenic mechanism for these two diseases, which are usually considered as closely related. Associations found for Caucasian

populations may not apply for other ethnic groups, and vice versa. For example, Grave's disease is closely related to B8/DR3 in Caucasian populations but to DR5 and DR8 in Japanese populations.[251] Moreover, no uniform associations are observed among patients classified as having "organ-specific autoimmune diseases" or among those having "generalized autoimmune diseases," suggesting that each autoimmune disease has, at least in part, a distinct genetic background, although one frequently sees simultaneous expression of multiple organ-specific autoimmune diseases in a given individual and overlap of serologic findings. For example, there is a high incidence of pernicious anemia in patients with Hashimoto's disease and, vice versa, of Addison's disease in those with autoimmune thyroid disease, as well as of rheumatoid factor and arthritis in patients with SLE. Furthermore, patients with organ-specific disorders are slightly more prone to developing cancer in the affected organ, whereas generalized lymphoreticular neoplasia shows up regularly along with organ-nonspecific disease. The genetic, environmental, and immunologic factors predisposing to these combined abnormalities are not known. A high frequency of generalized autoimmune disease also accompanies deficiencies in certain complement components.[252] Thus, patients with C2 deficiency, an autosomal recessive trait, often have vasculitis, skin rashes, recurrent infections, and a general picture similar to that of SLE. Similarly, a high incidence of SLE or like syndromes characterizes patients with C1r, C1s, or C3 deficiencies. Many autoimmune diseases also affect more females, suggesting a linkage with the X-chromosome, although this association may be hormonally related (see below).

Considering the clinical spectrum of autoimmune disease and the mode of inheritance, it is unlikely that just one gene alone is responsible for susceptibility to the development of autoimmune disease. Nevertheless, typing for MHC specificities, particularly those encoded by the putative immune response D/DR locus of HLA, should eventually provide diagnostic benefits relative to clinical autoimmune disorders. These benefits include the better definition of homogeneous subgroups of patients with a given disease, a more accurate prognosis for such patients, identification of individuals likely to develop the disease, an indication of expected severity, and development of preventative measures via genetic counseling. Of the possible ways in which HLA genes might regulate susceptibility to disease, the most logical are effects on the magnitude of humoral and cellular responses and on immunoregulation (helper, suppressor, and cytotoxic T-cell functions); metabolic influences, especially on steroid hormones; and changes in antigen handling by phagocytic cells. Of particular interest is a recent report describing defects in Fc-receptor function associated with the HLA B8/DR3 haplotype.[253] The possibility also exists that some of the associations between HLA and disease simply represent strong linkage disequilibrium between susceptibility genes and certain HLA haplotypes.

Table 6—HLA-DR and Diseases*

	Antigen	Relative risk
Multiple sclerosis	DR2	4.1
Optic nephritis	DR2	2.4
Goodpasture's syndrome	DR2	15.0
C2 deficiency	DR2	Linked to A25, B18
Dermatitis herpetiformis	DR3	15.4
Celiac disease	DR3	10.8 (also DR7)
Sicca syndrome	DR3	9.7
Addison's disease	DR3	6.3
Graves' disease	DR3	3.0
Juvenile diabetes	DR3	5.6 (also DR4)
Myasthenia gravis	DR3	2.5
SLE	DR3	5.8
Idiopathic membranous nephropathy	DR3	12.0
Rheumatoid arthritis	DR4	4.2
Pemphigus	DR4	14.4
IgA nephropathy	DR4	4.0
Hydralazine-SLE	DR4	5.6
Hashimoto's disease	DR5	3.2
Pernicious anemia	DR5	5.4
Juvenile rheumatoid arthritis	DR5	5.2

* From Dausset and Contu.[247]

Genes coding for V regions (antigen binding site) or C regions (effector function such as complement fixation and binding to cellular Fc receptors) of Ig also have an apparent association with particular diseases, including autoimmune diseases, as the importance of Ig allotypic markers in determining susceptibility to autoimmune disorders suggests. For example, expression of rheumatoid factors in crosses of 129 and C57BL/6 mice depends in part upon a gene linked to the C locus.[254] Thus, high levels of IgA anti-IgG2a (Igh-1) autoantibodies, like those found in the serum of the 129 strain, appear only in Igh-1^{aa} mice, whereas IgM anti-IgG1 of the C57BL/6 type is detectable mainly in Igh-1^{bb} mice, and both types of rheumatoid factors are depressed in heterozygous Igh-1^{ab} animals. In other experimental murine systems, autoimmune manifestations and allotypes have been linked with antibody production against autologous erythrocytes[255] and AChRs.[256] Similarly, in humans Gm allotypic homozygosity has been related to the risk of anti-γ-globulin development,[257] and the presence of certain Gm allotypes was associated with SLE,[258] autoimmune chronic active hepatitis,[258] myasthenia gravis,[259] insulin-dependent juvenile

onset diabetes with serum anti-insulin antibodies,[260] and Graves' disease.[261,262] Combined assessment of HLA haplotype and of Gm allotype in Japanese families that had more than two first-degree relatives affected by Graves' disease provided an excellent predictor of risk for this disease, since all affected individuals had a given combination of these two markers, although siblings who shared the disease-associated haplotypes did not necessarily suffer from the disease.[261] Thus, one may expect that HLA and Ig allotyping, along with establishing other genetic markers and environmental factors, would allow fairly accurate prediction of autoimmune diseases in the future. In regard to allotypic Ig markers and diseases, it should be noted that idiotypic determinants coded by V genes have been linked to heavy chain C region allotypic markers of mice.[263,264] Since idiotypic determinants on lymphocyte membranes appear to have fundamental roles in immune regulation, the development of techniques for their assessment, such as hybridoma technology, which makes monoclonal idiotypes and anti-idiotypes available, may provide further means of improving genetic analysis of autoimmune disorders.

Genes controlling and otherwise active in autoimmunity have also been studied in animals with spontaneous or induced autoimmune diseases, particularly mice with spontaneous lupus-like syndromes. The H-2 haplotypes, lymphocyte surface alloantigens, and IgG allotypes of this kind of mice are shown in Table 3. Unfortunately, these SLE strains show no consistency or uniformity in any one of these markers. Of the two models used to determine the genetic factors associated with murine SLE, one results from crossing the several SLE-prone strains, then analyzing their F_1 hybrids in hope of finding common genetic denominators among these strains. The second model involves analysis of F_2 hybrids and recombinant inbred strains so as to interrelate the individual immunopathologic and histocompatibility traits of SLE-prone strains. In initial studies by Adams and associates,[265-268] offspring of (NZB × NZW)F_1 backcrosses with NZB and of (NZB × NZW)F_1 out-crossed with NZC mice were studied, and the genes determining expression of lupus nephritis and of autoimmune anemia, respectively, were assessed. Three genes determine the occurrence of lupus nephritis (Lpn genes) in the NZB × NZW hybrid mice; the NZB strain contains one (Lpn-1), and the NZW strain contains the other two (Lpn-2, Lpn-3). Of the two genes governing autoimmune anemia (Aia-1, Aia-2) in the NZB and NZB × NZC hybrid mice, both are in the NZB strain, and one (Aia-2) is also in the NZC strain. Thus, the autoimmune diseases of these mice clearly depend on combinations of genes that are not pathogenic individually. Of these five genes, only one, Aia-2, is tightly linked to the MHC in these investigators' opinion. According to Adams,[265,266] of the three genes governing lupus nephritis, none can be a heavy chain V gene because these are on murine chromosome 12[269] (in humans on chromosome 14[270,271]), whereas Lpn-1 and Lpn-2 are on chromosome 17, and Lpn-3 is not linked to the heavy chain allotype, as clearly shown. Moreover, Lpn-1 and Lpn-2 are not kappa light chain V genes, since these are located on murine chromosome 6[272] (in man on chromosome 2[273]). The finding that Aia-1, governing autoimmune anemia, is on chromosome 4 again precludes its being a heavy chain or kappa light chain V gene. Similarly, these genes are not related to murine lambda light chain gene, since this gene is located on chromosome 16[274] (in humans on chromosome 22[273]). Therefore, the evidence indicates involvement in murine SLE of classes of genes additional to MHC and V genes. Studies by Raveche[275] and associates similarly showed that anti-thymocyte production is controlled by a single co-dominant gene and that an independent dominant gene controls the production of autoantibodies to ssDNA. Apparently neither gene is H-2–linked. At present, the products of such co-dominant (produce their effect in the heterozygous state), non-MHC, non-V genes are unknown. Additional studies in F_2 crosses of autoimmune mice performed by Dixon and associates[149,152] and in recombinant inbred strains by Raveche and Steinberg[151] and Riblet and associates[151,276] clearly demonstrate that murine SLE is not the result of an autoimmune gene that predisposes an individual to a wide variety of autoimmune phenomena, but rather of multiple abnormal genes that are independently inherited and independently expressed, free from any link with a particular H-2 haplotype or immunoglobulin genes.

Further analysis[149] of these SLE mice shows that individual accelerating factors characteristic for each strain account for differences in the onset and severity of disease as well as mortality rates peculiar to each (Table 3). In the BXSB mouse, the accelerating factor is associated with the Y chromosome but not with sex hormones and results in much earlier disease and death in males than females. In the MRL mice the accelerating factor is the autosomal recessive lpr gene, which accounts not only for proliferation of $Lytl^+$ T cells but also for a significantly accelerated onset of disease in homozygous MRL/Mp-lpr/lpr mice, compared with congenic MRL/Mp-+/+ that do not have the lpr gene. The significance of these genetically determined accelerating factors in the expression of murine SLE is indicated in F_1 hybrids of BXSB mice and in transfers of the lpr gene of

MRL/1 mice to other SLE and normal strains. When the BXSB mouse is used as mother, it complements the predisposition to lupus in both NZB and NZW strains and produces F_1 hybrids quite similar to the traditional (NZB × NZW)F_1 mice with female offspring dying first, but BXSB females crossed with normal strains produce F_1s with little or no disease.[149,152] However, when the BXSB is used as a father in crosses with all other genetically predisposed SLE strains such as NZB, NZW, and MRL/l, the male offspring develop disease much earlier than the females, as it is observed in the BXSB strain. Similarly, establishment of the lpr gene in a homozygous state on NZB or MRL/n late-SLE developing strains, results in acceleration of the onset and course of SLE; for example, in NZB mice the 50% mortality drops from 16 months to less than 5 months and in MRL/n mice from 17 months to 5 months. But in spite of inducing lymphoproliferation, the lpr gene does not cause early SLE in normal mice without the SLE background to influence it. In New Zealand hybrid mice, the female hormones (see below) apparently hasten the onset of disease and death in females, compared with males.[277] Thus, murine SLE is caused by many independently segregating genetic factors, which in the presence of an endogenous or exogenous accelerator express themselves early; whereas in the absence of the accelerator they appear late in life. Future analysis of certain genetic markers whose location on a given chromosome is known and of their possible segregation or association with autoimmune phenomena and autoantibody production in appropriate recombinant and F_2 mice may pinpoint the exact location of the multiple abnormal genes responsible for this disease and provide the basis for further genetic characterization of persons with such multifactorial diseases as SLE.

Hormonal Factors in Autoimmunity

Sex hormones, as well as X-chromosome- or Y-chromosome-linked genes, may influence the expression of autoimmune diseases. It is well-known that hormones of the hypophysis, thyroid, parathyroid, adrenals, and gonads clearly affect the homeostasis of the lymphoid system and responses to antigens by as yet undefined mechanisms. Within the intricate homeostatic role that hormones play in lymphocyte function, the effects of the gonads on the immune response and autoimmune disease are particularly apparent. In general, females are far more susceptible to most connective tissue diseases than males. For example, the incidence of SLE in women after puberty is nine times that in men.[278] No explanation is readily apparent for this sex difference, but experimental and clinical studies in man and animals tend to incriminate, at least in part, female sex hormones rather than X-chromosome-associated genes. Consistently, females and castrated males, both in lower animals and man, have higher levels of Ig and higher specific immune responses than sexually normal males, although the direct immunosuppressive effects of testosterone or immunoenhancing effects of estrogens have not been shown conclusively.[279] Recent findings of elevated estriol levels in SLE patients with manifestations of Klinefelter's syndrome[280,281] and of absence of SLE in the castrated female monozygotic twin of a lupus victim[282] suggest further that chronic estrogenic stimulation may play an important role in the prevalence of SLE in females. Indeed, although the total amount of estrogens recovered from female human SLE subjects is normal, estradiol activity may be enhanced due to abnormalities in female hormone metabolic patterns. Thus, Lahita and Kunkel[283] found that women with SLE had elevations in the 16a-hydroxylated compounds of 16a-hydroxyestrone and estriol in their serum, compared with normal subjects.

