Leukapheresis in Man. III. Hematologic Observations in Patients with Leukemia and Myeloid Metaplasia

By Howard R. Bierman, G. J. Marshall, K. H. Kelly and R. L. Byron

"The proper study of mankind is Man."—Alexander Pope

The study of leukocyte behavior in man by leukapheresis was undertaken 10 years ago with the awareness that it would be much more difficult and slower than could be achieved in animals. However, since the ultimate aim was to study leukocyte dynamics in the leukemic patient in comparison with the hematologically normal subject, the most direct attack appeared advisable.

The immediate changes in circulating leukocyte numbers during leukapheresis are due to changes in distribution from one hematopoietic compartment to another and probably do not reflect significant leukocyte proliferation at that time. Consequently, the term replenishment was employed. However, in the days following leukapheresis, when leukocyte production or lack of it becomes apparent in regard to marrow and blood constituency, the term proliferation was used.

The prolonged selective withdrawal of leukocytes from the peripheral blood of hematologically normal man usually results in prompt granulocytosis. Despite the removal of 5.0 to 172.0 x 10⁶ leukocytes representing 22 to 615 per cent of the initial circulating leukocyte number, the replenishment of circulating leukocytes from the extracirculatory reservoirs exceeded the number removed in 40 of 47 studies. The readily available reservoir (RAR) of these patients was estimated to be at least 60 times greater than the circulating leukocyte number. A characteristic later increase in granulocytopenesis in the marrow, associated with the elaboration of a circulating granulocytopenetic stimulant termed Leukopoietin, was observed in these patients.

Eighteen similar studies have been completed in 11 patients with leukemia and one patient with agnogenic myeloid metaplasia. The findings differ so markedly from the observations in normal subjects, and those suggested from animal data and with isotope labeling, that a detailed report is warranted.

This report represents the first measurements in human leukemia subjects...
of the size of the readily available extracirculatory leukocyte reservoir (RAR),
the rate of replenishment of the circulating blood, and the behavior of hematopoiesis following leukocyte withdrawal.

**Patients and Methods**

**Patients**

Eleven patients with leukemia and one with myeloid metaplasia were studied on 18 occasions (table 1). Five patients had chronic granulocytic leukemia, five acute granulocytic leukemia, and one chronic lymphocytic leukemia, determined by repeated hemograms, bone marrow aspirates, and the clinical courses.

Because leukapheresis was an investigative procedure, it was not employed until all conventional modes of therapy had been exhausted and the course of the disease indicated refractiveness to continued therapy. No radiation or chemotherapy was given during the leukapheresis. All patients volunteered freely after they and their relatives had been informed of the possible hazards of the procedure. (We were, of course, not aware at that time of the relative safety of the procedure.) Consequently, a number of these patients were acutely ill, and approaching the end of the natural course of leukemia. All patients were under continuous hospital observation for at least 1 month prior to the first leukapheresis.

**Methods**

The primary purpose of leukapheresis was to remove large numbers of leukocytes rapidly without injury to the remaining hematopoietic elements.

The patient was placed supine in bed on a specially adapted, elevated platform. The level of the right atrium was approximately 4 feet above the inlet orifice of the Fractionator to assure adequate flow by gravity. Blood was obtained from a 16-gauge indwelling femoral arterial needle and led by non-wettable plastic tubing through a filter of 100-mesh siliconized nylon directly to the ADL-Cohn Fractionator, which was employed as a continuous flow centrifuge and separated whole blood into plasma, erythrocytes, platelets and leukocyte fractions.1,2,10,11

During the separation of the leukocytes and platelets from the blood in the Fractionator, the erythrocytes and plasma were recombined under sterile conditions and returned to the patient via an indwelling catheter inserted into the subclavian vein or superior vena cava. The rate of inflow was adjusted to equal that of the outflow. A slow, constant drip of physiologic saline solution containing 1 mg. of heparin per ml. entered the outflow blood immediately distal to the arterial needle and prevented clotting. Five to 1500 ml. of bank blood were employed initially to maintain a constant hematocrit during the initial part of the procedure. This quantity of blood was usually involved in the extracorporeal circuit prior to the return of the reconstituted blood to the patient.

