Systemic Lupus Erythematosus

By Joseph J. Bunim, A. McGehee Harvey, Alfred J. Bollet, T. F. Hilbish, Eugene Van Scott, Leon Sokoloff, and George Brecher

Dr. Joseph J. Bunim: The patient whose course we shall discuss today offers an unusual opportunity to study the history of lupus erythematosus. The life history of this child is almost coincident with the natural history of this disease. We are grateful to Dr. Bernard Benjamin of Brooklyn, New York, for this referral, and for his accurate and complete records.

Dr. Alfred J. Bollet: The patient is a 7-year-old girl admitted to the Clinical Center with a history of intermittent febrile episodes accompanied by arthritis of 4 years' duration.

At the age of 2½ months, following an episode of pneumonia treated with penicillin, the patient developed an erythematous rash on the cheeks and nose and a persistent cough. This rash has varied in severity but has never entirely disappeared. At the age of 2 years she developed deformed, thickened fingernails and clubbing of her fingers, which have also persisted. Frequent cultures of the nails failed to reveal fungi, and the cause of these changes remained obscure.

At the age of 3 years, redness, swelling, tenderness, and pain on motion of the right knee appeared for 24 hours, and 3 months later fever and painful swelling of both elbows and the left wrist. Within a week there were stiffness of the spine and pain in the temporomandibular joints. Subsequently, the feet, knees, and ankles were involved. The rash on her face spread and became more erythematous. Diagnoses of Still's disease and discoid lupus erythematosus were made.

Treatment with cortisone abolished the fever; the joint symptoms and the rash subsided but did not entirely disappear. Facial rounding and edema developed, but the dose of cortisone could not be lowered below 200 mg./day without return of joint pain and some fever. This regimen was continued for 2 years, when hydrocortisone was substituted in a minimum maintenance dose of 60 mg./day. Because of persistent activity of the disease process, an L.E. cell preparation was done, but was negative. The patient was referred to the Clinical Center for treatment with the new steroids.

Her past history was negative except for measles at age 4 and varicella at age 5. There was no family history of arthritis or related diseases.

On examination at the time of admission, the patient was a very small, thin, alert white girl in no discomfort, but coughing occasionally. The blood pressure was 110/70 mm. Hg, temperature 98.7° F., pulse 110. There was an erythematous rash on the left cheek and left elbow that was slightly raised and indurated and showed dilated follicular pores, follicular keratoses, and some central atrophy. Small acniform lesions were also present on the face. A rough, reddened patch was present on the hard palate. Small cervical, axillary, and inguinal nodes were palpable. No retinopathy was noted. Moist rales were heard over the right middle lobe. The heart was negative, the liver and spleen were not palpable, and there was no swelling or tenderness of any joint. There was clubbing of the fingers with dystrophic and hypertrophic nail changes (fig. 1).

Laboratory data at the time of admission included a normal urinalysis, hematocrit value of 42 per cent, white blood cell count of 13,200, with 87 per cent polymorphonuclear cells and

1 metamyelocyte (subsequently 4,700–8,300, with similar differential count), sedimentation rate 53 mm./hr. (Westergren), C-reactive protein negative, blood urea nitrogen 12 mg. per cent, fasting blood sugar 56 mg. per cent, sodium 140, potassium 4.6, chlorides 104 mEq./L., CO₂ 26 mEq./L., calcium 10.5, phosphorus 4.4 mg. per cent, alkaline phosphatase 2.2 B-L units; albumin 3.6, globulin 4.4 Gm. per cent, and bilirubin 0.4 and uric acid 2.3 mg. per cent. Roentgenograms revealed areas of fibrosis and reticular mottling in both lung fields, some delay in bone development, and negative gastrointestinal tract. Electrocardiogram was normal.

It was thought that the patient had developed systemic lupus erythematosus. The L.E. preparation had been negative in the past, but after 2 negative tests, 3 subsequent smears were positive. The pulmonary findings could be part of systemic lupus or could be related to chronic pulmonary infection following the episode of pneumonia in infancy.

