IS LEUKEMIA A DISEASE OF THE RETICULO-ENDOTHELIAL SYSTEM?

By Bruce K. WiseMAN, M.D.

At the twenty-second year milestone following discovery of a rewarding treatment of pernicious anemia by Minot and Murphy, there is little doubt that the problem presented by leukemia is more important than any other in the field of hematology. Whether the increasing incidence in this disease is actual or only apparent due to more refinements in diagnosis (especially the widespread use of bone marrow biopsy) and more physicians interested in hematology is debatable. In any case, the frequency with which this diagnosis is made is undoubtedly rising. This fact is highlighted by the observation that little or no real progress has been made in pathogenesis or treatment, since with unimportant exceptions, the efficiency of treatment by blood transfusions and x-ray therapy is still supreme (and unsatisfactory) and the prognosis for longevity remains unchanged. These facts suggest that a fresh, if not new, point of view with respect to this disease would not be undesirable. The present observations in a series of clinical and hematologic studies of monocytic leukemia may suggest an important role of the reticulo-endothelial system in the mechanism of the production of leukemia.

The Reticulo-Endothelial System

Although ameboid cells in the connective tissues, distinct from the blood cells, were described as long ago as at least 1863, it remained for Aschoff in 1913, working with vital staining methods using lithium carmine, to recognize that the phagocytic cells described by various cytologists under varying names were widespread throughout the body, forming a system of cells. Almost at the same time, hematologists were struggling with the problem of the identity of the monocyte, thought to be a white blood cell with exceedingly well developed powers of phagocytosis but resembling the neutrophilic leukocyte on the one hand and the lymphocyte on the other. These conflicting observations were resolved by Schilling-Torgan by establishing that the monocyte is a separate cell type. This was the general situation until 1925 when abundant evidence began to accumulate from the study of inflamed tissue and especially from tissue culture technics that monocytes and clasmatocytes were capable of transformation from one to the other (table 1). Recently, in our laboratory, this transformation has been convincingly demonstrated by Houghton with a single cell tissue culture technic. This observation has been further strengthened by the identification of transitional types of mononuclear phagocytic cells in human blood which, when strained supravitally, have characteristics of both monocytes and clasmatocytes (see also fig. 6).

At present, therefore, it seems to some of us rather convincingly demonstrated that the monocyte is a derivative of the reticulo-endothelial system and that this system, having a blood as well as a tissue component, greatly exceeds in extent and

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importance that which was originally indicated by the concept of Aschoff and Kiyono. Monocytic leukemia, therefore, may be regarded as fundamentally and in fact as a leukemic reticulo-endotheliosis. Monocytic leukemia might, therefore, furnish a valuable approach to the study of the various reactions and potentials of the reticulo-endothelial system of cells when under intense stimulation.

Reactions of the Reticulo-Endothelial System Terminating in Monocytic Leukemia

During the past seventeen years in our clinic at Columbus, 192 cases of monocytic leukemia have been studied. Many of these have shown the most unusual cytologic reactions in our entire experience with the blood dyscrasias of all types. This has recently been the subject of comment.\textsuperscript{12} Cases initially appearing to be

Table 1.—Historical Development of Identity and Relationships of Monocyte Clasmatocyte and Fibroblast

