MEDICAL GRAND ROUNDS

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CLINICAL SYNDROMES

WITHIN THE SPECTRUM OF LUPUS ERYTHEMATOSUS

by

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CLINICAL SYNDROMES WITHIN THE SPECTRUM OF LUPUS ERYTHEMATOSUS

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I.

INTRODUCTION

As an organ containing specialized cells with highly specialized functions, the skin frequently reflects abnormalities in other organ systems. Because the gross morphologic patterns of the skin are so readily visible, they have been subjected to a bewildering array of descriptive names which often fail to convey any understanding of the disease process involved. Consequently the name as well as the pathologic change to which it applies is often ignored. However, the discerning clinician uses skin disease as a clue to the nature of the host's response to the local or underlying systemic disease processes. The purpose of this review is to analyze an intimate relationship of skin and systemic disease.

Lupus erythematosus is perhaps one of the best examples of a systemic disorder in which a careful assessment of the cutaneous component of the disease can yield valuable diagnostic and prognostic information. This review will describe the gross, histologic and immunopathologic features of lupus skin disease, emphasizing the relationship between the cutaneous manifestations and certain systemic aspects of clinical syndromes within the LE spectrum. Immunologic abnormalities that characterize these syndromes will be described. Finally, possible pathogenic mechanisms of the specific types of LE skin disease will be proposed as explanation of how the skin may reflect the state of immunologic imbalance in lupus erythematosus.

In order to put the relationship between certain clinical and immunologic abnormalities of LE into the proper perspective, it is necessary to summarize our current understanding of lupus erythematosus and to review briefly the relationship between autoimmunity and abnormalities in the intrinsic controls of the immune response.

II.

A REVIEW OF BASIC LYMPHOCYTE BIOLOGY[1] AND THE CURRENT CONCEPTS OF IMMUNOREGULATION

Lymphocyte precursors arise as undifferentiated pluripotential cells in the bone marrow (fig. 1). After leaving the bone marrow, one of two different routes of differentiation may be followed. They may go to the liver, a recently proposed mammalian equivalent to the bursa of Fabricius[2] where they differentiate into B-lymphocytes, or this early differentiation process may occur within the bone marrow. These B-lymphocytes then go to the peripheral lymphoid tissue in the gut, the lymph nodes and the spleen where they participate in the formation of germinal centers. B-lymphocytes or B-cells have the function of carrying out aspects of humeral immunity. They do this by the production and secretion of immunoglobulin antibody products. B-cells are characterized by the fact

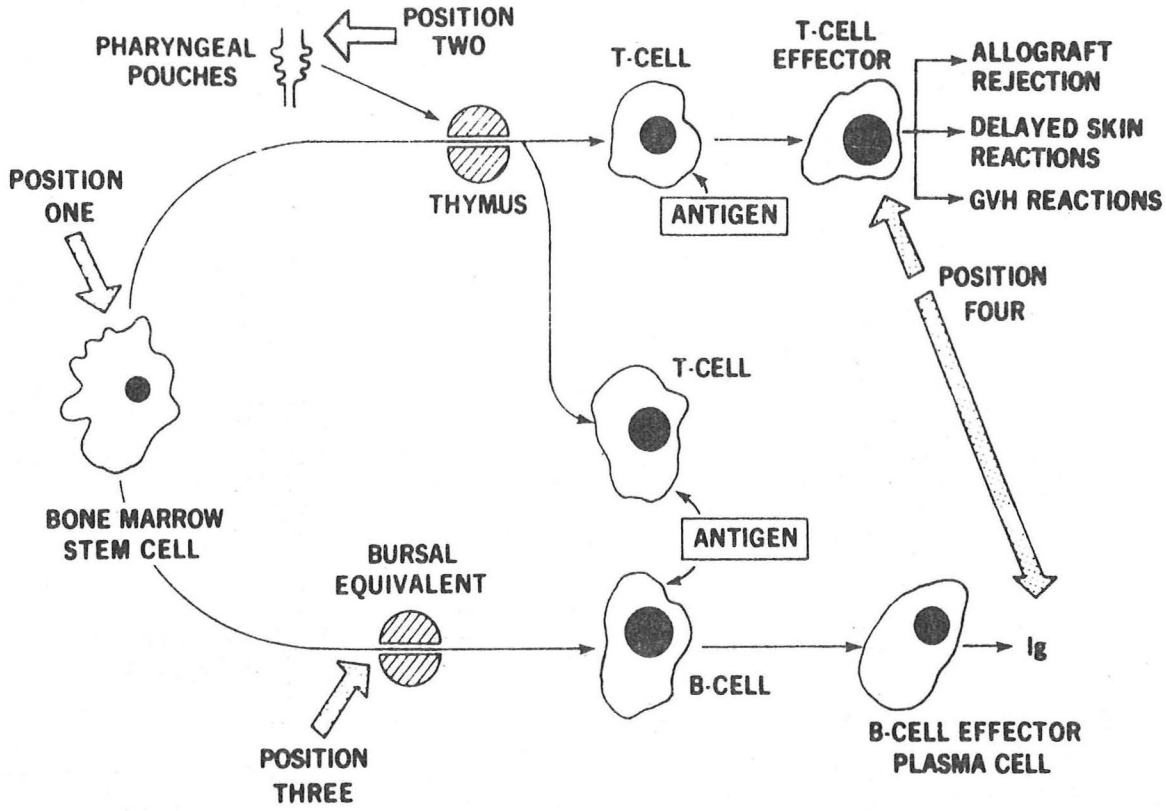

Fig. 1. Scheme of immunodifferentiation, cellular interaction and cellular biosynthesis

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[1]Cooper, M.D., Perey, D.Y., Peterson, R.D.A. and Good, R.A. The two component concept of the lymphoid system. Immunologic Deficiency Disease in Man, ed. D. Bergsma, R.A. Good, New York, National Foundation Press, 1968.

[2]Owen, J.J., Cooper, M.D., Raff, M.C. In vitro generation of B lymphocytes in mouse foetal liver, a mammalian "bursa equivalent". Nature 249:361-363, 1974.

that they maintain in their surface membranes representatives of the immunoglobulin of the specific antibody that they secrete.[3,4]

The other route of differentiation for these bone marrow precursor cells is to physically migrate through the thymus where they come under some very important microenvironmental influences. In the thymus gland, products produced by thymic epithelium, including putative thymic hormone (thymosin),[5,6,7] contribute to the differentiation of these cells. When they emerge from the thymus they have a totally different set of characteristics and perform and subserve a different set of immunologic functions. They also migrate to peripheral lymphoid organs (spleen and lymph nodes) where they occupy anatomically specific areas - and where they take on the characteristic functions of T-lymphocytes. Approximately 75-80% of the lymphocytes in the peripheral blood are T-lymphocytes. The T-lymphocytes do not have antibody production as one of their responsibilities, but rather, they mediate aspects of cellular immunity. These include delayed hypersensitivity, allograft rejection, and immune surveillance against malignancy. They do this not by the production of antibodies but by the production of a variety of soluble factors called lymphokines which include many factors such as blastogenic factor, macrophage inhibitory factor, cytotoxic factor, etc. (Table 1).[8] They do not have surface immunoglobulin detectable by ordinary methods, but T-cells can be identified by the presence of surface receptors for

Table 1 – Mediators Elaborated by Activated Lymphocytes

1. Macrophage migration inhibitory factor (MIF)
2. Polymorphonuclear leukocyte inhibitory factor (LIF)
3. Macrophage-activating factor (indistinguishable from (MIF)
4. Chemotactic factors for: macrophages, neutrophils, eosinophils, and lymphocytes
5. Cytotoxic factor or lymphotoxin
6. Growth inhibitory factors: clonal inhibitory factor and proliferation inhibitory factor
7. Skin reactive factors
8. Blastogenic or mitogenic factors for lymphocytes
9. Interferon
10. Transfer factor

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[3]Pernis, B., Farris, L., Awante, L. Immunoglobulin spots on the surface of rabbit lymphocytes. J. Exp. Med. 132:1001-1018, 1970.

[4]Froland, S., Natvig, J.B., Berdal, P. Surface-bound immunoglobulin as a marker of B lymphocytes in man. Nature (New Biol) 234: 251, 1971.

[5]Dardenne, M., Papiernik, M., Bach, J-F and Stutman, O. Studies on thymus products. III. Epithelial origin of the serum thymic factor. Immunology 27:299-304, 1974.

[6]Basch, R.S. and Goldstein, G. Induction of T-cell differentiation in vitro by thymin, a purified polypeptide hormone of the thymus. Proc. Nat. Acad. Sci. USA 71:1474-1478, 1974.

[7]Trainin, N. Thymic hormones and the immune response. Physiological Reviews 54:272-315, 1974.

[8]Dumonde, D.C., Wolstencroft, R.A., Panayi, G.S., Matthew, M., Morley, J., Howson, W.T. Lymphokines: non-antibody mediator of cellular immunity generated by lymphocyte activation. Nature (Lond) 224:38-42, 1969.

sheep red blood cells. Whether they, in fact, have surface immunoglobulin is a somewhat controversial point, but certainly by immunofluorescence one does not find Ig on the surface of these cells.

T-CELL REGULATION OF THE HUMORAL RESPONSE[9,10]

In addition to subserving certain effector functions, such as delayed hypersensitivity, T-cells have another very important function. T-cells regulate and control the immune response. They are, according to Gershon, the grand conductor of the immunologic orchestra. The first regulatory function for T-lymphocytes was described by Henry Claman[11] who observed that T-cells were required along with B-cells to get a maximum antibody response to sheep red blood cells. This function has subsequently been termed "helper function". More recently, considerable evidence has been presented to suggest that T-cells also have a negative influence on B-cell function[12]. This phenomenon has been called T-cell suppression. So T-cells can act in a positive way or a negative way that can either help or suppress antibody production by B-cells. On the other hand, B-cells themselves apparently do not exert much discrimination. Indeed, there is considerable evidence that normal individuals have B-cells in their circulation that are capable of mounting an immune response to autoantigens such as thyroglobulin[13] and DNA[14]. Therefore, the concept that the elimination of self-recognition lymphocytes during fetal development as suggested by Burnet and Fenner[15] in the clonal selection theory, cannot provide a full explanation for the apparent immunologic nonreactivity against self-antigens *in vivo*. It now seems likely that self-tolerance to many autoantigens is maintained by a state of active autoregulation in which autoantigen recognition cells are continuously inhibited by suppressor T-cells[16].

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[9]Dutton, R.W. and Hunter. The effects of mitogen-stimulated T cells on the response of B cell to antigen and the mechanism of T cell stimulation of the B cell response. In Cellular Selection and Regulation in the Immune Response, Ed. G.M. Edelman, Raven Press, New York, 1974.

[10]Gershon, R.K. T cell control of antibody production. In Contemporary Topics in Immunobiology, Vol. 3, pp. 1040, Ed. M.D. Cooper and N.L. Warner, Plenum Press, New York, 1974.

[11]Claman, H.N. and Chaperon, E.A. Immunologic Complementation between Thymus and Marrow Cells - A Model for the Two-Cell Theory of Immunocompetence. Transpl. Rev. 1:92, 1969.

[12]Gershon, R.K. and Kondo, K. Cell interactions in the induction of tolerance: The role of thymic lymphocytes. Immunology 18:723-735, 1970.

[13]Bankhurst, A.D., Torrigiani, G., Allison, A.C. Lymphocytes binding human thyroglobulin in healthy patients and its relevance to tolerance for autoantigens. Lancet 1:226-230, 1973.

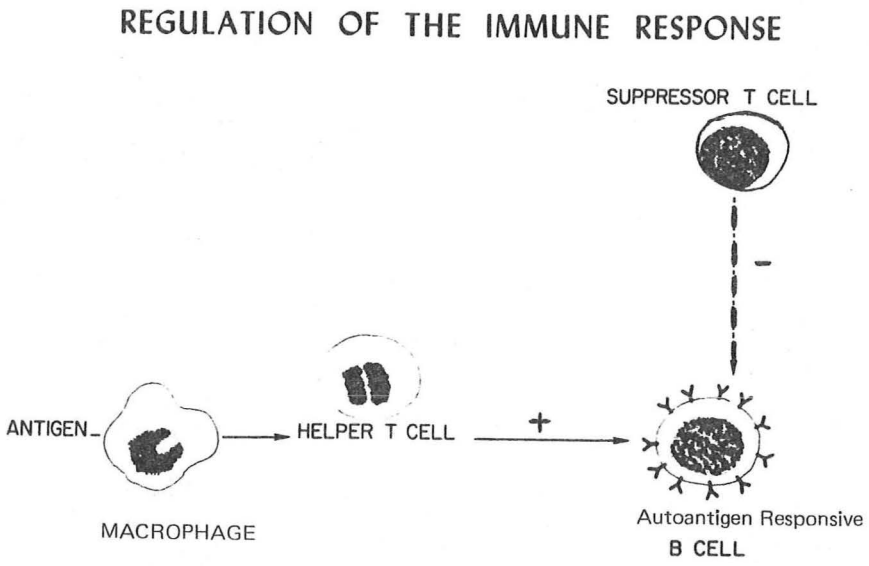
[14]Bankhurst, A.D. and Williams, R.C. DNA-binding lymphocytes in systemic lupus erythematosus. Clin. Res. 23:103A, 1975.

[15]Burnet, F.M. and Fenner, F. The Production of Antibodies, 2nd ed. Melbourne, Australia, MacMillan and Co., 1949.

[16]Allison, A.C. Mechanisms of tolerance and autoimmunity. Ann. Rheum. Dis. 32:283-293, 1973.

Apparently, the regulatory mechanism does not reside with the B-cell but with the play of influence that comes onto and into the surface membrane of that B-cell largely through the action of T-cells and T-cell factors (fig. 2).

FIGURE 2



III.

PROPOSED IMMUNOLOGIC DEFECT IN SLE

Recently it has been proposed that the immunologic abnormality in patients with SLE and in the lupus-like disease of New Zealand (NZ) mice is due to deficiencies in T-cell dependent immunoregulatory mechanisms, leading to a loss of self-tolerance and a state of immune imbalance. This imbalance is characterized by excessive B-cell activity and antibody production and depressed T-cell activity or cell mediated immunity. The evidence for this concept has come largely from animal studies, particularly those involving the New Zealand (NZ) mice.[17]

NEW ZEALAND MOUSE DISEASE: A MODEL FOR SLE.

The New Zealand black (NZB) and NZB/W F_1 hybrid mice are inbred-mouse strains with autoimmune diseases remarkably similar to SLE.[18,19,20] Genetic, immunologic and viral factors are all implicated in their disease.[21,22] The NZB parental strain develops Coombs-positive hemolytic anemia, membranous glomerulonephritis, skin lesions and lymphoid infiltration of many internal organs. Many of the parental New Zealand white (NZW) mice have chronic destructive skin lesions[23] but otherwise have no overt autoimmune disease. The cross NZB-by-NZW leads to a first generation hybrid (NZB/W F_1) which develops antinuclear antibodies[24] and antibodies to native DNA (nDNA),[25] subepidermal immunoglobulin deposits in

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[17]Talal, Norman. Autoimmunity and lymphoid malignancy in New Zealand Black Mice. In: Prog. in Clinical Immunol. ed. R.S. Schwartz 2:101-120 Grune and Stratton, New York, 1974.

[18]Howie, J.B., Helyer, B.J. The immunology and pathology of NZB mice. Adv. Immunol. 9:215-266, 1968.

[19]Mellors, R.C. Autoimmune and immunoproliferative diseases of NZB/B1 and hybrids. Int. Rev. Exp. Pathol. 5:217-252, 1966.

[20]Lambert, P.H., Dixon, F.J. Pathogenesis of the glomerulonephritis and NZB/W mice. J. Exp. Med. 127:507-512, 1968.

[21]Talal, N. Immunologic and viral factors in the pathogenesis of systemic lupus erythematosus. Arthritis Rheum. 13:887-894, 1970.

[22]Lambert, P.H. and Dixon, F.J. Genesis of antinuclear antibody in NZB/W mice: role of genetic factors and of viral infections. Clin. Exptl. Immunol. 6:829-839, 1970.

[23]de Vries, M.J. and Hijmans, W. Pathological changes of thymic epithelial cells and autoimmune disease in NZB, NZW and (NZB x NZW) F_1 mice. Immunol. 12:179-195, 1967.

[24]Norins, L.C. and Holmes, M.C. Antinuclear factor in mice. J. Immunol. 93:148-154, 1964.

[25]Steinberg, A.D., Pincus, T., Talal, N. DNA-binding assay for detection of anti-DNA antibodies in NZB/NZW F_1 hybrid mice. J.J. Immunol. 114:133-137, 1975.

apparently normal skin[26] and immune complex mediated glomerulonephritis.[20,27] A Gross-type murine leukemia virus is involved in the immune complex glomerulonephritis.[28] However, most of the antibody eluted from the kidney reacts with nuclear antigens[29] and as in human lupus erythematosus, both nDNA and anti-nDNA are present in the glomerular eluate.[27,29]

The immunologic dysfunction in New Zealand mice can best be characterized as an immunologic imbalance with excessive B-cell activity and depressed T-cell activity. The earliest evidence of this immunologic abnormality appears in the thymus and the thymus derived lymphocytes. These T-cell and thymic abnormalities develop before the onset of autoantibody production by B-cells, which begins at 3 to 4 months of age.

Long before the concept of suppressor T-cells emerged, deVries and Hijmans,[23] described a deficiency of differentiated epithelial cells in the thymus of these NZ mouse strains. These morphologic abnormalities in the thymus were identified in newborn animals. The authors suggested that preventing auto-reactivity of lymphoid cells was a possible function of the thymus. In NZB/W mice thymectomized at birth, the spontaneous development of antinuclear antibodies is considerably enhanced and in some other inbred strains of mice, neonatal thymectomy induces the appearance of antinuclear antibody.[30,31,32]

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[26]Gilliam, J.N., Hurd, E.R., Ziff, M. Subepidermal deposition of immunoglobulin in (NZB x NZW) F_1 hybrid mice. J. Immunol. 114:133-137, 1975.

[27]Koffler, D., Schur, P.H., Kunkle, H. Immunological studies concerning the nephritis of systemic lupus erythematosus. J. Exp. Med. 126:607-623, 1967.

[28]Mellors, R.C., Shirai, T., Aoki, T., et al. Wild-type gross leukemia virus and the pathogenesis of the glomerulonephritis in New Zealand mice. J. Exp. Med. 133:113-132, 1971.

[29]Dixon, F.J., Oldstone, M.B.A., Tonietti, G. Pathogenesis of immune complex glomerulonephritis of New Zealand mice. J. Exp. Med. 134 (suppl): 65-71, 1971.

