SOME OBSERVATIONS ON THE PATHOGENESIS OF SYSTEMIC LUPUS ERYTHEMATOSUS

STEPHEN C. GOLD, M.D., M.R.C.P.

The exact mechanism involved in the mesenchymal tissue reactions occurring in collagen diseases in general and systemic lupus erythematosus in particular is speculative. The term “fibrinoid” was originally coined by Neumann who described it in serous inflammations of mucous, synovial and endothelial surfaces. It was originally postulated that “fibrinoid” changes of collagen noted a sensitivity reaction as it was seen following the Arthus phenomenon. As a result one finds that the appearance of such changes were always interpreted as being the results of such a sensitivity reaction (Gerlach (1), Klinge (8, 9)). Subsequently it appeared that these changes are nonspecific and merely indicate tissue damage; thus “fibrinoid” changes have been seen after squeezing the skin, at the base of a peptic ulcer, after prolonged passive hyperaemia and in hypostatic conditions.

It has been postulated that the tissue changes of systemic lupus erythematosus must represent damage by either a toxin, enzyme or possibly an antibody. A constant pathological finding is hyper-γ-globulinaemia and it is probable that the increase of γ-globulin is associated with increased, either quantitatively or qualitatively, antibody. On the premise that a factor in this globulin fraction of serum could be responsible for the observed tissue changes it was decided, by means of intracutaneous injection of serum from patients in an acute phase of systemic lupus erythematosus into the skin of rabbits, to discover if any comparable changes would occur therein. If an agent which might affect healthy collagen in either a toxic manner or by enzymic processes was present in such a serum, it is possible that detectable changes in the animals’ connective tissue might develop. Accordingly, serum from three acute patients was injected into three sites on the flank of three separate rabbits; the injected areas were excised after six, twelve and twenty-four hours respectively and, along with control sites, subjected to histological study. Sections were stained by Haematoxylin and Eosin and the period acid/Schiff methods. All tissues examined, when compared with the control areas, showed no points of difference—there was no suggestion of “fibrinoid” change of collagen or of metachromasia of ground substance. It is probable therefore, that so far as rabbits’ connective tissue is concerned, there is no factor in the serum of patients with acute systemic lupus erythematosus which affects dermal collagen to produce “fibrinoid” or other changes.

The next step to take was to study the effect of patients’ serum on normal human skin. It was thought, however, that to inject serum of such a nature
into healthy persons might be courting disaster and the following scheme was devised. Fresh skin obtained at surgical operations from young adults was cut into centimetre squares, superfluous fat was removed and these small pieces were immersed in the particular serum. The specimens were kept at 37°C and were removed from the incubator for fixing and sectioning, after six, twelve and twenty-four hours respectively. These tissues were studied in the same manner as previously and again, when compared with controls, no histological changes were apparent.

The negative findings of these experiments will probably discount the observed changes being due either to a toxin or an enzyme for it is probable that had such a process occurred evidence would appear in one or both the above experiments. Should the changes be the result of an antibody/antigen reaction occurring in fixed tissues, particularly should this antibody be an auto-antibody, one would, of course, not expect to see changes develop in the above experiments.

The presence of auto-antibodies in systemic lupus erythematosus has been described by Zoutendyk and Gear (12, 13) and Marshall et al. (10). These workers have commented on the frequency with which the Coombs’ test was positive in the blood of these patients, while Gold (2) produced some evidence correlating red cell sensitization with L.E. cell formation and, furthermore, remarked on an occasional high degree of cold auto-agglutination.

There is thus strong evidence that patients severely ill with the systemic disease may show auto-antibody formation. Although the erythrocyte is an inert cell, while the leukocyte is viable, there is much to suggest that the L.E. cell phenomenon is also one of auto-sensitization. According to observations made with a phase-contrast microscope (Smith (11)) the following series of events can be seen during the formation of an L.E. cell:

One lobe of a polymorph becomes swollen, separates from the other lobes and is eventually extruded (this free lying nuclear lobe probably represents the haematoxylin body of Gross). A second polymorph may be seen to approach this extruded lobe and then to envelop it; in so doing the nuclear lobes of this second cell appear to become compressed around the apparently ingested body to give the characteristic “horseshoe” appearance. In fact, this body is not ingested but only enveloped for not infrequently it may be released and apparently expelled from this second leukocyte.

Such events can be correlated with observations on hematoxylin bodies by means of spectro-photometry. It has been shown that they contain nucleic acid and, by histochemical stains (Feulgen and methyl-green extinction), most of it is deoxyribose nucleic acid in a depolymerized state. This alteration is not due to anoxia and, furthermore, the material is not digested by ribose nuclease (Klemperer et al. (6, 7)). It seemed, from these observations that a disturbance of nucleic acid metabolism affecting the one lobe of a polymorph cell was the essential first stage in this process.

It is suggested that the L.E. phenomenon is a direct correlation of the Coombs’ test. The “L.E. factor” represents auto-antibody in patients’ serum and the cell nucleus is the antigen. It should be remembered that there is much evidence to support the concept of the “L.E. factor” being an antibody. Haserick et al.
(5) showed that it resided in the γ-globulin fraction and would disappear during remissions and he also (Haserick (3)) showed that it was destroyed by heating to 65°C but would persist for months if stored in a refrigerator. Antigenically it is a distinct fraction of γ-globulin (Haserick and Lewis (4)) and will stimulate production of a specific antibody if injected into the rabbit.

Fig. 1. Suggested mechanism of L.E. cell formation. a. Healthy polymorph in surrounding milieu of auto-antibody. b. One nuclear lobe has become swollen and stains abnormally. c. The swollen lobe is ejected from parent polymorph. d. Nuclear lobe becomes sensitized on its surface with auto-antibody. e. Second healthy polymorph is attracted to the sensitized body. f. Complete envelopment of sensitized body by second polymorph to produce L.E. cell.

The following hypothesis is presented to explain the means of L.E. cell formation:

1. Auto-antibodies present in patients' serum cause a reaction to occur between one lobe of a polymorph nucleus (as evidenced by swelling and alteration of staining reactions revealing depolymerization of nucleic acid).
2. This altered lobe is now foreign to the cell and becomes extruded.
3. The extruded lobe is in intimate contact with "L.E. factor" present in the surrounding serum and becomes sensitized by it (compare Coombs' test).
4. The sensitized mass is now coated with antibody and attracts a healthy polymorph towards itself.
5. The final envelopment of the hematoxylin body by the apparently healthy polymorph represents the final stage of reaction between the sensitized lobe (covered with antibody) and the healthy polymorph (representing the original antigen).

Whether this enveloping polymorph always rejects the ingested lobe is uncertain and whether it, as a result of this reaction, becomes affected to produce a subsequent hematoxylin body itself is speculative.
SUMMARY

There is no evidence of a toxic or enzymic factor present in patients' serum being responsible for the observed tissue changes in acute systemic lupus erythematosus.

There is indication that auto-antibodies are present and it is suggested that L.E. cell formation may be a process akin to red cell sensitization (positive Coombs' test).

REFERENCES