As in human SLE, studies in the murine SLE model of (NZB × NZW)F_1 mice implicate sex hormones as accelerating factors in autoantibody levels and the overall earlier mortality in females than males. Castrated (NZB × NZW)F_1 males resemble the females, in that they have an accelerated autoimmune disease detectable at the age of six months.[277] However, testosterone or dihydrotestosterone inhibits the onset of this autoimmune disease in females or castrated male (NZB × NZW)F_1 mice following subcutaneous implantation of the androgens in silastic tubes.[277,284-286] On the other hand, although prepubertal castration of female (NZB × NZW)F_1 mice is without effect, estrogen administration accelerates overt disease in both males and females. The modes by which sex hormones modify the (NZB × NZW)F_1 disease are explained variously as effects on antigen presentation and handling by the immune system and androgen-induced enhancement of suppressor T-cell activity[287] or of tolerance inducibility.[228]

The accelerating effects of female factors such as estrogens is by no means applicable in all human and animal autoimmune diseases. For example, the incidence of ankylosing spondylitis, possibly an autoimmune disease, is higher in males than females. Moreover, in murine models of spontaneous SLE other than the NZB × NZW, the females are not hardest hit. For example, in the MRL/l mouse, sex hormones appear to have little effect, since the fe-

males die only slightly earlier than the males and, in contrast, in BXSB males the disease develops much earlier (50% mortality at 6 months of age) than in females (50% mortality at 18 months of age).[288,289] In this last strain, the male sex-determined accelerated autoimmunity is Y-chromosome-linked and not hormonally mediated. This conclusion is based on the following: 1) castration of males has no effect on the course of the disease[300]; 2) the disease is inherited in a Y-linked or holandric fashion (father to son) in F_1 crosses of BXSB males with other autoimmune strains[149,152,289]; and 3) transfer of early, severe SLE by male BXSB bone marrow or spleen cells is independent of the lethally irradiated BXSB recipient's sex.[211] Interestingly enough, a human counterpart of BXSB male-predominant disease was recently described by Lahita and Kunkel in familial studies of patients with SLE (personal communication). They observed that full expression of SLE predominated in fathers and sons, whereas female members, despite having some autoantibodies, lacked fully expressed SLE with associated glomerulonephritis.

Viral Factors in Autoimmunity

Viruses are frequently associated with autoimmune diseases of humans and animals. Such infectious agents may be acquired by horizontal or vertical transmission, and they may promote autoimmune reactions by many and varied mechanisms; among them are polyclonal activation of lymphocytes, release of subcellular organelles after cellular destruction, associative recognition phenomena in which insertion of viral antigens into cellular membranes may promote reactions against pre-existing self-components, and direct infection and thus functional impairment of certain subsets of regulatory cells such as suppressor T cells.

EBV is most prominently considered as a cause of human autoimmune diseases because of its ubiquity, persistence, and ability to act on the immune system. For example, EBV acts as a polyclonal B-cell activator stimulating mitoses and Ig secretion[200] as well as promoting autoantibody production, especially rheumatoid factor, during the course of primary infection.[201,291] The serum of rheumatoid patients contains an antibody that recognizes unique EBV-induced antigens (RAP, rheumatoid arthritis precipitation, and RANA, rheumatoid arthritis nuclear antigen) present in extracts of an EBV-carrying B type lymphoblastoid cell line of human origin.[292,293] Additionally, T cells from these patients have less capacity to suppress EBV-induced B-lymphocyte transformation than their normal counterparts.[203] Based on both these findings, this virus could be involved in the pathogenesis of rheumatoid arthritis. However, seroepidemiologic studies indicate that 1) as a group, subjects with rheumatoid arthritis have the same exposure to EBV as individuals without this disease; 2) antibodies to EBV-associated antigens are not a unique characteristic of such patients but can be found, albeit to a lower degree, in normal persons[294–297]; 3) no evidence proves entry by EBV into the joint space; 4) arthritis does not accompany certain EBV syndromes such as infectious mononucleosis; 5) in patients with early (less than 6 weeks) rheumatoid arthritis there is no elevation of anti-EBV antibodies, and in one patient with early rheumatoid arthritis no serologic evidence of prior EBV infection or antibody to RANA antigen was detected.[298] These findings refute a primary role for EBV in the etiology of rheumatoid arthritis.

Myxoviruses, hepatitis viruses, cytomegaloviruses, Coxsackie viruses, retroviruses, and others have also been incriminated as causative agents of autoimmune diseases in humans.[167,299] Most of these viruses induce autoantibodies during natural infections and also autoimmune-disease-like immunopathologic characteristics such as vasculitis and glomerulonephritis, which, however, appear to be caused primarily by specific virus–viral antibody immune complexes rather than by autoantibody–antigen complexes. An oncornavirus-associated etiology for human SLE, although claimed, has not been demonstrated.[300–302] Thus, although particles resembling viruses have been observed in lymphocytes[303] and kidneys[304] of SLE patients, it is generally agreed that these particles are artifacts or cell structures that have no relationship to viruses.[304] Moreover, isolation of C-type viruses or antigens thereof from spleens[305] and placentas[306] of SLE patients is disputed[307]; C-type virus antigens, in spite of claims to the contrary,[308,309] are not conclusively established as components of glomerular immune complex deposits, and repeated attempts to demonstrate specific antibodies against C-type viruses in serum of humans, including SLE patients, have failed.[310,311] Although increased titers of antibodies against certain viruses, such as measles have been found in serum of SLE patients, compared with normals, this finding has been considered nonspecific—the result of these patients' hypergammaglobulinemia.[312] Despite these negative results, the search for a virus associated with human SLE continues.

As is obvious, the relationship between virus and autoimmune disease is best examined in animal models that share characteristics in common with the disease in humans. Thus, a viral etiology has been es-

tablished in the disease of Aleutian minks involving a small DNA virus[313]; in equine infectious anemia stemming from a transmissible C-type viruslike agent that has been isolated[314]; and possibly in canine SLE comprising anti-DNA antibodies, rheumatoid factor, anti-red blood cell antibodies, hypergammaglobulinemia, LE cells, and C-type virus.[299,315,316]

Viruses and their antigenic components correlate best with the pathogenesis of autoimmune disease in the murine SLE model. An initial report[317] that NZB disease could be transferred to normal mice with cell-free extracts and filtrates of NZB splenocytes was unconfirmed.[318,319] Subsequent research demonstrated that NZB mice express infectious xenotropic type-C RNA virus throughout life and in high titers.[299,320,321] The virus is not found in the mouse itself but becomes apparent after co-cultivation of its tissue homogenates with heterologous cells such as those from cats. The correlation between high titers of xenotropic virus production *in vitro* by tissue homogenates of NZB mice and autoimmunity then suggested a cause-and-effect relationship. This concept was strengthened when viral antigen–antiviral antibody immune complexes were recovered from the renal lesions in NZB and (NZB × NZW)F_1 mice.[322,323] The failure to transmit autoimmune disease with cell-free filtrates was explained by the fact that xenotropic C-viruses cannot productively infect mouse cells, only cells of heterologous species. Subsequently, the magnified expression of xenotropic virus in NZB mice was established as a genetically determined trait controlled by two independently segregating, autosomal dominant loci (Nzv-1 and Nzv-2).[321] This demonstration has facilitated genetic analysis of the relationship between xenotropic virus and autoimmunity. The murine hybrid chosen for study of this relationship was NZB × SWR because NZB mice are homozygous for the dominant alleles of viral expression, whereas SWR mice are homozygous for the recessive alleles and do not spontaneously develop autoimmune disease.[324,325] Analysis of the F_1, F_2, and backcross progeny of NZB × SWR mice demonstrated the following: 1) some progency whose tissue homogenates express titers of xenotropic virus as high as those of the NZB parent fail to develop signs of autoimmunity; 2) virus-negative offspring from these crosses still develop autoantibodies; 3) the phenotypic expression of virus does not correlate with the incidence of glomerular lesions; and 4) levels of the viral antigen gp70 do not correlate with the development of nephritis in these crosses.

Gp70, the major glycoprotein component of the envelope of C-type RNA viruses is found in tissue and serum of virtually all mice. Structural studies of serum gp70 indicate that it is the same in all strains and resembles the gp70 of the NZB xenotropic virus.[326] Its presence is independent of the expression of complete retrovirus particles, and it appears to be produced primarily in the liver. Gp70 has also been implicated in the pathogenesis of spontaneous lupus nephritis because of the high concentrations in the serum of these mice and deposits of gp70 in diseased glomeruli along with specific antibody, complement, and nuclear antigens and antibodies.[323,327,328] However, similarly high levels of identical gp70 have been detected in several immunologically normal strains of mice,[327] indicating that gp70 *per se* is not the factor that determines disease expression.

Compared with normal strains of mice, only SLE mice produce antibodies against xenotropic gp70 and contain circulating gp70–anti-gp70 complexes.[329] Notably, the presence of such complexes is related to the expression of glomerulonephritis in (NZB × NZW)F_2 mice.[330] The gp70 that participates in the formation of immune complexes is no different antigenically or structurally, by tryptic peptide map analysis, from the free xenotropic gp70 found at varying levels in the serum of all murine strains.[331] Thus, the high serum levels of xenotropic gp70, in themselves, apparently do not cause murine nephritis, but rather the unique ability of autoimmune mice to respond to this autoantigen is the critical factor. To summarize, these studies indicate that although xenotropic virus and viral antigens may participate secondarily in the formation of immunopathologic lesions in the NZB mouse and its crosses, they are not a primary cause.

Chronic viral infections may have an additional secondary role in autoimmune diseases if their superimposition on an autoimmune genetic background accelerates autoimmunity. For example, lymphocytic choriomeningitis (LCM) virus,[332] polyoma virus,[332] and retrovirus[333] infections all induce or elevate antinuclear antibodies and SLE-like disease in mice. Although these viruses probably act in part by causing anti-virus antibody and immune complexes to form, parallel stimulation of antinuclear and of other autoantibodies must be considered as potential means of enhancing SLE. Neonatal LCM virus infection changes the 50% mortality point caused by SLE-like disease from 16 to less than 5 months in the NZB female, from 18 to 9 months in the BXSB female, and from 17 to 12 months in the MRL/Mp-+/+ mice. In contrast, normal C3H and SWR mice infected neonatally with LCM virus and examined from birth to 2 years of age do not develop the fatal SLE-like disease. The transient appearance of autoreactive splenic T cells within 3 days after injection of LCM virus has been reported in adult mice, and this

Table 7—Means of Treatment for Autoimmune Diseases

Currently available	Experimental
Replacement therapies (insulin in diabetes, B_{12} in pernicious anemia, thyroxine in myxedema, etc.)	Inhibitors of complement peptides
Antiinflammatory agents	Induction of tolerance to autoantigens
Cytostatic agents	Autoantigen-specific suppressor T cells and their products
Plasmapheresis and lymphoplasmapheresis	Anti-idiotypic antibodies to autoantibodies
Total lymphoid irradiation	Bone marrow transplantation
	Thymic hormones and peptides
	Prostaglandins
	Dietary restriction (low caloric uptake, low fatty acids)
	Androgens
	Alpha-fetoprotein

phenomenon may account for the expression of enhanced autoimmunity in mice with immune disregulation. Consequently, viruses may induce aberrant responses and autoaggression with subsequent development of autoimmune manifestations via their polyclonal B-cell activating potential, their cytolytic capacity, their possible tropisms for certain subpopulations of lymphoid cells, and their possible capacity to associate with and convert autoantigens to foreign antigens.

Treatment of Autoimmune Diseases

Both nonspecific and specific means for treating patients with autoimmune diseases already exist or are in the planning stage (Table 7). These treatments are based on current knowledge about the immunologic and serologic abnormalities associated with these diseases as well as the mechanisms that mediate inflammatory processes.

Replacement therapies are now being used to treat most organ-specific autoimmune diseases, ie, insulin in juvenile diabetes, vitamin B_{12} in pernicious anemia, anti-thyroid drugs for Graves' disease, thyroxine in primary myxedema, etc. Anticholinesterase drugs are commonly administered for therapy of myasthenia gravis; and, in some instances, thymectomy has proven beneficial, perhaps due to a postulated presence in that organ of an antigen that cross-reacts with AChRs or of cells that enhance production of anti-AChR antibodies.

Several nonspecific *means for intervention and/or modification of inflammatory responses* and of their biologically active mediators have been developed and used extensively, since autoantibody, immune complexes and/or complement mediate most autoimmune diseases, and most involve the attraction of inflammatory cells (polymorphonuclear cells, macrophages), release of hydrolases, and subsequent tissue damage. Corticosteroids are of primary use in autoimmune diseases, especially SLE, rheumatoid arthritis, and myasthenia gravis. In rheumatoid arthritis, in addition to steroids, antiinflammatory drugs such as salicylates, indomethacin, and others are widely prescribed as well as antimalarial drugs, penicillamine, and gold salts, the latter three of which act by relatively unknown mechanisms. Additionally, *immunosuppressive or cytostatic drugs* such as cyclophosphamide, azathioprine, and methotrexate are used in many disorders including rheumatoid arthritis, SLE, chronic active hepatitis, and autoimmune hemolytic anemias. *Plasmapheresis or lymphoplasmapheresis*[334] are also tried for severe forms of rheumatoid arthritis, Goodpasture's syndrome, myasthenia gravis, and SLE but, in many instances, with limited success, because of a rather quick rebound of autoantibody levels following the completion of therapy.

