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SYSTEMIC LUPUS ERYTHEMATOSUS*

BY

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The story of systemic lupus erythematosus opens in 1872 with Kaposi's paper, "Neue Beiträge zur Kenntniss des Lupus Erythematosus." What manner of man was its author?

When we turn back the leaves of history an unexpected or forgotten but brilliant page breaks to the view. England was settling with Victorian stoicism to the fourth year of Mr. Gladstone's first ministry; Europe was gasping at the fall of France and the failure of the banks; in Vienna the sun shone. This was the hour of Johann Strauss and Fanny Elssler, this the first years of the Ringstrasse and the New Opera House. Vienna, at that time a city of 600,000 souls, was astir. Brückner had just been appointed to the Conservatorium, and Brahms had finally returned to this cultural centre of Europe and of the world. One of his friends, Billroth, was professor of surgery; with him Brahms would often spend a musical evening playing duets before Billroth's great contemporaries.

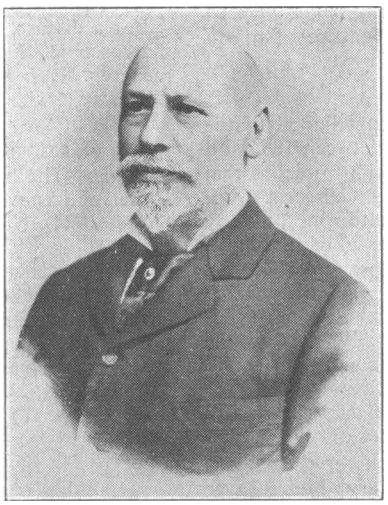

FIG. 1.—Moritz Kaposi.

In these days, when we turn our thoughts westward across the Atlantic for refreshment and quickening, we sometimes overlook the greatness of this Viennese school of medicine founded by a Dutchman, van Swieten, whom the wise Maria Theresa invited to lead the new faculty within the University. His famous contemporary was Leopold Auenbrugger. The new school soon acquired a substantial centre in the 2,000-bedded Allgemeine Krankenhaus, the development of which the Emperor Joseph II entrusted to Peter Frank, a versatile genius who, among many activities, founded a corps of police surgeons, revolutionized and rationalized the treatment of the insane, and sponsored Jennerian vaccination. On these sturdy foundations the great era of Viennese medicine began during the nineteenth century under the direction of Rokitansky, Skoda, and Hebra.

Moritz Kaposi

Ferdinand von Hebra was Skoda's pupil and was encouraged by him to undertake the systematic study of diseases of the skin, thereby laying the foundation of dermatology as a separate discipline. In his turn Moritz Kaposi (Fig. 1) was Hebra's pupil and eventually his son-in-law and successor as professor of dermatology. Thus in 1872 we find the brilliant pupil already preparing, with his father-in-law, the textbook on diseases of the skin which they published three years later (Hebra and Kaposi, 1875). He also found time to review Hebra's (1845) earlier work on lupus erythematosus and to widen and enrich our knowledge of this disease.

Hebra and Kaposi built on the work of Théodore Biett (1828), who wrote an early account of the skin lesions of lupus erythematosus in the textbook edited by Cazenave and Schedel (1838). An even earlier account was given by a distinguished French physician, Pierre Rayer, whose contributions to medicine have, I believe, received too little attention in this country. In 1827, under the title of "Flux Sebace," he described the sebaceous origin and typical distribution of the scaly eruption. He was also author of a book on diseases of the kidney. Perhaps he was overshadowed by our own Richard Bright, whose contemporary he was. Cazenave developed Biett's ideas and, impressed by the destruction and scarring of the advanced disease, classed it with lupus vulgaris. In 1851 he coined the unfortunate term "lupus erythematodes," which has the single virtue of being grammatically more correct than our present usage.

When Kaposi published his paper in 1872 he was, I believe, aware that he was breaking new ground and not just extending a furrow. He included the word "Kenntniss" in the title: he was widening the understanding of lupus erythematosus, not merely adding to the list of physical signs. His account, bedevilled a little by the minutiae of skin lesions and their Latin classification, is thorough and in places has a modern tang: indeed, considering the few clinical tools which he commanded, I am reminded of some words which "Q" wrote about a minor poet of the seventeenth century: "A wonderful performer, Traherne, on an instrument of at most a few strings."

Kaposi refers to observations over the previous 20 years. "Lupus erythematosus," he says, "is not only

*The first of two Lumleian Lectures (abridged) delivered before the Royal College of Physicians of London on April 2 and 4, 1957.

a local disease of the skin but various and severe general symptoms may develop in connexion with or as a consequence of the affliction which may even endanger the life of the patient." He describes in detail the two classes of rash which Hebra (1845) had depicted in his Atlas, L.E. discoides and L.E. discretus et aggregatus, the former being relatively benign, localized, and chronic, the latter more widely distributed and potentially dangerous, since it may become generalized with severe constitutional disturbance. His enumeration of the signs and symptoms of this generalized disease is surprisingly comprehensive. He describes the "aching, boring, deep-seated pains in the bones," nodules the size of hazel nuts, swellings around joints with associated changes in the skin, adenitis, and a terrible complicating erysipelas. "During this phase, patients exhibit symptoms of a severe and generalized febrile disease. They lie on their backs, have a hot dry skin, dry fissured tongue, general prostration, and are more or less unconscious. In the course of two to three weeks death ensues, being preceded by increased mental disturbance, coma, or by pleuro-pneumonia." To his eye, there could be another ending: ". . . . the fever vanishes, the tongue becomes moist, the swelling of the face diminishes, the crusts fall off, and the patients recover."

