Although the cause and fundamental nature of the syndrome of systemic lupus erythematosus are still obscure, newer contributions have broadened the existing concept of this disorder. Interest in the disease has been stimulated in recent years, and improved methods of diagnosis have resulted in a significant increase in the number of cases recognized. How much of this is real is not known, but it is apparent that it can no longer be regarded as a rare disease.

Among the more important advances have been a better understanding of the natural history of the disease lupus erythematosus; the demonstration that the mesenchymal tissues throughout the body and vascular system are the principal sites of attack; the recognition of a number of characteristic, though not necessarily specific, pathologic tissue changes; and the introduction of the “L.E. test” as a valuable aid in diagnosis. In order to gain a better understanding of the broad scope and development of the modern concept of this rather complex disorder, it is essential that brief reference be made to the historical background.

DEVELOPMENT OF MODERN CONCEPT

The earliest reference to the dermal lesions of lupus erythematosus was that of Biett in 1828. While more detailed descriptions were made by Hebra and by Cazenave, the attention of these authors was confined entirely to the skin. Recognition of the systemic nature of the disease came with the descriptions of Kaposi and of Osler. The latter emphasized not only the systemic manifestations and widespread visceral involvement but he also drew attention to the fact that the disease might run its full course without ever exhibiting cutaneous lesions.

After the turn of the century, emphasis was placed mainly on comprehensive reviews of the subject and recognition of additional features. Jadassohn drew attention to the frequent involvement of the joints, kidneys, serous and mucous membranes, followed some years later by the addition of leukopenia and thrombocytopenia to the syndrome. Libman and Sacks described a nonbacterial, verrucose endocarditis and noted periarterial fibrosis of small vessels of the spleen, while Gross reported on the occurrence of myocardial lesions and con-
glomerate deposits or clumps of nuclear material in tissues, now known as “hematoxylin bodies.” In 1935 Baehr, Klemperer and Schifrin described a variety of vascular lesions, including the so-called “wire-loop” changes in the glomeruli of the kidneys. They suggested that lupus erythematosus was primarily a disease of the small vessels.

The observation that lupus erythematosus was a systemic disease affecting tissues of mesenchymal origin, was made by Denzer and Blumenthal in 1937. Subsequently Banks and Klemperer, Pollack and Baehr enlarged on this theme, and linked together a group of disorders under the common term, “collagen diseases.” They included lupus erythematosus, polyarteritis nodosa, dermatomyositis and scleroderma; other authors have since added rheumatoid arthritis and rheumatic fever. Thus there evolved the concept of a group of reactive diseases affecting tissues of mesenchymal origin, in which systemic lupus erythematosus emerged as the principal member. Perhaps the most interesting of recent developments has been the introduction of the L.E. cell phenomenon as an aid in diagnosis, by Hargraves, Richmond and Morton. As an aftermath, there have been brought to light a number of other syndromes the relationships of which to lupus erythematosus have not yet been clarified. It is likely that the scope of the disease may be broadened even further.

INCIDENCE

Accurate figures concerning the incidence of lupus erythematosus cannot be given. Undoubtedly many cases have gone unrecognized in the past and much of the increase in the number of cases reported in recent years has been due to improved methods of diagnosis. Whether there has been an actual increase in the incidence, corresponding to the greater use of chemotherapeutic agents, is open to speculation. Some observers have indicated an incidence approaching that of rheumatic fever, which is not surprising for hospitals admitting largely adult patients. However, it would not apply to children’s institutions, where rheumatic fever is most commonly encountered, and cannot be regarded as representative of the general population.

While females are predominantly affected, an increasing number of cases are being observed in males, in some series reaching as high as 10 to 30% of the cases. The disease reaches its greatest incidence in young adult life, but no age is exempt. Racial immunity is unknown. A distinct familial tendency may be observed and instances of more than one case in a family have been recorded, as well as the association in different members of a family of lupus erythematosus, rheumatoid arthritis or what may appear to be idiopathic thrombocytopenic purpura. The significance of this association is not clearly understood.