All procedures were carried out under local anesthesia with mild barbiturate or meperidine sedation. During the procedure the patients conversed freely with the laboratory personnel, read books or occupied themselves with puzzles, etc. Mothers were present when children were the subjects and assisted in amusing the child during the procedure.

Blood counts were determined with National Bureau of Standards certified hemocytometers and Trenner automatic filling capillary pipettes. An average of duplicate counts was employed by the method previously described,12 with an accuracy of ± 8.5 per cent. Platelet counts were performed by the direct method. A microhematocrit technic was employed for estimation of the packed erythrocyte volume.13 The blood volume was computed as 8 per cent of the body weight.

Two to six marrow aspirations were performed for each study. Multiple samples from various areas of the pelvis were obtained on each aspiration.14 The activity and maturation of erythropoiesis, leukopoiesis, megakaryocytopenesis, and other cellular elements was
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<th>L. of Blood Fractionated</th>
<th>Rate of Flow (ml/min.)</th>
<th>Duration (min.)</th>
<th>Total Leukocyte Number in PB x 10^11</th>
<th>Total Leukocytes Removed PB x 10^11</th>
<th>Fraction of Initial PB Leukocytes Removed (%)</th>
<th>Fraction of Blood Volume Removed in 1 hr.</th>
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recorded. Whenever possible, the size of lymph nodes, spleen, or liver was documented by actual measurement.

RESULTS

Eighteen leukaphereses were performed on 11 patients with leukemia and one patient with myeloid metaplasia for 94 to 275 minutes; 93 to 168 x 10⁶ leukocytes were removed (table 1). The number of leukocytes withdrawn represented 16 to 247 per cent of the initial total circulating leukocyte number. The rate of blood flow through the Fractionator varied from 15 to 75 mL/minute which permitted separation of leukocytes from the whole blood at 167 to 4770 leukocytes/mm² for each minute of flow (table 2). The recovery of both mature and immature leukocytes²,⁷ was greater in this study than in the study of hematologically normal subjects. The recovered leukocytes averaged 86.5 per cent (53 to 114 per cent) of the number delivered to the instrument (table 3).

Changes in Leukocyte Concentration

A decrease in leukocyte concentration was observed during leukapheresis in 17 of the 18 studies (table 2). At the end of leukapheresis, all but two studies evidenced a fall (table 2). In one patient (MES) the circulating leukocyte concentration increased at the end of two procedures (table 2 and fig. 1). All 12 patients subsequently exhibited a decrease in circulating leukocyte concentration 4 to 24 hours following the procedure, with a continued decline for 72 hours in six studies (fig. 2).

Calculations

The rate of replenishment was calculated from the lowest point of leukocyte concentration (usually 4 to 24 hours following the procedure) over the period necessary to reach a level within 10 per cent of the initial count. If the count was rising but failed to reach the necessary level, the curve was extrapolated to the initial value.

Changes in Cell Type

The changes in leukocyte concentration in all instances were due to the dominant cell type (table 4). No significant change in the ratios of the various leukocytes occurred nor was there a significant shift toward greater or lesser immaturity.

Return of Leukocyte Concentration Following Leukapheresis

In seven studies the leukocyte concentration did not return to the control level. In four studies the leukocyte concentration returned to within 10 per cent of the initial count in 24 to 72 hours and in the remaining seven studies the white blood cell concentration returned within 4 to 22 days following leukapheresis (table 2).

Rate of Replenishment of Granulocytes in Granulocytic Leukemia

Rates of replenishment of circulating immature granulocytes were calculated in 13 studies and ranged from 6.3 x 10⁶ to 21.89 x 10¹¹/day. Since both children
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<th>Lowest Level during Leukapheresis X 10^4</th>
<th>Maximum Decrease as % of Initial PB Leukocyte Count</th>
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<th>Received into Fract. X 10¹¹</th>
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and adults were investigated, these data were converted to per Kg. of body weight per day of 0.12 to 52.2 x 10⁶ (table 4).

