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Animal Models of Human Systemic Lupus Erythematosus[1]

DAVID P. HUSTON, M.D., AND ALFRED D. STEINBERG, M.D.

The Arthritis and Rheumatism Branch, National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Bethesda, Maryland

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Systemic lupus erythematosus (SLE) is a human autoimmune disease of unknown etiology. Clinical, serologic, immunologic, and pathologic findings are highly variable in different patients and at different times in the same patient. Murine and canine animal models of SLE have been found with clinicopathologic abnormalities resembling those observed in humans. Each animal model has unique characteristics; taken together they reflect the spectrum of disease in human SLE.

Investigations in the animals have suggested that genetic, hormonal, immunologic, viral, and other environmental factors contribute to and modify the expression of disease. Where analogous studies are available for humans, the same factors have been found to modify disease expression in a similar fashion. Together, these studies have helped to clarify the multifactorial basis for SLE.

The best characterized abnormalities are immunologic. These include excessive B cell function with the formation of large amounts of autoantibodies, and T cell abnormalities which include defects in T cell regulatory function as well as certain T cell effector functions.

The animal models of SLE also serve as convenient test subjects for newer therapeutic modalities. It is hoped that further study of the animal models will provide a more rational approach to therapeutic modulation of disease in humans with SLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune multisystem disease characterized in humans and certain animals by dermatitis, photosensitivity, alopecia, arthritis, serositis, fever, anemia, glomerulonephritis, and/or central nervous system aberrations. Serologic abnormalities include depressed complement and antibodies to nuclear constituents, leukocytes, and erythrocytes. Although SLE has long been considered an autoimmune disease on the basis of a plethora of autoantibodies, the cause of this illness has remained elusive with investigators having implicated genetic, viral, and immunologic factors. Since the spectrum of disease is immense, SLE may actually represent many different diseases with a similar common pathway of illness. Alternatively, relatively few diseases may be represented, the differences explained by genetic and/or environmental factors.

Our working hypothesis has been that SLE is a multifactorial disease in both humans and animals (Table 1). Some factors may be necessary, but not sufficient, for the disease expression. Different factors may carry different wieght in different individuals, and understanding of the contributing factors has evolved from studies utilizing animal models.

[1]This is the third in a series of articles on Animal Models of Human Diseases. Anthony Schwartz, D.V.M., Ph.D., is guest editor.

Address reprint requests to: David P. Huston, M.D., and Alfred D. Steinberg, M.D., National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20014

TABLE I
Pathogenetic Factors in Autoimmunity with Special Reference to Systemic Lupus Erythematosus

Factor	Human	New Zealand Mice	Canine
Genetic	B-cell antigen association Family studies	Limited number of autosomal genes	?
Immune	B-cell excesses T-cell deficiencies	B-cell excesses T-cell deficiencies	?
Viral and other "Environmental" Factors	Viruses and other environmental insults may stimulate the immune system, especially B-cell function	C-type virus may act as a B-cell mitogen	? Vertically transmissible virus

MRL/l and BXSB mice have not been studied.

In 1959, Bielchowsky found that New Zealand Black (NZB) mice die prematurely with hepatosplenomegaly and autoimmune hemolytic anemia, the first report of a spontaneously occurring autoimmune disease in an experimental animal [1]. Subsequently, Helyer and Howie observed the spontaneous appearance of a different autoimmune disease in New Zealand Black × New Zealand White (NZB × NZW) F_1 hybrid mice, characterized by antinuclear antibodies, lupus erythematosus cells (LE cells), glomerulonephritis, and premature death secondary to renal failure, features not unlike those found in human SLE [2]. A similar SLE-like disease has been found in dogs [3] and in the past two years, additional mouse models of SLE have been reported [4]. Studies utilizing these SLE animal models have led to a better understanding of not only human SLE, but of a variety of autoimmune phenomena, as well as associations between autoimmunity and neoplasia.

Features of the NZB Murine Model

NZB mice spontaneously develop autoimmune hemolytic anemia, immune complex renal disease, and excessive lymphoreticular proliferation. The anti-erythrocyte antibody is initially detected after three months of age by the direct antiglobulin test (Direct Coomb's) and after several more months may be detected by the indirect antiglobulin test (Indirect Coombs). These antibodies are initially of the IgG subclasses [5]; some are directed against cryptic antigenic determinants, such as the X-antigen which is exposed only after partial digestion of the erythrocyte membrane [6]. Only NZB mice and their hybrids are capable of generating these anti-X-antibodies [7]. Furthermore, these antibodies are represented in IgG_1, IgG_{2a}, and IgG_{2b} subclasses, suggesting that more than one clone of antibody producing cells is active, making a clonal malignancy unlikely [8]. This activation of polyclonal antibody responses to cryptic autoantigen may represent activation of repressed anti-self clones of lymphocytes.

