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SYSTEMIC LUPUS ERYTHEMATOSUS: Recent developments

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I. INTRODUCTION

Lupus Erythematosus has for many years fascinated internists, dermatologists, rheumatologists, nephrologists, neurologists, immunologists and others, all of whom have given testimony of their interest and contributions in the vast literature accumulated on the subject. It would not do justice to this effort to attempt to cover all of the writing in this brief presentation. Those who wish to inform themselves of the older literature are referred to the excellent reviews in the following:

1. Talbott, J.H. and Ferrandis, R.M. Collagen diseases. Grune & Stratton, New York, 1956.

2. Dubois, E.L. Lupus erythematosus. McGraw-Hill Book Company, New York, 1966.

The latter which covers material from 1453 references truly contains all the information up to 1966. Therefore the present discussion will be devoted mainly to the literature of the last 3 or 4 years. A selected review covering the SLE literature of 1970 and 1971 has recently been published.

3. Wallace, S.L., Diamond, H., and Kaplan, D. Recent advances in rheumatic diseases: the connective tissue diseases other than rheumatoid arthritis in 1970 and 1971. Ann. Int. Med. *77:*455, 1972.

In an effort to further reduce the material, to make it manageable, it was decided arbitrarily to exclude the literature pertaining to viruses, virus-like structures and anti-viral antibodies. The reasons for this are two-fold: a) an extensive presentation of the "virus" material has recently been made to this audience and published,

4. Ziff, M. Viruses and connective tissue diseases. Ann. Int. Med. *75:*951, 1971.

and b) in spite of the intensive efforts of numerous investigators, it is the judgment of the present reviewer that this approach has yielded very little worthwhile reporting.*

II. CASE HISTORIES AND TEACHING SLIDES

Because it is desirable in this type of conference to give an overview of salient clinical features, case histories have been chosen to illustrate several points and some slides will be shown which will

*The hope of finding an etiologic agent has again waned after an initial flurry of enthusiasm. However, the view that infection and probably common viruses play some contributory role is a well justified, widely held assumption. The current views on the pertinent pathogenic mechanisms will be discussed below.

depict well established manifestations of this disease. They will serve perhaps to inform some of the younger members of the audience and to remind others of the multiple facets that characterize this disease.

Case 1. Case of a young woman who developed lupus nephritis, CNS involvement, myositis, was treated with cyclophosphamide and went into complete remission.

[redacted]

This young [redacted] woman first presented in [redacted] of 1965, at the age of 15, with a two months history of arthritis involving PIP joints and knees, fever and a malar rash. She was anemic (Hgb 8.2) and the LE prep was positive. A kidney biopsy showed diffuse mesangial involvement, focal areas of proliferative glomerulitis and interstitial inflammation. Her course was characterized by persistent fever, arthalgias, and convulsions. In [redacted] 1965, she was admitted to psychiatry in a state of disorientation and organic psychosis secondary to SLE. She was treated with prednisolone, 6-mercaptopurine and thorazine. She developed large decubital ulcers. This hospital stay lasted until [redacted] of 1966. In [redacted] 1966, she developed muscle tenderness and weakness. In [redacted] 1967, hospitalized with marked weakness, elevated SGOT, aldolase and CPK. EMG consistent with polymyositis. She was febrile, Hgb 8, C3 76 mg%, urinary protein 5 gm/24 hrs. She also was markedly hyperglycemic requiring insulin 80 u per day. Treatment consisted of prednisolone 40 mg and cytoxan 2 mg/kg. After discharge she was maintained on cytoxan. Prednisolone was reduced to 10 mg daily and insulin was stopped when no longer needed. Cytoxan was maintained for two years with patient now in complete remission. The drug was finally discontinued when the patient developed herpes zoster. Several months after stopping the cyclophosphamide the patient became pregnant. She went through a normal pregnancy and delivered twins at term with no problems. She continues to take prednisolone 5 mg daily and her antinuclear test is still positive.

Case 2. A patient presented with arthritis, Raynaud's Syndrome and pericarditis; she then developed hemolytic anemia and was found to have Hodgkins' lymphoma.

[redacted]

This [redacted] girl first presented at the age of 16, complaining of joint pains and cold sensitivity. She improved but continued to have Raynaud's phenomenon for which she was treated with aldomet. She had positive LE, antinuclear and sensitized sheep cell reactions. About 2 years later she developed pericarditis which was treated with prednisone. During this time the diagnosis was first mixed connective tissue disease and later probable SLE. She did well

until early 1972, when she began to loose weight and developed anemia with low serum iron which did not respond to Fergon. In [redacted] 1972, she was found to have a Coombs negative hemolytic anemia and marked hypoalbuminemia. Hgb was 5.6, serum albumin 1.9. The anemia was difficult to control requiring high doses of steroids. She had a positive Schirmer test and punctate staining of the cornea suggesting Sjögren's syndrome. A mediastinal mass was discovered on chest X-Ray and lymph node biopsy revealed she had Hodgkins' disease from which she eventually died.

Case 3. A young girl had lupus involving the skin and kidney with progressive loss of renal function. She did well after kidney transplantation but 1 1/2 years later developed an intracranial tumor.

[redacted]

This [redacted] girl was twelve years old when she developed a rash over the malar area and hands. The diagnosis of lupus erythematosus was made in Lubbock and she was treated with steroids with some improvement. A year later she developed an ear infection and the rash returned. A few months later she began to have edema and gained 30 pounds of weight. She was then referred to [redacted] in [redacted] 1970. She was found to be in terminal renal failure and required hemodialysis. In [redacted] 1970, she received a kidney transplant from a cadaveric donor. In [redacted] 1971 she underwent bilateral nephrectomy for control of hypertension. After this she did well for 1 1/2 years when she began noticing left-sided weakness and twitching. An intracranial tumor was found which was treated by irradiation. She has recovered most of her neurologic function and her kidney transplant is functioning well.

Case 4. This patient with SLE developed recurrent leukopenia and infections. The leukopenia which was associated with autoantibodies was controlled on prednisolone.

[redacted]

This 36 year old [redacted] woman developed lupus erythematosus 7 years ago with arthalgia, fever, skin rash and cervical adenitis but no evidence of renal disease. She had elevated ESR, positive LE prep and latex test, decreased serum complement and leukopenia. She had two hospital admissions for fever and exacerbation of skin rash. In [redacted] 1970, she was seen with weakness, anorexia, severe rash after sun exposure. Temperature was 105; WBC 1200. She developed a supraclavicular cellulitis and pneumococal septicemia. At the time her leukopenia was noted she was found to have autoantibodies against her own white blood cells. During the course of steroid treatment over a period of 6 weeks these antibodies disappeared.

Steroid treatment was maintained as required to control WBC above 4000. Subsequently she developed skin lesions on hands and face for which she was treated with hydroxychloroguine with excellent response. She is now in remission on prednisolone 5 mg/day.

Case 5. An elderly woman developed manifestations of lupus erythematosus after treatment with procainamide.

[redacted]

A 69 year old [redacted] woman who had a history of hypertension and Graves' disease treated by thyroidectomy was admitted for shortness of breath, paroxysml nocturnel dyspnea and chest X-Ray compatible with a congestive state. She was treated for congestive heart failure and because of frequent PVCs was started on procainamide. About a year later she was seen in rheumatology clinic complaining of polyarthragia. ESR was 90, latex negative, LE prep positive and ANA 3+; Coombs' test was reactive. She developed pain and swelling in both wrists and knees and procainamide was discontinued. Her final hospital admission was 2 months later when she developed gangrene of the L foot and sepsis. She received procainamide for 1 week. At autopsy it was found she had a sterile pericarditis, with hematoxylin bodies consistent with the procainamide-induced lupus erythematosus syndrome.

The slides to be shown illustrate the following:

1. Skin lesions of SLE
2. LE cells
3. Antinuclear fluorescence patterns
4. Lupus nephritis
5. Immunofluorescence in the skin

III. IMMUNOLOGY AND PATHOGENESIS

It has been known for a long time that patients with SLE produce a variety of abnormal antibodies. It has been clearly established that some of these are of pathogenic significance. Increasingly also, evidence is accumulating of immunologic pathogenesis in the sister diseases, rheumatoid arthritis, polymyositis and scleroderma.

A wide range of aberrations in the functions of the immune apparatus has been found in patients with SLE. This has included *a defect in phagocytosis,*

5. Brandt, L., Hedberg, H. Impaired phagocytosis by peripheral blood granulocytes in Systemic Lupus Erythematosus. Scand. J. Haemat. *6:*348, 1969.

defective delayed hypersensitivity,

6. Abe, T. and Homma, M. Immunological reactivity in patients with systemic lupus erythematosus. Humoral antibody and cellular immune responses. Acta. Rheum. Scand. *17:*35, 1971.

7. Horwitz, D.A. Impaired delayed hypersensitivity in systemic lupus erythematosus. Arth. Rheum. *15:*353, 1972.

abnormalities in the production of immunoglobulins,

8. Smith, C.K. and Cassidy, J.L. Type I dysgammaglobulinemia, systemic lupus erythematosus and lymphoma. Am. J. Med. *48:*113, 1970.

and *in complement components.*

9. Pondman, K.W., Stoop, J.W., and Cormane, R.H., et al: Abnormal C´1 in a patient with systemic lupus erythematosus. J. Immunol. *101:*8111, 1968.

10. Moncada, B., Day, N.K.B., Good, R.A., and Windhorst, D.B. Lupus-erythematosus-like syndrome with a familial defect of complement. New Eng. J. Med. *286:*698, 1972.

11. Day, N.B.K., Geiger, H., Stroud, R., de Bracco, M., Mancado, B., Windhorst, D., and Good, R.A. C1r deficiency in human serum: a possible inborn error associated with cutaneous and renal disease. J. Clin. Invest. *51:*1102, 1972.

12. Agnello, V., de Bracco, M.E. and Kunkel, H.G. Hereditary C2 deficiency with some manifestations of systemic lupus erythematosus. J. Immunol. *108:*837, 1972.

This is a relatively recent area of investigation and the frequency and distribution of such defects in patients with SLE is not yet known. Some of the defects are probably isolated findings. Patients appear to have one defect or another. In one report, delayed hypersensitivity skin tests for most antigens were similar in SLE patients and controls.

13. Block, S.R., Gibbs, C.B., Stevens, M.D., Shulman, L.E. Delayed hypersensitivity in systemic lupus erythematosus. Ann. Rheum. Dis. *27:*311, 1968.

Hereditary complement component defects are rare and it is argued that if SLE has developed in one case in association with an inborn deficiency of Clr and in another with absence of C2, it is most likely not due to chance.

Several authors have speculated that autoimmunity may be a consequence of immunologic deficiency states

14. Fudenberg, H.H. Are autoimmune diseases immunologic deficiency states? Hospital Practice, Jan. 1968, p. 43.

or of loss of homeostasis which requires a controlling function on the part of the thymus,

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

or of a combination of factors where "infections with common viruses would lead to autoimmunity in susceptible hosts with genetically altered cellular and humoral immunity."