ETIOLOGY

There is little to support an early concept that the disease is due to tuberculosis or other bacterial infections, although these may occur as complications. Among the various theories concerning its pathogenesis, present evidence would seem to favor an immuno-chemical abnormality, associated with a disturbed antibody-producing mechanism as the most important factor. This is supported by (a) the increased production of the gamma-globulins, (b) the frequent occurrence of biologic false-positive serologic tests for syphilis, (c) the occasional presence of auto-antibodies for erythrocytes, (d) the L.E. phenomenon, (e) the occasional demonstration of an abnormal circulating anticoagulant, (f) the frequent sensitivity of these individuals to sunlight, blood transfusions, chemotherapeutic agents and antibiotics, and (g) the more recent observation of syndromes resembling lupus erythematosus which appear to have been precipitated by hydralazine, phenylbutazone, tetanus antiserum or other agents. An instance of the disease developing after a reaction to one of various antigenic materials is obviously difficult to evaluate, either as a direct cause or as a precipitating factor in
predisposed individuals.\textsuperscript{23,24} Nevertheless, such an association is indicative of an abnormal immunologic mechanism.

\section*{CLINICAL MANIFESTATIONS}

There is no good classification of lupus erythematosus other than the separation into chronic discoid and systemic forms of the disease. The importance of this differentiation is one of prognosis, because the discoid form is more chronic and relatively benign. The relationship of the two forms has been much debated, but it is significant that occasional progression of the discoid form to the systemic form has been observed by competent clinicians. Added to this are recent reports of systemic manifestations observed in patients with chronic discoid lupus erythematosus.\textsuperscript{25}

\textbf{Clinical Varieties}

Rather than enumerate the varied manifestations of this disease, it may be preferable to consider the different clinical syndromes which may present during the initial stages, depending on the system principally affected. However, it must be remembered that in well-established cases it is usual for more than one system to be affected, a feature which should direct attention to the disorder. The presence of a skin lesion makes early diagnosis relatively easy, but it may be absent in nearly half the cases. A history of photosensitivity or the occurrence of vasomotor (Raynaud-like) phenomena, which often precede the onset of the disease by many years, should also alert one to the possibility.

\textbf{Rash:} Somewhat more than half of the cases may be expected to conform to the classical description of systemic lupus erythematosus, with an erythematous eruption, characteristically over the face and exposed area of the neck and chest. It may however be much more generalized. The rash may be a simple erythema, macular, scaling with keratotic plugs, or occasionally bullous. Ulceration of mucous membranes or mucocutaneous junctions is not infrequent. Pyrexia, musculoskeletal symptoms and evidence of other system involvement usually complete the picture.

\textbf{Fever:} Some patients may exhibit little more than intermittent fever, with or without chills, excessive weakness and fatigue. Certainly many of these were formerly classed as pyrexia of unknown origin, until such time as involvement of other systems would direct attention to the correct diagnosis.

\textbf{Arthralgia:} In a rather large group of patients the presenting complaint is an acute arthralgia or a frank polyarthritis, with joint pain, swelling and limitation of movement. The joint manifestations resemble, and cannot be differentiated from, those of rheumatic fever or early rheumatoid arthritis. Some joint deformity may also be evident, but a destructive arthritis of the type seen in chronic rheumatoid arthritis is unusual. Instances of systemic lupus erythematosus with a destructive and deforming polyarthritis of the chronic rheumatoid type, associated with subcutaneous rheumatoid nodules, have been recorded. However, the accuracy of the diagnosis and the differentiation from actual rheumatoid arthritis in such cases is extremely difficult and may be open to doubt. Myositis with severe wasting and contractures of the skeletal muscles may also be observed.

\textbf{Cardiac, Pulmonic:} Another group of patients may exhibit principally visceral lesions, with serous membrane involvement as the initial symptom, most commonly a pleurisy or less often a pericarditis. Involvement of the lung parenchyma is not unusual, either an interstitial pneumonia or a pneumonitis, and may be followed by varying degrees of interstitial fibrosis. Involvement of the heart with nonbacterial, verrucose endocarditis may be accompanied by valvular murmurs but these are uncommon. Cardiac insufficiency, secondary to hypertension or myocardial involvement, has been observed but is not common in the early stages.