By nine to eighteen months of age the anti-erythrocyte antibodies are of the IgG and IgM classes and directed against both cryptic and non-cryptic antigens [9]. The mice develop severe anemia with reticulocytosis, spherocytosis, decreased *in vivo* erythrocyte survival, increased erythrocyte osmotic fragility, marked splenomegaly, and extramedullary hematopoiesis. In some of these mice a membraneous and/or a proliferative glomerulonephritis may be found, often without clinically significant deterioration of renal function [9]. A minority of NZB mice are found to have LE cells or positive fluorescent antinuclear antibody tests [10] though they do spontaneously develop antibodies to single-stranded DNA. In addition, they produce large amounts of IgM antibodies to thymocytes [11]. These naturally occurring thymo-

cytotoxic antibodies (NTA) increase in titer as the NZB mice age and may play an important role in the development of autoimmunity. Most of the NZB mice die of their autoimmune hemolytic anemia by 18–20 months of age, while some of the mice die with lymphoid malignancies.

Features of the NZB/NZW F_1 Murine Model

The mating of NZB mice with non-autoimmune New Zealand White mice results in an F_1 hybrid in which the predominant autoimmune phenomenon is changed from the NZB hemolytic anemia to a severe proliferative glomerulonephritis. In addition, these F_1 mice all develop LE cells and high titers of antinuclear antibodies, making them a better model for human SLE than NZB mice. (NZB × NZW) F_1 and (NZW × NZB) F_1 mice had very similar clinical and serological abnormalities, making extremely unlikely the possibility that murine SLE was either sex-linked or transmitted via a maternal-fetal interaction in utero or via colostrum [12]. Ovum transplantation studies confirmed these findings [13]. However, comparison of (NZB × NZW) F_1 littermates revealed that the females have a more rapid progression of disease with death by nine to twelve months of age secondary to renal failure; the male littermates live 100–150 days longer, having a more gradual progression of disease [14].

By one month of age, female (NZB × NZW) F_1 mice may have detectable antinuclear antibodies which increase with age and are heterogeneous, consisting of antibodies to single- and double-stranded DNA and RNA, nucleic acid-protein complexes, and nuclear proteins. After four months of age the LE cells may be found. Between six and nine months of age, immunoglobulins and complement can be detected in glomeruli of (NZB × NZW) F_1 mice by immunofluorescence [15]. Electron microscopic studies reveal electron dense deposits (immune complexes) initially in the mesangium followed by subendothelial deposits and then subepithelial deposits. Later there is diffuse proliferation of Bowman's Capsule with basement membrane thickening, focal necrosis, and glomerular sclerosis. These histologic findings are associated with progressive proteinuria, azotemia, and death by nine to twelve months of age [16]. Death due to a lymphoid malignancy is seen less often than in NZB mice, possibly due to an early death from renal failure.

Since female (NZB × NZW) F_1 mice have an accelerated form of SLE, sex hormones have been suspected of playing a significant role on the expression of disease. Recent studies have supported this theory. Comparison of age-matched male and female castrated and/or sex hormone treated (NZB × NZW) F_1 mice, followed with serial determinations of urinary protein, serum anti-DNA antibody titers, and longevity, revealed that androgens exert a protective effect [17]. When pre- or post-pubertally castrated female mice were treated with androgens (in subcutaneous continuous-release capsules), they had reduced proteinuria and prolonged survival, although post-pubertal treatment with androgens had little effect on anti-DNA antibody production. Estrogens do not appear to be as important in accelerating disease as androgens are in retarding autoimmunity; however, administration of an estrogen inhibitor has retarded disease, leaving an accelerating role for estrogens as a possibility [18].

Genetic Factors in New Zealand Murine Models

Genetic analyses of the inheritance of autoimmune traits have been performed by mating NZB mice with other New Zealand strains and with non-New Zealand strains. Crosses of NZB and NZC (New Zealand Chocolate) mice and F_1 backcrosses to the

NZC suggested that both a dominant and a recessive gene are responsible for anti-erythrocyte antibodies [19,20]. Crosses of NZB and AKR (non-autoimmune, non-New Zealand) mice and F_1 backcrosses to the AKR suggested that three to five unlinked genes control the production of anti-erythrocyte antibodies, and that one of the genes is on the X chromosone [21,22]. These and additional crosses all suggest that more than one gene, at least one of which may not be uniquely associated with the NZB strain, is involved in the phenotypic expression of Coomb's positivity [23].

Furthermore when (NZB × NZW) F_1 mice were studied, the NZW contributed a modifying gene that in the presence of the NZB gene allowed for a positive anti-nuclear antibody response [10]. Recent evidence suggests that a single dominant gene controls the spontaneous expression of anti-single-stranded DNA antibodies, one of the anti-nuclear antibodies [24].

