History of Lupus

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PRESCIENTIFIC PERIOD

Lupus (wolf) was an ancient Roman family name, and there was a St. Lupus who lived in central France around AD 600. How the name of this large carnivore came to have a disease association is obscure. The earliest known medical use of lupus appeared in a 10th-century biography of St. Martin, who had lived in 4th-century Gaul. The Bishop of Liege was healed at St. Martin’s shrine in Tours:

He was seriously afflicted and almost brought to the point of death by the disease called lupus… The location of the disease … was not to be seen, nonetheless, a sort of thin red line remained as a mark of the scar.3

Toward the end of the 12th century, Rogerius Frugardi, a Salernitan surgeon, introduced the term noli me tangere (touch me not) to designate a facial ulcer. He also stated, “Sometimes lupus arises in the thighs and the lower legs [and is] distinguished from cancer.” This distinction was clarified somewhat by his student, Roland of Parma: “In the early stages it [cancer] is called sclerosis [hardening] or negrosis [blackening]. After it begins to rot it is called cancrena [gangrene?]; finally it is called carcinoma [cancer].” This progressive lesion is also named according to its location. On the face he used Roger’s term, noli me tangere, on the trunk, cingulum [girdle]. “However, in the lower body, as in the feet, thighs and hips, it is called lupula [little she-wolf] and it is incurable … in this place.”4

Lupus remained associated with ulcerated lesions of the legs until the 16th century, after which it was considered primarily a facial lesion. Most authors considered it to be a distinctive disease rather than a phase of an evolving ailment, but no one described lupus in sufficient detail for a modern diagnosis to be inferred. Various ailments likely bore the name. Paracelsus (1493–1541) presented an example of the undefined use of the term:

The art of medicine resides in recognizing the site wherein lies the cure, such as cancer, lupus, gout, plague, fever, hydrops, polyuria, menses, worms, etc.5

DIFFERENTIATION FROM TUBERCULOSIS

Discussion of whether this skin disease is merely a manifestation of tuberculosis, which itself was just being defined, began early in the 19th century. According to the dermatologist Thomas Bateman (1778–1821), his mentor, Robert Willan (1757–1812), defined lupus:

… to comprise, together with the “noli me tangere” affecting the nose and lips, other slow tubercular affections, especially about the face, commonly ending in ragged ulcerations of the cheeks, forehead, eyelids, and lips, and sometimes occurring in other parts of the body, where they gradually destroy the skin and muscular parts to a considerable depth.6

In 1853 Sir James Paget (1814–1899), calling the lesion a “rodent ulcer,” identified noli me tangere as a neoplasm.7

In 1845 Ferdinand von Hebra (1816–1880, Vienna) proposed a classification of skin diseases based on abnormalities of specific components of the skin. Under “hyperactivity of sebaceous glands” he
described "seborrhea congestiva," which a few years later was renamed lupus érythémateux. Here is his description:

One sees at the beginning of this illness—mainly on the face, on the cheeks and the nose in a distribution not dissimilar to a butterfly—on an erythematous but not infiltrated base the sebum filled openings of the sebaceous glands as white flat dots.

Laurent T. Biett (1761–1840, Paris) in 1833 may have described the same disease as "érythème centrifuge," but this was first published in 1851 (Fig. 1.1) by his student Pierre L. Cazenave (1795–1877, Paris):

It is a very rare occurrence, and appears most frequently in young people, especially in females, whose health is otherwise excellent. It attacks the face chiefly. It generally appears in the form of round red patches, slightly elevated, and about the size of a 30 sous piece; these patches generally begin by a small red spot, slightly papular, which gradually increases in circumference, and sometimes spreads over the greater part of the face. The edges of the patches are prominent, and the centre, which retains its natural color, is depressed …

At a meeting in 1851, Cazenave also described a case and after giving credit to Biett for having described a variety of lupus as érythème centrifuge, introduced the term lupus érythémateux.

In the 1856 edition of his textbook, Cazenave wrote extensively about lupus erythematosus (LE). He mentions the potential occurrence of "fever and even pain," but his presentation is entirely dermatologic. Cazenave is the first to note alopecia as a symptom. He does not mention the "butterfly rash," but states that the eruption "is very common on the face and the nose." He emphasizes that lesions heal with scarring but do not ulcerate, which is an important distinction from lupus vulgaris (LV), and states that these patients are not necessarily scrofulous (Fig. 1.2).

The distinction from scrofulous (i.e., tuberculous) was important because lupus was considered a tuberculous disease, with tuberculous having a different meaning in this prebacteriologic time. According to Erasmus Wilson (1809–1884; 1862, London):

Destruction, then, we may take as the leading character of lupus. A further inquiry into the nature of lupus is served, however, to show that this destructive disease was preceded by a circumscribed thickening and prominence of the skin, commonly termed a tubercle, hence, lupus is considered as a tuberculous affection of the skin … Now, the destructive action implied by the term lupus was, in the first instance, intended to be restricted to that form of tubercle which commonly issues in destructive ulceration, but as cutaneous diseases came to be more carefully observed, it was perceived that there existed a kind of tubercle which did not of a necessity ulcerate, which was chronic and lasting in its nature, and which … left behind it a deep pit or a strongly marked cicatrix … This form of cutaneous disease … has been distinguished by Cazenave under the name of lupus erythematosus.

Unfortunately, Wilson then confuses this finding with a syphilitic lesion. However, the fact that the medieval description of lupus depended mainly on ulceration makes it likely that the nonulcerative lupus was first recognized in the 1830s.

Moriz (Kohn) Kaposi (1837–1902, Vienna), with his publications in 1869 and especially in 1872, called attention to LE. He confirmed Wilson’s observation that LE occurs more frequently in women and considered that it also is more likely to be severe in them. Kaposi believed that tuberculosis and LE may occur in the same patient but
was convinced that LE is not a manifestation of tuberculosis. He became quite annoyed at the confusion:

… the disease called lupus erythematosus does not have the least in common with lupus vulgaris, and it is not enough to criticise even leading surgeons for confusing these two entirely different processes that have not the least in common, and even less to justify many dermatologic specialists who assume transitional or mixed forms of lupus erythematosus and lupus vulgaris, as has occurred recently.15

From 1866 to 1871, Kaposi made the diagnosis of LE in 22 patients and diagnosed LV (cutaneous tuberculosis) in 279. He introduced the term discoid for lesions that expand from single foci and discrete and aggregate for lesions that enlarge by the merger of multiple pinhead-size foci.14 Subsequently, he altered the latter term to disperse and aggregate.18 Confusion resulted from Kaposi’s intention for disperse to refer to cases in which the lesions were not limited to the head when systemic symptoms (Fig. 1.3) were observed only in patients with disperse skin lesions:

