Inhibition of Leukocyte Agglutination by Serum from Patients with Systemic Lupus Erythematosus: A Manifestation of the L.E. Cell Phenomenon

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LEUKOCYTES maintained in suspension in vitro tend to undergo spontaneous agglutination due to cell death, lysis and nucleoprotein "clot" formation. Further study of this phenomenon was prompted by the observations that although in the presence of quinacrine and normal serum, leukocyte agglutination occurs regularly and is grossly complete after two hours incubation at 37 C, agglutination fails to occur in the presence of serum containing the L.E. cell factor. The possibility suggested itself that this might represent a macroscopic expression of the L.E. cell phenomenon—a test which could have practical applications in clinical diagnosis and might lead to increased insight into the mechanism of formation of L.E. cells.

The studies herein reported have been concerned with the biochemistry underlying the observed leukocyte-agglutination-inhibition (LAI) as well as the testing of this LAI reaction to determine its correlation with the L.E. cell phenomenon and its applicability as a clinical laboratory procedure.

MATERIALS AND METHODS

All tests were performed with a system consisting of serum and various modifying agents in the following proportions:

- Serum or other supporting media .................................................. 0.5 ml.
- Cell suspension (100,000-300,000/mm³) ......................................... 0.1 ml.
- Quinacrine or other modifying agent .............................................. 0.1 ml.
- Second modifying agent .................................................................. 0.1 ml.

Total volume .................................................................................. 0.8 ml.

Aqueous sodium ethyl mercuri thiosalicylate in a final concentration of 1:20,000 was added. This mixture was incubated in a glass tube at 37 C for 3 hours. In the biochemical studies, the composition of each of the ingredients of the mixture was varied in accordance with the plan of each experiment. These variations will, for the most part, be apparent in the descriptions of the experiments.

Serum protein fractions used in some of the experiments were prepared from normal and from L.E. sera by fractional precipitation with ammonium sulfate, by zone electrophoresis in a starch block, and by the method of Simkin et al.

Cell suspensions of human origin, whatever the cell type, were all prepared in similar manner from citrated venous blood. Donors were selected with the dual criteria of leukocytosis and rapid erythrocyte sedimentation in mind.

Red cells were allowed to separate out by gravity, and the plasma layer (containing mainly white cells and platelets) was withdrawn. The cells were separated from the

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INHIBITION OF LEUKOCYTE AGGLUTINATION

plasma by centrifugation at 1000 rpm for five minutes, and were washed three times with at least 10 volumes of physiologic saline solution. (Care must be taken not to centrifuge too fast during these washings, as rupture of the cells can lead to spontaneous agglutination.) After the third washing, the cells were re-suspended in sufficient volume of physiologic saline solution (containing 1/20,000 sodium ethyl mercuri thiosalicylate) to make the final leukocyte concentration between 100,000 and 300,000 per cubic millimeter. Leukocyte suspensions may be kept at 4 C. for as long as one week and remain usable.

Calf thymocyte suspensions were prepared by scraping a freshly cut surface of fresh calf thymus, suspending the scrapings in physiologic saline, and washing as for leukocytes.

In the clinical studies, the system employed is as follows:

Serum (or plasma) ........................................... 0.5 ml.
Cell suspension (human-leukemic or otherwise, 100-300,000/mm.)........... 0.1 ml.
Quinacrine hydrochloride (2 mg./ml. in 0.15 M phosphate buffer at pH 7.0) ................. 0.1 ml.
Sodium oxalate ................................................... 0.1 ml.

Tubes were gently agitated and were incubated at 37 C. for three hours. At the end of that time the tubes were examined for leukocyte agglutination which was scored as follows:

0. Completely homogeneous cloudy suspension after gentle agitation of tube.
1. Tiny shreds in otherwise homogeneous cloudy suspension.
2. Several larger fibrous masses in cloudy suspension.
3. Single large “clot” against cloudy background.

Tests were considered invalid unless a negative control (known normal serum) was at least grade 3. Grades 0 or 1 were considered as positive; grade 2 as doubtful and to be repeated. All determinations were done in duplicate.

