RES MEDICA
Journal of the Royal Medical Society

Systemic Lupus Erythematosus

R. McD. Fox

Abstract
A Review based on a Dissertation read before the Society on Friday. 29th November, 1964.

Not even the most enthusiastic student of systemic lupus erythematosus (SLE) would claim that it is a common disease, but it is an interesting one not only because it can mimic almost every other known disease, but also because it combines many of the features of commoner but equally ill-understood connective tissue disorders. Among these are rheumatic fever and rheumatoid arthritis. Another impetus to research is the nature of the victims— most of these unfortunate people are girls and young women.

ISSN: 2051-7580 (Online) ISSN: 0482-3206 (Print)
Res Medica is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

Res Medica, Spring 1965, 4(4): 12-14
doi: 10.2218/resmedica.v4i4.436

Systemic Lupus Erythematosus

A Review based on a Dissertation read before the Society on Friday, 29th November, 1964

R. McD. FOX

Not even the most enthusiastic student of systemic lupus erythematosus (SLE) would claim that it is a common disease, but it is an interesting one not only because it can mimic almost every other known disease, but also because it combines many of the features of commoner but equally ill-understood connective tissue disorders. Among these are rheumatic fever and rheumatoid arthritis. Another impetus to research is the nature of the victims—most of these unfortunate people are girls and young women.

SLE can present in many ways, but most commonly the patient's first complaint is of fever, joint pains, malaise or of the rash which gave the disease its name. But the organs most severely affected are the heart and kidneys, and in the acute attack the patient may die of cardiac or renal failure. More commonly, however, the disease progresses in a series of remissions and exacerbations, and even in the untreated patient it may be several years before death ensues.

Recently-developed techniques have shown that the relatively benign skin condition, discoid lupus (a slowly expanding rash which appears in areas exposed to sunlight), is a manifestation of the same pathological process which leads to the malignant systemic condition. About 50% of patients with this fairly common condition eventually develop some of the clinical or laboratory features of systemic lupus.

DIAGNOSIS :

When one is faced with systemic lupus in the differential diagnosis, some simple tests may be helpful. Often protein is found in the urine. The cellular elements of the blood are usually depressed, and there may be evidence of haemolysis. (In 30% of cases the Coombs Test is positive). The erythrocyte sedimentation rate is raised. LE cells may be seen in the peripheral blood. The plasma gamma-globulin is much in excess of the normal 10 - 15% of the total protein, and electrophoresis shows a peak in the low-molecular-weight division of the gamma-globulins.

PATHOLOGY :

The tissue damage appears to be related to changes in the connective tissue. Many of the bizarre signs and symptoms of SLE are caused by abnormalities in small blood vessels. The basement membranes of the renal glomeruli are also liable to severe damage, which accounts for the proteinuria almost invariably found at some stage of the disease.

There are four distinctive features which may be seen in the lesions :

(1) Degeneration of connective tissue, with deposition of fibrin-like material.
(2) Infiltration with lymphocytes and plasma cells.
(3) Aggregations of material with the staining properties of nucleoprotein (haematoxylin bodies).
(4) Polymorphs with similar material in their cytoplasm (LE cells).

A major advance in the knowledge of SLE was the discovery that these patients often have a positive Wassermann Reaction in the absence of spirochaetal infection. This Biological False Positive Test seemed to indicate the presence of abnormal antibodies, and led to the discovery that the plasma of these patients contains antibodies to a number of organs including heart, kidney and thyroid. There were also antibodies to specific cells, including leukocytes, erythrocytes and platelets, and to subcellular elements like mitochondria, microsomes and DNA. The obvious deduction was that the tissue damage is caused by these abnormal antibodies.

By immuno-fluorescent techniques it was shown that abnormal quantities of gamma-globulin are present in the lesions, together with complement, a substance often associated with antibody-antigen reactions. The fibrinoid material in the connective tissue was shown to consist largely of gamma-globulin. The nuclear material of haematoxylin bodies and LE cells was shown to be combined with gamma-globulin. Attention was drawn to the presence of lymphocytes and plasma cells in the lesions. Both of these are believed to synthesise gamma-globulin.

PATHOGENESIS :

All this seemed irrefutable evidence that antibody-antigen reactions were occurring at these sites.

The most celebrated attempt to explain these immunological phenomena was that of Sir Macfarlane Burnet. He suggested that a cancer-like mutation may occur in an immunologically active cell so that it and its progeny (which he likes to call a 'forbidden clone') synthesise abnormal antibodies. These antibodies react with the body's own tissues. Burnet produced histological evidence to support his theory that the original change occurs in the thymus gland.

The evidence for Burnet's theory rests largely on the experimental condition, Runt Disease. This is produced by suppressing the immune mechanism of an animal by means of drugs or radiation, so that it no longer rejects foreign proteins. When immunologically active cells from another animal are injected, these synthesise antibodies against the tissues of the host. So an artificial 'clone' of cells is produced, reproducing the circumstances envisaged by Burnet. This disease unfortunately bears little resemblance to the naturally occurring disorders.