The spontaneous production of anti-thymocyte antibodies (NTA) has been studied using NZB and DBA/2 (non-autoimmune, non-New Zealand) mice, their F_1 and F_1 backcrosses [24]. Analysis suggests that NTA production is inherited as a single codominant trait. Whether the quantity of autoantibody production is controlled by gene dosage effects or by regulatory genes is uncertain.

The occurrence of lupus glomerulonephritis in (NZB × NZW) F_1 mice appears to be dependent on the interaction of at least two dominant or codominant genes, at least one gene from each parent [25]. However, since a multitude of immune complexes may contribute to lupus nephritis, this phenotypic expression of autoimmunity may be the most difficult to subject to genetic analysis.

These and many other genetic studies have suffered from the lack of a primary gene product for study. Therefore investigators have had to choose phenotypic markers which vary with age. However, recent advances in immunogenetics have resulted in the identification of proteins encoded for in specific genes located both in and outside the major histocompatability complex (H-2) of mice. It is hoped that immune response gene products will provide better markers for the genetic analysis of autoimmunity in the future.

Viruses and New Zealand Murine Models

The role of viruses in the etiology and/or pathogenesis of autoimmunity in NZB and (NZB × NZW) F_1 mice is uncertain. A C-type virus can be isolated from these mice and passed to other species but not other mice (xenotropic virus). In addition, viral antigen-antibody complexes can be found in (NZB × NZW) F_1 glomeruli [26]. Infection of (NZB × NZW) F_1 mice with lymphocytic choriomeningitis virus or polyoma virus accelerates disease [27], while infection with lactic dehydrogenase virus or treatment with viral-like statalon retards disease [28]. This suggests that viruses can at least alter the expression of autoimmunity. Recent studies suggest that more than one virus may combine genomes, resulting in a "new" or "pseudotype" virus [29]. Such a "new" virus can be hypothesized as contributing to the development of autoimmunity. On the other hand, many strains of mice have similar viruses without autoimmune disease [30]. Thus the debate continues as to the role of viruses as well as genetics in the development of autoimmunity; most likely both contribute.

IMMUNOLOGIC ABNORMALITIES IN NEW ZEALAND MICE

Three broad categories of cell types are thought to be fundamental for an effective immune response. One of these cells is the macrophage, an antigen processing and presenting cell; the other two are lymphocytes. The lymphocytes which arise in bone marrow and migrate directly to peripheral lymphoid organs where they aggregate in

germinal centers and can be stimulated to synthesize and secrete antibody are called B cells. These B cells are distinguished by the presence of immunoglobulin on their membrane surfaces when stained with fluorescenated anti-immunoglobulin. Lymphocytes which arise in the bone marrow but are modified by passage through the thymus before they migrate to peripheral lymphoid organs are called T cells. T cell functions include the cell-mediated immune response of delayed hypersensitivity and allograft rejection. In addition, T cells can function as regulators of both B cell antibody production and T cell cell-mediated immune responses. This regulation can take the form of enhancing (helper T cells) or suppressing (suppressor T cells) immune responses. These regulatory interactions can result from direct interaction of regulatory T cells, or their products, with effector T or B cells; in addition, the regulator T cells or their products can activate third-party T cells and macrophages which then interact with the effector T or B cells. Thus, an aberration of macrophages, B cells, and/or T cells could result in altered immune responses.

The autoimmune diseases of New Zealand mice appear to reflect such aberrations. Although clinically normal for the first three months of life, there are numerous immunoregulatory abnormalities which can be detected. NZB B cells produce excessive amounts of IgM at birth and continue to produce more IgM than other mice throughout their lives [31]. This excessive IgM production is reflected in excessive spontaneous production of antibodies to nucleic acids [32] and T cells [33]. Since IgM does not cross the placental barrier, the early occurrence of these autoantibodies in New Zealand mice indicates synthesis by the young mouse rather than passive transfer in utero. Furthermore, when compared to normal mice, NZB or (NZB × NZW) F_1 mice less than ten weeks of age had excessive antibody responses to the heterologous antigens of sheep erythrocytes [34], bovine serum albumin [35], and bovine gamma globulin [36]. In addition to excessive B cell activity, the T cell regulation of B cell function is shifted toward decreased suppression in New Zealand mice [37]. The spontaneous evolution of autoantibodies and hyperresponsiveness to heterologous antigens could reflect an excessive helper T cell activity, defective suppressor T cell activity, or both.

The induction of tolerance to foreign antigens results in a hyporesponsive state to repeated antigen exposure. Compared to normal mice, autoimmune New Zealand mice by five weeks of age are defective in their ability to develop tolerance to bovine serum albumin [35], heterologous gamma globulin [36], polynucleotides [38–42], and gross viral antigen [43]. In many cases, development of tolerance has been shown to be dependent on T suppressor cells [44–47]. Thus, at a time when the (NZB × NZW) F_1 mouse has lost self-tolerance as manifest by autoantibodies, it has also lost experimental tolerance to heterologous antigen, suggesting an early loss of suppressor function. Furthermore, neonatal thymectomy accelerates the development of autoimmunity [48]. This concept was further supported by the demonstration that thymuses from two-week-old (NZB × NZW) F_1 mice, transplanted into neonatally thymectomized (NZB × NZW) F_1 mice, induced the recipients to regain the capacity to develop tolerance to bovine gamma globulin, while anti-DNA titers were suppressed [49].