Before coming to the next great figure I must mention that in 1884 Jonathan Hutchinson described "chilblain lupus," the first reference we have to the sensitivity to cold and the Raynaud phenomenon, a feature of many cases to-day.

William Osler

With the papers which William Osler contributed to the *American Journal of the Medical Sciences* between 1895 and 1903, we arrive in modern times. It is difficult to realize that 60 years have elapsed since he wrote of the "Visceral Complications of Erythema Exudativum Multiforme": "By exudative erythema is understood a disease of unknown aetiology with polymorphic skin lesions—hyperemia, edema, and hemorrhage—arthritis occasionally, and a variable number of visceral manifestations of which the most important are gastro-intestinal crises, endocarditis, pericarditis, acute nephritis and hemorrhage from the mucous surfaces." He mentions the tendency to remission, the variability in the skin eruptions, and the fact that the disease may run its full course to death without skin involvement.

The physical description of systemic lupus erythematosus began in the early years of the nineteenth century: Pierre Rayer (1827) and Théodore Biett (1828) crystallized the first nebulous thoughts about the skin changes. Moritz Kaposi (1872) added another dimension (Table I). William Osler (1895) put the disease in its medical perspective and began that hunt for its causes which later workers, notably Klemperer and his co-authors (1942a, 1942b), have continued to the present.

TABLE I.—*Early Titles Applied to Lupus Erythematosus*

Flux sebace (Pierre Rayer), 1827.
Erythème centrifuge (Théodore Biett), 1828.
Hypertrophia folliculorum (Robert Willis), 1841.
Seborrhoea congestiva (Ferdinand von Hebra), 1845.
Lupus erythematodes (Cazenave), 1851.
Herpes cretace (Devergie), 1854.
Erysipelas perstans faciei (Moritz Kaposi), 1872.
Exudative erythema (William Osler), 1895.
Ulerythema centrifugum (Unna), 1896.

Apart from a comprehensive review by Jadassohn in 1904, little was heard of the systemic features of the disease until in 1924 Libman and Sacks published their famous description of four cases of non-bacterial endocarditis, two of which had the typical skin lesions of lupus. Neither they nor Gross (1932), who subsequently drew attention to the peculiar changes in the myocardium and the pericardium, appear to have been aware of Osler's contribution.

In 1941 Klemperer, Pollack, and Baehr (see Asboe-Hansen, 1954) reintroduced the term "fibrinoid degeneration," first mentioned by Neumann in 1880 and again used by Klinge in 1933, in describing the most significant finding in the hypersensitivity state. A year later these authors (1942a), under the title of "Diffuse Collagen Disease," introduced the concept that a fundamental alteration of the collagenous elements of connective tissue is responsible for the seemingly heterogeneous organ lesions of systemic lupus erythematosus and allied diseases. They never intended the term to be a diagnostic label but used it merely to stress the significance of connective-tissue involvement and encourage its study.

In 1948 Hargraves, Richmond, and Morton discovered the L.E. cell in the bone marrow of patients with systemic lupus, introducing not only a valuable diagnostic aid but a new and important facet of the problem comparable perhaps with Kaposi's contribution three-quarters of a century earlier.

Dr. William Osler began his Goulstonian Lectures to the Royal College of Physicians in 1885 as follows: "It is of use, from time to time, to take stock, so to speak, of our knowledge of a particular disease, to see exactly where we stand in regard to it, to inquire to what conclusions the accumulated facts seem to point, and to ascertain in what direction we may look for fruitful investigations in the future." It is in this spirit that I have undertaken the study of systemic lupus erythematosus, approaching it as a practising physician faced with a disease the interest and popularity of which are evidenced by the already vast and accumulating literature.

Morbid Anatomy

For a disease so widespread and so frequently deadly, the macroscopic findings at necropsy are often surprisingly meagre. Even histological changes may have to be sought diligently. The lesions are capricious in distribution and variable in their severity. Some viscera, however, are more prone to exhibit the distinctive features.