[30]Brezin, C., Cannat, A. and Sekiguchi, M. The presence of serum antinuclear antibodies in mice thymectomized at birth. Rev. Franc. Clin. Biol. 10:839, 1965.

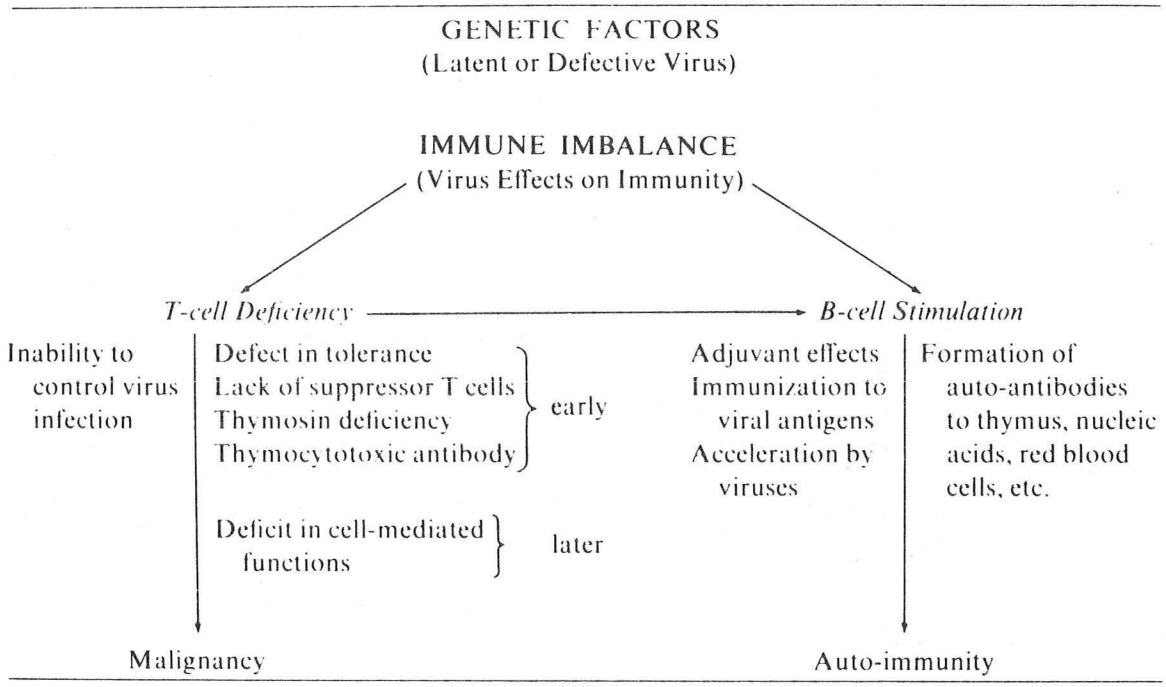
[31]Howie, J.B. and Helyer, B.J. Experimental and clinical studies. In: The Thymus. G.E.W. Wolstenholme and R. Porter, eds. Little, Brown, Boston, 1966, p. 360.

[32]Taegue, P.O., Friou, G.J., Myers, L.L. Antinuclear antibodies in mice. I. Influence of age and possible genetic factors on spontaneous and induced responses. J. Immunol. 101:791, 1968.

Most recently, a deficiency of suppressor T-cells in young NZB/W mice has been suggested by several studies,[33,34] and Bach and co-workers[35] have found evidence of an early loss of thymic hormone (thymosin) activity in these animals. Studies by Talal and associates[36] have shown that thymosin treatment of NZB/W mice from 2 weeks of age preserved T-cell suppressor function and delayed the formation of antibodies to DNA and RNA.

These results suggest that a deficiency of thymic hormone may contribute to the suppressor T-cell loss and emergence of auto-antibody producing B-cells. A proposed concept of pathogenesis is presented schematically in Table 2. As a consequence of genetic or viral factors, a state of immune imbalance arises with its consequent changes in T and B cell functions. The ultimate pathological consequences are lymphoid malignancy and autoimmunity.

TABLE 2



[33]Allison, A.C., Denman, A.M., Barnes, R.D. Cooperating and controlling functions of thymus-derived lymphocytes in relation to autoimmunity. Lancet 2:135-140, 1971.

[34]Hardin, J.A., Chused, T.M., Steinberg, A.D. Suppressor cells in the graft-vs-host reaction. J. Immunol. 111:650, 1973.

[35]Bach, J.F., Dardenne, M., Salomon, J.C. Studies of thymus products. IV Absence of serum 'thymic activity' in adult NZB and (NZB x NZW) F_1 mice. Clin. Exp. Immunol. 14:247-256, 1973.

[36]Talal, N., Dauphinee, M., Pillarisetty, R. and Goldblum, R. Effect of thymosin on thymocyte proliferation and autoimmunity in NZB mice. Ann. N.Y. Acad. Sci. 249:438-449, 1975.

COMPARISON OF NZ MOUSE DISEASE WITH LUPUS ERYTHEMATOSUS.

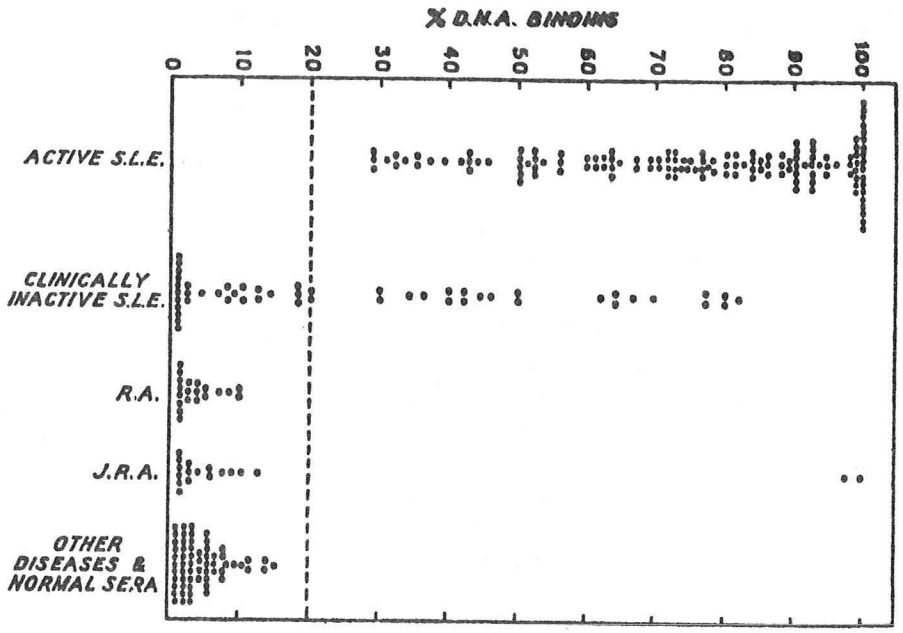
The most striking similarity between human SLE and disease in New Zealand mice is the formation of antibodies to native or double stranded DNA (anti-nDNA). Anti-nDNA antibodies have been found to be the most specific of all auto-antibodies for lupus and to correlate best with disease activity, hypocomplementemia and proliferative glomerulonephritis (fig. 3).[37-45] Steinberg and Talal[25] found

FIGURE 3

Scattergram showing % D.N.A.-binding activity in 185 serum samples from 86 S.L.E. patients (divided into clinically active and inactive groups).

The 2 patients at first thought to have juvenile arthritis with high titers of anti-D.N.A. antibodies both subsequently developed S.L.E. with striking renal involvement.

From Hughes. (ref. 39)



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[37]Schur, P.H., Sandson, J. Immunologic factors and clinical activity in systemic lupus erythematosus. N. Engl. J. Med. 278: 533-537, 1968.

[38]Pick, A.I., Levo, Y. and Weiss, C.H. The value of anti-DNA antibody titers in the early diagnosis, treatment and follow-up of systemic lupus erythematosus. Isreal J. Med. Sci. 10:725-730, 1974.

[39]Hughes, G.R.V. Significance of anti-DNA antibodies in systemic lupus erythematosus. Lancet 2:861, 1971.

[40]Webb, J., and Whaley, K. Evaluation of the native DNA-binding assay for DNA antibodies in systemic lupus and other connective tissue diseases. Med. J. Aust. 2:324-328, 1974.

[41]Webb, J., Whaley, K. and Lee, P. Clinical significance of native DNA antibodies in systemic lupus erythematosus and other connective tissue diseases. Scot. Med. J. 19:171-175, 1974.

[42]Hughs, G.R.V. The diagnosis of systemic lupus erythematosus. Brit. J. Hematol. 25:409-413, 1973.

[43]Pincus. T., Schur, P.H., Rose, J.A., et al. Measurement of serum DNA-binding activity in systemic lupus erythematosus. N. Engl. J. Med. 281:701-705, 1969.

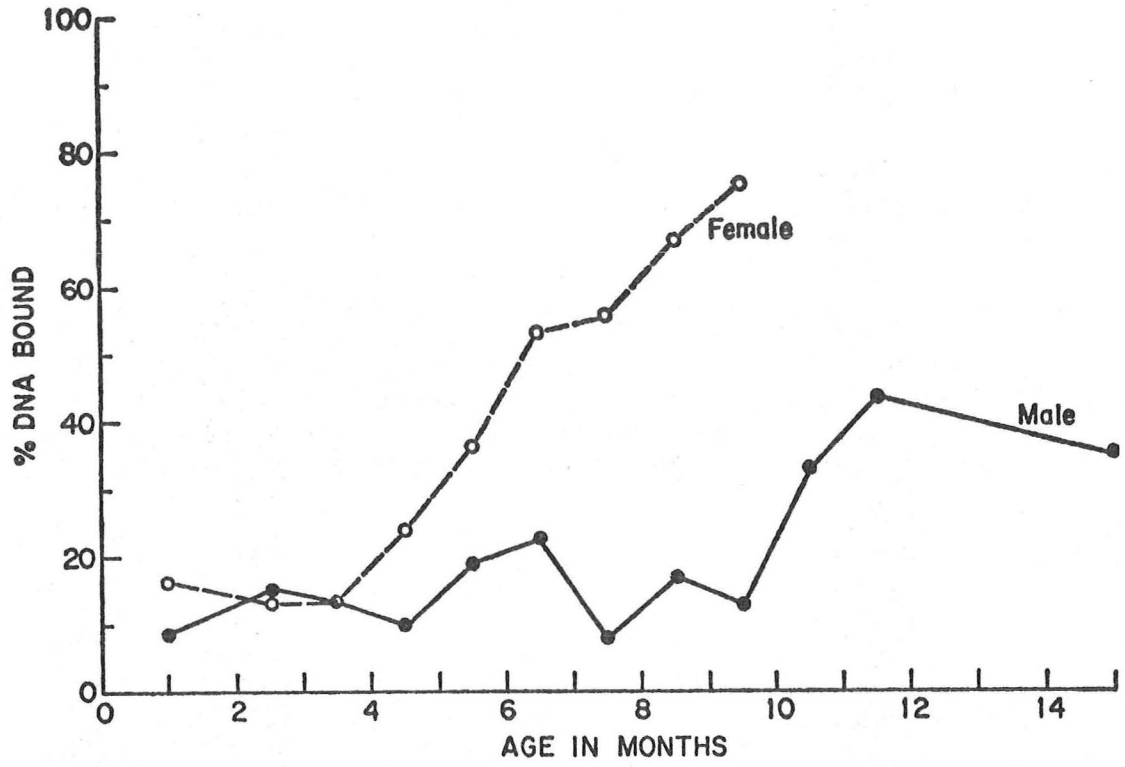
[44]Tan, E.M., Schur, P.H., Carr, R.I., et al. Deoxyribonucleic acid (DNA) and antibodies to DNA in the serum of patients with systemic lupus erythematosus. J. Clin. Invest. 45:1732-1740, 1966.

[45]Koffler, D., Carr, R., Agnello, V. et al. Antibodies to polynucleotides in human sera: antigenic specificity and relation to disease. J. Exp. Med. 134:294-312, 1971.

that NZB/W mice develop anti-nDNA antibodies which increase progressively with age (fig. 4). It is notable that with few exceptions, only patients and animals that spontaneously develop these remarkably similar autoimmune diseases produce antibodies to double-stranded (native) DNA. The antibody titers are significantly higher in the female NZB/W mice compared to the male animals. This observation correlates with the more severe renal disease and significantly shorter life-span of the female animals (See fig. 5).[46, 18] As mentioned before, anti-nDNA antibodies have been identified in the eluates from both NZB/W[20,29] and SLE kidneys.[27] These and other findings suggest that complement fixing nDNA:anti-nDNA complexes are almost certainly the predominant etiological factor in the diffuse proliferative nephritis of patients with SLE and NZB/W mice.

The reasons for the peculiar specificity of anti-nDNA antibodies for SLE remains unknown. DNA may be found in the plasma in a variety of situations associated with cellular breakdown, such as cytotoxic therapy in leukemia patients and in extensive burns.[47]

FIGURE 4



Anti-nDNA antibodies in male and females NZB/W F_1 mice.
From Steinberg, Pincus & Talal (ref. 25)

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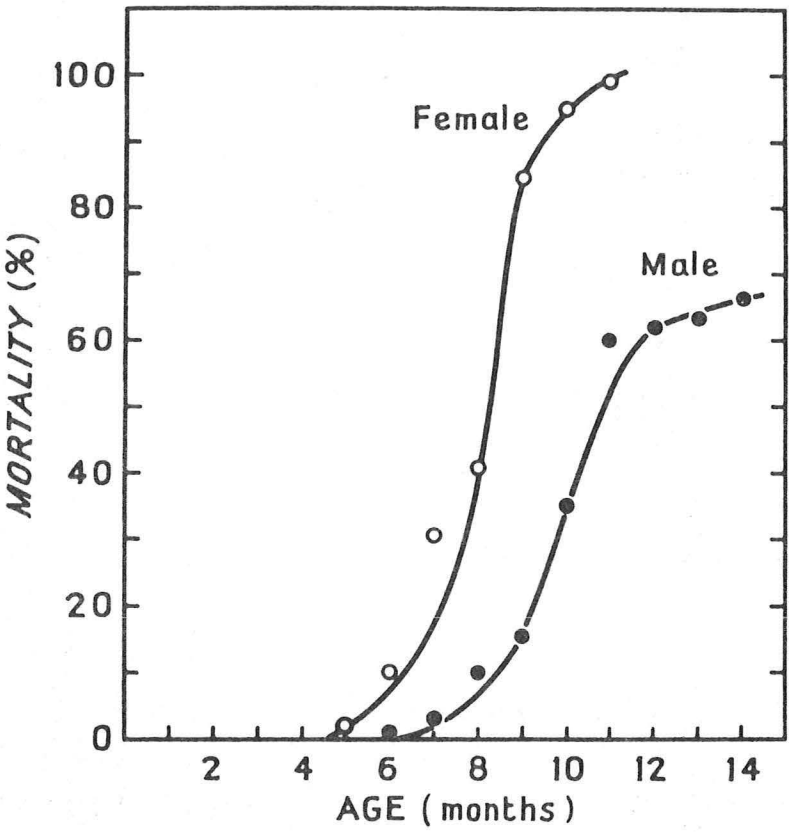
[46]Denman, A.M., Denman, E.J. and Holborow, E.J.: Lancet 2:841-843, 1966.

[47]Hughes, G.R.V., Cohen, S.A., Lightfoot, R.W., Meltzer, J.I. and Christian, C.L. The release of DNA into serum and synovial fluid. Arthritis Rheum. 14:259-266, 1971.

FIGURE 5



Cumulative mortality in 55 male and 45 female (N.Z.B. × N.Z.W.) F 1 hybrid mice.

From: Denman, A.M., Denman, E.J., and Holborrow, E.J.

Although the DNA antibodies cross-react with DNA from many sources, the phenomenon cannot, at present, be attributed to an outside source of DNA, such as a viral infection. The viruses that have been implicated in SLE have, in general, been RNA in type.[48, 49] There is evidence for an autogenous source of DNA, as small amounts of native DNA have been detected in normal human plasma.[50]

While RNA antibodies and antibodies to denatured DNA are also found in SLE, these are less specific for the disease[51] and have no particular pathogenic significance. Native or double stranded DNA is a poor immunogen and experimental attempts to induce anti-nDNA antibodies have had limited success.[52, 53] However, under special circumstances some mouse strains can be induced to produce anti-nDNA antibodies. For example, animals from certain inbred strains develop anti-DNA antibodies after repeated injections of bacterial lipopolysaccharides (LPS).[54] The DNA antibodies follow the appearance in the circulation of free DNA that is released from an unknown source after the LPS injection. The athymic or nude (nu/nu) mice develop DNA antibodies spontaneously.[55] These animals also develop renal disease. However, because of their short life span, progression to the advanced stage of disease seen in the NZB/W mice is not observed. These experiments suggest that the spontaneous development of anti-DNA antibodies may be due to the release of endogenous DNA in a host that is naturally, or rendered responsive to this type of antigen.

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[48]Phillips, P.E., Christian, C.L. Myxovirus antibody increases in human connective tissue disease. Science 168:982-984 1970.

[49]Hollinger, F.B., Sharp, J.T., Lidsky, M.D., Rawls, W.E. Antibodies to viral antigens in systemic lupus erythematosus. Arthritis Rheum. 14:1-11, 1971.

[50]Hunter, D., Dilley, J., Holman, H.R. Isolation and characterization of DNA, RNA and immune complexes from systemic lupus erythematosus and normal plasma. Arthritis Rheum. 16:554, 1973 (Abst).

[51]Koffler, D., Carr, R.I., Agnello, V., Fiezi, T. and Kunkel, H.G. Antibodies to polynucleotides: Distribution in human serums. Science 166:1648-1649, 1969.

[52]Plescia, O.J., Braun, W. and Palczuk, N.C. Production of antibodies to denatured deoxyribonucleic acid (DNA). Proc. Nat. Acad. Sci. U.S.A. 52:279, 1964.