\textbf{Renal:} In a small proportion of patients the initial complaint may be referable to the kidneys; the clinical manifestations and
urinary findings are those of glomerulonephritis or nephrotic syndrome. Depending on the severity of this involvement, varying degrees of renal insufficiency and hypertension may be anticipated.

NEUROLOGIC: Rarely, manifestations indicative of involvement of the nervous system may usher in the disease, including peripheral neuritis, cerebrovascular accidents and epilepsy.

HEMATOPOEITIC: Lastly, an unusual occurrence is for the disease to manifest itself as an acquired hemolytic anemia or a thrombocytopenic purpura.

DIAGNOSIS AND PROGNOSIS

When one considers the varied symptoms of the syndromes described, it is apparent that systemic lupus erythematosus can mimic many different diseases. The clinical symptomatology is gradually being broadened even further, to the point of becoming so all-inclusive as to raise the important question of whether the disorder is actually a disease entity. Problematic cases arise in which one cannot either positively identify or exclude lupus erythematosus. Unfortunately there is no simple answer. Specific diagnostic criteria have not been established and while a variety of lesions may be regarded as characteristic of the disease, none of them are entirely pathognomonic. At the present time it is the assessment of the over-all clinical picture and natural course of the disease, assisted by a variety of diagnostic aids, which enables one to arrive at the diagnosis in difficult cases. Even so, errors in diagnosis are to be expected. The changing concept of the disease makes it difficult to give an accurate prognosis in individual cases or to cite mortality rates. This is particularly true of early or mild cases, which sometimes appear to run a prolonged and relatively benign course.

PATHOLOGY

Space will not permit a detailed description of all the changes in the tissues which may be encountered in this disease. Many are nonspecific in character and are indistinguishable from similar changes occurring in other diseases. There are, however, a number of lesions which deserve special consideration and which should direct attention to the diagnosis. Even these are not altogether specific in themselves, but when considered in combination with the clinical findings are highly characteristic. Unfortunately, in some cases they are entirely absent, although the patients may have exhibited one of the classical syndromes before death.

A number of vascular lesions may be encountered, including a proliferative endarteritis, periarteritis or a panarteritis of the small vessels of the heart, lungs or kidneys. Fibrinoid degeneration (Fig. 1a) of small arterioles, especially those of the kidneys and other viscera is a frequent finding, and sometimes focal areas of fibrinoid necrosis within the tufts of the glomeruli (Fig. 1b). A more characteristic change is a hyaline thickening of the basement membrane of the glomerular capillary loops, the so-called "wire-loop" appearance (Figs. 2a and 2b). Equally significant is a periarterial fibrosis of the small arterioles of the malpighian corpuscles of the spleen (Fig. 3). These result from the deposition of collagenous material in concentric layers around the vessel, giving it an onion-skin appearance. In various organs (lymph nodes, spleen, heart-valves, lungs, etc.) there may be local or extensive areas of necrosis, in which are contained clumps or packets of structureless, hematoxylin-staining bodies (Figs. 4a and 4b). They are composed of nuclear material from degenerated cells, chiefly mesenchymal in origin, and represent a change comparable to the inclusion bodies of the L.E. phenomenon. In the heart there may be a nonbacterial, verrucose endocarditis of the heart valves (Fig. 5), composed largely of fibrinoid material and degenerated cells. Finally, a lesion of considerable interest is the demonstration of the so-called cytoid bodies in the retina (Fig. 6a). They appear as pale, fluffy lesions by ophthalmoscopic examination. While they may
be indistinguishable from the exudates of malignant hypertension, renal insufficiency or diabetes mellitus, they can be observed in the absence of these complications. Microscopically they consist of localized areas of degeneration and swelling in the superficial, nerve-fiber layer of the retina, with a sparse cellular infiltrate and structureless, basophilic or eosinophilic masses resembling degenerated, nuclear material (Fig. 6b). Their nature and significance are not clearly understood.