Lupus erythematosus may occur and progress with manifestations of a dissemi nated or universal acute or subacute febrile eruption, and may then frequently involve the entire body with intense local and general symptoms, indeed to endanger and destroy life.14

Of the 11 cases Kaposi described in 1872, four had pneumonia, three had arthralgias, and three had major adenopathy. Of the three who came to autopsy, two had pneumonia, one of whom also had amyloidosis, and one had tuberculosis. No renal disease was described. He was uncertain whether the relationship between the cutaneous and other findings was more than coincidental. The first American publication on LE, by W. H. Geddings in 1869, described the cutaneous findings of the first case in Kaposi’s 1872 publication.16

Many investigators recognized that the relative prevalence of LE and LV was influenced by socioeconomic factors, with LV particularly associated with poverty. Thus Jonathan Hutchinson (1828–1913, London) cited Wilson as having seen an equal number of cases of these two diseases among 10,000 dermatologic patients from among the “wealthier classes,” and attributed this to referral bias.17 One decade later, H. R. Crocker (1845–1909), another English dermatologist, found LV to be twice as prevalent as LE among 10,000 dermatologic clinic cases (1.27% versus 0.63%), whereas the opposite was true among 5000 private patients (0.98% versus 1.80%).18

Hutchinson in 1888 made the principal distinctions between the major members of the lupus family (Table 1.1). Hutchinson concluded:

The features which distinguish these two diseases ... are useful rather for the purposes of clinical diagnosis and arrangement than as implying essential differences ... The two are closely allied and ... are in a general way induced by a similar kind of causative influence ... . In the lupus family vulgaris and erythematosus stand as brother and sister, having many essential resemblances and many marked but superficial differences.

In his descriptions of the symmetry of LE lesions he substituted “the bat’s wing form” for von Hebra’s “butterfly.” Six years after the discovery of the tubercle bacillus, Hutchinson conceded that no one had detected them in cases of LE, “but this, no doubt is only a question of time.”12 Hutchinson was in a shrinking minority of advocates of a direct tuberculous etiology of LE. In view of the inability to recover tubercle bacilli from LE lesions, but with no persuasive alternative etiologic hypothesis, the most acceptable compromise was that LE “is a chronic inflammatory process produced by toxic substances of tuberculous origin.”19 Goeckerman20 in 1921 analyzed Mayo Clinic data and found tuberculosis equally prevalent among cases of discoid lupus erythematosus (DLE) and those with other dermatoses. In 1933 Harry Keil, a dermatologist in New York, in reviewing autopsy reports of cases of systemic LE, found that only 20% showed evidence of active or remote tuberculosis. He also concluded that the occurrence of the two diseases is coincidental and, in view of the prevalence of tuberculosis, not surprising.21

<table>
<thead>
<tr>
<th>Feature</th>
<th>Lupus Vulgaris</th>
<th>Lupus Erythematosus</th>
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<tbody>
<tr>
<td>“Apple jelly” growth</td>
<td>Characteristic</td>
<td>Little or none</td>
</tr>
<tr>
<td>Tendency to ulcerate</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Symmetric lesions</td>
<td>No</td>
<td>As a rule</td>
</tr>
<tr>
<td>Childhood occurrence</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>Almost equal</td>
<td>More common in women</td>
</tr>
<tr>
<td>Related to chilblains</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Fatal</td>
<td>Very seldom</td>
<td>Sometimes</td>
</tr>
</tbody>
</table>

Figure 1.3 Disseminated lupus erythematosus (LE) involving scalp, face, trunk, and extremities. (From Kaposi M: Neue Beiträge zur Kenntnis des Lupus erythematosus. Arch Derm Syphilol 4:36–78, 1872.)
Recognizing SLE

Between 1872 and the first of William Osler’s (1849–1919) three long articles describing a disease he initially called *erythema exudativum multiforme* (EEM), a few cases of LE were described in which some extracutaneous symptoms were present.22,23 In 1895, Osler described a disease:

… of unknown etiology with polymorphic skin lesions—hyperaemia, edema, and hemorrhage—arthritis occasionally, and a variable number of visceral manifestations, of which the most important are gastrointestinal crises, endocarditis, pericarditis, acute nephritis, and hemorrhage from the mucous surfaces. Recurrence is a special feature of the disease, and attacks may come on month after month, or even throughout a long period of years … The attacks may not be characterized by skin manifestations; the visceral symptoms alone may be present, and to the outward view the patient may have no indication whatever of erythema exudativum.24

The relevance of Osler’s contributions to the understanding of LE has been misinterpreted. In 1900 he acknowledged that the cases he was assembling were not uniform:

While I feel that in bringing together a somewhat motley series of cases I may only have contributed to make the “confusion worse confounded,” on the other hand there is, I think, a positive advantage in recognizing the affinities and the strong points of similarity in affections usually grouped as separate diseases.25

Therefore he withdrew the term EEM in favor of the less specific *erythema group*. At no time did he use the term LE.

In the last paper (1904), Osler summarized his 29 cases, and they differ significantly in gender and age from typical LE: 18 were male, 12 were between the ages of 3 and 12 years, and 19 had purpura and colic. All had some sort of cutaneous findings. The most frequent extracutaneous symptoms were arthralgia in 17 and nephritis in 14. None of the seven fatal cases came to autopsy. Osler made no etiologic hypotheses, but regarding pathogenesis he stated: “The essential process is a vascular change with exudate, blood, serum, alone or combined.”26

Osler’s three articles drew praise for calling attention to the association of cutaneous and visceral symptoms.27,28 The modern diagnosis of most of these patients undoubtedly would be Schönlein–Henoch purpura, a possibility about which Osler equivocated.25 Keil in 1937 became the first to point out that Osler’s 29 cases included two descriptions of typical acute (systemic) LE.29,30

Various modifications of *lupus erythematosus* came to be preferred over Osler’s erythema group. In 1908, Kraus and Bohac31 in Prague introduced the term *acute LE* to indicate the presence of both cutaneous and visceral symptoms. *Chronic LE* became a synonym for DLE. *Acute disseminated LE* was used for “cases which start acutely [i.e., with systemic symptoms], assume a disseminated [cutaneous] form and run acutely throughout.”32 That cutaneous lesions are not a prerequisite for a diagnosis of SLE was rediscovered in 193633 and emphasized in 1942.34 Although various authors used cumbersome descriptive terms, LE was never discarded. Brunsting35 in 1952 in Rochester, Minnesota, introduced *disseminated (systemic) LE*, and Harvey and colleagues36 in 1954 in Baltimore finally popularized the contemporary *systemic lupus erythematosus* (SLE) (Table 1.2).