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<thead>
<tr>
<th>Monocyte</th>
<th>Clasmatocyte</th>
<th>Connective Tissue</th>
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<tbody>
<tr>
<td>Blood</td>
<td>Clasmatocyte (Ranvier 1891)</td>
<td>Macrophage separated from microphage (Mechnikoff 1892)</td>
</tr>
<tr>
<td>Transitional Neutrophile (Ehrlich-Naegeli)</td>
<td>Adventitial Cells (Marchant 1890)</td>
<td>Adventitial cell and Polyblast identical (Goldman 1909)</td>
</tr>
<tr>
<td>Neutrophile does not contain azur granules (Michaelis &amp; Wolfe 1902)</td>
<td>Clasmat., Macrophage, Adventitial cell and Polyblast identical (Goldman 1909)</td>
<td>Histioyte &amp; R. E. System (Aschoff &amp; Kiyono 1913)</td>
</tr>
<tr>
<td>Independence of Monocyte &amp; Neutrophile (Pappenheim &amp; Ferrata 1911)</td>
<td>Polyblast (Maximow 1902)</td>
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<tr>
<td>Monocyte a separate cell type (Schilling-Torgau)</td>
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<td>Monocytic leukemia described (Schilling-Torgau &amp; Reschad 1913)</td>
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myeloid, or lymphatic leukemia but terminating as classic monocytic leukemia have been seen in addition to those which showed approximately equal numbers of all three cell types throughout the entire course of the disease. Instances in which there was an early stimulation of megaloblasts have been observed. Polycythemia vera coexisted in one case. In several instances, long remissions\textsuperscript{14} with near normal hematologic recovery occurred at a time when with marked anemia and thrombocytopenia existing the disease was thought to be far advanced. Examples of a few of these unusual hematologic reactions will be given in brief summarization.

Case Reports

Case 1. (Fig. 1). This patient, a colored male, age 28, was first seen on December 30, 1946, presenting marked generalized adenopathy and splenomegaly. The lymph nodes were exceedingly hard upon
palpation and the spleen quite nodular but also very hard. Repeated bone marrow aspirations from the sternum failed to show many free cells, the bone marrow content being chiefly reticulum cells and a few monoblasts. Bits of solid bone marrow tissue, however, consisted almost entirely of reticulum cells. An occasional megacaryocyte was seen and a fair sprinkling of myeloid cells in all stages of maturation. Lymph node biopsy showed complete loss of architecture, the cellular content being composed almost entirely of reticulum cells and monoblasts. Reference to figure 2 shows increasing difficulty in the supply of circulating blood elements, even before the application of the nitrogen mustard and deep x-ray therapy, which, incidentally, resulted in no visible decrease in the size of the adenopathy or splenomegaly.

This case is shown as an instance of reticulo-endothelial hyperplasia with very little tendency to do other than reduplicate its own type of cell. This, therefore,
would be an instance of almost "pure" reticulo-endotheliosis, and is to be contrasted especially with the following case.

*Fig. 2.* Graphic representation of the blood findings in a patient with aleukemic reticulo-endotheliosis. Case 2 of text. The differential cell-count of the bone marrow as obtained by the aspiration technic is shown in the vertical panel on the right. Nucleated red cells listed refer to the number encountered in counting 100 white blood cells.

*Case 2.* (Fig. 2.) This patient, a white male aged 84 years, has been ill for sixteen months, during which time his clinical and hematologic state has varied little. He has received blood transfusions about once a month to maintain his red cell count. There is no apparent physical deterioration and he goes about in the same fashion as almost any man of the stated age. Figure 2 shows the hematologic record...
for a typical month (March, 1947), during which time he received urethane. Although this medication apparently improved the levels of blood platelets and neutrophiles, it was discontinued because the patient definitely felt worse when he was on this form of treatment. Of importance to the present discussion is the fact, clearly shown on this graph, that the level of monocytes in the blood are very low with no immature forms present at all, while the bone marrow constantly shows a small, but definite, percentage of monoblasts which does not vary appreciably from time to time.

This case illustrates a minimal reaction of the reticulo-endothelial system in the direction of producing monoblasts with little tendency for maturation to monocytes. This is reflected in a clinical course that is unchanging, paralleling the stationary character of the hematologic reaction.

Case 3. (Fig. 3). This patient, a white female, aged 46 years, illustrates the transition from an aleukemic state, in which no qualitative or quantitative changes in the blood monocytes could be detected, to a frank monoblastic leukemia. Also illustrated is the deceptiveness of attempting to interpret the bone marrow findings as obtained by the aspiration technic when the marrow does not aspirate freely. Re-
peated samplings of the marrow were attempted from the sternum but only a few drops of acellular fluid were obtained on each occasion. In this material no free monoblasts and no increase in monocytes were obtained, as shown in figure 3 (right panel). Monoblasts first appeared in the blood seven days before death, but monocytes were never increased.