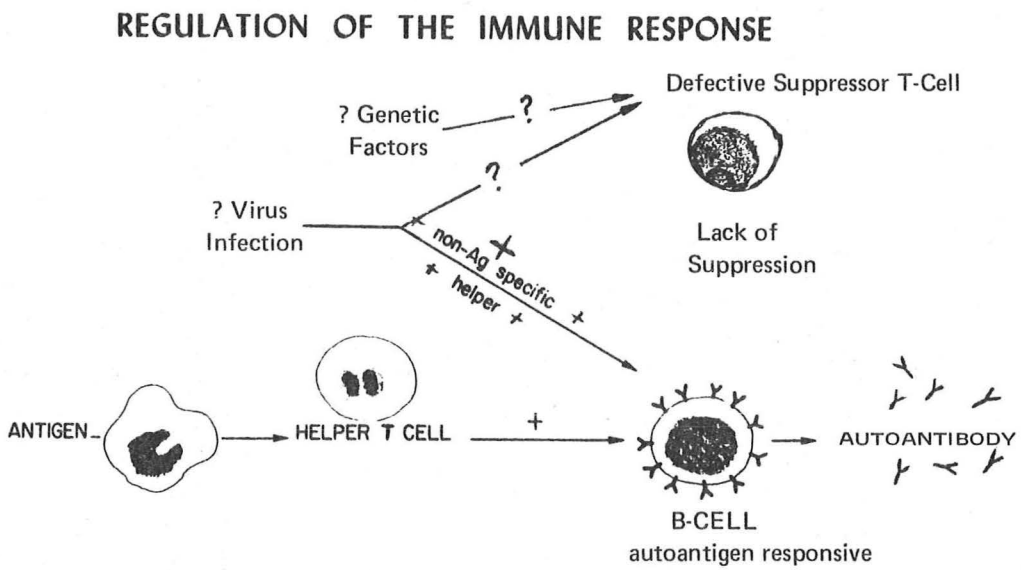
[53]Erlanger, B.F. and Beiser, S.M. Antibodies specific for ribonucleosides and ribonucleotides and their reaction with DNA. Proc. Nat. Acad. Sci. U.S.A. 52:68, 1964.

[54]Fournie, G.J., Lambert, P.H. and Miescher, P.A. Release of DNA in circulating blood and induction of anti-DNA antibodies after injection of bacterial lipopolysacchardies. J. Exp. Med. 140:1189-1206, 1974.

[55]Morse, H.C., Steinberg, A.D., Schur, P.H. and Reed, N.D. Spontaneous "autoimmune disease" in nude mice. J. Immunol. 113:688-697, 1974.

It has recently been shown that mice have a genetic X-linked factor that influences the immune response to synthetic polynucleotides.[22] In humans, there is also some evidence that the X chromosome carries determinants of serum immunoglobulin[56] and antibody levels.[57] Therefore, the appropriate X-linked genetic factors may play a permissive role in the development of anti-nDNA antibodies. One may speculate that in individuals with additional genetic or viral factors, the combination of abnormal T-cell control over the ever-present autoantigen responsive B-cells, and an autogenous source of DNA may produce anti-DNA antibodies in sufficient quantity to yield immune-complex disease (fig. 6).

FIGURE 6



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[56]Grundbacher, F.J. Human X chromosome carries quantitative genes for immunoglobulin M. Science 176:311-312, 1972.

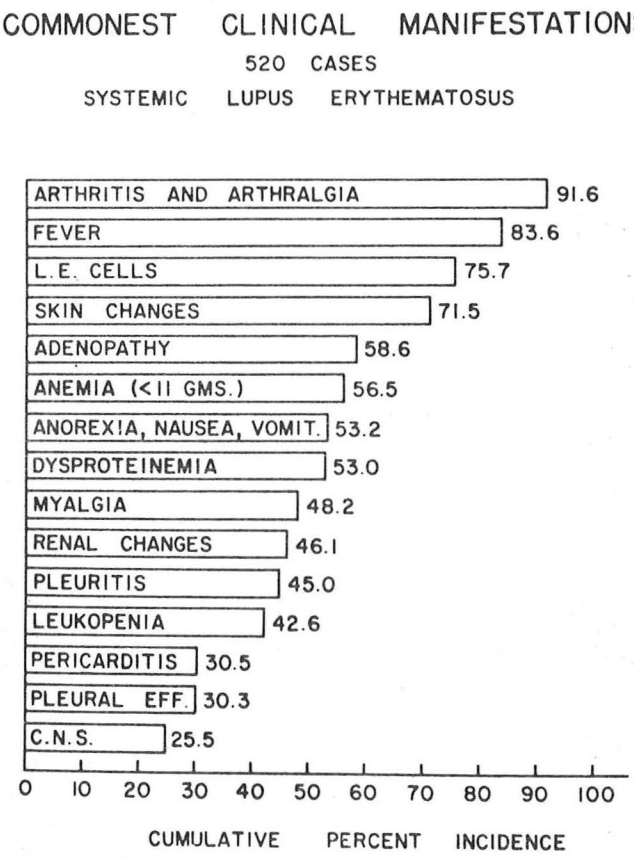
[57]Rhodes, K., Scott A., Markham, R.L. et al. Immunological sex differences. A study of patients with rheumatoid arthritis, their relations and controls. Ann. Rheum. Dis. 28:104-119, 1969.

IV

PATHOLOGY AND IMMUNOPATHOLOGY OF THE SPECIFIC OR DIAGNOSTIC LE SKIN LESIONS

Skin involvement is a major feature of lupus erythematosus. In 520 cases of SLE reported by Dubois and Tuffanelli,[58] skin changes were observed in over 70% (Fig. 7). Other large studies[59,60] have reported an incidence of disease-related cutaneous abnormalities in 75 to 80% of the cases. It has also been established that skin lesions cause the second most common initial

FIGURE 7



From: Dubois and Tuffanelli (ref. 58)

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[58] Dubois, E.L. and Tuffanelli, D.L. Clinical manifestations of systemic lupus erythematosus. JAMA 170:104-111, 1964.

[59] Estes, D. and Christian, C.L. The natural history of systemic lupus erythematosus by prospectus analysis. Medicine 50:85-95, 1971.

[60] Tay, C.H. Cutaneous manifestations of systemic lupus erythematosus. Aust. J. Derm. 11:30-41, 1970.

manifestation of SLE (See Table 3).

TABLE 3

Initial Manifestation of SLE in 150 Patients

Manifestation	Percent of patients
Arthritis or arthralgia	53
Cutaneous	19
Discoid Lesions 9%	
Malar Rash 9	
Other 1	
Nephritis	6
Fever	5
Epileptiform seizures	3
Raynaud's phenomenon	3
Pleurisy	3
Pericarditis	2
Anemia	2
Thrombocytopenic purpura	2
Biologic false positive Wassermann reaction	1
Jaundice	1

From: Estes and Christian (ref. 59)

These cutaneous manifestations can be classified as LE-specific or nonspecific (nondiagnostic). (See Tables 4 and 5).

TABLE 4

CLINICAL FEATURES OF THE LE SPECIFIC OR DIAGNOSTIC SKIN LESIONS IN LUPUS ERYTHEMATOSUS

I. Inflammatory dermal lesions with characteristic epidermal involvement.
   - A. Acute cutaneous LE (butterfly eruption) (60%)†
     Principal clinical features:
     1. Transient facial erythema and edema lasting hours to days.
     2. Resolution leaving postinflammatory hyperpigmentation but no scarring.
     3. Always evidence of extracutaneous involvement.
     4. Frequent correlation with a flare of systemic disease
     5. Frequently have elevated levels of anti-nDNA antibodies and renal disease.
     6. Usually subepidermal Ig in lesional skin and commonly in normal skin (pos LBT).
   - B. Subacute cutaneous LE
     Principal clinical features:
     1. Lesions more persistent, lasting weeks or months.
     2. Widespread distribution.
     3. Upon resolution, some residual telangiectasia but no atrophy.
     4. Association with extracutaneous involvement but skin disease may be the major and occasionally the only manifestation of LE.
     5. Results of anti-nDNA test and normal skin IF†† – variable; lesional skin IF – subepi Ig usually present.
   - C. Chronic cutaneous LE (chronic discoid LE or DLE) (15-25%)
     Principal clinical features:
     1. Lesions persist for months or years.
     2. Healing with scarring and atrophy.
     3. Usually confined to the head and neck – may occasionally be widespread.
     4. Occurrence most often without associated extracutaneous disease.
     5. Low titers of antinuclear and anti-nDNA antibodies demonstrable in a minority of patients with these lesions.
     6. Subepidermal Ig commonly found in lesions but rarely present in normal skin.
     7. Rare, if ever, simultaneous occurrence of active chronic DLE skin lesions and lupus nephritis.

II. Inflammatory lesions of the deep dermis and subcutaneous fat.
   - A. Lupus Panniculitis (LE profundus) (2%)
     Principal clinical features:
     1. Chronic, relatively non-tender, firm, subcutaneous nodules located over buttocks, thighs, upper arms, breast and cheeks.
     2. Erythematous but not scaley, possibly sclerotic or ulcerating overlying skin
     3. Presence of overt SLE in approximately 1/2 cases
     4. Typical DLE lesions often present
     5. Skin IF findings:
        a) normal skin – variable; subepi. Ig indicative of occult systemic disease
        b) lesional skin – vascular Ig deposits usually present

†(%) percentage incidence in SLE

††IF, immunofluorescence

TABLE 5

CLINICAL FEATURES OF THE NONSPECIFIC SKIN LESIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS

I. Vascular lesions (25-30%)†
   A. Lupus panniculitis (Lupus profundus) (1-2%)††
   B. Dermal vasculitis (10-20%)
   C. Thrombophlebitis (5%)
   D. Raynauds (15-20%)
   E. Livedo reticularis (10%)
   F. Chronic ulcers (2-8%)
   G. Rheumatoid nodules (5-10%)
   H. Peripheral gangrene (<5%)
   I. "Dagos-like" dermal infarcts (rare)†††

II. Mucous membrane lesions (7%)

III. Pigmentary abnormalities (10%)

IV. Sclerodactyly (10%)

V. Alopecia (40-60%)
   1. Frontal ("Lupus Hair")
   2. Diffuse
   3. Focal scarring (DLE)
      non-scarring (? alopecia areata)

VI. Calcinosis cutis (rare, except in lupus panniculitis)

VII. Urticaria and Erythema multiforme (7-14%)

VIII. Bullous lesions (rare)

†(%), estimated incidence in SLE

††lesion may be diagnostic (see Table 4)

†††Dubin, H.V., Stawiski, M.A.: Systemic Lupus Erythematosus Resembling Malignant Atrophic Papulosis. Arch. Int. Med. 134:321-323, 1974 (112)

CLINICAL FEATURES OF LE SPECIFIC OR DIAGNOSTIC SKIN LESIONS

Dermal inflammatory lesions with characteristic epidermal involvement can be recognized clinically and histologically as cutaneous LE. The dermal inflammatory lesions may be chronic, subacute or acute in nature, and the morphology of the lesion correlates with these time-related stages.

Chronic cutaneous LE or DLE is characterized by erythema, atrophy telangiectasia, scaling and both hyper- and hypopigmentation. The lesions are usually sharply circumscribed, pink to violacious in color and have central areas of scarring and peripheral areas of active inflammation. These lesions usually persist for months or years.[60,61] Upon healing, telangiectasias may be the

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[61]Dubois, E.L. (ed). Lupus Erythematosus: A review of the current status of discoid and systemic lupus erythematosus and their variants, ed. 2. Los Angeles, University of Southern California Press, 1974.

most prominent feature, but areas of atrophy and scarring are invariably present. Hyper- and hypopigmentation are especially pronounced in patients with black skin. Follicular dilatation with keratin plugging is usually seen. The lesions may be localized to the malar areas, nose or forehead. They are commonly seen in light exposed areas. The ears are often involved. The lesions tend to spread with an active peripheral margin, and heal with an atrophic, often depigmented, central scar. Occasionally these lesions are scattered over wide areas of the body, resulting in severe disfigurement. A hypertrophic, hyperkeratotic variety occurs which may look psoriasiform.

This chronic form of infiltrative, destructive skin lesion, commonly known as chronic discoid lupus or DLE, is often the only manifestation of lupus, and probably less than 5 to 10% of those patients with DLE lesion as the only manifestation of LE will subsequently develop overt evidence of extracutaneous involvement. However, 15 to 25% of patients with well documented systemic lupus have typical discoid type skin lesions at some time during the course of their disease[58,59] Patients with systemic lupus with this form of chronic destructive skin lesion have a more benign course and rarely develop severe renal disease.[62] Moreover, SLE patients occasionally develop discoid skin lesions after entering a phase of remission of their systemic disease.[63] Scott and Rees[64] concluded after following the course of 118 LE patients over an 8 year period that SLE patients with discoid-type skin lesions have a mild disease with a good prognosis. Such patients appear resistant to the development of the more serious immune complex mediated form of SLE that is often accompanied by severe renal disease.[62]

The lesions of subacute cutaneous LE are characterized by erythematous plaques often with minimal or absent scale. These lesions are also commonly located on the forehead, nose, cheeks, "V" area of the neck and back of the hands. They may occur in a localized or a disseminated form. The localized form may be impossible to differentiate from an early lesion of DLE. These lesions are less persistent than DLE, however, and usually resolve within a period of several weeks or a few months. The distribution of the lesions is symmetrical and often coincides with light exposed areas. In time, some superficial scaliness may appear, and the eruption may then similate acute guttate psoriasis. This type of cutaneous involvement usually occurs in patients with systemic disease. However, it may occasionally be the manor manifestation of LE with little or no evidence of extracutaneous disease.

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[62]Prystowsky, S.D. and Gilliam, J.N. Correlation of Clinical features with laboratory findings in lupus erythematosus: Discoid lupus erythematosus as a part of a larger disease spectrum. Arch. Dermatol. (in press).

[63]Ganor, S. and Sagher, F. Systemic lupus erythematosus changing to the chronic discoid type. Dermatologica 125:81-92, 1962.

[64]Scott A. and Rees, E.G. The relationship of systemic lupus erythematosus and discoid lupus erythematosus. Arch. Dermatol. 79:422-435, 1959.

Acute cutaneous LE or the typical butterfly rash occurs at some time in 50 to 60% of SLE patients.[58,59,60] The acute dermal inflammatory lesion is marked by edema and erythema. This lesion appears urticarial but is more persistent than the classic urticarial lesion. The acute lesions commonly affect the malar area, are abrupt in onset, and often last only a few days. They commonly coincide with systemic flares of the disease. The entire face may be involved with sparing of the lids, and periorbital areas or eyelid involvement may occur in a manner similar to that seen in dermatomyositis. In an occasional patient, the upper dermal edema is of such prominence that subepidermal vesicles develop which subsequently rupture and leave small erosions. Hyperpigmentation commonly follows and may be the principal change by the time the patient is seen. The facial and periorbital edema may be marked, appearing identical to that seen in dermatomyositis or early scleroderma.

Deep dermal and subcutaneous inflammatory lesions of lupus have been referred to as lupus erythematosus panniculitis or lupus profundus.[65,66] These lesions produce deep, firm nodules often without visible skin change. The lesions appear on the head, upper arm, chest, buttocks, and thighs. The overlying skin is usually indrawn and sometimes tethered to the firm underlying nodule. This type of lesion occurs in patients that often have DLE with mild systemic involvement.[67] Occasionally such lesions result in large areas of ulceration.[68]

HISTOLOGY OF LE SKIN DISEASE

The principal pathologic target of lupus erythematosus in most tissues is that epithelial - or endothelial - mesenchymal interface where basal lamina material is synthesized. The skin is no exception. The distinctive pathologic change of cutaneous LE is at the dermal-epidermal junction. Morphological changes noted by light, fluorescent, and electron microscopy suggest that the basal or germinal cell of the epidermis is the primary site of in-

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[65] Irgang, S. Lupus erythematosus profundus report of an example with clinical resemblance to Darier-Roussy sarcoid. Arch. Dermatol. 42:97-108,1940.

[66] Milner, ANP. Systemic lupus erythematosus with nodular lesions. Br. J. Dermatol. 65:204-211, 1953.

[67] Diaz-Jouanen, E., DeHoratius, R.J., Alarcon-Segovia, D. and Messner, R.P. Systemic lupus erythematosus presenting as panniculitis (lupus profundus). Ann. Intern. Med. 82:376-379, 1975.

[68] Winkelmann, R.K. Panniculitis and systemic lupus erythematosus. JAMA 211:472-475, 1970.

jury in cutaneous LE whether acute or chronic in nature.[69,70,71]

In the chronic cutaneous (discoid) LE lesion there is prominent hyperkeratosis and well developed follicular plugging. The nucleated layers of the epidermis are generally not thickened and may be slightly atrophic. The changes along the basal layer are characterized by loss of the normal organization and orientation of the basal cells, edema with vacuole formation between and sometimes within basal cells, partial obscuration of the dermal epidermal junction by a mononuclear infiltrate, evidence of increased melanogenesis, and interruption of pigment transfer leading to the accumulation of melanin beneath the epidermis. Prominent thickening of the PAS positive epidermal basement membrane is present in older lesions.

A mononuclear infiltrate localized to periappendigeal and perivascular areas is present in the dermis. The density of the dermal lymphocytic and histiocytic infiltrate varies considerably and can be related to the age of the lesion.[71] Plasma cells are rarely seen.

This combination of changes within the germinal layer of the epidermis is characteristic of a group of disorders including animal[72] and human[73] graft-vs-host disease, lichen planus, dermatomyositis,[74] poikiloderma of Jacobi,[75] and certain drug re-

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[69]Tuffanelli, D.L., Kay, D. and Kukuyama, K. Dermal-eipdermal junction in lupus erythematosus. Arch. Dermatol. 99:652-662, 1969.

[70]Montgomery, H. Dermatopathology. New York, Harper and Row Publishers, 1967, pp. 719-738.

[71]Clark, W.H., Reed, R.J. and Mihnn, M.C. Lupus erythematosus: Histopathology of cutaneous lesions. Human Path. 4:157-163, 1974.

[72]Stastny, P., Stembridge, V.A. and Ziff, M. Homologous disease in the adult rat, a model for antoimmune disease. I. General features and cutaneous lesions J. Exp. Med. 118:635-648, 1963.

[73]Lerner, K.G., Kao, G.F., Storb, R., Buckner, C.D., Cliff, R.A. and Thomas, E.D. Histopathology of Graft-vs-Host Reaction (GvHR) in Human Recipients of Marrow from HL-A Matched Sibling Donors: Transpl. Proc. 6:367-371, 1974.

[74]Janis, J.F. and Winkelman, R.K. Histopathology of the skin in dermatomyositis. Arch. Dermatol. 97:640-650, 1968.

[75]Lever, W.F. Histopathology of the skin. Philadelphia, J.B. Lippincott Co., 1967.

actions (arsenicals,[75] hydroyurea,[76] busulfan[77]) and vitamin B_{12} deficiency.[78] This subject has been thoroughly reviewed by Pinkus.[79] The common denominator for these morphologic changes appears to be basal layer injury.

The pathologic change in the acute LE skin lesions (typical butterfly rash) may be quite subtle. The initial impression when looking under low power is that the skin is virtually normal. However, careful examination at higher magnification will show distinctive changes. A series of small vacuoles may be noted within, above, and deep to the basal lamina. Lymphocytes will be scattered along the dermal-epidermal interface. The papillary dermis is edematous and the blood vessels are dilated.