Heart.—The heart sometimes shows a very striking lesion—the well-known verrucose endocarditis of Libman and Sacks (1924). These authors drew attention to a form of endocarditis which was associated with "a negative blood culture, cutaneous petechiae and some form of renal disease." One of their cases had vegetations on the tricuspid and pulmonary valves. Characteristically the vegetations tend to spread away from the contact margins of the cusps; they may extend on to the adjacent mural endocardium (Fig. 2). These non-bacterial vegetations, granular,

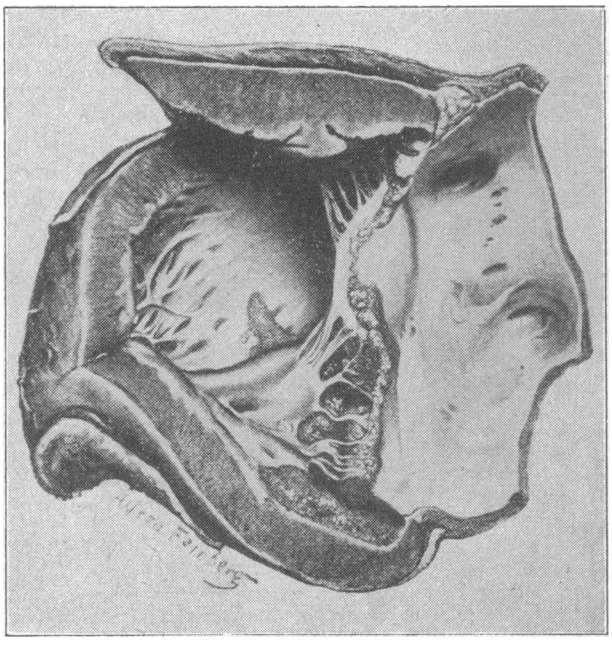

FIG. 2.—Characteristic vegetations in the mitral valve.

pink, or tawny in colour, and variable in size, are derived from pale thrombi deposited on an inflamed valve cusp. In the underlying cusp there is fibrinoid degeneration in the connective tissue with areas of necrosis which may become aggregated into the conglomerate masses of nuclear debris and basophilic fragments of cytoplasm known as haematoxyphil bodies. Myocarditis is found in about half of the cases and consists of foci of fibrinoid degeneration in the interstitial tissue, accompanied generally by a pronounced exudative reaction of leucocytes. Occasionally there may be myocardial infarction from arteritis and occlusion of a coronary vessel. Pericarditis is very frequent and an effusion may develop; this is rarely large and commonly takes the form of a fibrinous exudate which organizes to form adhesions.

Spleen.—This may be enlarged. The characteristic histological feature is the concentric fibrosis around the central arterioles (Fig. 3); the "onion skin" lesion. This appearance, however, is sometimes found in other and unrelated conditions.

Lung.—Pleurisy is common. There may be an effusion, usually serofibrinous and containing a few leucocytes. Organization naturally leads to adhesions. Terminal bronchopneumonia is common, but the lung also frequently exhibits a form of chronic interstitial pneumonitis whose similarity to other connective-tissue diseases depends upon a seemingly uniform and diffuse arteritis. Foldes (1946) and Baggenstoss (1952) have each described this condition, which may lead to collapse and, at times, to respiratory failure. The alveolar walls and perivascular connective tissues were the sites of low-grade inflammation with focal necrosis and alveolar thrombi leading to obliteration of the alveolar spaces.

Kidney.—Most cases of systemic lupus have some renal involvement. If severe, it is usually associated with a clinical picture of nephrosis. According to Harvey *et al.* (1954) there is a remarkable lack of correlation between the clinical and histological findings. Macroscopically the kidneys show no special feature. They may be swollen, with a few tiny petechiae on the surface.

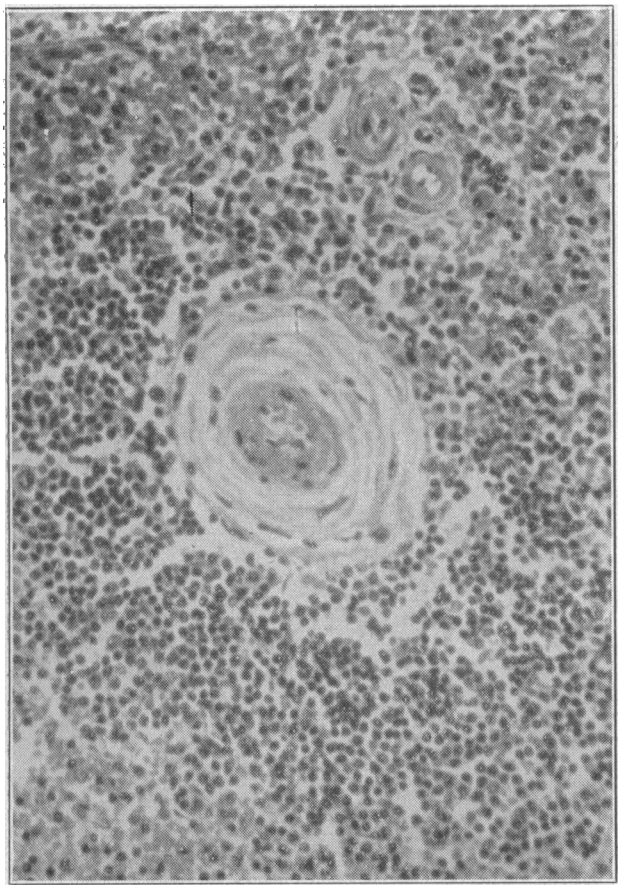

FIG. 3.—Concentric fibrosis around a central arteriole of the spleen. (×300.)

