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A RETROSPECTIVE STUDY OF PATIENTS WITH SYSTEMIC
LUPUS ERYTHEMATOSIS

by

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ABSTRACT

The current literature suggests that certain persons may be genetically predisposed to Systemic Lupus Erythematosus (SLE), and that these persons develop the disease when they are exposed to certain triggering agents. The purposes of this study were: (1) to determine if a person who might be predisposed to SLE could be recognized prior to the onset of the acute syndrome; and (2) to identify chemical agents which these persons might be unable to tolerate.

Sixteen case histories of persons with diagnosed SLE were examined to determine: (1) what clinical manifestations were in evidence before, or at the time the disease was recognized; (2) what indications there were that implicated genetic involvement; and (3) what part suspected triggering agents had played in the onset of symptoms.

It was found that persons who eventually developed SLE did display commonalities which could be considered in recognizing individuals with a subacute SLE or a lupus diathesis. Drugs, and other agents which have been suspected of influencing the onset of the disease were demonstrated in the medical histories of these patients.

Chapter 1

INTRODUCTION

The evolution of man is a continuing source of wonderment to students of physiology. Through the centuries of painful metamorphosis, each challenge thrown at man by his environment was met by a gradual genetic modulation that enabled man to survive In the past few decades we have devised techniques unprecedented in the entire previous experience of the species, to challenge the adaptability of the organism. We have designed molecules unique to human physiology and have intruded them into blood and tissue by techniques that are also unique in physiologic experience.... To these ingenious tactics of assault.... we have evolved defenses at all levels from the simplest reflex to the most complex immune reactions. It is quite evident that some of these unprecedented therapeutic intrusions will overtax the ability of the body to accomodate-- and it will react with displeasure if not violent rejection.¹

Systemic lupus erythematosus (SLE), is a clinical syndrome of unknown cause, characterized by multi-systemic involvement and subject to multiple exacerbations and remissions. Present knowledge indicates that some individuals may be genetically predisposed to developing the disease. This predisposition is called a lupus diathesis. A variety of stimuli is suspected of inciting the syndrome in susceptible persons. Among the suspected triggering agents are sunlight, multiple immunizations, radiologic exposure, infections, and certain chemicals. The chemical agents are classified into two groups: those which frequently induce a lupus-like syndrome in many individuals, and those

¹Robert H. Moser, M.D., F.A.C.P., Editor, Diseases of Medical Progress: A Study of Iatrogenic Diseases, Charles C. Thomas, Publisher, Springfield, Illinois, U.S.A., 1969, pp. xix-xx.

which exacerbate an existing SLE, but do not cause these symptoms in normal persons.

"There is some evidence that the actual incidence may also be rising."² This increase in reported incidence could be due to better diagnostic procedures, or to increased use of chemical agents which, though therapeutic for some conditions, may unmask a latent lupus diathesis. "Drug induced lupus erythematosus may be true lupus in which the etiologic agent can be identified...."³ If the etiological agent, or agents can be recognized; and the individual who may be susceptible can be identified prior to the onset of the syndrome, then the incidence of the disease can be reduced.

THE PROBLEM

This study was conducted to determine if (1) an individual with a lupus diathesis can be recognized prior to the onset of acute symptoms of the disease, and (2) the agents which might incite the development of symptoms in the susceptible individual can be identified.

²Joseph H. Oyama, M.D., "Diagnosis and Treatment of Lupus Nephritis," The Medical Clinics of North America, W. B. Saunders Co. Philadelphia, January 1971, Vol 55, No. 1, p. 71.

³Moser, *op. cit.*, p. xx.

THE PURPOSE

This study was undertaken in an attempt to (1) provide the nurse with knowledge which could assist her in recognizing the individual who may have a lupus diathesis, (2) increase her awareness of the symptoms which frequently precede the acute onset of SLE, and (3) enable her to identify the drugs, or other agents, which might be dangerous for this individual.

JUSTIFICATION FOR THE STUDY

A primary role of the nurse is that of patient's advocate. In part, she fulfills this obligation by functioning as an intelligent assistant to the physician. She may be the first member of the health team to become aware of a mounting toxicity to a drug. She may be the one who detects a pattern which has not been noticed before. The possibility that the physician may fail to obtain an accurate and complete medical history is apparent when hospital records are studied. In many instances, the physician must rely totally on the patient's memory, and the patient's judgment as to what is important enough to report. The physician must make his decisions based on that information which is available to him. The nurse who can make accurate observations, and interpret correctly what she has observed, can contribute valuable data which may be used by the physician on the patient's behalf.

A friend of the author's, diagnosed as having SLE in 1970, had been exhibiting manifestations of SLE at least thirteen years before the diagnosis was made. During these years she had taken many of the drugs which have been implicated in the induction or exacerbation of SLE; she had been subjected to some of the other suspected triggering agents such as immunizations and X-rays. She had also exposed herself to the sun regularly.

Had she been recognized as a susceptible person and the suspected triggering agents been avoided, would she have developed the disease? Would the onset have been delayed, or the symptoms less severe? With earlier diagnosis, and earlier initiation of proper treatment, she would have been spared much of the anxiety that accompanies poor health for which a cause or cure have not been found. She could also have avoided much physical discomfort as the disease progressed.

It was to increase the knowledge of this insidious disease through searching for commonalities in persons who have developed SLE, and examining any real or apparent association between exposure to suspected inciters and the onset of symptoms, that this study was done. The more knowledge the nurse possesses, the better equipped she will be to fulfill her role as patient's advocate.

METHODOLOGY

This was a retrospective study of 16 patients with diagnosed systemic lupus erythematosus. Permission was obtained from the physicians involved to examine the hospital charts covering admissions for this diagnosis between January 1965 and February 1971. Fifteen cases were studied in this way. Two of these were available for a personal interview and also filled out the questionnaire. (See questionnaire in Appendix). Two others filled out the questionnaire, but were not available to be interviewed. Information on one patient was obtained from the questionnaire only. At the time of the study, three of the patients were deceased.

The variables in relation to the sample studied were:

1. Chemical exposure to drugs which have been implicated in the occurrence of SLE or an SLE-like syndrome.
2. Radiologic exposure.
3. Immunologic exposure.
4. A relationship with the menstrual mechanism and the X chromosome. This factor was examined by noting any abnormalities in the function of the reproductive system of female patients.
5. Excessive exposure to sunshine which may have initiated a break in immunological tolerance.
6. Familial history of connective tissue diseases. Rheumatoid arthritis was chosen as an indicator of this factor because the LE cell phenomenon has not infrequently been found in patients with rheumatoid arthritis, and this diagnosis is distinct enough to be more reliable when referred to in case histories examined retrospectively than other diseases in this category.

The information obtained was analyzed to discover to what extent the patient had been exposed to these suspected agents and the association, if any, between the exposure of the patient to these agents and the onset, or recurrence of symptoms. The presence of rheumatoid arthritis and a dysfunction of the reproductive system were tabulated as a possible indication of a genetic predisposition, and for their value as a clue to identifying the susceptible person. The symptoms which were in evidence prior to the time a diagnosis was made were charted in an attempt to describe a model of masked or subacute SLE.

LIMITATIONS

This study was limited in that the information available was, in part, subject to the unreliability of memory. The experiences of the patient, which were recorded on the hospital chart, were all that could be verified beyond the possibility of error. Medical histories on the patient's chart were compiled from past medical records, and from what the patient remembered. Some omissions and discrepancies were noted when charts from several admissions were compared.

Chapter 2

REVIEW OF LITERATURE

HISTORY, INCIDENCE AND PREVELANCE

Lupus, which is the latin name for wolf, has been used since about 1230 as a term to describe cutaneous conditions which resemble the malar erythema of a wolf.... In 1851 Cazenave first used the term "Lupus erythematosus." Kaposi, in 1872, noted the systemic involvement in lupus.... Osler described the systemic complications of lupus and noted that they could occur in the absence of skin disease. The clinical recognition of SLE has changed greatly since Hargraves first described the LE cell test in 1948 and by the development of the immunofluorescent antinuclear factor test by Friou in 1957.⁴

Because of these recent developments, SLE is being diagnosed in persons with much more varied symptoms. The clinical picture is changing. Previously, a diagnosis of SLE was made primarily in young women who had a butterfly rash, and symptoms of systemic involvement. Studies indicate that the classic symptom, the butterfly rash, occurs in approximately 47% of the cases. SLE was once expected to be rapidly fatal. It is now considered a chronic disease, with periods of activity and remission.

The incidence of morbidity is estimated at one new case per 100,000 persons per year. A study of the prevalence rate in New York

⁴Peter H. Schur, "Systemic Erythematosus," Textbook of Medicine, 13th Ed. 1971, W. B. Saunders Co., Philadelphia, London, and Toronto, Vol I, p. 816.