Following initial observations, the dose of hydrocortisone was lowered. At a level of 30 mg./day she developed indurated, erythematous, slightly tender areas about both elbows. At 10 mg./day the manifestations of lupus flared up, with fever to 100.7 F., marked malaise, severe anorexia, and diffuse aches and pains that were most marked in the joints. The facial rash spread, and a 0.5 cm. superficial ulceration appeared in the right buccal mucosa. The cough increased in severity, and fine, moist rales were heard throughout both lung fields. Tenderness was noted over all joints with swelling about the elbows: The sedimentation rate rose to 88 mm./hr. (Westergren), and the C-reactive protein became 1+. The hydrocortisone was abruptly discontinued, and prednisone, 20 mg./day, was given. There was dramatic improvement, with an abrupt end to the fever, malaise, pain, and anorexia. The joint tenderness subsided, the rales diminished, and the facial rash and mucous membrane lesions gradually faded. The dose of prednisone was subsequently lowered to 15 mg. daily, and the patient continued to do well. She has become completely asymptomatic and remains well at this time.

*Dr. T. F. Hilbish:* This patient has small, reticular infiltrative lesions throughout both lung fields, most marked in the lower lobes and particularly on the left. The lung fields show very small linear bands of fibrosis. The heart is within the upper limits of normal.

The only other radiologic finding is retardation in bony development. Practically all the joints that were x-rayed showed some delay in bony growth. For example, the head of the radius is very small and undeveloped for the patient's age. X-rays of the bones in hands and feet also show developmental retardation.

*Dr. Bunim:* There are several points in this patient's story that are worthy of comment. First, how soon could the diagnosis of lupus erythematosus have been made from the clinical features?

She started with a pulmonary infection that was considered to be pneumonia and was treated with penicillin. This was soon followed by an erythematous rash. We have no direct information on this earlier infection, but we do have some notes from the physician who saw her at the age of 2 years and 9 months for a recurrence of pulmonary infection.

According to these notes, there were dullness and bronchial breathing over the left lobe of the lung posteriorly. A presumptive diagnosis of pulmonary tuberculosis was supported by a positive patch test, later shown to be a false positive reaction. X-ray of the chest showed enlargement of both hilar regions and numerous areas of infiltration in both lung fields, especially the left. The spleen was palpable 3 finger-breathings below the costal margin, the white count was 5,200, and the sedimentation rate was markedly elevated. Within 14 days after this examination the patient developed polyarthritis, which persisted for several years.
It seems, in retrospect, that the diagnosis could have been made at this time on the basis of repeated nonspecific pulmonary infections, splenomegaly, mucocutaneous eruption and erythematous skin rash, absence of leukocytosis, markedly elevated sedimentation rate, and polyarthritis.

Polyarthritis occurs in many patients with lupus erythematosus. Perhaps only half of them have joint pains and the other half have objective joint changes that may resemble acute rheumatic fever or a nondescript type of arthritis, but are most often indistinguishable from rheumatoid arthritis. For 2 years this child was considered a case of juvenile rheumatoid arthritis or Still’s disease. We now search for L.E. cells routinely at this institution in all cases of rheumatoid arthritis.

The nail changes are interesting. We have been unable to find any reference in the literature to nail changes in lupus erythematosus, but we have seen 2 other patients with systemic lupus at the Clinical Center with similar nail changes.

Dr. Benjamin, who referred this child to us, reports that with cortisone therapy the liver became enlarged and was 2 to 3 fingerbreadths below the costal margin. For a time the patient received cortisone in doses of 200 mg./day.

In a study of 38 children with rheumatic fever treated with cortisone, we were impressed that children, especially under 8 years of age, are likely to develop hepatomegaly as a side effect of cortisone. In about 50 per cent the liver became palpable at the end of the first week and remained enlarged for several weeks to several months after the drug was discontinued. Liver biopsies have shown fatty infiltration. Why adults escape this effect I do not know; but it is important in the management of children with rheumatic fever, for the large liver may be misinterpreted as evidence of congestive heart failure.