Many objections to Burnet's theory have been raised. If the connective tissue disorders are caused by abnormal antibodies, one might anticipate that symptoms could be induced in a normal subject by giving him gamma-globulin from a patient with SLE. Again one might expect the babies of mothers with SLE to be affected by the transplacental passage of antibodies. These phenomena do not normally occur in SLE.

Recent research on acute rheumatism and acute nephritis, two of the commonest diseases characterised by the presence of tissue-specific antibodies, has produced strong evidence of a different aetiology. Both these diseases are associated with preceding streptococcal infections. Kaplan has demonstrated that the Group A beta-haemolytic streptococci associated with acute rheumatism have constituents antigenically identical to substances in the sarcolemma of human heart muscle. He suggests that the antibodies produced in response to streptococcal infection may subsequently, in some individuals, attack the sarcolemma. Using similar techniques Markowitz and Lange showed cross-antigenicity between Type 12 Group A beta-haemolytic streptococci and glomerular basement membrane. This could account for the pathology of acute glomerulonephritis.

Although this evidence is striking it may not be relevant to disorders like SLE and rheum-

atoid arthritis. Rheumatic fever and acute nephritis are unique in being associated with preceding bacterial infections with specific organisms. Nevertheless, these results prompted Stevens to suggest that SLE too is a disease of cross-antigenicity. He deduced that the organism responsible was likely to be a commensal. In particular he incriminated an organism usually commensal in women of child-bearing age—the vaginal lactobacillus. No experimental evidence has been produced in support of this hypothesis.

Another setback for the 'forbidden clone' school of thought was the discovery that autoantibodies are a feature of many forms of tissue damage. For example, antibodies to liver are sometimes found for a short time in the course of infective hepatitis. Antibodies to heart can be demonstrated after myocardial infarction, and antibodies to thyroid after thyroidectomies. It seemed possible that the production of small amounts of autoantibody might be a normal sequel to tissue injury.

Richardson suggested that in SLE, as in infective hepatitis, a virus might be responsible for the antigenic changes. However, it seems unlikely that a virus alone could be responsible for the changes of SLE. Recent work on the normal response to tissue injury prompted Weissmann to suggest that connective tissue disorders might be the result of an inadequate response to cellular injury. He incriminates the subcellular organelle, the lysosome. Lysosomes are microscopic intracellular vesicles which contain proteolytic enzymes. Damage to the fragile lysosomal envelope causes the release of these enzymes, which denature surrounding proteins. The changes in the structure of the proteins renders them antigenic, and antibodies are synthesised in response to this stimulus. Weissmann believes that in patients with connective tissue disorders, lysosomes are abnormally fragile. He has demonstrated this *in vitro* and *in vivo*. The lysosomal envelope is strengthened by corticosteroids and antimalarials (such as chloroquine) and made more fragile by progesterone and certain oestrogens. Corticosteroids and antimalarials are valuable in the control of connective tissue diseases; in SLE exacerbations often occur in the second half of the menstrual cycle.

Any cellular damage results in the release of lysosomes, but in patients with connective tissue disorders widespread denaturation occurs because of an inability to stabilise the lysosomal membranes.

Much of this is speculation, but the lysosomal theory offers an attractive explanation for many of the features of SLE. If the enzymes were released directly into the bloodstream, as they would be if, say, polymorphs were involved, they would be likely to act mainly upon the cardiovascular system and on organs like the kidney. Connective tissue ground substance would be particularly susceptible because it has no protective membrane. The damage caused by the enzymes might result in the further release of lysosomes, so perpetuating the disease. The original cell injury could be caused by any harmful stimulus sufficient to interrupt the cell membrane. This could include the action of bacteria, viruses, ultraviolet light, and toxic drugs. Such agents as these could also be responsible for exacerbations.

TREATMENT:

The most valuable drugs in SLE are the corticosteroids, but the antimalarials and salicylates are useful, particularly during remissions. Some clinicians use cytotoxic drugs to reduce antibody synthesis, but their value is not established. Thymectomy has been tried, with disappointing results. Splenectomy may be necessary in cases of severe haemolytic anaemia.

SUMMARY:

The actiology of SLE is still unknown, but there is some evidence that the primary defect is an abnormal response to tissue injury.

I would like to thank Dr. D. L. Gardner for his help in the preparation of this article.

REFERENCES

BURNET, F. M. (1959). Clonal Selection Theory of Acquired Immunity. Nashville.

KAPLAN, M. H., et al. New Engl. J. Med. 1964, 271, 637.

MARKOWITZ, A.S., LANGE, C. F. J. Immunol. 1964, 92, 565.

RICHARDSON, Sir J. (1963). Connective Tissue Disorders. Blackwell.

STEVENS, K. (1964). Lancet ii, 506.

WEISSMANN, G. (1964). Lancet ii, 1373.