L.E. cell tests were performed by a clotted blood technic. In the case of the particular sera studied in table 1, a 1/4 dilution of normal serum in saline still produced significant agglutination, while a 15/16 concentration of the same serum yielded no agglutination when the mixture contained 1/16 part of L.E. serum.

Similar experiments have been performed with all nonagglutinating L.E.
sera studied. In 25 of 32 such sera it was possible to demonstrate a leukocyte-agglutination-inhibiting (LAI) factor in titers varying from 1:2 to 1:32. Seven of the 32 sera failed to inhibit leukocyte agglutination when diluted to any extent by normal serum.

2. Importance of quinacrine in leukocyte agglutination. A series of experiments was undertaken to determine whether quinacrine is essential to leukocyte agglutination in the system described (table 2). It was found that agglutination occurred in the absence of quinacrine when cell suspensions were more than a few hours old, when they had been prepared by rapid centrifugation of white cells, when serum-cell mixtures were allowed to incubate overnight, or when calf thymocytes were employed. Such agglutination was not, however, always predictable. The presence of quinacrine in the incubating mixture insured maximal agglutination within a reasonable time.

Employing leukocyte-serum suspensions which did not agglutinate spontaneously in the absence of quinacrine, solutions of methylene blue, toluidine blue and methyl green were added in final concentrations of 0.1 to 0.4 mg./ml. Leukocyte agglutination did not occur with any of these basic dyes.

3. Importance of serum in leukocyte agglutination. If physiologic saline is substituted for normal serum in the standard leukocyte agglutination system, gross agglutination does not occur. The ability of serum to induce maximal agglutination cannot be reproduced satisfactorily by comparable concentrations of albumin or gamma globulin.

Smears have been made from masses of agglutinated leukocytes (fig. 1).

<table>
<thead>
<tr>
<th>Normal serum diluted with saline</th>
<th>Full Strength</th>
<th>1/2</th>
<th>1/4</th>
<th>1/8</th>
<th>1/16</th>
<th>1/32</th>
<th>1/64</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.E. serum (M.Fl.) diluted with normal serum</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Numbers refer to grades of agglutination.

Table 1.—Inhibition of Leukocyte Agglutination by L.E. Serum

Table 2.—Factors Influencing Leukocyte Agglutination

Favoring | Inhibiting
---|---
Storage of suspensions | Fresh suspensions
Rough handling during preparation (rapid centrifugation, high temperatures, physical trauma, etc.) | Gentle handling
Prolonged incubation | Short incubation
Heterologous cells | Homologous cells
Protein component of all human serum | L.E. cell factor
Quinacrine |
INHIBITION OF LEUKOCYTE AGGLUTINATION

Fig. 1.—Leukocyte agglutination in presence of normal serum and quinacrine. Leukocytes from patient with chronic lymphocytic leukemia. Smear made from agglutinated mass. Fixation, methyl alcohol. Stain, Feulgen. Magnification, 500 x.

a. Remnant of lysed nucleus merges into background of nucleoprotein fibrils.
b. Intact nuclei out of focus in thick preparation.

In these, intact cells are seen to be trapped in the meshes of a network of fine, interlacing fibers. This fibrillar network is Feulgen-positive, and hence of nuclear origin. Studies of leukocyte suspensions by phase-contrast microscopy show that prior to agglutination many cells “explode.” The nuclei of these lysed cells stretch into long fibrous strands which bind the remaining cells together.

Suspensions of leukocytes in the absence of serum undergo the same changes. Strands of fibrillar nuclear material may be seen in smears from these cells. However, it seems that these fibers lack the tensile strength necessary to produce a firm “clot.” Microscopically, small aggregates are seen, but these are not visible on gross inspection of the suspension.

4. Nature of alteration of nucleoprotein found after LAI by L.E. serum. Suspensions of normal leukocytes incubated with quinacrine in L.E. serum were centrifuged. Smears made from the sediment and stained by the Jenner-Giemsa method (fig. 2) showed striking changes involving almost all of the cell nuclei. These were swollen and homogeneous; chromatin patterns were no longer evident. Many cells were disrupted with only the swollen, distorted nuclei remaining. In other cells the cytoplasm was strikingly reminiscent of those seen in included bodies of L.E. cells and in the free “L.E. bodies” or “hematoxylin bodies” often seen in L.E. cell preparations.