In general, the only histologic difference between the acute (butterfly) and chronic (discoid) cutaneous lesions of LE is in the degree or extent of the identical pathologic alteration. The chronic scarring discoid lesions with its dense cellular infiltrate that often persists for months or years stands at one end of a pathologic spectrum and the evansecent butterfly rash of SLE stands at the other.

Lupus panniculitis or profundus is the only LE-specific inflammatory lesion of the deep dermis and subcutaneous fat. The histology is that of a lymphocytic panniculitis. There has been disagreement concerning the histopathology of these lesions. Some authors[69,80] have reported the changes as specific and diagnostic; others[66,81-84] state that they are nonspecific. The most striking features are as follows: insignificant epidermal involvement, a perivascular lymphocytic infiltrate in the deep dermis and subcutaneous fat, vessel wall thickening and permeation by lymphocytes, absence of polymorphonuclear leukocytes, prominent fibrinoid degeneration of collagen, calcification[67,68] and deposition of immuno-

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[76]Kennedy, B.J., Smith, R., Goltz, R.W. Skin changes secondary to hydroxyurea therapy. Arch. Dermatol. 111:183-187, 1975.

[77]Kyle, R.A., Schwartz, R.S., Oliner, H.L. and Dameshek, W. A syndrome resembling adrenal cortical insufficiency associated with long term busulfan (Myleran) therapy. Blood 18:497-510, 1961.

[78]Gilliam. J.N. and Cox, A.J. Epidermal changes in B_{12} deficiency. Arch. Dermatol. 107:231-236, 1973.

[79]Pinkus, H. Lichenoid tissue reactions. Arch. Dermatol. 107:840-846, 1973.

[80]Fountain, R.B. Lupus erythematosus profundus. Br. J. Dermatol. 80:571-579, 1968.

[81]Jablonska S., Chorzelski, T., Stachow, A: Lupus erythematosus profundus, publication 55. Amsterdam, Excerpta Medica Foundation, 1962, nol. 1, pp. 698-700.

[82]Pascher, F., Sims, C.F., Pensky, N. Lupus erythematosus profundus (Kaposi-Irgang). J. Invest. Derm. 25:347-362, 1955.

[83]Frain-Bell, W., Forman, L. Systemic lupus erythematosus with nodular lesion. Brit. J. Derm. 68:102-103, 1956.

[84]Tuffanelli, D.L., DuBois, E.L. Cutaneous manifestations of systemic lupus erythematosus. Arch. Derm. 90:377-384, 1964.

globulin and complement in vessel walls detectable by direct immunofluorescence.[85]

IMMUNOPATHOLOGY

In 1963, Burnham, Neblett and Fine[86] applied the direct fluorescent antibody technique to biopsies from LE skin lesions and discovered a granular band of immunoglobulin localized to the dermal-epidermal junction. This has been repeatedly confirmed.[87-90] A subepidermal band of immunoglobulin is found in over 90% of the acute and chronic LE lesions.[91] Since this location corresponds to the principal site of injury in cutaneous LE, it was suggested that antibody or antigen-antibody complexes played a role in the pathogenesis. However, several findings since that time make the possibility of immune-xomplex mediated injury at the dermal-epidermal junction unlikely. For example, it is now well known that subepidermal deposits of immunoglobulin are present in clinically normal SLE skin[92-96] and that such deposits are inversely related

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[85]Tuffanelli, D.L. Lupus erythematosus panniculitis (profundus) Arch. Derm. 103:231-242, 1971.

[86]Burnham, T.K., Neblett, T.F. and Fine, G. The application of the fluorescent antibody technique to the investigation of lupus erythematusos and various dermatoses. J. Invest. Dermatol. 41:451-456, 1963.

[87]Tan, E.M. and Kunkel, H.G. An immunofluorescent study of the skin lesions in systemic lupus erythematosus. Arthritis Rheum. 9:37-46, 1966.

[88]Kay, D.M. and Tuffanelli, D.L. Immunofluorescent techniques in clinical diagnosis of cutaneous disease. Ann. Int. Med. 71:753-762, 1969.

[89]Burnham, T.K., Fine, G. and Neblett, T.R. Immunofluorescent "band" test for lupus erythematosus II. Employing skin lesions. Arch. Dermatol. 102:42, 1970.

[90]Cormane, R.H. "Bound" globulin in the skin of patients with chronic discoid lupus erythematosus and systemic lupus erythematosus. Lancet 1:534-535, 1964.

[91]Tuffanelli, D.L. Lupus erythematosus. Arch. Dermatol. 106:553-566, 1972.

[92]Percy, J.S., Smyth, C.J. The immunofluorescent skin test in systemic lupus erythematosus. JAMA 203:485-488, 1969.

[93]Jablonska, S., Chorzelski, T., Maciejowska, E. The scope and limitations of the immunofluorescence method in the diagnosis of lupus erythematosus. Br. J. Dermatol. 83:242-247, 1970.

[94]Grossman, J., Callerme, M.L., Condemi, J.J., Skin immunofluorescence studies on lupus erythematosus and other antinuclear antibody-positive disease. Ann. Intern. Med. 80:496-500, 1974.

[95]Burnham, T.K., Fine, G. The immunofluorescent "band" test for lupus erythematosus. Arch. Derm. 103:34-32, 1971.

[96]Nesbitt, L.T., Gum. O.B. Direct cutaneous immunofluorescent test in lupus erythematosus. South Med. J. 66:991-997, 1973.

to the occurrence of chronic LE skin lesions.[97] In addition, Cripps and Rankin[98] have shown that the appearance of subepidermal immunoglobulin follows the inflammatory response by several weeks. Finally, the histologic appearance of the LE skin lesions is more consistent with cell mediated injury, probably by T-cells.

ULTRASTRUCTURAL FINDINGS

Ultrastructural localization of immunoglobulin at the dermal-epidermal junction using the immuno-peroxidase method[99] confirms that most of the Ig deposits are in the superficial dermis. Deposits are also found along the basal lamina, along the collagen fibers, and on the plasma membrane of basal cells. Paramyxovirus-like inclusions have been identified in the normal and lesional skin of both the acute and chronic type lesions.[100-102]

A recent study has shown that these viral-like structures increase in areas of LE skin that have been subjected to ultraviolet irradiation.[103] The significance of these ubiquitous viral-like structures remains a mystery; however, that they are present in epithelial, endothelial, white blood cells[104] in both cutaneous

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[97]Gilliam, J.N., Cheatum, D.E., Hurd, E.R., Stastny, P., Ziff, M. Immunoglobulin in clinically uninvolved skin in systemic lupus erythematosus. J. Clin. Invest. 53:1434-1438, 1974.

[98]Cripps, D.J. and Rankin, J. Action spectra of lupus erythematosus and experimental immunofluroscence. Arch. Derm. 107: 563-567, 1973.

[99]Wolff-Schreiner, E., Wolff, K. Immunoglobulins at the dermal-epidermal junction in lupus erythematosus. Ultrastructural investigations. Arch. Derm. Forsch. 246:193-210, 1973.

[100]Nieland, N.W., Hashimoto, K., Masi A.T. Microtubular inclusions in normal skin of systemic lupus erythematosus patients. Arthritis Rheum. 15:193-200, 1972.

[101]Hashimoto, K., Thompson, D.F. Discoid lupus erythematosus electron microscopic studies of paramyxovirus-like structures. Arch. Dermatol. 101:565-577, 1970.

[102]Haustein UWE: Tubular structures in affected and normal skin in chronic discoid and systemic lupus erythematosus: electron microscopic studies. Brit. J. Derm. 89:1-13, 1973.

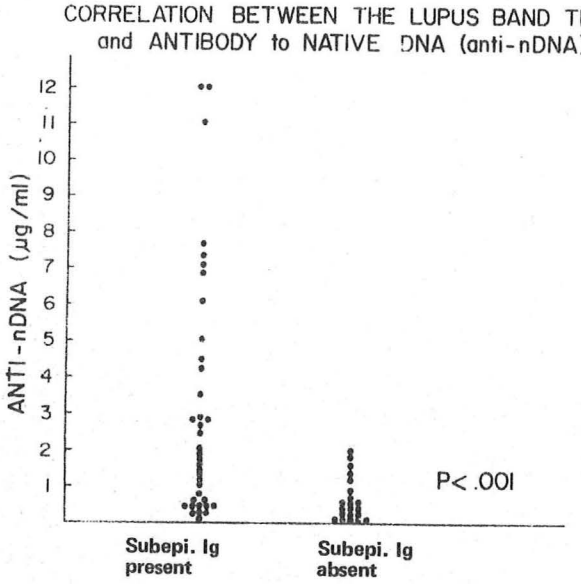
[103]Berk, S.H. and Blank, H. Ultraviolet light and cytoplasmic tubules in lupus erythematosus. Arch. Dermatol. 109:364-366, 1974.

[104]Prunieras, M., Grupper, C.H., Durepaire, R., Deltzer-Garelly, E., and Regnier M: Etude ultrastructural de la peau dams 42 cas de lupus erythematosus. La Presse Med. 78:2475-2479, 1970.

and extracutaneous sites emphazes the generalized nature of this disease even in those patients whose clinically apparent disease is limited to the skin.

Ultrastructural studies by Grisham and Churg[105] revealed subepidermal electron dense deposits in LE skin similar to the glomerular deposts commonly identified in renal biopsies from patients with lupus nephritis. These glomerular dense deposits are generally considered to be immune complexes. In the nephritis of SLE the predominate immune complex is nDNA:anti-nDNA. These findings together with the demonstration of antinuclear activity in SLE skin immunoglobulin eluates[106,107] suggests that the subepidermal immunoglobulin might contain nDNA:anti-nDNA complexes and that the presence of subepidermal deposits might correlate with the concentration and persistence of serum anti-nDNA antibodies. Recent studies[108, 109] have shown that SLE patients with significant elevations of serum anti-nDNA always have subepidermal immunoglobulin in apparently normal non-exposed skin whereas patients with low or undetectable anti-nDNA levels frequently do not. (fig. 8). In longitudinal studies[96] in which intermittent determinations

FIGURE 8



Scattergram showing serum DNA-binding (µ/gm DNA bound per ml serum) in 59 serum samples from 40 SLE patients divided into those with subepi. Ig in normal skin and those without subepi. Ig in normal skin.
From: Gilliam (ref. 108)

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[105]Grisham, E. and Churg, J. Ultrastructure of dermal lesions in SLE. Lab. Invest. 22:189-197, 1970.

[106]Landry, M., Sams, W.M. Basement-membrane antibodies in two patients with systemic lupus erythematosus. Lancet 1:821-822, 1972.

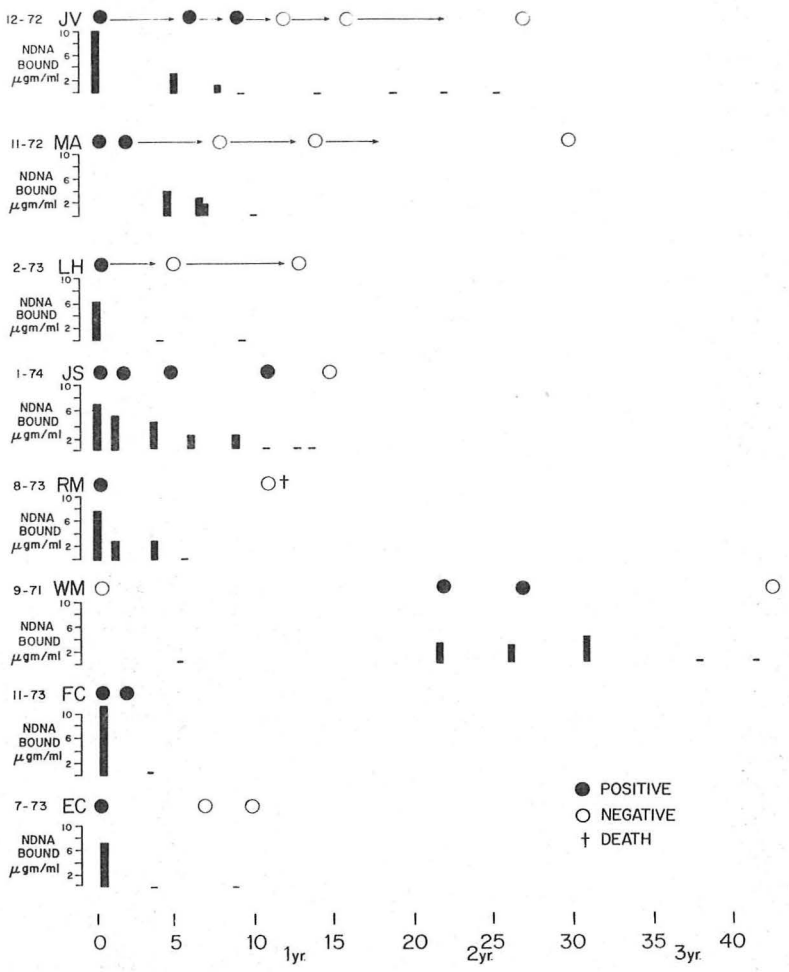
[107]Landry, M., Sams, W.M. Systemic lupus erythematosus. Studies of the antibodies bound to skin. J. Clin. Invest. 52:1871-1875, 1973.

[108]Gilliam, J.N., Hurd, E.R., Ziff, M. The effect of treatment on the lupus band test. Clin. Res. 22:158a, 1974 (abs).

[109]Gilliam, J.N., Smiley, J.D., Ziff, M. Immunoglobulin in clinically uninvolved skin in systemic lupus erythematosus: correlation with serum antibody to native DNA (in preparation).

of serum anti-nDNA antibodies and cutaneous immunofluorescence were performed we have found that the appearance of serum anti-nDNA antibody is followed in several weeks by the development of subepidermal deposits and also that the deposits in the skin may persist for several weeks after anti-nDNA antibodies have disappeared from the serum. (fig 9).[110]

FIGURE 9



Temporal relationship between anti DNA-antibody level ▌ and subepi. Ig (0, Ig absent; ● Ig present) arrows → indicate onset and duration of cyclophosphamide treatment.

From: Gilliam (ref. 110)

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[110] Gilliam, J.N., unpublished observations.

V.

MORPHOLOGIC FEATURES AND CLINICAL SIGNIFICANCE OF THE NON-SPECIFIC LE SKIN LESIONS

There are numerous nonspecific or nondiagnostic but LE related skin lesions. The presence of these lesions implies systemic disease. It is also important to recognize these because many are associated with a particular type of systemic involvement.

The vascular lesions of SLE are relatively common and give rise to a wide array of clinical syndromes as listed in Table 5. These tend to occur more commonly in certain SLE patients and when vascular syndromes do occur as a manifestation of SLE, they tend to be multiple and recurrent.[111]
111

Dermal vasculitis involving the arterioles, capillaries and venules of the dermis results in purpuric, papular and necrotic lesions. Occasionally hemorrhagic bullae occur. The hallmark of dermal vasculitis is palpable purpura. These lesions are often limited to the lower extremities. The presence of these lesions should lead to a consideration of a widespread small vessel vasculitis. Central nervous system disease has been commonly observed in patients with this type of skin involvement[111, 112] and splinter hemorrhages may be an associated feature.[113]

Recurrent superficial and deep thrombophlebitis may be an early sign of lupus as emphasized by Alarcon-Segovia.[114]

Raynaud's Phenomenon occurs in approximately 20% of SLE patients as opposed to over 90% in those with scleroderma and the mixed connective tissue disease (MCTD) syndrome described by Gordon Sharp.[115]

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[111]Mintz, G. and Fraga, A. Arteritis in systemic lupus erythematosus. Arch. Intern. Med. 116:55-66, 1965.

[112]Dubin, H.V., Stawiski, M.A. Systemic lupus erythematosus resembling malignant atrophic papulosis. Arch. Int. Med. 134:321-323, 1974.

[113]Fraga, A. and Mintz, G. Splinter hemorrhages in SLE. Arthritis Rheum. 9:648-649, 1966.

[114]Alarcon-Segovia, D. and Osmundson, P.J. Peripheral vascular syndromes associated with systemic lupus erythematosus. Ann. Intern. Med. 62:907-919, 1965.

[115]Sharp, G.C., Irvine, W.S., Laroque R.L. et al. Association of autoantibodies to different nuclear antigens with clinical patterns of rheumatic disease and responsiveness to therapy. J. Clin. Invest. 50:350-359, 1971.

Livedo reticularis[116] is a reddish-purple, blotchy, or reticulated pattern that is found chiefly on the trunk and extremities. It may involve the entire trunk or limb, or it may be present as discontinuous patches. The discoloration persists even after the skin has been warmed, unlike the physiologic livedo or cutis marmorata produced by cold in infants and young children. In addition to lupus, this pattern has been seen in patients with periarteritis, rheumatoid arthritis, drug induced vasculitis, rheumatic fever, thrombotic thrombocytopenic purpura, cryoglobulinemia and various DIC syndromes, particularly purpura fulminans. Livedo may be associated with tender subcutaneous nodules which on biopsy show a necrotizing vasculitis. Purpura may accompany these changes and may be followed by cutaneous infarction and ulceration.[117]

Chronic and recurrent leg ulcers may occasionally be the principal manifestation of lupus.[117-120] These ulcers usually occur over the pretibial and malleolar areas and are similar to those seen in rheumatoid arthritis. The ulcers may occur in unusual sites such as the plantar surface of the feet. As mentioned, ulcers may be associated with livedo reticularis and/or cryoglobulinemia. The most likely cause of the ulceration is vasculitis of small to medium muscular arteries with resultant cutaneous infarction.

Peripheral gangrene is an infrequent but well documented manifestation of lupus erythematosus.[121] The gangrene commonly has an insidious onset. The patients complain of coldness, tenderness and blush discoloration of the digit. Persistent cyanosis, severe pain and dry gangrene develop, often requiring amputation. The microscopic picture shows a chronic necrotizing vasculitis of small to medium muscular arteries. This change may also appear in association with livedo reticularis or Raynaud's phenomenon.[122]

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[116]Golden, R.L. Livedo reticularis in systemic lupus erythematosus. Arch. Dermatol. 87:67-69, 1963.

[117]Desser, K.B., Sartiano, G.P. and Cooper, J.L. Lupus livido and cutaneous infarction. Angiology 20:261, 1969.

[118]Kirsner, A.B., Diller, J.G. and Sheon, R.P. Systemic lupus erythematosus with cutaneous ulceration. JAMA 217:821-823, 1971.

[119]Goltz, R.W. and Smith, N.G. Recurrent lower leg ulcers in lupus erythematosus. Minn. Med. 41:348-349, 1958.