Additional evidence for defective suppressor T cell function has evolved from studies of such cells in normal mice. When spleen cells from normal mice are cultured with the mitogen concanavalin A (Con A), a subpopulation of T cells are activated. These Con A-activated T cells, and factors which these cells release into the culture supernatants, can suppress antibody responses *in vitro* [50–52]. Con A-activated spleen cells from four- and 18-week-old normal mice and (NZB × NZW) F_1 mice were

studied for their ability to suppress the pokeweed mitogen-driven splenic B cell generation of IgM *in vitro* [53]. The Con A-activated spleen cells and culture supernatants from young and old normal mice and young (NZB and NZW) F_1 mice were equally suppressive. However the Con A-activated cells, and culture supernatants, from old (NZB × NZW) F_1 mice were unable to suppress such IgM production. Conversely, the pokeweed mitogen-driven IgM responses of these old (NZB × NZW) F_1 mice were suppressible by normal or young (NZB × NZW) F_1 Con A-activated cells or factors. Thus, as the (NZB × NZW) F_1 mice aged they lost their capacity to generate suppressor activity, though their lymphocytes could still be suppressed by exogenously supplied suppressor signals. When Con A was administered to young (NZB × NZW) F_1 mice they retained their capacity to develop tolerance to bovine gamma globulin and their anti-DNA antibody titers decreased [54]. Furthermore, the administration of supernatants of Con A-activated spleen cells to (NZB × NZW) F_1 mice resulted in decreased immunoglobulin levels, anti-nuclear antibody, proteinuria, and renal pathology [55]; the active factor(s) involved were of very low molecular weight ($\leq$ 1000 daltons) with one of the major mechanisms of suppression being *in vivo* reduction in spleen cell number [56].

Recent investigations have suggested that the suppressor defect in New Zealand mice is due to a defect in one of two cells which synergize in the induction of suppression [57]. These investigations have been aided by the identification of unique antigenic markers (Ly antigens) on the surfaces of functionally different T cells [58]. Thymocytes are almost all Ly $1^+2^+3^+$ while peripheral helper T cells are Ly $1^+2^-3^-$ and suppressor T cells are Ly $1^-2^+3^+$. In normal mice a subpopulation of immature T cells, Ly $1^+2^+3^+$, can be induced by Ly 1^+ (helper) T cells to differentiate to Ly 2^+3^+ (suppressor) T cells [59]. Thus, a helper T cell not only enhances an effector function, but can also enhance feedback suppression of that same effector function, resulting in a controlled immune response. When NZB mice were compared to normal mice for the presence of Ly $1^+2^+3^+$ spleen cells which could be induced to become suppressor cells of a B cell antibody response to sheep erythrocytes, the NZB mice were markedly deficient in those cells by one month of age [60]. Furthermore, we have recently found that the naturally occurring anti-thymocyte antibody (natural thymocytotoxic antibody or NTA) of NZB mice is specific for undifferentiated thymocytes (presumably Ly $1^+2^+3^+$ T cells) since Con A-activated thymocytes are relatively resistant to lysis in NTA plus complement [61]. Perhaps the simultaneous occurrence of detectable NTA, the deficiency of Ly $1^+2^+3^+$ splenic precursor cells, and the onset of a progressive aberration in suppressor function in NZB mice can be pathophysiologically correlated. The accelerated loss of suppressor cell function by neonatal (NZB × NZW) F_1 female mice administered NTA certainly supports such theory [62]. Further progression of aberrant immunoregulation in (NZB × NZW) F_1 mice occurs as the mice develop clinical disease by about six months of age. The hyperresponsiveness to heterologous antigens seen at ten weeks of age changes to hyporesponsiveness suggesting a loss of T helper cells [63].

Thus, the abnormalities of B cell function appear to result from loss of first suppressor T cells and then helper T cells. Although such a functional loss could be explained solely on the basis of a physical loss of lymphocyte subsets, the decreased regulatory control may result from an inability of B cells, T cells, and/or macrophages to "communicate." A model for altered cell-to-cell "communication" has evolved from studies of the autologous mixed lymphocyte reaction. In normal mice, splenic cells can be stimulated to proliferate when cultured with autologous B cells [64]. However, the auto-immune New Zealand mice fail to generate a proliferative

response in an autologous mixed lymphocyte reaction. Furthermore, there is evidence to suggest that B cells of autoimmune New Zealand mice are spontaneously hyperactive [65].