City revealed 2.6 cases per 100,000 populations. It is estimated to occur between five and ten times more frequently among women than men. Although the disease has been diagnosed in persons at ages ranging from two to ninety-seven, the majority of persons are discovered to have SLE during the third or fourth decade of life. SLE has been diagnosed in all races, but "occurs more frequently in Negroes than in whites and is extremely rare among asians."⁵

ETIOLOGY

Systemic lupus erythematosus is believed to be based on autoimmunity. Autoimmunity is defined as "an abnormal state characterized by the presence of a self derived immunological mechanism which may lead to disease."⁶ According to our present knowledge, autoimmunization is probably controlled by two mechanisms; (1) a genetic one, and (2) acquired immunological tolerance."⁷ The autoimmune manifestations of SLE can be differentiated from organ specific autoimmune conditions in that the lesions are widespread. SLE produces a degeneration of the

⁵*Ibid*, p. 816.

⁶William Dameshek, "Autoimmunity: Theoretical Aspects," New York Academy of Science Annals, Vol 124, Published by The Academy of New York, June 30, 1965, p. 7.

⁷Peter A. Miescher, and Hans J. Muller-Eberhard, Textbook of Immuno-pathology, Vol II, Grune and Stratten, 1969, p. 678.

connective tissues throughout the body, with a particular affinity for the small blood vessels. As connective tissue is widely distributed in all tissue elements, and is involved in most of the functions of the body, destruction of, or lesions in, the basic structure of the tissues can have serious ramifications.

A considerable number of drugs have been implicated in the occurrence of SLE, or an SLE-like syndrome. Hydrazides, used to reduce blood pressure; anticonvulsants, used to control convulsive seizures; and procainamide, beneficial in correcting cardiac arrhythmias; are associated with triggering a lupus-like syndrome. In these instances the symptoms usually subside within a few weeks after the use of the drug is discontinued. "Other drugs, including penicillin, sulfonamides, and oral contraceptives are associated with true exacerbations of SLE, and do not cause SLE-type symptoms or positive tests in normal persons."⁸

The list of drugs in Table 1 was compiled from the drug index supplied by Moser⁹, and from the 1970 Physicians' Desk Reference.¹⁰

⁸Schur, *op. cit.*, p. 821.

⁹Robert H. Moser, M.D., Editor, Diseases of Medical Progress. A Study of Iatrogenic Diseases, Charles C. Thomas, Publisher, Springfield, Illinois, U.S.A., 1969, pp. 823-842.

¹⁰Physicians' Desk Reference to Pharmaceutical Specialties and Biologicals, Albert B. Miller, Publisher, Litton Publications, Inc., Oradell, New Jersey, 1970.

Table 1. Drugs Implicated in Producing a Lupus-Like Reaction or in Exacerbating the Symptoms of Systemic Lupus Erythematosus.

Chemical Name	Brand Name	Therapeutic Action
Griseofulvin	Fulvicin- U/F Grifulvin V Grisactin Grisiofulvin Ayerst	Antifungal Antibiotic
Hydralazine	Apresoline HGL Apresoline-Esidrix Ser-Ap-Es Serpasil-Apresoline	Antihypertensive agent with the dual capacity of reducing blood pressure and increasing renal flow.
Hydantoin Mephentyoin	Dilantin Phelantin Mesantoin	Anticonvulsant for grand mal siezures, psychomotor, focal and Jacksonian types of Epileptic Siezures.
Isoniazid (INH)	Di-Isoqacin Niadex Nydrasid Piasoxine Pasna Tri-Pack	Anti-Tuberculosis
Para-Aminosalic Acid Di-Isopacin	Para-Pas Parasal Pamisyl PAS (Pascorbic) Pasna Tri-Pac Rezipas	Ancillary treatment of pulmonary or extra-pulmonary tuberculosis.
Penicillin	Bicillin Crysticillin Sugracillin Etc.	Antibiotic for Penicillin susceptible organisms
Phenylbutazone	Butazolidin-Alka Butazolidin	Anti-inflammatory, Analgesic, antipyretic

Table 1. (continued)

Chemical Name	Brand Name	Therapeutic Action
Phenylthiazine	Compazine Largon Phenergan Sparine Stelazine Temaril Thorazine (Chlorpromazine)	Tranquilizer, potentiator, Anti-emetic, with sedative effect. Depresses cough reflex.
Procainamide HCL	Pronestyl	Corrects cardiac arrhythmias, particularly ventricular.
Sulfonamide Sulfathiazole Sulfadiazine	Eskadiazine Qynben Vaginal In- serts Quinette Suladyn Urobiotic	Treatment of infections due to Sulfa-sensitive organisms.
Tetracyclines	Achromycin Aureomycin Declomucin Kesso-Tatro Syrup Panmycin Rexamycin Rondomycin Mysteclin-R Signomycin Sumycin Terramycin Tetracydin Tetrex Tetraban Tetramex Urobiotic	Broad Spectrum Anti- biotic.
Trimethadione Paramethadione	Tridione Paradione	Petit Mal Epileptic seizures. May be employed in organic brain injury.

The Physicians' Desk Reference was used as the source of actions and uses. In addition to the drugs mentioned, Oyama implicates certain cosmetics, hair dyes and rinses¹¹, but is not specific as to brand names or chemical content. Schur reports that ovulation inhibitors often cause an exacerbation of SLE. He does not indicate which of the components, estrogen or progesterone, may be suspected, but relates this to the hypothesis that endocrine factors may influence the development of SLE.¹²

Dameshek states that there can be autoantibodies against lipoprotein present without any harmful results, but that these indicate the existence of functional clones of abnormal immunocytes.¹³ If certain other conditions are met, causing a modification of cellular reactions of the clones, the result may be a break in the immunologic tolerance between such clones and the host. The other conditions he suggests could be chemical or radiologic exposure, a connection with the break up of cells during menstruation, or an association with the

¹¹Joseph H. Oyama, M.D., "Diagnosis and Treatment of Lupus Nephritis," The Medical Clinics of North America, Jan. 1971, Vol 55, No. 1. W. B. Saunders Co., Philadelphia, p. 80.

¹²Schur, *op. cit.*, p. 817.

¹³The term clone represents all the descendants derived asexually from a single individual. In this case, the cells which are reproduced by the original abnormal immunocyte.

X chromosome.¹⁴

Other immunizing agents, such as multiple vaccinations, have been suspected of triggering SLE.¹⁵ Occasional reference is made to an association between the development of SLE and an identifiable infection. In regard to viral infections:

"Paramyxovirus-like particles have been found in biopsies from some SLE patients, and antibodies to viral RNA have been found in the sera from others. These data suggest that a viral infection, in genetically predisposed patients, may alter the delicate balance between immunity and tolerance, and may result in the development of antibodies to cell structures altered by virus; these antibodies then cross-react with the normal cell structure."¹⁶

GENETIC IMPLICATION

The genetic role in SLE has been supported in the laboratory through experiments with inbred mice. The high incidence of the disease in human females might reflect a genetic predisposition associated with the X chromosome. There is a higher incidence of other connective tissue diseases, such as rheumatoid arthritis, dermatomyositis, thyroiditis, rheumatic fever, and hemolytic anemia, in the families of SLE patients than in the general population.

¹⁴William Dameshek, "Autoimmunity: Theoretical Aspects," New York Academy of Science Annals, Vol 124, 1965, Published by the Academy, N. Y. June 30, 1965, p. 7.

¹⁵Miescher and Muller-Eberhard, *op. cit.*, p. 677.

¹⁶Schur, *op. cit.*, p. 817.

Another discovery which is supportive of the hypothesis that SLE is genetically predisposed is reported by Baron and others in studies of isoniazid absorption. It has been shown that polymorphism for isoniazid is an autosomal recessive trait. "Sulfadimidine (synthetic sulphonamethazine) and isoniazid are both polymorphically acetylated in the same way."¹⁷ Evidence has been reported by Baron and others to show that hydralazine is most probably a substrate for polymorphic acetylation in man.¹⁸

The very bizarre toxic effects of hydralazine which include a systemic LE-like syndrome and peripheral neuropathy, may well be more common in slow acetylators of the drug. Severe side effects of phenelzine, which is a substitute for hydralazine, were found only in slow acetylator subjects.¹⁹

Thus these three drugs, hydralazine, sulfadimidine, and isoniazid, known to arouse SLE-like reactions, are linked with a demonstratable genetic deviation.

¹⁷D. N. Baron, M.D., Path., and others, Editors, Recent Advances in Medicine, 15th Ed. Little Brown and Co., Boston, 1968, pp. 215.