[120]Baker, L.P. Disseminated lupus erythematosus with leg ulcers. Arch. Derm. Syph. 66:758, 1952.

[121]Cheah, J.S. Systemic lupus erythematosus in a Chinese woman presenting with gangrene of the fingers. Aus. N.Z. J. Med. 3:197-199, 1973.

[122]Kitchiner, D., Edmonds, J., Bruneau, C., Hughes, G.R.V. Mixed connective tissue disease with digital gangrene. Br. Med. J. 1:249-250, 1975.

Rheumatoid nodules occur in SLE in an incidence of approximately 5 to 7%.[123-124] These lesions may be clinically and histologically identical to typical rheumatoid nodules; however, they are often more superficially located and may contain hematoxylin bodies.[125] A deforming non-erosive arthritis is often seen in SLE patients with these lesions.[126,127]

Hair loss is the most common non-specific cutaneous sign of SLE.[128] Alopecia of three types is seen in lupus. A scarring type is seen in areas of scalp involvement by the chronic discoid skin lesions; a diffuse variety occurs during the acute toxic exacerbations of the systemic disease, a type of frontal alopecia associated with increased hair fragility results in short broken-off hairs producing a dishevelled appearance. This third type of alopecia is rather characteristic of LE. It is sometimes referred to as "lupus hair."[128]

Oral mucosal lesions are characterized by shallow ulcers or erosions of the buccal mucosa, whitish atrophic scars, and silvering of the lips. These white mucosal lesions are often misdiagnosed as leukoplakia.

Diffuse pigmentation may be seen in SLE but occurs more often in patients with scleroderma or scleroderma-like features. Adrenocortical function is normal.

Sclerodactyly may occur particularly in those with long standing Raynaud's phenomenon, and such patients often fit the clinical syndrome of mixed connective tissue disease described by Sharp.[129]

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[123]Dubois, E.L., Friou, G.J. and Chandor, S. Rheumatoid nodules and rheumatoid granulomas in systemic lupus erythematosus. JAMA 220: 515-518, 1972.

[124]Hahn, B.H., Yardley, J.H. and Stevens, M.B. "Rheumatoid" nodules in systemic lupus erythematosus. Ann. Inter. Med. 72:49-58, 1970.

[125]Steinberg, A.D. and Talal, N. The coexistence of Sjogren's Syndrome and systemic lupus erythematosus. Ann. Intern. Med. 74:55-61, 1971.

[126]Kramer, L.S., Ruderman, J.R., Dubois, E.L. et al. Deforming non-erosive arthritis of the hands in chronic systemic lupus erythematosus. Arthritis Rheum. 13:329-330, 1970.

[127]Aptekar, R.G., Lawless, O.J., Decker, J.L. Deforming non-erosive arthritis of the hand in systemic lupus erythematosus. Clin. Ortho. and Rel. Res. 100:120-124, 1974.

[128]Alarcon-Segovia D. and Cetina, J.A.: Lupus hair. Am. J. Med. Sci. 267:241-242, 1974.

[129]Sharp, G.C., Irvin, W.S., Tan. E.M., Gould, R.G. and Holman, H.R. Mixed connective tissue disease - an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA) Amer. J. Med. 52:148-159, 1972.

Calcinosis cutis occurs rarely in lupus.[130] It is a common finding in dermatomyositis, especially the childhood type, and it is not uncommon in scleroderma. Subcutaneous calcification is a feature of lupus panniculitis and soft tissue x-rays can be helpful in establishing a diagnosis.

Urticaria is sometimes related to an increased activity of the disease, and erythema multiforme in LE bears a similar relationship.[131, 132] Otherwise, these non-specific changes are of little prognostic significance.

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[130]Powell, R.J. Systemic lupus erythematosus with widespread subcutaneous fat calcification. Proc. Roy Soc. Med. 67:215-217, 1973.

[131]Rallison, M.L., Carlisle, J.W., Lee, R.E., Vernier, R.L. and Good, R.A. Lupus erythematosus and Stevens-Johnson Syndrome. Am. J. Dis. Child. 101:725-738, 1961.

[132]Rothfield, N. and Weissman, G. Bullae in systemic lupus erythematosus. Arch. Int. Med. 107:908-914, 1961.

VI.

CLINICAL SYNDROMES WITHIN THE LE SPECTRUM

In contrast to the extremely homogenous disease of inbred NZ mice, human SLE displays a wide variety of clinical patterns. However, individual patients acquire distinct forms of the disease and within certain limits, the clinical features of the disease for each patient remain essentially the same. Consequently, there are groups of patients within this disease spectrum with similar clinical features. Based upon the NZ mouse model, one would expect patients within each of these clinically homogenous groups to share certain characteristic immune responses since the clinical expression of this disease most likely depends upon the nature of the host's immune response. By examining the clinical, pathologic and immunologic features that define these syndromes, and by observing the course and the response to treatment of patients within these syndromes, one gets a much better understanding of the nature of the disease. In addition, by contrasting the clinical, pathologic and immunologic features of patients with different syndromes, one gains insight into the mechanisms involved in the production of specific components of the disease. To illustrate these points the contrasting features of patients with the following distinct clinical syndromes will be described: chronic cutaneous (discoid) LE without clinical evidence of extracutaneous disease, chronic cutaneous (discoid) LE with systemic involvement, and lupus nephritis. These will serve as markers along the LE spectrum with DLE at one extreme, lupus nephritis at the other and chronic cutaneous LE with systemic involvement somewhere in between. Related clinical syndromes and their relative position along this disease spectrum will also be described.

THE RELATIONSHIP BETWEEN CHRONIC CUTANEOUS LE AND SYSTEMIC LE

The chronic destructive skin lesions of LE identify the first two of these three syndromes. In contrast, patients in the third group, i.e. those with lupus nephritis, will invariably not have this type of skin lesion but often will have the acute and transient LE lesion with or without some nonspecific cutaneous lesion. This difference is a constant feature which reflects a characteristic difference in the host response, so it deserves special attention.

Whether DLE is fundamentally different from SLE has been previously debated.[133,134] It now seems clear that there is only a

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[133]Rothfield, N.F., March, C.H. Lupus erythematosus, dermatology in general medicine. First edition. T.B. Fitzpatrick, New York, McGraw-Hill Co., 1971 pp. 1513-1514.

[134]Rowell, N.R. Lupus erythematosus, Texbook of Dermatology. Second Edition, Ed. A. Rook, D.S. Wilkinson, F.J.G. Ebling. Oxford, Pub. 1972 pp. 1062-1064.

practical clinical difference between discoid LE and systemic LE and certainly no difference of a fundamental nature. Indeed, most patients with DLE have disease that remains confined to the skin, but some do have antinuclear antibodies;[135-139] in addition, a sensitive assay will show low levels of antibodies to native or doublestranded DNA;[140] furthermore, a small number (5%) will develop extracutaneous disease.[64] Conversely, approximately 15% of SLE patients will have DLE.[133] The familial occurrence of DLE and SLE has been reported.[141, 142] Hyperglobulinemia occurs in approximately 10% of DLE patients[64] compared with 50% in SLE patients.[61] It is obvious that the boundary between DLE and SLE is artificial in that examples of every possible graduation of involvement from patients with only cutaneous disease to those that have DLE plus overt widespread systemic disease are seen.

Until recently there have been no tests to indicate which DLE patients might be at risk to progress to systemic involvement; however, some recent evidence indicates that such patients will have subepidermal deposits of immunoglobulin in biopsies taken from uninvolved skin (positive "band test").[143] Other studies[144, 145]

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[135]Rothfield, N., March, C.H., Meischer, P., McEwen C. Chronic discoid lupus erythematosus: A study of 65 patients and 65 controls. New Engl. J. Med. 269:1155-1161, 1963.

[136]Burnham, T.K., Bank, P.W. Antinuclear antibodies. I. Patterns of nuclear immunofluorescence. J. Invest. Dermatol. 62:526-534, 1974.

[137]Beck, S.W., Rowell, N.R. Discoid lupus erythematosus: A study of the clinical features in 120 patients with observations of the relationship of this disease to systemic lupus erythematosus. Quartely J. Med. 35:119-136, 1966.

[138]Shrank, A.B., Doniach, D. Discoid lupus erythematosus. Correlation of clinical features with serum auto-antibody pattern. Arch. Dermatol. 87:677-685, 1963.

[139]Strejcek, J., Malina, L., Bielicky, T. Antinuclear factors, rheumatoid factors and Bordet-Wasserman reaction in chronic and systemic lupus erythematosus. Acta Derm. Venerol. 48:198-202, 1968.

[140]Hasselbacker, P. and LeRoy C. Serum DNA binding activity in healthy subjects and in Rheumatic Disease. Arthritis Rheum. 17: 63-71, 1974.

[141]Gallo, R.C. and Forde, D.L. Familial chronic discoid lupus erythematosus and hypergammaglobulinemia. Arch. Int. Med. 117:627-631, 1966.

[142]Leonhardt, T. Familial hypergammaglobulinemia and systemic lupus erythematosus. Lancet 273:1200-1203, 1957.

[143]Baart de la Faille-Kuyper, E.H. and Cormane, R.H. The occurrence of certain serum factors in the dermo-epidermal junction and vessel walls of the skin in lupus erythematosus and other (skin) diseases. Acta Derm-Venereol. (Stockholm) 48:578-588, 1968.

[144]Mandel, M.J., Carr, R.K., Weston, W.L., Sams, W.M., Jr., Harbeck, R.J., and Krueger, G.G. Anti-native DNA antibodies in discoid LE, Arch. Dermatol. 106:668-670, 1972.

[145]Davis, P., Atkins, B. and Hughes, G.R.V. Antibodies to native DNA in discoid lupus erythematosus. Brit. J. Derm. 91:175-181, 1974.

suggest that detection of anti-nDNA antibodies predicts impending systemic disease activity. As mentioned earlier, our data[146] indicates that both of these tests probably measure the same thing, i.e. serum anti-nDNA antibody. However, the skin "band test" or lupus band test (LBT) has the advantage of being much more sensitive, especially if the normal skin is obtained from a light exposed area.

CHRONIC CUTANEOUS LE WITH SYSTEMIC INVOLVEMENT

The clinical manifestations of 15 Parkland patients with DLE lesions is shown in Fig. 10. The most striking feature is the low incidence of clinically apparent renal disease. One patient had a renal biopsy 4 years ago with findings of membranous glomerulonephritis. Since then she has had moderate proteinuria without evidence of deterioration in renal function. She has been treated with intermittent steroid and chloroquine. The data from renal histologic and functional studies in 12 of the 15 patients in this group is shown in Table 6.

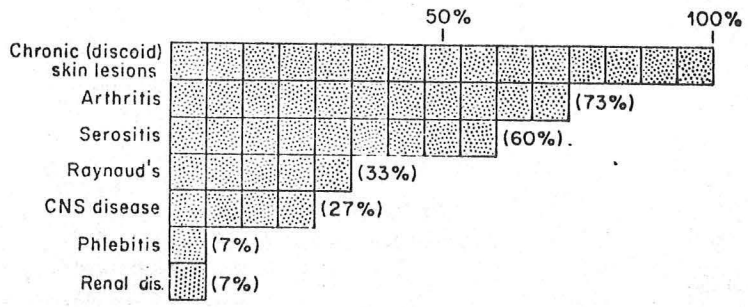
TABLE 6

RENAL BIOPSY FINDINGS AND RENAL FUNCTION IN SLE PATIENTS WITH DISCOID SKIN LESIONS

Proliferative Glomerulonephritis	0
Membraneous Glomerulonephritis	1
Mesangial Glomerulitis	2
Normal Biopsy	3
Normal Renal Function	6

FIGURE 10

CLINICAL MANIFESTATIONS OF SLE PATIENTS WITH DISCOID SKIN LESIONS



Clinical manifestations of 15 Parkland SLE patients with DLE lesions.
From: Gilliam (ref. 110)

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[146] Gilliam, J.N. The significance of cutaneous immunoglobulin deposits in lupus erythematous and NZB/W F_1 hybrid mice. Jour. Invest. Derm. 65, 1975. (in press)

The most common non-cutaneous manifestations in this group have been arthritis in 11 (73%), serositis - including both pleurisy and pericarditis - in 9 (60%) and Raynaud's phenomenon in 5 (33%). Except for a slight increase in the incidence of Raynaud's phenomenon, the incidence of other features is comparable to that found in unselected groups of SLE patients (fig. 7).

The DLE lesions in these SLE patients, though chronic and destructive, appear somewhat less aggressive and persistent when compared with many of the lesions in DLE patients without systemic involvement. Two deaths from sepsis with underlying vasculitis have occurred in this group. One of these developed an enormous area of necrosis with deep ulceration of the gluteal area. In retrospect, this might have been an aggressive ulcerative form of lupus profundus or lupus panniculitis as described by Winkelman.[69]

Antinuclear antibodies were present in over 90% of this group during periods of disease activity (Table 7). This is similar to the incidence of ANA positivity in SLE patients with active nephritis but it is vastly different from the low incidence found in DLE patients without systemic disease. Peripheral nuclear staining which occurs with anti-DNA antibody (See fig. 11) was seen exclusively in patients with lupus nephritis. Only speckled staining patterns were observed in the DLE group while both speckled and homogeneous patterns were found in the SLE group with DLE skin lesions.

TABLE 7

ANTINUCLEAR ANTIBODIES AND NUCLEAR STAINING PATTERNS IN PATIENTS WITH LUPUS ERYTHEMATOSUS

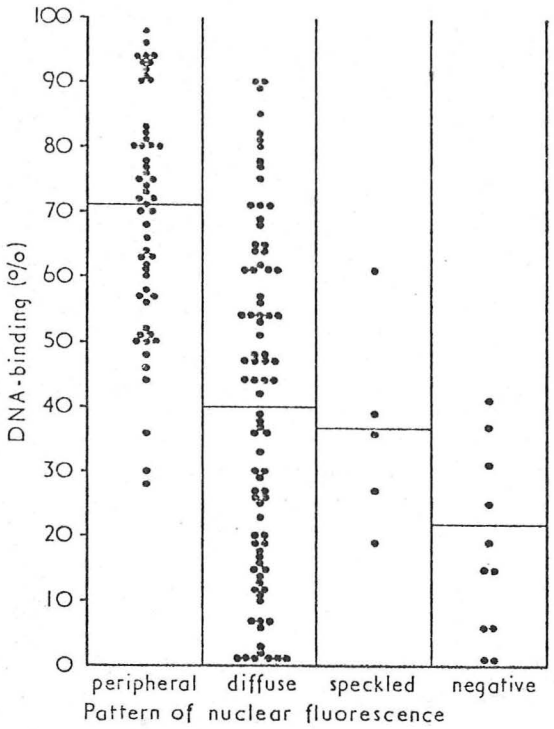
	No. tested	No. positive	% positive	Pattern P*	H†	S‡
Group I	80	3	4	–	–	3
		($p < .001$)				
Group II	15	14	93	–	9	5
		N.S.				
Group III	13	13	100	6	5	2

P* – peripheral

H† – homogeneous

S‡ – speckled

FIGURE 11



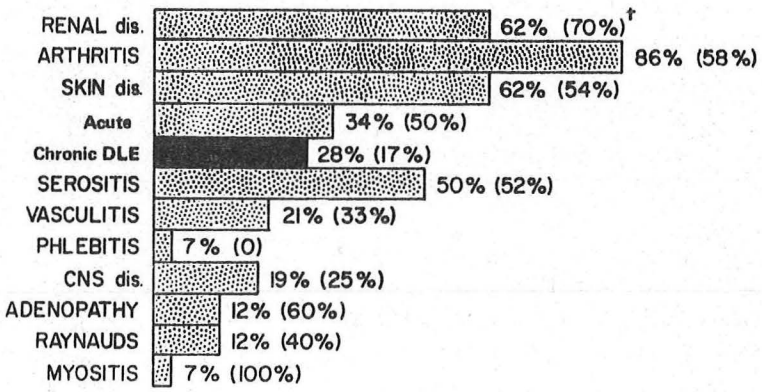
Relationship between patterns of nuclear fluorescence and percentage of DNA-binding in sera from SLE patients.

From: Luciano and Rothfield (ref. 147)

In an earlier study[97] we observed a low incidence of subepidermal Ig in biopsies from uninvolved skin of SLE patients with DLE lesions (fig. 12). We found that only 17% of the SLE

FIGURE 12

CLINICAL FEATURES OF 42 SLE PTS. IN RELATION TO THE % LBT POS. †



†(%) = percentage incendena of LBT positive patients
From: Gilliam et. al.

patients with DLE lesions had Ig in uninvolved non-exposed skin compared to an overall incidence of 55%. Table 8 compares the incidence of band positivity between DLE patients without systemic disease (Group I), SLE patients with DLE (Group II) and SLE patients with biopsy-proven proliferative glomerulonephritis (Group III). None of the DLE patients had subepidermal Ig in normal skin and only three of 15 (20%) of the SLE patients with DLE were positive. In contrast, 13 of 14 (93%) of the patients with lupus nephritis had subepidermal Ig deposits in normal non-exposed skin. The difference between groups I and II is not significant, but there is a highly significant difference between groups II and III.

TABLE 8

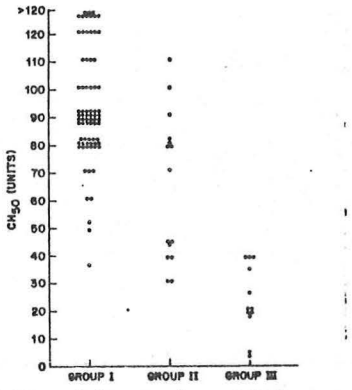
SUBEPIDERMAL IMMUNOGLOBULIN DEPOSITS IN VISIBLY NORMAL SKIN (POSITIVE LUPUS BAND TESTS) IN GROUP I, GROUP II AND GROUP III PATIENTS

	No. tested	No. LBT positive	% LBT positive	
Group I	27	0	0	
Group II	15	3	20	$p < .001$
Group III	14	13	93	

Group I - DLE
Group II - DLE with extra-cutaneous involvement
Group III - Lupus Nephritis
From: Prystowsky and Gilliam (Ref. 62)

Comparison of the total hemolytic complement levels between these three groups (fig. 9) shows that, as expected, DLE patients have normal complement values, approximately one-half of the SLE patients with DLE lesions had moderately low levels during periods of active disease, and all of those with active lupus nephritis had moderate to marked hypocomplementemia.