**Case 4.** (Fig. 4). Demonstrated here is a case of monoblastic leukemia in which, during the early phases of the disease, an appreciable number of megaloblasts were found in the bone marrow, when monoblasts were not apparent in this tissue. When leukemia first became clearly evident, small numbers of monoblasts began to appear in the marrow but megaloblasts were no longer to be found. Later, large numbers of monoblasts were present in both blood and bone marrow.

The data in this case suggest a low grade stimulation of the reticulo-endothelial system, in the early phases of which pathologic megaloblasts were the first abnormal free cells to appear in proximity to reticulo-endothelial tissue; later, the stimulus resulted in more directional changes in terms of formation of monoblasts.

**Case 5.** (Fig. 5). This case of monocytic leukemia is remarkable because of the coincident polycythemic levels of red blood cells. The patient had a large spleen (extending to the level of the umbilicus) which was removed at another hospital, the tissues being unfortunately lost. When first seen in this clinic the usual clinical signs of polycythemia vera were present, i.e., cherry red mucous membranes, liver-like tongue, distended dark retinal veins, chronic conjunctivitis, etc. There was no adenopathy.
The initial blood examination (fig. 5) showed high levels for all the circulating blood elements including reticulocytes. However, the only pathologic white cells found were monoblasts although young and mature monocytes were distinctly plentiful. Radiation therapy with radioactive phosphorus as shown presumably has decreased the monoblasts in the blood almost to the vanishing point so that now the patient shows little else than the classic hematologic and clinical signs of polycythemia vera.

We interpret these bizarre hematologic events to be the result of increased stimulatory effects upon the reticulo-endothelial system with dominate effect upon the
intersinusoidal reticulo-endothelial system capillaries (red cell-forming precursory tissues) of the marrow, producing increased numbers of mature erythrocytes. Elsewhere, this stimulus results in a monocytic response resembling the average

**Fig. 6.** Graphic representation of the blood findings in a case of myeloblastic leukemia, later terminating as monoblastic leukemia. Case 6 of text. White cells in semi-logarithmic scale.

case of monocytic leukemia except for the unusually favorable response to radiation therapy.

*Case 6. (Fig. 6).* This patient initially presented with the peripheral blood and bone marrow findings of myeloblastic leukemia. As shown in figure 6, neutrophilic leukocytes constituted 80 per cent of the circulating level of 50,000 white blood cells, indicating that our diagnosis of the immature cells present
at that time as myeloblasts and not monoblasts was probably correct. Subsequently, and coincidently, with radiation therapy as shown, the myeloid reaction completely disappeared to be replaced by a blood and bone marrow picture of monocytic leukemia which persisted until death. Autopsy findings in this and the preceding cases were those usually noted in monocytic leukemia described in a previous publication from this and other laboratories. There is some evidence here that myeloblastic leukemia may be one manifestation of reticulo-endothelial disease. If the myeloblasts did not arise originally from reticulo-endothelial stimulation, it is difficult to understand why the proliferation of these cells did not persist with the advent of the monocytic reaction.

Cases similar to the above, in which the initial cell stimulation consisted of lymphocytes with immature lymphoid elements present, and others in which im-

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**Fig. 7.** Clasmatocytic leukemia characterized by many transitional phagocytic mononuclear cells. Hematologic graph of a case of reticulo-endothelial leukemia. Case 7 of text. White cells in semi-logarithmic scale.
mature elements of all three types of white blood cells were increased in approximate equal proportions, have been previously described and reported from this laboratory and need not receive additional emphasis in this communication.

Case 7. (Fig. 7). This patient furnishes, through the observed hematologic reactions during her illness, additional evidence that the reticulo-endothelial system may undoubtedly undergo stimulatory changes resulting in a leukemia of reticulo-endothelial cells. In this chart, only morphologically classic monocytes are labeled as such, represented by the heavy solid line. However, the dotted line of the graph represents phagocytic cells, many of which had predominating monocytic characteristics as well as cells that were definitely clasmocytes and endothelial cells. There is little doubt that this was a leukemia of reticulo-endothelial elements in which monocytes participated as one of the pathologic cells. Blood cultures were sterile and there was no evidence of bacterial endocarditis or other sepsis.

