PROGRESS IN CLINICAL RHEUMATOLOGY VOLUME 1

Edited by

ALAN S. COHEN, M. D.

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Preface

The rheumatologic literature has expanded enormously in the past 20 years. There exist a multiplicity of medical journals both in the United States and abroad, and many original articles in the field are published in general research or clinically oriented journals as well. *Progress in Clinical Rheumatology* is designed to provide timely and comprehensive reviews of major clinical topics; of investigative topics relevant to our understanding of the clinical state of the art; and to bring to bear our understanding of basic considerations on the clinical and therapeutic aspects of the particular disorder.

In this first volume, each of the above has been attempted. Chapter 1 presents an in depth review, based on animal models and basic modern immunologic science, of the conceptualization of systemic lupus erythematosus. Dr. Steinberg, a major contributor to our understanding of this increasingly complex area, gives the reader a clear understanding of current concepts of host factors, immune factors, and genetic factors as primary or secondary phenomena in SLE.

In Chapter 2, Drs. Nepom and Schaller analyze in detail their extensive personal experience with childhood SLE. They review not only the clinical manifestations, but laboratory studies, modes of treatment and prognosis, as well as neonatal lupus.

Chapter 3 combines the physiologic and therapeutic approaches. Drs. Kahaleh and LeRoy review not only the natural history and clinical manifestations of the disease, but stress the basic factors that may be related to its pathogenesis. The vascular disorder in scleroderma is lucidly discussed as well as the fibrotic, collagen related aspects and immunologic phenomena that occur.

In recent years aggressive treatment for rheumatoid arthritis has been increasingly emphasized. Drs. Klinenberg, Reichman, and Clements appropriately entitle this "Investigational Therapy" and expound in a precise fashion the current status of the use of azathioprine, 6 mercaptopurine, cyclophosphamide, chlorambucil, methotrexate, thoracic duct drainage, apheresis (plasmapheresis, cryopheresis, etc), and total lymphoid irradiation. They provide us with information about the mechanism of action, toxicity, and therapeutic results that will be a springboard for the understanding of future studies.

Another disease in which technology has made a major impact albeit in diagnosis rather than therapy, is ankylosing spondylitis. Drs. Khan and Kushner after a useful clinical review evaluate the current approach to the diagnosis of spondylitis. Radiographs, computerized tomography, radionuclide scintigraphy, thermography, nuclear magnetic resonance, and finally the role of HLA-B27 testing are discussed. The use of sensitivity-specificity testing allows a clearer appreciation of the value of the HLA-B27 test.

Finally, Drs. Goldenberg and Rice review one of the most treatable forms of articular disease, acute gonococcal arthritis. They update what had been controversial regarding the sequential clinical stages of the disease and discuss diagnosis and treatment. Of particular note is their review of the new data on the microbial and host features of disseminated gonococcal disease and the role of immune mechanisms, and then discussion of a new laboratory model. It is through studies such as these, that we shall obtain a better understanding of the epidemiology of this worldwide disorder.

Thus the reviews in Volume I of *Progress in Clinical Rheumatology* deal with problems in the major connective tissue diseases, i.e. rheumatoid arthritis, systemic lupus erythematosus, scleroderma, ankylosing spondylitis, and infectious arthritis.

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Contents

Alfred D. Steinberg

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Modern Concepts of Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a spontaneously occurring nonspecific disorder of the organs that has a tremendous variability of expression. People of all ages may be affected; however, females between the ages of 12 and 40 are most often afflicted. In addition to the spontaneous occurrence of SLE, the disease may be induced in humans by administration of certain drugs. Not only humans develop SLE; but also many other mammals, including dogs, mink, and mice, develop the syndrome. We will try herein to describe the current conceptual framework for the development of autoimmune diseases in general and systemic lupus in particular. Next, we will describe the information available from studies of animals with SLE as a background for discussing the human disorder. Human SLE will be described in terms of immune regulatory abnormalities, organ pathology, current approaches to treatment, and potential newer modalities.

THE CONCEPTUAL FRAMEWORK FOR THE DEVELOPMENT OF AUTOIMMUNE DISEASES

How does an autoimmune disease occur? Does each have the same general basis? Do all patients with SLE have the same regulatory defect or the same pathogenetic mechanisms? These questions cannot be answered definitively at present. Nevertheless, a substantial increase in the knowledge of immunology and molecular biology allows us to consider the general problem of autoimmune disorders.