FIGURE 9

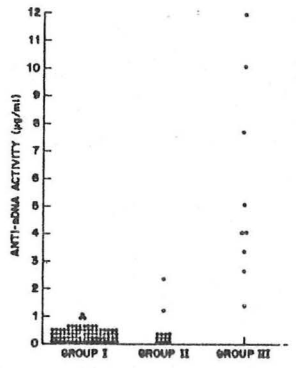


Total hemolytic complement (CH_{50}) in DLE (Group I) SLE with DLE lesions (Group II) and LE nephritis (Group III)

Norm > 60 units
From: Prostowsky and Gilliam

Fig. 10 gives the anti-DNA values for patients in these three. groups. The vales are expressed as gm of DNA bound per ml of serum shown on the vertical axis. Binding of more than 1.5 to 2.0 μg of DNA per ml is probably significant in this assay. All the DLE patients (group I) were negative, and only one SLE patient with DLE had DNA antibodies. This was the patient previously mentioned with membranous glomerulonephritis. On the other hand, most of the patients with proliferative glomerulonephritis (group III) had significantly elevated levels of anti-DNA antibodies. Similar findings have been reported by numerous investigators.[46,47,42,43,146] Table 9, taken from a paper by Luciano and Rothfield,[147] shows the relationship between certain clinical or laboratory manifestations of SLE and serum antibody to native DNA. In that study, a positive correlation between anti-nDNA antibodies and nephritis, hypocomplementemia and peripheral or rim pattern antinuclear antibodies was demonstrated. In view of our data, it is interesting that they found no correlation between serum anti-nDNA antibodies and skin disease. Estes and Christian[59] conducted, a computerized prospective 8 year study of the natural history of SLE. They compared the percent survival after 5 years between groups of patients with certain clinical manifestations of LE. Figure 11 is taken from that study. The overall 5-year survival was 76.9%. Notice that almost 100% of the 21 patients with discoid lesions were alive five years after the onset of their disease. Patients with acute and subacute cutaneous LE lesions had a 65% survival, and those with renal disease, 55%.

FIGURE 10



DLE (Group I) SLE with DLE lesions
(Group II) and LE nephritis (Group III)

Serum DNA Binding in μg/ml
From: Prostowsky and Gilliam

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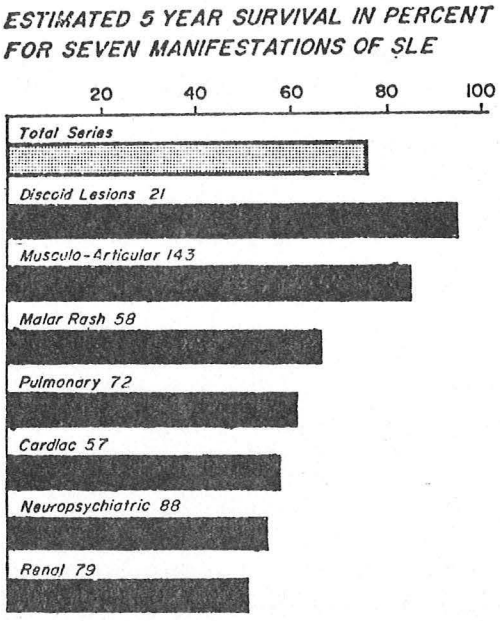
[147]Luciano, A. and Rothfield, N.F. Patterns of nuclear fluorescence and DNA-binding activity. Ann. Rheum. Dis. 32:337-341, 1973.

TABLE 9
CORRELATION OF ANTI-nDNA ANTIBODIES WITH CLINICAL AND LABORATORY PARAMETERS IN 34 PATIENTS WITH SLE

Positive Correlation	No Correlation
Arthritis	Fever
Nephritis	Rash
Anemia	Serositis
LE cells	Lymphadenopathy
Hypocomplementemia	Coombs' antibody
Rim pattern ANA	Leukopenia
	Thrombocytopenia
	Rheumatoid factor
	Hypergammaglobulinemia

From: Luciano and Rothfield (Ref. 147)

FIGURE 11



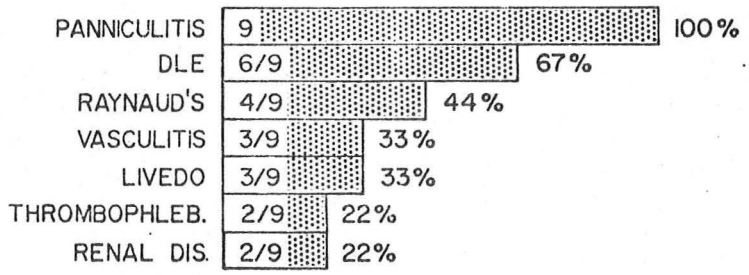
From: Estes and Christian (Ref. 60)

LUPUS PANNICULITIS (LUPUS PROFUNDUS)

Persistent subcutaneous nodules have been a recognized feature of LE for 35 years.[65] However, until recently[67,68] panniculitis as a manifestation of lupus erythematosus has been dealt with almost exclusively in the dermatologic literature.[148-150] The relationship of lupus profundus to other clinical presentations of lupus erythematosus is still not well defined. Approximately 40 to 50% of patients with LE panniculitis have or will develop manifestations suggestive of systemic disease.[67,151] In contrast, systemic manifestations are found in less than 10% of DLE patients followed for five years.[64] Figure 12 gives the incidence of the common clinical manifestations of 9 patients with lupus panniculitis. This data was obtained from a recent report of 6 cases,[67] plus 3 patients followed in the Parkland Clinic. A constant and well recognized feature is the common occurrence of DLE in these patients. Zweiman and associates[151] have pointed out that renal involvement has occurred in a minority of reported cases, and death from renal failure appears to be uncommon. The incidence of vascular involvement of various types is impressive in this small group. Data from

FIGURE 12

CLINICAL MANIFESTATIONS OF PATIENTS WITH LUPUS PANNICULITIS (LUPUS PROFUNDUS)



From: Gilliam (ref. 68) - 6 cases
Parkland (3 - cases)

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[148]Arnold, H.L. Lupus erythematosus profundus: Commentary and report on four more cases. Arch. Derm. 73:15-33, 1956.

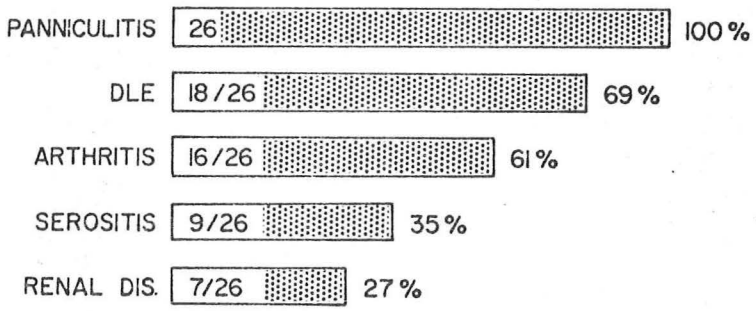
[149]Thurston, C.S., Curtis, A.C. Lupus erythematosus profundus (Kaposi-Irgang). Arch. Derm. 93:577-582, 1966.

[150]Epstein, M.T. Lupus erythematosus panniculitis. Brit. J. Derm. 85:292-294, 1971.

a larger number of patients reported by Zweiman[151] are shown in Figure 13. Again the most striking features are the high incidence of DLE lesions and the relatively low incidence of renal disease. In general, patients with LE panniculitis appear to have a relatively benign form of SLE similar to that seen in SLE patients with chronic scarring or discoid-type skin lesions.

FIGURE 13

CLINICAL MANIFESTATIONS OF PATIENTS WITH LUPUS PANNICULITIS (LUPUS PROFUNDUS)



From: Zweiman, 17 cases (ref. 151)
Diaz-Jouanen, 6 cases (ref. 68)
Parkland, 3 cases (ref. 110)

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[151]Zweiman, B., Tomar, R.H. and Gross, P.R. Lupus erythematosus profundus following thrombocytopenic purpura. Arch. Dermatol. 111:347-351, 1975.

MIXED CONNECTIVE TISSUE DISEASE SYNDROME

Sharp and coworkers[115] have recently described a group of patients designated as having a mixed connective tissue disease (MCTD) syndrome with benign features compatible with SLE but suggestive of scleroderma and/or polymyositis. Table 9 lists the characteristic clinical features of these patients. Arthritis, swollen hand or sclerodactyly, Raynaud's phenomenon, abnormal esophageal motility, myositis and lymphadenopathy were the most prominent features. Most of these patients had marked hypergammaglobulinemia and they all had high titers of antibody to a saline soluble (extractable) nuclear antigen, referred to as ENA. In addition, all of these MCTD patients had a speckled nuclear staining pattern on the fluorescent ANA test, normal serum complement levels and an absence of renal disease. Since half of the patients with typical features of SLE also had similar ENA antibody titers, attempts were made to differentiate the antibody of MCTD from SLE by enzymatic treatment of the extractable nuclear antigen (ENA) with RNAase.[129] The antigen-antibody reaction in SLE was unaffected by RNAase treatment of the ENA. However, such treatment greatly reduced or abolished the reaction in MCTD. This indicated that patients with the MCTD syndrome had antibody to an RNAase sensitive antigenic component of the ENA, whereas the ENA antibody in typical SLE recognized an RNAase insensitive component. ENA subsequently was shown to consist of at least 2 distinct antigens (Table 10). One is

TABLE 9

CLINICAL CHARACTERISTICS OF TWENTY-FIVE PATIENTS WITH MIXED CONNECTIVE TISSUE DISEASE

Characteristic	Per Cent
Arthritis, arthralgias	96
Swollen hands	88
Raynaud's phenomenon	84
Abnormal esophageal motility	77
Myositis	72
Lymphadenopathy	68
Fever	32
Hepatomegaly	28
Serositis	24
Splenomegaly	21
Renal disease	0*
Anemia	48
Leukopenia	52
Hypergammaglobulinemia	80

*At the time this manuscript was being completed renal disease developed in one patient; the nature of the disease had not been elucidated.
From: Sharp et al, (ref. 115)

TABLE 10

ANTIBODIES TO NUCLEAR CONSTITUENTS IN SLE SERA

1. Native DNA
2. Single-stranded DNA
3. Nucleoprotein
4. RNAase res. ENA (Sm antigen)
5. RNAase sens. ENA (RNP)
6. Nucleolar RNA

ENA < 4, 5

sensitive to ribonuclease (RNase) and trypsin and appears to be a ribonucleo-protein (RNP), and the other is resistent to RNase and appears to be identical to the previously described Sm antigen.[129, 152-154] In patients with the MCTD syndrome the antibody is invariably directed to the RNase-sensitive RNP antigen and not the RNase-resistent Sm antigen. Since the clinical course of patients with this syndrome appears to be benign and many of the manifestations disappear with steroid therapy, this finding is significant. While doing direct immunofluorescent staining of SLE skin, we occasionally observed speckled epidermal nuclear staining. We found that this phenomenon correlates with high titer antibodies to both the RNase sensitive (RNP) and RNase resistant (Sm) ENA.[155] This finding brought to our attention a group of patients with anti-RNP antibodies which seems to fall within the spectrum of LE but has certain distinctive clinical and laboratory features. Figure

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[152]Tan, E.M. and Kunkel, H.G. Characteristics of a soluble nuclear antigen precipitating with sera of patients with systemic lupus erythematosus. J. Immunol. 96:464-471, 1966.

[153]Northway, J.D., Tan. E.M. Differentiations of antinuclear antibodies giving speckled staining patterns in immunofluorescence. Clin. Immunol. Immunopath. 1:140-154, 1972.

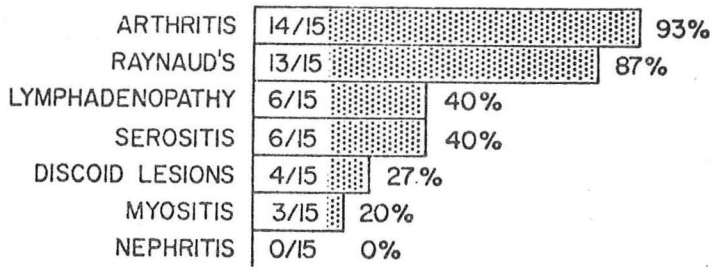
[154]Reichlin, M. and Mattioli, M. Correlation of a precipitin reaction to an RNA-protein antigen and low prevalence of nephritis in patients with systemic lupus erythematosus. N. Engl. J. Med. 286:908:911, 1972.

[155]Gilliam, J.N., Smiley, J.D. and Ziff, M. Correlation between serum antibody to extractable nuclear antigen and immunoglobulin localization in epidermal nuclei. Clin. Res. 22:611A, 1974.

14 shows the clinical features of our patients with this cutaneous marker for the mixed connective tissue disease syndrome. The most helpful features are Raynaud's (often with sclerodactyly and finger-tip ulcerations) and marked lymphadenopathy. None of the patients in this group have significant LE renal disease, a finding which agrees with the observations of Sharp and coworkers[129] and with Reichlin and Mattioli.[154] It is interesting that almost 1/3 of our patients have chronic scarring discoid skin lesions. Two had DLE for one and three years without evidence of systemic involvement prior to the onset of arthritis and and Raynauds, which marked the clinical appearance of the MCTD syndrome. Dubois[156] reported the clinical and laboratory findings in a group of SLE patients with coexistent scleroderma (see Table 11). The general features of his patients

FIGURE 14

CLINICAL FEATURES OF PATIENTS WITH THE MIXED CONNECTIVE TISSUE DISEASE SYNDROME



From: Gilliam (ref. 155)

TABLE 11

CLINICAL AND LABORATORY FINDINGS IN 11 PATIENTS WITH COEXISTANT PSS+ AND SLE COMPARED WITH TYPICAL SLE

	SLE	PSS+ + SLE
Raynauds	20%	82%
Hyperglobulinemia	32%	91%
Arthritis	92%	73%
DLE	10%	45%
Serositis	35%	45%
Myalgia	48%	18%
Lupus Nephropathy	46%	18%

+PSS, progressive systemic sclerosis
(modified from Dubois et. al. Med. 50:199, 1971)

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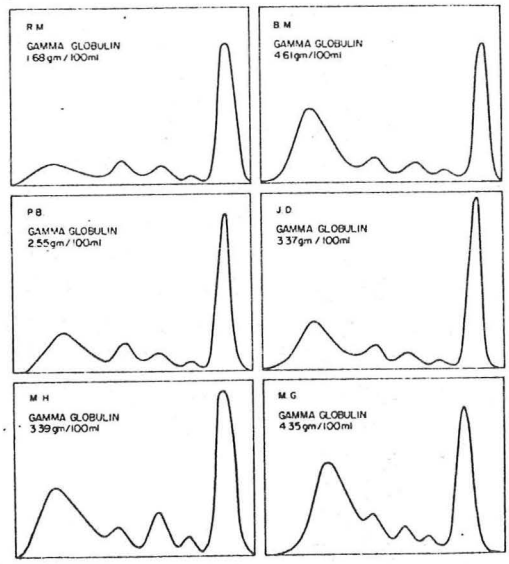
[156]Dubois, E.L., Chandor, S., Friou, G.J. and Bischel, M. Progressive systemic sclerosis (PSS) and localized scleroderma (morphea) with positive LE cell test and unusual systemic manifestations compatible with systemic lupus erythematosus (SLE). Medicine 50:199-222, 1971.

are similar to our patients with MCTD. DLE-type skin lesions were found in 45% of the patients and nephropathy in only 18%. Two of his patients had pulmonary fibrosis, and recently Sharp[157] has shown that patients with the MCTD syndrome have a high incidence of pulmonary involvement with impaired diffusion capacity in 67% and findings of restrictive lung disease in 50%.

In addition to the invariable presence of RNP antibody, two other laboratory features are significant. First, marked hypergammaglobulinemia is common (see fig. 15) and as shown in fig. 16, significant levels of anti-nDNA have not been detected in the patients with RNAase-sensitive ENA antibodies. Patients with RNase-resistant ENA antibodies often have nDNA antibodies. All of the patients with elevated levels of anti-nDNA, shown as open circles in fig. 16, had significant renal disease.

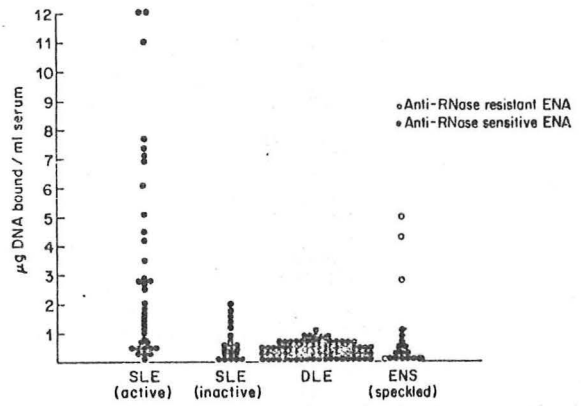
FIGURE 15



Serum protein electrophoretic pattern from 5 patients with MCTD (BM, PB, JD, MH, MG) RM is a black woman with inactive SLE.

FIGURE 16

ANTIBODY TO NATIVE DNA (anti-nDNA) IN PATIENTS WITH LE AND PATIENTS WITH SPECKLED EPIDERMAL NUCLEAR STAINING (ENS)



Scattergram showing serum DNA binding (µg/ml) in active SLE, inactive SLE, DLE and patients with epidermal nuclear staining (ENS). The patients with antibody to RNAase sen. ENA are classified as MCTD

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[157]Sharp, G., Irvin, W., May, C., Holman, H., McDuffie, F., Hess, E. and Schmid, F. Association of antibodies to ribonucleoprotein and Sm antigens with mixed connective tissue disease (MCTD), system lupus erythematosus (SLE) and other rheumatic diseases. Clin. Res. 23:50A, 1975.

Several investigators have now confirmed Sharp's orginal observations[152,155,156,158] and it seems likely that further such studies may reveal other antigen-antibody systems that are related to distinct clinical syndromes within the spectrum of LE. Since the mixed connective tissue disease syndrome has many features of typical SLE, the early differentiation of this group with a less aggressive clinical course, absence of renal disease, and good response to steroids is important for prognostic purposes. ENA (RNP) antibodies appear to provide an easily detectable immunological marker for such cases.

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[158]Parker, M.D. Ribonucleoprotein antibodies: Frequencies and clinical significance in systemic lupus erythematosus, scleroderma, and mixed connective disease. J. Lab. Clin. Med. 82:769-775, 1973.

ANA NEGATIVE SLE-LIKE SYNDROMES WITH ANTIBODY TO CYTOPLASMIC ANTIGENS

Maas and Schubothe[159] described 21 patients with an SLE-like syndrome who showed only antimitochondrial antibodies without evidence of liver disease, antinuclear factor or LE cells. Their major manifestation was chronic recurrent attacks of pyrexia. In addition, there were varying combinations of polyarthritis, muscle aching, pericarditis and myocarditis, pleuritis, pleural effusions, and pulmonary infiltrates. These patients have not had LE cells or antinuclear antibodies. Guardia and associates[160] have recently reported a milder and less persistent version of this syndrome from Barcelona. The antimitochondrial antibody titer in the sera of their patients correlated with disease activity. The cause of this new SLE-like syndrome, the stimulus to mitochondrial-antibody synthesis, and the long-term outcome of the disease are as yet unknown.