LABORATORY AIDS TO DIAGNOSIS

Except for the demonstration of leukopenia, or less often thrombocytopenia, other
hematologic changes are of secondary importance. The electrophoretic pattern of the serum proteins is abnormal in a large proportion of cases (Fig. 7c) and consists principally of an increase in the gamma-globulin fraction.26,27 When present, this change does not differ in any specific manner from that seen in rheumatoid arthritis or chronic liver disease. It is probably responsible for many of the abnormal serologic reactions which may be demonstrated in patients with the disease. Included among these are auto-agglutinins to erythrocytes, biologic false-positive serologic tests for syphilis, and pos-
tive reactions in Coombs’ test, cephalin-
cholesterol flocculation test, formol-gel test,
sensitized sheep cell agglutination test and
the L.E. test. In the occasional instance one
may be able to demonstrate the presence of
cryoglobulins or an unidentified circulating
anticoagulant.

The most fascinating of these various ab-
normalities is undoubtedly the L.E. phe-
nomenon. It is an in-vitro phenomenon
which can readily be demonstrated in clotted venous blood, although a variety
of different techniques have been described.
The fundamental nature of the reaction is
not known except that it is dependent on
the so-called L.E. factor present in the
gamma-globulins, which behaves as a
lysin to leukocytes.

Two structures are regarded as character-
istic of this phenomenon: (1) the L.E. cell,
and (2) the rosette (Fig. 8). The L.E. cell
usually consists of a mature neutrophil con-
taining within its cytoplasm, one or more
large, amorphous inclusion bodies of de-
polymerized, nucleoprotein material. Its
development has been studied in living,
wet-film preparation and recorded with
motion pictures. Shortly after blood is
withdrawn, some of the leukocytes undergo
swelling of the cytoplasm and nuclei. The
detail of the nuclear chromatin becomes
less distinct and assumes a smoky appear-
ance. At this point the cell membrane rup-
tures and releases the altered nuclear seg-
ments, which then behave as foreign ma-
terial. Actively mobile leukocytes are at-
tracted to these nuclear masses and many
of them are phagocytized, forming the
characteristic L.E. cell. The rosette is
merely an attempt on the part of many
cells to engulf larger masses of the nuclear
debris. Of the two structures, the L.E. cell
is the more significant.

Although opinion has been divided con-
cerning the significance of the L.E. test,
recent studies would appear to indicate that
even this reaction cannot be regarded as
entirely specific for systemic lupus erythe-
matosus. Certainly it is observed most
frequently in this disease, being positive
in the majority of acute cases (Table I). Its
occasional demonstration in other related
Fig. 4. a (Upper). Structureless "hematoxylin-bodies" in section of lung (x500). b (Lower). Masses of hematoxylin-staining bodies in area of necrosis of lymphnode (x500).

syndromes, to be discussed, does not detract from its value as a diagnostic aid. Neither does it imply that identically the same factor is responsible for the changes in all instances, although the mechanism of production of the phenomenon may be the same.

**SYNDROMES POSSIBLY RELATED**

**Systemic Rheumatoid Disease**

A number of authors have drawn attention to a severe and sometimes fulminating form of rheumatoid disease, which appears to carry a uniformly serious prognosis.34,35
TABLE 1
L.E. CELL PHENOMENON
(800 Patients, 1400 Tests*)

<table>
<thead>
<tr>
<th>Disorders</th>
<th>Patients</th>
<th>Positive Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute systemic L.E.</td>
<td>43</td>
<td>40</td>
</tr>
<tr>
<td>Subacute systemic L.E.</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Discoid L.E.</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Polyarteritis</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>200</td>
<td>17</td>
</tr>
<tr>
<td>Cirrhosis (all types)</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Lymphomas (all types)</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Acquired hemol. anemia</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Phenylbutazone therapy</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Hydralazine therapy</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>450</td>
<td>0</td>
</tr>
</tbody>
</table>

* Author's data plus additions to date.