Once visceral symptoms began to be associated with cutaneous LE, the question of whether they are causally related had to be resolved. Consequently, a gap between the first description of many findings and the recognition that they are a component of LE exist. Kaposi had mentioned the occurrence of fever and pneumonia in 1872, but Kraus and Bohac31 concluded in 1908 and 1909 from their eight cases that pneumonia may be a component of LE and that fever is not necessarily a result of infection.

In 1911, Emanuel Libman (1872–1946, New York) hospitalized a 10-year-old girl who had been ill for 10 weeks with polyarthralgia, followed by precordial pain, dyspnea, and oliguria. “There was an erythematous eruption of butterfly pattern, which resembled acute lupus erythematosus disseminatus.” Blood cultures were sterile. Hematuria and a precordial rub developed during a febrile 8-week course. The autopsy revealed “endocarditis of a peculiar type, particularly because of the unusual manner of spread of the endocardial lesions along the posterior wall of the left ventricle,” as well as glomerulonephritis. This case was first reported in 1924 as the fourth of four cases of nonbacterial valvar and mural endocarditis treated by Libman and autopsied by Benjamin Sacks.36 Cases 1 and 2 had already been reported in 1923.30 Two of the four had the butterfly facial eruption and three had nephritis. Libman and Sacks pointed out “the similarity of certain of the symptoms to those observed in the erythema group of Osler,” but declined to make a definite diagnosis of SLE in any case.

Dermatologists, on reviewing published cases in 1936, came to the confusing conclusion that the “Libman-Sacks syndrome is a subvariety of the Osler erythema group,” but probably not LE.37 An internist and a pathologist finally stated unequivocally in 1940 that this form of endocarditis is a manifestation of SLE, irrespective of the presence of characteristic skin lesions.38 Libman–Sacks endocarditis has become a less common pathologic finding since the introduction of corticosteroid therapy, with 59% of cases of SLE reported from 1924 to 1951 versus 36% of cases from 1953 to 1976.39

At least two of the patients in whom Osler found signs of nephritis did have LE.40,41 Sequeira and Baaleen42 in 1902 in London found proteinuria in 5 of 10 cases of disseminated (cutaneous) LE, of whom the one fatal case had a pathologic diagnosis of nephritis. Similar single cases were published in the next few years. Keith and Rowntree43 in 1922 in Rochester, Minnesota, pointed out that nephritis is “a common complication of disseminated LE.” In a pathologic study of 23 cases of SLE, Baehr and colleagues44 in 1935 in New York differentiated a type of nephritis in 13 cases (56%), which they considered to be peculiar to LE:

The commonest and most characteristic glomerular alteration was a peculiar hyaline thickening of the capillary walls … The thickened wall appears rigid, as if made of heavy wire. We have, therefore, called it the “wire loop lesion.” … It is quite different from the hyaline degeneration seen in glomeruli of arteriosclerotic kidneys or of chronic glomerulonephritis. It apparently represents a toxic degenerative process.41

Nevertheless, renal failure was not considered a principal cause of death in LE, probably because early death usually resulted from infection. The importance of renal involvement was recognized by Harvey and colleagues42 who found that in two-thirds of their autopsied cases “SLE alone was responsible for varying degrees of renal damage.” They pointed out “the inability to correlate the degree of renal involvement disclosed clinically and the extent of renal damage at postmortem examination.” Libman and Sacks,46 incidentally to their description of the cardiac lesion, also described a splenic abnormality:

The greater part of each malpighian body [lymph follicle] was occupied by a number of arterioles, each of which was surrounded by a broad zone of hyaline-like connective tissue. The arteriolar lumen in each instance was diminished in caliber.
symptom was alluded to only incidentally before 1951, when it was also pointed out that seizures may precede diagnosable SLE for years. Harvey and colleagues attributed seizures to SLE in 11% of their patients. According to Bowen (1896), “I have often met with cases of extreme melancholia in the subjects of this disease [LE] and in a number of instances the mind has become really affected.” Toxic delirium was described, but the range of psychotic manifestations that may occur was not comprehensively reviewed until 1960. Cerebral vasculitis to which the various manifestations might be attributed was described by Jarcho in 1936 in Baltimore and Daly in 1945 in Minneapolis. Paraplegia because of spinal vasculitis was identified in 1953.

Attention to ocular symptoms antedates modern descriptions of cerebral symptoms. Retinal vasculitis was demonstrated pathologically in the 1930s. Whether these patients actually had SLE is equivocal, but this allegation has repeatedly been made. Peripheral Raynaud phenomenon was associated with SLE by MacLeod in 1908 in London. Until the 1940s abnormalities of cerebral function were generally attributed to fever or uremia. Although seizures are the most frequent cerebral manifestation of SLE, this symptom was alluded to only incidentally before 1951, when it was also pointed out that seizures may precede diagnosable SLE for years.

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## Table 1.2 First Descriptions as Components of SLE

<table>
<thead>
<tr>
<th>Component</th>
<th>Author, Year</th>
<th>Site</th>
<th>Reference</th>
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<tbody>
<tr>
<td><strong>Clinical</strong></td>
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<tr>
<td>Butterfly rash</td>
<td>Von Hebra (1845)</td>
<td>Vienna</td>
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<tr>
<td>Panniculitis</td>
<td>Kaposi (1869)</td>
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<td>Arthralgia</td>
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<td>Adenopathy</td>
<td>Kaposi (1872)</td>
<td>Hamburg</td>
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<td>Nephritis</td>
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<tr>
<td>Purpura</td>
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<td>Psychosis</td>
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<td>Pneumonia</td>
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<td>Raynaud phenomenon</td>
<td>MacLeod (1908)</td>
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<td>Photosensitivity</td>
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<td>Thrombocytopenia</td>
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<td>&quot;Wire loop&quot; glomeruli</td>
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<td>&quot;Onion skin&quot; splenic lesion</td>
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<td>Hypergammaglobulinemia</td>
<td>Coburn and Moore (1943)</td>
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<td>LE cell</td>
<td>Hargraves (1969)</td>
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<td>Lupus anticoagulant</td>
<td>Conley and Hartman (1952)</td>
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<td>Antinuclear antibody</td>
<td>Miesscher and Faauconnet (1954)</td>
<td>Geneva, Switzerland</td>
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<tr>
<td>“Lupoid” hepatitis</td>
<td>Cowling and Mackay (1956)</td>
<td>Melbourne, Australia</td>
<td>55</td>
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</table>

**BFP,** Biologically false positive; **LE,** lupus erythematosus.

Kaiser in 1942 in Baltimore studied this “onion skin” periarterial splenic fibrosis in detail and found it in 83% of cases of SLE but in only 3% of other diseases:

*Its discovery post mortem should at least raise the suspicion of that diagnosis … [and] its coincidence with the other well recognized lesions of the connective tissue such as verrucous endocarditis and the "wire loop” glomerular changes can serve to strengthen the post mortem diagnosis of disseminated lupus erythematosus.*

Abdominal symptoms were recognized as peritonitis, which tended to be associated with pleurisy, but there were no primarily gastrointestinal (GI) findings.