We have also seen marked liver enlargement as a result of prednisone treatment in children with acute rheumatic fever or rheumatoid arthritis. Therefore, I think this side effect will probably be seen commonly in prednisone, cortisone, and hydrocortisone therapy.

In our other patients with lupus erythematosus, prednisone had about 4 times the potency of cortisone (by weight). One patient required 150 mg. of cortisone plus 40 units of corticotrophin daily for control of symptoms, but as little as 5 mg./day of prednisone was adequate. Because the drug requirement was so low, it was discontinued, whereupon the patient immediately developed a relapse. Now he is very comfortable again on 10 mg. of prednisone daily. Several physicians have reported similar experiences.

Even with 60 Gm. of hydrocortisone, this child continued to have active disease, for which she was referred to the Clinical Center. Now she is completely symptom-free at 15 mg. of prednisone daily, a 4:1 ratio, but the control is maximum rather than barely satisfactory. It remains to be seen whether she will require more prednisone when she goes home and becomes more active.

Finally, I would like to discuss the question of transition from discoid lupus to systemic lupus erythematosus. The impression that discoid lupus does not go on to systemic lupus is not true. As early as 1937, Dr. Keil of New York noted a transition from the discoid to the systemic type, with clinical and histopathologic confirmation. In our own limited experience we have seen 6 such patients; the interval from the appearance of discoid to systemic lupus ranged from 2 to 31 years. In Dr. Harvey’s series there were 3 such patients. Patients with a discoid lesion should therefore be followed very carefully as potential cases of systemic lupus.

If a patient has both systemic lupus erythematosus and an intercurrent infection like pneumonia and is treated with antibiotics alone without concomitant adrenal cortical steroids of some type, he may succumb. Consequently, it is extremely important to keep patients with discoid lupus under surveillance and to administer steroid therapy at the first sign of severe systemic involvement.

Dr. Eugene Van Scott: Lupus erythematosus was first described, roughly 125 years ago, when medicine was largely a descriptive science. The definitive descriptions of the gross, and later microscopic, characteristics of the skin lesions are examples of astute, detailed obser-
vations. The disease was first recognized as a primary skin disease, manifested by chronic patches of scaling erythema that often eventuated into scarring and atrophy of the involved skin. About 50 years later the disseminated form of the disease was described. It was noted that a certain number of individuals with skin lesions acquired a serious systemic illness.

Without precise figures, I think we can reasonably agree that the chronic discoid form tends to remain confined to the skin, with a very small percentage eventuating in the systemic disease. Whether to stress and study the similarities of these two states and their transitions or to stress and study their differences is perhaps of more than theoretic interest; the current tendency is to study the similarities. An important clue to the more serious systemic illness may lie in the fact that so many chronic discoid cases never disseminate.

One particular phenomenon found in this condition, ultraviolet sensitivity, is important at least in stimulating further thought. It is common knowledge that exposure to sunlight has a pronounced adverse effect on patients with either systemic or localized cutaneous lupus erythematosus. Indeed, some subjects without L.E. develop skin eruptions from sunlight, and microscopically the lesions are indistinguishable from L.E. One of the effects of ultraviolet light in suberythema general body exposures is to produce a picture that resembles adrenal insufficiency. These effects include a fall in blood pressure lasting 24 hours, a low fasting blood sugar, a flat glucose tolerance curve, and an increased readiness to skin pigmentation. Is this observation related to why L.E. is made worse by ultraviolet light and is improved by adrenal steroid therapy?

Second, light sensitivity is pronounced in pellagra, in which the chronic skin eruption grossly and microscopically often resembles lupus erythematosus. We know that this photosensitivity is related to a nicotinic acid deficiency. The classic corn diet possesses a pyridine-containing antagonist of nicotinic acid. Sulfapyridine is also a competitor of nicotinic acid, and the sulfa drugs as a group are capable of inciting or exacerbating cases of L.E., and of photosensitizing normal skin.