¹⁸Polymorphism refers to the property of a certain substance of crystalizing in two or more different forms or systems. Acetylation refers to the combination of an acetyl radical with an organic compound. This results in inactivating the compound. Slow acetylation would result in higher levels of free compound in the blood and urine of the patient taking a certain drug. In the instance of isoniazid, which has bacteriostatic action against microbacterium tuberculosis strain H-37R, this would result in higher blood levels of the drug in the patient who is slow to acetylate, than in the patient with a faster acetylation rate, other factors being equal.

¹⁹*Ibid*, p. 216.

CLINICAL MANIFESTATIONS

General symptoms include fatigue, weight loss, arthralgias, rashes, and fever. Other symptoms are dependent upon which organs are involved. Pleuritic pain is common and may be the first clue to the diagnosis of SLE. Joint changes as seen in rheumatoid arthritis are uncommon, but if they do exist, these "destructive joint lesions suggest a diagnosis of rheumatoid arthritis or 'rhus' (rheumatoid arthritis-lupus) overlap syndrome."²⁰

The butterfly rash is no longer considered essential to the diagnosis. Rashes occur most often on areas which have been exposed to sunlight and may recede and recur. Patchy loss of hair is frequent, and often undetected. Small ulcerations resulting from an underlying vasculitis may develop on the fingertips, and painful ulcers are seen frequently on buccal mucosa and gums. "Purpura and ecchymoses usually reflect an underlying blood platelet and clotting problem, renal insufficiency, or the side effects of corticosteroids."²¹

Kidney involvement may be the presenting manifestation of SLE, and occurs in about half of the patients. The same is true of those who develop cardiovascular involvement.

²⁰Schur, *op. cit.*, p. 818.

²¹*Ibid*, p. 818.

Neurologic and psychologic manifestations may complicate the natural fears and anxieties which accompany a chronic illness. Organic, neurological disturbances may manifest as irritability, confusion, hallucinations, and obsessional and paranoid reactions.

The psychosis of SLE may easily be confused with, and in fact is difficult to differentiate from, a steroid-induced psychosis; other symptoms and signs of active SLE usually accompany the organic disease. Organic brain damage most commonly manifests itself as convulsions, which occur in at least 15 percent of the patients. Other neurologic findings, found less frequently, have included peripheral neuropathy, hemiparesis, motor aphasia, ptosis, diplopia, and nystagmus.²²

A circulating anticoagulant which may be present.... either as antibody to factor VIII or more commonly as an inhibitor to the formation of "prothrombinase" results in prolonged clotting and prothrombin times and may be associated with mild or, rarely, severe hemorrhages.²³

This complicates menses, which may be irregular, heavy, or both. Patients with SLE usually can go through a pregnancy successfully if they do not have renal involvement. There is some risk of miscarriage during the first three months, and a much greater probability that there will be post partum exacerbation. "Occasionally a coagulation abnormality may be the first sign of SLE, for the prothrombin deficiency and inhibitors in one patient studied.... were detected eight years before other signs of the disease appeared."²⁴

²²*Ibid*, p. 819.

²³*Ibid*, p. 820.

²⁴Baron and others, *op. cit.*, p. 85.

Table 2. Frequency of Clinical Symptoms in Systemic Lupus Erythematosus.

	Percent		Percent
Arthritis, Arthralgia	91	Pulmonary	
		Pleurisy	49
Fever	84	Effusion	29
		Pneumonia	30
Skin	76		
Butterfly rash	47	Cardiac	
Photosensitivity	32	Pericarditis	33
Alopecia	20	Murmurs	29
Raynaud's phenomenon	18	EKG changes	18
Purpura	15		
Urticaria	7	Adenopathy	46
Renal	54	Splenomegaly	10
Nephrotic syndrome	21	Hepatomegaly	23
Gastrointestinal	55	Central nervous system	30

Peter H. Schur, "Systemic Lupus Erythematosus," Textbook of Medicine, 13th Ed. 1971, W. B. Saunders Co., Philadelphia, London, and Toronto, Vol 1, p. 818.

Abnormal immunologic reactions may precede symptoms for years. For example, a biologic false positive test for syphilis, noted in fifteen percent of the patients with SLE. The LE cell phenomenon, although of historical significance, is not always present in SLE, and is sometimes found in rheumatoid arthritis, lupoid hepatitis, and drug

reactions, which must be ruled out before diagnosis is made. The more sensitive antinuclear antibody detection technique (ANA) is more reliable. Antinuclear antibodies occur in other conditions, but are present in higher titers in patients with SLE than in other disorders.

"Antibodies to DNA are a positive indication of SLE."²⁵

Table 3. Laboratory Abnormalities in Systemic Lupus Erythematosus.

	Percent
Hematologic	
Anemia	71
Leukopenia	57
Thrombocytopenia	10
Hemolytic anemia	2
Circulating anticoagulant	1
Rheumatoid factors	14
Biologic false positive test for syphilis	15
Hypoalbuminemia	48
Hypergammaglobulinemia	62
LE cell test	83
Antinuclear factors	99.5
Anti-DNA antibodies	61
Hypocomplementemia	95

Schur, *op. cit.*, p. 820.

²⁵Schur, *op. cit.*, p. 821.

Chapter 3

PRESENTATION OF DATA

Of the sixteen patients whose case histories were studied, 15 were female and one was male; 15 were white, one was Indian. The range in age at the time the diagnosis was made was 17 to 73. The mean age was 44.7. Table 4, page 20, lists the presenting symptoms which were noted before, or at the time the diagnosis was made. The patients experienced these complaints in various degrees of intensity. It is possible that some symptoms may have been present but were not recorded.

A patient was credited with having a menstrual dysfunction if she reported difficulty during pregnancy, an unexplained miscarriage, ovarian cysts or tumors, irregular menses, or a hysterectomy. One patient's history indicated a pregnancy, but she had no children. She was not credited with a dysfunction as the reason for her childlessness was not explained.

A patient was credited with anemia if the chart stated that anemia existed. Detailed study of the patient's blood was not done. Any indication of pathology of the gingiva, dental abscess, or loss of teeth was counted in the general category of oral pathology. The American Dental Association, in its publicity campaign for better dental health, states that a large percent of teeth are lost because of disease of the gums; therefore, if the patient was edentulous, this was included in the tabulation.

Table 4. Occurrence of Manifestations of Systemic Lupus Erythematosus which were present in the patients studied prior to the time the diagnosis was made.

	Case No.																Total	Percent
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16		
Arthritis, Arthralgia	x		x	x	x	x	x	x	x	x	x	x	x	x		x	14	87.5
Fever	x		x	x					x		x		x	x		x	8	50
Skin																		
Butterfly rash, other	x			x	x			x	x				x				6	37.5
Photosensitivity	x			x	x		x								x		5	31.25
Alopecia			x							x							2	12.5
Raynaud's phenomenon																	0	0
Purpura			x		x			x					x			x	5	31.25
Urticaria											x						1	6.25
Renal dysfunction					x		x		x		x	x	x				6	37.5
Menstrual dysfunction		x	x		x	x	x	x		x	x	x					9	56.25
Gastrointestinal	x		x	x			x	x		x			x			x	8	50
Pulmonary			x	x		x	x	x	x				x		x		8	50
Anemia	x		x		x				x	x	x		x			x	8	50
Drug reactions		x			x	x	x				x	x	x	x	x		9	56.25
Cardiac			x			x	x			x		x		x			6	37.5
Central nervous system					x		x								x		3	18.75
Adenopathy		x				x	x				x	x	x				6	37.5
Splenomegaly	x																1	6.25
Hepatomegaly																	0	0
Peripheral neuropathy				x		x					x	x					4	25
Fatigability	x		x					x	x	x	x						6	37.5
Weight loss	x		x			x				x	x						5	31.25
Oral pathology	x	x					x			x							4	25
Myositis	x						x			x	x						4	25
Visual complaints		x	x	x	x	x				x	x		x				8	50
Total	11	5	12	8	10	9	12	7	7	11	13	7	11	4	4	5		

CASE NO. 1

This patient, a white female, was seventeen years of age at the time the diagnosis of SLE was made. The presenting symptoms were weakness, fatigability, rapid weight loss, nausea, fever, peridonditis, progressive leukopenia, anemia, erythema nodosum of the right ankle, myositis, splenomegaly, and arthralgia of the wrists and fingers.

Approximately six weeks before the onset of SLE, she began running a temperature of 103 to 104. She was diagnosed to have a dental abcess. Declomycin was prescribed. The temperature persisted for ten days. Approximately a month following this episode, she suffered a severe sunburn involving her face, forearms, and neck. Several days later she became ill with the symptoms which led to the diagnosis of SLE. No family history or past history was available.