16. Talal, N. Immunologic and viral factors in the pathogenesis of systemic lupus erythematosus. Arth. Rheum. *13:*887, 1970.

The theme of a *genetic factor in human SLE* was reviewed by Leonhardt as follows:

(1) evidence of *familial aggregation* of SLE,

(2) presence of *hypergammaglobulineima in relatives*,

(3) presence of *antinuclear antibodies in relatives*,

(4) presence of other *abnormal antibodies* (rheumatoid factor, biologic false positive serologic reaction for syphilis) *in relatives*,

17. Leonhardt, E.T.G. Family studies in systemic lupus erythematosus. Clin. Exp. Immunol. *2:*743, 1967.

In agreement with the above, in another study IgG measured by radial diffusion was found elevated in relatives of SLE patients and significantly different from the IgG levels of spouses.

18. Larsen, R.A. Family studies in systemic lupus erythematosus (SLE). VII. Serum immunoglobulins: IgG concentrations in relatives and spouses. J. Chron. Dis. *25:*205, 1972.

Another approach to the question of genetic predisposition for the development of SLE is offered by the study of *histocompatibility antigens*. This is particularly attractive because of the known linkage between histocompatibility loci and genetic loci governing the immune response in mice and guinea pigs, as well as loci coding for susceptibility to certain oncogenic viruses in mice.

An abnormal distribution of HL-A antigens has been found.

19. Waters, H., Konrad, P. and Walford, R.L. The distribution of HL-A histocompatibility factors and genes in patients with systemic lupus erythematosus. Tissue Antigens *1*:57, 1971.

20. Grumet, E.K., Conkell, A., Bodmer, J.G., Bodmer, W.E. and Dewitt, H.O. Increased incidence of two leukocyte antigen specificities in systemic lupus erythematosus. New Eng. J. Med. *285*:193, 1971.

This was true also in our series of black patients with SLE.

21. Stastny, P. The distribution of HL-A antigens in black patients with systemic lupus erythematosus (SLE). Arth. Rheum. *15*:455, 1972 (Abstr.).

The question has been raised whether autoantibodies known to be present in these patients do not produce false results in HL-A typing. In support of this view, in our series, the frequency of "null" genes was reduced in the SLE group compared to the controls.

The discovery of the *LE phenomenon* paved the way for the eventual realization of the importance of antibodies against nuclear constituents in SLE. The account of the events that led to the discovery of the LE phenomenon in the course of bone marrow studies beginning in 1943, makes fascinating reading.

22. Hargraves, M.M. Discovery of the LE cell and its morphology. Mayo Clin. Proc. *44*:579, 1969.

It was not at first realized that the phenomenon required a period of *in vitro* incubation. Soon it was realized that a complex immunologic phenomenon was involved. The primary reaction was that of antinuclear antibodies with nuclear constituents.

The *immune response against nuclear antigens* has been studied extensively. A variety of antibodies against nucleic acids are found,

23. Levine, L. and Stollor, B.D. Nucleic acid immune systems. Prog. Allergy *12*:161, 1968.

cellular immunity to nuclear antigens may also develop.

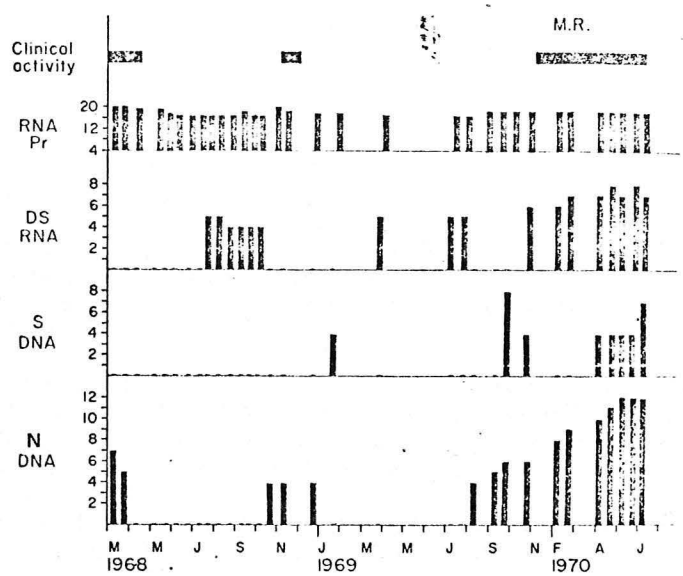
24. Goldman, J.A., Litwin, A., Adams, L.E., Krueger, R.C. and Hess, E.V. Cellular immunity to nuclear antigens in systemic lupus erythematosus. J. Clin. Invest. *51:*2669, 1972.

It was shown that anti-native DNA (NDNA) and certain anti-double-stranded RNA antibodies also reacted with single-stranded DNA (SSDNA) In most sera anti-NDNA reacted more avidly with SSDNA. It made no difference whether the SSDNA was derived from mammalian, bacterial or viral sources.

25. Koffler, D., Carr, R.I., Agnello, V., Feizi, T. and Kunkel, H.G. Antibodies to polynucleotides: distributions in human serums. Science *166:*1648, 1969.

Anti-NDNA antibodies were closely associated with disease activity and were rarely found in conditions other than SLE. Anti-SSDNA and DSRNA were also frequently increased during periods of active SLE but also were found high during periods of quiesence. They were frequently present in sera from patients who did not have SLE.

26. Koffler, D., Carr, R., Agnello, V., Thoburn, R., and Kunkel, H.G. Antibodies to polynucleotides in human sera; antigenic specificity and relation to disease. J. Exp. Med. *134:*294, 1971.



Three episodes of clinical activity associated with rises in anti-NDNA antibo... The third clinical episode of activity shows parallel increases in SDNA, DSRNA, and NDNA antibody titers. Anti-DSRNA antibodies persist during quiescent periods. Note anti-nucleoprotein antibodies persist in high titer throughout the course of the disease.

Figure 1.
(from Koffler, Carr, Agnello et al. J. Exp. Med. *134:*294, 1971)

Three out of 25 SLE patients in whom serial studies were available never developed anti NDNA antibodies even in the presence of severe renal disease. It was suggested that other antigen-antibody systems must have played a role in the renal disease developing in these patients.

Table 1. Incidence of Antibodies to Polynucleotides

(modified from Koffler et al, J. Exp. Med. *134*:294, 1971.)

Diagnosis	Number Tested	Percent Positive NDNA	SDNA	RNAPr
Normal	110	0.3	3.7	0
Hospital pts.	65	0	16.8	3.1
SLE	60	60.0	87.0	66.6
Procainamide	19	0	52.6	0
Rheumatoid Arth.	32	3.1	59.5	15.5
Chr. Glomerulonephritis	40	2.5	7.5	2.5
Chr. Active hepatitis	43	2.3	58.2	0

A number of other publications deal with antibodies to DSRNA and to ribonucleoprotein,

27. Schur, P.H., Stollar, B.D., Steinberg, A.D. and Talal, N. Incidence of antibodies to double-stranded RNA in systemic lupus erythematosus and related diseases. Arth. Rheum. *14*:342, 1971.

28. Reichlin, M. and Mattioli, M. Correlation of precipitin reaction to an RNA protein antigen and a low prevalence of nephritis in patients with systemic lupus erythematosus. New Eng. J. Med. *286*:908, 1972.

29. Mattioli, M. and Reichlin, M. Characterization of a soluble nuclear ribonucleoprotein antigen reactive with SLE sera. J. Immunol. *107*:1281, 1971.

Soluble ribonucleoprotein antigen is reactive with SLE sera by precipitin analysis and by complement fixation. This antibody is

found also in other connective tissue diseases. It is associated with the "speckled" pattern of nuclear fluorescence.

Anti-RNA antibodies in SLE sera were inhibited by viral RNA.

30. Talal, N., Steinberg, A.D. and Daley, G.C. Inhibition of antibodies binding polyinosisus-polycytidylic acid in human and mouse lupus sera by viral and synthetic ribonucleic acids. J. Clin. Invest. *50:*1248, 1971.

The authors speculate that this antibody may be induced by virus infection.

Another way DNA may be altered to make it antigenic could be by irradiation with ultraviolet light.

31. Tan, E.M. and Stoughton, R.B. Ultraviolet light alteration of cellular deoxyribonucleic acid *in vivo*. Proc. Natl. Acad. Sci. USA *62:*708, 1969.

Release of DNA was found to be a common phenomenon following a variety of causes of cellular injury.

32. 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. Arth. Rheum. *14:*259, 1971.

Release of DNA after trauma, infection, steroid therapy in SLE patients with anti-DNA antibodies may provide opportunity for the *in vivo* formation of immune complexes.

Such complexes in the sera of patients with SLE can be demonstrated by precipitin reaction with Clq in gel diffusion.

33. Agnello, V., Winchester, R.J. and Kunkel, H.G. Precipitin reactions of the Clq component of complement with aggregated gamma globulin and immune complexes in gel diffusion. Immunology *19:*909, 1970.

34. Agnello, V., Koffler, D., Eisenberg, J.W., Winchester, R.J. and Kunkel, H.G. Clq precipitins in the sera of patients with systemic lupus erythematosus and other hypocomplementeuric states: characterization of high and low molecular weight types. J. Exp. Med. *134:*(Suppl.) 228, 1971.

Circulating complexes reacting with Clq were associated with disease activity and *in vivo* complement depression.

Cold insoluble complexes (cryoglobulin) in 11 of 31 patients with SLE consisted mainly of IgG and Clq. Presence of these complexes was associated with decrease in the serum levels of C3.

35. Stastny, P. and Ziff, M. Cold-insoluble complexes and complement levels in systemic lupus erythematosus. New Eng. J. Med. *280:*1376, 1969.

The *in vivo* reaction of antinuclear antibodies with LE cell formation in synovial fluid has been reported.

36. Hunder, G.G., and Pierre, R.V., *In vivo* LE cell formation in synovial fluid. Arth. Rheum. *13:*448, 1970.

Another type of reaction thought to represent *in vivo* binding has been observed in renal biopsies of patients with SLE.

37. McCoy, R.C. Nuclear localization of immunoglobulins in renal biopsies of patients with lupus nephritis. Am. J. Path. *68:*469, 1972.

Homogeneous, nuclear rim and speckled patterns were observed. Since nuclear localization of immunoglobulins was seen in areas of histologically uninvolved parenchyma their significance is at present unknown.