The rates of replenishment of the PMN’s were 0.01 to 7.05 x 10⁶ per Kg. per day. The PMN in the leukemic patients is therefore generally replenished at a slower rate than in the normal subject (0.07 to 23.7 x 10⁶ per Kg. per day³).

In the single patient with myeloid metaplasia, the rates of replenishment of immature granulocytes and PMN’s were respectively 0.045 and 0.039 on the first study and 0.089 and 0.092 x 10⁶ per Kg. per day on the second study. The data for immature granulocytes and PMN’s were essentially the same in these two studies although approximately two and three times as many PMN’s were removed as immature granulocytes.

Changes in Marrow Aspirates

Marrow aspirates were obtained before, during and at frequent intervals up to 96 hours following leukapheresis. The marrow aspirates were hypercellular on 15 occasions, primarily involving the predominant cell line. On three occasions hypocellularity had been induced by previous radiation or chemotherapy.

In general, only minimal marrow changes were observed. No stimulation of leukopoiesis occurred during or following leukapheresis in marked contrast to the findings in normal subjects.²,³ The cellularity and differential counts were within the range of biologic variation. In Study #3 increased eosinopoiesis was observed 24 hours after the procedure, and in Study #11 a decided plasmacytosis developed. An increase in tissue mast cells in the particles was noted 96 hours after the procedure in Study #14.
<table>
<thead>
<tr>
<th>Leukocytes Removed X 10^9</th>
<th>Immature Leukocytes X 10^9/cu.mm.</th>
<th>Time to Return in Days</th>
<th>Rate of Replenishment /Day X 10^9 /Day/Kg. X 10^9</th>
<th>PMN X 10^9/cu.mm.</th>
<th>Time to Return in Days</th>
<th>Rate of Replenishment /Day X 10^9 /Day/Kg. X 10^9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run #</td>
<td>Immature</td>
<td>PMN</td>
<td>Initial</td>
<td>Nadir</td>
<td>Return</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.9</td>
<td>1.1</td>
<td>9.0</td>
<td>3.0</td>
<td>NR</td>
<td>—</td>
</tr>
<tr>
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<td>1.9</td>
<td>204.0</td>
<td>114.0</td>
<td>180.0</td>
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<td>3.9</td>
<td>68.0</td>
<td>44.0</td>
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<td>1 hr.</td>
</tr>
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<td>22.0</td>
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<tr>
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<td>1.3</td>
<td>158.2</td>
<td>32.6</td>
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<td>—</td>
</tr>
<tr>
<td>6</td>
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<td>115.0</td>
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</tr>
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<tr>
<td>8</td>
<td>11.0</td>
<td>1.4</td>
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<td>50.0</td>
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<td>0.8</td>
<td>0.1</td>
<td>14.5</td>
<td>2.0</td>
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<td>3.5 hrs.</td>
</tr>
<tr>
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<td>1.7</td>
<td>0.01</td>
<td>22.2</td>
<td>9.6</td>
<td>NR</td>
<td>—</td>
</tr>
<tr>
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<td>0.01</td>
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<tr>
<td>17</td>
<td>0.3</td>
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<td>7.0</td>
<td>0.1</td>
<td>7.0</td>
<td>6.0</td>
</tr>
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<td>18</td>
<td>18.05</td>
<td>0.1</td>
<td>50.0</td>
<td>150.0</td>
<td>21.0</td>
<td>26.7</td>
</tr>
</tbody>
</table>

*Increased to 6.6 x 10^9 on the 16th day with development of pneumonia.
†Lymphocytes.
NR = no return.
Effect of Splenectomy

One subject, PAL, who had an aggressive granulocytic leukemia, underwent three leukaphereses (fig. 3). Two studies were performed prior to and one after splenectomy. The first study, during which $7.78 \times 10^{11}$ leukocytes were removed in 132 minutes (116 per cent of the initial total circulating leukocyte number), resulted in a decrease of leukocyte concentration from 134,200 per cu. mm. to 50,000 per cu. mm. during the procedure. The immature granulocytes fell from 115,000 to 35,000 per cu. mm. and never returned to more than 69,300 per cu. mm. by the 10th day, when the PMN's had returned to the initial level of 15,000 per cu. mm. after having declined to 5,000 during the procedure.