Regarding cerebral involvement, Osler considered as “peculiarly obscure” the delirium in one (case 1) and recurrent episodes of hemiplegia and aphasia (case 15), which he speculated “were associated with changes in the brain of essentially the same nature which subsequently occurred … in the skin. They remind one somewhat of the attacks of recurrent aphasia with paralysis in cases of Raynaud’s disease.” Whether these patients actually had SLE is equivocal, but this allegation has repeatedly been made. Peripheral Raynaud phenomenon was associated with SLE by MacLeod in 1908 in London. Until the 1940s abnormalities of cerebral function were generally attributed to fever or uremia. Although seizures are the most frequent cerebral manifestation of SLE, this symptom was alluded to only incidentally before 1951, when it was also pointed out that seizures may precede diagnosable SLE for years.
The absence of anemia in early descriptions of SLE can be attributed to the rudimentary state of hematologic methods. However, it is surprising that “secondary anemia often with a normal leukocyte count” was not described until 1924. A case with leukopenia was cited by Goecckerman in 1923. However, Rose and Pillsbury in 1939 in Philadelphia were the first to consider this “the principal feature of the blood picture.” Purpura had been described by Kaposi and by Osler, but the thrombocytopenia with which it occurs was not recognized until the 1930s. Conversely, the infrequency of purpura among platelet-deficient patients was pointed out in 1951.

**Lupoid Hepatitis**

In the mid-1950s a syndrome was recognized manifested by progressive liver disease usually associated with arthralgia and/or fever and a significantly elevated serum gamma globulin concentration that occurred predominantly in young women. Bearn and colleagues (New York) among 26 cases of liver disease (23 female) had 8 cases (mean age 17) that had both fever and arthritis, a mean serum globulin content of 7 g%, and hyperbilirubinemia. The possibility that these were instances of SLE was not entertained. In 1955 Kofman and colleagues (Chicago) evaluated patients with SLE for evidence of liver disease. The serum globulin concentration exceeded 3 g% in 22 of the 25 cases. The investigators concluded that the numerous abnormal hepatic function test results in most cases reflected globulin abnormalities related to SLE rather than liver disease. Coincidentally, physicians in Melbourne, Australia, demonstrated the LE cell phenomenon in patients with chronic hepatitis that they presumed to be viral. In 1956, Ian R. Mackay (Melbourne) introduced the term lupoid hepatitis for this association. Bartholomew and colleagues (Mayo Clinic) found the serum gamma globulin concentration in seven cases consistently greater than 3.1 g%. Various early histopathologic descriptions of the liver ranged from minimal changes to postnecrotic cirrhosis. In 1956 the first instance of lupoid hepatitis in a case of possibly drug-related SLE was also reported; a sulfonamide was implicated. Mackay and colleagues (1959) proposed that the etiology may be “mediated via abnormal immunologic responsiveness with auto-destruction of host tissues.”

**SEROLOGIC ASPECTS**

The Wassermann test for syphilis was devised in 1906 and rapidly gained wide use. It soon was discovered that some, mainly tropical, diseases were negative. The latter author suggested that this result is evidence that LE is not a manifestation of tuberculosis because falsely positive reactions had not been reported in the latter disease. The incidence of biological false-positive (BFP) reactions has ranged from less than 3% to 44% of cases of SLE. The test results in most cases reflected globulin abnormalities related to SLE rather than liver disease. The specificity of the reaction, and Rothfield and colleagues in 1961 showed that LE cells are formed by a factor in the blood of patients with LE. Then in 1950 he showed that this factor is a gamma globulin. In the same year Klempner and colleagues in New York discovered “hematoxylin bodies.” These appeared to be identical with the phagocytosed substance within LE cells in various tissues obtained at autopsy of cases of SLE. This strengthened the hypothesis that the LE cell reaction is related to the pathogenesis of the disease. LE cells were also demonstrated in vivo in the content of artificially raised blisters. Peripheral blood replaced bone marrow as the source of LE cells, and of several techniques the one described by Zimmer and Hargraves in 1952 was generally adopted.

Reliance on the LE cell to diagnose SLE began to diminish after a few years. Goslings and colleagues in 1956 demonstrated LE cells in 16% of cases of rheumatoid arthritis, increasing doubt about the specificity of the reaction, and Rothfield and colleagues in 1961 showed that LE cells cannot be detected in approximately one-fourth of the cases of SLE, proving poor sensitivity. In 1954 investigators in Switzerland found that isolated cell nuclei can absorb the serum factor that induces LE cell formation. They therefore postulated that the factor is an antibody against a component of the nucleus. In 1957, Friou and colleagues at Yale devised a technique to demonstrate the antibody semiquantitatively by indirect immunofluorescence microscopy. The reactive substance was identified in 1959 as a DNA-histone nucleoprotein, and Beck in 1961 in London showed that at least three fluorescent staining patterns could be distinguished. In the next decade, refined laboratory methods permitted the discovery of numerous antibodies, some of which could be correlated clinically with subsets of SLE and other diseases. The discovery of the LE cell had initiated the discipline of immunopathology.

In 1957, three laboratories almost simultaneously demonstrated a factor in the serum of some cases of SLE that reacts specifically with DNA. Tan and colleagues in 1966 in New York detected anti-DNA antibodies in SLE sera. Koffler and colleagues in 1969 in New York found that the detection of native double-stranded DNA (dsDNA) is more specific for SLE but less sensitive than antibody to denatured ssDNA. Schur and colleagues in 1971, using more sensitive techniques, confirmed the specificity of the reaction with dsDNA but obtained positive reactions in only half of SLE sera. Tan and Kunkel in 1966 in New York detected a cytoplasmic (RNP) antigen in SLE serum that...
they designated Sm. It was the first antibody to a nonhistone nuclear antigen and highly specific for SLE, although it was found in only one-third of cases.

The next discoveries about the antibody systems related to SLE were gained from the development of techniques to extract uncomplexed histones from nuclei and recombinating them with DNA, free of other components. Histones are small basic proteins associated with nucleic acids in cell nuclei. Some extracted recombinant antigens, depending on the precise histone structure, can be used to detect antihistone antibodies. The important findings were that antihistone antibodies occur more frequently in drug-induced than in idiopathic SLE, and that lupus-inducing drugs vary in their ability to induce these antibodies, with procainamide doing so most consistently.

The role of antinuclear antibodies (ANAs) in SLE became uncertain when clinically typical cases in which ANAs could not be detected began to be described. These cases comprise fewer than 5% of cases of SLE, and most have antibody reactive against the cytoplasmic RNA antigen Ro.