Mattoli and Reichlin[161] have described three ANA negative patients with lupus-like features that had antibodies to a newly discovered cytoplasmic nonribosomal antigen. One of their patients had sufficient findings for the clinical diagnosis of SLE with photosensitivity, butterfly rash, polyarthritis, pleuritis, leukopenia and Raynaud's phenomemon.

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[159]Maas, D., and Schubothe, H.: Lupus erythematosus-like syndrome with antimitochondrial antibodies, (orig. in German) Dtsch, Med. Wochenschr, 98:131-139, 1973.

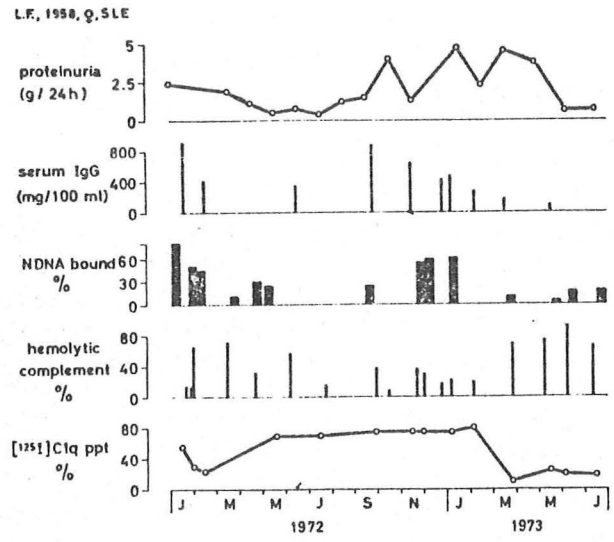
[160]Guardia, J., Gomez, J., Martin, C., Martinez-Vazquez, J.M., Barcardi, R., Tornos, J.: Pericarditis, pleural effusion, and pneumonitis with transient mitochondrial antibodies. Br. Med. Jour. 1:370-371, 1975.

[161]Mattioli, M. and Reichlin, M.: Heterogeneity of RNA protein antigens reactive with sera of patients with systemic lupus erythematosus. Arthritis Rheum. 17:421-429, 1974.

THE SYNDROME OF LUPUS NEPHRITIS

The clinical syndrome of lupus nephritis (proliferative glomerulonephritis) stands at the opposite end of the LE spectrum from DLE. It is characterized clinically by the abrupt appearance of polyarthritis, fever, leukopenia, alopecia and an evanescent butterfly rash in a young woman. This is the prototype of typical SLE. The serologic hallmark of this form of LE is anti-nDNA antibody.[162,147] Additional clinically relevant information comes from an assessement of proteinuria, renal function and the serum complement level. This is illustrated in Figure 17, which is taken from a recent paper by Nydegger and coworkers.[163] This shows the relationship between circulating immune complexes (measured with a radiolabeled Clq binding technique), total hemolytic complement, anti-nDNA, serum IgG and proteinuria. Periods of active disease were associated with increases in [^{125}I] Clq binding, decreased complement levels, elevated levels of anti-nDNA and serum IgG. The accumulative effect of several episodes of active disease on glomerular injury is reflected by the progressive rise in proteinuria which lags behind the serologic changes. This is analogous to the relationship between serum anti-nDNA levels (shown as solid bars) and subepidermal Ig in normal skin (solid circle-Ig

FIGURE 17



Comparison of the evolution of various parameters for SLE disease activity in the follow-up study of a 15-yr-old girl. Periods with normal hemolytic complement activities are characterized by low [^{125}I]C1q binding activities. Low CH_{50} activity, proteinuria, and high titered anti-DNA antibodies are further characterizing periods associated with increased [^{125}I]C1q binding.
From: Nydegger (ref. 163)

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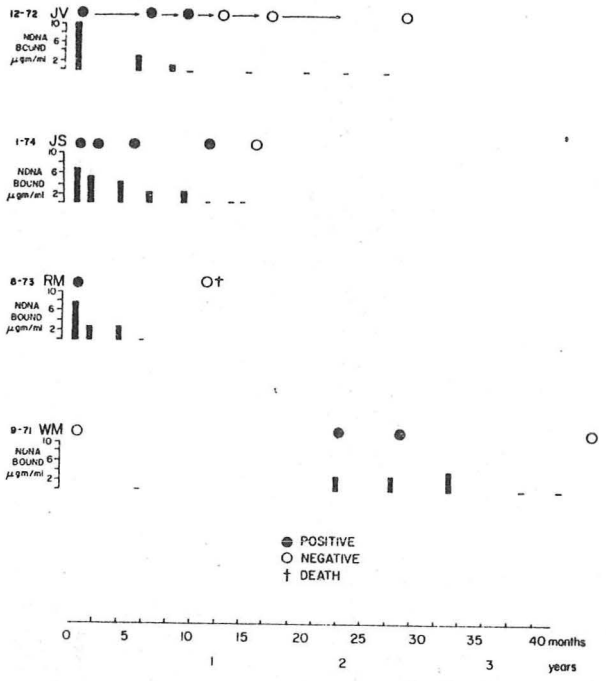
[162]Harbeck, R.J., Bardana, E.J., Kohler, P.F. and Carr, R.I. DNA:Anti-DNA Complex: Their detection in systemic lupus erythematosus sera. Journ. Clin. Invest. 52:789-795, 1973.

[163]Nydegger, U.E., Lambert, P.H., Gerber, H. and Miescher, P.A. Circulating immune complexes in the serum in systemic lupus erythematosus and in carriers of hepatitis B antigen. Jour. Clin. Invest. 54:297-309, 1974.

present, open circle Ig absent) shown again (fig. 18) here for comparison. The presence of subepidermal Ig in normal nonexposed skin (positive "band" test) has been correlated with hypocomplementemia,[94] serum antibody to nDNA[155] and proliferative glomerulonephritis.[97] Figure 19 shows the results of serial determinations on a group of band positive SLE patients.[166] The arrows at the top indicate the onset and duration of cyclophosphamide (solid line)

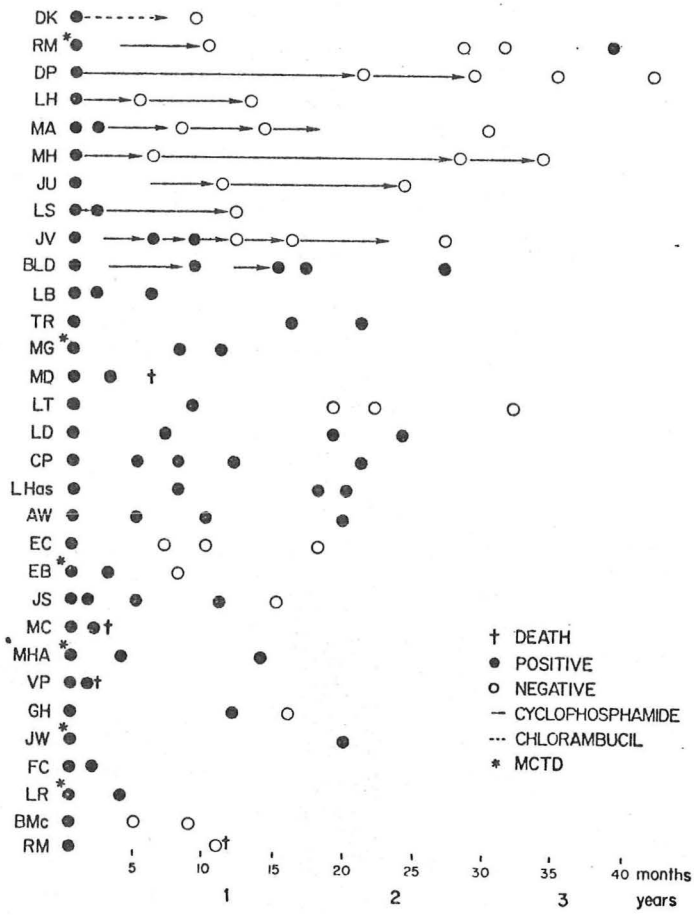
FIGURE 18



Temporal relationship between serum anti-nDNA antibodies and subepidermal Ig in normal skin.
O - Subepidermal Ig absent
● - Subepidermal Ig present

FIGURE 19

Serial Determinations on Lupus Band Test Positive Subjects



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[164]Gilliam, J.N., Cheatum, D.E., Hurd, E.R. and Ziff, M. The prognostic significance of the LE fluorescent band test. Arthritis Rheum. 16:545-546, 1973.

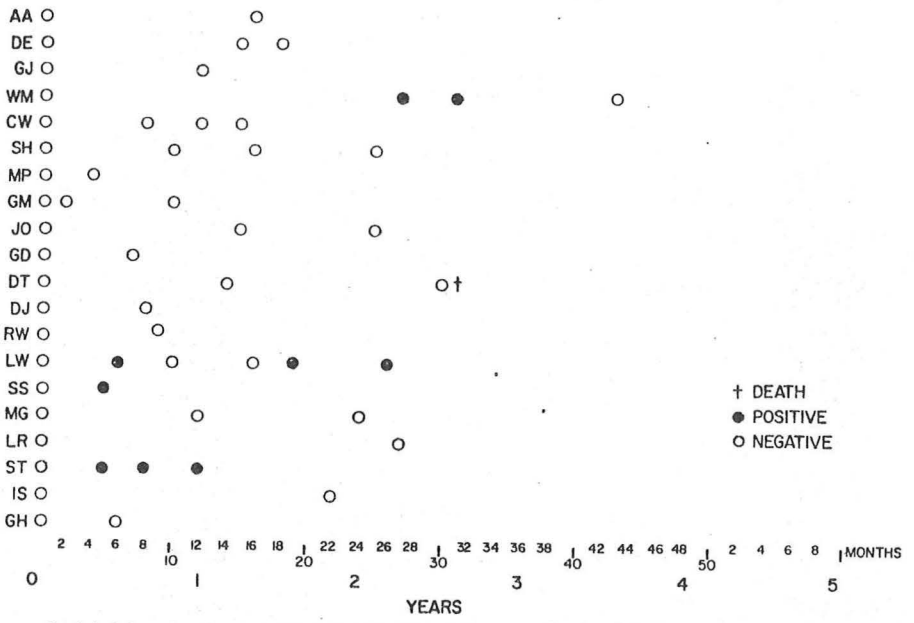
[165]Nesbitt, L.T., Gum, O.B. Direct cutaneous immunofluorescent test in lupus erythematosus. South Med. J. 66:991-997, 1973.

[166]Gilliam, J.N., Hurd, E.R., and Ziff, M. Immunoglobulin in clinically uninvolved skin in systemic lupus erythematosus: effect of immunosuppressive therapy. J. Rheum. (Suppl. No. 1), 1:4, 1974.

or chlorambucil (broken line) administration. All patients were taking prednisone in an average dose of 25 mg. daily. Notice that 9 out of 10 patients treated with alkalating agents plus steroid became negative. In contrast, only 3 patients on steroids alone became negative during the same period of observation. Figure 20 gives similar data on band negative SLE patients. All of these patients were on low doses of prednisone. Three of the 4 patients that developed positive tests experienced well-documented episodes of disease activity characterized by hypocomplementemia and elevated levels of anti-nDNA antibodies during the one to two month period prior to testing. All evidence seems to indicate that the subepidermal accumulation of Ig depends upon the presence of DNA antibodies or DNA:anti-DNA immune complexes in the serum. To test the possibility that a variety of immune complexes might also accumulate in the subepidermal region, 23 non-SLE patients with clinical and laboratory evidence of circulating immune complexes

FIGURE 20

SERIAL DETERMINATIONS ON LUPUS BAND TEST NEGATIVE SUBJECTS



Serial determinations on 20 band negative (absence of subepi. Ig in normal skin) SLE patients.

were tested (Table 11). All of these patients had arthritis and arthralgia. Most had low complement levels, urticaria or cutaneous vasculitis, and several had clinical evidence of glomerulitis. However, none of these patients had cutaenous Ig deposits.

TABLE 11

FLUORESCENT ANTIBODY (FA) STAINING OF CLINICALLY NORMAL SKIN OF NON-SLE PATIENTS WITH PROBABLY CIRCULATING IMMUNE COMPLES

Diagnosis	No. Tested	No. with Subepi. Ig
Hepatitis and arthritis (Australia antigen pos.)	8	0
Glomerulonephritis (post. streptococcal)	8	0
Secondary syphilis	4	0
Cryoglobulinemia (mixed type) with hypocomplementemia	3	0

Active discoid LE is not part of lupus nephritis, although such patients have been observed to develop DLE lesions on remission of the acute phase of their illness.[63] This has occurred in two of the Parkland cyclophosphamide treated SLE patients. Both patients developed DLE lesions several months after all evidence of systemic disease activity, anti-nDNA antibodies and subepidermal Ig in normal skin had disappeared. Even though easily recognized skin lesions are uncommon in patients with lupus nephritis the highly specific immunofluorescence findings in the apparently normal skin more than compensates for the absence of diagnostic gross changes. At least 90% of SLE patients with nephritis will have subepidermal deposits of immunoglobulins.[132] The specificity of this finding for SLE is supported by the data in Table 12. Of 155 patients with a var-

TABLE 12

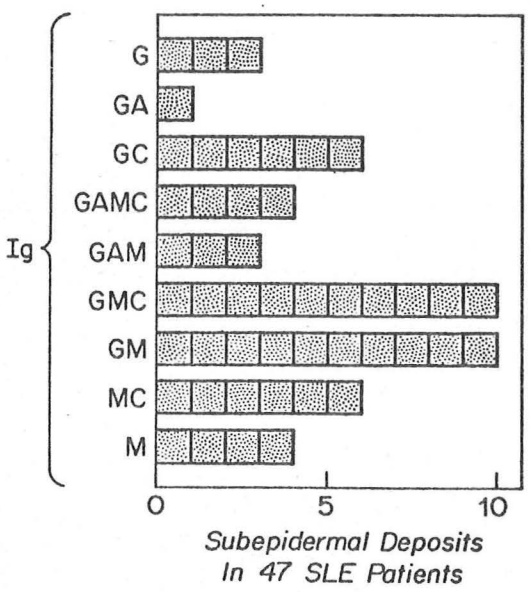
DIRECT CUTANEOUS IMMUNOFLUORESCENCE IN 155 PATIENTS WITH CONNECTIVE TISSUE DISEASES

Diagnosis	No. of Patients	No. with Subepi. Ig*	%
SLE	87	47	53
Scleroderma	11	0	–
Polymyositis	10	0	–
DLE	27	0	–
Rheumatoid arthritis (ANA pos.)	10	1	10
Sjogren's	2	0	–
Raynauds	1	0	–
Drug-induced LE	7	0	–

*Subepi. Ig – subepidermal immunoglobulin (The Lupus band)

iety of rheumatic disease only one non-SLE patient had subepidermal Ig deposits. This patient had a positive antinuclear antibody test and significantly elevated anti-nDNA antibodies without clinical evidence to suggest a diagnosis of LE. Her test for rheumatoid factor was negative. Rochmis and associates[167] have found anti-nDNA antibodies in 4% of sera from a large group of rheumatoid arthritis (RA) patients. All of the RA patients with antiDNA antibodies had normal or elevated complement levels and there was no evidence of renal disease. So a low incidence of band positive RA patients might be expected. Its significance in regard to renal disease in these patients is unknown. It is of interest that our band positive RA patient had only IgM in the subepidermal zone. This finding may be associated with a benign course. Figure 21 gives the prevalence of different Ig classes in the band positive patients. IgM has been found alone in 10 patients. In six of these, sequential studies have shown only IgM on each determination. None of these have had evidence of active renal disease or deterioration of renal function. In contrast, all of the patients with lupus nephritis have had IgG and usually IgG and IgM in their subepidermal deposits. The full significance of these findings is not yet established.

FIGURE 21



Frequency - distribution of Ig classes (G, A, M) in the subepidermal deposits of 47 SLE patients

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[167] Rochmis, P.G., Palefsky, H., Becker, M., Roth, H. and Zvaifler, N.J. Native DNA binding in rheumatoid arthritis. Ann. Rheum. Dis. 33:357-360, 1974.

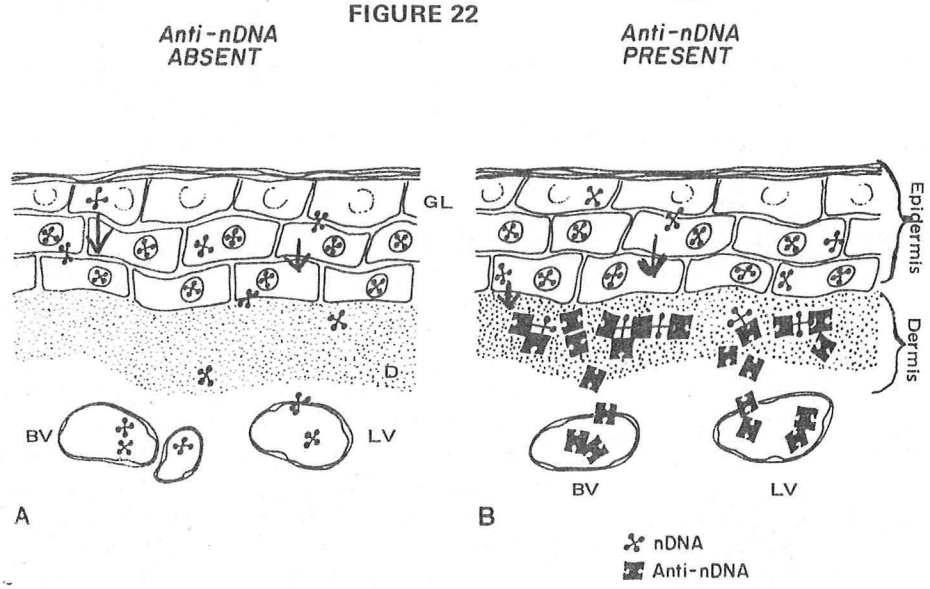
VII.