CASE NO. 2

Patient number two, an Indian female, was under treatment in a hospital for a penicillin allergy at the time the diagnosis of SLE was made. She was forty-eight years old. She had been treated for tuberculosis from 1961 to 1963. In 1963 she was diagnosed to have luetic aoritis and was treated repeatedly with penicillin. She had a hysterectomy for vaginal bleeding after the SLE had been recognized. In June of 1969 she had a separation of the wound resulting in a large ventral

hernia.

Other physical findings include: marked scarring of the fundi oculi from old hemorrhage, a vertical nystagmus, a scar from a scalene node biopsy on the right side of the neck, slight vein distention, cirrhosis of the liver, luetic heart disease with congestive failure, she was edentulous, and at the time of her admission in January of 1970 she had bronchopneumonia. There was no family history available.

CASE NO. 3

Patient No. 3, a white female 54 years old, was admitted with fever of undetermined origin, chest pains, weakness, arthritis, swelling of the ankles and wrists, faintness, nausea, and weight loss. These symptoms had developed progressively over the five month period prior to her admission. She reported that her hair had become more coarse in texture. Laboratory examination revealed normocytic anemia, elevated sedimentation rate, moderately severe hypoproteinemia, hypergamma-globinemia, and leukopenia. A positive LE cell preparation confirmed the diagnosis of SLE.

Physical examination revealed a small amount of pleural effusion, extremities distorted by arthritis, skin generally mottled, alopecia, and two large ecchymosis over each wrist. An electrocardiogram exposed a sinus tachycardia. She had had a hysterectomy for excessive vaginal bleeding.

This patient was re-admitted to the hospital 15 months later with her lupus out of control. She reported recurrence of her symptoms had begun approximately eight months earlier after she had taken declomycin and an unidentified cough syrup for a cold. It was discovered that an error had been made in her prescription and that she had been taking stelazine rather than sterane for the past six months.

There was no family history available.

CASE NO. 4

Patient number four, a white female, was diagnosed to have SLE when she was thirty-six years old. The chief complaint at that time was chest pain, cough and a low grade temperature. She was found to have pleuritis with light pleural effusion. She had previously been diagnosed to have rheumatoid arthritis, and was now complaining of increased pain and joint distress. Telangiectatic blood vessels in the typical butterfly pattern were across her nose. She had osteoporesis with minimal narrowing of the proximal interphalangeal joints of the hands and some impairment of the sense of touch.

The history of arthralgias dated back four years. At one time she had had joint pain with some mild swelling which persisted for six months. During this period, she complained of blurred vision in her right eye. Photosensitivity affecting face, arms, and neck dated back three years, as did a history of headache, neck pain, low back pain, and

substernal or retrosternal pyrosis. She had been treated with gold for rheumatoid arthritis with quite dramatic results, but has no deformity of the permanent sort to support the diagnosis of rheumatoid arthritis.

Both parents are reported to have rheumatoid arthritis.

CASE NO. 5

This patient, a 30 year old white female, was admitted in a comatose state, having had three grand mal seizures in the past twelve hours. She was found to have the typical butterfly patterned rash on her face, papilladema and fundiscopic findings typical of nephritis or lupus, hemolytic anemia, marked leukopenia, and glomerulonephritis.

Approximately six weeks earlier, and shortly after the birth of her first child, she had developed a breast abscess. This was treated with a ten day course of oral penicillin. Her history indicated she had had acute glomerulonephritis, followed by a chronic state of glomerulonephritis with hypertension.

She had been treated again one month after the breast abscess had cleared, this time for what was felt to be a sinusitis. The symptoms were headache, and swelling of the eyes and face, plugging of the nose, and severe pain around the face. She was given tetracycline for seven days. The first three or four days brought improvement, then her symptoms returned and she was re-admitted to the hospital. Physical findings at this time included temperature of 102, an asymptomatic

cholelithiasis, pale skin with typical butterfly rash pattern on face, papilledema bilaterally with a few streaked hemorrhages (choked ocular discs), edema of the eyelids, puffiness of cheeks, and erythema on eyelids and soles of the feet. She was anemic.

Her history at this time reported an extreme photosensitivity. Ten days prior to this admission she had experienced severe exaggeration of redness, and burning of skin of face after exposure to sunlight for approximately two hours. At this time she was on tetracycline 250 mgm four times a day.

This patient was admitted again one month after the diagnosis of SLE had been made. She now had in addition to her previous symptoms polyarthralgia, mild dyspnea on exertion, and definite swelling of the ankles. She now reported an allergy to sulfa, which caused a skin rash.

Five weeks later she was admitted again with a recurrence of her symptoms following treatment for a Barthalon duct abcess with terramycin.

CASE NO. 6

This white female was diagnosed to have SLE at the age of fifty. She reported that she has had difficulty breathing for several years, with pain in the low posterior portions of the right chest, a nagging cough for the past two weeks, some wheezing, and recent weight loss.

The history records periods of chest pain when lying down, when belching, or when excited. She had bilateral pneumonitis two years ago for which the organism was not identified. She had taken steroids many years ago which had caused her to swell, and she is allergic to penicillin. She has been treated for essential hypertension, has had a cystocele repair, an appendectomy and an oophorectomy for a cyst. Other complaints are periodic pain and stiffness in the hips and knees, numbness in the right leg, and tremors of the left hand. Her last menstrual period was five years ago. She is a para IV, gravida VI, with two miscarriages.

Physical examination shows evidence of inactive rheumatoid changes on wrists and fingers. X-rays show cardiomegaly with bilateral pleural effusion. She has varicose veins. Examination of the fundus of the eye revealed marked nitching.

CASE NO. 7

Patient number seven, a white female, was diagnosed to have SLE at age thirty-eight. This was four years before the hospital admission for menopausal symptoms and arthritis, probably secondary to lupus. The history of her symptoms at the time the diagnosis was made was not available.

The patient reported a history of a rash on her face and arms from sunlight. She had had a hysterectomy when she was twenty-eight.

The pathology was not reported. She has had nine pregnancies with three miscarriages, and one stillbirth. She stated that she has had arthritis for the past several years, with pain in her back and morning stiffness. She is edentulous. Electrocardiogram and chest X-rays reveal cardiomegaly and non-specific ST wave changes with an incomplete right bundle block. The vaginal examination revealed "lumpy-bumpy" areas in the vaginal vault and the left labia majora.

This patient's history revealed many and varied medical problems, and numerous operations. She reported episodes of fainting without warning for the last year and one half, with no associated convulsions. She is allergic to kantrex, penicillin, sulfa, streptomycin, achromycin, codiene, lysol, and soap.

CASE NO. 8

This white female patient was diagnosed to have SLE when she was fifty-seven. She had had rheumatoid arthritis for over twenty years with considerable deformity and disability. She had been treated with gold which had no effect and butozoladin with only slight relief. She has marked malar and palmer erythema. Her complaints included nausea and vomiting, and fatigue.

A thyroidectomy for hyperthyroidism had been done seven years ago. Her last menstrual period was at the age of forty. An ovarian tumor had been removed twenty years ago. She is a gravida one, para

zero. The family history reveals that her sister has rheumatoid arthritis.

At the time of this admission the patient was diagnosed to have hypercortisonism with Cushingoid syndrome, probable heart failure, and probably pleural effusion.

CASE NO. 9

This patient, a white male, was diagnosed to have SLE at the age of seventy-three. For several months the patient had been running a low grade fever and complaining of progressive weakness and stiffening of the joints. He had been treated with antibiotics (unidentified) on several occasions for a urinary infection which did not respond satisfactorily to the therapy.

This man has had classic lesions of chronic discoid lupus over the malar regions for approximately twenty years. This was reported to have waxed and waned. When he was admitted he had a rash on both malar regions. He had been diagnosed to have pulmonary emphysema for a number of years. Pleural effusion developed during the last two months. Fluid aspirated from the thoracic cavity showed no abnormal cells.

At the time of his final admission to the hospital, his diagnosis was SLE, uremia, and hemolysis, which is disintegration of blood. He had rheumatoid type swelling of the knees, elbows, and wrists.

CASE NO. 10

This white female was diagnosed to have SLE at the age of forty-one. She was admitted with retrosternal distress, dyspnea, some nausea and vomiting, and diaphoresis. Physical findings at that time included an intermittant pre-systolic gallop at the lower left sternal border, and a very soft, grade one or less, over-apical systolic murmur. She was anemic. The admitting diagnosis was possible pericarditis and acute myositis.

This patient's medical history disclosed an oophorectomy for an endometrial cyst at the age of eighteen followed by a pan hysterectomy for menometrorrhagia at the age of twenty-three. She frequently had experienced a pain in the neck which radiated to the anterior chest, and was accompanied by nausea and vomiting. She had had transient arthralgia with swelling of the ankles and frequent puffiness of the eyelids. Alopecia, loss of hair, was very evident. Four years earlier this patient had undergone a gingivectomy for acute and chronic inflammation and hyperkeratosis of the gingival mucosa. Recently she had complained of gross fatigue.