Total lymphoid irradiation (TLI), initially one of the treatments for malignant hematologic disorders, is now adapted successfully in treating intractable cases of rheumatoid arthritis[335,336] as well as lupus of both humans and experimental animals[172] and may be applicable to many other autoimmune diseases. This treatment consists of repeated irradiation of all lymphoid organs (150–220-rad separate doses, for a total of 2000 rads) over a relatively short period of time (2–3 weeks) with shielding of bone marrow. Adverse side effects appear to be very limited, although the immunosuppressive effects of TLI are long-lasting.

Contemplated treatments for autoimmune diseases include administration of the following: 1) Chemical *inhibitors* of the *complement system*, especially of its biologically active peptides C3a and C5a. 2) *Autoantigens* coupled with tolerance-inducing carriers such as isologous IgG, D-glutamic acid, D-lysine (D-GL), or syngeneic lymphocytes. This approach was successfully used in inducing tolerance to autoantigens in murine SLE models.[337,338] 3) Autoantigen-specific or -nonspecific *soluble suppressive factors* from cloned suppressor T cells or Con A-activated T lymphocytes. Crude supernatants of Con A-activated normal lymphocytes inhibit the ex-

pression of disease in NZB × NZW mice when given repeatedly.[339,340] 4) *Anti-idiotypic antibodies* against the idiotype of autoantibodies. This approach has been tried with some success in animal models of autoimmune disease, such as rats with experimental thyroditis,[341] rabbits and rats with tubulointerstitial nephritis,[342,343] and rabbits with experimental myasthenia gravis.[344] However, such means may have limited success for the following reasons; first, most autoantibody responses are polyclonal and may lack any cross-reactive idiotype; second, anti-idiotypic suppression is allotypically restricted and therefore may act on one person but not others with the same disease; and third, xenoanti-idiotypic antibodies given over long periods of time may cause adverse effects such as serum sickness. 5) *Bone marrow* transplanted from normal persons to those with autoimmune disease. As shown in murine SLE models,[211,214] lethally irradiated SLE mice transplanted with bone marrow derived from normal histocompatible mice do not develop lupus, in contrast to recipients of syngeneic bone marrow. This finding strongly suggests that the cause of SLE is genetically determined hematopoietic abnormalities of lymphoid cells, not nonlymphoid environmental factors. Therefore, when bone marrow transplantation can be achieved safely across histocompatibility barriers, such an approach may be useful in some cases of severe SLE and probably other autoimmune disorders. 6) *Thymic hormones*, although tried in humans and animals with SLE, have very little, if any, effect.[185,186] 7) *Prostaglandin* (PGE_1). This agent in pharmacologic amounts prolongs the survival of $(NZB \times NZW)F_1$ and MRL/1 mice by inhibiting immune complex–mediated glomerulonephritis and massive T-cell proliferation in the latter strain.[345–347] The mode by which these beneficial effects are mediated is unknown but may include increased clearance of immune complexes by PGE_1-activated mononuclear phagocytes or suppression of the antibody responses to retroviral envelope antigens. PGE_1 exerts beneficial effects in SLE-prone mice if given very early in life before overt disease is expressed. 8) *Dietary restriction*. In a number of studies, special diets and dietary caloric restriction, especially those low in dietary fat and essential fatty acids, have proved helpful for murine SLE.[348,350] 9) *Androgens*. As discussed, androgens can retard SLE in $(NZB \times NZW)F_1$ mice; however, usage of androgens in humans has the serious limitation of producing significant virilization. Unfortunately, derivatives of ethinyltestosterone, such as danazol, which are mildly anabolic and have markedly attenuated androgenic effects are ineffective in murine SLE models.[284] 10) *Alpha-fetoprotein*. AFP, a glycoprotein produced in quantity by the fetal liver, exerts significant suppression on both humoral and cellular immune responses. Recent studies indicated that AFP has a significant inhibitory effect on the binding of anti-AChR antibody to its antigen and can prevent the development of experimental autoimmune myasthenia gravis in rabbits.[351]

Conclusions

Here we present some of the intellectual avenues involved in the acquisition of our present understanding of autoimmune disorders and the reasons for their occurrence. The pursuit of knowledge in this field brings together penetrating research into immunology, pathology, endocrinology, virology, genetics, and molecular biology. The role of self-recognition in the immune system has been discussed in light of recent experimental data. These findings indicate that, under certain conditions, recognition of self-determinants is not totally forbidden or harmful. Thus, before T cells can differentiate to become effector cells, they must recognize both foreign antigen and self-MHC determinants. Furthermore, homeostasis of immunity and control of immune responses appear to involve a complex web that interconnects all lymphocytes and their antigen receptors via self-V–anti-self-V domain Ig determinants, the so-called idiotype–anti-idiotype network. Since autorecognition is, apparently, a normal event in a functioning immune system, the proposal that autoimmune diseases may result in part from an imbalance or aberration of complementary idiotypic–anti-idiotypic responses is reasonable.

Although autorecognition can be physiologically normal, the fact remains that an individual generally does not respond overtly against most of its own constituents. The process of inducing tolerance to self, as derived from experimental studies of tolerance induction to foreign antigens, is attributable to numerous mechanisms for which the most acceptable explanations are clonal silencing and/or engagement of suppressor T cells, the latter mechanism presumably acting by the idiotype–anti-idiotype circuit. It is generally agreed that immature immunocytes are much more susceptible to tolerance induction than mature cells. Since the turnover of B cells is very rapid, one can logically conclude that the process of inducing tolerance to self is a continuous event that occurs repeatedly throughout the life span of an individual whenever primitive cells with a genetic commitment to self-reactivity emerge from the hematopoietic organs, where they have the opportunity to meet self-

antigens in situ. Foreign antigens do not, usually, induce tolerance, because they pass through a succession of lymph nodes, where they have optimal opportunity to meet tolerance-resistant mature immunocytes.

Why the phenotypically apparent self-tolerance mechanism sometimes fails and permits destructive autoimmunity is unknown. However, genetic factors combined with a variety of primary or secondary immunologic abnormalities, as well as hormonal abnormalities and infectious agents such as viruses, may promote the development of autoimmune diseases. The abnormal genes responsible for expression of autoimmune syndromes have not yet been identified, but studies in animal models of SLE have shown that many independently segregating genes could be responsible for the formation of the various autoantibodies. Despite the observed association, albeit minimal, between most autoimmune diseases of man and certain MHC and Ig genes, the genes controlling expression of autoantibodies in murine SLE have not been closely linked to any particular H-2 type or allotypic marker. Further studies aiming at the precise chromosomal assignment and location of autoimmunity-promoting genes will be of extreme importance in our attempts to understand the pathogenesis of these disorders and possibly to evolve genetic engineering techniques that halt their progress.

Neither the etiologic events nor the actual immunologic abnormalities leading to autoimmunity are well defined; in particular, the organ-specific autoimmune diseases for which few animal models are available remain virtually unexplored. From studies of SLE in humans and mice one can list many abnormalities at both the B- and T-cell levels. Originally, the prevailing view was that the characteristic B-cell hyperactivity of this disease was secondary to suppressor T-cell abnormalities. However, this explanation now seems doubtful. Transplantation experiments between some SLE murine strains and their normal congenic or histocompatible counterparts indicate that hematopoietic stem cells and precursors of B cells can transfer the disease in the absence of T cells, thus suggesting a primary B-cell defect as the responsible agent for this disease. Some T-cell abnormalities of such mice develop independently of associated B-cell abnormalities in appropriate crosses, and vice versa. Assuredly, the possibility that T cells may express some inhibitory effects on expression of the primary B-cell defect cannot be excluded. Defects in tolerance induction to foreign antigens have been observed in all SLE strains of mice. The reasons for such a defect as well as the relevance to lack of tolerance to self-antigens are not clear, but the rapid transition of immunocytes from the immature state, in which they are easily made tolerant, to one of maturity refractory to being made tolerant is a possibility worthy of consideration. Evidence is available for such a rapid transition in subsets of B cells from NZB mice.

Whatever the basic genetic and molecular immunologic defects, such defects may not become overt until late in life unless accelerating factors are superimposed. These accelerating factors may be endogenous and genetic in nature. One example is the Y-chromosome-linked accelerating gene(s) of BXSB mice that predisposes to a much earlier development of SLE in male than in female mice; another such example is the lpr gene of MRL mice that predisposes, possibly by inducing proliferation of helper T cells, to the earlier expression of disease in MRL/Mp-lpr/lpr mice compared with congenic MRL/Mp-+/+ mice that lack the lpr gene, in which the disease develops later. Accelerating factors of autoimmunity may also be female hormones and some exogenous factors such as viruses and bacteria that may activate polyclonally self-reactive B cells.

Of medical treatments for autoimmune diseases, most are nonspecific and burdened with undesirable side effects. Perhaps further understanding of normal and abnormal immunoregulation will result in means of specifically eliminating or turning off emerging clones of autoantibody-secreting cells without otherwise compromising the host. Such means, for example, may include autoantibody-specific suppressor T-cell factors and anti-idiotypic antibodies against autoantibodies. In concluding, a noteworthy proposal from some investigators, based on the idiotype-anti-idiotype concept, is that iatrogenically induced autoimmunization may benefit certain patients.[352,353] Observations in experimental systems have shown that autoanti-idiotypic immunity may obliterate undesirable immune reactivity, as, for example, in allotransplantation,[354] or may, conversely, induce immunity to particular antigens on target organs with the appropriate receptors. For example, anti-idiotypic antibodies to anti-insulin antibodies may mimic the action of insulin,[355] and anti-idiotypic antibodies to monoclonal antibodies specific for *Trypanosoma rhodesiense* may induce antigen-independent immunity in mice.[356]

References

1. Ehrlich P, Morgenroth J: The Collected Papers of Paul Ehrlich—1900. Edited by F Himmelweit. Oxford, Pergamon Press, republished 1956, pp 205–255
2. Weigle WO: Analysis of autoimmunity through ex-