Discussion

Doubt that monocytes are derivatives of the reticulo-endothelial system, and that monocytic leukemia is therefore not a disease of this system of cells has often been expressed, chiefly because reticulo-endothelial hyperplasia is not always demonstrable in this disease. It should be pointed out, however, that numerical increase in the reticulum and specific endothelial cells probably will not be apparent unless maturation of these elements is obstructed. That is to say, when cell division and maturation occur uninhibited, hyperplasia of that cell type often is not apparent by microscopic examination of the tissue in question; the numerical increase is noted only in the end-state cell. An excellent example of a tissue reaction supporting this statement is furnished by almost universally accepted observations in pernicious anemia. During the phase of relapse, megaloblastic hyperplasia with the separate power of division of the cell intact is outstanding in the near absence of maturative principle. When the maturative principle is supplied, however, megaloblasts rapidly disappear, so that within forty eight hours and thereafter, no greater number of megaloblasts can be found in the bone marrow than is apparent in a normal resting marrow. Within seven days, however, mature red blood cells are being supplied to the circulation in maximum numbers; i.e., only the end cell product is visibly increased, although little doubt can be entertained that these new red cells are taking origin primarily from the megaloblasts. There is little reason therefore to demand visible evidence of reticulo-endothelial hyperplasia in monocytic leukemia to satisfy the hypothesis that in this disease the monocytes take origin from the reticulo-endothelial system. In a blood cell strain, it is only the cell in the end-stage of maturation that regularly shows appreciable and visible quantitative increase under conditions of stimulation, not the precursor cells.

If this statement is accepted, it follows that there is no valid reason to discount the distinct possibility that leukemias of all cell types are primarily diseases of the reticulo-endothelial system. The case studies cited in the foregoing part of this paper offer some evidence that under an unknown type of stimulus to the reticulo-endothelial system (as indicated by the advent of monocytic leukemia at some phase of the disease), there may be formed large numbers of myeloblasts, lymphoblasts and even megaloblasts. It is possible in the cited cases that hyperplasia of one or another of the types of cells occurred because maturative substance for that
cell type was temporarily deficient. Eventually, the body resources were able to mobilize adequate quantities of maturing substances for this cell type, the final failure coming in inability to supply sufficient cell maturing factor for monocytes, thus in the end determining the death of the individual from monoblastic leukemia.

This discussion leads to the following suggestions of a possible mechanism for the production of leukemia.

1. Leukemia, irrespective of cell type, may be the result of unknown stimulatory effects upon the reticulo-endothelial system.

2. The type of leukemia observed may be determined by the failure of the body to supply specific maturative substance or substances at one or more phases in development in that cell strain in quantity to keep up with the particular intensity
of reticulo-endothelial stimulation operating at that time in that individual organ-

3. Specific cytologic maturative substances may be multiple in types and chemi-
cal identity and failure of supply of one type may not necessarily prejudice ade-
quate supplies of another type. "The chain breaks at its weakest link."

4. The bizarre varieties of leukemia regularly seen in all hematologic labora-
tories may result from multiple mixed failures of maturation factor varying as to
type specificity and as to degree.

This explanation of the production of leukemia, although admittedly specula-
tive, satisfactorily accounts for many if not all of the puzzling features regularly
encountered in patients with this disease by using only one basic mechanism with-
out recourse to multiple theories. The concept of specific cell maturation substances
is cytologically correct and the existence of one such substance for megaloblasts
has been proved. In addition to the need for more information relating to other
maturative factors, more facts are needed with respect to influences that are stimu-
latory to the reticulo-endothelial system. Particularly, in this regard is there need
for additional study of lipid metabolism and the influence of lipids upon this system
of cells.18, 18-20 (fig. 8).

SUMMARY

1. Evidence is given from case study of reticulo-endothelial disease supporting
the concept that monocytic leukemia is one form of reticulo-endotheliosis.

2. On the basis of varied types of cell reactions seen in monocytic leukemia, it is
suggested that all forms of leukemia may be hematologic varieties of reticulo-
endotheliosis.

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