As a result of a personal interview, and the questionnaire, the following information was obtained. She had had a severe attack of pericarditis following pneumonia when she was twenty-eight. She has lipoid tumors of the breasts and left arm. She remembers having had

at least seventeen X-rays, and more than sixty-two immunizations. She was in the habit of sunbathing regularly prior to her diagnosis, and although she did not display a photosensitivity, she reported that she would consistently feel poorly after a day of boating or other lengthy exposure to the sun. She had suffered a severe sunburn as a child, and had had episodes of blurred vision, itching, swelling and redness of the eyes.

Of the drugs which have been implicated in triggering lupus, she has taken stelazine, thiorazine, penicillin, butazolidin-alka, and norflex. Norflex is not listed in Table 1, but is described as a substitute for hydralazine. She has an uncle who has rheumatoid arthritis.

CASE NO. 11

This white female was diagnosed to have SLE when she was thirty-six. Upon admission, this patient stated she had had "blood trouble" for three years. This was characterized by high temperatures and a consistently high white cell count. She had had swelling of glands in the left axilla, lumbar pain, chills, and weakness. She reported numbness in the right side of her face which usually would last several hours, and some soreness and aching in arms and shoulders. She reported that her elbows had been sore, and her hands swollen for approximately two years. She was earlier diagnosed to have rheumatoid

arthritis, and had had gold therapy in the past. Her weight loss over the past two years amounted to fifty pounds.

Her history discloses that her menses was never regular, and that she had a marked bloody discharge throughout her entire pregnancy two years ago. She was hospitalized during most of her pregnancy with a fever of questionable origin. Other symptoms were a marked tenderness in both flanks, pain and swelling in the coccyx, sore and swollen knees, large lymph glands in both axillary areas, and deformities of both hands. Her laboratory examinations showed anemia, elevated sedimentation rate, and many pus cells in the urine. She reported an allergy to sulfa, which caused hives. During this hospitalization, she received achromycin 500 mgns. three times before it was discontinued.

This patient was admitted to the hospital ten months later having fainted following a tooth extraction. Plethora of the face suggested a butterfly lesion over both malar regions. There were multiple dilated capillaries in all areas of the skin. There was tenderness in bilateral flank areas. Her temperature ranged from 100 to 101. She was discharged with the diagnosis of syncope, probable cause, SLE.

Three days later she was re-admitted after having a convulsive seizure of the grand mal type. She was treated with prednisone and dilantin, improved, and was discharged with advice to continue taking both of these drugs.

She was next admitted, seven days later, with a status epilepticus of approximately twelve hours duration. She was treated with calcium and dilantin by intramuscular injection every two hours, high doses of corticosteroids intravenously, and finally intravenous pentathol. She expired without regaining consciousness.

Her autopsy showed severe encephalopathy secondary to SLE, obliterative fibrous pleuritis, pericarditis, ascites, terminal bronchopneumonia, a dermoid cyst of the right ovary, and hydropic degeneration of the kidney with wire loop phenomena. It was also noted on the autopsy report that the exposed areas of her skin appeared to be normally suntanned.

CASE NO. 12

Patient number twelve is a white female who was diagnosed to have SLE at the age of sixty-seven. She was admitted with midback pain related to osteophoresis of the spine. The bone marrow study showed massive hemosiderosis with some LE cells. The presence of albumenurea with cellular elements indicated some renal involvement. She reported an allergy to penicillin, and that she had had a hysterectomy for adenomosis of the uterus at the age of forty-six.

She was later admitted with osteoporosis of the dorsal spine and compression fractures of four dorsal vertebrae, paronchitis of the fifth toe, right foot, and an infection of the left index finger.

The infections were incised and drained, and she was fitted with a brace for her back. She was discharged taking prednisolone, darvon compound and rondomycin.

This lady filled out the questionnaire. The information obtained disclosed that she had had over eighteen immunizations, approximately twenty-five X-rays, no severe sunburn, and no habit of sunbathing. She reports having had pleurisy, arthritis in both hands and legs in the past, and a pericarditis when she was fifty-one. The irregular heart beat which was a residual of this illness was treated with vistaril, pronestyl, and peritrate. She reported having had occasional episodes of neuritis.

CASE NO. 13

This white female was diagnosed to have SLE when she was sixty-four. She was admitted for diagnosis as a result of symptoms indicating decreased renal function. She was anemic, had occasional low grade fever, and transient raised erythematous skin lesions, transitory polyarthralgia, chest pain with right pleuritis and ascites.

Nine months previously, this patient had been hospitalized with extensive bilateral pneumonia. She was treated with numerous antibiotics. Among them were penicillin and tetracycline. She developed a rash which was attributed to an allergy to one or both of these drugs. She later took tetracycline again, and it was discontinued because of

itching. She became anemic, and required six units of blood.

Eight months after this illness she developed a cough and hoarseness, with purulent sputum. She became febrile. Erythromycin 250 mg. four times a day was prescribed. Three days later she developed redness and swelling in the anterior portion of her left leg and foot. She had two well circumscribed lesions on the left anterior tibial surface which resembled purpura. There were enlarged tender nodes in the left inguinal area.

Her past history notes that she was diagnosed to have arthritis approximately a year before the diagnosis of SLE was made. She reacted to the prescribed indocin with nausea, vomiting, headache, dizziness, sore red eyes, weakness, cough and some question of pleurisy. She has had an appendectomy and a cholecystectomy, and she has an exophthalmic goiter. She is the mother of seven children. No menstrual abnormalities were noted.

Physical examination revealed a discoid atelectasis in the lower lobe of the right lung, a small hiatus hernia, and a defect in the duodenum consistent with a small benign ulcer. Renal biopsy shows extensive hyalinization of the glomeruli with endothelial cell proliferation and membrane thickening. There was infiltration with polymorphonuclear leukocytes.

CASE NO. 14

Fourteen years ago this patient was diagnosed to have SLE. She was then thirty-six. She reported, on the questionnaire, that she was treated for a sinus infection with penicillin. Three months later she began experiencing stiffness in her arms and legs upon awakening, and running a low grade fever. This, according to the patient, progressed into lupus, with involvement of the heart.

She reported twenty-seven or more immunizations, "too many X-rays to estimate," and a mild case of rheumatoid arthritis in her mother. She has suffered severe sunburn, and has been in the habit of sunbathing regularly. She reports allergies to penicillin, sulfa, and codiene.

This patient, at the time the data was being collected, was being treated for cancer of the endometrium with radiation therapy. She was judged to be a poor surgical risk because she had been on long term cortisone therapy. She has had pericarditis, and frequent sinusitis, which was treated with nasal decongestants and unidentified antibiotics. She was reported to have some non-specific ST and T wave changes in her cardiac rhythm, and some lupus nephritis. She had recently had acute gastroenteritis.

CASE NO. 15

Patient number fifteen, a white female, was diagnosed to have SLE when she was fifty. Information about the symptoms which led to the diagnosis was not available. This patient filled out the questionnaire and the following facts were disclosed. She reported having had approximately eight immunizations, and an estimated fifty X-rays, not including dental X-rays. She states she has had a severe sunburn, that she has a photosensitivity, and has never sunbathed regularly. She states she has had no problems with her menstrual cycle.

Her medical history includes a toxic encephalitis following an immunization shot for influenza. This was complicated by thrombophlebitis and pulmonary embolism. She reports many recurrences of pulmonary embolism and chronic pleurisy. When she was ten years old she had scarlet fever which was complicated by "what the doctors, at that time, called brain fever."

She stated that penicillin is the only drug to which she is allergic. She has taken plaquenil for approximately three years.

CASE NO. 16

This patient, a white female, was eighteen years old at the time a positive LE cell preparation was obtained. She had been complaining of nausea, vomiting, and pain in the extremities for several

weeks. An atrophic, tenangiectatic patch was observed on the dorsus of her left hand. Her laboratory examinations revealed anemia. She had a history of recurrent arthritis with fever of two years duration. She was hospitalized briefly for the laboratory work-up. No further information was available.

SUMMARY

Tabulation of the symptoms which were present at the time SLE was identified in these patients reveals the following rate of occurrence. Arthralgia, or arthritis was reported in fourteen (87.5%) of the cases. Fever was listed in eight (50%). Of the skin manifestations, eleven (68.7%) patients had observable involvement. Six (37.5%) of these had rashes, five (31.25%) experienced photosensitivity, two (12.5%) had alopecia, none displayed Raynaud's phenomenon, five (31.25%) had discernable purpura, and one (6.25%) described the cutaneous manifestation as urticaria.