From this chain of relationships arises the obvious question whether L.E. is related to defective metabolism of nicotinic acid or tryptophane, a normal precursor of nicotinic acid. Would some related compound be useful in the treatment of lupus erythematosus?

Third, it has been shown that ultraviolet light causes loss of specific absorption spectra of purines and pyrimidines, and depolymerizes deoxyribose nucleic acid. Very probably a depolymerization of DNA occurs in L.E., accounts for some histologic changes in several tissues, and is also a biochemical prerequisite for the L.E. phenomenon and the L.E. cell.

Several phenomena, then, suggest that the metabolism of nicotinic acid, nucleic acids, and the function of the adrenal cortex may be somehow interrelated in the biochemical pathology of lupus erythematosus.

Dr. Naomi Kanof: I would like to discuss 2 aspects of this disease in the patient presented. One concerns the nail changes. I have never seen a patient whose disease onset was as early as in this child, and I am therefore not able to recall changes of similar nature. But in adult patients this bulbous distortion of the fingers is not uncommon, and is an unfavorable prognostic sign, suggesting an acute process.

Every internist and dermatologist who is concerned with this disease comes to a very firm conclusion regarding its evolution and then has an experience to shake his conclusion. One patient mentioned by Dr. Bunim was undeniably a case of chronic discoid lupus erythematosus. But the fact that the child was only 9 years old seemed noteworthy. Chloroquine therapy was started. Within 3 weeks the patient was desperately ill, one of the most severe cases of fulminating lupus erythematosus I have ever seen.

On the other hand one sees patients with polymorphous eruptions from light of 20 years' duration with histopathology indistinguishable from disseminated L.E., and with leukopenia, increased sedimentation rate, and a history of epilepsy. They may fare very well even on exposure to ultraviolet light.

This field is ripe not only for the biochemist, as Dr. Van Scott mentioned, but also for the immunologist.
Professor Flarer of Padua University has pointed out that the degree of erythema is unrelated to the degree of scarring, and that the intensity of the disease is unrelated to the sequence of events in chronic discoid L.E. He has suggested that there are probably several types of erythema, a concept that may have an important relationship to the mechanisms of lupus erythematosus.

The second important consideration is that of Gold, who considered the development of the L.E. cell an immunologic reaction. If this is a disease of immunologic mechanism, its course is unique. More common in progression of an immunologic disease is the process in syphilis, in which the invasion of organisms is followed by an acute reaction without destruction of tissue; after many years, the number of organisms lessens, the tissue response intensifies, and subsequently the tissue itself is destroyed. In lupus erythematosus the progression is from the indurated and scarring lesion to the disseminating and fulminating disease.

*Dr. Leon Sokoloff:* It is one of the peculiarities of disseminated lupus erythematosus that anatomic changes are inconstant, of varying character, and, in large part, lacking in diagnostic specificity. Virtually any organ may be involved. Not infrequently the pathologist is unable to detect appreciable changes in patients who have had the most profound clinical symptoms. Probably the most characteristic lesions are observed in the circulatory system—the heart, small arteries, arterioles, and glomerular capillaries. For purposes of simplification, the vascular lesions may be placed in 2 categories, the luminal and the mural, and they may be illustrated in the renal glomerulus.