Microscopically the important lesions are found in the glomeruli and consist of haematoxyphil bodies (Fig. 4), focal necroses, and deposition of hyaline material in the tuft. The

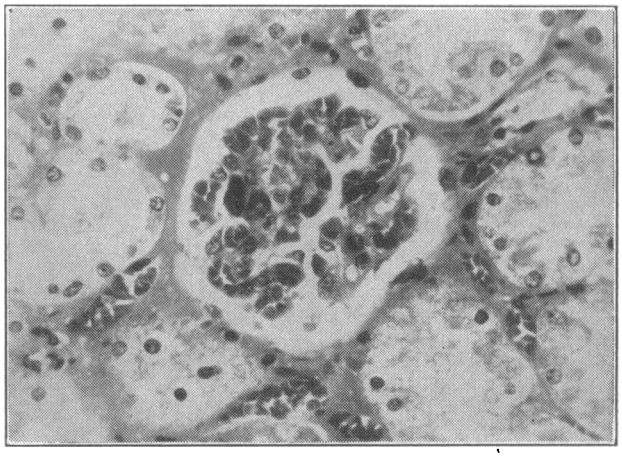

FIG. 4.—Kidney. Haematoxylin body in a glomerulus. (×350.)

haematoxyphil bodies, which stain purple with haematoxylin and eosin, are quite small and may be of any shape; occasionally large masses may arise from the fusion of several smaller bodies. They may occur as isolated bodies in the lumen of glomerular capillaries or in association with the second feature, focal areas of tuft necrosis. The third feature, capillary loop thickening, may affect the whole or part of the glomerular tuft. This thickening is a hyaline deposit which gives a positive histochemical test for protein. The hyaline material may clothe capillary loops, lie between them, or appear within their lumen. A point stressed by Smith (1955) is that the association of this hyaline protein material with haematoxyphil bodies is virtually diagnostic of systemic lupus. Histochemical studies strongly suggest that both haematoxyphil bodies and hyaline material result from breakdown of nucleoprotein.

The renal arterioles may show necrotic lesions; sometimes there is an arteritis resembling polyarteritis nodosa. There is indeed considerable overlapping of the renal histology in these so-called collagen diseases. One of our cases of systemic lupus (Case 31) showed at necropsy widespread lesions of polyarteritis nodosa. The kidneys shared in this arteritis but showed no wire-looping and no haematoxyphil bodies. On the other hand, I have seen a case of scleroderma which showed all the renal lesions regarded as typical of systemic lupus together with other visceral lesions of polyarteritis. Another example of this overlap occurs in the report by Gillespie and Poteliakhoff (1951) of a case of asthma with eosinophilia. Necropsy revealed an eosinophilic polyarteritis associated with Libman–Sacks endocarditis; there was no wire-looping of glomerular tufts.

Nervous System.—Lesions in the central nervous system appear to be predominantly related to vascular damage. Until recently there was no reference to involvement of the peripheral nerves. Bailey, Sayre, and Clark (1956) reported five cases of peripheral neuritis with necropsy in two. Focal degeneration of nerves and posterior root ganglia were demonstrated at necropsy with secondary diffuse degeneration of the posterior columns and, in one case only, vascular lesions. The authors consider that vascular changes alone do not account for the neuritis in all cases. One of our cases (Case 31) had peripheral neuritis, and sections showed a widespread polyarteritis involving many tissues, including the spinal cord (Fig. 5) and peripheral nerves (Fig. 6).

Skin.—In the skin there is a lymphocytic infiltration mainly around the blood vessels and sweat glands (Fig. 7).

The elastic and collagen fibres in the dermis show degenerative changes with the appearance of fibrinoid. Oedema at the junction of epithelium and connective tissue may lead to liquefaction necrosis of the basal layer of the epithelium with the formation of bullae.

Nature of Fibrinoid.—Much attention has been focused on fibrinoid material. Its presence in the lesions of systemic lupus, polyarteritis, and allied conditions has led to much speculation regarding some common basis for the so-called collagen diseases. The fact that these diseases share common pathological features does not justify the assumption of a common aetiology. The capacity of connective tissue to react to injury is limited to a few basic patterns ; it is therefore inevitable that the changes produced by these diseases should have some resemblance to each other.

Klemperer, Pollack, and Baehr (1942a) originally used the term " collagen disease " to focus attention on changes in the extracellular connective tissues in systemic lupus and scleroderma. Among those changes, alteration of collagen fibres and the presence of fibrinoid, believed to derive from altered collagen, were prominent. The term "collagen diseases," stressing as it does the changes in a particular fibrous protein and ignoring those in other connective-tissue elements, must therefore be used only as Klemperer *et al.* intended—to draw attention to the importance of the connective tissues as the site of morbid changes in these diseases and not to imply their aetiological or pathogenetic identity.