THE IMMUNOLOGIC RELATIONSHIP BETWEEN CUTANEOUS AND SYSTEMIC LE

PROPOSED MECHANISM OF SUBEPIDERMAL IMMUNOGLOBULIN ACCUMULATION

The serum concentration of antibody to native DNA, its duration in the circulation, and local factors affecting epidermal turn-over appear to be important determinants for the accumulation of Ig at the dermal-epidermal junction. It is well known that during the initial phases of keratinization the nuclei of the cells in the granular layer (upper layer of epidermis) are broken down.[75] Tracer studies[168] have shown that DNA is not incorporated into the stratum corneum. It has been assumed that some of this nuclear material may gain access to the dermis and be removed via blood or lymphatic vessels. Therefore, during the process of normal keratinization, epidermal nuclear material, including fragments of double-stranded DNA, may be liberated. This might explain the observation of Hunter, Dilley, and Holman[50] of native DNA in normal human plasma. If the epidermis is a normal source of endogenous nDNA, then subepidermal accumulation of immunoglobulin would be expected in conditions which characteristically have serum antibody to nDNA, i.e., systemic lupus erythematosus and the autoimmune disease of NZB/W_1 mice (See fig. 22).

FIGURE 22



A. Liberation of epidermal nuclear material at the granular layer (GL) during the process of normal keratinization may result in backdiffusion of nDNA (✣) into the dermis (D). Under normal circumstances this nDNA would pass through the subepidermal zone and be removed by the blood (BV) and lymphatic (LV) vessels.
B. When anti-nDNA (▩) is present the epidermal nDNA (✣) and anti-nDNA precipitate in the subepidermal zone.

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[168] Fukuyama, K. and Bernstein, I.A. Autoradiographic studies of the incorporation of thymidine - H3 into deoxyribonucleic acid in the skin of young rats. Invest. Derm. 36:321-326, 1961.

Natali and Tan[169] have shown that a subepidermal band of immunoglobulin accumulates at sites of UV-irradiation in mice which have been induced to make antibody to UV-altered DNA (UV-DNA). Their experiments demonstrate that under these conditions an epidermal nuclear antigen (UV-DNA) is released and precipitates along the dermal-epidermal junction if the corresponding antibody (anti-UV-DNA) is present. In SLE and in the NZB/W mice, the accumulation of subepidermal immunoglobulin is also enhanced by UV exposure.[170] However, in these spontaneously acquired diseases, UV exposure is not required for subepidermal Ig deposits to appear, and antibody to UV-altered DNA is not a characteristic feature. Therefore, though the mechanism may be similar, a different antigen-antibody system, namely nDNA:anti-DNA, is involved.

In addition to the serum DNA antibody concentration, the local concentration or rate of release of antigen must also play an important role in determining whether detectable amounts of subepidermal antigen-antibody complexes appear. The rate of epidermal nDNA release is probably influenced by many factors that alter epidermal proliferation. This may partially explain the difference between the incidence of the band in light-exposed versus light-protected sites and between lesional and nonlesional skin.

PROPOSED MECHANISM OF LE SKIN DISEASE

The exact relationship between immune complex formation in SLE skin and the development of inflammatory skin lesions is not known. However, we now know that the incidence of chronic LE skin lesions varies inversely with the incidence of serum antibodies to nDNA and subepidermal Ig in normal skin. We also know that the persistent destructive LE skin lesions are not seen in patients with diffuse proliferative glomerulonephritis, marked elevations of anti-nDNA, and heavy subepidermal Ig deposits in uninvolved skin. These facts, plus the absence of histologic or immunopathologic data to implicate antigen-antibody complex mediated injury and the presence of pathologic features which sug-m gest a cell mediated immune response, lead to the conclusion that LE skin disease is caused by the activation of an antigen responsive T-cell. The chronic nature of these lesions suggests persistent or continual liberation of the antigenic stimulus which could be epidermal DNA. This would explain why UV-irradiation[98,171] and trauma[172] of uninvolved DLE skin can initiate new lesions by increasing the local release of antigen.

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[169]Natali, P.G., and Tan, E.M.: Experimental skin lesions in mice resembling systemic lupus erythematosus. Arthritis Rheum. 16:579-589, 1973.

[170]Fogleman, J. and Gilliam, J.N.: Local effect of trauma and ultraviolet light (UVL) on subepidermal accumulation of immunoglobulin (Ig) in female NZB/W (B/W) F. mice. Clin. Rev. 23:23A, 1975.

[171]Freeman, R.G., Knox, J.M. and Owens, D.D.: Cutaneous lesions of lupus erythematosus induced by monochromatic light. Arch. Derm. 100:677-682, 1969.

[172]Lodin, H.: Discoid lupus erythematosus and trauma. Acta Derma. 43:142-148, 1968.

EVIDENCE FOR THE ROLE OF CELL MEDIATED AUTOIMMUNITY IN LE

Attempts to examine cellular (T-cell) hypersensitivity to DNA in patients with SLE by intradermal testing[173,174,175] have been inconclusive. (Table 13) *In vitro* studies of lymphocyte

TABLE 13

Cell-mediated Immunity (CMI) in SLE

1. Lymphocyte response to phytomitogens and PPD is generally intact
2. Skin reactivity to PPD, *Trichophyton*, and *Candida* probably impaired
3. CMI to nucleic acids present in a few patients
4. Lymphocytotoxic antibodies specific for T cells are present
5. Lymphocytes lyse spontaneously with rabbit complement
6. Mixed lymphocyte reaction is blocked due to lymphocyte coating by antibod
7. T cells are reduced in a few patients

From: Talal (17)

responses to DNA have also yielded variable results.[176-179] However, one gains the overall impression from the data in the literature that some SLE patients have DNA responsive lymphocytes. In general, the *in vitro* lymphocyte response has failed to correlate with the presence *in vivo* of anti-nDNA antibodies. Indeed,

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[173] Hahn, B.H., Bagby, M.K., Osterland,C.K.: Abnormalities of delayed hypersinsitivity in systemic lupus erythematosus. Amer. J. Med. 55:25-31, 1973.

[174] Friedman, E.A., Bardawil, W.A., Merrill, J.P., et al: "Delayed" cutaneous hypersensitivity to leukocytes in disseminated lupus erythematosus. N. Engl. J. Med. 262:486-491, 1960.

[175] Bennet, J.C., Holley, H.L.: Philadelphia and London, W.B. Saunders Company, 1961, pp. 205-209.

[176] Azoury, F.J., Jones, H.E., Derbes, V.J., et al: Intradermal tests and antibuclear factors in systemic lupus erythematosus. Ann. Int. Med. 65:1221-1228, 1966.

[177] Patrucco, A., Rothfield, N.F., Hirshhorn, K.: The response of cultured lymphocytes from patients with systemic lupus erythematosus to DNA. Arthritis Rheum. 10:32-37, 1967.

[178] Barfield, H., Atoynatan, T: Cellular immunity in systemic lupus erythematosus (SLE) to nuclear antigens. Arthritis Rheum. 14:369, 1971 (Abst).

[179] Goldman, J.A., Litwin, A., Adams, L.E., et al: Cellular immunity to nuclear antigens in systemic lupus erythematosus. J. Clin, Invest. 51:2669-2677, 1972.

Federlin and Helmke[180] found that lymphocytes from SLE patients with significant levels of serum anti-nDNA antibodies were unresponsive to DNA. However, most studies have failed to relate the presence or absence of DNA-responsive lymphocytes to clinical or serologic features of the disease.

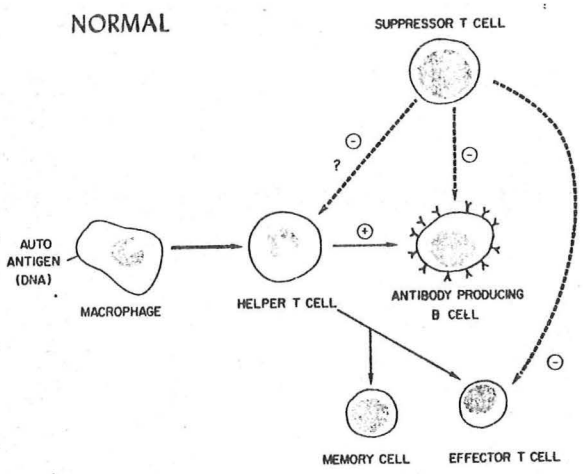
In two studies[181,182] intradermal skin testing with DNA in LE patients has shown a higher incidence of delayed type hypersensitivity in the DLE patients than in SLE patients. These are interesting findings in view of the clinical observations of a higher incidence and increase in severity of cutaneous LE in patients with mild inactive SLE and low or undetectable DNA antibodies.

THE SIGNIFICANCE OF LE SKIN DISEASE IN ASSESSING THE IMMUNOLOGIC IMBALANCE IN LE

If one assumes that tolerance to DNA is normally maintained by T-cell suppression of DNA-responsive B and T lymphocytes (Fig. 23); then DLE might be due to a moderate impairment of

FIGURE 23

REGULATION OF THE IMMUNE RESPONSE



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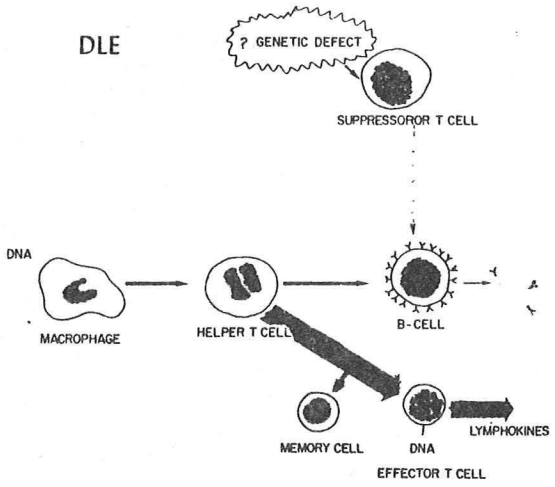
[180] Federlin, K. and Helmk, K.: Depression od cellular hypersensitivity to DNA in systemic lupus erythematosus. The Lancet. II:596, 1972.

[181] Jones, H.E., Derbes, V.J., Gum, O.B., Azoury, F.J.: Skin test with nuclear factors in systemic lupus erythematosus. Arch. Dermatol. 99:559-564, 1967.

[182] Fardal, R.W. and Winkelman, R.K.: Hypersensitivity to deoxyribonucleic acid in cutaneous disease, Arch. Derm. 91:503-511, 1965.

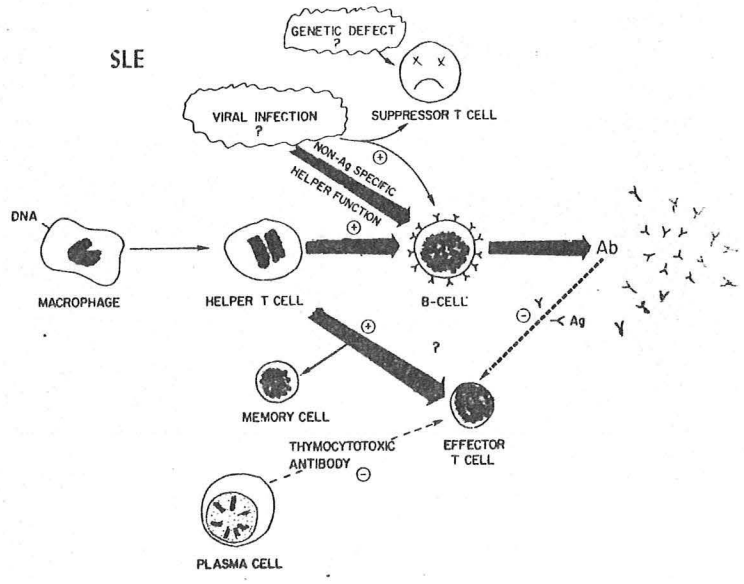
this suppressor activity in conjunction with genetic factors that result in a state of T-cell hyper-responsiveness to DNA. DNA-responsive T-cells would encounter DNA in the dermis and be stimulated to secrete lypmhokines, leading to skin lesions. In this case, the B-cell produces minimal amounts of antibody to DNA. (Fig. 24).

FIGURE 24
REGULATION OF THE IMMUNE RESPONSE



SLE may be due to a similar but more severe defect of T-cell suppressor function, perhaps because of a superimposed virus infection. The resulting release of DNA responsive T and B lymphocytes with the addition of a persistent viral infection may supply the B-cell with a non-antigen specific "helper" effect. This added stimulus, plus the loss of T-cell suppression, may allow DNA responsive B-cells and ultimately plasma cells to produce large amounts of anti-DNA antibody which forms nephrotoxic DNA:anti-DNA complexes (Fig. 25).

FIGURE 25
REGULATION OF THE IMMUNE RESPONSE



On the other hand, the DNA-responsive effector T-cells may be blocked by such large amounts of immune complexes or antibody so that LE skin disease is either prevented or reduced to the characteristic transient and hypocellular lesions of acute LE. The effector T-cell function may be further reduced, in a more general way, by the thymocytotoxic antibodies which are commonly present in active SLE.[184-186] This generalized impairment of cell mediated immunity would allow the persistence of the viral infection with maintenance of this state of immunologic imbalance.

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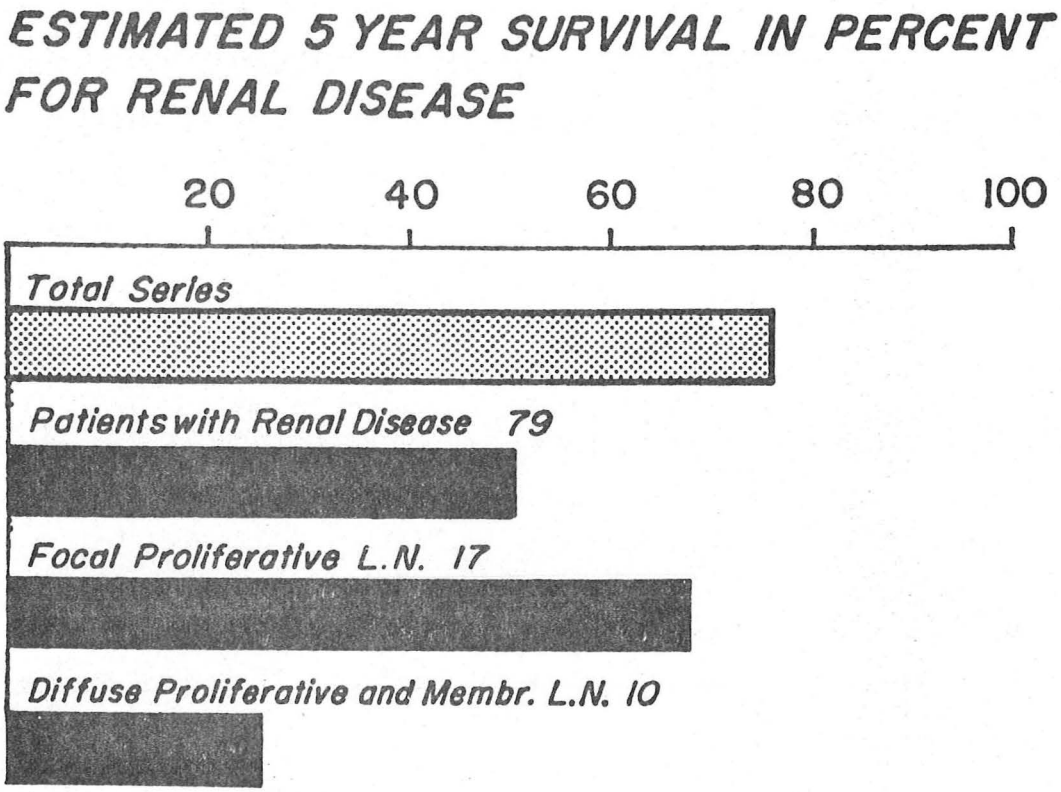
[184] Stastny, P. and Ziff, M.: Antibodies against cell membrane constituents in systemic lupus erythematosus and related diseases. I. Cytotoxic effect of serum from patients with systemic lupus erythematosus (SLE) for allogeneic and for autologous lymphocytes. Clin, Exp. Immunol. 8:543, 1971.

[185] Butler, W.T., Sharp, J.T., Rossen, R.D., Lidsky, M.D., Mittal, K.K., and Sard, D.A. Relationship of the clinical course of systemic lupus erythematosus to the presence of circulating lymphocytotoxic antibodies. Arth. Rheum. 15:251, 1972.

[186] Stastny, P. and Ziff, M. Direct lysis of lymphocytes by complement in patients with systemic lupus erythematosus. Arth. Rheum. 14:733, 1971.

Table 9S1-8. CUTANEOUS MANIFESTATIONS OF SLE IN 150 PATIENTS[1860]

Manifestation	Percent
Malar rash	39
Alopecia	37
Dermal vasculitis	21
Raynaud's phenomenon	21
Purpura	17
Discoid lesions	14
Hives or angioneurotic edema	13
Rheumatoid nodules	11
Mucous membrane lesions	7



COMMON CLINICAL MANIFESTATIONS IN PATIENTS WITH SPECKLED EPIDERMAL NUCLEAR STAINING (ENS)

Clinical Manifestation	%
Arthritis/Arthralgia	90
Raynauds	72
Sclerodactyly	55
Polyserositis	50
Weakness/Myalgia	44
Alopecia or Skin Rash	44
Adenopathy	28

CLINICAL FEATURES OF PATIENTS WITH ANTIBODIES TO RNase SENSITIVE AND RNase RESISTANT ENA

	Anti-ENA	
Clinical Features	RNase Sensitive	RNase Resistant
Raynauds	(13/15) 87%	(1/5) 20%
Lymphadenopathy	(6/15) 40%	(1/5) 20%
Serositis	(6/15) 40%	(1/5) 20%
Myositis	(3/15) 20%	(0/5) 0%
Nephritis	(0/15) 0%	(4/5) 80%

UNCOMMON LABORATORY FINDINGS IN ANTI-ENA AND SENS* POSITIVE PATIENTS

Laboratory Findings	%
Serum anti-nDNA	24
Pos. RA Latex test	24
Hypocomplementemia	19
Pos. Coombs test	19
Pos. LE Cell Test	10
Azotemia	10

*SENS – speckled epidermal nuclear staining

LABORATORY FINDINGS IN PATIENTS WITH SERUM ANTI-ENA ANTIBODIES AND SENS*

Laboratory Findings	%
Positive FANA (speckled)	100
Hypergammaglobulenemia	81
Subepi. Ig (normal skin)	45

*SENS – speckled epidermal nuclear staining

LABORATORY FINDINGS IN PATIENTS WITH ANTIBODIES TO RNase SENSITIVE AND RNase RESISTANT ENA

	Anti-ENA	
Laboratory Findings	RNase Sensitive	RNase Resistant
Hypergammaglobulinemia	(12/15) 80%	(4/5) 80%
Elevated anti-nDNA	(0/15) 0%	(4/5) 80%
Hypocomplementemia	(3/15) 20%	(4/5) 80%
Subepidermal Ig	(5/15) 33%	(4/5) 80%