The luminal change is characterized by formation of hyaline thrombi in some of the capillaries of the tuft. At one time, these thrombi were regarded as an extrusion of a mural deposit into the lumen. More recently, it has been recognized that the thrombi may be quite discrete (fig. 2) and occur independently of the so-called wire-loop change in the walls of the capillaries (fig. 3). The hyaline material appears similar to fibrin and, for this reason, it is often referred to as a fibrinoid substance. A unique feature of the fibrinoid material in disseminated lupus erythematosus has been described recently by Dr. Klemperer and his associates in New York City as an inclusion of homogeneous material that is stained somewhat blue by

---

**Fig. 2.** Thrombi in some of the capillaries may be quite discrete.

**Fig. 3.** Thrombi may occur independently of the so-called wire-loop change in the walls of the capillaries.
hematoxylin. According to these investigators, this “hematoxylin body” is derived from degraded cell nuclei; the deoxyribonucleoprotein becomes depolymerized progressively and is transformed, thereby, into the fibrinoid substance. The hematoxylin body corresponds to the central inclusion of the L.E. cell. When present, the body is regarded as a specific and characteristic feature of disseminated lupus erythematosus.

The mural change is characterized by the deposition of a fibrinoid substance in the wall of the capillaries and other vessels. Similar material may also be seen, at times, in extravascular connective tissues as well.

The sequence of events is interpreted morphologically by the group at Mt. Sinai Hospital as follows. Disseminated lupus erythematosus involves an abnormality of deoxyribonucleoproteins. Certain connective tissue cells die and their deoxyribonucleic acids become depolymerized. The fibrinoid substance resulting from this degradation is formed within the blood stream and finds its way into the walls of the blood vessels and surrounding tissues. There it evokes a variety of nonspecific inflammatory reactions. When the heart is involved, verrucous endocarditis, interstitial myocarditis, and pericarditis develop. In the visceral circulation, arteritis may appear, accompanied by a variable inflammatory reaction. In its most extreme forms, the arteritis cannot be distinguished from polyarteritis nodosa. In the kidneys, glomerulonephritis develops frequently.

Despite these observations, vascular lesions are not observed frequently in many of the lesions of lupus erythematosus. The cutaneous, choroid, muscle, and synovial lesions are inflammatory and rarely present vascular changes. It has long been recognized that waxing and waning pneumonia may dominate the clinical course of lupus erythematosus. At necropsy, banal bacterial types of pneumonia, with or without organization, are frequent. Recently a number of observers have suggested that there is a more specific pattern of pulmonary inflammation in the disease, characterized by an interstitial reaction, with edema and inflammatory infiltration in the walls of the smaller air spaces. This interesting suggestion warrants further investigation.

Dr. George Brecher: The first set of L.E. preparations on this patient made from the buffy coat of heparinized blood was negative. The second set of preparations was positive, with both Hargraves’ test on clotted blood and Conley’s test in which buffy coat smears are made from incubated, heparinized blood after rotation with added glass beads. In general, Conley’s test appears to increase the amount of L.E. material, without necessarily increasing the number of L.E. cells. We believe Conley’s test matches Hargraves’ in sensitivity, but is more easily read because the amount of L.E. material serves as a signal to search assiduously for L.E. cells. Moreover, L.E. cells are more readily identified because of better preservation of cellular detail.

On occasion, L.E. material is plentiful and L.E. cells are not found. It is not known why L.E. material is phagocytized in one patient and not in another. Since it is not present in control subjects, it probably has some specific meaning. It seems best at this time, however, to require the presence of L.E. cells for a positive test. Occasionally only 1 or 2 L.E. cells are found in a single preparation even on repeated trials. To my knowledge, none of the numerous modifications of the L.E. test has solved the problems posed by the presence of L.E. material without L.E. cells or by the finding of a single positive test.

Dr. A. McGehee Harvey: During the last 6 or 8 years I have seen a great number of patients with this disease, and have developed a somewhat different concept of its natural history than is ordinarily described. I think that in many respects the patient we have seen today furnishes a good text for presenting this concept.

First of all, the course of this disease in the majority of the cases is a very chronic one. It is characterized by exacerbations and remissions. Furthermore, in any 1 exacerbation, only 1 or several organ systems may be involved. In this manner, the disease unfolds over a period of years with a number of seemingly unrelated episodes of illness, leading the unwary physician to overlook its presence for many years.
The appearance of chronic lesions, particularly on the face, for many years before any other manifestations of the disease appear, has been discussed today. Also, we have seen patients who had arthritis for many, many years before they developed other manifestations of the disease. One may observe patients in whom the disease apparently began with a hemolytic type of anemia or thrombocytopenic purpura or repeated epileptiform convulsions as the only clinical evidence of illness for as long as 10 or 12 years.