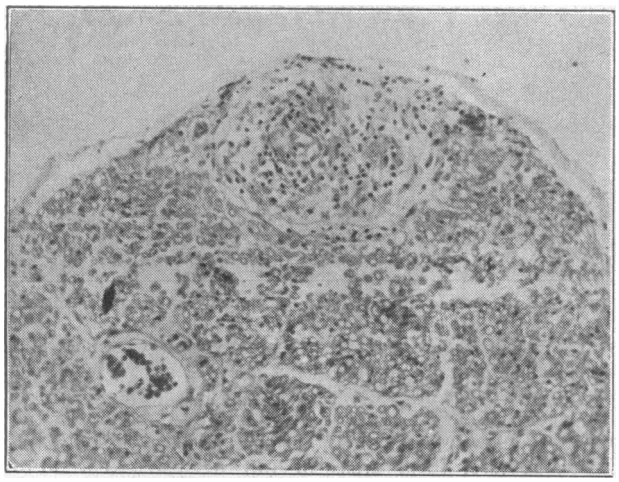

FIG. 5.—An acute arteriolitis in one of the anterior roots of the spinal cord. (×150.)

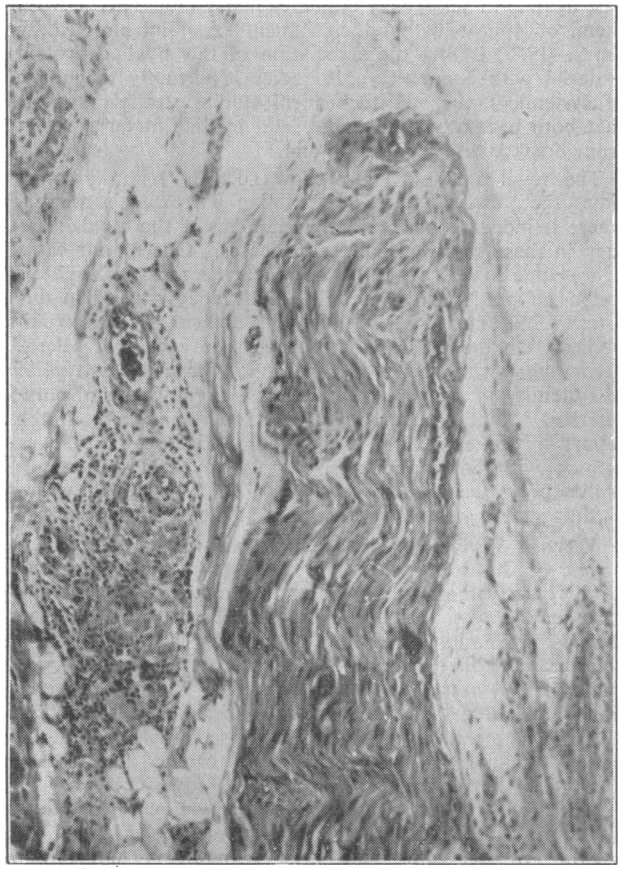

FIG. 6.—Showing an arteriolitis in a vessel in the sciatic nerve. (×110.) The arteriolitis is to the left of a nerve bundle.

Clinical Pathology

The clinical laboratory plays an essential part in the diagnosis and management of patients suffering from S.L.E. Most of the abnormalities are well documented ; I shall therefore refer only to those of particular clinical importance or of controversial significance.

Anaemia is common, typically of the normocytic, normochromic type, and of moderate degree ; it usually improves as the disease is controlled by therapy. Since we are dealing mainly with women whose iron balance is frequently precarious, iron deficiency may also be present at any stage, but particularly in patients who have passed through a long period of rheumatoid arthritis. In the quieter phases parenteral iron may relieve the deficiency ; it is less effective in the active stages. Both types of response are exemplified in Case 33.

Case 33.—A woman, who developed rheumatoid arthritis at 46, was first seen six years later. She had severe arthritis with a haemoglobin of 69%. After intravenous iron the haemoglobin rose to 79%, with disappearance of slight microcytosis and central pallor. Later she relapsed, her haemoglobin fell to 48%, and L.E. cells were found ; the red cells were now normal in size and staining. The introduction of cortisone was followed by improvement in the general condition and in the haemoglobin level, which reached 90% in three months.

