A small proportion of patients with acute or chronic leukemia has an extraordinarily high blood leukocyte count. These high counts can result in a very high fractional volume of leukocytes (leukocrit), which is also a function of the mean leukocyte volume in different types of leukemia. Despite a high fractional volume of leukocytes, bulk viscosity of blood is usually not increased because a decrement in the fractional volume of erythrocytes accompanies the increase in leukocytes. Nevertheless, the excessive numbers of leukocytes present two major problems: first, they can seriously affect flow in the circulation of the lung, brain, and less often, other organs by obstructing microchannels or by forming aggregates and white thrombi in small veins. Moreover, leukemic blasts may compete for oxygen in the microcirculation and they may be invasive, damaging vessel walls. Second, their rapid destruction in response to cytotoxic drugs causes metabolic disturbances, especially uric acid accumulation, which can lead to obstructive uropathy.

A small proportion of cases of leukemia is associated with an extraordinary concentration of leukocytes in the blood (Fig. 1). These cases present special problems to the therapist because of the effects of leukemic blast cells in the circulation of the lung, brain, and other organs, and the metabolic effects that result when massive numbers of leukemic cells in blood, marrow, and tissues are killed simultaneously by cytotoxic drugs. In some cases, leukocyte counts are so high that blood viscosity increases above normal values. In most cases, bulk viscosity of blood is not increased above normal, although viscosity can be high in the microcirculation. Other characteristics of leukemic blast cells, such as high oxygen consumption and invasiveness, may interact with a flow alteration to lead to vascular damage and organ malfunction.

CELL DEFORMABILITY AND THE VOLUME FRACTION OF CELLS AS DETERMINANTS OF VISCOSITY

The contribution of blood cells to the bulk viscosity of blood at high flow rates is a function of two factors: the deformability of individual cells and the volume fraction of blood that the cells represent. The viscosity increases logarithmically as the fractional volume of red cells (erythrocrit) increases. Leukocytes are less deformable than are red cells,\(^1\)\(^-\)\(^5\) thus, viscosity increases even more dramatically as the fractional volume of leukocytes (leukocrit) increases (Fig. 2). The distinction between the viscosity of red cell and white cell suspensions becomes evident when the observed leukocytocrit measured in a high-speed microcytocrit centrifuge exceeds 15 ml/dl. The observed leukocrit is greater than the true leukocrit because of the trapped plasma between the poorly deformable leukocytes. The true leukocrit can be calculated from the product of the cell packing factor (0.7) and the observed leukocrit. In the case of the red cells, the true erythrocrit and observed erythrocrit are nearly identical.

RELATIONSHIP OF WHITE CELL NUMBER TO THE FRACTIONAL VOLUME OF THE LEUKOCYTE SUSPENSION

A very high concentration of leukocytes is required to produce a true leukocrit of over 10 ml/dl. The concentration of leukocytes that results in a given true leukocrit is a function of the mean cell volume of the
leukocyte (Fig. 3). Leukemic lymphocytes have a mean cell volume that ranges from 190 to 250 cu μm, leukemic lymphoblasts from 250 to 350 cu μm, and leukemic myeloblasts from 350 to 450 cu μm. Thus, it takes nearly twice the number of leukemic lymphocytes than leukemic myeloblasts to result in a given increase in leukocrit. This difference in cell diameter and volume explains, in part, the rarity of hyperleukocytic syndromes in chronic lymphocytic leukemia even at lymphocyte counts of over several hundred thousand cells per microliter (Table 1). Specific differences in the invasiveness of cells or other factors are also important.

THE RELATIONSHIP OF ERYTHROCIT TO LEUKOCIT

In the chronic leukemias, both myelogenous (CML) and lymphocytic (CLL), there is a strong inverse relationship of erythrocyt with observed leukocrit. As leukocrit rises, erythrocyt falls (Fig. 4). In CML, erythrocyt falls 1.1 ml/dl for each increment in leuko-
I... CML and CLL patients (No. = 80).

HYPERLEUKOCYTIC HEALTHY LEUKEMIA SUBJECTS

<table>
<thead>
<tr>
<th>Type</th>
<th>No.</th>
<th>Probable Cases</th>
<th>Possible Cases</th>
<th>Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>179</td>
<td>3 (2%)</td>
<td>6 (3%)</td>
<td>9 (5%)</td>
</tr>
<tr>
<td>CML</td>
<td>85</td>
<td>12 (14%)</td>
<td>1 (1%)</td>
<td>13 (15%)</td>
</tr>
<tr>
<td>ALL</td>
<td>143</td>
<td>4 (3%)</td>
<td>2 (1%)</td>
<td>6 (4%)</td>
</tr>
<tr>
<td>CLL</td>
<td>89</td>
<td>0</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Data represent cases seen at the University of Rochester Medical Center from 1970 to 1981. Nine patients with CML were under 20 yr of age. Eight had the Ph' chromosome in their cells. Five of the 8 patients had white cell counts over 300,000/μl and had signs of the hyperleukocytic syndrome. Thus, about 10% of adults with CML had signs of the hyperleukocytic syndrome, whereas over 50% of children with CML had such signs.

crit of 1.0 ml/dl, and in CLL erythrocrit falls 1.5 ml/dl for each 1.0 ml rise in leukocrit. Since white cells influence bulk viscosity of blood in about the same manner as red cells until the observed leukocrit exceeds 15 ml/dl, and the fall in erythrocrit usually exceeds the rise in leukocrit, a rise in bulk viscosity of blood is very rare in hyperleukocytic leukemias and is confined virtually to cases of CML (Fig. 5).