Remissions may last a long time and may vary in degree. The disease may go from a state of fulminating intensity to a period in which the patient is entirely free of any symptom for a long time.

We believe that this is probably a more common disease than any of us realize even now, and that it may go on for many years in a very mild relapsing course. An example is a patient who came into the hospital recently for treatment of severe hypertension. She had never had any complaints concerning her skin or any difficulty other than the hypertension, which developed following pregnancy. The intern who saw this patient knew that she was going to receive hypotensive drugs, one of which is accompanied at times by a rheumatic-like picture, occasionally with the finding of L.E. cells. He saw a very small erythematous lesion on the patient’s forehead and ordered an L.E. cell test, which was positive.

Often the manifestations in the beginning are so vague that it is hard to date their onset. When a given manifestation appears, it is natural to make the diagnosis referable to that single organ system. As Dr. Bunim has already stated, many of these patients in the beginning are said to have rheumatoid arthritis.

Many physicians dismiss the possibility of systemic lupus erythematosus unless all the classical manifestations are present in a single period of activity of the disease, but we have seen patients who developed a skin lesion in the beginning and had cutaneous lesions for 10 or 12 years before they developed any other manifestations. Some patients had other manifestations for 10 or 12 years before they ever had any cutaneous lesions, and still other patients ran the full course of the disease without cutaneous manifestations at any time.

It is important, I think, to recognize the minor phases of the illness. For instance, the patient may say that he has always been sensitive to sunlight, or that all of his life he has had recurrent aches in his joints, although they were never severe enough to warrant consulting a physician. The patient may fail to describe a previous attack of pleurisy or a previous episode of cutaneous difficulty unless specifically asked about it because he does not recognize its possible relation to the current complaint.

The clinical diagnosis of systemic lupus, I think, can be made consistently only when the observer appreciates the chronic course of this disease, with episodic periods of illness that may seem entirely unrelated; and that with a disease apparently involving only a single system, such as arthritis, it is important to inquire specifically about previous illnesses that may be related. What has happened in the past may make the current event more meaningful.

Figure 4 shows the sex, race, and age incidence at onset in a number of patients that we have observed. I would like to call your attention to 2 points: most of the patients are females, and in most of them the disease begins in the second, third, or fourth decades.

Studies reported elsewhere indicate the frequency with which various systems are involved in the total course of the illness in these
patients. Joint manifestations are frequently seen. Cutaneous manifestations are also common, and it is important to point out that mucous membrane lesions do occur, as exhibited by this patient. Frequently there may be involvement of a wide variety of other organs.

One tends to think of skin lesions in relation to this disease as being those that are classically described, but the skin lesions are multiform. Almost any type of lesion may be seen. One thing that has impressed us greatly is the frequency of urticarial lesions and also of lesions resembling angioneurotic edema.

Reference has been made to pulmonary lesions. Dr. Hilbish described the common type of lesion, usually in the lower lung fields. Pulmonary changes are more frequent than has been commonly recognized. They may be chronic in nature. The symptoms of pulmonary difficulty are out of proportion to any objective findings on physical examination. The patient may be tachypneic, dyspneic, somewhat cyanotic, while on examination of the lungs only a few scattered rales may be heard. In going over all our films on these patients, we were impressed with the frequency of elevation of the diaphragm and plate-like areas of atelectasis in the lower portions of the lung fields.

Retinal cytoid bodies are commonly seen. They are exudative lesions in the nerve fiber layer of the retina that resemble cells microscopically. They are not specific for lupus. They have the same appearance as the cotton wool exudates in hypertensive disease and diabetic retinitis.

