Critique of the Concept of the "Pre-L.E." Cell

By Frances Pascher and Alexander Borota

The term "PRE-L.E. CELL" was first introduced to describe altered polymorphonuclear leukocytes in L.E. preparations of peripheral blood and these were interpreted as probable morphologic stages in the development of the L.E. (Hargraves) cell. This concept was subsequently accepted by a number of authors. The object of the present report is to show that these cells are not specific since we have been able to demonstrate them in normal individuals and in patients with a wide variety of cutaneous and visceral disorders, as well as in subjects with systemic lupus erythematosus.

Procedure

During the past seven years, more than 1500 samples of peripheral blood were examined for the presence of L.E. cells by the technics of Huserick, Mathis, Moffatt-Barnes or Magath. Until two years ago at least two of these methods were used concurrently for comparative purposes. Since then the Magath modification of the two-hour-clot method has been used almost exclusively. Specimens were drawn from 750 individuals with diverse cutaneous and visceral disorders and from 11 healthy volunteers.

Findings

Cells resembling the so-called pre-L.E. forms were found in most of these cases. The affected cells were often somewhat reduced in size, but occasionally some were found to be larger than average. The cell wall was intact in some; in others it was partially or totally wanting. Granules, when retained, were, as a rule, reduced in number, somewhat coarser and altered tinctorially. Where the granules were lost, the cytoplasm had a pale-pink translucent appearance. The most striking changes were in the structure and staining capacity of the nuclei. These ranged from indentifiable neutrophilic leukocytes in which the sole change was an attenuation or loss of nuclear filaments connecting the lobes of the nucleus to structures of doubtful origin with a single ball of pycnotic material. The chromatia was often arranged in rounded, intensely basophilic pycnotic spheres from two to six in number. In some instances the clumps of chromatia were uneven in size, in others they were singularly uniform. Vacuolization and expansion of one or more of these spheres or balls of chromatia, leaving only a remnant of basophilic material within the cell, were also noted. Cells in which the chromatia was about to be extruded could also be demonstrated.

Counts of these cell forms, henceforth to be referred to as decomposition forms (Abbauformen) were made in 55 cases. The findings are summarized in table 1.
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Figs. 1-6.—Decomposition forms (Abbauformen) appear to correspond to "pre-L.E. cells" (x 1830).

1.—A polymorphonuclear leukocyte showing attenuation and partial loss of filaments connecting the lobes of the nucleus.

2.—The nucleus of the polymorphonuclear leukocyte is separated into clumps of chromatin of uneven size. The cytoplasm appears more granular; the cell outline is well defined.

3.—The pycnotic nuclear material is arranged in dense basophilic balls.

4.—The nuclear material is condensed and is arranged in eight small balls of chromatin resembling shot.

5.—Note the uniform size and shape of the nuclear material. One of the balls of chromatin is about to be extruded.

6.—The chromatin appears ready to coalesce into a single ball. The cell outline is no longer distinct.
Table 1.—Incidence of Decomposition Forms in L.E. Preparations

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of cases</th>
<th>No. of Decomposition Forms/500 W.B.C.</th>
<th>L.E. Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lupus erythematosus</td>
<td>2</td>
<td>2</td>
<td>+</td>
</tr>
<tr>
<td>Subacute lupus erythematosus</td>
<td>2</td>
<td>4</td>
<td>+</td>
</tr>
<tr>
<td>Disseminated lupus erythematosus</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Chronic discoid lupus erythematosus</td>
<td>16</td>
<td>0 to 10; Av. 3</td>
<td></td>
</tr>
<tr>
<td>Lupus erythematosus? dermatitis?</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Polymyositis (various forms)</td>
<td>4</td>
<td>0 to 9; Av. 3</td>
<td></td>
</tr>
<tr>
<td>Chronic rheumatoid arthritis</td>
<td>1</td>
<td>10</td>
<td>+</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>3</td>
<td>0 to 3</td>
<td></td>
</tr>
<tr>
<td>Fever undetermined origin</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pericarditis</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Asthma, hypertension</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Primary anemia</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Infectious mononucleosis</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Diverticulosis</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Scleroderma</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Leukoplakia</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Decomposition forms were found in 17 different disorders, 30 times in negative L.E. preparations and 3 times in association with the L.E. cell. The highest incidence, 9 to 10 of these forms to 500 normal leukocytes, occurred in two cases of rheumatoid arthritis and in one case of chronic discoid lupus erythematosus. The average number was 2/500 leukocytes. No decomposition or L.E. cells were found in a single case of chronic glomerular nephritis, septic mastitis, thrombophlebitis, acute sinitis, coronary thrombosis, Raynaud's disease, muscle spasm, hypoglycemia, exfoliative dermatitis and psoriasis.