The introduction in 1963 of a convenient pathologic technique complemented the ever-increasing number of serologic tests. The "lupus band test" determines by immunofluorescence microscopic examination of skin biopsies whether immunoglobulins are deposited at the dermoepidermal junction. In DLE it is positive in lesional but not in uninvolved skin. It also is positive in the "normal" skin of at least half of the cases of SLE. It has proven not to be a highly specific finding because it occurs in approximately 15% of cases of rheumatoid arthritis and in various bullous dermatoses.

**EPIDEMIOLOGY**

In contrast to DLE, until the 1950s SLE was considered a rare disease. At the Johns Hopkins Hospital as of 1936, five cases were found among 7500 autopsies. Twelve cases were diagnosed at the University of Pennsylvania Hospital from 1932 to 1938. The large referral clientele of the Mayo Clinic included 154 cases from 1918 through 1937 and 132 cases from 1938 to 1947. At Columbia-Presbyterian Hospital in New York, 44 cases were recognized from 1937 through 1952. SLE was diagnosed in 11 cases at the Los Angeles County Hospital from 1946 to 1949, but 44 cases were diagnosed the next 2 years. Dubois attributed the increase to the use of the LE cell test and better diagnostic acumen. On the other hand, the incidence of hospitalization for SLE in a Swedish city remained approximately 1 per 100,000 from 1938 to 1939 and 1948 to 1949 but increased to 4.8 per 100,000 from 1954 to 1955. These authors considered this increase genuine, although unexplained. The first survey of a circumscribed population in which case findings included 7500 autopsies. Twelve cases were diagnosed at the University of Pennsylvania Hospital from 1932 to 1938. The large referral clientele of the Mayo Clinic included 154 cases from 1918 through 1937 and 132 cases from 1938 to 1947. At Columbia-Presbyterian Hospital in New York, 44 cases were recognized from 1937 through 1952. SLE was diagnosed in 11 cases at the Los Angeles County Hospital from 1946 to 1949, but 44 cases were diagnosed the next 2 years. Dubois attributed the increase to the use of the LE cell test and better diagnostic acumen. On the other hand, the incidence of hospitalization for SLE in a Swedish city remained approximately 1 per 100,000 from 1938 to 1939 and 1948 to 1949 but increased to 4.8 per 100,000 from 1954 to 1955. These authors considered this increase genuine, although unexplained.

The main symptom that the popular press has associated with LE is corticosteroids than do other manifestations. The 10-year survival of the patient cohort begun by Dubois’ group, which was treated from 1950 to 1971 with multiple agents, was 87%, but only 65% in those with renal involvement.

**SLE AND “COLLAGEN DISEASE”**

Development of the modern pathogenetic concept of SLE required the retraction of two principles: Giovanni B. Morgagni (1682–1771, Padua) who had concluded in 1761 that every disease resides primarily in a certain organ, and Paul Ehrlich (1854–1915, Frankfurt) who in 1901 concluded that an organism cannot react against any of its own constituents. The former was first contradicted by the German pathologist, Fritz Klinke (1892–1974), who showed from 1928 to 1934 that the form of a disease had no logic until it became apparent that the widespread lesions were identical in that they were mere local expressions of a certain well-defined optical and tinctorial alterations in the collagenous fibers and ground substance.

This is the origin in 1942 of the term collagen disease, which initially was limited to SLE and scleroderma.

Ehrlich’s doctrine was first questioned by Wilhelm Gennerich, a German dermatologist, who in 1921 speculated about the etiology of SLE:

Lymphocytic [leukocytic] ferments are liberated by the disintegration of lymph nodes. They act on the organism as denatured protein and in sufficient quantity cause anaphylaxis. Furthermore, the liberated ferments exert their biologic effect, which seemingly consists of sensitizing the vascular endothelium and destroying certain components of connective tissue cells, especially, predisposed components of the skin and eventually also of all parenchymatous organs, if an abundant accumulation (acute LE) of the ferments develops in the blood.

This hypothesis gained acceptance in the 1940s because of the research of Arnold Rich (1893–1968, Baltimore), who advocated that the primary lesions of SLE-affected endothelium and collagen occur by anaphylaxis. The initiator of such hypersensitivity, however, remained obscure. Gross in 1932 in New York had described microscopic “granular hematoxylin-stained bodies” in the hearts of cases of Libman–Sacks endocarditis. In 1950 Klemperer and colleagues detected these abnormalities “in 32 of 35 cases of this disease, often widely distributed throughout the body.” Whether they were (or contained) the pathogen could not be ascertained.

**PHOTOSENSITIVITY**

The main symptom that the popular press has associated with LE is aggravation of the disease by exposure to bright sunlight. This was first described by a Viennese dermatologist in 1921 regarding a fair-complexioned woman on whom DLE developed after intensive sun...
exposure. After several months, when the lesions had diminished, she received one ultraviolet irradiation to the back. On the next day there was a significant proliferation of lesions in the irradiated area.\textsuperscript{36} Rasch\textsuperscript{126} in 1926 in Copenhagen stated that he had seen many such cases since 1907, with the lesions typically limited to the uncovered skin. He concluded that LE (i.e., SLE) “is very decidedly aggravated by light, in fact caused by it.”

Rose and Pillsbury\textsuperscript{70} in 1939 in Philadelphia take precedence in the description of exacerbations of SLE after exposure to sun or therapeutic ultraviolet light as well as photosensitivity long preceding the development of recognized symptoms of this disease. Reports of the prevalence of photosensitivity have varied considerably: for example, 11% of 105 cases\textsuperscript{36} and 32.7% of 520 cases.\textsuperscript{127}

**DRUG-INDUCED AND AGGRAVATED LUPUS ERYTHEMATOSUS**

Sulfonamides (initially sulfanilamide) began to be used to treat DLE in 1938\textsuperscript{26} and a few years later also SLE, with some benefit described. In 1945 florid SLE developed in a young soldier who was being treated with sulfadiazine for presumed pyelonephritis.\textsuperscript{128} Gold\textsuperscript{10} in 1951 in London hypothesized that the aggravation of LE by sulfonamide treatment, as had recently been reported, is because of the sensitization of patients by prior exposure to these drugs.

Gold compounds also acquired a reputation for exacerbating pre-existing SLE. Their use in treating DLE began and ended long before their use in rheumatoid arthritis. The initial rationale also had been the presumed tuberculous etiology of the disease.\textsuperscript{131} A review in 1927 concluded that “in the treatment of lupus erythematosus we possess a systemic remedy of real efficacy. When one considers how refractory and unresponsive to therapeutic endeavor lupus erythematosus has been, … the results now achieved are all the more gratifying.”\textsuperscript{132} As recently as 1956, a therapeutic comparison of gold sodium thiosulfate and chloroquine, the latter first advocated for DLE in 1954,\textsuperscript{133} showed similar efficacy.