The patient presented today had a high serum globulin level. A striking feature of this disease is the frequency of abnormal protein changes in the blood. The patients almost uniformly have an elevated sedimentation rate and an elevated serum fibrinogen level. On several occasions a circulating anticoagulant has been demonstrated.

The elevation in serum globulin is frequent, particularly the gamma globulin fraction. A very large percentage of these patients have positive cephalin flocculation and positive thymol turbidity tests and other protein abnormalities. Of course, it is a protein in the serum that is responsible for the formation of the L.E. cell.

It has been known for many years that patients with systemic lupus may have a false serologic test for syphilis. With the advent of the treponemal immobilization test, it has become possible to recognize with certainty a truly false positive serologic test. In the series of patients we have observed, a false positive serologic test for syphilis was found in about 20 per cent of the cases.

Dr. J. Earle Moore has been interested for a number of years in the persistent false serologic test for syphilis with the object of determining its significance. Not under consideration is the acute false positive test that develops in acute situations like malaria and pneumonia and disappears in a matter of a few weeks or months. Of private patients in the upper socioeconomic class tested by Dr. Moore, 40 per cent had a false serologic test for syphilis. In over 60 per cent of the cases the test was simply a routine examination. That is, the patient applied for a job, got married, had a baby, was inducted into the Army, or something of that sort, and all were in perfect health so far as they knew. Thirty-seven per cent had some type of illness, but it was usually a minor illness of vague nature for which the cause could be determined.

Dr. Moore and his group now have well over a hundred of these patients who have been classified as false positive reactors: they had no likely exposure to syphilis, had 2 negative treponemal immobilization tests, and had no evidence of syphilis on physical examination. The false positive test was chronic, in that positivity was known for 2 to 20 years, with an average of over 6 years.

The sex distribution of these false reactors is almost identical with that of the series of cases of proved lupus erythematosus I showed you previously. The age distribution for the discovery of the false positive serologic tests is similar to that for the onset of symptoms of lupus.

Of 44 men in Dr. Moore’s series, 1 has developed known rheumatoid arthritis, 9 have developed a series of illnesses in which the diagnosis was probably collagen vascular disease,
and 1 now has systemic lupus proved by a positive L.E. cell test.

Of the 104 women, 9 have now developed proved systemic lupus erythematosus. By "proved" I mean that they have developed L.E. cells while under observation. Six have developed a clinical picture indistinguishable from rheumatoid arthritis. Another 36 have developed a series of illnesses that seem clinically to be systemic lupus erythematosus, but as yet no L.E. cells have been found. Furthermore, 43 of these patients also have developed some type of serum protein abnormality, usually an elevation of serum globulin.

Table 1 shows the clinical manifestations in the patients who have been classified as probably having systemic lupus erythematosus. There have been episodes of fever in 12 and episodes of arthritis or arthralgia in 13. Other manifestations included splenomegaly, serositis, and Raynaud's phenomena, which may develop in patients with systemic lupus.

Each of these patients has had at least 2, and usually several, of the 17 different manifestations listed, with an average of 3.8 episodes. An abnormal cephalin flocculation developed in 76 per cent, a positive thymol turbidity test in a large portion and elevation of the serum globulin level in a large portion.

One patient described by Moore started out with a protein abnormality of the blood (the false positive serologic test for syphilis), and 12 years later developed positive L.E. cell tests, with various illnesses in between. This sequence brings out a very important point in regard to the diagnosis of this disease and the determination of when there is local lupus, so to speak, and when there is systemic lupus. From this study of false biologic reactors it becomes obvious that the L.E. cell phenomenon may be a relatively late event in the disease, so that a negative L.E. cell test in no way excludes the diagnosis.