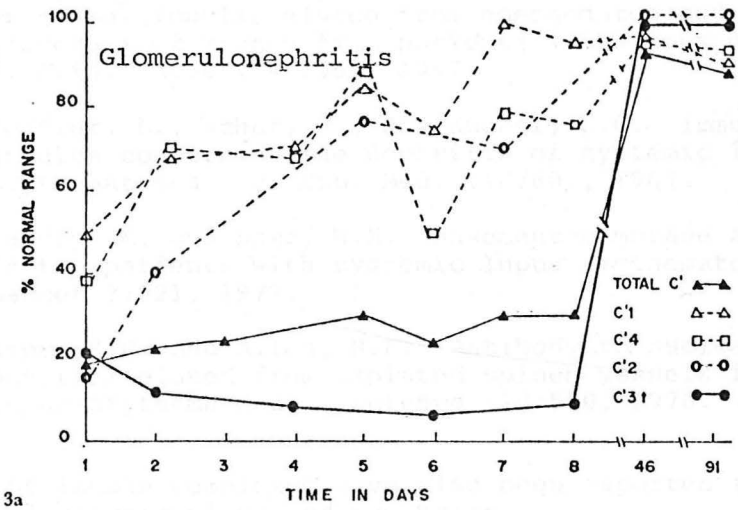
In vivo formation of antigen-antibody complexes is thought to be causally related to the *depressed levels of complement in SLE.*

38. Gewurz, H., Pickering, R.J., Mergenhagen, S.E. and Good, R.A. The complement profile in acute glomerulonephritis, systemic lupus erythematosus and hypocomplementemic chronic glomerulonephritis. Contrasts and experimental correlation. Int. Arch. All. App. Immun. *34:*556, 1968.

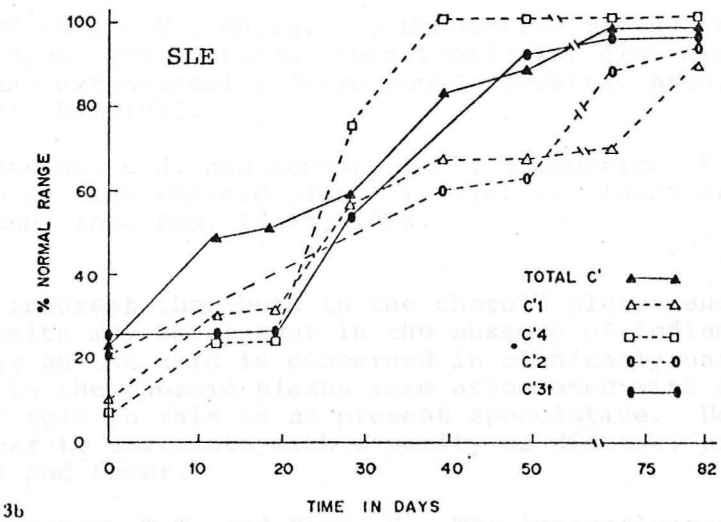
39. Lewis, E.J., Carpenter, C.B. and Schur, P.H. Serum complement component levels in human glomerulonephritis. Ann. Intern. Med. *75:*555, 1971.

40. Pickering, R.J., Michael, A.F., Jr., Herdman, R.C., et al: The complement system in chronic glomerulonephritis: three newly associated aberrations. J. Pediatr. *78:*30, 1971.

Detailed study of complement components in the course of SLE, acute glomerulonephritis and hypocomplementemic chronic glomerulonephritis has revealed different profile. In SLE the early complement components Cl and C 4 are markedly depressed. In AGN and hypocomplementemic chronic GN there is predominant and persistent reduction of the late component C3.



3a



3b

Sequential hemolytic C′ profiles. (a) An 8-year-old girl with acute glomerulonephritis (AGN). In the convalescent interval C′ 1, C′ 4 and C′ 2 titers returned to normal, while the C′ 3t titer remained depressed. The time indicates days after hospital admission. (b) A 10-year-old girl with systemic *lupus erythematosis* (SLE). In the convalescent interval each of the classical C′ component titers returned to normal concomitantly.

Figure 2.

Elution studies of deposits in kidney, skin and spleen have demonstrated the presence of antinuclear antibodies.

41. Krishman, C. and Kaplan, M.H. Immunopathologic studies of systemic lupus erythematosus. II. Antinuclear reaction of gamma-globulin eluted from homogenates and isolated glomeruli of kidney from patients with lupus nephritis. J. Clin. Invest. *46:*569, 1967.

42. Koffler, D., Schur, P., and Kunkel, H.G. Immunological studies concerning the nephritis of systemic lupus erythematosus. J. Exp. Med. *126:*607, 1967.

43. Landry, M. and Sams, W.M. Basement-membrane antibodies in two patients with systemic lupus erythematosus. Lancet *1:*821, 1972.

44. Svec, K.H. and Allen, S.L. Antibody to nuclear material eluted from isolated spleen vessels in systemic lupus erythematosus. Science *170:*550, 1970.

Deposits of immune complexes have also been reported in the heart, joints, and choroid plexus of the brain.

45. Grishman, E., Churg, J., Connective tissue in systemic lupus erythematosus demonstration of disseminated vascular and extravascular "wire loop" deposits. Arch. Path. *91:*156, 1971.

46. Atkins, C.J. and Kondon, J.J., Quismorico, F.P. and Friou, G.J. The choroid plexus in systemic lupus erythematosus. Ann. Int. Med. *76:*65, 1972.

It is of interest that both in the choroid plexus and in the skin such deposits may be present in the absence of inflammatory changes and as far as the skin is concerned in clinically uninvolved tissue. Deposits in the choroid plexus were associated with mental symptoms but their role in this is at present speculative. Deposits in the skin appear to correlate with severity of disease, presence of nephritis and fever.

47. Burnham, T.K. and Fine, G. The immunofluorescent "band" test for lupus erythematosus. 3. Employing clinically normal skin. Arch. Dermatol. *103:*24, 1971.

48. Gilliam J.N., Cheatum, D.E., Hurd, E.R., and Ziff, M. The prognostic significance of the LE fluorescent band test. (to be published)

Presence of DNA in the complexes deposited in the kidney of patients with SLE nephritis has been demonstrated by direct immunofluorescent staining.

49. Andres, G.A., Accinni, L., Beiser, S.M., Christian, C.L., Cinotti, G.A., Frlanger, B.F., Hsu, K.C. and Seegal, B.C., Localization of fluorescein-labeled antinucleoside antibodies in glomeruli of patients with active systemic lupus erythematosus. J. Clin. Invest. *49:*2106, 1970.

Since the complement system is thought to be involved in the development of the inflammatory changes leading to tissue damage in SLE nephritis the *relative complement-fixing activity of antinuclear antibodies* in patients with and without clinical renal disease was studied. High complement-fixing activity was found in the nephritis group and low in the others. The latter were mainly patients with rheumatoid arthritis and patients with drug-induced anti-nuclear antibodies.

50. Tojo, T. and Frion, G.J. Lupus nephritis: varying complement fixing properties of immunoglobulin G antibodies to antigens of cell nuclei. Science, *161:*904, 1968.

51. Cossio, P.J. Complement-fixing ability of antinuclear factors. Studies in adult and juvenile rheumatoid arthritis and systemic lupus erythematosus. Ann. Rhem. Dis. *30:*640, 1971.

The *IgG subclass of anti-nuclear and anti-DNA antibodies* was studied. A predominance of IgG 1 and IgG3, the types which fix complement most efficiently, was found in anti-DNA antibodies. Diffuse and speckled anti-nuclear antibodies were predominantly anti-IgG3. It was speculated that a property in IgG1 other than complement fixation may be important for the development of clinical nephritis.

52. Kacaki,J.N., Callerame, M.L., Blomgren, S.E. and Vaughan, J.H. IgG subclasses of antinuclear antibodies and renal deposits: comparison of systemic lupus erythematosus (SLE) drug-induced lupus (P-SLE) and rheumatoid arthritis. Arth. Rheum. *12:*671, 1969.

53. Schur, P.H., Monroe, M., and Rothfield, N. The γG subclass of antinuclear and antinucleic acid antibodies. Arth. Rheum. *15:*174, 1972.

Properdin was found in the kidneys of 6 out of 7 patients with lupus nephritis and in the dermal-epidermal junction in one of two SLE patients with an erythematosus rash. The presence of properdin suggests activation of complement by the alternate pathway which does not require C1, C4 and C2.

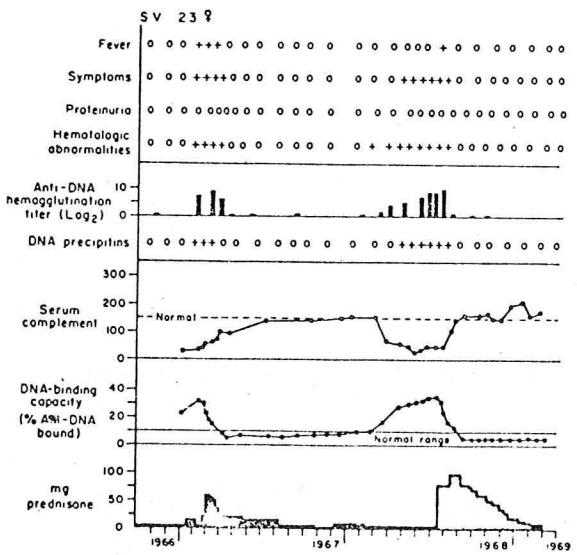
54. Rothfield, N., Ross, H.A., Minta, J.O. and Lepow, I.A. Glomerular and dermal deposition of properdin in systemic lupus erythematosus. New. Eng. J. Med. *287:*681, 1972.

Properdin has also been reported in the glomeruli of patients with acute poststreptococcal glomerulonephritis and chronic membrano-proliferative glomerulonephritis.

55. Westberg, N.G., Naff, G.B., Boyer, J.T. et al, Glomerular deposition of properdin in acute and chronic glomerulonephritis with hypocomplementemia. J. Clin. Invest. *50:*642, 1971.

Serological studies, immunofluorescence studies and immunochemical assay of glomerular eluates have indicated that several antigen-antibody systems may be involved in the pathogenesis of SLE nephritis.

56. Koffler, D., Agnello, V., Thoburn, R. and Kunkel, H.G. Systemic lupus erythematosus: prototype of immune complex nephritis in man. J. Exp. Med. *134:* (Suppl.) 169, 1971.



Serial study of a patient (S. V.) with SLE, showing two clinical exacerbations associated with increases in the titer of anti-NDNA antibodies and serum complement depression. Antibodies were assayed by agar gel precipitation, hemagglutination, and an ammonium sulfate precipitation test using tritiated actinomycin-labeled DNA (AM-DNA). No proteinuria was observed.

Figure 3.
(from Koffler, et al J. Exp. Med. *134:*(Suppl.) 1971)

The *antibodies against antigens of cell membranes* found in SLE sera constitute yet another type of antibody which probably plays a role in the pathogenesis of this disease.

57. Mittal, K.K., Rossen, R.D., Sharp, J.T., Lidsky, M.D. and Butler, W.T. Lymphocyte cytotoxic antibodies in systemic lupus erythematosus. Nature *255:*1255, 1970.

58. Terasaki, P.I., and Mattironi, U.D. Cytotoxins in disease. Auto cytotoxins in lupus. New Eng. J. Med. *283:*724, 1970.