Despite the lack of any effective treatment for SLE, as of 1937:

*The general opinion that this method of treatment [gold] is contraindicated for acute and subacute disseminated lupus erythematosus is well founded on sad experience … The capillaries seem unduly sensitive not only to gold therapy but also to a wide variety of therapeutic agents … This is understandable in the case of therapy with gold preparations, since it affects the structures (capillaries) attacked by lupus erythematosus itself.*\textsuperscript{134}

It still was deemed necessary in 1949 to warn that “gold is especially dangerous in the acute phases and probably should never be used.”\textsuperscript{126} This danger never was well documented.

Chronologically, the first commonly used drugs that were implicated to possibly induce rather than aggravate SLE were hydralazine (1954),\textsuperscript{135} the hydantoins (1957),\textsuperscript{138} and procainamide (1962).\textsuperscript{139} In the case of hydralazine, the development of symptoms clearly was related to the chronic use of large doses to control hypertension. The first reported manifestation was arthritis, and additional symptoms more definitely suggestive of SLE developed if hydralazine was not discontinued. Comens and Schroeder\textsuperscript{140} in 1956 found that, although LE cells were not found consistently in patients whose symptoms suggested SLE, these cells could also be demonstrated in some asymptomatic patients who were taking hydralazine. A Mayo Clinic study (1965) compared 50 cases of “hydralazine syndrome” with 100 hypertensive patients who were receiving another therapy. The authors concluded from the prehydralazine histories that “antedating manifestations possibly suggesting lupus diathesis” were nearly six times as frequent in the hydralazine cases as in the controls. Hence, this drug probably uncovers an “underlying lupus diathesis.”\textsuperscript{84,85}

Diphenylhydantoin and Mesantoin were the first, but not the only, anticonvulsants to be related to the induction of SLE.\textsuperscript{138,142} Because seizures may be an early manifestation of this disease, the possibility that certain drugs “uncover” SLE gained support from these observations.

By far the most unequivocal inducing agent has been the antiarhythmic drug procainamide. Dubois\textsuperscript{143} in 1969 compared 33 well-documented cases against his cohort of 520 cases of idiopathic SLE. This supported the impression that the drug-induced disease tends to exhibit fewer and milder symptoms, particularly lacking GI, renal, and neurologic involvement. In a prospective study, Blomgren and colleagues\textsuperscript{144} in 1969 in Rochester, New York, showed that ANA developed within 6 months in half of the patients who were placed on procainamide, “making it unlikely that the drug simply unveils a latent predisposition to idiopathic lupus erythematosus.”

**DIAGNOSTIC CRITERIA**

Valid, agreed-on diagnoses are essential for epidemiologic and therapeutic research. The method for developing disease-specific diagnostic criteria was pioneered in 1944 for rheumatic fever.\textsuperscript{145} When the technique was applied to LE in 1971, the extraordinarily large number of 74 clinical and laboratory items were considered and refined into 14 diagnostic criteria, one of which was the presence of DLE.\textsuperscript{146} The revision of 1982 placed greater reliance on serologic findings, and the number of criteria was reduced to 11. The presence of at least four criteria was required in both schemes. Using the revised set, false-negative diagnoses decreased without a change in the small percentage of false-positive diagnoses.\textsuperscript{147}

**RELATIONSHIP OF DISCOID LUPUS ERYTHEMATOSUS TO SLE**

Agreement with Kapossi’s belief that DLE and SLE are expressions of the same disease has waxed and waned. For example, MacLeod\textsuperscript{148} in 1913 in London concluded:

*Lupus erythematosus of the acute disseminated type has from time to time been found to occur in association with more or less general toxemia … The circumscribed cases have probably a different etiology from those of the acute disseminated type.*

Reliance on skin lesions to diagnose SLE was abandoned reluctantly. According to a 1952 textbook, “Diagnosis may be impossible until the appearance of the characteristic rash.”\textsuperscript{149} Of the pre-1938 cases of SLE diagnosed at the Mayo Clinic, the onset was considered to be with DLE in 47%. This decreased to 17% of those seen in the next decade, perhaps because of greater experience.\textsuperscript{83} Keil\textsuperscript{35} in 1937 pointed out the lack of correlation between the severity of cutaneous and internal manifestations and considered it probable that the two are variants of the same disorder. However, Baehr and colleagues\textsuperscript{130} still held in 1951 that “disseminate lupus erythematosus bears no relationship whatever … to the benign indolent skin lesion known to dermatologists as discoid lupus.” Among Dubois’\textsuperscript{84} 520 cases of SLE (1950–1963), 10.8% initially had discoid lesions, and thrice as many as had a “butterfly rash.”\textsuperscript{142} According to a more recent multicenter study, 13% of 353 cases of SLE “at some time during the course of their illness” manifested discoid lesions.\textsuperscript{150} Conversely, none of 120 cases of DLE developed systemic findings during a 5-year follow-up.\textsuperscript{152} The two opinions were moderated by Burch and Rowell\textsuperscript{153} in 1968 in Leeds, England, who theorized that there is a different polygenic
predisposition for the development of DLE and SLE: “When a genuine transition from DLE to SLE occurs, the affected patient is genetically predisposed to both diseases.” The question remains open.

FOUR SUBSETS OF LUPUS ERYTHEMATOSUS

Antiphospholipid Syndrome
In 1941 Pangborn in Albany, New York, discovered that the substance in the beef heart extract that was used in the complement fixation test for syphilis was a phospholipid. Keil had recently surmised that the “false positive” reactions in cases of SLE were not merely coincidental. However, evidence of a mechanism to explain “biologic false positive” reactions did not accrue until 1983, when a sensitive method to test for antiphospholipid [antiphospholipid] antibodies was devised.156

In 1948, Conley and colleagues in Baltimore demonstrated an endogenous circulating anticoagulant in nonhemophilic bleeding patients. Four years later two cases of SLE with hemorrhaging attributed to such an anticoagulant were briefly described. Lee and Sanders in 1955 in New York found that this substance is not a rarity in SLE, but that it usually does not cause bleeding. This observation was followed in 1963 by the surprising discovery that the anticoagulant may be associated not only with bleeding, but also with thromboses.157 In 1975 spontaneous abortion during the course of SLE was first associated with the lupus anticoagulant; and this relationship was subsequently confirmed prospectively.161 In 1988 antiphospholipid antibodies associated with syphilis were differentiated from those related to SLE.162

Lupus Erythematosus Profundus
The term lupus erythematosus profundus was coined by Samuel Irgang in 1940 in New York to differentiate from DLE cases with nodular lesions in the deeper portions of the skin with little epidermal involvement. Such a case had been described by Kaposi in 1869, and this manifestation has been called Kaposi–Irgang syndrome in the dermatologic literature. The first American report is attributed to Fordyce in 1924 in New York. Before the 1940s this variant probably was usually misdiagnosed as sarcoid. Winkelmann in 1970 suggested that LE panniculitis would be a more accurate term, endorsing the pathologic interpretation of Fountain in 1968 in London.