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Until recently, it was thought that anti-self reactions were abnormal and detrimental. More recently, however, it has become apparent that self-self recognition plays an important role in normal immune responsiveness and homeostasis. Cells of the immune system recognize specific major histocompatibility complex (MHC) encoded recognition structures during the process of responding to specific foreign antigens. Antibodies to foreign antigens (Ab_1) give rise to antibodies specific for themselves (Ab_2). Such anti-idiotype antibodies have the capacity to regulate immune responses to the antigen to which Ab_1 reacts. Ab_2 can recognize cells with receptors that bear the idiotype of Ab_1 as well as recognizing secreted Ab_1. Therefore, there is a great range of possible regulatory interactions in this system. In addition, antibody itself (Ab_1) is capable of exerting feedback regulation. Both antibodies and cells, thus, can recognize self-determinants and play a role in normal regulatory processes.

How does this new knowledge affect our concepts of autoimmune diseases? It makes us realize that autoimmunity is common, normal, and not pathological (Table 1-1). Only when autoimmune reactions lead to tissue damage or some other pathological disorder is the process abnormal and disease inducing. In other words, autoimmunity is not at all abnormal. It is part of the normal regulatory activity of the immune system. As a result, autoimmune reactions and autoimmune phenomena are not, in themselves, pathological. This recognition makes us distinguish between noninjurious and injurious autoimmune phenomena. As a corollary, there may be autoimmune phenomena that do not serve any normal regulatory processes but that are not injurious. For example, many healthy people have antibodies reactive with nuclear antigens, immunoglobulins, thyroid antigens, etc. but do not suffer obvious ill effects of such antibodies. These people may be viewed as manifesting abnormal autoimmune phenomena without manifesting illness. The recognition of nonpathogenic autoantibodies allows us to appreciate that patients with SLE may have many deleterious autoantibodies but that some of their autoantibodies may not be pathogenic. Thus, from the viewpoint of understanding pathogenesis, special emphasis must go to those antibodies that induce injury and/or inflammation. Similarly, those are the antibodies against which therapy must be directed. The same holds for nonantibody-mediated inflammatory processes.

THE MULTIFACTORIAL NATURE OF DISEASE INDUCTION

Common sense and numerous observations point to multiple factors in the development of many diseases. It is clear that miliary tuberculosis (TB) is "caused" by the tubercle bacillus. It is also clear that Ashkenase Jews rarely develop miliary TB and that on exposure to TB, Eskimos and Alaskan Indians often develop miliary TB. Therefore, other factors, in this case

Table 1-1
Concepts of Immune Regulation and Their Relationship to Autoimmunity and Autoimmune Diseases

1. Self–self interactions form the bases for both normal immune reactions and normal immune regulation.
2. These self–self interactions include self-recognition by parts of the immune activity on the basis of that recognition.
3. Since #2 represents an autoimmune response, autoimmune responses are part of normal physiology.
4. Diseases associated with autoimmune responses can result from a variety of different types of abnormalities
   a. A defect in the afferent limb of the immune system initiated without a requirement for a specific external agent
      With important genetic requirements
      Without important genetic requirements
   b. A defect in the afferent limb of the immune system initiated by a specific external agent
      With important genetic requirements
      Without important genetic requirements
   c. A defect in effector mechanisms of immunity initiated without a requirement for a specific external agent
   d. A defect in effector mechanisms of immunity initiated by a specific external agent
   e. Combinations of a–d
5. Many autoimmune diseases are multifactoral in etiology and/or disease expression.
   a. Genetic—Disease is often polygenic
      —Individual genes predispose to particular abnormalities
   b. Environmental factors—Stimulate the immune system (specifically or polyclonally)
      —Interfere with normal immune regulation
   c. Hormonal factors—Modify disease manifestations

apparently genetic factors, may predispose to, or protect against, the development of a disease. This is true whether or not there is a specific "etiologic" organism. Additional factors clearly predispose to miliary TB. These include, but are not limited to, degree of crowding, alcoholism, nutritional status, immunosuppressive events, immunostimulatory events, and prior exposure. In other words, miliary TB may be viewed as multifactorial in etiology, despite the necessary requirement for the tubercle bacillus. In fact, the genetic factors may be so important in some populations that it may be viewed as a genetic disorder as much as an infectious disorder. One could even do genetic analyses of populations and families and try to determine the genetic basis for susceptibility. The take-home message is that even for a disease with known "triggers," multiple factors may determine whether the disease will be manifested.