In this syndrome patients with otherwise typical rheumatoid arthritis, after running a chronic course for a period of 5 to 30 years, often characterized by severe articular deformities, contractures and subcutaneous rheumatoid nodules, begin to manifest signs of widespread visceral disease. These may include involvement of the heart, lungs, serous membranes, kidneys and other visceral structures. Some of the patients have exhibited the L.E. phenomenon, while others have not, yet the clinical course and pathologic changes observed at necropsy are remarkably similar. These resemble the changes commonly found in other conditions grouped under the term, collagen diseases, notably lupus erythematosus, polyarteritis nodosa, dermatomyositis, and sclerodema. The concentration of gammaglobulin in the serum is usually considerably increased (Fig. 7d). Whether these findings represent true manifestations of a severe type of rheumatoid process, or the superimposition of another related disease, has yet to be determined. In still another group of patients with chronic rheumatoid arthritis, the L.E. phenomenon may be demonstrated even though there has been no evidence of severe visceral involvement. The test has sometimes become positive after the institution of therapy with adrenal steroids and at a time when the patient is subjectively improved, or in others during the severe relapse that may follow the withdrawal of steroid therapy.

![Fig. 5. Verrucose (Libman-Sacks) endocarditis at margins of mitral valve.](http://pediatrics.aappublications.org/)
FIG. 6. a (Upper). Fluffy, white lesions (cytoid bodies) of retina. b (Lower). Microscopic appearance of cytoid bodies; expanded lesions in the superficial, nerve-fiber layer of retina (×200).

Chronic Hepatitis with Cirrhosis

A previously unrecognized form of hepatitis has recently been described, characterized by recurring jaundice over a period of years, and progressing to an advanced cirrhosis. Young women are principally affected though not exclusively so. In addition to enlargement of the liver and spleen, the patients may develop esophageal varices, spider telangiectases, ascites, edema and in some cases transient joint lesions and hirsutism with amenorrhea. Carbohydrate
Fig. 7. Patterns of serum proteins by filter paper electrophoresis: (a) normal, (b) acute systemic lupus erythematosus, (c) acute systemic lupus erythematosus, (d) systemic rheumatoid disease, (e) chronic hepatitis with cirrhosis (juvenile), and (f) hydralazine syndrome.

<table>
<thead>
<tr>
<th>Figure in Text</th>
<th>Total Protein</th>
<th>Albumin</th>
<th>Alpha1</th>
<th>Alpha2</th>
<th>Beta</th>
<th>Gamma</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>6.75</td>
<td>4.46</td>
<td>.27</td>
<td>.54</td>
<td>.74</td>
<td>.74</td>
</tr>
<tr>
<td>7b</td>
<td>7.10</td>
<td>4.54</td>
<td>.28</td>
<td>.50</td>
<td>.71</td>
<td>1.07</td>
</tr>
<tr>
<td>7c</td>
<td>7.75</td>
<td>3.49</td>
<td>.31</td>
<td>.70</td>
<td>.62</td>
<td>2.63</td>
</tr>
<tr>
<td>7d</td>
<td>6.94</td>
<td>1.87</td>
<td>.49</td>
<td>.62</td>
<td>.35</td>
<td>3.61</td>
</tr>
<tr>
<td>7e</td>
<td>8.13</td>
<td>1.63</td>
<td>.24</td>
<td>.24</td>
<td>.33</td>
<td>5.69</td>
</tr>
<tr>
<td>7f</td>
<td>7.13</td>
<td>3.78</td>
<td>.28</td>
<td>.86</td>
<td>.71</td>
<td>1.50</td>
</tr>
</tbody>
</table>
tolerance may be reduced and there may be an increased excretion of adrenal corticoids in the urine. The concentration of gammaglobulin in the serum tends to be increased considerably more than is usual in lupus erythematosus (Fig. 7e, Table II). Three such cases, exhibiting a positive L.E. phenomenon, have been observed (Table I). Necropsy revealed advanced cirrhosis as the principal pathologic change, but none of the lesions distinctive of lupus erythematosus. Therapy with adrenal steroids in this particular group of patients has been of limited benefit only.