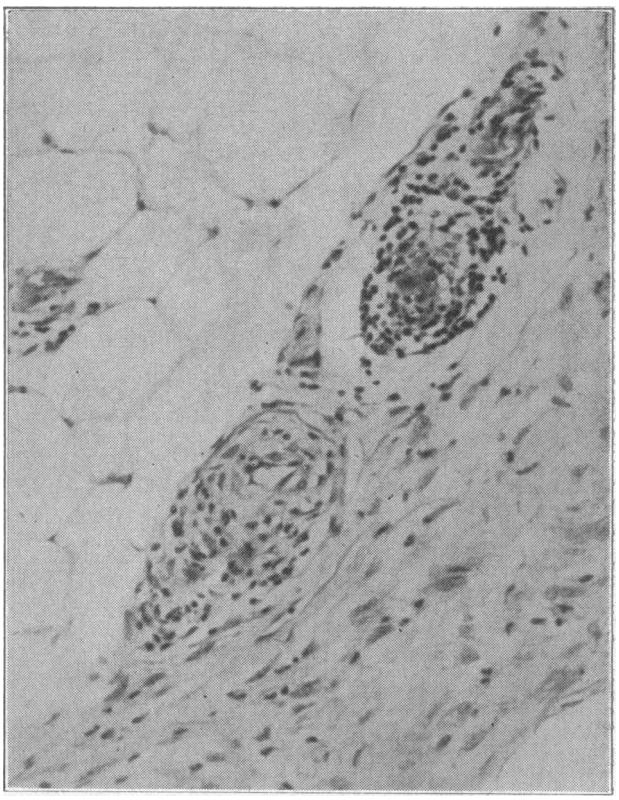

FIG. 7.—Biopsy showing lymphocytic infiltration around vessels in the deep part of the dermis. (×210.)

Anaemia was present at some time in every one of our cases. During the benign phases normal haemoglobin levels were sometimes found, particularly when iron deficiency has been relieved. It invariably accompanied relapse. I regard the absence of anaemia as a favourable portent, even when the clinical picture points to deterioration.

Case 38.—A woman developed a vague febrile illness after dental extraction, thought at first to be subacute bacterial endocarditis. Eventually L.E. cells were discovered. Despite constitutional upset and severe Raynaud's phenomenon necessitating bilateral cervical sympathectomy, the haemoglobin was only reduced on one of many estimations. Three and a half years later she was in good general health and improving steadily. Her haemoglobin was 102% and L.E. cells were not present.

The genesis of this normocytic, normochromic anaemia is obscure. We find no regular or significant abnormality in the sternal marrow. Hypoplasia is reported, but the diagnosis of this from examination of aspirated marrow is notoriously unreliable. The fact that the red-cell count may become normal during steroid therapy, that the marrow can respond to the development of haemolytic anaemia by gross hyperplasia, and that, in the analogous refractory anaemia of rheumatoid disease, the count can be raised to normal by giving cobalt, suggest defective regulation of haemopoiesis as an explanation rather than a specific deficiency or depression by hypothetical toxins.

Overt haemolysis is not usually an important feature, though in the more acute phases excessive red-cell destruction, recognizable only by shortening of the life-span of transfused erythrocytes, may be of clinical significance and analogous to that sometimes found in advanced renal failure and malignant disease.

Frank haemolytic anaemia is a well-recognized, if uncommon, manifestation, and may be the presenting feature. Splenectomy for the relief of "idiopathic" acquired haemolytic anaemia has sometimes (Dameshek, 1955) been followed by widespread evidence of systemic lupus.

The haemolytic anaemia has been attributed to hypersplenism, which was defined by the late Sir Lionel Whitby (Hayhoe and Whitby, 1955) as "the state in which an enlarged and overactive spleen is primarily responsible for the development of neutropenia, anaemia, or thrombocytopenia or a combination of these cytopenias." Any other possible cause should be carefully excluded before falling back on this explanation; such another cause, red-cell antibody, can be revealed by the Coombs test in S.L.E. Furthermore, Dameshek (1955), who has nurtured the concept of hypersplenism, declares that "an all-important feature of hypersplenism is that splenectomy shall result in the correction of the cytopenia." In very few reported cases has it done so, and our experience accords with that of Chertkow and Dacie (1956), who have treated various types of auto-immune haemolytic anaemia and report that steroid therapy is more effective than splenectomy in arresting haemolysis.

The white-cell count is frequently low. Michael *et al.* (1951) found a leucopenia at some time in 68 of 111 cases. Seven out of the 12 of our patients, who had five or more counts performed, showed levels below 5,000 at some time. On the other hand, several had, in the absence of infection, a leucocytosis which persisted during clinical remission. At the time when L.E. cells were found, only 17 of 37 of our cases showed leucopenia. The importance of leucopenia is sometimes overstressed, and a normal or raised white count in no way invalidates the diagnosis.

Gross thrombocytopenia has occasionally been reported and lesser degrees of platelet depression are fairly common, though probably without clinical significance. Michael *et al.* (1951) found a count below 150,000 in about half of the 83 patients examined. Gross haemorrhagic manifestations may usher in the disease, and in any case of "idiopathic" thrombocytopenic purpura L.E. cells must be looked for. While remission of the purpura has usually followed removal of the spleen, generalization of the systemic lupus has sometimes seemed to be precipitated by the operation (Dameshek and Reeves, 1956).

Case 31.—A woman of 39 suffered from a cutaneous anaphylactoid purpura for eight years, with two episodes of abdominal pain and bloody diarrhoea, before the emergence of a dusky red facial rash followed by peripheral neuropathy, the finding of L.E. cells, and a positive skin biopsy established the diagnosis.

This case raises the question whether renal failure, which the textbooks tell us is the only dangerous complication of anaphylactoid purpura, is not in fact a later manifestation of systemic lupus.