Careful study of a large number of such smears failed to reveal any typical L.E. cells or rosette formation. These findings were in striking contrast to control preparations made from identical cell suspensions in identical L.E. sera, but without quinacrine. Such control smears showed the majority of
We are indebted to Drs. G. Godman and Arlene Deitch for these cytochemical analyses.


1. Lymphocyte nuclei in various stages of development into "L.E. bodies."

Cells to have normal nuclear structure. However, rosette formation occurred around fragments of altered nuclear material, and L.E. cells were always easily demonstrable.

Smears made from leukocyte suspensions in quinacrine and L.E. serum were subjected to cytochemical analysis. The obvious nuclear alterations were found to be identical with those of typical L.E. bodies.*

5. Agglutination of various cell types. Cell suspensions for study of leukocyte agglutination have been prepared from normal blood, and from blood from various disease states in which the white cells are quantitatively and qualitatively altered. Pathologic leukocytes from cases of myeloid metaplasia, "spent" polycythemia vera, chronic granulocytic leukemia, chronic lymphocytic leukemia, myeloblastic leukemia, monocytoid myeloblastic leukemia and lymphoblastic leukemia have been employed. All these cells behaved similarly, in normal serum as well as in L.E. serum, insofar as agglutination or inhibition of agglutination was concerned.

However, examination of smears made from various cell suspensions incubated in L.E. serum disclosed certain differences. Mature (or nearly mature) granulocytes and lymphocytes from various leukemic and leukemoid states uniformly showed nuclear swelling and homogenization, as seen in normal leukocytes (fig. 2). Blast cells and other immature leukocytes failed to show this change. These cells agglutinated in normal serum and failed to do so in L.E. serum, exactly as did more mature cell types, yet did not show the characteristic morphologic changes of LAI when studied by con-

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INHIBITION OF LEUKOCYTE AGGLUTINATION

ventional methods. Cytochemical measurements of blast cells which have been subjected to the LAI reaction have not yet been performed.

6. Inhibition of agglutination by deoxyribonuclease (DNA-ase) and its relationship to LAI. Addition of DNA-ase to the reaction mixture containing leukocytes, normal serum and quinacrine effectively prevented leukocyte agglutination. Smears made after incubation revealed morphologic changes quite distinct from those seen in the absence of DNA-ase. In place of the dense meshwork of interlacing nucleoprotein fibrils, only a few wisps of poorly staining fibrillar material remained. Many of the intact cells were shrunken and pyknotic. These smears were distinctly different, not only from those made from nucleoprotein "clots," but also from those made from leukocyte suspensions in quinacrine and L.E. serum.

DNA-ase is inactive in the absence of magnesium ions. Magnesium can be removed effectively from serum by the addition of sodium oxalate, which leads to the precipitation of MgC₂O₄. The addition of 0.1 ml. of 0.1 M Na₂C₂O₄ to the standard system containing leukocytes, normal serum, quinacrine and DNA-ase reversed the inhibition of agglutination by DNA-ase. Sodium oxalate had no effect, however, on LAI in the presence of L.E. serum.

In the course of these studies, a few human sera were found which did not exhibit the L.E. cell phenomenon, but which did not support leukocyte agglutination. Smears from suspensions of leukocytes in these sera bore striking resemblances to smears made in the presence of DNA-ase. When sodium oxalate was added to these sera, leukocyte agglutination occurred.

7. Effect of blood coagulation upon LAI. Blood serum and routinely prepared blood plasma (whether heparinized, oxalated or citrated) gave comparable results in the LAI system. Serum and plasma obtained from the same L.E. patient at the same time produced LAI to the same titer.

However, under certain circumstances, differences between plasma and serum from active L.E. patients could be demonstrated (table 3). Blood was drawn through a siliconized needle into a siliconized syringe. Nine milliliters of this blood were added immediately to 1 ml. of 3.8 per cent sodium citrate in a siliconized tube. Blood and anticoagulant were mixed by inversion and immediately centrifuged at 4 C. at 2500 rpm for 30 minutes. Recalcification of the resulting platelet-poor plasma produced clotting but virtually no prothrombin consumption after one hour.