In addition to the humoral defects discussed above, there are also abnormalities of cell-mediated immunity which develop after the first 2–3 months of life [66–70]. By six months of age they develop increased cytotoxic responses to alloantigen both *in vivo* and *in vitro* [71]. Furthremore, spleen cells from six-month-old (NZB × NZW) F_1 mice generated a greater graft-versus-host (GVH) reaction then spleen cells from one-month-old mice in neonatal allogeneic hosts [72]; when young cells were mixed with the old cells, the GVH reaction was decreased. By nine months of age, their cytotoxic cell-mediated immunity changes from a hyper- to a hyporesponsive state [71]. Furthermore, by 12 months of age the (NZB × NZW) F_1 spleen cells give a poor GVH reaction in neonatal allogeneic recipients [72]; however by admixing a non-stimulatory number of cells from six-month-old mice with the cells from 12-month-old mice resulted in a GVH reaction suggesting the 12-month-old mice were deficient in helper cells.

Recently a model for suppression of T cell responses to alloantigen has suggested a further defect in the regulation of cell-mediated immune responses in New Zealand mice [73]. Mice, immunized with allogeneic spleen cells, have splenic T cells which, on restimulation with the immunizing alloantigen, elaborate factor(s) which suppresses cytotoxic immune responses *in vitro*. The NZB mice, although having the ability to elaborate such suppressive factor(s), are resistant to their suppressive effects. This may represent a defect analogous to that seen with B cell suppression in which there is a functional deficiency of cells through which feedback suppression can be mediated.

Thus, the aberrations of the immune system in autoimmune New Zealand mice can be viewed as an imbalance in normal regulatory mechanisms which culminates in uncontrolled autoantibody production and resultant immune complex disease resembling human SLE. The terminal malignancies which can develop may reflect the combination of abnormal lymphocyte functions and the propensity toward chromosomal abnormalities seen in these mice [74]. The role of genetic and viral factors are probably of key etiologic importance and need to be more clearly defined. The more recent elucidation of genetic control of both qualitative and quantitative immune responses to antigenic stimulation further supports the importance of genetic factors [75–79]. The genetic component could reflect the effects of a virus integrated into and indistinguishable from the mouse genome. In addition, the modifying effects of virus infection on the expression of autoimmunity [27,28] suggest that viruses can stimulate or inhibit T and B cell functions, possibly by a direct effect on the lymphocytes. In fact, propensity to produce antibodies to T cells and DNA are inherited as independent traits [24]. Regardless of the underlying etiologies of the various defects, the consequences are the appearance of autoantibody-producing cell clones and a loss of regulatory and effector T cell functions (Table 2). The ultimate pathological consequences are autoimmunity and lymphoreticular malignancies.

Non-New Zealand Murine Models

Two new inbred mouse strains, MLR/1 and BXSB, have been developed as models for autoimmunity and SLE [4]. These mice share many of the features of autoimmune New Zealand mice [78]: B cell hyperactivity, autoantibodies, circulating immune complexes, abnormal immunoglobulins, depressed serum complement,

TABLE 2
Immunologic Features

	Active SLE	NZB	(NZB × NZW) F_1
1. Spontaneous B-Cell Hyperactivity	+	+	+
2. Impaired 1° Antibody Responses	+	+	+
3. Impaired 1° Cell Mediated Immunity	+	+	+
4. Relatively Normal 2° Immune Responses (Antibody and Cell Mediated)	+	+	+
5. Impaired Autologous MLR	+	+	?
6. Impaired Suppressor Function	+	+	+
7. Impaired Helper Cell Function	Variable	+	+

MRL/1 and BXSB mice and canine SLE have not been studied.

immune complex glomerulonephritis, and thymic cortical atrophy. In addition the MRL/1 mice develop arthritis. While NZB and (NZB × NZW) F_1 female mice have accelerated disease activity compared to males, the incidence and severity of disease is equal in male and female MRL/1 mice and is greatest in BXSB males. Furthermore the MRL/1 and BXSB mice have a more accelerated onset of disease than New Zealand mice, with a 50 percent mortality by six months of age.

Serum concentrations of immunoglobulin in BXSB and MRL/1 mice increase with age and are five to nine times those of six-month-old normal mice. In addition, MRL/1 mice have large quanitites of cryoglobulins. As the MRL/1 and BXSB mice age, 23 percent and 43 percent, respectively, develop monoclonal gammopathies. Abnormal autoantibody titers to nucleic acids and to double- and single-stranded DNA increase with age; they are higher in MRL/1 than BXSB mice, and are associated chronologically with rising titers of circulating immune complexes and falling serum complement levels and the onset of clinical disease. Anti-thymocyte antibodies are elevated in BXSB mice but are of low titer in MRL/1 mice although both have thymic atrophy.