Renal dysfunction was evidenced in six (37.5%) of the patients, menstrual deviations and drug reactions were reported in nine (56.25%). Gastrointestinal symptoms occurred in eight (50%) patients, as did pulmonary pathology, anemia, and visual complaints. Six (37.5%) manifested cardiac involvement, and adenopathy. Six (37.5%) complained of excess fatigue. Weight loss was recorded in five (31.25%) of the cases. Peripheral neuropathy, oral pathology, and myositis were symptoms in

four (25%). Central nervous system dysfunction occurred in three (18.75%). One (6.25%) patient was observed to have splenomegaly, and none displayed a hepatomegaly which was reported.

The number of symptoms per patient ranged from four to thirteen. Table 4, on page twenty, may be referred to for an individual analysis of the frequency of occurrence.

Chapter 4

INTERPRETATION OF DATA

The purpose of this study was to attempt to determine if a person who might be predisposed to SLE could be recognized prior to the onset of acute symptoms. This was to be considered by examining the clinical manifestations as well as evidence of genetic predisposition. The second purpose was to identify those agents these persons might be unable to tolerate.

CLINICAL COMMONALITIES

The commonalities demonstrated by the patients in this study in regard to their clinical manifestations approximate the descriptions presented in the literature. Fourteen of the sixteen suffered from arthritis or arthralgia. If this were found to occur in connection with exposure to some suspected triggering agent, rejection by the body of that agent should be considered. Joint pain and stiffness is often treated lightly as a sign of age in older people. It receives more attention if it occurs in the young. Rothfield states that "if a child treated for rheumatoid arthritis demonstrates a leukopenia, SLE should be considered."²⁶

²⁶Naomi F. Rothfield, M.D., "Diagnosis of Lupus Erythematosus Rheumatoid Arthritis in Children," The Pediatric Clinics of North America, Vol XVIII, No. 1, A Symposium on Laboratory Diagnosis, guest Ed. Philip A. Brunell, M.D., W. B. Saunders Co., Philadelphia, Feb. 1971.

The next most frequently reported symptoms involved the skin. Eleven patients in all had developed rashes, photosensitivity, alopecia, purpura, or urticaria. Inasmuch as SLE was believed to be a disease of the skin before the involvement of other organs was recognized, this finding is in harmony with the classic clinical picture.

Menstrual dysfunctions and drug reactions had occurred in nine of the case histories. Abnormalities of the menstrual mechanism, the X chromosome, and genetic deviations of certain clotting factors have been suggested as causes of SLE. Is it possible that evidence of menstrual dysfunction, unexplained accidents of pregnancy, or the presence of clotting inhibitors signal the approach of a break in the immunological tolerance which would initiate the acute syndrome? Baron and others states that:

Occasionally a coagulation abnormality may be the first sign of this condition (SLE), for prothrombin deficiency and inhibitors in one of the patients studied by Biggs and Denson (1964) were detected eight years before other signs of the disease appeared.²⁷

Patient number one, married at sixteen, assumed she was pregnant when her symptoms began. It was not stated that she had been taking ovulation inhibitors, which have been suspected of inducing SLE. Neither was it noted that a change in her menstrual pattern had occurred. It is known that the onset, or exacerbation of symptoms of SLE is not

²⁷D. N. Baron, M.D., D.Sc., M.R.C.P., and others (editors), Recent Advances in Medicine, 15 ed., Little Brown and Co., Boston, 1968.

uncommon following pregnancy. Patients number five and eleven of this study began to experience their presenting symptoms soon after the birth of their first child.

In this study sixty percent of the women demonstrated some type of dysfunction involving the reproductive cycle before the diagnosis was made. Patient number two required a hysterectomy for excessive bleeding after she was diagnosed, and patient number fourteen was being treated for cancer of the endometrium at the time this data was being collected.

Drug reactions are clearly a warning that further invasion by that chemical will not be tolerated. It might also be an indication that the body's general adaptive ability is weakening, and therefore, exposure to other chemical agents might be dangerous as well.

Eight patients demonstrated gastrointestinal symptoms. The same number reported pulmonary pathology, anemia, fever, and visual complications. Gastrointestinal symptoms are varied both in type and intensity. Beeson observes that "acute SLE may present with an abdominal picture requiring differentiation from pancreatitis."²⁸ He also states that "SLE sometimes compromises the blood supply to the small intestines causing malabsorption."²⁹ This could be a consideration

²⁸Paul B. Beeson, M.D., and Walsh McDermott, M.D., Textbook of Medicine, 13th Ed., Vol 2, W. B. Saunders Co., Philadelphia, 1971, p. 1318.

²⁹*Ibid*, p. 1310.

in the weight loss which is common to SLE patients.

Pulmonary manifestations included pleural effusion, pleurisy, pulmonary embolism, pneumonia, pneumonitis, and emphysema. As the process of SLE weakens the small blood vessels and connective tissue, the lungs can be expected to function less efficiently, and to be more susceptible to invasion of organisms.

Anemia is consistent with the clinical picture which includes suppression of any or all formed elements of the blood. Polycytopenia would have been a more inclusive criterion for studying this manifestation. The fever is frequently of undetermined origin. Once the syndrome is recognized, the cause for the elevation in temperature is less obscure. Visual complaints are the result of telangiosis in the fundus of the eye, as evidenced by choked optic discs, hemorrhage, and abnormal exudates.

Indications of renal involvement were observed in six of the patients studied. The same number presented cardiac symptoms, and complained of fatigue. As SLE produces degeneration of small blood vessels and connective tissue, the kidneys are particularly vulnerable. Kidney involvement is frequent in the diagnosed cases, and is responsible for more than fifty percent of the mortality rate.

If the heart is the major organ which is involved, the patient is frequently diagnosed first to have pericarditis. Minor arrhythmias may be discovered when the patient does not display more severe cardiac

symptoms. "SLE may present many findings of bacterial endocarditis.... A positive test for L.E. factor and negative blood cultures are the usual criteria for differentiation."³⁰ Fatigue is the companion of disease, easily understood where there is anemia, multisystemic involvement, and anxiety. A complete medical history would most probably reveal that this symptom occurred in one hundred percent of the patients studied.

Six patients also showed indication of adenopathy. The severity of this symptom varied from enlargement of lymph nodes to an adenopathy of the uterus serious enough to necessitate a hysterectomy. Five patients recorded weight loss. This symptom could be attributed to gastrointestinal pathology, or with loss of appetite due to general malaise.

Oral pathology, periferal neuropathy, and myositis were identified in four of the patients. All of these manifestations occur because of disease of the capillaries and the connective tissue of the organs involved. Symptoms indicating pathology of the central nervous system occurred in three patients. Alopecia was recorded in two. Loss of hair, until recently has not been associated with this syndrome. Considering the popularity of wigs, and the likelihood that a woman with thinning hair and patchy baldness will be wearing a wig, this

³⁰*Ibid*, p. 1103.

manifestation can easily be overlooked.

Two patients were found to have had thyroidectomies, and one was reported to have an exophthalmic goiter. The possibility presents itself that thyroiditis, another connective tissue disease, might in some cases present an overlap syndrome similar to that which sometimes occurs with SLE and rheumatoid arthritis. If this could be proved the evidence would support the theory of genetic predisposition. Splenomegaly, found only once in this study, brought the total of presenting symptoms to eleven for patient number one.

In the population studied, no patient exhibited less than four manifestations of SLE at the time the disease was recognized. It is probable that others were present, but were either not observed, or were not associated with SLE. More than two-thirds of the population were tabulated with seven to thirteen specific symptoms. This supports the theory that a person who is developing SLE could be recognized prior to the onset of acute symptoms. As Oyama suggests:

The introduction of corticosteroids into the management of SLE and its complications has resulted in reduction of acute mortality, and the increased life span of the patients with SLE has allowed the full evolution of the disease process to become more fully known."³¹

³¹Joseph H. Oyama, M.D., "Diagnosis and Treatment of Lupus Nephritis," The Medical Clinics of North America, Vol LV/No. 1, Symposium on Diseases of the Kidney, Robert M. Kark, M.D., Guest Editor, W. B. Saunders Co., Philadelphia, London, and Toronto, Jan. 1971, p. 71.

This means that with our present knowledge of the disease, we no longer have to wait until the typical butterfly pattern of rash develops for the disease to be recognized. Treatment, in the form of protection from the agents which might escalate the symptoms, can be offered the individual before he becomes acutely ill.

THE ROLE OF SUSPECTED TRIGGERING AGENTS

The second objective of this study was to observe the role suspected triggering agents appear to have played in regard to the onset or exacerbation of symptoms. Implication of these agents in the development of symptoms increased the evidence that they are to be considered a potential hazard to persons with an acute, or subacute SLE.