perimental models of thyroiditis and allergic encephalomyelitis. Adv Immunol 1980, 30:159-273
3. Irvine, JW: Autoimmunity in endocrine disease, Immunology 80—Progress in Immunology IV. Edited by M Fougereau, J Dausset. London, Academic Press, 1980, pp 930-958
4. Talal N: Autoimmunity and lymphoid malignancy: Manifestations of immunoregulatory disequilibrium, Autoimmunity—Genetic, Immunologic, Virologic, and Clinical Aspects. Edited by N Talal. New York, Academic Press, 1977, pp 184-206
5. Burnet FM: Autoimmunity and aging,[4] pp 513-530
6. Ammann AJ: Immunodeficiency disorders and autoimmunity,[4] pp 479-512
7. Raum D, Donalson VH, Alper CA, Rosen FS: Genetics of complement, The Menarini Series on Immunopathology. Edited by PA Miescher, L Bolis, G. Torrigiani. Basel, Schwabe, 1981, pp 162-183
8. Weksler ME: The senescence of the immune system. Hosp Pract 1981, 16:53-64
9. Koffler D: Systemic lupus erythematosus. Sci Am 1980, 243:52-61
10. Kunkel HG: The immunopathology of SLE. Hosp Prac 1980, 15:47-56
11. Theofilopoulos AN, Dixon FJ: The biology and detection of immune complexes. Adv Immunol 1979, 28:89-220
12. Petz LD: Autoimmune and drug-induced immune hemolytic anemias, Manual of Clinical Immunology. Edited by NR Rose, H Friedman. Washington, DC, American Society for Microbiology, 1980, pp 726-743
13. Wilson CB, Dixon FJ: The renal response to immunological injury, The Kidney. Vol. 2. Edited by BM Brenner, FC Rector Jr. Philadelphia, WB Saunders Company, 1976, pp 838-940
14. Adams DD: Thyroid-stimulating autoantibodies. Vitam Horm 1980, 38:119-203
15. Kidd A, Okita N, Row VV, Volpe R: Immunologic aspects of Graves' and Hashimoto's diseases. Metabolism 1980, 29:80-99
16. Cahill Jr CF, McDevitt HO: Insulin-dependent diabetes mellitus: The initial lesion. N Engl J Med 1981, 304:1454-1465
17. Blecher M, Bar RS: Receptors and Human Disease. Baltimore, Williams and Wilkins, 1981
18. Lindstrom J: Autoimmune response to acetylcholine receptors in myasthenia gravis and its animal model. Adv Immunol 1979, 27:1-50
19. De Baets M, Elewaut A, Dacremont G, Vermeulen A: Autoantibodies to the thyrotropin receptor and their significance in autoimmune thyroid disease, Recent Progress in Diagnostic Laboratory Immunology. Edited by R Nakamura. New York, Masson, 1982, pp 37-51
20. Roths J: Insulin receptors in diabetes. Hosp Pract 1980, 15:98-103
21. Kahn CR, Flier JS, Bar RS, Archer JA, Gorden P, Martin MM, Roth J: The syndrome of insulin resistance and acanthosis nigricans. N Engl J Med 1976, 294:739-745
22. Venter JC, Fraser CM, Harrison LC: Autoantibodies to β_2-adrenergic receptors: A possible cause of adrenergic hyporesponsiveness in allergic rhinitis and asthma. Science 1980, 207:1361-1363
23. Fraser CM, Venter JC, Kaliner M: Autonomic abnormalities and autoantibodies to beta-adrenergic receptors. N Engl J Med 1981, 305:1165-1170
24. Tan EM: Autoantibodies to nuclear antigens (ANA): Their immunobiology and medicine. Adv Immunol 1982 (In press)
25. Winchester RJ, Winfield JB, Siegal F, Wernet P, Bentwich Z, Kunkel HG: Analyses of lymphocytes from patients with rheumatoid arthritis and systemic lupus erythematosus: Occurrence of interfering cold-reactive antilymphocyte antibodies. J Clin Invest 1974, 54:1082-1092
26. Stastny P, Ziff M: Antibodies against cell membrane constituents in systemic lupus erythematosus and related diseases. Clin Exp Immunol 1971, 8:543-550
27. Winfield JB, Winchester RJ, Wernet P, Fu SM, Kunkel HG: Nature of cold-reactive antibodies to lymphocyte surface determinants in systemic lupus erythematosus. Arthritis Rheum 1975, 18:1-8
28. Bluestein HG: Neurocytotoxic antibodies in serum of patients with systemic lupus erythematosus. Proc Natl Acad Sci USA 1978, 75:3965-3969
29. Lafer EM, Rauch J, Andrzejewski C, Mudd D, Furie B, Furie B, Schwartz RS, Stollar BD: Polyspecific monoclonal lupus autoantibodies reactive with both polynucleotides and phospholipids. J Exp Med 1981, 153:897-909
30. Lafer EM, Moller A, Nordheim A, Stollar BD, Rich A: Antibodies specific for left-handed Z-DNA. Proc Natl Acad Sci USA 1981, 78:3546-3550
31. Lerner MR, Steitz JA: Snurps and scyrps. Cell 1981, 25:298-300
32. Yang VW, Lerner MR, Steitz JA, Flint SJ: A small nuclear ribonucleoprotein is required for splicing of adenoviral early RNA sequences. Proc Natl Acad Sci USA 1981, 78:1371-1375
33. Alarcon-Segovia D, Ruiz-Arguelles A, Fishbein E: Antibody to nuclear ribonucleoprotein penetrates live human mononuclear cells through Fc receptors. Nature 1978, 271:67-69
34. Zvaifler NJ: Rheumatoid arthritis,[4] pp 569-595
35. Carson DA, Pasquali JL, Tsoukas CD, Fong S, Slovin SF, Lawrence SK, Slaughter L, Vaughan JH: Physiology and pathology of rheumatoid factors. Springer Seminars in Immunopathology 1981, 4:161-179
36. Cohn M: Immunology: What are the rules of the game? Cell Immunol 1972, 5:1-20
37. Jerne NK: The somatic generation of immune recognition. Eur J Immunol 1971, 1:1-9
38. Cohn M, Langman R, Geckeler R: Diversity 1980,[3] pp 153-201
39. Honjo T, Nakai S, Nishida Y, Kataoka T, Yamawaki-Kataoka Y, Takahashi N, Obata M, Shimizu A, Yaoita Y, Nikaido T, Ishida N: Rearrangement of immunoglobulin genes during differentiation and evolution. Immunol Rev 1981, 59:33-67
40. Adams JM: The organization and expression of immunoglobulin genes. Immunology Today 1980, 1:10-17
41. Klinman NR, Wylie DE, Teale JM: B Cell development. Immunology Today 1981, 2:212-216
42. De Freitas AA, Coutinho A: Very rapid decay of mature B lymphocytes in the spleen. J Exp Med 1981, 154:994-999
43. Zinkernagel RM, Callahan GN, Klein J, Dennert G: Cytotoxic T cells learn specificity for self *H-2* during differentiation in the thymus. Nature 1978, 271:251-253
44. Bevan MJ, Fink PJ: the influence of thymus *H-2* antigens on the specificity of maturing killer and helper cells. Immunol Rev 1978, 42:4-19
45. Wekerle H, Ketelsen VP: Thymic nurse-Ia-bearing epithelium involved in T-lymphocyte differentiation. Nature 1980, 283:402-404
46. Bevan MJ: In a radiation chimera, host *H-2* antigens determine immune responsiveness of donor cytotoxic cells. Nature 1977, 269:417-418
47. Zinkernagel RM, Doherty PC: MHC-restricted cyto-

toxic T cells: Studies on the biological role of polymorphic major transplantation antigen determining T cell restriction-specificity, function and responsiveness. Adv Immunol 1979, 27:51-177
48. Bevan MJ: Thymic education. Immunology Today 1981, 2:216-219
49. Doherty PC, Bennink JR: Monitoring the integrity of self: Biology of MHC-restriction of virus-immune T cells. Fed Proc 1981, 40:218-221
50. Langman RE: The role of the major histocompatibility complex in immunity: A new concept in the functioning of a cell-mediated immune system. Rev Physiol Biochem Pharmacol 1978, 81:1-35
51. Von Boehmer H, Haas W, Jerne NK: Major histocompatibility complex-linked immune-responsiveness is acquired by lymphocytes of low-responder mice differentiating in thymuses of high-responder mice. Proc Natl Acad Sci USA 1978, 75:2439-2442
52. Miescher PA: The Menarini Series on Immunopathology, Edited by P Miescher, L Bolis, G Torrigiani. Basel, Schwabe, 1981, pp 9-18
53. Hood LE, Weissman IL, Wood WB: Cell-cell recognition occurs through complementary molecular interactions, Immunology. Edited by M Forker, M Moore, J Hall. Menlo Park, Benjamin/Cummings Publishing, 1978, pp 332-343
54. Katz DH: Lymphocyte Differentiation, Recognition and Regulation. New York, Academic Press, 1977
55. Katz DH, Benacerraf B: The function and interrelationship of T cell receptors, Ir genes and other histocompatibility gene products. Transplant Rev 1975, 22:175-195
56. Rosenthal AS: Determinant selection and macrophage function between antigen presenting cells and primed T lymphocytes. Immunol Rev 1978, 40:136-152
57. Benacerraf B: Role of MHC gene products in immune regulation. Science 1981, 212:1229-1238
58. Shearer GM, Schmitt-Verhulst AM: Major histocompatibility complex restricted cell-mediated immunity. Adv Immunol 1977, 25:55-91
59. Matzinger P: A one-receptor view of T-cell behavior. Nature 1981, 292:497-501
60. Williamson AR: Three-receptor, clonal expansion model for selection of self-recognition in the thymus. Nature 1980, 283:527-532
61. Krawinkel U, Cramer M, Kindred B, Rajewsky K: Isolated hapten-binding receptors of sensitized lymphocytes: V. Cellular origin of receptor molecules. Eur J Immunol 1979, 10:815-820
62. Cayre Y, Palladino MA, Marcu KB, Stavnezer J: Expression of an antigen receptor on T cells does not require recombination at the immunoglobulin J_H-Cμ locus. Proc Natl Acad Sci USA 1981, 78:3814-3818
63. Wigzell H, Binz H: Lymphocyte receptors,[3] pp 94-104
64. Blanden RV: How do immune response genes work? Immunology Today 1980, 1:33-36
65. Ohno S, Matsunaga T, Epplen JT, Hozumi T: Interaction of viruses and lymphocytes in evolution, differentiation and oncogenesis,[3] pp 577-598
66. Oudin J, Michel M: Idiotypy of rabbit antibodies: I. Comparison of idiotypy of antibodies against *salmonella typhi* with that of antibodies against other bacteria in the same rabbits, or of antibodies against *salmonella typhi* in various rabbits. J Exp Med 1968, 130:595-617
67. Kunkel HG, Mannik M, Williams RC: Individual antigenic specificity of isolated antibodies. Science 1963, 140:1218-1219
68. Eichmann K: Expression and function of idiotypes on lymphocytes. Adv Immunol 1978, 26:195-254
69. Jerne NK: Towards a network theory of the immune system. Ann Immunol (Paris) 1974, 125C:373-389
70. Jerne NK: The immune system: A web of V domains. Harvey Lect 1975, 93-110
71. Davie JM: Anti-idiotypic reagents. J Immunol Methods 1980, 38:1-7
72. Herzenberg LA, Herzenberg LA: Mouse immunoglobulin allotypes: Description and special methodology, Handbook of Experimental Immunology. Edited by DM Weir. Oxford, Blackwell Scientific Publications, 1973, pp 13.1-13.18
73. Lieberman R: Genetics of Ig CH (allotype) locus in mouse. Springer Seminars in Immunopathology 1978, 1:7-30
74. Consenza H, Kohler H: Specific inhibition of plaque formation to phosphorylcholine by antibody against antibody. Science 1972, 176:1027-1029
75. Makela O, Karjalainen K: Inherited immunoglobulin idiotypes of the mouse. Immunol Rev 1977, 34:119-138
76. Daugharty H, Hopper JE, MacDonald AB, Nisonoff A: Quantitative investigations of idiotypic antibodies: I. Analysis of precipitating antibody populations. J Exp Med 169, 130:1047-1062
77. Geha RS, Weinberg RP: Anti-idiotypic antisera in man: I. Production and immunochemical characterization of anti-idiotypic antisera to human antitetanus antibodies. J Immunol 1978, 121:1518-1523
78. Eichmann K, Kindt TJ: The inheritance of individual antigenic specificities of rabbit antibodies to streptococcal carbohydrates. J Exp Med 1971, 134:532-552
79. Kunkel HG, Agnello V, Joslin RF, Winchester RJ, Capra JD. Cross-idiotypic specificity among monoclonal IgM proteins with anti-γ-globulin activity. J Exp Med 1973, 137:331-342
80. Pasquali JL, Fong S, Tsoukas C, Vaughan JH, Carson DA: Inheritance of immunoglobulin M rheumatoid factor idiotypes. J Clin Invest 1980, 66:863-866
81. Vincent A: Idiotype restriction in myasthenia gravis antibodies. Nature 1981, 290:293-294
82. Bona CA, Heber-Katz E, Paul WE: Idiotype-anti-idiotype regulation: I. Immunization with a levan-binding myeloma protein leads to the appearance of auto-anti-(anti-idiotype) antibodies and to the activation of silent clones. J Exp Med 1981, 153:951-967
83. Lindenmann J: Homobodies: Do they exist? Ann Immunol (Paris) 1979, 130C:311-318
84. Kluskens L, Kohler H: Regulation of immune response by autogenous antibodies against receptor. Proc Natl Acad Sci USA 1974, 71:5083-5087
85. Goidl EA, Schrater AF, Siskind GW, Thorbecke GJ: Production of auto-anti-idiotypic antibody during the normal immune response to TNP-Ficoll: II. Hapten-reversible inhibition of anti-TNP plaque forming cells by immune serum as an assay for auto-anti-idiotypic antibodies. J Exp Med 1979, 150:154-165
86. Brown JC, Rodkey LS: Autoregulation of antibody response via network induced auto-anti-idiotype. J Exp Med 1979, 150:67-85
87. Cosenza H: Detection of anti-idiotype reactive cells in the immune response to phosphorylcholine. Eur J Immunol 1976, 6:114-116
88. Golub ES: Idiotypes and the network hypothesis. Cell 1980, 22:641-642
89. Hiernaux J: Anti-idiotypic networks. Fed Proc 1981, 40:1484-1488
90. Kohler H: Idiotypic network interactions. Immunology Today 1980, 1:18-21
91. Kohler H, Levitt D, Bach M: A non-galilean view of the immune network. Immunology Today 1981, 2:58-60