Figure 6 provides an estimate of the minimum apparent viscosity of blood at a given erythrocrit and observed leukocrit. In moderately anemic subjects, observed leukocrits over 20%-25% must be present to result in an objective increase in bulk viscosity of blood. Transfusion of large quantities of red cells before the leukocyte count is reduced also can result in hyperviscosity in hyperleukocytic leukemia and can be deleterious. Effects of leukocytes in the circulation: pathogenesis of the hyperleukocytic syndrome

Histopathologic studies indicate that aggregates of blast cells and thrombi, perhaps initiated by blast cell
aggregates, may lead to occlusion of small veins in the lung, brain, or other sites.11,17

Viscosity of blood in the microcirculation may play a role in the development of the syndrome. Viscosity in the microcirculation is a function of the plasma viscosity and the deformability of individual cells in capillaries: leukocyte passage should transiently raise the viscosity in such small channels. Moreover, flow in microchannels will fall if the diameter of poorly deformable white cells approaches that of the channel. The flow patterns of leukemic leukocytes in the microcirculation have not been studied. What vessels leukemic cells enter, and what their effects may be, can only be surmised. In vitro studies using Micropore filters and micropipettes suggest that leukemic leukocytes have properties that could lead to occlusion of vessels if the vessel caliber is 75% or less of the leukemic cell diameter. Theoretical considerations suggest that flow should be reduced in channels that are only slightly larger than the diameter of the leukocyte.4,5 With high leukocyte counts, chronically decreased flow may decrease oxygen transport to tissues, since the probability of leukocytes entering microchannels should be increased as a function of white cell count. Moreover, leukemic blast cells have an oxygen consumption rate that could contribute to deleterious effects in the microcirculation.7 By competing with tissue cells in areas of obstructed flow, oxygen tension and supply can be further reduced. In some cases the invasiveness of the leukemic blast cells may be important. This feature of the cells can lead to injury or disruption of vascular walls.37 Rare cases of leukemia have features of the hyperleukocytic syndrome without markedly elevated leukocyte counts, suggesting that special features of leukemic cells may contribute to the syndrome also. This finding may be particularly true of leukemic monoblasts and promonocytes.

CLINICAL SIGNS OF HYPERLEUKOCYTIC LEUKEMIA

High leukemic blast cell counts in AML, CML, and ALL may be associated with pulmonary signs such as tachypnea, dyspnea, and hypoxia.13,16,18,23 A rapid decrease in blood oxygen, which occurs in vitro in the presence of hyperleukocytosis makes PO2 measurements difficult;1,24 however, true hypoxia has apparently been observed. Nervous system signs such as stupor, delirium, dizziness, tinnitus, ataxia, visual blurring, papilledema, retinal vein distention, retinal abnormalities, or intracranial hemorrhage have been associated with hyperleukocytosis.10,12,13,25,27,38 Pneumorrhagia and vascular insufficiency have been reported. Sudden death can occur, usually as a result of intracranial hemorrhage. Thus, hyperleukocytosis should be treated promptly.11,12,17 Cytotoxic drugs may precipitate symptoms or signs that mimic hyperleukocytosis, perhaps as a result of loss of deformability of drug-injured leukemic blast cells or because of the release of procoagulants.30

TREATMENT OF HYPERLEUKOCYTOSIS

A specific white cell count cannot be used to define hyperleukocytosis or to determine the approach to therapy. In patients with acute leukemia or with the accelerated phase of CML, leukemic blast cell counts of over 50,000/μl usually require prompt treatment to decrease the cell count. Patients with leukemia and hyperleukocytosis can be treated with leukapheresis and cytotoxic therapy.10,25,31,35 A single, efficient leukapheresis usually will decrease the white cell count by 20%-60% in a few hours. Since blast cells are not adherent to glass wool, a centrifuge technique rather than a filtration technique should be used. Leukapheresis can (1) reverse the hyperleukocytic syndrome rapidly, (2) be used immediately without having to wait for the result of allopurinol to reduce the risk of uric acid nephropathy, and (3) decrease the tumor cell mass so as to minimize the extent of cytolysis-induced hyperuricemia, hyperkalemia, and hyperphosphatemia. Chemotherapy with hydroxyurea in CML or in the accelerated phase of CML, with cytosine arabinoside and anthracycline antibiotics in AML, or with vincristine, L-asparaginase, and prednisone in ALL should be used concomitantly to further reduce the leukocyte count and enhance the efficiency of leuko-
pheresis by inhibiting proliferation and thereby influx of new cells into the circulation.

In ALL, because of the extreme risk of excessive cytolysis, lower doses of cytotoxic drugs should be used until the white cell count is decreased. Early cranial irradiation has been recommended for children who are too small to have leukapheresis or for adults with severe CNS manifestations. Exchange transfusion can also be used in small children in whom leukapheresis may be difficult.

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MA Lichtman and JM Rowe