How does this apply to SLE? It appears that SLE is a disorder in which multiple factors combine to determine whether disease will be expressed and to what extent. In some individuals, the genetic predisposition may be so strong that trivial environmental factors or even no environmental factors may be necessary for the disease to be expressed. In other individuals, the genetic predisposition may be modest; moderately strong environmental factors may be required for disease expression. Additional factors, such as sex hormone metabolism and state of the immune system, may be sufficient to allow or prevent disease expression. Clues to the multifactorial nature of SLE in a given individual and to the differing factors in different individuals come from studies of mice that spontaneously develop SLE.

MURINE SYSTEMIC LUPUS

For physicians who are interested only in the management of human SLE, there is a strong tendency to skip over sections such as this. That is a most unfortunate tendency since more is known about murine SLE, and what is known can be applied to human lupus. Unlike other diseases in which there are animal models that provide little insight into the human disorder, murine SLE occurs spontaneously, has characteristics of humans with SLE, and responds to therapy the way patients do.[1] Most important, the ability to dissect the genetic basis for illness and the pathogenesis of immune abnormalities is much easier and more advanced in murine systemic lupus. One cannot, therefore, be a fully informed physician of patients with SLE without a working knowledge of the disease as it occurs in mice.

Mice with systemic lupus come in different sizes and colors. Their MHC types may be different.[1-4] In other words, the genetic basis for illness may be different in different mice with lupus (Table 1-2). The most commonly studied mice have been the New Zealand black (NZB), (NZB × NZW) F_1, MRL-*lpr*/*lpr*, and BXSB. These mice have differences in the pace of illness and sex hormone effects. The BXSB mice have a male-oriented illness; the males have accelerated disease relative to the females. Some factor associated with the Y chromosome of the BXSB mouse appears to be responsible. Sex hormones are not able to reverse this male disease.[5] However, whereas the BXSB Y chromosome leads to disease in BXSB mice and in male offspring of BXSB males with autoimmune-prone females, the BXSB Y chromosome does not lead to accelerated disease in offspring of BXSB fathers and non-autoimmune-prone mothers.[6] Therefore, the BXSB Y chromosome factor is an accelerating factor rather than a lupus-inducing factor.

Another accelerating factor is the *lpr* gene. Originally described on the MRL background, this gene has now been bred onto many backgrounds.[4] In homozygous form, this gene leads to lymphoproliferation. The proliferating cell is a dull Ly 1 + T cell (helper phenotype).[7] Eventually, massive lymph-

Table 1-2
Heterogeneity of Murine Lupus

Feature	NZB	(NZB × NZW)F_1	MRL-MP/*lpr*/*lpr*	BXSB
Genetic	At least 6 autosomal genes	Multiple genes, some from NZW	Multiple background genes, *lpr* major accelerator	Multiple background genes, y chromosome gene major accelerator
Major histocompatibility	d/d	d/z	k/k	b/b
Sex	Little effect Recessive gene for androgen insensitivity	Marked effect Androgens protect Estrogens worsen	Androgens protect slightly	Marked acceleration in males, not hormonal
Immunoglobulins	↑ IgM	↑ IgM, ↑ IgG_2	↑ IgG_1, ↑ IgG2a	↑ IgG_1, ↑ IgG2b
Lymphoid organs	Lymphoid hyperplasia	Lymphoid hyperplasia	Marked ↑ T cells	Moderate ↑ B cells
Effects of *xid*	Prevents disease	Prevents disease	Retards disease	Prevents disease
Disease manifestations	Anti-T cell antibodies Coombs-positive hemolytic anemia Late life renal disease Splenic hyperdiploidy Death occurs after 1 year	Anti-DNA, LE cells Membranoproliferative glomerulonephritis Sjögren's syndrome Females die in first year of life	Marked lymphadenopathy Anti-DNA, anti-Sm Arthritis and anti-Ig Membranoproliferative glomerulonephritis Vasculitis Males and females die in first year of life	Immune complex glomerulonephritis Degenerative coronary artery disease Serologically less abnormal than others Moderate adenopathy Males die in first year of life

adenopathy and splenomegaly result. Female sex hormones are an accelerating factor and androgens are a retarding factor in (NZB × NZW) F_1 mice.[8,9] Females have much more rapid onset of disease and death than their male counterparts; however, that difference can be reversed by opposite sex hormone treatment. NZB mice tend to have late onset "middle-age" lupus with only a small difference between males and females. Some of these features are summarized in Table 1-3.