Subacute Cutaneous Lupus Erythematosus
“Subacute cutaneous LE,” described by Sontheimer and colleagues in 1979 in Dallas, appears to be clinically intermediate between DLE and SLE. The lesions may be preceded by those of DLE and coincide with these at some time in about 20% of cases. They differ from discoid lesions because they are annular or resemble psoriasis, lack follicular plugging, and are less likely to heal with scarring. Patients are more frequently light sensitive than those with either DLE or SLE. About half fulfill the diagnostic criteria for SLE. Most cases are ANA positive but resemble “ANA-negative SLE” because they are anti-Ro positive. Occurrence as a drug-induced phenomenon was first described in 1985, associated with hydrochlorothiazide.

Neonatal Lupus Erythematosus
The innocuous transplacental transfer of the LE factor (anti-DNA antibody) was demonstrated in 1954. In the same year a case of transient DLE was described in an infant whose mother subsequently developed SLE. Since then, neonatal DLE has usually been found to resolve within the first year. In 1957 a woman with SLE delivered a boy who had complete heart block and died on the second day. His myocardium was found to contain hematoxylin bodies. By 1977, sufficient cases of neonatal complete heart block had been described that this became recognized as the most characteristic sign of neonatal LE, occurring in approximately half of these infants. The other frequent findings are cutaneous lesions. SSA (anti-Ro) antibody was pointed out in 1981 to be the most consistent serologic finding in both neonatal DLE and SLE.

HOW DID SLE EVOLVE FROM THE REALM OF DERMATOLOGY TO INTERNAL MEDICINE?
With few exceptions, such as the clinical observations of Osler and of Libman, the delineation and treatment of LE remained in the domain of dermatologists until the 1940s. There are two complementary explanations for this. (1) SLE was recognized by its cutaneous findings and linking it, albeit equivocally, to DLE, a cutaneous disease. SLE was diagnosed much less frequently than DLE, and its visceral manifestations were considered secondary to the cutaneous findings. The 1939 edition of Sutton and Sutton’s Diseases of the Skin contained 13 pages on DLE and SLE, whereas the 1944 edition of Comroe’s Arthritis and Allied Conditions had three. It only became accepted in the 1940s that SLE may occur without skin lesions, which is one factor that moved the disease toward the internist. (2) A medical specialty, when it is circumscribed by more than the patient’s age or gender, results from particular technical and/or therapeutic expertise. Although the beginnings of rheumatology may be placed in the late 1920s, its pioneers had neither technical nor therapeutic superiority over other internists. This changed abruptly with the almost simultaneous discovery of two diagnostic methods: the rheumatoid factor and the LE cell in 1948, and cortisone therapy in 1949, followed in 1950 by the establishment of the Institute of Arthritis and Metabolic Diseases in the National Institutes of Health. The LE cell test increased the diagnosis of SLE, and corticosteroids meant not only that these patients could be helped, but that the treatment required specialized knowledge, enhancing the status of rheumatology.

Interest in LE has shifted from clinical description to immunologic research, with the still frustrated goal of elucidating the etiology, whether it is single or multiple. The continued intensification of scientific interest is reflected in the listing of articles in the Index Medicus. These have been increasing steadily, from 8 columns in 1960 to 21 in 1982, 25 in 1987, 31 in 1992, and 47 in 1997 to thousands of references in 2006 (personal observation).

Disseminated LE originally meant that the skin lesions were extensive. This term became ambiguous when it became applied to patients who had both cutaneous and visceral symptoms. The therapeutic history of DLE is longer than that of SLE but similarly reveals frustrations. Jonathan Hutchinson (1828–1913, London) wrote in 1880 pertaining to the skin disease:

*We must improve the patient’s state of nutrition with tonic, good food, bracing air, cod-liver oil, and the judicious use of stimulants. To all these, arsenic—the specific for psoriasis—may usually with much advantage be added…. We must abstain from enfeebling the health by iodides and mercury.*

Hutchinson was more aggressive when it came to topical treatment: “The new cell growth must be destroyed, eradicated without delay and without flinching,” which he sought to achieve with caustics or a cautery. According to Pereira’s Elements of Materia Medica and Therapeutics (1846), arsenic, while recognized as a poison, had various medicinal uses: orally as arsenious acid (hydrate of arsenic oxide) and topically in lard as arsenic iodide. “In various chronic affections of the skin: particularly the scaly diseases (lepra and psoriasis), eczema, and impetigo, arsenic is one of our most valuable agents.” Doses: 1/16 to 1/8 grain (4–8 mg) in a pill or as a solution of potassium arsenide were typical doses without specified frequency.
In contrast, Louis Duhring (1845–1913), Professor of Dermatology at the University of Pennsylvania, in 1881 advocated the internal use of either potassium iodide or iodide-soaked starch and believed that “mercurial ointment is of service in some cases.” He cautioned that caustics should be a last resort because their use has been “without notable success.”

Henry Radciff Crocker (1845–1909), Professor of Dermatology at University College Hospital in London, by 1903 began to lose confidence in arsenic:

> While the long-established position of arsenic, and its wide-spread use by the mass of the profession for almost every cutaneous disease, and its undoubted merits for some diseases, entitled it to the first consideration, most dermatologists would agree that it was often a most disappointing drug … Its local action was shown by its effect on psoriasis patches actually present. It did not prevent others from forming even in the neighborhood.… The general indications for all acute and widespread inflammations of the skin, irrespective of the diagnosis, are rest and equability of the temperature. Putting the patient in bed without other treatment would cure and ameliorate many more extensive cases of dermatitis.

Therapeutic hopes had not advanced 40 years later. Robert Koch (1843–1910) discovered the tubercle bacillus in 1882 and found in 1890 that an in vitro (but not in vivo) culture of Mycobacterium tuberculosis was killed by a solution of gold cyanide that was more dilute than any other substance he tested, at 1 : 2 million. It soon became widely believed that discoid lupus, because of some similarity of appearance with cutaneous tuberculosis (LUV), is a variant of the latter disease.

Walther Pick, a staff member of A. L. Neisser’s dermatology department in Breslau, in 1901 published the most thoughtful argument against the tuberculous etiology of LE. It was supported by tuberculin skin tests on 29 LE patients of whom only 15 reacted, and all of whom had clinical evidence of tuberculosis. This disparity was perhaps the first objective evidence that DLE must have an alternative diagnosis to being a manifestation of tuberculosis. His reasoning was ignored for decades. Most other investigators argued for or against a tuberculous etiology based on clinical statistics.