The immune complex proliferative glomerulonephritis of both strains is characterized by the presence of high concentrations of antibodies to nucleic acids, double- and single-stranded DNA in the renal eluates. Immunofluorescence staining of the kidneys reveal striking deposits of immunoglobulin and complement involving both the capillary loops and the mesangium. Lymphoid hyperplasia is most marked in MRL/1 mice. Initial studies suggest that different proliferating subpopulations of lymphocytes may be involved in each strain.

The similarities and differences of autoimmune MRL/1, BXSB and New Zealand mice may allow genetic manipulations which will provide a better understanding of the etiology of SLE. However, it should be realized that these new murine models have not yet been extensively studied immunologically. Further data will need to be gathered before their relativity to human disease is established. Nevertheless, these mice provide an added spectrum of disease models of human SLE. The MRL/1 mice may represent the SLE-Sjogren's mix of human disease, while the BXSB mice may provide further insight into the role of genetic or hormonal sex-linked influences on the development of autoimmunity and neoplasia.

Canine Model

Canine SLE commonly presents as Coomb's positive hemolytic anemia, thrombocytopenia, arthritis, and glomerulonephritis; less frequently the dogs have a facial rash, alopecia, serositis, leukopenia, hepatosplenomegaly, and/or lymphodenopathy

[3]. Antibodies to single-stranded DNA and double-stranded RNA and positive LE preparations are common. Antibodies to double-stranded DNA are infrequent. All breeds of dogs can be affected, with disease especially severe in young females.

Since canine SLE was first described by Lewis, Schwarts, and Henry in 1965, studies have concentrated on genetic and viral contributions to the development of disease. Three separate breeding lines were studied with 95 percent of the F_1 offspring developing serologic abnormalities by 18 months of age; however, none of these F_1 hybrids developed clinical SLE over seven years [79,80]. F_1 backcross and outcross breedings failed to support a genetic basis for the serologic abnormalities.

These studies did, however, suggest the natural vertical passage of an infectious agent. Experimental vertical transmission was subsequently demonstrated when cell-free filtrates of SLE dog spleens were infused into normal puppies and mice [81]. Some of these recipients developed serologic abnormalities. Dogs receiving normal spleen cell-free filtrates remained normal if housed separately. Natural horizontal transmission was suggested when three of the recipients of normal spleen cell-free filtrates developed abnormal serologic studies when housed with recipients of SLE spleen cell-free filtrates.

Of the mice which received SLE dog spleen cell-free filtrates, 6 percent developed lymphoid malignancies [81]. Cell-free filtrates of these tumors were then given to normal dogs and syngeneic normal mice. Postive LE preparations were induced in the dogs, and lymphoid tumors and antibodies to nucleic acids in the mice. One of the murine tumors was a plasmacytoma (SP-104) which produced monoclonal IgA against double-stranded DNA [82]. The relevance of these findings to humans was supported by the finding that rabbit fluorescein-conjugated antibody to the purified SP-104 virus stained lymphocytes from human SLE patients; in addition, anti-lymphocyte antibodies from an SLE patient's sera could be absorbed with SP-104 [83].

Although these studies support the role of a transmissable agent in the pathogenesis of canine SLE, the clinical features still have not been transmissable, supporting the concept of a multifactorial etiology of SLE. However, due to frequent canine-human interaction, the theoretical consequences of an infectious (presumably viral) agent which can be transmitted between species are of epidemiologic importance [84].

Human SLE

The available evidence strongly suggests that human SLE is multifactorial in etiology. Genetic factors have long been thought to be important. Recent studies of families of patients with SLE have been reinforced by the finding that particular B cell alloantigens occur with increased frequency in patients with SLE [85]. This is analogous to the NZB mouse which spontaneously develops a lupus-like illness and which has a limited number of genes predisposing to autoimmune features [19–25]. Genetic factors also are important in BXSB and MRL/1 mice and in SLE dogs.

Environmental factors such as viral infection (which may actually be endogenous rather than exogenous) under certain circumstances seem to influence the appearance of autoimmune manifestations [86]. Although the environmental factors may be heterogenous, and their mechanisms of action diverse, the most likely deleterious action is an adjuvant-like effect upon the immune system. In other words, any factor which will stimulate the immune system, especially the B cell antibody-producing part of the immune system, would exacerbate a tendency toward autoantibody production.

Humans and mice with SLE appear to have generalized hyperactive B cell function

[87,65]. Patients with active SLE have B cells and their progeny which produce antibody to a variety of chemical haptens. Their increase in numbers of antibody-forming cells is not limited to those producing autoantibodies, supporting the idea of generalized B cell activation. Patients with active disease appear to be especially abnormal with regard to IgG antibody-forming cells. Those with inactive disease may have normal or increased numbers of IgM antibody-forming cells, but not increased IgG antibody-forming cells. This further points to a pathogenic role for IgG antibody excess associated with active SLE as has been suggested for (NZB × NZW) F_1 mice [15,16].