Sixty percent of random sera tested had antibody reacting with allogeneic lymphocytes. These reactions were specific as demonstrated by absorption experiments. The antigens involved were not correlated with the HL-A antigens detected. Twelve patients were shown to have autoantibodies reacting with their own lymphocytes. The antibodies were active at 37°C suggesting they were also operative *in vivo*.

59. 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.

The presence of circulating lymphocytotoxic antibodies correlated with clinical activity of SLE.

60. 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.

Lymphocytes from patients with active lupus underwent lysis when exposed to rabbit complement. This was shown to be due to *in vivo* coating of the lymphocytes by autoantibodies. The *direct lymphocyte lysis test* (DLL) was found to correlate with clinical activity and leukopenia. Serial studies showed that it became normal after steroid therapy. The DLL test was negative in patients leukopenic due to the effect of immunosuppressive drugs.

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

The possible role of lymphocytotoxic antibodies in the initiation or amplification of the immunologic abnormalities in SLE will be further discussed below in relation to findings in mice with a lupus-like disease.

IV. ANIMAL MODELS

New Zealand black (NZB) and hybrid NZB x NZW/F1 mice develop spontaneously an *immune complex nephritis, antibodies to nuclear antigens and Coombs positive hemolytic anemia.* This disease of inbred mice resembles closely human SLE, including the presence of *typical LE cells.*

62. Howie, J.B. and Helyer, B.J. The immunology and pathology of NAB mice. Adv. Immunol. *9:*215, 1968.

Lymphoid infiltration of the salivary glands suggesting Sjögren's Syndrome has also been described.

63. Kessler, H.S. A laboratory model of Sjögren's Syndrome Amer. J. Path. *52:*671, 1968.

Development of *malignant lymphoma* is a later development in a high percentage of the affected animals.

Because of the striking similarities with human lupus many have felt that an understanding of the condition occurring in NZ mice would be useful.

NZ mice have been found to have multiple immunological abnormalities in both antibody production and cellular immunity. Antibody responses to many antigens including the Gross leukemia virus that infects them, as well as most other strains, are excessive.

64. Talal, N., Steinberg, A.D., Jacobs, M.E., Chused, T.M. and Gazdar, A.F. Immune cell cooperation. Viruses and antibodies to nucleic acids in New Zealand Mice. J. Exp. Med. *134:*(Suppl.) 52, 1971.

Cellular immune mechanisms by contrast, appear to be deficient. They have a decreased ability to induce graft-versus-host disease, to undergo blastogenic transformation after stimulation by mitogenic agents *in vitro* and to reject allografts of skin or tumors.

65. Cantor, H., Asofsky, R. and Talal, N. Synergy among lymphoid cells mediating the graft-versus-host reaction produced by cells from NZB/Bl mice. J. Exp. Med.*131:*223, 1970.

66. Leventhal, B.G. and Talal, N. Response of NZB and NZB x NZW spleen cells to mitogenic agents. J. Immunol. *104:*918, 1970.

67. Teague, P.O., Yunis, E.J., Rodey, G., Rish, H.J., Stutman, O., and Good, R.A. Autoimmune phenomena and renal disease in mice. Lab. Invest. *22:*121, 1970.

68. Rodey, G.E., Good, R.A. and Yunis, E.J. Progressive loss *in vitro* of cellular immunity with aging in strains of mice susceptible to autoimmune disease. Clin. Exp. Immunol. *9:*305, 1971.

A defect in circulating B-cells has also been reported.

69. de Jesus, D.G., Holborow, E.J. and Brown, J.C. A defect of B-lymphocyte transport of aggregated HGG into germinal centres in NZB and NZB x NZW F1 hybrid mice. Clin. Exp. Immunol. *11:*507, 1972.

NZ mice carry the common Gross leukemia virus, but unlike other strains which contain the virus, break tolerance and produce antibodies to Gross antigens giving rise to immune complexes which deposit in the kidney.

70. Mellors, R.C., Shirai, T., Aoki, T., Huebner, R.J. and Krawczyuski, K. Wild-type Gross leukemia virus and the pathogenesis of the glomerulonephritis of New Zealand mice. J. Exp. Med. *133:*113, 1971.

71. Mellors, R.C. Wild-type Gross leukemia virus and heritable autoimmune disease of New Zealand mice. Am. J. Clin. Path. *56:*270, 1971.

In addition NZB x NZWF1 mice spontaneously produce antinuclear and anti-nucleic acid antibodies which have been shown to parallel the appearance and incidence of glomerulonephritis.

72. Lambert, P.H. and Dixon, F.J. Genesis of antinuclear antibody in NZB/W mice - role of genetic factors and of viral infections. Clin. Exp. Immunol. *6:*829, 1970.

The appearance of these antibodies and the immunologic disease could be accelerated by immunization with nucleic acids or by viral infections.

73. Tonietti, G., Oldstone, M.B.A. and Dixon, F.J. The effect of induced chronic viral infections on the immunologic disease of New Zealand mice. J. Exp. Med. *132:*89, 1970.

Elution of IgG from nephritic kidneys of NZ mice and absorption of the eluted material with selected antigens has indicated that their immune complex nephritis involves at least two kinds of antigen-antibody complexes. Almost half of the eluted IgG was reactive with nucleoproteins, 7 to 21% was reactive with Gross antigen. When the mice were infected experimentally with LCM or with Polyoma virus some of the IgG eluted from the nephritic kidneys reacted with the corresponding virus.

74. Dixon, F.J., Oldstone, M.B.A. and Tonietti, G. Pathogenesis of immune complex glomerulonephritis of New Zealand mice. J. Exp. Med. *134:* (Suppl.) 65, 1971.

Autoantibodies against lymphocytes of the T-cell variety have been found in NZB mice.

75. Shirai, T. and Mellors, R.C. Natural thymocytotoxic autoantibody and reactive antigen in New Zealand Black and other mice. Proc. Nat. Acad. Sci. *68:*1412, 1971.

Coating of lymphocytes with these naturally occurring antibodies was shown to affect the circulation and tissue distribution in a manner very similar to the effect of a heterologous anti-lymphocyte serum. It is speculated therefore, that such autoantibodies against lymphocytes may play a role in the development of the immunological defects which characterize these mice.

76. Shirai, T. Yoshitki, T. and Mellors, R.C. Effects of natural thymocytotoxic autoantibody of NZB mice and of specifically prepared antilymphocyte serum on the tissue distribution of ^{51}Cr-labeled lymphocytes. J. Immunol. *110:*517, 1972.

A spontaneous disease resembling systemic lupus erythematosus has been described in dogs.

77. Lewis, R.M., and Schwartz, R.S. Canine systemic lupus erythematosus. J. Exp. Med. *134:*417, 1971.

Pathogenesis of Lupus Nephritis in NZ mice

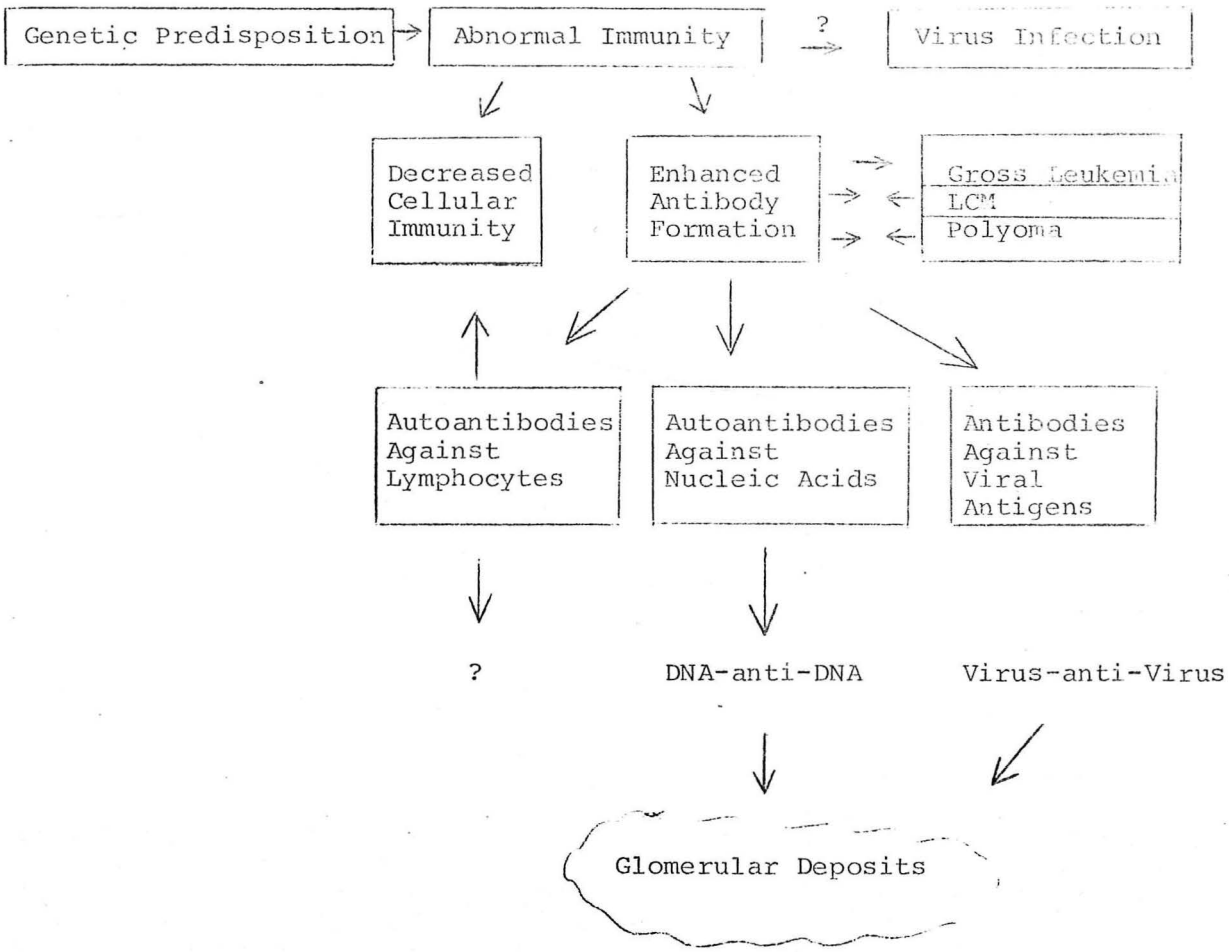


Figure 4.

V. CLINICAL MANIFESTATIONS

A study of SLE in populations in New York City and in Jefferson County, Alabama showed that the incidence and prevalence of SLE and the mortality rate from this disease were three times higher for Negro females than for whites in both localities.

78. Siegel, M., Holley, H.L. and Lee, S.L. Epidemiologic studies in systemic lupus erythematosus. Arth. Rheum. *13:*802, 1970.

A committee of the American Rheumatism Association has set forth preliminary *criteria for the classification of SLE* for the purpose of clinical trials, population surveys and other studies. The proposed criteria are based on 14 manifestations, 4 or more being required to classify a patient as having SLE.