When it became apparent that the return of the immature granulocyte concentration in the blood was much slower than anticipated and that the rate of return was constant enough over a sufficient period to permit a valid estimate of replenishment during that period, a second leukapheresis was performed when the PMN concentration reached the pre-leukapheresis level.

The second leukapheresis, performed 10 days after the first, removed $3.47 \times 10^{11}$ leukocytes in 116 minutes (104 per cent of the initial total circulating leukocyte number), similar to the first, resulting in a decrease of leukocyte concentration from 69,300 to 33,000 per cu. mm. during the procedure. The immature granulocytes fell from 44,000 to 17,000 per cu. mm. which returned to 44,000 per cu. mm. in 24 hours. The PMN concentration fell from 10,000 to 7,000 per cu. mm. with slow return thereafter. When the returning leukocyte
concentration was projected, it reached the initial level at 19.8 days and it was planned to wait for the slow return to obtain a good estimate of leukocyte replenishment. However, on the 12th day after the second leukapheresis, the patient experienced sharp left upper quadrant pain which became progressively more severe and excruciating. Diagnosis of a splenic infarct was confirmed at splenectomy.

On the 16th postoperative day, 28 days after the second leukapheresis, the white blood count was noted to begin to climb precipitously. Twenty-six days after the second leukapheresis, the third leukapheresis was performed. In 124 minutes, $14.65 \times 10^{11}$ leukocytes were removed (109 per cent of the initial total circulating leukocyte number). Immature granulocytes fell from 235,000 to 50,000 per cu. mm. during the procedure and returned to the initial level 6 days later. The PMN's fell from 20,000 to 7,500, returning to the 20,000-per-cu. mm. level halfway through the 10th day.

Changes in Chronic Lymphocytic Leukemia

One patient, THO, with chronic lymphocytic leukemia, had an initial leukocyte count of 182,700/mm³, 99 per cent of which were small lymphocytes. A progressive decline in the peripheral leukocyte concentration occurred during leukapheresis and continued for 72 hours, finally stabilizing at 50,000/mm³. There was a slow but irregular rise to 150,000/mm³ 21 days
LEUKAPHERESIS IN MAN III

Fig. 3.—Response to leukapheresis of one leukemic subject (PAL) before and after splenectomy. The periods of leukapheresis are shown by vertical bands.

after the nadir. The lymphadenopathy and hepatosplenomegaly decreased to normal within 5 days; this state persisted until the leukocyte concentration again exceeded 120,000/mm³. No changes in lymphocyte morphology were observed during or following leukapheresis.

Platelets

In the 13 studies where sufficient data were available and the platelet count was stable prior to the study, a decrease in platelet concentration occurred either during or immediately following leukapheresis. In eight of the studies the platelet level returned to the initial concentration within 7 hours; in four the concentration was restored by 9 days and in one patient there was no return (table 5). There was considerable oscillation in the platelet levels during and immediately following the procedure but stabilizing soon thereafter (fig. 1). Platelet behavior in the leukemic was comparable to that noted in the normal subjects.

In eight studies in which the platelet level returned to the initial level within 7 hours, 94 to 303 per cent of the initial total circulating platelet concentration was removed. Therefore, the platelet reservoir in these patients was probably no greater than twice the circulating number. In those five patients in whom the return was slower, the platelet reservoir would be less than twice the circulating concentration.