A large number of T cell defects has been described in patients with SLE. Such defects include reduced numbers of T cells [88,89], impaired delayed hypersensitivity reactions [90,91], impaired response to T cell mitogens (including non-specific mitogens, allogeneic cells, and antigens to which the cells had been sensitized) [91–93], and impaired generation of suppressor cells [94]. Cells which contain large quantities of T cell surface membrane antigens are preferentially lost [95,96]. These studies point to a loss of a particular subpopulation of T cells. At least some of the cells lost appear to be those capable of being activated to become suppressor cells. The defect in suppression is an inability to produce suppressive signals rather than a defect in responsiveness to suppressive signals. These findings are quite analogous to those found in (NZB × NZW) F_1 mice.

Active SLE patients, like NZB mice, also have marked defects in the autologous mixed lymphocyte reaction [97]. With such a defect in T cell-B cell "communication," it is not surprising that so many abnormalities have been reported in active SLE and in New Zealand mice.

Plasma and sera from many patients with active SLE, but not from normals or patients with inactive SLE, were found to contain antibodies reactive with T cells by indirect immunofluorescence, using the fluorescence-activated cell sorter and the technique of flow microfluorometry [95]. These antibodies were largely of the IgM class. They stained almost all T cell, whether from normals or patients with SLE. In addition, patients with active SLE were found to have a decrease in T cells with high density of T cell antigen (brightly staining cells) suggesting *in vivo* elimination by the antibodies reactive with such T cells. The mechanism of *in vivo* elimination remains unknown; it probably is alteration in circulatory pathways and removal of antibody coated cells by the reticuloendothelial systems as occurs in New Zealand mice [67,98]. *In vitro* treatment of normal T cells with anti-T cell antibodies from most patients with SLE led to killing of between 20 percent and 25 percent of T cells, but only if complement was added [96]. Although the antibodies are capable of binding to *all* T cells, there is a preferential killing of only a subpopulation of these T cells. Plasma from patients with active SLE, in which anti-T cell antibodies were present, inhibited the development of suppressor activity in the cultures of normal T cells activated by Con A [96]. Absorption of the plasma containing anti-T cell antibodies with T cells, but not non-T cells, could eliminate the suppressor-inhibiting activity of the SLE plasma containing anti-T cell antibodies. The IgM, but not the IgG, fraction of the plasma was shown to possess the inhibiting property and complement was found to be necessary for the maximal effect of such anti-T cell antibodies. Anti-T cell antibodies found to occur spontaneously in New Zealand mice have also been found to preferentially kill suppressor cell precursors. This is true whether the antibodies were studied *in vitro* or whether they were injected *in vivo* [61,62]. In patients with SLE, there appears to be an analogous defect. The deficiency in generation of

suppressor T cells of SLE patients can be reproduced in a normal human T cell population by incubating them with IgM anti-T cell antibodies obtained from patients with active SLE. These observations suggest the possibility that, as in NZB mice, such antibodies may be the cause of some of the observed T cell defects in patients with SLE. In addition, the class of SLE anti-T cell antibodies, IgM, is the same as that found in NZB mice [33].

Studies to date suggest that different mechanisms may be operative in different patients with SLE or in the same patient at different times. The various animal models cover the spectrum of human SLE and support the possibility of a heterogeneous group of disorders with different genetic and immunologic bases as well as different responses to a variety of environmental stimuli.

THERAPY

The treatment of human SLE has been guided for the most part by experimental studies in autoimmune New Zealand mice. Therefore we will concentrate on those studies. The therapeutic approaches to the autoimmune diseases of New Zealand mice can emphasize either prophylaxis or treatment. Many of the prophylactic studies are directed more toward understanding pathogenesis than toward treatment. Certainly the breeding studies of NZB mice suggest that the manifestations of autoimmunity can be genetically modified. However, since our understanding of human immunogenetics does not yet allow us to predict who will develop SLE, such maneuvers are not yet applicable to the human illness.

Implication of a viral etiology has led to therapeutic trials in (NZB × NZW) F_1 mice with the anti-viral agent Ribavirin [99]. The Ribavirin-treated mice lived longer and had decreased proteinuria and antibodies to DNA; however, it is not clear that the drug's beneficial effects are a result of the antiviral properties of the drug.

Attempts to modify the immune system have included treatment with immunosuppressive agents (Table 3). NZB mice have been treated with anti-lymphocyte serum with suppression of the autoimmune hemolytic anemia, but with little favorable effect on hyperglobulinemia, lymphoid infiltrates, or renal disease [100]. Similar therapy of (NZB × NZW) F_1 mice was found to accelerate disease [101,102], though this may have been due to formation of antibodies to the heterologous serum proteins with resultant additional immune complexes which could be prevented by induction

TABLE 3
Modification of Early Disease

	Human	Murine	
	Active Disease	NZB	(NZB × NZW)F_1
1. Genetic	?	↑ or ↓	↑ or ↓
2. Viral	?	↑ or ↓	↑ or ↓
3. Immunologic Adjuvants	↑	↑	↑
4. Immune Suppressors	↓	↓	↓
5. Sex Hormones: Androgens	?	?	↓
Estrogens	↑	↑	↑
6. Corticosteroids	↓	↓	↓
7. Cytostatic, Cytotoxic Drugs	?	↓	↓

↑ = Worsening of disease

↓ = Suppression of disease

MRL/l and BXSB mice and canine SLE have not been comprehensively studied.