92. Geha RS: Regulation of the immune response by idiotypic-anti-idiotypic interactions. N Engl J Med 1981, 305:25-28
93. Hiernaux J, Bona C: Immune network, Lymphocyte regulation by antibodies. Edited by C Bona, P-A Cazenave. New York, J Wiley and Sons, 1981, pp 269-297
94. Janeway CA, Sakato N, Eisen HN: Recognition of immunoglobulin idiotypes by thymus-derived lymphocytes. Proc Natl Acad Sci USA 1975, 72:2357-2360
95. Nisonoff A, Greene MI: Regulation through idiotypic determinants of the immune response to the p-azophenylarsonate hapten in strain A mice,[3] pp 57-80
96. Sunday ME, Benacerraf B, Dorf ME: Hapten-specific T cell responses to 4-hydroxy-3-nitrophenyl acetyl: VIII. Suppressor cell pathways in cutaneous sensitivity responses. J Exp Med 1981, 153:811-822
97. Coutinho A: The self-nonself discrimination and the nature and acquisition of the antibody repertoire. Ann Immunol (Paris) 1980, 131D:235-253
98. Triplett EL: On the mechanism of immunologic self recognition. J Immunol 1962, 89:505-510
99. Rosenberg LT, Tachibana DK: Activity of mouse complement. J Immunol 1962, 89:861-867
100. Winchester G: Acquired self tolerance to the intracellular liver protein F (Abstr). J Supramol Struct 1979, 11(Suppl):274
101. Burnet FM: The Clonal Selection Theory of Acquired Immunity. London, Cambridge University Press, 1959
102. Jerne NK: The natural selection theory of antibody formation. Proc Natl Acad Sci USA 1955, 41:849-857
103. Owen RD: Immunogenetic consequences of vascular anastomoses between bovine twins. Science 1945, 102: 400-401
104. Billingham RE, Brent L, Medawar PB: Actively acquired tolerance of foreign cells. Nature 1953, 172: 603-606
105. Nossal GJV, Pike BL: Antibody receptor diversity and diversity of signals,[3] pp 136-152
106. Metcalf ES, Schrater AF, Klinman NR: Murine models of tolerance induction in developing and mature B cells. Immunol Rev 1979, 43:142-183
107. Teale JM, Layton JE, Nossal GJV: *In vitro* model for natural tolerance to self-antigens: Inhibition of the development of surface immunoglobulin-negative lymphocytes into T-independent responsive B cells by antigen. J Exp Med 1979, 150:205-217
108. Teale JM, Klinman NR: Tolerance as an active process. Nature 1980, 288:385-387
109. Sidman CL, Unanue ER: Receptor-mediated inactivation of early B lymphocytes. Nature 1975, 257: 149-151
110. Raff MC, Owen JJT, Cooper MD, Lawton R, Megson M, Gathings WE: Differences in susceptibility of mature and immature mouse B lymphocytes to anti-immunoglobulin-induced immunoglobulin suppression *in vitro*. J Exp Med 1975, 142:1052-1064
111. Nossal GJV, Pike BL: Functional clonal deletion in immunological tolerance to major histocompatibility complex antigens. Proc Natl Acad Sci USA 1981, 78: 3844-3847
112. Green DR, Gershon RK, Eardley DD: Functional deletion of different Ly-1 T-cell-inducer subset activities by Ly-2 suppressor T lymphocytes. Proc Natl Acad Sci USA 1981, 78:3819-3823
113. Golub ES: Suppressor T cells and their possible role in the regulation of autoreactivity. Cell 1981, 24:595-596
114. Gershon RF: Suppressor T cells: A miniposition paper celebrating a new decade,[3] pp 373-388
115. Cantor H, Gershon RK: Immunological circuits: Cellular composition. Fed Proc 1979, 38:2058-2064
116. Gershon RK, Eardley DD, Durum S, Green DR, Shen F-W, Yamauchi K, Cantor H, Murphy DB: Contrasuppression: A novel immunoregulatory activity. J Exp Med 1981, 153:1533-1546
117. Ledbetter JA, Rouse RV, Micklem HS, Herzenberg LA. T cell subsets defined by expression of Lyt-1,2,3 and the Thy-1 antigens: Two parameter immunofluorescence and cytotoxicity analysis with monoclonal antibodies modifies current views. J Exp Med 1980, 152:280-295
118. Sercarz EE, Yowell RL, Turkin D, Miller A, Araneo BA, Adorini L: Different functional specificity repertoires for suppressor and helper T cells. Immunol Rev 1978, 39:108-136
119. Flood PM, Kripke ML, Rowley DA, Schreiber H: Suppression of tumor rejection by autologous anti-idiotypic immunity. Proc Natl Acad Sci USA 1980, 77:2209-2213
120. Bigazzi PE, Kosuda LL, Hsu KC, Andres GA: Immune complex orchitis in vasectomized rabbits. J Exp Med 1976, 143:382-404
121. Sandberg HO, Closs O: The humoral immune response to alpha, beta, and gamma crystallins of the human lens. Scand J Immunol 1979, 10:549-553
122. Farrell C, Bloth B, Nielson H, Daugharty H, Lundman T, Svehag S-E: A survey for circulating immune complexes in patients with acute myocardial infarction. Scand J Immunol 1977, 6:1233-1240
123. Reinherz EL, Kung PC, Goldstein G, Schlossman SF: Further characterization of the human inducer T cell subset defined by monoclonal antibody. J Immunol 1979, 123:2894-2896
124. Reinherz EL, Kung PC, Goldstein G, Schlossman SF: A monoclonal antibody reactive with the human cytotoxic/suppressor T cell subset previously defined by a heteroantiserum termed TH_2. J Immunol 1980, 124: 1301-1307
125. Moretta L, Ferrarini M, Cooper MD: Characterization of human T-cell subpopulations as defined by specific receptors for immunoglobulins. Contemp Top Immunobiol 1978, 8:19-53
126. Bach M-A, Bach J-F: The use of monoclonal anti-T cell antibodies to study T cell imbalances in human diseases. Clin Exp Immunol 1981, 45:449-456
127. Fauci AS: Assays for suppressor cells, Manual of Clinical Immunology. Second Edition. Edited by NR Rose, H Friedman. Washington, DC, American Society for Microbiology, 1980, pp 297-303
128. Aoki N, Pinnamaneni KM, DeGroot LJ: Studies on suppressor cell function in thyroid diseases. J Clin Endocrinol Metab 1979, 48:803-810
129. Fauci AS, Steinberg AD, Haynes BF, Whaley G: Immunoregulatory aberrations in systemic lupus erythematosus. J Immunol 1978, 121:1473-1479
130. Berrih S, Gaud S, Bach MA, Kung P, Goldstein G, Le Brigand H, Binet JP, Bach J-F: Evaluation of T cell subsets in myasthenia gravis, using anti-T cell monoclonal antibodies. Clin Exp Immunol 1981, 45: 1-8
131. Breshnihan B, Jasin HE: Suppressor function of peripheral blood mononuclear cells in normal individuals and in patients with systemic lupus erythematosus. J Clin Invest 1977, 59:106-113
132. Abdou NI, Sagawa A, Pascual E, Hebert J, Sadeghee S: Suppressor T cell abnormality in idiopathic systemic lupus erythematosus. Clin Immunol Immunopathol 1976, 6:192-199
133. Sakane T, Steinberg AD, Green I: Studies of immune functions of patients with systemic lupus erythematosus: I. Dysfunction of suppressor T cell activity

related to impaired generation of, rather than response to, suppressor cells. Arthritis Rheum 1978, 21:657–664
134. Sagawa A, Abdou NI: Suppressor-cell dysfunction in systemic lupus erythematosus: Cells involved and *in vitro* correction. J Clin Invest 1978, 62:789–796
135. Alarcon-Segovia D, Ruiz-Arguelles A: Decreased circulating thymus-derived cells with receptors for the Fc portion of immunoglobulin G in systemic lupus erythematosus. J Clin Invest 1978, 62:1390–1394
136. Miller KB, Schwartz RS: Familial abnormalities of suppressor-cell function in systemic lupus erythematosus. N Engl J Med 1979, 301:803–809
137. Raveche ES, Steinberg AD: Lymphocytes and lymphocyte function in systemic lupus erythematosus. Semin Hematol 1979, 16:344–370
138. Sakane T, Steinberg AD, Green I: Failure of autologous mixed lymphocyte reactions between T and non-T cells in patients with systemic lupus erythematosus. Proc Natl Acad Sci USA 1978, 75:3464–3468
139. Sakane T, Steinberg AD, Reeves JP, Green I: Studies of immune functions of patients with systemic lupus erythematosus. Complement-dependent immunoglobulin M anti-thymus-derived cell antibodies preferentially inactivate suppressor cells. J Clin Invest 1979, 63:954–965
140. Sakane T, Steinberg AD, Reeves JP, Green I: Studies of immune functions in patients with systemic lupus erythematosus. T-cell subsets and antibodies to T-cell subsets. J Clin Invest 1979, 64:1260–1269
141. Nakamura Z-I, Asano T, Yano K, Ofuji T: Reevaluation of suppressor cell function in systemic lupus erythematosus. Clin Immunol Immunopathol 1982, 24:72–82
142. Okada J, Stastny P: Antibodies against T cells, B cells and monocytes in patients with SLE (Abstr). Arthritis Rheum 1981, 24:S76
143. Krakauer RS, Waldmann TA, Strober W: Loss of suppressor T cells in adult NZB/NZW mice. J Exp Med 1976, 144:662–673
144. Cantor H, McVay-Boudreau L, Hugenberger J, Naidorf K, Shen FW, Gershon RK: Immunoregulatory circuits among T-cell sets: II. Physiologic role of feedback inhibition *in vivo*: Absence in NZB mice. J Exp Med 1978, 147:1116–1125
145. Theofilopoulos AN, Shawler DL, Eisenberg RA, Dixon FJ: Splenic immunoglobulin-secreting cells and their regulation in autoimmune mice. J Exp Med 1980, 151:446–466
146. Creighton WD, Katz DH, Dixon FJ: Antigen-specific immunocompetency, B cell function, and regulatory helper and suppressor T cell activities in spontaneously autoimmune mice. J Immunol 1979, 123:2627–2636
147. Shirai T, Hayakawa K, Okumura K, Tada T: Differential cytotoxic effect of natural thymocytotoxic autoantibody of NZB mice on functional subsets of T cells. J Immunol 1978, 120:1924–1929
148. Klassen LW, Krakauer RS, Steinberg AD: Selective loss of suppressor cell function in New Zealand mice induced by NTA. J Immunol 1977, 119:830–837
149. Theofilopoulos AN, Dixon FJ: Etiopathogenesis of murine SLE. Immunol Rev 1981, 55:179–216
150. Eisenberg RA, Theofilopoulos AN, Andrews BS, Peters CJ, Thor L. Dixon FJ: Natural thymocytotoxic autoantibodies in autoimmune and normal mice. J Immunol 1979, 122:2272–2278
151. Raveche ES, Novotny EA, Hansen CT, Tjio JH, Steinberg AD: Genetic studies in NZB mice: V. Recombinant inbred lines demonstrate that separate genes control autoimmune phenotype. J Exp Med 1981, 153:1187–1197
152. Dixon FJ, McConahey PJ: Genetic background of murine SLE, The Menarini Series on Immunopathology, Edited by PA Miescher, L Bolis, G Torrigiani. Basel, Schwabe, 1981, 125–134
153. Altman A: B cell-specific immunoregulatory lymphokines. Immunology Today 1982 (In press)
154. Primi D, Hammarstom L, Smith CIE, Moller G: Immunological unresponsiveness of self-recognizing B lymphocytes to the PBA property of a soluble T cell factor. Cell Immunol 1978, 41:320–329
155. Pure E, Isakson PC, Takatsu K, Hamaoka T, Swain SL, Dutton RW, Dennert DG, Uhr JW, Vitetta ES: Induction of B cell differentiation by T cell factors. I. Stimulation of IgM secretion by products of a T cell hybridoma and a T cell line. J Immunol 1981, 127: 1953–1958
156. Elvin EH van, Veen FM van der, Rolink AG, Issa P, Duin TM, Gleichmann E: Diseases caused by reactions of T lymphocytes to incompatible structures of the major histocompatibility complex: V. High titers of IgG autoantibodies to double-stranded DNA. J Immunol 1981, 127:2435–2433
157. Veen JPW van der, Rolink AG, Gleichmann E: Diseases caused by reactions of T lymphocytes to incompatible structures of the major histocompatibility complex: III. Autoantibodies to thymocytes. J Immunol 1981, 127:1281–1286
158. Elven EH van, Agterberg J, Sadal S, Gleichmann E: Diseases caused by reactions of T lymphocytes to incompatible structures of the major histocompatibility complex: II. Autoantibodies deposited along the basement membrane of skin and their relationship to immune complex glomerulonephritis. J Immunol 1981, 126:1684–1691
159. Shulman HM, Sullivan KM, Weiden PL, McDonald GB, Striker GE, Sale GE, Hackman R, Tsoi M-S, Storb R, Thomas ED: Chronic graft-versus-host syndrome in man: A long-term clinicopathologic study of 20 Seattle patients. Am J Med 1980, 69:204–217
160. Allison AC: Autoimmune diseases: Concepts of pathogenesis and control,[5] pp 91–139
161. Weigle WO: Recent observations and concepts in immunological unresponsiveness and autoimmunity. Clin Exp Immunol 1971, 9:437–447
162. Weigle WO: The immune response of rabbits tolerant to bovine serum albumin to the injection of other heterologous serum albumins. J Exp Med 1961, 114: 111–125
163. Weigle WO, High GJ, Nakamura RM: The role of mycobacteria and the effect of proteolytic degradation of thyroglobulin on the production of autoimmune thyroiditis. J Exp Med 1969, 130:243–262
164. Worlledge SM, Carstairs, KC, Dacie JV: Autoimmune hemolytic anemia associated with α-methyldopa therapy. Lancet 1966, 2:135–139
165. Weistein A: Drug induced systemic lupus erythematosus, Progress in Clinical Immunology. Edited by RS Schwartz. New York, Grune and Stratton, 1980, pp 1–21.
166. Feizi T, Taylor-Robinson D, Shields MD, Carter RA: Production of cold agglutinins in rabbits immunized with human erythrocytes treated with *Mycoplasma pneumoniae*. Nature 1969, 222:1253–1256
167. Williams RC Jr: Infection and autoimmunity,[4] pp 457–478
168. Cossio PM, Diez C, Szarfman A, Kreutzer E, Candiolo B, Arana RM: Chagasic cardiopathy: Demonstration of a serum gamma globulin factor which reacts with endocardium and vascular structures. Circulation 1974, 49:13–21
169. Szarfman A, Cossio PM, Diez C, Arana RM, Sadum