Patient number one was treated with declomycin for a dental abcess which appeared to have been diagnosed on the basis of facial pain and a fever. Neither her temperature, nor her pain responded as expected to the antibiotic. Her body responded by displaying a sensitivity to sunlight. Within six weeks she had developed enough symptoms of SLE that the disease process was recognized and confirmed.

Patient number two had been treated over a long period of time for luetic heart disease with penicillin. She had been treated for tuberculosis, most probably with isoniazid (INH) and para-aminosalic acid (PAS) for two years. She was in the hospital because of an acute

allergic reaction to penicillin when her SLE was diagnosed.

Patient number three was enjoying a remission of her symptoms until she took declomycin for a cold. She was also given a cough syrup. If this cough syrup were phenergan, another suspected agent would have been involved. It was discovered that the patient's prescription for sterane, a steroid, had been mistakenly filled with stelazine, which is a brand name for phenylthiazine, a tranquilizer which has been suspected of inducing SLE.

Patient number four had been diagnosed to have rheumatoid arthritis, but had no deformity of the permanent sort to support this diagnosis. She had been treated with gold for the arthritis, and dramatic results were recorded. Schur focuses attention on gold salts as a chemical capable of influencing the onset of SLE.³²

Patient number five developed a breast abcess shortly after the birth of her first child. For this she was given a ten day course of oral penicillin. She next was given tetracycline for seven days for sinusitis. She appeared to respond for three or four days, then her symptoms returned. She was next given terramycin for a Bartholin duct abcess. Within six weeks from the original complaint, the patient was admitted to the hospital in a comatose state, and diagnosed as having

³²Peter H. Schur, "Systemic Lupus Erythematosus," Textbook of Medicine, 13th Ed., Vol I, W. B. Saunders Co., Philadelphia, London, and Toronto, 1971, p. 816.

acute SLE.

Patient number six was allergic to penicillin. She had been treated for hypertension. The drug was not identified. Hydralazine would have to be ruled out.

Patient number seven reports allergies to sulfa, penicillin, and achromycin in addition to allergies to chemicals not included in this study.

Patient number eight had been treated with gold with no effect and with butazoladin-alka with very little improvement.

Patient number nine was given many unidentified antibiotics for a urinary infection. It was noted that he did not respond as expected to the drugs used.

Patient number ten reported a large number of immunizations, and seventeen X-rays. She has taken stelazine, thorazine, penicillin, butazoladin-alka, and norflex. Personal interview revealed that she has an idiosyncratic result from tranquilizers.

Patient number eleven was given gold therapy for rheumatoid arthritis. Her history shows treatment for other conditions with achromycin and dilantin. The dilantin was given for the convulsions which occurred as her condition began to deteriorate rapidly. It did not succeed in reversing the course of the disease.

Patient number twelve reported a penicillin allergy prior to her diagnosis of SLE. Six years before the disease was identified, she

had had an attack of pericarditis. She had been taking pronestyl since that time to control the irregular heart beat which was a residual of that episode. She estimates she has had twenty-five X-rays.

She was recently hospitalized for compressed fractures of the spine due to osteoporosis. At this time, two small infected areas were incised and drained. She was sent home with a prescription for rondomycin to heal the infection. Her response to the rondomycin was not ascertained. Several days later this patient cancelled her appointment for an interview because she did not feel well enough to talk. This may be of no significance, however, she had expressed interest in cooperating with this study.

Patient number thirteen was hospitalized nine months before the recognition of her disease with pneumonia. She was treated with numerous antibiotics including penicillin and tetracycline. These were discontinued when she developed a skin rash and itch. She was given tetracycline again, and developed only an itch. Eight months later erythromycin was prescribed for a cough. Within three days well described purpura developed on her left leg and foot, and the lymph nodes in her left inguinal area became enlarged and tender. The onset of acute SLE followed, promptly.

Patient number fourteen reports the development of the symptoms of SLE within three months after receiving a shot of penicillin. Since her diagnosis was made fourteen years ago, she has been treated with

unidentified antibiotics for pericarditis and sinusitis. In answer to the questionnaire, she listed a minimum of twenty-seven immunizations, "too many X-rays to estimate", and an allergy to penicillin and sulfa.

Patient number fifteen reports approximately eight immunizations, over 50 X-rays, and an allergy to penicillin.

Patient number sixteen had no history of drug consumption available to be used in this study.

In this population, the anti-bacterial agents were most widely implicated. This may be because they are more frequently prescribed than the other drugs. Every patient except number eight and sixteen reported minimal or extensive use of antibiotics. Because their use was not reported on the records available, it need not be assumed that these persons have never been exposed to these agents. Nine patients are credited with taking one or more forms of tetracycline, and nine also have taken penicillin. Sulfa was reported by two. As this drug is no longer being used, these were reported because the patient stated he was allergic to sulfa. INH and PAS were assumed to have been used by one patient. In addition to this, two patients reported using antibiotics which they were unable to identify.

Of the drugs prescribed to alleviate the symptoms of arthritis or arthralgia, three patients had been treated with gold injections, and two had tried butazolidin-alka. Two patients reported the use of tranquilizers. One had used both stelazine and thorazine, the other

had taken stelazine by mistake. One patient reported having taken pronestyl to control a cardiac arrhythmia. Two patients had taken antihypertensive drugs. One specifically identified norflex. One patient's record reports the use of dilantin, and four have records of multiple immunizations and numerous X-rays.

ADDITIONAL OBSERVATIONS

The population dealt with in this study was drawn from a limited geographical area. It included only a sample of the persons who had been treated for SLE during a six year period, in one city in eastern Montana. Other cases were brought to the attention of the researcher, but could not be included in the study for various reasons. This area has a population of approximately 350,000. The prevalence rate for this area then would be 4.57 cases per 100,000, based only on the cases included in this study. With the other known cases, it would be higher. The prevalence rate reported in the study done in New York City was 2.6 cases per 100,000.

Does this information indicate the existence of a geographical or climatic influence on the development of SLE, or does it reflect the improvement in diagnostic procedures and treatment which has resulted in reduced mortality?

SLE is reported to occur more frequently in the Negro race, and almost never among asians. This area has a minimum population from

both of these races. SLE occurs more frequently among women than men. This area has a higher population of men than women. If the people living in this area spend more time enjoying the sunshine than those do who live in New York City, then exposure to the sun may be a factor.

It was also noted that the only male in this study developed SLE in his seventh decade. Could the onset of the disease in any way be related to a deficiency in male hormones?

Chapter 5

SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

SUMMARY

The first purpose of this study was to investigate the commonalities of persons who develop Systemic Lupus Erythematosus (SLE) in order that such persons might be recognized prior to the onset of acute symptoms, and protected from receiving medications which might escalate the syndrome. The second purpose was to determine to what degree the drugs, or other triggering agents which have been suspected of complicity in the onset of exacerbation of the symptoms of SLE, played a part in the medical histories of the cases studied.

The information was obtained by studying hospital records of 15 persons admitted with a diagnosis of SLE between January 1965, and February 1971. A questionnaire (see Appendix) was filled out by four patients. For one of these, the questionnaire was the only source of information. The other three had hospital records available. Two persons were personally interviewed by the author, in addition to filling out the questionnaire.

The sample dealt with in this study was drawn from a limited geographical area - all patients having been treated in one city in eastern Montana. Some of the information used is subject to the unreliability of memory. Discrepancies and omissions were noted when

the records were studied.

The literature suggests that SLE is based on autoimmunity. Autoimmunity is believed to be controlled by two mechanisms, a genetic determination, and an acquired immunological tolerance. The genetic theory, which is offered to explain why some persons will respond to specific stimuli with symptoms of SLE while others will not, is based upon the following observations. There seems to be more connective tissue diseases in the families of persons with SLE than in the population as a whole. Persons who are slow acetylators of certain drugs have been found to have developed symptoms of SLE after taking these drugs, while persons who acetylate at a faster rate do not. Rate of acetylation of some drugs has been linked to a recessive gene. The frequent occurrence of menstrual dysfunctions, and the preponderance of females who acquire the disease, have led to suspicion that the X chromosome may be involved. Genetic deviation in clotting factors of patients with SLE have been demonstrated.

Acquired immunological tolerance is related to the increased use of chemical agents for therapeutic effects. It is suspected that persons with a lupus diathesis develop the disease when the body is exposed to drugs, or other chemical agents which it is unable to tolerate.

The investigator found sufficient clinical manifestations of the disease were observable in the population studied at the time the

diagnosis was made, to support the supposition that these patients might have been recognized as being SLE inclined prior to the onset of acute symptoms.

Incomplete as the information regarding use of suspected triggering agents was, no patient except the one for which no record other than that of symptoms was available, indicated a history of using less than two of the chemical agents implicated in the onset of symptoms.