A portion of the original blood specimen was allowed to clot in an ordinary glass tube. Serum obtained from this sample was compared in the LAI system with platelet-poor plasma prepared as described. The leukocyte suspension

<table>
<thead>
<tr>
<th>Reaction Mixture</th>
<th>Agglutination Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum + Platelet-poor plasma (see text for preparation)</td>
<td>Platelet-poor + quinacrine</td>
</tr>
</tbody>
</table>

Table 3.—Effect of Blood Coagulation on LAI.
used in this experiment was especially chosen to be extremely poor in platelets.

Under these conditions, a distinct difference between LAI activity of plasma and serum was apparent: serum showed complete inhibition of agglutination, while plasma failed to show any inhibition.

B. Clinical Studies

LAI tests have been performed during the period of this study on 1183 specimens of human serum. Simultaneous L.E. cell tests were performed on each sample of blood. The results of these tests are shown in table 4. Of 1183 LAI tests performed, 108 were positive. Ninety-five of these positive LAI tests were on bloods with positive L.E. cell tests. Only on 13 occasions was the LAI test reported as positive while the L.E. cell test was negative. One of these blood samples was from a patient who was later found to have systemic lupus, and whose subsequent L.E. cell tests were positive. Review of the L.E. cell preparations which had been reported as negative in this case showed a few suggestive “L.E. bodies” but no true L.E. cells.

These 1183 tests included 164 from 34 patients with clinically accepted systemic lupus. The L.E. cell tests in this group were positive 111 times (68 per cent) and negative 53 times (32 per cent). With one exception (see preceding paragraph) the negative tests were obtained in patients in clinical remission or in the stage of renal failure. In this group of 164 blood samples, the LAI test was positive 96 times (59 per cent) and negative 68 times (41 per cent). Fifty-two of the 68 negative tests were from the L.E.-cell-negative group; the remaining 16 showed weakly positive L.E. cell tests.

DISCUSSION

A. Mechanism of LAI

1. Relationship of LAI to the L.E. cell phenomenon. It has been established that the essential manifestation of the L.E. cell phenomenon is a peculiar alteration of desoxyribonucleoprotein. Early evidence suggested that the major alteration is a depolymerization of the nucleic acid moiety of this molecule; more recent studies would seem to indicate that the more important change is in the protein of DNA-protein. In either case, there can be little doubt that the affected nucleoprotein is drastically altered with regard to its physicochemical characteristics: the fact that it is recognizable by ordinary staining technics is sufficient evidence of that.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>L.E. Cells</th>
<th>LAI Negative</th>
<th>LAI Positive</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.E.</td>
<td>Negative</td>
<td>52</td>
<td>1</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>16</td>
<td>95</td>
<td>111</td>
</tr>
<tr>
<td>Total L.E.</td>
<td></td>
<td>68</td>
<td>96</td>
<td>164</td>
</tr>
<tr>
<td>Other</td>
<td>Negative</td>
<td>1007</td>
<td>12</td>
<td>1019</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total Control</td>
<td></td>
<td>1007</td>
<td>12</td>
<td>1019</td>
</tr>
</tbody>
</table>
Leukocyte agglutination, in the system studied herein, is also a phenomenon involving DNA-protein. Inhibition of such agglutination must be due to some alteration of the DNA-protein. When inhibition is brought about by L.E. serum—i.e., serum which is known to be capable of altering DNA-protein in a specific way—a relationship must be presumed to exist between the alteration which produces the L.E. cell phenomenon and the alteration which prevents agglutination.

Corroborative evidence of this relationship has been obtained from two independent sources. Cytochemical studies indicate that the nuclear changes of cells exposed to LAI are identical with DNA-protein changes found in typical L.E. cells. Clinical studies have shown such good correlation between LAI and the L.E. cell phenomenon when applied to a large number of unknown blood samples that a relationship must be presumed to exist on this basis alone.