The material used for defining the criteria consisted of 245 patients with unequivocal SLE, 204 with probable SLE, 234 patients with classical or definite RA and 217 patients with other non-rheumatic diseases, submitted by 52 rheumatologists.

79. Cohen, A.S., Reynolds, W.E., Franklin, E.C., et al: Preliminary criteria for the classification of systemic lupus erythematosus. Bull. Rheum. Dis. *21:*643, 1971.

In testing the criteria it was observed that certain manifestations such as facial erythema, discoid lupus, Raynaud's, alopecia, photosensitivity, oral and pharyngel ulceration (which constitute the first 6 of the 14 manifestations listed) had to be specifically mentioned and sometimes were not excluded in routine clinical records.

80. Gibson, T.P., Dibons, G.F. Use of the American Rheumatism Association's preliminary criteria for the classification of systemic lupus erythematosus. Am. Int. Med. *77:*754, 1972.

Overlap Syndromes and Mixed Connective Tissue Disease

It is well known that in certain patients either at one time or in successive stages in the course of their illness manifestations occur which are characteristic of more than one of the connective tissue diseases. Thus patients with lupus erythematosus develop chronic deforming arthritis indistinguishable from rheumatoid arthritis; patients with rheumatoid arthritis develop positive LE tests or patients combine at one time features of lupus, scler-

oderma and polymyositis.

In one report, a 41 year old woman had destructive arthritis, subcutaneous nodules, high titer rheumatoid factor, and also photo sensitivity, a malar rash, glomerulonephritis, positive LE preparation and high titer anti-DNA antibodies.

81. Kantor, G.L., Bichel, Y.B. and Barnett, E.V. Coexistence of systemic lupus erythematosus and rheumatoid arthritis. Am. J. Med. *47:*433, 1969.

It was concluded that she had both diseases, an example of the overlap syndrome.

One should not, however, use this term as a waste-basket or an excuse for carelessness in arriving at a diagnosis. Furthermore, in each case, if an overlap does exist, the components should be clearly identified.

It has been suggested that the occurrence of such patients emphasizes the close association of the disorders that present in combination. Such associations exist also at the histologic level. In one report patients with definite SLE were found to have rheumatoid nodules or rheumatoid granulomas, proven by biopsy.

82. Dubois, E.L., Friou, G.J. Rheumatoid nodules and rheumatoid granulomas in systemic lupus erythematosus. J.A.M.A. *220:*515, 1972.

Salivary gland swelling and pain occurred in association with exacerbations of SLE.

83. Katz, W.A. and Ehrlich, G.E. Acute salivary gland inflammation associated with systemic lupus erythematosus Ann. Rheum. Dis. *31:*384, 1972.

Full blown Sjögrens' syndrome associated with SLE was recognized in 8 patients.

84. Steinberg, A.D. and Talal, N. The coexistence of Sjögrens' syndrome and systemic lupus erythematosus. Ann. Int. Med. *74:*55, 1971.

The overlap of SLE with Scleroderma and polymyositis is also well documented. In one group, patients with scleroderma have positive

LE tests and certain systemic manifestations suggestive of SLE.

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

In another group of patients, the basic diagnosis is SLE, but in addition they have Raynaud's phenomenon, skin changes compatible with scleroderma and muscle weakness, elevation of serum enzymes, as well as EMG changes and biopsy findings of polymyositis (see case 1, this protocol).

Sharp and co-workers, have described 25 patients with a *mixed connective tissue syndrome* characterized by the presence of high titer antibodies against an extractable nuclear antigen (ENA). Clinically these patients had a combination of features of SLE, scleroderma and polymyositis. Renal disease was usually absent and most of the manifestations have responded to steroid therapy. The antibodies to ENA which characterize this group of patients will be further discussed in section VII.

86. 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). Am. J. Med. *52:*148, 1972.

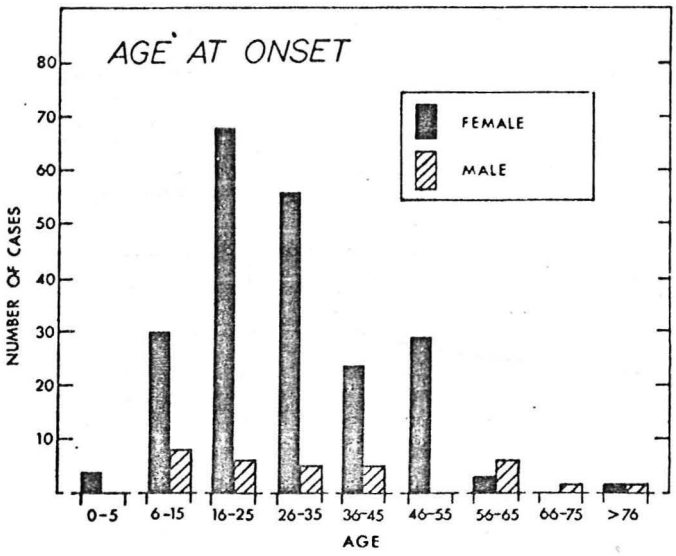
Table 2. **Clinical Characteristics of Twenty-Five Patients with Mixed Connective Tissue Disease**

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, Am J. Med. *52:*148, 1972)

The *age of onset of SLE* has varied from 2 years to beyond 76.



Age at onset of 242 cases of SLE of all ages.

Figure 5.
(from Meislin, et al. Pediatrics *42*:37, 1968.)

The peak incidence occurred in girls during adolescence. In this, as well as in other series, the marked predominance of females disappears after age 50.

In *children SLE* was characterized by a higher incidence of hepatosplenomegaly (69% compared to 35% in adults) and a poor prognosis, although the overall incidence of renal disease was about the same.

87. Meislin, A.G. and Rothfield, N. Systemic lupus erythematosus in childhood; analysis of 42 cases with comparative data on 200 adult cases followed concurrently. Pediatrics *42*:37, 1968.

Table 3.

CLINICAL MANIFESTATIONS IN 42 CHILDREN COMPARED WITH 200 ADULTS WITH SLE

Manifestation	*Children* (%)	*Adults* (%)
Joints	90	91
Skin	79	84
Hepatosplenomegaly or lymphadenopathy	69	35
Renal disease	69	51
Hematologic	52	45
Cardiac	38	49
Neurological	38	30
CNS	29	22
Pulmonary	26	43
GI	24	14
Psychiatric	24	24

Table 4.

LABORATORY MANIFESTATIONS IN CHILDREN AND ADULTS WITH SLE

Manifestation	*Children* (%)	*Adults* (%)
Anemia	69	45
Leukopenia	53	31
Positive Coombs test	44	25
Thrombocytopenia	31	10
Rheumatoid factor	29	23

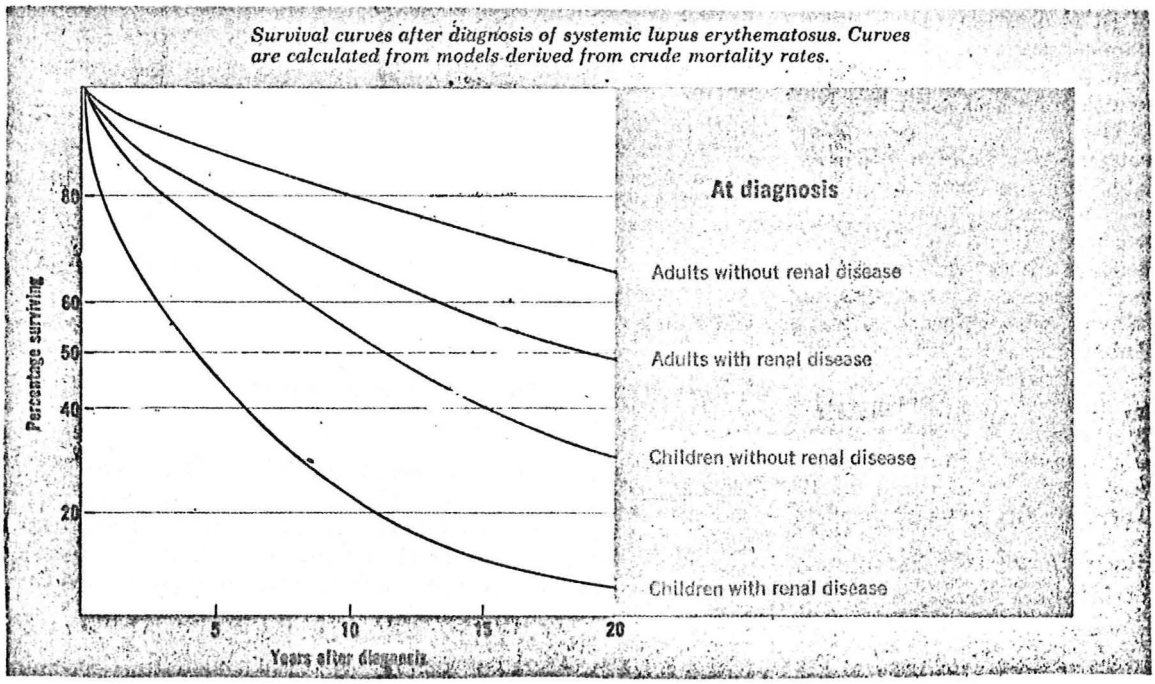


Figure 6.
(from Meislin, et al., Pediatrics *42*:37, 1968)

In the elderly, on the other hand, the disease tended to be more insidious and benign. Nine patients were studied with onset of SLE beyond the age of 60. The clinical picture was that of a polymyalgia rheumatica-like syndrome.

88. Foad, B.S., and Sheon, R.P. Systemic lupus erythematosus in the elderly. Arch. Int. Med. *130:*743, 1972.

The *initial manifestations* and *major clinical manifestations* in one series comprising 150 patients with SLE are given on the following two tables.

Table 5.

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

Table 6.

Major Clinical Manifestations of SLE in 150 patients

Manifestation	Percent
Musculo-articular	95
Cutaneous	81
Fever	77
Neuropsychiatric	59
Renal	53
Pulmonary	48
Cardiac	38

(from Estes et al, Medicine *50:*85, 1971)

Almost 3/4 of the patients *presented* with *articular* or *cutaneous* manifestations. The interval between initial discoid skin lesions and onset of multisystem disease ranged from a few months to 20 years. Nine patients (6%) presented with lupus nephritis, 7 of these had the nephrotic syndrome at onset.

89. Estes, D. and Christian, C.L. The natural history of systemic lupus erythematosus by prospective analysis. Medicine *50:*85, 1971.

Muscular-articular symptoms were observed at some time in almost all patients.

In another report, 19 out of 25 SLE patients had frank arthritis. This was usually mild and not followed by joint destruction. Four patients, all on steroids, developed aseptic necrosis of the femoral head.

90. Labowitz, R., and Schumacher, R.H., Jr. Articular manifestations of systemic lupus erythematosus. Ann. Int. Med. *74:*911, 1971.

The *synovial fluid* in SLE with arthritis was usually clear and viscous, contained few WBC and had low complement. Three kinds of fluids were observed: (1) *transudates*, seen in patients with edema, (2) *exudates* with high protein and complement, and (3) *exudates with low complement* but different from RA fluids in that polymorphonuclear leukocytosis and rheumatoid factor were not found.