Biochemical Changes

Of the six studies in which satisfactory data were obtained, one patient (END) exhibited a fall in serum potassium from 4.6 to 3.2 mEq./L. This
Table 5.—Changes in Platelet Concentration during Leukapheresis in 13 Studies

<table>
<thead>
<tr>
<th>Run #</th>
<th>Total PB in PB X 10^11</th>
<th>Total Removed PB X 10^11</th>
<th>Fract. Initial PB Platelets Removed (%)</th>
<th>Platelet Concentration in PB X 10^11</th>
<th>Time of Return to Initial Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>8.43</td>
<td>74</td>
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</tr>
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<td>2</td>
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<td>19.0</td>
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<tr>
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</tr>
<tr>
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</tr>
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<td>9</td>
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<tr>
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<td>5.40</td>
<td>94</td>
<td>102.5</td>
<td>75.0</td>
</tr>
</tbody>
</table>

The same patient also had a decrease in serum proteins from 8.1 gm. to 5.2 gm. 24 hours after completion of the procedure. Administered supplemental potassium probably was responsible for preventing a deficit produced by massive withdrawal of potassium-rich leukocytes.\(^1\)\(^1\) No significant changes in serum sodium or chlorides were observed.

**DISCUSSION**

The classical concept of leukemia as a disease entity of excessive proliferation of leukocytes suggests that the reservoirs should be discharging leukocytes into the circulation at a rapid rate. Consequently, one would have expected that the removal of 0.13 to 1.14 volumes of circulating leukocytes per hour would either induce a greater increase in circulating leukocyte number than in the hematologically normal subjects,\(^1\) or perhaps fail to alter the leukocyte concentration significantly. In the hematologically normal man, leukapheresis results in an increase in the circulating leukocyte concentration. We were therefore surprised to observe the contrary response—a decrease in circulating leukocyte concentration during leukapheresis and often a continued and prolonged decline days after the procedure. Since the exact mechanisms of replenishment, proliferation, and readjustment of leukocyte levels in the
blood from other sources in man is not known, one can only interpret the findings in light of the pertinent information available, taking care to avoid assumptions or inferences from the literature which may not be valid in man.

Craddock, Adams, Perry, Skoog, and Lawrence\(^6\) reported a transient leukopenia in normal dogs with leukapheresis only when the rate of removal exceeded 1.5 to 3 volumes of the circulating leukocytes/hour. This could not be confirmed by Ingram\(^7\) in healthy dogs or by ourselves in the hematologically normal human subject.\(^1\) In the leukemic patients the response to leukapheresis appeared related to the number of leukocytes removed, rather than to blood volumes removed per hour.

The hematodynamic behavior in these leukemic patients suggested that either the readily available leukocyte reservoir (RAR) was possibly smaller than in the normal subject, or that the transfer of cells from the RAR to the circulation might be unable to respond as promptly or vigorously as in normal subjects. This delayed response was apparently independent of the initial leukocyte blood concentration (13,300 to 563,000/mm\(^3\)) or marrow hypercellularity or the degree of blood or tissue saturation.

In the hematologically normal subject, the initial leukocyte concentration was regained from elevated levels and maintained within a few hours after leukapheresis, whereas in the leukemic patients there was a continued decline from the initial level after leukapheresis, pointing to a defect in the transfer mechanism of leukocytes from the RAR into the circulation which prevented the re-establishment of the initial level since ample cells remained in the extracirculatory depots. It is of interest, therefore, that in the patient (MES) who had the lowest initial leukocyte concentration (13,300/mm\(^3\)), the increase during leukapheresis was comparable to the response in the normal subject, yet promptly after leukapheresis the progressive decline in the leukocyte concentration characteristic of leukemic patients was observed. Apparently these two phenomena, during and following leukapheresis, may represent separate mechanisms.

Contrary to common belief, immature granulocytes enter the blood regularly and circulate freely in normal subjects.\(^15\) The leukocyte concentrations obtained during leukapheresis in normal subjects illustrate the vast numbers of myelocytes and metamyelocytes that were readily available.\(^1,2\) The tissue-blood barrier in non-leukemic subjects apparently regulates the flow of immature granulocytes into the blood at an approximate ratio of 1,000 PMN’s: 10 metamyelocytes: 5 myelocytes: 1 promyelocyte. The ratio of PMN’s to immature granulocytes is greater in the blood than in the marrow, suggesting preferential passage of readily available PMN’s from the marrow.