The sedimentation rate is usually very rapid and remains high during remissions. It exceeded 50 mm. in 1 hour in 38 of 42 of our cases at the time when L.E. cells were first found.

Serum protein changes are usual, with reduction or reversal of the albumin/globulin ratio. Electrophoresis shows a fall in albumin with sometimes a slight rise in α_2- and usually a big rise in γ-globulin. These changes are in no way specific and are so frequent in rheumatoid disease as to be valueless for distinguishing cases of systemic lupus. In a patient without rheumatic symptoms this electrophoretic pattern would be hardly more suggestive of lupus than a very high sedimentation rate.

The Rose test was positive in 20 out of 25 of our patients. The fact that this test is usually done when the patient has joint symptoms may explain this high proportion. It was, however, also positive in two patients, one of whom had only extremely slight and vague aches and pains and the other had none at all. Hess (1957), who reviews the literature, reports an overall figure of 46% of positive results in systemic lupus. She also draws attention to the close association with joint involvement.

Patients with S.L.E. seem prone to form abnormal plasma proteins of the antibody type. These give rise to a variety of clinical phenomena, the commonest being the biological false-positive test for syphilis. A positive reaction was found in 44% of cases by Montgomery and McCreight (1949) by repeated testing. In our series one test only was performed and 1 out of 14 gave a positive result. Most interesting are those apparently healthy people who give a persisting false-positive reaction. Moore and Lutz (1955) and Moore (1956) have reported 148 such cases followed for from 1 to 20 years. Ten have developed proved S.L.E.; in 45 this is strongly suspected; 13 others show either rheumatoid features or are undiagnosed with a bizarre type of illness. Thus almost half the cases have already developed an illness of the systemic lupus type.

At the Royal National Hospital the Berger 2 modification of the Kahn reaction is performed upon all new in-patients. The records since 1950 contain 25 patients with unexplained positive tests. All were among the 2,100 diagnosed as having rheumatoid arthritis; not one was found in the 990 patients with other chronic rheumatic diseases. This is a statistically significant difference. The average sedimentation rate of the sero-positive cases was 9 mm. in 1 hour higher than that of a random sample of 300 sero-negatives: we shall follow the future of these cases with great interest.

Other abnormal proteins occasionally reported include circulating anticoagulants (Frick, 1955), cold agglutinins (Gold and Gowing, 1955), and cryoglobulins (Barr *et al.*, 1950). Frequent reactions after blood transfusion and the development of multiple antibodies are reported. Nine of our patients received blood, three on several occasions. Apart from slight pyrexia, none showed reaction in the ordinary sense of rigor, collapse, or haemolysis. One case of haemolytic anaemia had many transfusions without incident, though the effect on her haemoglobin was very transient.

The L.E. cell phenomenon (Hargraves *et al.*, 1948) is now widely used as a diagnostic test. Many techniques have been evolved, the essence of the test remaining the same—namely, the lysis and ingestion of dead nuclear material by intact white cells, usually polymorphs, under the influence of a factor present in the serum in systemic lupus, with the production of a characteristic bloated cell. The test is negative in a small proportion, probably 5–10% (Haserick, 1951)

of undoubted cases of S.L.E. False positives are very rare. They have been reported in severe drug reactions, particularly to penicillin (Walsh and Zimmerman, 1953). I suspect that some cases at least reflect insufficiently strict criteria for identification, and in others perusal of the notes shows that clinical features, very suggestive of the early stages of systemic lupus, were present before the allegedly offending drug was given. Many "false-positive" reactions stem from failure to recognize how chronic and how restricted a condition systemic lupus can be: it is the authors' view of the natural history of the disease that is false and not the test. From a practical point of view, I feel that the finding of L.E. cells is diagnostic of S.L.E. in the broad sense; it does not at once imply a severe illness running a malignant course. Their absence, however, does not exclude the diagnosis, nor does their persistence during remissions, either natural or induced, affect the prognosis.

Natural History

The term "disseminated," which Kaposi used in 1875 to indicate extension of the rash and the development of constitutional symptoms, is open to objection and should be abandoned. It implies the scattering of the seeds of disease from a local focus, as in disseminated miliary tuberculosis. It is a fundamental feature of our present views of systemic lupus that the disease exhibits a widespread and simultaneous involvement of the connective tissues as a whole. "Systemic" epitomizes this idea.

The distinction between acute, subacute, and chronic seems to me both arbitrary and artificial in such a protean disease. Systemic lupus is in some ways analogous to hypertension, which may be an observation without symptoms, a benign clinical state, or a malignant illness. I would like to suggest that systemic lupus may usefully be described as "benign" or "malignant."

The recognition of the benign or malignant phase is essentially a matter of clinical judgment, resting upon a balanced assessment of the case as a whole and not on any single symptom, sign, or laboratory finding. Features suggesting the malignant phase are severe constitutional disturbance, with weight loss and fever, serous membrane involvement, falling haemoglobin level, or frank blood dyscrasia; affection of the central nervous system; or persistent renal disease (Table II). The benign phase commonly declares itself as an arthritis of the rheumatoid type, as chronic discoid lupus, or perhaps as a false-positive Wassermann reaction. The coexistence of chronic skin and joint manifestations does not necessarily imply a malignant course, though it does suggest that the patient is near to the precipice.