E: Antibodies against endocardium, vascular structures, and interstitium of striated muscle that cross-react with *T. cruzi* and *T. rhodisiense*. J Parasitol 1974, 60:1024
170. Lewis DE, Giorgi JV, Warner NL: Flow cytometry analysis of T cells and continuous T cell lines from autoimmune MRL/1 mice. Nature 1981, 289:298-300
171. Theofilopoulos AN, Eisenberg RA, Bourdon M, Crowell Jr JS, Dixon FJ: Distribution of lymphocytes identified by surface markers in murine strains with SLE-like syndromes. J Exp Med 1979, 149:516-534
172. Theofilopoulos AN, Balderas RS, Shawler DL, Izui S, Kotzin BL, Strober S, Dixon FJ: Inhibition of T cell proliferation and SLE-like syndrome of MRL/1 mice by whole body or total lymphoid irradiation. J Immunol 1980, 125:2137-2142
173. Theofilopoulos AN, Balderas RS, Shawler DL, Lee S, Dixon FJ: The influence of thymic genotype on the SLE-like disease and T cell proliferation of MRL/Mp-*lpr/lpr* mice. J Exp Med 1981, 153:1405-1414
174. Altman A, Theofilopoulos AN, Weiner R, Katz D, Dixon FJ: Analysis of T cell function in autoimmune murine strains: Defects in production of and responsiveness to interleukin-2. J Exp Med 1981, 154:791-808
175. Dauphinee MJ, Kipper SB, Wofsy D, Talal N: Interleukin 2 deficiency is a common feature of autoimmune mice. J Immunol 1981, 127:2483-2487
176. Watson J, Mochizuki D: Interleukin 2: A class of T cell growth factors. Immunol Rev 1980, 51:257-278
177. Glimcher LH, Steinberg AD, House SB, Green I: The autologous mixed lymphocyte reaction in strains of mice with autoimmune disease. J Immunol 1980, 125: 1832-1838
178. Glimcher LH, Longo DL, Green I, Schwartz RH: Murine syngeneic mixed lymphocyte response: I. Target antigens are self Ia molecules. J Exp Med 1981, 154:1652-1670
179. Bach JF, Dardenne M, Salomon JC: Studies on thymus products. IV. Absence of serum thymic activity in adult NZB and (NZB × NZW)F_1 mice. Clin Exp Immunol 1973, 14:247-256
180. Talal N, Dauphinee M, Pillarisetty R: Effect of thymosine on thymocyte proliferation and autoimmunity in NZB mice. Ann NY Acad Sci 1975, 249:438-449
181. Steinberg AD, Law LD, Talal N: The role of NZB/NZW F_1 thymus in experimental tolerance and autoimmunity. Arthritis Rheum 1970, 13:369-377
182. Kysela S, Steinberg AD: Increased survival of NZB/W mice given multiple syngeneic young thymus grafts. Clin Immunol Immunopathol 1973, 2:133-136
183. Knight JG, Adams DD: Failure of transferred thymus cells to suppress or prevent autoantibody production in NZB and NZB × NZW mice. J Clin Lab Immunol 1978, 1:151-158
184. Hoffman AA, Harbech RJ: Immunoregulation in New Zealand mice: I. Failure of the transfer of syngeneic spleen or thymus cells to influence the natural disease in New Zealand mice. Arthritis Rheum 1979, 22:412-418
185. Gershwin ME, Steinberg AD, Ahmed A, Derkay C: Study of thymic factors: II. Failure of thymosin to alter the natural history of NZB and NZB/NZW mice. Arthritis Rheum 1976, 19:862-866
186. Mehta J, Knotts L, Craig C, Burkholder S, Miller C, Hahn B: Effect of altered lymphocyte function on immunologic disorders in NZB/NZW mice: III. Acceleration of disease by thymosin. Arthritis Rheum 1978, 21:196-203
187. Roubinian JR, Papoian R, Talal N: Effects of neonatal thymectomy and splenectomy in survival and regulation of autoantibody formation in NZB/NZW F_1 mice. J Immunol 1977, 118:1524-1529
188. Steinberg AD, Roths JB, Murphy ED, Steinberg RT, Raveche ES: Effects of thymectomy and androgen administration upon the autoimmune disease of MRL/Mp-*lpr/lpr* mice. J Immunol 1980, 125:871-873
189. Gershwin ME, Ohsugi Y, Ahmed A, Castles JJ, Scibienski R, Ikeda RM: Studies of congenitally immunologically mutant New Zealand mice: IV. Development of autoimmunity in congenitally athymic (nude) New Zealand Black × White F_1 hybrid mice. J Immunol 1980, 125:1189-1195
190. Goodman MG, Weigle WO: Role of polyclonal B-cell activation in self/non-self discrimination. Immunology Today 1981, 2:54-57
191. Moller G: B lymphocyte activation. Immunology Today 1981, 2:181-184
192. Fish F. Ziff M: The *in vitro* and *in vivo* induction of anti-double-stranded DNA antibodies in normal and autoimmune mice. J Immunol 1982, 128:409-414
193. Izui S, Lambert P-H, Fournie GJ, Turler H, Miescher PA: Features of systemic lupus erythematosus in mice injected with bacterial lipopolysaccharide. Identification of circulating DNA and renal localization of DNA-anti-DNA complexes. J Exp Med 1977, 145: 1115-1130
194. Izui S, Eisenberg RA, Dixon FJ: IgM rheumatoid factors in mice injected with bacterial lipopolysaccharides. J Immunol 1979, 122:2096-2102
195. Dresser DW: Most IgM-producing cells in the mouse secrete auto-antibodies (rheumatoid factor). Nature 1978, 274:480-483
196. Izui S, Kobayakawa T, Louis J, Lambert P-H: Induction of thymocytotoxic autoantibodies after injection of bacterial lipopolysaccharides in mice. Eur J Immunol 1979, 9:338-341
197. Meredith PJ, Kristie JA, Walford RL: Aging increases expression of LPS-induced autoantibody-secreting B cells. J Immunol 1979, 123:87-91
198. Kobayakawa T, Louis J, Izui S, Lambert P-H: Autoimmune response to DNA, red blood cells, and thymocyte antigens in association with polyclonal antibody synthesis during experimental African *trypanosomiasis*. J Immunol 1979, 122:296-301
199. Ortiz-Ortiz L, Parks DE, Rodriguez M, Weigle WO: Polyclonal B lymphocyte activation during *Trypanosoma cruzi* infection. J Immunol 1980, 124:121-126
200. Rosen A, Gergely P, Jondal M, Klein G, Britton S: Polyclonal Ig production after Epstein-Barr virus infection in human lymphocytes *in vitro*. Nature 1977, 267:52-54
201. Slaughter L, Carson DA, Jensen FC, Holbrook TL, Vaughan JH: *In vitro* effects of Epstein-Barr virus in peripheral blood mononuclear cells from patients with rheumatoid arthritis and normal subjects. J Exp Med 1978, 148:1429-1434
202. Thorley-Lawson D, Chess L, Strominger J: Suppression of *in vitro* Epstein-Barr virus infection, a new role for adult human T lymphocytes. J Exp Med 1977, 146:495-508
203. Tosato G, Steinberg AD, Blaese R: Defective EBV-specific suppressor T-cell function in rheumatoid arthritis. N Engl J Med 1981, 305:1238-1243
204. Izui S, Eisenberg RA, Dixon FJ: Subclass-restricted IgG polyclonal antibody production in mice injected with lipid A-rich lipopolysaccharides. J Exp Med 1981, 153:324-338
205. Izui S, McConahey PJ, Dixon FJ: Increased spontaneous polyclonal activation of B lymphocytes in mice with spontaneous autoimmune disease. J Immunol 1978, 121:2213-2219

206. Moutsopoulos HM, Boehm-Truitt M, Kassan SS, Chused TM: Demonstration of activation of B lymphocytes in New Zealand Black mice at birth by an immunoradiometric assay for murine IgM. J Immunol 1977, 119:1639–1644
207. Manny N, Datta SK, Schwartz RS: Synthesis of IgM by cells of NZB and SWR mice and their crosses. J Immunol 1979, 122:1220–1227
208. Taurog JD, Moutsopoulos HM, Rosenberg YJ, Chused TM, Steinberg AD: CBA/N x-linked B-cell defect prevents NZB B-cell hyperactivity in F_1 mice. J Exp Med 1979, 150:31–43
209. Kemp JD, Cowdery JS, Steinberg AD, Gershon RK: Genetic control of autoimmune disease: Interactions between *xid* and *lpr*. J Immunol 1982, 128:388–392
210. Eastcott JW, Schwartz RS, Datta SK: Genetic segregation of B-cell hyperactivity and autoimmunity in crosses of NZB mice (Abstr). Fed Proc 1981, 40:1058
211. Eisenberg RA, Izui S, McConahey PJ, Hang L, Peters CJ, Theofilopoulos AN, Dixon FJ: Male determined accelerated autoimmune disease in BXSB mice: Transfer by bone marrow and spleen cells. J Immunol 1980, 125:1032–1036
212. Morton JI, Siegel BV: Transplantation of autoimmune potential: I. Development of antinuclear antibodies in *H-2* histocompatible recipients of bone marrow from New Zealand Black mice. Proc Natl Acad Sci USA 1974, 71:2162–2165
213. Akizuki M, Reeves JP, Steinberg AD: Expression of autoimmunity by NZB/NZW marrow. Clin Immunol Immunopathol 1978, 10:247–250
214. Morton JI, Siegel BV: Transplantation of autoimmune potential: IV. Reversal of the NZB autoimmune syndrome by bone marrow transplantation. Transplantation 1979, 27:133–134
215. Jyonouchi H, Kincade PW, Good RA, Fernandes G: Reciprocal transfer of abnormalities in clonable B lymphocytes and myeloid progenitors between NZB and DBA/2 mice. J Immunol 1981, 127:1232–1235
216. De Heer DH, Edgington TS: Evidence for a B lymphocyte defect underlying the anti-X anti-erythrocyte autoantibody response of NZB mice. J Immunol 1977, 118:1858–1863
217. Rosenthal AS: Regulation of the immune response—Role of the macrophage. N Engl J Med 1980, 303: 1153–1156
218. Unanue ER: Cooperation between mononuclear phagocytes and lymphocytes in immunity. N Engl J Med 1980, 303:977–985
219. Frank MM, Hamburger MI, Lawley TJ, Kimberly RP, Plotz PH: Defective reticuloendothelial system Fc-receptor function in systemic lupus erythematosus. N Engl J Med 1979, 300:518–523
220. Finbloom DS, Plotz PH: Studies of reticuloendothelial function in the mouse with model immune complexes: II. Serum clearance, tissue uptake, and reticuloendothelial saturation in NZB/W mice. J Immunol 1979, 123:1600–1603
221. Braverman IM, Slesinski J: Study of autoimmune disease in New Zealand mice: IV. Immunologic reactivity and reticuloendothelial function. J Invest Dermatol 1970, 55:317–324
222. Thomas HI, Weir DM: The *in vitro* activity of peritoneal exudate cells from New Zealand Black mice (NZB/B_1) in the presence of ^{125}I-BSA (bovine serum albumin). Clin Exp Immunol 1972, 12:263–272
223. Morgan AG, Steward MW: Macrophage clearance function and immune complex disease in New Zealand Black/White F_1 hybrid mice. Clin Exp Immunol 1976, 26:133–136
224. Morton JI, Siegal BV: Reticuloendothelial activity in New Zealand Black mice. Proc Soc Exp Biol 1970, 133:1055–1059
225. Magilavy DB, Rifai A, Plotz PH: An abnormality of immune complex kinetics in murine lupus. J Immunol 1981, 126:770–774
226. Lu, CY, Calamai EG, Unanue ER: A defect in the antigen-presenting function of macrophages from neonatal mice. Nature 1979, 282:327–329
227. Lu CY, Beller DI, Unanue ER: During ontogeny Ia-bearing accessory cells are found early in the thymus but late in the spleen. Proc Natl Acad Sci USA 1980, 77:1597–1601
228. Laskin CA, Taurog JD, Smathers PA, Steinberg AD: Studies of defective tolerance in murine lupus. J Immunol 1981, 127:1743–1747
229. Staples PJ, Talal N: Relative inability to induce tolerance in adult NZB and NZB/NZW F_1 mice. J Exp Med 1969, 129:123–139
230. Amagai T, Cinader B: Resistance of MRL/Mp-*lpr*/*lpr* mice to tolerance induction. Eur J Immunol 1981, 11:923–926
231. Goldings EA, Cohen PL, McFadden SF, Ziff M, Vitetta ES: Defective B cell tolerance in adult (NZB × NZW)F_1 mice. J Exp Med 1980, 152:730–735
232. Santoro TJ, Scott DW, Pisetsky DS: The induction of tolerance and suppression in autoimmune MRL mice using hapten-modified self. J Immunol 1981, 127: 690–693
233. Hang L, Izui S, Theofilopoulos AN, Dixon FJ: Transfer of male BXSB SLE disease by T-depleted male bone marrow cells. J Immunol (Manuscript in preparation)
234. Forni L, Coutinho A, Kohler G, Jerne NK: IgM antibodies induce the production of antibodies of the same specificity. Proc Natl Acad Sci USA 1980, 77: 1125–1128
235. Urbain J, Cazenave PA, Wikler M, Franssen JD, Mariame B, Leo O: Idiotypic induction and immune networks,[3] pp 81–93
236. Bluestone JA, Sharrow SO, Epstein SL, Ozato K, Sachs DH: Induction of anti-*H-2* antibodies without alloantigen exposure by *in vivo* administration of anti-idiotype. Nature 1981, 291:233–235
237. Binz H, Frisch K, Necht H, Wigzell H: Some studies on idiotypes and anti-idiotypic reactions and receptors in anti-allo-MHC T-cell immunity. Ann Immunol (Paris) 1979, 130C:273–279
238. Alevy YG, Witherspoon C, Bellone CJ: Anti-TMA immunity in mice: III. Induction of L-Tyrosine-p-Azophenyltrimethylammonium (tyr(TMA)) specific helper T cells by the monovalent antigen or idiotypic antisera. J Immunol 1981, 126:2390–2396
239. Sege K, Peterson PA: Use of anti-idiotypic antibodies as cell-surface receptor probes. Proc Natl Acad Sci USA 1978, 75:2443–2447
240. Schreiber AB, Couraud PO, Andre C, Vray B, Strosberg AD: Anti-alprenolol anti-idiotypic antibodies bind to β-adrenergic receptors and modulate catecholamine-sensitive adenylate cyclase. Proc Natl Acad Sci USA 1980, 77:7385–7389
241. Rose NR, Bigazzi PE, Warner NL: Genetic Control of Autoimmune Disease. Developments in Immunology. Vol 1. Edited by NR Rose, PE Bigazzi, NL Warner. New York, Elsever/North-Holland, 1978
242. Klein J: Biology of the mouse histocompatibility-2 complex. Principles of immunogenetics applied to a single system. New York, Springer-Verlag, 1975
243. McDevitt HO: The role of *H-2* I region genes in regulation of the immune response,[3] pp 503–512