---

**Table 1.—"Probable" Systemic Lupus Erythematosus: Clinical Manifestations in Twenty-One Patients.*

<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>No. of cases showing specified symptom or sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>12</td>
</tr>
<tr>
<td>Arthralgia or arthritis</td>
<td>13</td>
</tr>
<tr>
<td>Ocular lesions</td>
<td>6</td>
</tr>
<tr>
<td>Splenomegaly; serositis; cutaneous lesions</td>
<td>5 each</td>
</tr>
<tr>
<td>Raynaud's phenomenon; significant malaise</td>
<td>4 each</td>
</tr>
<tr>
<td>Major phlebothrombosis; psychoses; nephritis</td>
<td>3 each</td>
</tr>
<tr>
<td>Photosensitivity; mucosal lesions; chorea;</td>
<td></td>
</tr>
<tr>
<td>hematuria</td>
<td>2 each</td>
</tr>
<tr>
<td>Thrombocytopenic purpura; convulsions; nephritis</td>
<td>1 each</td>
</tr>
</tbody>
</table>


Each patient has had at least 2 and usually several of the 17 manifestations listed; and the 21 patients have had a total of 75 of these symptoms or signs (i.e., 3.57 per patient).

---

**Fig. 5.** Survival after diagnosis in 99 cases of systemic lupus erythematosus seen from 1949 through 1953. (From Harvey, A. M. and associates. Medicine 33: 201, 1954, published by The Williams and Wilkins Company.)

**Fig. 6.** Intervals from onset to diagnosis of systemic lupus erythematosus. (From Merrell, M. and Shulman, L. E., J. Chron. Dis. 1: 12, 1955, published by The C. V. Mosby Company.)
Finally, I would like to review what has happened to a hundred of our patients, studied since 1949, who have been treated with one of the adrenal hormones during periods of activity of the disease. Figure 5 shows a survivorship curve that was constructed by Dr. Merrill of the Department of Biostatistics. The duration of disease in these patients was considered from the time the diagnosis was made, not the time of the first manifestation of illness.

In the first 3 months after diagnosis, 13 per cent of the patients died, but after that there has been a rather steady curve, which indicates that about 10 per cent of the original group have died each succeeding year. That leaves 52 per cent of these patients surviving a full 4 years after the diagnosis was made.

Dr. Ragan and his co-workers published an analysis of prognosis several years ago in which 38 per cent survived for 4 years from the time of onset of the first symptom until death. This 4-year survival of 38 per cent is considerably less than in our series; and ours is weighted in the opposite direction, since duration of life was calculated from date of diagnosis. Figure 6 shows the intervals of time from time of onset to time of diagnosis of the disease, illustrating again the chronic nature of this disease. Many of these patients had manifestations for 5, 10, or 15 years before the diagnosis was finally established.

REFERENCES


A group of 239 patients with toxemia of pregnancy occurring during the first gestation has been followed from periods of 5 to 10 years. All but 11 had subsequent pregnancies. Although a higher percentage suffered recurrent toxemia, only 27 (or 11.3 per cent of the total) were found to have permanent hypertensive disease. The expected incidence of hypertension for young women of this age is 8.4 per cent according to Master and his group. The authors believe that in all likelihood this figure is higher than the true incidence of hypertensive disease in women of this age, because many of the observations of Master and his group were made at a time these women were applying for jobs and when slight elevation of blood pressure is common. The authors conclude that toxemia of pregnancy results in increased incidence of hypertensive disease, that the more severe the initial illness (excluding eclampsia) the more likely there is to be eventual permanent vascular damage. Repeated pregnancies and recurrent episodes of toxemia may have some relationship to the later occurrence in hypertensive disease, in that most women developing permanent elevation of blood pressure did so after 3 pregnancies and at least 2 bouts of toxemia.
Systemic Lupus Erythematosus
JOSEPH J. BUNIM, A. MCGEHEE HARVEY, ALFRED J. BOLLET, T. F. HILBISH, EUGENE VAN SCOTT, LEON SOKOLOFF and GEORGE BRECHER

Circulation. 1956;14:125-134
doi: 10.1161/01.CIR.14.1.125
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1956 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/14/1/125.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/