DISCUSSION

Identification of “pre-L.E. cells” as decomposition forms was based on their striking resemblance to decomposition forms (Abbauformen) described some years ago, in the course of in vitro studies of cellular disintegration in peripheral blood, without relation to the L.E. phenomenon. Hargraves incidentally noted similar forms in L.E. preparations which he considered unrelated to lupus erythematosus (fig. 23). Rasponi likewise voiced the opinion that the term “pre-L.E.” cell does not apply “to the roundish cells with the small, unique, multiple, homogenous, strangely chromatophilic corpuscles” and that if the term is used at all, it should be reserved for the rosette stage of the L.E. body. One may add that the resemblance of the nuclear alterations shown in figures 3 to 6 to nuclear pycnosis, which has been accepted as a sign of cell degeneration in tissue, is also striking.
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the sake of completeness it should be mentioned that Diggs, Sturm and Bell\textsuperscript{16} have used the term pre-L.E. cell in a different sense, namely to designate the earliest demonstrable stage of the specific nucleolytic process that they regarded as characteristic of the L.E. phenomenon.

These specimens were also shown to Dr. Marion B. Salzberger and to a number of outstanding hematologists\textsuperscript{*} who concurred in the opinion that these forms were artifacts attributable to degeneration. One must bear in mind that there is ample time for decomposition to set in during the course of making an L.E. preparation since one is dealing with an in vitro phenomenon that requires at least 3/4 of an hour, and as a rule two or more hours, for optimal development. Koeffier\textsuperscript{17} has shown that a two-hour interval is sufficient for the development of degenerative changes in neutrophilic leukocytes in vitro. Lymphocytes and monocytes, on the other hand, are more resistant, while eosinophiles seem to withstand disintegration best.

We find it difficult on morphologic grounds to distinguish "pre-L.E. cells" from decomposition forms. Examination of the descriptive data and photomicrographs in our study discloses a striking resemblance to the data and photomicrographs in the original report by Stitch et al.\textsuperscript{1} Moreover, this report dealt only with seven cases of systemic lupus erythematosus. There is no evidence that samples from patients with other diseases or from normal individuals were examined. Our study disclosed that the very same forms were demonstrable not only in systemic lupus erythematosus but also in localized as well as in systemic conditions, in cutaneous disorders as well as in visceral diseases and in association with negative as well as positive L.E. tests. These forms were also demonstrated in 11 healthy volunteers.\textsuperscript{18} Quantitative estimates, moreover, disclosed no significant variation in the incidence of these forms in the different conditions studied. Nor did the incidence vary to any great extent with the technic employed.\textsuperscript{18}

The intensely basophilic, dense, homogenized nuclear material of decomposition forms appears different from the much less compact, pale-staining nuclear material which makes up the inclusion body of the L.E. cell. Cytoc
chemical studies also indicate that the two may be distinct. It has been shown that whereas the regressive changes of nuclear pycnosis are characterized by concentration of histone and loss of other protein\textsuperscript{15,19} in the lupus body there is apparent loss of stainable histone and an increase of total protein. Some qualitative and quantitative differences in desoxyribose-nucleic acid have also been noted.\textsuperscript{20} Because of the apparent morphologic and histochemical differences it is felt that these nonspecific forms cannot be regarded as precursors of the L.E. cell.

Whether or not decomposed polymorphonuclear leukocytes provide some or all of the nuclear material for the inclusion body of the L.E. cell, and in that sense are pre-L.E. cells, has to be considered. Snapper\textsuperscript{21} is of the opinion that lupus serum can alter desoxyribose nucleic acid of dead, but not of living, cells. Kurnick,\textsuperscript{22} on the other hand, among others, is of the

\textsuperscript{*}We are indebted to Marcel Bessis, Nathan Rosenthal (deceased) and Alexander S. Wiener for their help in this study.
opinion that the plasma factor can penetrate the cell wall and induce nucleolysis of the otherwise intact polymorphonuclear leukocyte. In either event the consensus is that the development of the typical inclusion body depends on the presence of the highly specific L.E. factor.

**SUMMARY AND CONCLUSION**

1. Cells with morphologic features apparently identical with the so-called pre-L.E. cell were demonstrated in L.E. preparations in healthy subjects and in individuals suffering from diverse cutaneous and visceral disorders, as well as in patients with systemic lupus erythematosus.

2. These cells appear to be decomposition forms without diagnostic significance, resulting from nonspecific autolytic process that sets in and progresses in the course of setting up the L.E. preparation.

**SUMMARIO IN INTERLINGUA**

1. Cellulas con aspectos morphologic apparentemente identic con le si-appellate cellulas pre-L.E. esseva demonstrate in preparatos ab subjectos normal e ab subjectos con varie disordines cutanee e visceral, tanto ben como in patientes con systemic lupus erythematose.

2. Il pare que iste cellulas es formas de decomposition sin valor diagnostic, resultante ab non-specific processos autolytic que es initiate e que progrede in le curso del preparativos pro le demonstration del phenomeno de L.E.

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