244. Dausset J, Svejgaard A: HLA and Disease. Edited by J Dausset, A Svejgaard. Copenhagen and Baltimore, Munksgaard/Williams and Wilkins, 1977
245. Brewerton DA: HLA-B27 and the inheritance of susceptibility to rheumatic disease. Arthritis Rheum 1976, 19:656–668
246. Schlosstein L, Terasaki PI, Bluestone R, Pearson CM: High association of an HLA-A antigen, W27, with ankylosing spondylitis. N Engl J Med 1973, 288: 704–706
247. Dausset J, Contu L: The MHC and immune response in man,[13] pp 513–529
248. Svejgaard A, Morling N, Platz P, Ryder LP, Thomsen M: HLA and disease,[3] pp 530–540
249. Winchester RJ, Kunkel HG: The human Ia system. Adv Immunol 1979, 28:221–292
250. Bernoco D, Terasaki PI: HLA-D and disease,[41] pp 3–11
251. Volpe R: The genetics and immunology of Graves' and Hashimoto's diseases,[241] pp 43–53
252. Raum D, Donaldson VH, Alper CA, Rosen FS: Genetics of complement and complement deficiencies,[3] pp 1244–1262
253. Lawley TJ, Hall RP, Fauci AS, Katz SI, Hamburger MI, Frank MM: Defective Fc-receptor functions associated with the HLA-B8/DRW3 haplotype: Studies in patients with dermatitis herpetiformis and normal subjects. N Engl J Med 1981, 304:185–192
254. Van Snick JL: A gene linked to the Igh-C locus controls the production of rheumatoid factor in the mouse. J Exp Med 1981, 153:738–742
255. Cox KO, Cox J, Thomas WR, Watkins MC: Experimental erythrocyte autoimmunity: I. Mice congenic for immunoglobulin allotypes vary in production of autoantibodies but produce suppressor cells not restricted by allotypes. Immunology 1980, 40:171–176
256. Berman PW, Patrick J: Linkage between the frequency of muscular weakness and loci that regulate immune responsiveness in murine experimental myasthenia gravis. J Exp Med 1980, 152:507–520
257. Mentnech MS, Pearson DJ, Elliot JA, Taylor G, Major PC: Correlation of *Gm* allotype with the incidence of anti-IgG antibody in coal worker's pneumoconiosis. Clin Immunol Immunopathol 1980, 17:274–279
258. Nakao Y, Matsumoto H, Miyazaki T, Nishitani H, Takatsuki K, Kasukawa R, Nakayama S, Izumi S, Fujita T, Tsuji K: IgG heavy chain allotypes (*Gm*) in autoimmune diseases. Clin Exp Immunol 1980, 42: 20–26
259. Nakao Y, Matsumoto H, Miyazaki T, Nishitani H, Ota K, Fujita T, Tsuji K: *Gm* allotypes in myasthenia gravis. Lancet 1980, 1:677–680
260. Nakao Y, Matsumoto H, Miyazaki T, Mizuno N, Arima N, Wakisaka A, Okimoto K, Akazawa Y, Tsuji K, Fujita T: IgG heavy-chain (*Gm*) allotypes and immune response to insulin in insulin-requiring diabetes mellitus. N Engl J Med 1981, 304:407–409
261. Uno H, Sasazuki T, Tamai H, Matsumoto H: Two major genes, linked to HLA and *Gm*, control susceptibility to Graves' disease. Nature 1981, 292:768–770
262. Farid MK, Sampson L, Noel EP, Marshall WH: *Gm* phenotypes in autoimmune thyroid diseases. J Immunogenet 1977, 4:429–432
263. Schwartz M, Lifshitz R, Givol D, Mozes E, Haimovich J: Cross-reactive idiotypic determinants on murine anti-(T,G)-A-L antibodies. J Immunol 1978, 121:421–426
264. Pawlak LL, Mushinski EB, Nisonoff A, Potter M: Evidence for the linkage of the IgCH locus to a gene controlling the idiotypic specificity of anti-p-azophenylarsonate antibodies in strain A mice. J Exp Med 1973, 137:22–31
265. Adams DD, Knight JG: H-gene theory of inherited autoimmune disease. Lancet 1980, 1:396–398
266. Adams DD, Adams Y, Knight JG, Loghem E van: Genetics of autoimmune disease in the New Zealand mice and in man,[7] pp 135–147
267. Knight JG, Adams DD: Three genes for lupus nephritis in NZB × NZW mice. J Exp Med 1978, 147: 1653–1660
268. Knight JG, Adams DD, Purves HD: The genetic contribution of the NZB mouse to the renal disease of the NZB × NZW hybrid. Clin Exp Immunol 1977, 28: 352–358
269. Eustachio P, Pravtcheva D, Marcu K, Ruddle FH: Chromosomal location of the structural gene cluster encoding murine immunoglobulin heavy chains. J Exp Med 1980, 151:1545–1550
270. Croce CM, Shander M, Martinis J, Cicurel L, D'Ancona GG, Dolby TW, Koprowski H: Chromosomal location of the genes for human immunoglobulin heavy chain. Proc Natl Acad Sci USA 1979, 76:3416–3419
271. Shander M, Martinis J, Croce CM: Genetics of human immunoglobulins: Assignment of the genes for μ, α, and γ immunoglobulin chains to human chromosome 14. Transplant Proc 1980, 12:417–420
272. Susan D, D'Eustachio P, Leinwand L, Seidman J, Keithley D, Ruddle FH: Chromosomal assignment of the mouse κ light chain genes. Proc Natl Acad Sci USA 1979, 76:2735–2739
273. Erikson J, Martinis J, Croce CM: Assignment of the genes for human immunoglobulin chains to chromosome 22. Nature 1981, 294:173–175
274. D'Eustachio P, Bothwell ALM, Takaro TK, Baltimore D, Ruddle FH: Chromosomal location of structural genes encoding murine immunoglobulin light chains. J Exp Med 1981, 153:793–800
275. Raveche ES, Steinberg AD, Klassen LW, Tjio JH: Genetic studies in NZB mice: I. Spontaneous autoantibody production. J Exp Med 1978, 147:1487–1502
276. Bocchieri MH, Cooke A, Smith JB, Weigert M, Riblet RJ: Independent segregation of NZB autoimmune abnormalities in NZB × C58 recombinant inbred mice. J Immunol 1982 (In press)
277. Roubinian JR, Talal N, Greenspan JS, Goodman JR, Siiteri PK: Effect of castration and sex hormone treatment on survival anti-nucleir acid antibodies, and glomerulonephritis in NZB/NZW F_1 mice. J Exp Med 1978, 147:1568–1583
278. Dubois EL: The clinical picture of systemic lupus erythematosus, Lupus Erythematosus. 2nd Edition. Edited by EL Dubois. Los Angeles, University of Southern California Press, 1974, pp 232–242
279. Cohn DA: High sensitivity to androgen as contributing factor in sex differences in the immune response. Arthritis Rheum 1979, 22:1218–1233
280. Stern R, Fishman J, Brusman H, Kunkel HG: Systemic lupus erythematosus associated with Klinefelter's syndrome. Arthritis Rheum 1977, 20:18–22
281. Michalski JP, Snyder SM, Leod RL, Talal N: Monozygotic twins with Klinefelter's syndrome discordant for systemic lupus erythematosus and symptomatic myasthenia gravis. Arthritis Rheum 1978, 21: 306–309
282. Yocum MW, Grossman J, Waterhouse C, Abraham GN, May AG, Condemi JJ: Monozygotic twins discordant for systemic lupus erythematosus. Arthritis Rheum 1975, 18:193–199