**Complication of Therapy with Hydralazine**

This syndrome is of particular interest, especially in relation to the possible pathogenesis of rheumatoid arthritis and lupus
erythematous. It has been observed in patients suffering from essential hypertension with no previous history of rheumatic complaints. The syndrome has been recorded in 5 to 8% of cases under treatment with large doses of hydralazine over a prolonged period, usually a year or longer. It has not been observed following administration of other antihypertensive agents.

Affected patients may exhibit simply the manifestations of rheumatoid arthritis, or a clinical picture resembling that seen in systemic lupus erythematosus. There may be involvement of joints, serous membranes and viscera, and in some instances the L.E. phenomenon may be demonstrated (Table I). The serum proteins have not been significantly altered (Fig. 7f). Thus far, cessation of hydralazine therapy has been followed by regression of the complicating symptoms, while resumption of the treatment may again precipitate the syndrome. The prolonged period of administration which seems to be necessary to produce this complication suggests that the complication is a result of the toxicity of the drug rather than of hypersensitivity. Adrenal steroids appear to be beneficial in the treatment of severely ill patients.

Reactions to Penicillin and Phenylbutazone

In a small proportion of patients who exhibit manifestations of hypersensitivity following the administration of various agents, such as penicillin and phenylbutazone (Table I), severe reactions may be observed in the skin, joints and serous membranes, and sometimes accompanied by a positive L.E. test. These reactions differ from the complications of treatment with hydralazine in that symptoms come on rather acutely, usually within 10 to 14 days of the institution of therapy. The reactions are reversible, but in severe cases treatment with adrenocorticotropin or the adrenal steroids may be indicated.

SUMMARY

Attention is drawn to the difficulties that may be encountered in the positive identification and classification of many patients suspected of suffering from systemic lupus erythematosus. Much of this is due to a lack of specific criteria, either clinical or pathologic, for the diagnosis of the disease. The problem has been made more difficult by the recognition of a number of other syndromes that bear a superficial resemblance to systemic lupus erythematosus, yet differ in clinical manifestations, natural course, prognosis and other respects.

A feature common to the group is the presence of the L.E. cell phenomenon. The related conditions differ from lupus erythematosus in that the L.E. phenomenon may only be demonstrable intermittently especially during severe exacerbations of the disease, while at the same time disturbances in the electrophoretic pattern of the serum proteins may be much more profound.

In systemic rheumatoid disease the prognosis without steroid therapy is better than in systemic lupus erythematosus, although the morbidity may be great.

The reactions which follow administration of certain chemotherapeutic agents are of considerable interest, particularly in view of the similarity to lupus erythematosus and rheumatoid arthritis, and the reversibility on withdrawal of the offending agent.

The relationship of these syndromes to each other and to classical systemic lupus erythematosus has not yet been resolved, and inclusion of them under the diagnosis of systemic lupus erythematosus at this time must be regarded as premature.

ACKNOWLEDGMENTS

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OGRYZLO – SYSTEMIC LUPUS ERYTHEMATOSUS

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UROLITHIASIS IN CHILDHOOD, N. A. A. Myers. (Arch. Dis. Childhood, 32:48, February, 1957.)

An account of 85 children with urolithiasis admitted to The Hospital for Sick Children, Great Ormond Street during a 20-year period is provided. Stones in the urogenital system were found in four groups of patients: in those with congenital anomalies, in patients with errors of metabolism such as cystinuria and oxaluria, other recognizable causes such as neurogenic bladder and nephrocalcinosis, and those with unknown causes comprising 46 of the cases. The clinical and radiologic findings are discussed and chemical analyses of the calculi in 59 cases are tabulated. Hematuria was the predominating presenting symptom and urinary infection was frequent. Nephritis is an unfortunate erroneous diagnosis which is to be avoided by remembering this possible confusion and employing urologic investigation in suspicious circumstances.
SYSTEMIC LUPUS ERYTHEMATOSUS AND SYNDROMES POSSIBLY RELATED
M. A. Ogryzlo and H. A. Smythe
Pediatrics 1957;19;1109

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