Based on the erroneous premise that dilute potassium gold cyanide kills tubercle bacilli in living tissue, such a solution was administered intravenously in 1913 to 20 cases of LV by physicians in Neisser’s dermatology department. Some involution of the lesions was observed, but it was uncertain to which part of the molecule this should be attributed. A pharmacologist then determined that it must be the gold because it kills tubercle bacilli in a higher dilution than potassium cyanide.

A few months after this optimistic report, a physician at another German clinic reported his results with this treatment of 15 cases; two underwent skin biopsies that revealed unaltered tubercles, but in one patient with disseminated LE a nearly fatal reaction occurred. In the next two decades about a dozen organic and inorganic gold compounds were synthesized to treat all forms of tuberculosis.

William H. Goeckerman (1884–1954, Mayo Clinic) in 1923 broached treatment of SLE: “In view of this extremely grave prognosis, it is permissible to assume some risk in the therapeutic management of these cases.” In the 1920s and 1930s belief in the curability of systemic diseases by the removal of presumed pyogenic foci was at its height. Thus Goeckerman merely stressed that in cases of SLE this must be done “with the utmost caution with the patient under a strict hospital regimen. Tuberculous adenitis is so commonly associated with disseminate lupus erythematosus that it seems to play some part in its cause.” Roentgen-ray irradiation may be tried, but he does not mention the administration of gold or arsenic.

In 1927 Jay F. Schamberg (1871–1934) and Carroll Wright (Philadelphia) introduced gold therapy for LE to the United States in the form of its thiosulfate. Based on 25 cases, “when one considers how refractory and unresponsive to therapeutic endeavor lupus erythematosus has been in the past, the results now achieved are all the more gratifying.”

Gold therapy was adopted rapidly. Harvey Towle (Boston) in 1931 culled 420 gold-treated cases of LE from publications, of whom half were “cured.” He pointed out the following:

> There have been many brilliant results, but now that time has elapsed, we are seeing recurrences.… Very few cases are more than one or 2 months old when reported.… Gold therapy does at least tend to influence lupus erythematosus favorably, but there is doubt as to the permanency of the alleged cures.… One also gets the impression that accidents are all too frequent under present conditions.

In 1936 Wright published a follow-up of 76 patients that included some of the earliest treated. Cure or great improvement was achieved in 71%. Nine patients have remained free of symptoms for 4 to 7 years. However, 17% suffered one or more relapses, some of whom responded to retreatment with gold, whereas 19% experienced a toxic reaction.

In 1938 Obermayer and Becker (Chicago) introduced ammonium succinimido-aurate:

> Although of equal therapeutic effectiveness, the marked advantage of aurate over gold sodium thiosulfate consists of the paucity and mildness of the untoward reactions.… The contraindications remain the same for both chemicals, namely, their use in the treatment of the acute disseminated form of the disease. It is our opinion that in this acute type treatment should be limited to bed rest and large doses of quinine by mouth.

This paper provides the most comprehensive international bibliography on dermatologic gold therapy.

Harry Keil (New York) proposed the following:

> The symptom complex considered typical of the acute process of lupus erythematosus may appear in the course of the discoid form under the influence of certain agents that are incapable of reproducing these clinical features in the course of other diseases (for example, gold therapy in pulmonary tuberculosis). This peculiarity suggests a constitutional background, and there is evidence linking it with an unstable vascular system involving principally the smaller vessels… The use of preparations of gold is probably a nonspecific form of medication. Nevertheless, it occasionally leads to brilliant results in the treatment of LE.… The therapy must be employed with extreme circumspection.

Maurice Tolman (Boston, 1938) carefully identified 122 cases of DLE. Of 68 patients who were treated with gold sodium thiomolate 62% were either “cured” or “markedly improved.” Benefit was not related to the number of injections. Recurrences occurred in 21%, and the lesions disseminated during treatment in six cases.

Paul E. Bechet (New York, 1942) advised that “Gold should never be used in lupus disseminatus of the acute variety with constitutional symptoms or in lupus erythematosus complicated by pulmonary tuberculosis because of the possible danger of activating the tuberculous processes.” It still was deemed necessary in 1949 to warn that “gold is
especially dangerous in the acute phases and probably should never be used.”

The administration of salts of bismuth, first used in France for DLE in 1927, had even less pharmacologic basis than gold. The first animal experiments were conducted in 1842 by M. J. Orfila (1787–1853), and bismuth was first used therapeutically in syphilis in 1889. When arsenicals were introduced in 1910 to treat syphilis, bismuth continued to be used as alternative therapy, even with penicillin in the 1940s. In the hope of inducing fewer toxic effects than with gold, R. M. Mackenna (London) in 1929 suggested that the “therapeutic action of bismuth is to inhibit the reaction of the lesions to the toxins (or bacteria) which cause the disease, and that therefore cases which have been apparently cured will probably relapse.” He used several bismuth compounds to treat 24 cases of DLE, with “four apparent cures.”

In 1934 A. G. Smith (Glasgow) compared a cohort of 12 DLE patients he treated with gold sodium thiosulfate (Sanocrysin) with 12 similar patients he treated with injections of a suspension of bismuth and quinine (Quinby). The results were essentially the same: 5 cures and 3 greatly improved of the 12 gold recipients, and 4 cures and 5 greatly improved of the 12 treated with bismuth. However, five of the gold cases, but none who received bismuth, developed some toxic effect. Furthermore, gold is more expensive and should be given in hospital, whereas bismuth can be administered to outpatients. Tolman (1938) confirmed these results in 43 cases in which bismuth salicylate was used. Neither author commented on the duration of benefit.

Fear of gold therapy is suggested in the discussion of a 1937 paper in a dermatology society meeting on how to differentiate early signs of DLE from SLE. Of nine discussants only one mentions gold at all. It is to be avoided because it may further depress bone marrow function, it may increase the severity of the vascular lesions and it is certainly capable of increasing the severity of renal damage.

Gold chloride had been introduced by H. Haxthausen, a Danish dermatologist, in 1926. Only his closing statement in a 1930 paper is noteworthy here as a sign of attitudes subsequently to change:

There is good reason why the simple salt should be preferred. It is much cheaper, and the solution may be prepared in any drugstore.

In the concentration employed (0.1 per cent), gold chloride is strongly bactericidal, so that sterilization of the solution is not required.

In 1956 a comparison of gold thiosulfate and chloroquine found that symptoms of LE resolved more slowly on gold, but benefits persisted longer on chloroquine, which was better tolerated. Thus the inferior safety of gold therapeutics ended reliance on metallotherapy.

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