CONCLUSIONS

Based on the findings of this study, the following inferences can be made.

SLE is usually diagnosed during an acute phase, months or even years after clinical symptoms have been noted. It is the involvement of a major organ such as the kidneys, heart, lung, or brain which usually focuses attention upon the disease. Not infrequently previous acute manifestations were not recognized to be part of a multi-systemic disease. The key to recognizing a subacute SLE appears to be in correlating symptoms which at first may appear to be insignificant, or unrelated. MacBryde, in describing the significance of areas of purpura on the buccal mucosa, states that, "the diagnosis (of SLE) will depend upon finding one or more other protean manifestations."³³

³³Cyril Mitchell MacBryde, Signs and Symptoms, 4th Ed., J. B. Lippincott Co., 1964, p. 140.

Several factors seem to be important when considering the iatrogenic aspects of SLE. There is a wide range recorded for the age of onset of the disease. This may mean that some individuals possess a higher degree of adaptability to chemical invasion than others. It may also be dependent upon the number and type of exposures to inducing agents. Persons who are now in their fifth, sixth, or seventh decade were less likely to have received multiple immunizations in their infancy and childhood, or to have been X-rayed routinely in their early life, or to have been given antibiotics for many, and often minor infections. These therapeutic intrusions, expected at first to usher in the golden age of health and longevity, were developed and their use escalated, after this older generation had reached adulthood. In effect then, these agents have been available to all of the population, except the very young, for approximately the same number of years.

Information was insufficient in regard to the patient's exposure to X-rays, immunizations, or sunburn to draw concrete conclusions. All patients may be assumed to have had X-rays and immunizations. The four for whom an estimated number was obtained recorded a sufficient number that these agents cannot be cleared of suspicion on the basis of this study. The data obtained in regard to exposure to the sun seems to indicate that photosensitivity is more likely to be a result of SLE than a factor contributing to its development.

The findings of this study support the suspicion that use of certain drugs do contribute to the exacerbation of the syndrome. Antibiotics were associated with the onset or exacerbation of symptoms in all but three of the patients studied. This may be related to the frequency with which antibiotics are used. Other agents, such as hydralazine, tranquilizers, and gold injections seemed to have a less volatile effect. Samter suggests that in some cases, rather than certain drugs inducing the symptoms of SLE, "it may be that the drug is used to treat the clinical disorders which are manifestations of SLE itself."³⁴

An unexpected finding is that the drugs being studied, when given to a patient with SLE, do not have the same therapeutic effect that they have for other persons. This raises the question that persons with SLE or a lupus diathesis may possess the proclivity for idiosyncratic reaction to drugs.

The data indicates that dysfunction of the reproductive system is connected with SLE in some way. If the underlying cause is related to circulating anticoagulants, or clotting inhibitors, the theory that genetic factors are involved would be supported. If the problem is caused by lesions in the connective tissue of the reproductive organs, then this would be an indication of a disease which already exists. In

³⁴Max Samter, M.D., (ed) Immunological Diseases, 1st Ed., C. V. Mosby Co., St. Louis, 1967, p. 744.

either case, these findings would help to identify the SLE patient.

The author concludes on the basis of this study, that it is possible to recognize a subacute SLE if a sufficiently complete medical history is available. The data also implies that for these persons, agents suspected of triggering the syndrome can be identified, and should be avoided whenever possible.

RECOMMENDATIONS

In view of the apparent significance of the data obtained here, the following recommendations were made.

1. That this study be repeated, using a larger sample, and a longer period of time to obtain a more complete medical history.
2. That a study be done to determine the rate at which clinical manifestations of SLE occur in the general population. A longitudinal study of those found to have five or more symptoms could prove to be interesting and informative.
3. That a study be made of women who display menstrual dysfunctions or who have had accidents of pregnancy. It might be observed if the mask of pregnancy is in any way related to the mask of SLE.
4. That a genetic study of males who develop SLE be conducted. This should disprove, or reveal complicity involving the X chromosome. Examination of the level of male hormone production might yield significant data.

5. That a study be done of the incidence and prevalence of SLE over a widespread area, to determine if there is a geographical or climatic factor involved in the occurrence of SLE.
6. It is further recommended that a tool be developed for use in identifying the individual who may have a lupus diathesis.

APPENDIX

LETTER TO DR. MILLER

307 Yerger Drive
Bozeman, Montana 59715
October 11, 1970

Dear Dr. Miller:

I am writing to request the name of the urinary antiseptic you mentioned in connection with Lupus Erythmatosis. I would also like the name of the book in which these findings have been published.

For my research project I am considering this subject. I feel it might be approached by studying past medical histories of patients with diagnosis of Lupus Erythmatosis, and also by doing follow up studies on persons who have taken the drug suspected of inducing Lupus Erythmatosis.

I am just beginning to develop this idea. Any suggestions you might have would be appreciated.

Thank you for your cooperation. I was fascinated by the information you presented in your lecture at M. S. U. I hope I may have the opportunity to listen to you again.

Sincerely,

Paula Cummings

REPLY FROM DR. MILLER

The L.E. like state is induced is Hydralazine
(Apresoline). other drugs that have been implicated
are hydantoin derivatives, chlorpromazine, penicillin
& procainamide, phenylbutazone, sulfadiazine
for references

1. Side Effects of Drugs by L. Mayler
Excerpta Medical Foundation
Volume 1 N.Y., N.Y. 1958-60
page 209.
2. The Modern Complications Medical Practice
by Sparr Druce & Stratton
page 22-24
3. Textbooks of Immunopathology
by Peter Miescher
Druce & Stratton

J. Alan Miller MD

LETTER TO PATIENTS

Billings, Montana
February 21, 1971

Dear Mrs. _____:

Inasmuch as I have not been successful in contacting you since the day I talked to you while you were still a patient in the hospital, I have decided to write to you and send this questionnaire, asking if you could spare a few minutes of your time to fill it out, and return it to me in the envelope provided.

As I told you when I talked with you in the hospital, the information I am asking for is to be used strictly to study the early medical histories of persons who subsequently develop Systemic Lupus Erythematosus. Your name will not be used in connection with any information you may give. Do not sign the questionnaire.

Your cooperation in this matter will be greatly appreciated.

Sincerely,

Paula Cummings, R.N.

Paula Cummings is a graduate student of Nursing at Montana State University. The information she wishes to obtain will be used to further knowledge in Nursing, and for no other purpose. Your name will not be used in association with any information you may give her.

Elizabeth Diegel, R.N.
Educational Director of Clinical
Nursing
Billings Deaconess Hospital

LETTER TO PATIENTS

Billings, Montana
February 21, 1971

Dear Mrs. _____:

I am a graduate student in Nursing at Montana State University, presently doing clinical work at the Billings Deaconess Hospital. Dr. _____ has given me your name, and his permission to contact you and ask you if you will take a few minutes of your time to fill out the enclosed questionnaire.

The information asked on this form is to be used to study the early medical histories of persons who have subsequently developed Systemic Lupus Erythematosus. Your name will not be used in connection with the information you give. Do not sign the questionnaire.

Your cooperation in this matter will be greatly appreciated. An envelope is enclosed for your convenience in returning the questionnaire to me.

Sincerely,

Paula Cummings, R.N.

Paula Cummings is a graduate student in Nursing at Montana State University. The information she wishes to obtain will be used to further knowledge in Nursing and for no other purpose. Your name will not be used in association with any information you may give her.

Elizabeth Diegel, R.N.
Educational Director of Clinical
Nursing
Billings Deaconess Hospital

QUESTIONNAIRE

1. What is your age? _____ race? _____ sex? _____
2. List the immunizations you have had. yes no how many

Smallpox	_____	_____	_____
Diphtheria	_____	_____	_____
Scarlet Fever	_____	_____	_____
Tetanus	_____	_____	_____
Rocky Mountain Spotted Fever	_____	_____	_____
Measles	_____	_____	_____
Mumps	_____	_____	_____
Influenza	_____	_____	_____
Pertussis (Whooping Cough)	_____	_____	_____
Polio	_____	_____	_____
Yellow Fever	_____	_____	_____
Other	_____	_____	_____
3. Have you or any of your family had Rheumatoid Arthritis? _____
4. Have the symptoms of your disease ever seemed to have been altered by any phase of your menstrual cycle? _____
5. Estimate how many X-rays of all types that you have had. _____
6. Have you ever had a severe sunburn? _____ Were you ever in the habit of sunbathing regularly? _____
7. Have you ever been treated for high blood pressure? _____
8. List as many as you can remember of the illnesses you have had, and state how you were treated for these conditions.
9. When were you informed that your illness had been diagnosed as Systemic Lupus Erythematosus? _____
10. If drug reaction, what drug was implicated? _____

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