Mode of Onset.—Malaise with loss of weight and an irregular fever, joint pains, and skin lesions, either together or independently, are perhaps the commonest initial complaints. Such symptoms may disappear spontaneously, only to recur later with increased severity. Evidence of dysfunction in any system may, however, be the presenting feature.

Table III indicates the mode of presentation in our 49 cases.

Age, Sex, and Race.—In most of the larger series (Jessar *et al.*, 1953; Dubois, 1956; Shearn and Pirofsky, 1952; Harvey *et al.*, 1954) females constitute between 80 and 90% of the total. There were 39 women in our 49 cases. In 25 the onset occurred between the ages of 30 and 50. Brunsting *et al.* (1950) claims that females with red hair and light-sensitive complexions are more susceptible. On the other hand, the pigmented skin of the negro does not protect (Shearn and Pirofsky, 1952).

Family History.—Several instances of familial occurrence are reported, notably by Brunsting *et al.* (1950) and Shearn and Pirofsky (1952), and both Haserick (1951) and Jessar *et al.* (1953) have found patients with systemic lupus in families in which other members have chronic discoid lupus and rheumatoid arthritis.

Past History.—Most of the patients in our series had excellent health before developing the disease. In the few instances in which recurrent chest infections were reported, these may well have been early manifestations. The possible influence of gold will be discussed fully later.

Incidence.—Undoubtedly many cases of systemic lupus have gone unrecognized in the past. In 1894 Morris stoutly maintained that no dermatologist in this country had met a patient with Kaposi's disease. Twenty years ago a case of systemic lupus was a great rarity in the medical wards. Today it seems more common than rheumatic fever. Dubois (1953) reported only 11 patients diagnosed in the Los Angeles County Hospital during 1948 and 1949, but 44 in the next two years. This increase, coinciding with the development of a new diagnostic test, need not indicate a change in incidence. Nevertheless, many observers are convinced that the disease is becoming more common.

TABLE II.—*Course of the Disease*

Malignant course from onset	11 (4 male, 7 female)
Benign course at first	38 (6 „ 32 „)
Subsequent course of the 38 cases initially benign:	
Have entered the malignant phase	22
Have so far remained benign	14
Developed another benign feature (chronic arthritis following discoid lupus)	2

TABLE III.—*Mode of Onset in 49 Cases (10 men and 39 women)*

Chronic arthritis	29	Neuropathy	1
Arthralgia	10	Pleurisy	1
General illness	6	Raynaud's phenomenon	1
Rash	4		

The onset of arthralgia was accompanied in two patients by general illness and in one by neuropathy. The average age of onset of the earliest features was 43 years (range 13–69).

Prognosis

"The essence of prognosis," says Hippocrates in the introduction to *The Prognostics*, lies in recognizing "the nature of the affection." The more we study the natural history of this disease with its infinite variations the less inclined are we to foretell the future. Personal experience and the facts of contemporary history combine to paint a sombre picture. Approximately 80% of patients in the series reported have died within five years of coming under supervision; death within one year is not uncommon (Table IV).

TABLE IV.—*Prognosis of Benign and Malignant Phases*

11 *cases initially malignant:*
- 4 died after 9 months to 5 years, average 2 years.
- 7 alive after 6 months to 7 years, average 2½ years.

38 *cases initially benign:*
- 16 remained benign for 1 to 21 years. Average 9½ years. (1 died of lymphosarcoma.)
- 22 became malignant after 1 to 25 years, average 6½ years.
  - 8 died after 6 months to 5 years, average 3 years.
  - 14 alive after 6 months to 5 years, average 2 years.

Perhaps the most accurate picture emerges from a comparison of two large series. The first, by Jessar *et al.* (1953) includes 103 patients followed up before the era of the L.E. cell and hormone therapy; their starting-point was the onset of the disease. In the second series of Harvey *et al.* (1954) 99 patients, 75 of whom were treated with hormones, were followed between 1949 and 1953; their starting-point was the first diagnosis. Both report an unfavourable prognosis. Of Jessar's patients, 38% were alive at the end of four years as compared with 52% of Harvey's. Of all the survivors in any one year about 10% died in the subsequent 12 months. To attribute this difference to hormone treatment is tempting but facile; no comparable figures exist for untreated patients in the same era of diagnosis, nor could such a control series be justified.

Dubois (1956) is more encouraging. In an earlier series the median duration of life of 59 untreated or inadequately treated patients was 24 months. In the recent series of 138 patients adequately treated and ill for 24 months or more, less than 10% have died. Interpreting these figures with caution, hormone treatment does appear to prolong expectancy of life. The more effective treatment of secondary infection by antibiotics under a steroid cover may also be a factor.

[*The second lecture, with a list of references, will appear in our next issue.*]