The available evidence thus indicates that LAI is a manifestation of the same nucleoprotein alteration which characterizes the L.E. cell phenomenon. Hence, it can be said that LAI and the L.E. cell phenomenon both detect the same thing—the presence of a unique abnormal component of the plasma gamma globulins which has become known as the L.E. cell factor.

2. Does quinacrine inhibit the L.E. cell phenomenon? Quinacrine hydrochloride is a standard (though not an essential) ingredient in the LAI reaction mixture. If, as has just been shown, LAI can be equated with the L.E. cell phenomenon, it is apparent that quinacrine does not inhibit this phenomenon, but rather even enhances it.

These findings must now be reconciled with those of Dubois, to the effect that addition of quinacrine HC1 in concentrations above 20 mg./100 ml. to leukocytes suspended in L.E. serum effectively prevented the L.E. cell phenomenon. Concentrations of quinacrine employed in the present studies were substantially the same as those used by Dubois, so that this factor can be eliminated as a source of the discrepancy.

Microscopic study of these preparations has, it is true, shown a complete absence of true L.E. cells; it must be presumed that this is the basis for the presumed inhibition of the L.E. cell phenomenon. But the essential manifestation of the L.E. cell phenomenon, the nucleoprotein alteration, has been shown to have taken place to an extensive degree. A secondary manifestation, phagocytosis, is indeed inhibited in the presence of quinacrine. Whether this absence of phagocytosis is simply due to an absence of viable cells, or to some other more complicated mechanism, is not clear.

3. Leukocyte agglutination in normal serum. The nature of the processes which occur during leukocyte agglutination is also not clear. The element (or elements) of normal serum which are necessary for agglutination have not been definitely identified, nor has the manner in which they react with DNA-protein. This problem is now under study. Preliminary data suggest that the mucoprotein fraction (a2-globulin) is the active fraction of serum. It is possible that this material combines with DNA-protein, producing the long-chain, viscous material which forms the basis of the "nucleoprotein clot." When the precise nature of this compound is understood, it may be
possible to understand the way in which the L.E. cell factor interferes with its formation, and hence the nature of the combination between the L.E. cell factor and the DNA-protein.

B. Application of LAI to the Problem of the L.E. Cell

1. Is desoxyribonuclease (DNA-ase) a factor in the L.E. cell phenomenon? The original cytochemical data on the "hematoxylin bodies" of systemic lupus and on the L.E. cell suggested that depolymerization of DNA was a factor in the phenomenon. This gave rise to studies of DNA-ase in the disease and to a theory of the mechanism of the L.E. cell phenomenon in which DNA-ase had a central role.

Recent cytochemical studies by Godman, Deitch and Klemperer suggest a different interpretation—namely, that the protein moiety, rather than the DNA, of DNA-protein, is primarily affected by the L.E. cell phenomenon. These workers, using new technics, find no evidence of significant nucleic acid depolymerization. Obviously, if there is no depolymerization, the depolymerizing enzyme cannot play an important role.

The present studies offer some additional evidence favoring this latter view. Leukocyte agglutination is inhibited both by L.E. serum and by DNA-ase, but the two agents appear to act in quite different ways. The morphology of cells whose agglutination has been inhibited by L.E. serum is characteristic. The morphology of cells whose agglutination has been inhibited by DNA-ase shows no similarity. LAI by L.E. serum is not affected by magnesium-binding substances; such substances completely prevent the agglutination-inhibiting action of DNA-ase (whether of human or animal origin).

Available evidence thus suggests that DNA-ase activity is not an important element of LAI and hence, by extension, not importantly involved in the L.E. cell phenomenon.

2. Role of blood coagulation in the L.E. cell phenomenon. The importance of blood coagulation in the L.E. cell phenomenon has been stressed previously. It has been shown that some substance derived (at least partially) from blood platelets—either plasma thromboplastin or a precursor—is a necessary part of the L.E. cell reaction mixture. But since this work was completed, it has become known that damage to leukocytes is an essential precursor of the L.E. cell phenomenon. The question has been raised as to whether the element of leukocyte damage might in reality have been a controlling factor in the work which purported to show the effects of blood coagulation.