91. Pekin, T.J. and Zvaifler, N.J. Synovial fluid findings in systemic lupus erythematosus. Arth. Rheum. *13:*777, 1970.

Cutaneous manifestations, most frequently observed were *malar rash* and *alopecia*. *Dermal vasculitis* was manifest by chronic *ulceration* and digital *gangrene*. Also seen were *erythema nodosum, bullous lesions, Raynaud's phenomenon, purpura, discoid lesions, hives, rheumatoid nodules* and *ulcerative lesions of the mucous membranes*.

In another report it was pointed out that ulcerations on the legs in patients with SLE showed an apparent correlation with serum complement levels, titer of antinuclear antibodies and overall clinical activity.

92. Kirsner, A.B. and Diller, J.G. Systemic lupus erythematosus with cutaneous ulceration. Correlation of immunologic factors with therapy and clinical activity. J.A.M.A. *217:*821, 1971.

Neuropsychiatric manifestations occurred in 59% of the above patients. The most common were disorders of mental function and grand mal seizures. The findings are similar to those of a previous series.

93. Johnson, R.T. and Richardson, E.P. The neurological manifestations of SLE. A clinical-pathological study of 24 cases and review of the literature. Medicine *47:*337, 1968.

Other neurologic manifestations observed were *cranial nerve signs, hemiparesis, tremor* and *peripheral neuropathy*. The *spinal fluid*

was abnormal in half the patients with neurologic manifestations, with increased protein and mild increase in lymphocytes. *EEG* abnormalities were common but diffuse and nonspecific.

Studies of serum *complement* and CSF complement suggested that determination of C4 and C2 was a sensitive indicator of CNS disease in patients with SLE. Spinal fluid C4 measured by a hemolytic assay was found decreased in 11 patients with CNS disease and normal in 7 patients with active SLE without CNS disease. C4 in spinal fluid was very unstable even at -50°C. Such determinations are at present not practical for routine studies.

Minor *retinal lesions* are not uncommon in SLE. A patient was reported who became blind from progressive lupus retinopathy.

95. Bishko, F. Retinopathy in systemic lupus erythematosus. A case report and review of the literature. Arth. Rheum. *15:*57, 1972.

Clinical renal disease was present in 53% of the patients. That figure is quite similar to the frequency observed in several other series.

96. Comerford, F.R., Cohen, A.S. The nephropathy of systemic lupus erythematosus. Medicine *46:* 425, 1967.

97. Zweiman, B., Dornblum, J., Cornog, J. and Hildreth, E.A. The prognosis of lupus nephritis. Role of clinical-pathologic correlations. Ann Int. Med. *69:*441, 1968.

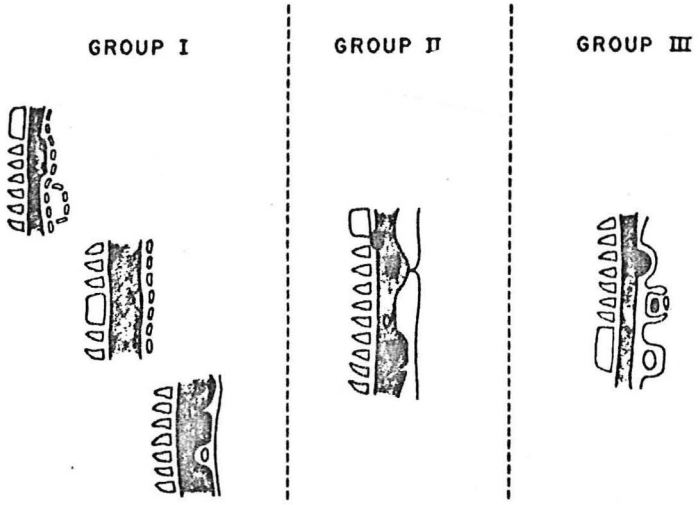
98. Pollak, V.E. and Pirani, C.L. Renal histologic findings in systemic lupus erythematosus. Mayo Clinic Proc. *44:*630, 1969.

99. Baldwin, D.S., Lowenstein, J., Rothfield, N.F., Gallo, G. and McCluskey, R.T. Clinical course of the proliferative and membranous forms of lupus nephritis. Ann Int. Med. *73:*929, 1970.

100. Cheatum, D.E., Hurd, E.R.J., Strunk, S.W. and Ziff, M., Renal histology and clinical course of systemic lupus erythematosus: a prospective study (submitted for publication)

It is now well recognized that different patterns of renal disease exist in SLE and that they have widely different clinical course, prognosis and are different also in their response to therapy.

Peripheral Glomerular Loop in Systemic Lupus Erythematosus



Diagrammatic representation of the three varieties of involvement of the peripheral glomerular capillary wall utilized in the classification of ultrastructural abnormalities in the glomerulus in Systemic Lupus Erythematosus. The basement membrane is represented by the central band, the epithelial foot processes are to the left, and the endothelial cytoplasm to the right. The small black areas represent the dense deposits. Group I cases are those in which dense deposits are not seen in relation to the glomerular basement membrane, which however may be nodular or thickened. Group II cases are those in which intramembranous or subepithelial dense deposits occur, but subendothelial dense deposits are not seen. Group III cases are characterized by the presence of subendothelial dense deposits, between the peripheral capillary wall basement membrane, and the endothelial cytoplasm. Apparent phagocytosis of dense material by endothelial cytoplasm, a feature of Group III cases, is also illustrated.

Figure 7.

(from Comerford et al, Medicine *46:*425, 1967)

In the Parkland series (Ref. 100) 30 patients with SLE were followed over a mean period of 9.4 years. The renal biopsy findings and subsequent course were as follows:

Table 7.

30 PMH Patients with SLE with Kidney Biopsy at Onset of Study Followed for Periods Ranging from 11 Months to 15.5 years (mean 9.4 years.

Renal Biopsy Classification	Number	Clinical Course
Normal Kidney	11	7 died of non-renal causes*
Mesangial Glomerulitis	4	all alive
Membranous Glomerulonephritis	2	all alive
Focal Proliferative Glomerulonephritis	5	2 died of renal and 2 of non-renal causes
Diffuse Proliferative Glomerulonephritis	8	6 died of renal disease

*Five of these patients died with neurologic or psychiatric symptoms.

The study of immunoglobulin and complement deposition in kidney biopsies by immunofluorescence was found to be a useful adjunt to diagnosis.

101. Koffler, D., Agnello, V., Carr, R.I. and Kunkel, H.G. Variable patterns of immunoglobulin and complement deposition in the kidneys of patients with systemic lupus erythematosus. Amer. J. Path. *56:*305, 1969.

102. McIntosh, R.M., Tinglof, B., Kaufman, D., Dornfeld, L., Gonick, H., Smith, F.G. and Vernier, R.L. Immunohistology in renal disease. Diagnostic, prognostic, therapeutic and etiologic value and limitations. Q.J. Med. *40:*385, 1971.

Fluorescence was sometimes observed in early cases of SLE when findings by light microscopy and urinary abnormalities were minimal. Distinct patterns of distribution of immunofluorescence staining were described.

Pulmonary complications of SLE were observed in 48% or 72 patients

out of the 150. *Pleural effusion* was seen in 60 patients. *Lupus pneumonitis* in 14 patients. X-Ray evidence of *pulmonary fibrosis* developed in 9 patients.

Pleural fluids were found to be exudates (>3.0 gm% protein) in 9 out of 10 cases. In most of them the glucose concentration was above 55 mg%. Rheumatoid pleural effusions had previously been found to have markedly low glucose levels (<20 mg%).

103. Carr, D.T., Lillington, A. and Mayne, J.G. Pleural-fluid glucose in systemic lupus erythematosus. Mayo Clin. Proc. *45:*409, 1970.

Pleural fluid CH50, C1q, C3 and C4 were low in SLE and RA compared to levels found in malignant pleural effusions or in congestive heart failure.

104. Hunder, G.G. and McDuffie, F.C. Pleural fluid complement in systemic lupus erythematosus and rheumatoid arthritis. Am. Int. Med. *76:*357, 1972.

Cardiac manifestations of SLE occurred in 38% of the patients. These patients had pericarditis, myocarditis, and congestive heart failure.

In another report, 4 patients with SLE from 16 to 38 years old, were found to have coronary artery disease with angina and myocardial infarctions.

105. Bonfiglio, T.A., Botti, R.E. and Hagstrom, J.W.C. Coronary arteritis, occlusion, myocardial infarction due to lupus erythematosus. Am. Heart J. *83:*153, 1972.

The *hematologic manifestations* consisted of anemia (73%) leukopenia (66%) and thrombocytopenia (19%). The direct Coombs test was positive in 27%. Severe leukopenia was rare. Thrombocytopenia required splenectomy in 4 patients.

In another study anti-platelet antibodies were found in 78% of SLE patients, but only 14% were thrombocytopenic.

106. Karpatkin, S., Strick, N., Karpatkin, M.B. and Siskind, G.W. Cumulative experience in the detection of anti-platelet antibody in 234 patients with idiopathic thrombocytopenic purpura, systemic lupus erythematosus and other clinical disorders. Am. J. Med. *52:*776, 1972.

Using a complement fixation technique, platelet antibodies were found by us, in 23 out of 25 SLE patients tested.

107. Stastny, P. and Ziff, M. Complement fixation with platelets in systemic lupus erythematosus. Clin.Res. *14:*42, 1971 (Abstr.)

The development of malignant lymphoma in patients with SLE was reported (see also case 2 and case 3 in this protocol).

108. Nilsen, L.B., Missal, M.R. and Condemi, J.J. Appearance of Hodgkin's disease in a patient with systemic lupus erythematosus. Cancer *20:*1920, 1967.

109. Lipsmeyer, E.A. Development of malignant cerebral lymphoma in a patient with systemic lupus erythematosus treated with immunosuppression. Arth. Rheum. *15:*183, 1972.

A certain number of SLE patients exacerbate during the first two trimesters of pregnancy and in the post-partum period. In one study fetal wastage was high (2 stillbirths, 1 abortion, 4 premature deliveries, in 11 pregnancies). Pregnancy did not appear to affect the course of SLE except in the patients with active lupus nephritis.

110. McGee, C.G. and Makowski, E.L. Systemic lupus erythematosus in pregnancy. Am. J. Obst. Gynec. *107:*1008, 1970.

The use of oral contraceptives was associated with exacerbations of SLE.

111. Chapel, T.A. and Burns, R.E. Oral contraceptives and exacerbation of lupus erythematosus. Am. J. Obst. Gynec. *110:*336, 1971.

VI. DRUG-INDUCED LUPUS ERYTHEMATOSUS

Certain drugs have the ability to induce in normal individuals many of the serological and clinical manifestations of SLE. A fine difference can be drawn between drugs that induce lupus through

peculiar pharmacologic properties and others that bring out an underlying dormant SLE or exacerbate SLE through an allergic reaction.