TABLE 4
Treatment of Kidney Disease

Therapy	Human	(NZB × NZW) F_1 Mice		
		Before	Early	Late
1. Corticosteroids	?	+	+	0
2. Immunosuppressive Drugs	?	+	+	0
3. Ribavirin	?	+	+	?
4. Prostaglandins	?	+	+	?
5. CONS[a]	?	+	+	-
6. Anti-thymocyte Globulin	?	+	+	0
7. Tolerance to Nucleic Acids	?	+	0	0
8. Androgens	?	+	+	?
9. Lymphoid Ablative Procedures	?	+	+	?

+ = Effective
0 = No change
- = Worsening
[a]CONS = Supernate of Concanavalin A activated cells
MRL/1 and BXSB mice and canine SLE have not been comprehensively studied.

of tolerance to these serum proteins prior to administering the anti-thymocyte serum [103].

Recent studies suggest that treatment with exogenously produced suppressor factors [55,56], prostaglandins [104], or cyclophosphamide and induction of tolerance to nucleic acids [105] may all lead to prolonged survival in (NZB × NZW) F_1 mice. None of these modalities are currently applicable to the treatment of human diseases, though they may be important therapeutic regimens in the future (Table 4).

Corticosteroids have been effective treatment for autoimmune hemolytic anemia of NZB mice [106], and the symptoms of canine SLE. Corticosteroids, azathioprine, and cyclophosphamide, given singly or in combination of two or three drugs, have all been efficacious treatments for glomerulonephritis in (NZB × NZW) F_1 mice if given prior to the development of irreversible renal disease [107–109]; however, their benefit if started after the development of advanced renal disease was marginal [110].

TABLE 5
Clinical Features of SLE

	Human	Murine				
	Active Untreated	NZB	(NZB × NZW) F_1	MRL/1	BXSB	Canine
1. Immune Complex Renal Disease	+	Variable	+	+	+	+
2. Hemolytic Anemia	<10%	+	<10%	0	+	+
3. Rash	+	0	0	0	0	+
4. Alopecia	+	0	0	0	0	+
5. Arthritis	+	0	0	+	0	+
6. Serositis	Variable	Variable	Variable	Variable	Variable	Variable
7. Splenomegaly	Variable	+	+	+	+	+
8. Lymphoid Infiltrates into Organs	Variable	+	+	+	+	+
9. CNS Involvement	Variable	?	+	?	?	?

+ = Present in the majority
0 = Rare or absent

TABLE 6
SLE Serological Features

	Human	Murine				
	Active Untreated	NZB	(NZB × NZW)F_1	MRL/1	BXSB	Canine
1. L E Cells	+	~20%	+	?	?	+
2. ANA	+	+	+	+	+	+
3. Anti-dsDNA	+	~20%	+	+	+	Rare
4. Anti-ssDNA	+	+	+	+	+	+
5. Anti-RNA	+	+	+	?	?	+
6. Anti-erythrocyte	~20%	+	Variable	10%	20%	+
7. Anti-T Cell	+	+ Earlier than in (NZB × NZW)F_1	+	10%	40%	?
8. Hyperglobulinemia	+	+	+	+	+	+

+ = Present in the majority

Therapeutic trials of similar drug regimens in the treatment of the glomerulonephritis of human SLE have yet to demonstrate clear-cut efficacy.

Another adjunct to treatment of canine and human SLE has been plasmapheresis [111,112]; theoretically the removal of circulating autoantibodies and immune complexes, coupled with immunosuppression, would reverse and/or prevent immune complex function and its subsequent pathology.

Although the majority of symptoms and some signs of human, murine, or canine SLE are responsive to corticosteroids, these drugs have a significant morbidity. In addition there is still no treatment which dramatically alters the advanced life-threatening features of SLE.

How Good are the Models?

Among the various animal models of human SLE one can find almost all of the clinical, serological, pathological, epidemiologic, viral, genetic, and immune abnormalities found in patients with SLE (Tables 5, 6). Different models fit different types of patients. NZB and BXSB mice are the best models of autoimmune hemolytic anemia. (NZB × NZW) F_1 mice best represent lupus glomerulonephritis. MRL/1 mice best represent Sjogren's Syndrome. In contrast to these inbred murine models, dogs represent an outbred model of SLE. Of all these models, New Zealand mice have been most completely studied. It is hoped that all these animals will provide a clearer understanding of the etiology and pathogenesis of SLE and result in more effective therapy.

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