Of considerable interest are mice about which little has been written. These (NZB × normal) F_1 mice develop autoantibodies but usually live a normal life span. The (NZB × MRL) F_1 mice develop a milder disease than either parent. This stands in contrast to the (NZB × NZW) F_1 female, which gets a more severe disease than either parent. Gene interactions, thus, may give rise to either accelerated or retarded disease in offspring. These results have particular importance for human family and population studies. In

Table 1-3
Genetics of Murine Autoimmunity: Relationship to Human SLE

	Murine system	Human SLE
NZB	Inherited autoimmune traits with a lack of sex differences[4]	Familial incidence of SLE[2] Concordance in identical twins[3]
F_1 hybrids with NZB	Androgens suppress and mask genetic mechanisms[4]	Female predominance in SLE[1,2]
BXSB	Male-linked inheritance[1,30,39]	Inheritance of male predominant SLE[7]
Recombinant inbreds, lines of NZB × Normal	Independent inheritance of many autoimmune traits[8]	Familial members of SLE patients develop some autoimmune features without clinical SLE
F_1 and backcross analysis	Dominant and recessive inheritance of autoimmune traits with additional modifying genes. Many genes show gene dosage effects	Dominant inheritance of ANA and Anti-ssDNA.[5] Two genes may give greater abnormality than one.
Modifying factors *xid* gene retards	Predisposing factors.[37,56,71,90] Retarding factors[32,34]	B-cell hyperactivity in SLE[36,94]

addition, in mice it is clear that high titers of autoantibodies may be associated with a normal life span without therapy.

A careful analysis of the genetic basis for disease in NZB mice by use of F_1 and backcross mice has indicated that genes for anti-DNA and anti-T-cell antibodies are unlinked and coded for by single dominant or codominant genes.[10] Additional genes from the NZW mouse contribute to disease in the (NZB × NZW) F_1.[11] More recently, studies of recombinant inbred lines of mice derived originally from NZB and normals have indicated that multiple genes are responsible for the full disease of NZB mice. At least six genes contribute to the disease of NZB mice.[12] A similar analysis of background genes in MRL and BXSB mice would be helpful.

In addition to those factors mentioned previously, congenital factors other than mammalian genes may be critical to the expression of disease. An oncornavirus may cause accelerated disease by virtue of increasing the load of pathogenic immune complexes.[13,14] Such a virus in an animal with a defect in tolerance, thus, could induce antiviral antibodies and exacerbate immune complex disease. Although such a virus is not necessary for disease,[15] it could be a factor similar to other viral infections.[16] Another factor is a maternally transmitted antigen, which is present in some, but not all, mice. This antigen may result from cytoplasmic genetic material, which is passed on from the mother's egg. Mice with the antigen may be protected from the full expression of autoimmune disease.

The detailed analysis of the cellular bases for illness in the different strains of mice that develop lupus is beyond the scope of this chapter. It is helpful, nevertheless, to point out some of the findings. First, the role of the thymus in retarding or preventing disease in the different strains may be very different. Neonatal thymectomy of MRL-*lpr*/*lpr* mice has a profoundly ameliorating effect on disease. These mice, which ordinarily die at about 6 months of age, are essentially cured by neonatal thymectomy.[17] In contrast, neonatal thymectomy causes accelerated disease in BXSB males.[18] In our hands, neonatal thymectomy has a less dramatic retarding effect in NZB mice and an accelerating effect in (NZB × NZW) F_1 mice. The mouse strains, thus, must differ in terms of the cellular basis for illness if neonatal thymectomy can have such dramatically different effects in the different strains. These differences are explainable. The proliferation observed in MRL-*lpr*/*lpr* mice is primarily one of T cells. These T cells cannot proliferate without a thymus; therefore, neonatal thymectomy prevents disease. A corollary is that the autoantibody production is T-cell dependent. In contrast, most of the proliferation of BXSB mice is of B cells. The thymus ordinarily holds the proliferation of these B cells in check, albeit not completely. Neonatal thymectomy allows the B cells to proliferate in an uninhibited fashion; this gives rise to massive lymphoproliferation and markedly increased autoantibody production.