112. Alarcón-Segovia, D., Drug-induced lupus syndromes. Mayo Clin. Proc. *44*:664, 1969.

Table 8.

Drugs that "Cause" SLE

Hydralazine	Dilantin
Isoniazid	Mesantoin
Procainamide	Phenothiazines

Drugs that Produce Allergic Reactions Resembling SLE

Penicillin	Tetracycline	Methyldopa
Sulfonamides	Streptomycin	Oral Contraceptives

Table 9.

Clinical Manifestations in Spontaneous and Drug-Induced SLE

Clinical Manifestation	Spontaneous	Cause of SLE	
		Hydralazine	Procainamide
		% of patients	
Arthritis or Arthralgia	92	74	67
Fever	84	40	38
Adenopathy	59	-	5
Erythematous Rash	58	20	9
Myalgia	48	6	19
Renal	46	20	2
Pulmonary	45	10	46
Pericarditis	30	3	15
Hepatomegaly	23	2	25
Convulsions	14	-	-

(from Alarcón-Segovia et al, Mayo Clin. Proc. *44*:664, 1969.)

Females predominated (89%) in spontaneous SLE, but not in the drug-induced disease. Hydralazine-lupus 64% females, procainamide-induced disease 50%. Drug-induced disease tended to occur at a later age. The mean age for SLE was 27.5 years, hydralazine-LE, 52.8 years and procainamide-LE 55.2 years.

Procainamide is the most potent drug capable of inducing a lupus syndrome. It is estimated that over 1/2 million patients per year take the drug. The syndrome has been extensively studied.

113. Dubois, E.L. Procainamide induction of systemic lupus erythematosus-like syndrome. Presentation of six cases, review of literature, and analysis and follow-up of reported cases. Medicine *48:*217, 1969.

114. Condemi, J.J., Blomgren, S.E. and Vaughan, J.H. The procainamide-induced lupus syndrome. Bull. Rheum. Dis. *20:*604, 1970.

115. Hope, R.R. and Bates, L.A. The frequency of procainamide-induced systemic lupus erythematosus. Med. J. Anst. *2:*298, 1972.

116. Blomgren, S.E., Condemi, J.J., Vaughan, J.H., Procainamide-induced erythematosus. Clinical and laboratory observations. Am. J. Med. *52:*338, 1972.

The most frequent clinical manifestation, apart from arthalgia has been *pulmonary involvment.* This has given rise to pleuritic chest pain, cough, hemoptisis, dyspnea, and X-Ray changes. *Pericardial friction rubs* and *fever* have also been common. Life-threatening pericardial tamponade has been reported.

117. Donlan, C.J., Jr., and Forker, A.D. Cardiac tamponade in procainamide induced lupus erythematosus. Chest *61:*685, 1972.

In other such cases the offending drug was isoniazid..

118. Greenberg, J.H., Lutcher, C.L. Drug-induced systemic lupus erythematosus. A case with life-threatening pericardial tamponade. J.A.M.A. *222:*191, 1972.

Most patients with drug-induced lupus *do not develop renal disease.*

LE preparations and antinuclear tests are positive but antibody to native-DNA has been absent and serum complement levels have remained normal.

Recent reports have implicated other drugs in the development of lupus-like syndromes (quinidine, chlorpromazine, penicillamine).

119. Kendall, M.J., and Hawkins, C.F. Quinidine-induced systemic lupus erythematosus. Postgraduate Med. J. *46:*729, 1970.

120. Fabius, A.J.M. and Gaulhofer, W.K. Systemic lupus erythematosus induced by psychotropic drugs. Acta. Rheum. Scand. *17:*137, 1971.

121. Berglund, S., Gottfries, C.G., Gottfries, J. et al, Chlorpromazine-induced antinuclear factors. Acta. Med. Scan. *187:*67, 1970.

122. Dubois, E.L. Tallman, E., Wonka, R.A. Chlorpromazine-induced systemic lupus erythematosus: Case report and review of the literature J.A.M.A. *221:*595, 1972.

123. Oliver, I., Liberman, U.A. and DeVries, A. Lupus-like syndrome induced by penicillanine in cystinuria. J.A.M.A. *220:*588, 1972.

The observation that some patients continue to have symptoms long after discontinuation of the drugs has been cited in favor of a latent "lupus diathesis" being unveiled by the drug. Against this notion is the fact that almost one-half of all the patients taking procainamide develop antinuclear antibodies.

124. Molina, J. Dubois, E.L., Bilitch, M., Blaud, S.L. and Frion G.J. Procainamide-induced serologic changes in asymptomatic patients. Arth. Rheum. *12:*608, 1969.

125. Blomgren, S.E., Condemi, J.J., Bignall, M.C. and Vaughan, J.H. Antinuclear antibody induced by procainamide, a prospective study. New Eng. J. Med. *281:*64, 1969.

It has also been possible to induce antinuclear antibodies in normal mice.

126. Ten Veen, J.H. and Feltkamp, T.E.W. Studies on drug induced lupus erythematosus in mice. I. Drug induced antinuclear antibodies (ANA) Clin. Exp. Immunol. *11:*265, 1972.

In studying the mechanism of development of hydralazine-lupus in 12 such patients it was observed that a number of patients had hemagglutinating antibodies against the drug and their lymphocytes showed blastic transformation after incubation with it.

127. Hahn, B.H., Sharp, G.C., Irvin, W.S., Kantor, O.S., Gardner, C.A., Bagby, M.K., Perry, H.M. and Oslerland, C.K. Immune response to hydralazine and nuclear antigens in hydralazine-induced lupus erythematosus. Ann Int. Med. *76:*365, 1972.

It was shown that in genetically *slow acetylator* individuals antinuclear antibodies developed after a lower total dose of hydralazine.

Table 10.

Relation between amount of hydralazine ingested and presence of ANA among slow and fast acetylators

Hydralazine ingested (Gm.)	*ANA negative*	*ANA positive*	*ANA positive (%)*
Slow acetylators			
200- 399	6	9	60
400-1,199	4	10	71
1,200-3,000	1	3	75
Fast acetylators			
200- 399	8	0	0
400-1,199	6	3	33
1,200-3,000	1	6	86

Four of the 9 ANA-positive slow acetylators with an exposure of 200 to 399 Gm. and 8 of the 10 with exposures of 400 to 1,199 Gm. were hydralazine toxic.

128. Perry, H.M.,Jr., Tan, F.M., Carmody, S. and Sakamoto, A. Relationship of acetyl transferase activity to antinuclear antibodies and toxic symptoms in hypertensive patients treated with hydralazine. J. Lab. Clin. Med. *76:*114, 1970.

It has been shown that hydrazides can alter nucleoproteins and that sera from patients treated with isoniazid reacted with hydrazide-altered soluble nucleoprotein. It was postulated that similar alteration of nucleoproteins occurrs *in vivo* and leads to the development of antinuclear antibodies.

129. Alarcon-Segovia, D., Fishbein, E. and Betancourt, V.M. Antibodies to nucleoprotein and to hydrazide-altered soluble nucleoprotein in tuberculous patients receiving isoniazid. Clin.Exp. Immunol. *5:*429, 1969.

VII. LABORATORY TESTS

Biologic false positive serologic tests for syphilis are well known in SLE. In some patients these tests were present long before the onset of clinical symptoms. Specific anti-treponema antibody

reactions are useful to distinguish the biologic false positive from true cases of syphilis. In the fluorescent treponema antibody absorption test (FTA-Abs) SLE sera produce false positive reactions which can be recognized by their beaded appearance instead of the usual homogeneous pattern of fluorescence.

130. Kraum, J.J., Haserich, J.R. and Lantz, M.A. Fluorescent treponemal antibody-absorption test reactions in lupus erythematosus. New Eng. J. Med.*282:*1287, 1970.

The measurement of antibodies to nucleic acids and serum complement determinations were found useful in the management of patients with SLE.

131. Schur, P.H. and Sandson, J. Immunologic factors and clinical activity in systemic lupus erythematosus. New Eng. J. Med. *278:*533, 1968.

The methodology and significance of the fluorescent antinuclear antibodies was reviewed. Different antinuclear sera produced different staining patterns because they contained immunoglobulin with affinity for different nuclear constituents.

Nuclear rim, peripheral or shaggy (DNA)

Homogeneous (Nucleoprotein)

Speckled (Saline-soluble nuclear proteins)

Nucleolar (Antigen of nucleoli)

Most sera produced mixed patterns which made their interpretation difficult. When purified antigens are available other methods of analysis (precipitin analysis, complement fixation, hemagglutination, binding of radioactive antigen) can be used.

132. Beck, J.S. Antinuclear antibodies: methods of detection and significance. Mayo Clin. Proc. *44:*600, 1969.

Antinuclear factor was found in 46% of 60 patients with chronic pulmonary tuberculosis. The role of isoniazid was not excluded.

133. Lindquist, K.J., Coleman, R.E. and Osterland, C.K. Autoantibodies in chronic pulmonary tuberculosis. J. Chron. Dis. *22* 717, 1970.

Radioactive DNA binding was measured by an ammonium sulfate precipitation method. A mixture of serum and radioactive DNA in half-saturated ammonium sulfate contains insoluble radioactivity only if DNA is bound to immunoglobulins. It was shown that the reactivity towards DNA is located in the Fab fragment of SLE IgG, not in the Fc portion of the molecule.

134. Pincus, T. and Kaplan, A.P. True antibodies to DNA in systemic lupus erythematosus activity of Fab and F(ab´)2 fragments. Nature *227* 394, 1970.

The radioactive-DNA binding procedure has become a clinical test which is now widely used.

135. Pincus, T., Schur, P.H., Rose, J.A., Decker, J.L. and Talal, N. Measurement of serum DNA-binding activity in systemic lupus erythematosus. New Eng. J. Med. *281* 701, 1969.

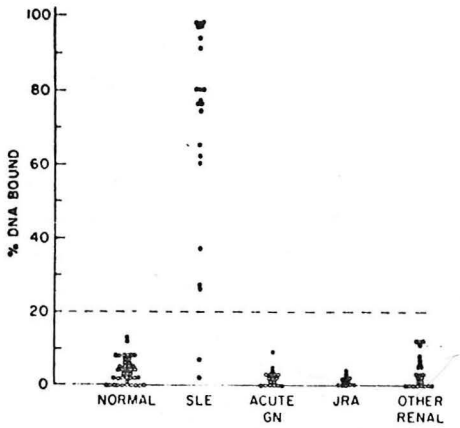
136. Pincus, T., Immunochemical condition affecting the measurement of DNA antibodies using ammonium sulfate precipitation. Arth. Rheum. *14* 623, 1971.

137. Hughes, G.R.V., Cohen, S.A. and Christian, C.L. Anti-DNA activity in systemic lupus erythematosus. Ann Rheum. Dis. *30*:259, 1971.