In the present studies, LAI activity of serum and of platelet-poor plasma was tested against a substrate of cells which were almost completely free of platelets. The results clearly demonstrated the importance of clotting in LAI, and hence in the L.E. cell phenomenon. In addition, the role of clotting can be further defined: its action is on the plasma, not on the cells.

Other applications of this method to research problems undoubtedly exist. It is currently being used as a source of "L.E. bodies" in large number for cytochemical examination. The varying behavior of abnormal leukocytes when subjected to this reaction may provide some clues as to the nature of the differences in their nucleoprotein structure.
INHIBITION OF LEUKOCYTE AGGLUTINATION

C. Clinical Application of LAI

At first glance, the LAI reaction offers considerable advantage over the standard methods of testing for L.E. cells. Multiple tests can be set up almost as easily as a single one. Interpretation is simple, and does not require a microscope or special cytologic training.

However, in its application, the test has fallen somewhat short of these expectations. Although its correlation with the L.E. cell test is excellent (table 4), it erred on the positive side in 12 cases out of 1019 (an incidence of 1.2 per cent) and on the negative side in 16 cases out of 111 (14 per cent). To translate into more general terms: if the LAI reaction were used as a substitute for the L.E. cell test, it might be expected to yield an occasional false positive result, and to miss about one case of systemic L.E. out of seven.

As an adjunct to the standard L.E. cell test, the LAI reaction serves a useful purpose by permitting rapid screening of large numbers of blood samples.

CONCLUSIONS AND SUMMARY

Dying leukocytes suspended in normal serum tend to agglutinate spontaneously into a firm "clot." This phenomenon is associated with cell lysis and the formation of long fibrous strands of DNA-protein. It seems likely that nuclear DNA-protein actually combines in some way with a fraction of the serum proteins (possibly mucoprotein).

Such leukocyte agglutination is inhibited by serum containing the L.E. cell factor. LAI is associated with nuclear changes which are characteristic of the L.E. cell phenomenon, and it is most probable that it is an expression of the L.E. cell phenomenon.

An understanding of the chemistry of LAI may lead to useful information as to the fundamental mechanism of the L.E. cell phenomenon. Without such understanding, LAI has been used to obtain collateral information concerning the L.E. cell phenomenon: namely, to rule out any important role for DNA-ase, and to confirm the importance of blood platelets. It has also been used to prepare "pure cultures" of L.E. bodies for cytochemical study.

On a clinical level, LAI may prove a useful adjunct to the standard L.E. cell tests. However, its lower level of sensitivity and occasional "false positive" reactions make it inadequate as a primary test in systemic lupus.

SUMMARIO IN INTERLINGUA

Moribunde leucocytos, suspendite in sero normal, tende a agglutinar se in un firme glomere. Iste phenomeno es associate con lyse cellular e le formation de longe caudas de proteina a acido disoxyribonucleic (ADN). Il pare probable que le complexo proteina-ADN se combina de facto in un manera o un altere con un fraction de proteina seral (possibilemente mucoproteina).

Iste agglutination leucocytic es inhibite per sero que contine le factor del cellulas de lupus erythematose (L.E.). Le inhibition del agglutination leucocytic (IAL) es associate con alterationes nucleari que es characteristic del phenomeno de L.E., e il es probabilissime que illo es un expression del phenomeno de L.E.
Le clarification del chimismo de IAL va forsam resultar in importante informationes relative al mechanismo fundamental in le phenomeno de L.E. In le absentia de un tal clarification, IAL ha essite utilisate pro obtener informationes collateral con respecto al phenomeno de L.E., i.e. le exclusion del possibilitate de un rolo importante de disoxyribonuclease e le confirmation del importantia del plachettas. Illo ha etiam essite usate in le preparation de "culturas pur" de corpores de L.E. pro le objectivos de studios cytochimic.

Ab le puncto de vista clinic, il es possibile que IAL va provar se un adjuncto utile al test standard pro cellulas de L.E. Tamen, su nivello inferior de sensibilitate e le occnrrentia de tempore a tempore de reactiones false positive rende lo inadequate como test primari pro lupus systemic.

REFERENCES

Inhibition of Leukocyte Agglutination by Serum from Patients with Systemic Lupus Erythematosus: A Manifestation of the L.E. Cell Phenomenon

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