Immune Abnormalities That Lead to Disease versus Those That Result from Disease

In the mice, it is relatively easy to study individuals prior to the onset of clinical illness and then after illness occurs. Such studies clearly indicate that there are many immune abnormalities. Those that are found at the time of clinical illness, however, may not be those that set off the process. This concept is especially important because patients with SLE are rarely studied prior to the onset of symptoms. Abnormalities observed at the time of active disease are given great importance with regard to pathogenesis of the disorder. Some of these may, in fact, serve to perpetuate the disease process. They may not have been important, however, in its initiation. Antigen nonspecific suppressor function thus falls prematurely early in the life of the (NZB × NZW) F_1 mouse but rises abnormally after the onset of disease.[19] It is possible that the abnormality observed at the time of illness—increased suppression—is important in perpetuating the process; however, it has nothing to do with its initiation. In fact, increased suppressor function probably results from the markedly increased immune reactivity that is observed as autoimmune disease develops. The marked hyperactivity is, however, not adequately controlled by the reactive suppressor factors.

What can be said of the early abnormalities of mice with murine lupus? It appears, in general, that all have a stem-cell disorder. That is, they have defects that may be expressed in mature cells of the immune system but that are encoded in the stem cells and that can be transferred with stem cells.[20–24] The precise defects may be different in the different mice. A defect associated with T-cell proliferation, thus, is associated with MRL-*lpr*/*lpr* stem cells.[25] Similarly, a defect for interference with normal tolerance is characteristic of NZB pre-T-cell stem cells.[26] In both cases, the stem cells must be acted on by a thymus for the defect to be expressed. In contrast, non-T cells appear to be critical to the failure of normal tolerance and disease expression in the BXSB male.[27] The defects in the mature lymphoid cells thus may differ even though the information for the defects may be present in the stem cells in all of the mice.

Many abnormalities are observed late in the course of disease. These include autoantibody production, immune complex renal disease, impaired responsiveness to T-cell mitogens, and impaired IL-2 production. Impaired immune responsiveness to exogenous stimulation is found in association with vigorous immune activity during the course of the autoimmune process. In other words, at the same time that there is vigorous B-cell activity and production of autoantibodies, immune responsiveness to stimulation with nonspecific mitogens or foreign antigens may be markedly impaired. This paradox may be viewed teleologically as follows: the body is preoccupied with making autoantibodies and autoimmune responses and cannot be bothered with the new stimuli. At a more mechanistic level, two explanations are available. First, the autoimmune process leads to the production of vigorous

immunosuppressive signals, which impair the responses to foreign antigens and mitogens. Second (and not mutually exclusive), pre-B-cell stem-cell pool is preempted by the maturation into autoantibody-producing cells and the T cells are functionally inactivated by suppressor factors, many secreted by nonlymphoid mononuclear cells. Additional factors occur in some, but not all individuals: anti-T-cell antibodies interfere with T-cell regulation. These various defects may be partly overcome by treatment with immunosuppressive regimens (including cortiocosteroids and cyclophosphamide) to restore more normal immune function. The problem, therefore, is not just a deficiency of adequate numbers of particular lymphocytes but active interference with normal cellular function.

HUMAN SYSTEMIC LUPUS ERYTHEMATOSUS: APPROACH BASED ON THE MURINE STUDIES

In the next several sections, information regarding human SLE lymphocytes will be put forth. An attempt will be made throughout to place the data in the perspective derived from the murine studies. This perspective includes the idea that different individuals with SLE may have different genetic and cellular bases for illness, that immune abnormalities observed during the course of active disease may not be those that induced the disease, and that many immune abnormalities may actually result from the disease process. Finally, throughout it must be appreciated that most studies of humans have been limited to the sampling of peripheral blood, whereas those of animals involve lymphoid organs such as spleen and lymph nodes and sophisticated transfer studies between experimental animals.

Lymphoid Cells in Patients with Systemic Lupus Erythematosus

Patients with active SLE often have leukopenia.[28] Although this leukopenia is accounted for on an absolute basis primarily by a reduction in granulocytes, there is also an absolute reduction in lymphocytes. There is thus the paradox of an increased percentage of lymphocytes in the differential but a decreased absolute number of lymphocytes on the basis of lymphocytes for each cubic millimeter of peripheral blood. Individuals vary greatly. Some patients have a leukocytosis, even without steroid therapy. Others have profound leukopenia, which may actually improve with immunosuppressive drug therapy.

Peripheral blood lymphocyte counts may be greatly depressed, in the normal range, or increased. In active disease, the average lymphocyte count was reduced approximately 70 percent, with approximately equal reductions in B and T cells.[29] That led to relative increase in cells of the monocyte–