283. Lahita RG, Bradlow HL, Kunkel HG, Fishman J: Alterations of estrogen metabolism in systemic lupus erythematosus. Arthritis Rheum 1979, 22:1195-1198
284. Steinberg AD, Melez KA, Raveche ES, Reeves JP, Boegel WA, Smathers PA, Taurog JD, Weinlein L, Duvic M: Approach to the study of the role of sex hormones in autoimmunity. Arthritis Rheum 1979, 22:1170-1176
285. Roubinian JR, Talal N, Siiteri PK, Sadakian JA: Sex hormone modulation of autoimmunity in NZB/NZW mice. Arthritis Rheum 1979, 22:1162-1169
286. Roubinian JR, Papoian R, Talal N: Androgenic hormones modulate auto-antibody responses and improve survival in murine lupus. J Clin Invest 1977, 59: 1066-1070
287. Weinstein Y, Berkovich Z: Testosterone effect on bone marrow, thymus, and suppressor T cells in the (NZB × NZW)F_1 mice: Its relevance to autoimmunity. J Immunol 1981, 126:998-1002
288. Theofilopoulos AN, McConahey PJ, Izui S, Eisenberg RA, Pereira A, Creighton WD: A comparative immunologic analysis of several murine strains with autoimmune manifestations. Clin Immunol Immunopathol 1980, 15:258-278
289. Murphy ED, Roths JB: A Y chromosome associated factor in strain BXSB producing accelerated autoimmunity and lymphoproliferation. Arthritis Rheum 1979, 22:1188-1194
290. Eisenberg RA, Dixon FJ: Effect of castration on male-determined acceleration of autoimmune disease in BXSB mice. J Immunol 1980, 125:1959-1961
291. Fong S, Tsoukas CD, Frincke LA, Lawrence SK, Holbrook TL, Vaughan JH, Carson DA: Age-associated changes in Epstein-Barr virus-induced human lymphocyte autoantibody responses. J Immunol 1981, 126:910-914
292. Ferrell PB, Tan EM: Epstein-Barr (EB) virus antibodies in rheumatoid arthritis. Springer Seminar on Immunopathology 1981, 4:181-191
293. Depper JM, Zvaifler NJ: Current comment: Epstein-Barr virus—Its relationship to the pathogenesis of rheumatoid arthritis. Arthritis Rheum 1981, 24:755-761
294. Catalano MA, Carson DA, Slovin SF, Richman D, Vaughan JH: Antibodies to Epstein-Barr virus-determined antigens in normal subjects and in patients with seropositive rheumatoid arthritis. Proc Natl Acad Sci USA 1979, 76:5825-5828
295. Alspaugh MA, Henle G, Lennette ET, Henle W: Elevated levels of antibodies to Epstein-Barr virus antigens in sera and synovial fluids of patients with rheumatoid arthritis. J Clin Invest 1981, 67:1134-1140
296. Ferrell PB, Aitcheson CT, Pearson GR, Tan EM: Seroepidemiological study of relationship between Epstein-Barr virus and rheumatoid arthritis. J Clin Invest 1981, 67:681-687
297. Venables P, Roffe LM, Erhardt C, Maini RN, Edwards JMB, Porter AD: Titers of antibodies to RANA in rheumatoid arthritis and normal sera. Arthritis Rheum 1981, 24:1459-1464
298. Silverman SL, Schumacher HR: Antibodies to Epstein-Barr viral antigens in early rheumatoid arthritis. Arthritis Rheum 1981, 24:1465-1468
299. Levy JA: C-type RNA viruses and autoimmune disease,[4] pp 403-453
300. Markenson JA, Phillips PE: Type C viruses and sytemic lupus erythematosus. Arthritis Rheum 1978, 21:266-270
301. Schwartz RS: Viruses and systemic lupus erythematosus. N Engl J Med 1975, 293:132-136
302. Phillips PE: The virus hypothesis in SLE. Ann Intern Med 1975, 83:709-715
303. Lewis RM, Tanneberg W, Smith C, Schwartz RS: C-type viruses in systemic lupus erythematosus. Nature 1974, 252:78-79
304. Grausz H, Earley LE, Stephens BG, Lee JC, Hopper Jr JH: Diagnostic importance of virus-like particles in the glomerular endothelium of patients with systemic lupus erythematosus. N Engl J Med 1970, 283: 506-511
305. Strand M, August JT: Type C RNA virus gene expression in human tissue. J Virol 1974, 14:1584-1596
306. Imamura M, Phillips PE, Mellors RC: The occurrence and frequency of type C virus-like particles in placentas from patients with SLE and from normal subjects. Am J Pathol 1976, 83:383-394
307. Phillips PE, Hargrave-Granada R: Type C oncornovirus isolation studies in SLE: II. Attempted detection by viral RNA-dependent DNA polymerase assay. Ann Rheum Dis 1978, 37:225-233
308. Mellors RC, Mellors JW: Antigen related to mammalian type-C RNA viral p30 proteins is located in renal glomeruli in human systemic lupus erythematosus. Proc Natl Acad Sci USA 1976, 73:233-237
309. Panem S, Ordonez NG, Kirstein WH, Katz AI, Spargo BH: C-type virus expression in systemic lupus erythematosus kidneys. N Engl J Med 1976, 295:470-475
310. Barbacid M, Bolognesi D, Aaronson SA: Humans have antibodies capable of recognizing oncoviral glycoproteins: Demonstration that these antibodes are formed in response to cellular modification of glycoproteins rather than as consequence of exposure to virus. Proc Natl Acad Sci USA 1980, 77:1617-1621
311. Snyder Jr HW, Fleissner E: Specificity of human antibodies to oncovirus glycoproteins: Recognition of antigen by natural antibodies directed against carbohydrate structures. Proc Natl Acad Sci USA 1980, 77:1622-1626
312. Pincus T, Steinberg HD, Blacklow NR, Decker JL: Reactivities of systemic lupus erythematosus sera with cellular and virus antigen preparations. Arthritis Rheum 1978, 21:873-879
313. Porter DD, Larsen AE, Porter HG: The pathogenesis of Aleutian disease of mink: I. *In vivo* viral replication and the host antibody response to viral antigen. J Exp Med 1969, 130:575-589
314. Hensen JB, McGuire TC: Equine infections anemia. Prog Med Virol 1974, 18:143-159
315. Lewis RM, Schwartz RS: Canine systemic lupus erythematosus: Genetic analysis of an established breeding colony. J Exp Med 1971, 134:417-438
316. Quimby FW, Schwartz RS: The etiopathogenesis of systemic lupus erythematosus. Pathobiol Ann 1978, 8:35-59
317. Mellors RC, Huang CY: Immunopathology of NZB/BL mice. VI. Virus separable from spleen and pathogeneic for Swiss mice. J Exp Med 1967, 126:53-62
318. Russell PJ, Hicks JD, Boston LE, Abbott A: Failure to transfer haemolytic anaemia or glomerulonephritis with cell-free material from NZB mice. Clin Exp Immunol 1970, 6:227-239
319. Schaap OL, Groot ER de, Loghem JJ van: Failure to induce autoimmune phenomena in mice by administration of highly purified C-type particles from NZB mice. Pathol Microbiol 1975, 42:171-187
320. Datta SK, Schwartz RS: Mendelian segregation of loci controlling xenotropic virus production in NZB crosses. Virology 1977, 83:449-452
321. Datta SK, Schwartz RS: Genetics of expression of xenotropic virus and autoimmunity in NZB mice. Nature 1976, 263:412-415
322. Mellors RC, Shirai T, Aoki T: Wild-type Gross leukemia virus and the pathogenesis of the glomerulonephritis of New Zealand mice. J Exp Med 1971, 133:113-132
323. Yoshiki T, Mellors RC, Strand M, August JT: The viral envelope glycoprotein of murine leukemia virus and the pathogenesis of immune complex glomeru-

lonephritis of New Zealand mice. J Exp Med 1974, 140:1011-1027
324. Datta SK, Manny N, Andrzejewski C, Andre-Schwartz J, Schwartz RS: Genetic studies of autoimmunity and retrovirus expression in crosses of New Zealand Black mice: I. Xenotropic virus. J Exp Med 1978, 147:854-571
325. Datta SK, McConahey PJ, Manny N, Theofilopoulos AN, Dixon FJ, Schwartz RS: Genetic studies of autoimmunity and retrovirus expression in crosses of New Zealand Black mice: II. The viral envelope glycoprotein gp70. J Exp Med 1978, 147:872-881
326. Elder JH, Jensen FC, Bryant ML, Lerner RA: Polymorphism of the major envelope glycoprotein (gp70) of murine C-type viruses: Virion associated and differentiation antigens encoded by a multi-gene family. Nature 1977, 267:23-28
327. Andrews BS, Eisenberg RA, Theofilopoulos AN, Izui S, Wilson C, McConahey PJ, Murphy ED, Roth JB, Dixon FJ: Spontaneous murine lupus-like syndrome. Clinical and immunopathological manifestations in several strains. J Exp Med 1978, 148:1198-1215
328. Lerner RA, Wilson CB, Del Villano BC, McConahey PJ, Dixon FJ: Endogenous oncornaviral gene expression in adult and fetal mice: Quantitative, histologic, and physiologic studies of the major viral glycoprotein, gp70. J Exp Med 1976, 143:151-166
329. Izui S, McConahey PJ, Theofilopoulos AN, Dixon FJ: Association of circulating retroviral gp70-anti-gp70 immune complexes with murine systemic lupus erythematosus. J Exp Med 1979, 149:1099-1116
330. Izui S, McConahey PJ, Clark JP, Hang LM, Hara I, Dixon FJ: Retroviral gp70 immune complexes in NZB × NZW F_2 mice with murine lupus nephritis. J Exp Med 1981, 154:517-528
331. Izui S, Elder JH, McConahey PJ, Dixon FJ: Identification of retroviral gp70 and anti-gp70 antibodies involved in circulating immune complexes in NZB × NZW mice. J Exp Med 1981, 153:1151-1160
332. Tonietti G, Oldstone MBA, Dixon FJ: The effect of induced chronic viral infections on the immunologic diseases of New Zealand mice. J Exp Med 1970, 132: 89-109
333. Crocker BP, Del Villano BC, Jensen FC, Lerner RA, Dixon FJ: Immunopathogenicity and oncogenicity of murine leukemia viruses: I. Induction of immunologic disease and lymphoma in (BALB/c × NZB)F_1 mice by Scripps leukemia virus. J Exp Med 1974, 140:1028-1048
334. Abdou NI, Lindsley HB, Pollock A, Stechschulte DJ, Wood G: Plasmapheresis in active systemic lupus erythematosus: Effects on clinical, serum, and cellular abnormalities. Clin Immunol Immunopathol 1981, 19:44-54
335. Kotzin BL, Strober S, Engleman EG, Calin A, Hoppe RT, Kansas G, Terrell CP, Kaplan HS: Treatment of intractable rheumatoid arthritis with total lymphoid irradiation. N Engl J Med 1981, 305:969-976
336. Trentham DE, Belli JA, Anderson RJ, Buckley JA, Goetzl EJ, David JR, Austen FK: Clinical and immunological effects of fractionated total lymphoid irradiation in refractory rheumatoid arthritis. N Engl J Med 1981, 305:976-982
337. Borel Y, Young MC: Nucleic acid-specific suppressor T cells. Proc Natl Acad Sci USA 1980, 77:1593-1596
338. Borel Y, Lewis RM, Andre-Schwartz J, Stollar BD, Diener E: Treatment of lupus nephritis in adult (NZB × NZW)F_1 mice by cortisone-facilitated tolerance to nucleic acid antigens. J Clin Invest 1978, 61:276-282
339. Krakauer RS, Strober W, Rippeon DL, Waldmann TA: Prevention of autoimmunity in experimental lupus erythematosus by soluble immune response suppressor. Science 1977, 196:56-59
340. Steinberg AD, Krakauer R, Reinertsen JL, Klassen LW, Infeld D, Reeves JP, Williams GW, Antonovych T: Therapeutic studies in NZB/NZW mice: VI. Age-dependent effects of Concanavalin A stimulated spleen cell supernate. Arthritis Rheum 1978, 21:204-209
341. Zanetti M, Bigazzi PE: Anti-idiotypic immunity and autoimmunity: I. *In vitro* and *in vivo* effects of anti-idiotypic antibodies to spontaneously occurring autoantibodies to rat thyroglobulin. Eur J Immunol 1978, 11:187-195
342. Brown CA, Carey K, Colvin RB: Inhibition of autoimmune tubulointerstitial nephritis in guinea pigs by heterologous antisera containing antiidiotype antibodies. J Immunol 1979, 123:2102-2107
343. Neilson EG, Phillips SM: Suppression of interstitial nephritis by auto-antiidiotypic immunity. J Exp Med 1982, 155:179-189
344. Newson-Davis J: Immune mechanisms in myasthenia gravis. Immunology Today 1981, 2:1-3
345. Izui S, Kelley VE, McConahey PJ, Dixon FJ: Selective suppression of retroviral gp70-anti-gp70 immune complex formation by prostaglandin E_1 in murine systemic lupus erythematosus. J Exp Med 1980, 152: 1645-1658
346. Kelley VE, Winkelstein A, Izui S, Dixon FJ: Prostaglandin E_1 inhibits T-cell proliferation and renal disease in MRL/1 mice. Clin Immunol Immunopathol 1981, 21:190-203
347. Zurier RB, Damjanov I, Miller PL, Biewer BF: Prostaglandin E_1 treatment prevents progression of nephritis in murine lupus erythematosus. J Clin Lab Immunol 1978, 1:95-98
348. Hurd ER, Johnston JM, Okita JR, MacDonald PC, Ziff M, Gilliam JN: Prevention of glomerulonephritis and prolonged survival in New Zealand Black/New Zealand White F_1 hybrid mice fed an essential fatty acid-deficient diet. J Clin Invest 1981, 67:476-485
349. Fernandes G, Yunis EJ, Good RA: Influence of diet on survival of mice. Proc Natl Acad Sci USA 1976, 73:1279-1283
350. Izui S, Fernandes G, Hara I, McConahey PJ, Jensen FC, Dixon FJ, Good RA: Low-calorie diet selectively reduces expression of retroviral envelope glycoprotein gp70 in sera of NZB × NZW F_1 hybrid mice. J Exp Med 1981, 154:1116-1123
351. Brenner T, Abramsky O: Immunosuppression of experimental autoimmune myasthenia gravis by alpha-fetoprotein rich formation. Immunology Lett 1981, 3:163-167
352. Wigzell H, Binz H, Frischknecht H, Peterson P, Sege K: Possible roles of auto-anti-idiotypic immunity in auto-immune disease,[241] pp 327-338
353. Nisonoff A, Lamoyi E: Implications of the presence of an internal image of the antigen in anti-idiotypic antibodies: Possible applications to vaccine production. Clin Immunol Immunopathol 1981, 21:397-406
354. Anderson L, Auguet M, Wight E, Anderson R, Binz H, Wigzell H: Induction of specific immune unresponsiveness using purified mixed leukocyte culture-activated T lymphoblasts as autoantigen: I. Demonstration of general validity as to species and histocompatibility barriers. J Exp Med 1977, 146:1124-1137
355. Schechter Y, Maron R, Elias D, Cohen IR: Autoantibodies to insulin receptor spontaneously develop as anti-idiotypes in mice immunized with insulin. Science 1982, 216:542-545
356. Sacks DL, Esser KM, Sher A: Immunization of mice against African trypanosomiasis using anti-idiotypic antibodies. J Exp Med 1982, 155:1108-1119