138. Hughes, G.R.V., Significance of anti-D.N.A. antibodies in systemic lupus erythematosus. Lancet *2* 861, 1971.

139. Pincus, T., Hughes, G.R.V., Pincus, D., Tina, L.U. and Bellanti, J.A. Antibodies to DNA in childhood systemic lupus erythematosus. J. Pediatrics *78* 981, 1971.

Since antibodies to NDNA are highly specific for SLE and correlate with clinical activity and renal disease their measurement is particularly useful.



Antibodies to DNA in sera of 44 normal children, of 22 children with systemic lupus erythematosus *(SLE)*, of 18 with acute glomerulonephritis *(GN)*, of 12 with juvenile rheumatoid arthritis *(JRA)*, and of 24 patients with other renal diseases.

Figure 8.
(from Pincus, et al J. Pediatrics *78:*981, 1971)

Antibodies to the *extractable nuclear antigen (ENA)* were determined by hemagglutination. The highest titers were found in patients having a mixed connective tissue syndrome with features of SLE, scleroderma and myositis. Interestingly antibody to ENA was found in 86% of patients with SLE nephritis who responded to steroid treatment and in only 8% of those who did not.

140. Sharp, G.C., Irvin, W.S., Gould, R.G. and Tan, E.M. Specific antibody to the extractable nuclear antigen (ENA) in the mixed connective tissue disease syndrome. J. Clin. Med. *74:*1010, 1969.

141. Sharp, G.C., Irvin, W.S., LaRogue, R.L., Velez, C., Daly, V., Kaiser, A.D. and Holman, H.R. Association of autoantibodies to different nuclear antigens with clinical patterns of rheumatic disease and responsiveness to therapy. J. Clin. Invest. *50:*350, 1971.

VIII. THERAPY

The general management of patients with SLE has been described in two review articles.

142. Dubois, E.L. Management and prognosis of systemic lupus erythematosus. Bull. Rheum. Dis. *18:*477, 1967.

143. Rothfield, N.F. General considerations in the treatment of systemic lupus erythematosus. Mayo Clin. Proc. *44:*691, 1969.

General measures such as avoidance of sunlight, rest, the use of salicytates for joint pains, the avoidance of pregnancy during the early period of the disease and in patients with nephropathy are well known.

Antimalarials such as chloroquine and hydroxychloroquine are very effective for control of some of the cutaneous manifestations and are thought to have a steroid sparing effect. Unfortunately a high percentage of patients taking these drugs develop retinopathy. It is mandatory if these drugs are used at all, to have the patients carefully followed by a competent ophthalmologist and the drugs must be discontinued at the first sign of macular retinopathy.

144. Carr, R.E., Henkind, P., Rothfield, N. and Siegel, I.M. Ocular toxicity of antimalarial drugs: long-term follow-up. Am. J. Ophtal. *66:*738, 1968.

145. Percival, S.P. and Behrman, J. Opthalmological safety of chloroquine. Brit. Ophtal. *53:*101, 1969.

Corticosteroids are of definite benefit for many of the manifestations of the disease with the exception of the two most serious and often fatal complications: lupus nephritis and lupus CNS disease. The use of steroids for the control of acute SLE, serositis, etc. is well known. The use of complement levels and titers of antinuclear and anti-DNA antibodies as a guide to long term therapy has been advocated.

The use of an alternate day steroid regimen where the total 48 hour amount is given as a single dose every other morning has been shown to decrease some of the undesirable side effects. This mode of therapy however, has not been found effective for patients with systemic disease (Ref. 142). In one study 6 patients with lupus nephritis were given 100-120 g prednisone every other day for 6-8 months with beneficial results.

146. Ackerman, G.L. Alternate day steroid therapy in lupus nephritis. Ann. Intern. Med. *72:*511, 1970.

Immunosuppressive drugs have been used quite extensively for the treatment of lupus nephritis. Evaluation of these efforts is difficult. Systemic lupus erythematosus is a disease that presents in many ways and spontaneous remissions are frequent. Better understanding of the different histologic forms of lupus nephropathy has helped,but controlled studies are badly needed.

Azathioprine has been used in several studies. It is felt to improve or help stabilize many patients who previously were not controlled on steroids alone.

In one study kidney biopsies after therapy showed a decrease in acute proliferative glomerular disease and an increase in glomerular sclerosis.

147. Drinkard, J.P., Stanley, R.M., Dornfeld, L.L. et al, Azathioprine and prednisone in the treatment of adults with lupus nephritis. Medicine *49:*411, 1970.

148. Shelp, W.D., Bloodworth, J.M.B., Jr., and Rieselbach, R.E. Effect of azathioprine on renal histology and function in lupus nephritis. Arch. Intern. Med. *128:*566, 1971.

149. Hayslett, J.P., Kashgarian, M., Cook, C.D. and Spargo, B.H. The effect of azathioprine on lupus glomerulonephritis. Medicine *51:*393, 1972.

Abrupt withdrawal of azathioprine resulted in severe exacerbation of SLE.

150. Sztejnbok, M., Stewart, A., and Diamond, H., et al Azathioprine in the treatment of systemic lupus erythematosus: a controlled study. Arth. Rheum. *14:*639,1971.

Similarly, withdrawal of cyclophosphamide brought about exacerbations, occurring from 21 to 200 days after stopping the drug, which were quite refractory to treatment.

151. Aptekar, R.G. Exacerbation of SLE nephritis after cyclophosphamide withdrawal. New Eng. J. Med. *286:*1159, 1972.

Azathioprine has been given to SLE patients for prolonged periods of time with relatively little toxicity.

152. Sharon, E., Greenwald, R., Solish, G. et al Adverse effects of azathioprine (Az) in patients with systemic lupus erythematosus (SLE). Clin. Pharmacol. The. *13:*152, 1972.

Adverse effects observed consisted of bone-marrow depression, increased incidence of infections and gastrointestinal intolerance.

Cyclophosphamide has been used in part because it was found to be very effective in controlling the nephritis of NZB/NZW F1 mice.

The reports in human SLE are in general favorable but based mostly on case reports or small uncontrolled series.

153. Cameron, J.S., Boulton-Jones, M., and Robinson, R., and Ogg,C. Treatment of lupus nephritis with cyclophosphamide. Lancet *2:*846, 1970.

154. Hadidi, T. Cyclophosphamide in systemic lupus erythematosus. Ann. Rheum. Dis. *29:*673, 1970.

A controlled trial of 10 weeks duration consisted of 6 patients receiving placebo, while 7 patients were treated with cyclophosphamide. Both groups were permitted up to 30 mg of prednisone daily. Improvement in the treatment group was observed in the following parameters: Anti-DNA, serum complement, urinary sediment, proteinuria and extra-renal manifestations of SLE. Creatine clearance was unchanged. A correlation between dose of cyclophosphamide (less than 2mg/Kg had little effect) and clinical improvement further suggested that the observed changes were due to the drug.

155. Steinberg, A.D., Kaltreider, H.B. and Staples, P.J., et al, Cyclophosphamide in lupus nephritis: a controlled trial. Ann Intern. Med. *75:*165, 1971.

A number of individuals have expressed concern about the use of these very potent drugs for treatment of non-malignant diseases. Severe bone-marrow depression, life-threatening infections and the possibility of enhancement of neoplasia, as reported in transplant recipients, constitute formidable dangers that have to be weighed against the severity of the condition to be treated. In a brief communication dealing with these problems Schwartz and Gowans have formulated tentative guidelines.

156. Schwartz, R.S. and Gowans, J.D.C. Guidelines for the use of cytotoxic drugs in rheumatic disease, Arth. Rheum. *14:*134, 1971.

(1) A life-threatening or seriously crippling disease should be present.

(2) The lesions to be treated should be reversible.

(3) The patient should have failed to respond or developed intolerable side effects with conventional therapy.

(4) There should be no clinically active infection.

(5) There should be no hematologic contraindication to treatment with a cytotoxic drug.

(6) Meticulous follow-up especially for signs of acute and long-term toxicity is mandatory.

(7) Methods of objective evaluation of the course of the disease should be used.

(8) The patients should be informed of the reasons for this form of therapy and its possible hazards; signed consent should be obtained.

(9) Therapeutic protocols should be submitted to peer group review.

The basic prinicples and the mechanisms by which these drugs may be of benefit in clinical immunology have been reviewed.

157. Schwartz, R.S. Therapeutic strategy in clinical immunology New Eng. J. Med. *280:*367, 1979.

158. Winkelstein, A. Principles of immunosuppressive therapy, Bull. Rheum. Dis. *21:*627, 1971.

A critical review of the literature on the use of immunosuppressive drugs in a variety of diseases has appeared.

159. Skinner, M.D. and Schwartz, R.S. Immunosuppressive therapy, New Eng. J. Med. *287:*221, 1972.

Transcripts of an NIH conference dealing with immunosuppressive therapy have been published.

160. Steinberg, A.D., Platz, P.H., Wolff, S.M. et al Cytotoxic drugs in treatment of non-malignant diseases. Ann. Int. Med. *76:*619, 1972.

Because it is not directed at the etiology of the disease and because it often inhibits useful as well as harmful immune and inflammatory responses, immunosuppressive therapy is nonspecific.

Therapeutic results in lupus nephritis are very difficult to evaluate. There are marked variations in severity natural history and clinical forms of SLE which make studies consisting of small groups of patients difficult to interpret.

There is no evidence that leukopenia is required to obtain a beneficial effect from cytotoxic drugs.

Cyclophosphamide can produce hemorrhagic cystitis,

161. Anderson, E.E., Cobb, O.E., Glenn, J.F. Cyclophosphamide hemorrhagic cystitis. J. Urol. *97:*857, 1967.

and fibrosis of the bladder can develop.

162. Johnson, W.W., Meadows, M.C. Urinary-bladder fibrosis and telangiectasia associated with long-term cyclophosphamide therapy. New Eng. J. Med. *284:*290, 1971.

Amenorrhea, destruction of the ovary, as well as sterility and testicular atrophy are common and bothersome problems.

163. Miller, J.J., Williams, G.F., Leissring, J.C. Multiple late complications of therapy with cyclophosphamide, including ovarian destruction. Am. J. Med. *50:*530, 1971.

164. Fairley, K.F., Barie, J.V. and Johnson, W. Sterility and testicular atrophy related to cyclophosphamide therapy. Lancet *1:*568, 1972.

165. Qureshi, M.S.A., Goldsmith, H.J., Remmington, J.H. and Cox,P.E. Cyclophosphamide therapy and sterility. Lancet *2:*1200, 1972.

Patients with advanced renal disease should probably not be exposed to the risks that immunosuppressive entail.

Such patients can now be adequately and sometimes very successfully treated by chronic hemodialysis and kidney transplantation.

166. Buda, J.A., Lattes, C.G. and Grant, J.P. et al. Feasibility of renal transplantation in systemic lupus erythematosus. Surg. Forum *21*:252, 1970.

167. Fries, J.F., Siegel, R.C. and Coplon, N.S. Hemodialysis and transplantation in lupus nephritis. Arth. Rheum. *16*:117, 1973 (Abstr.).