The marrow in normal man is the sole granulopoietic site and also serves as the largest single reservoir for both immature and mature granulocytes. Probably not all the PMN’s in the marrow are readily available and the mechanism of discharge in man is unknown. Although the number of granulocytes in tissues other than the marrow are in low concentration, the mass of tissue is 70 to 100 times greater and these cells cannot be arbitrarily ignored although their availability is unknown.

Donohue et al.\(^16,17\) have estimated the number of granulocytes in the
marrow, employing the erythron as a reference. The assumptions required for
this estimate have been seriously questioned.18 Radioisotope labeling of
granulocytes with tritiated thymidine, radiophosphorus, and diisopropyl-
fluorophosphate (P32), by both in vivo and in vitro technics, have resulted in
widely variable and conflicting data in man.7-9,19 The interpretation of the
curves has presented considerable difficulty despite computer analysis and
repeated attempts to fit the data into many simple models, confirming the
suspicion of many investigators that leukopoiesis is an imperfectly understood
complex system.

Athens et al.,9 employing diisopropylfluorophosphate (DFP32) in vitro
labeled leukocytes, confirmed the rapid disappearance of these leukocytes as
demonstrated previously. With epinephrine and exercise, 20 per cent of the
cells remained unaccounted for and were not readily available. The readily
available reservoir in these studies was termed marginal granulocyte pool
(MGP), which was estimated to be 34.6 ± 15.6 x 10⁷ per Kg. body weight.
The circulating granulocyte pool was measured at 30.7 ± 11.8 x 10⁷ per Kg.
body weight. In addition to the large standard deviation and the 20 per cent
of the cells unaccounted for, it should be emphasized that there are marginal
cells in considerable number which are not released upon the administration of
epinephrine. Often repeated infusions of epinephrine at 2 to 5 minute intervals
were unable to fully mobilize the marginal cells.20 Furthermore, at these
periods beyond 5 minutes, the homeostatic mechanism of the blood involving
histamine21 comes into play.

Athens et al.21 in further studies found the granulocyte turnover rate to be
179.9 ± 74.3 x 10⁷ per Kg./day, a value at the lower border of magnitude
of that previously reported, employing three different non-isotope methods.22
Again the variations were marked and the same reservations with this method
must be considered.

The value of leukapheresis in man is that it yields data free of the complica-
tion of isotope labeling, and critical assumptions are unnecessary, thus per-
mitting additional data for comparison with that obtained by more compli-
cated methods.

The RAR of these leukemic patients ranged from 1 to 12 times as large as
the total leukocyte number of the peripheral blood, as compared to greater
than 60 times in normal subjects. However, because of the elevated peripheral
blood leukocyte concentration, the sum of the blood and the RAR in the
leukemic subject is equal to, or only slightly greater than, the normal, a
surprising finding. This strongly suggests that the majority of the extra-
circulatory leukocytes in granulocytic leukemia are not readily available to
the blood and resist release by vigorous methods which are successful in
the normal subject.12

Thus, the picture of hypercellular granulocytic leukemia cannot be explained
alone by an excessive rate of proliferation. It is conceivable that one of the
major defects in leukemia is a block in the rapid mobilization of cell reservoirs.
If granulocytes cannot readily enter the peripheral blood, an increase in the
tissue reservoirs will result, creating a picture of hypercellularity which has
been previously assumed to reflect an increased rate of proliferation. The appearance of increased numbers of granulocytes in the blood must be a late phenomenon. By the time the peripheral blood count in granulocytic leukemia exhibits increased numbers of immature granulocytes, the marrow has been engorged for some time.

Although the rate of division of each immature granulocyte may be at or less than its counterpart in the normal subject,22 the sum of all the accumulated cell divisions may eventually lead to increased numbers of dividing cells which was previously misinterpreted as representing an increased rate of cell proliferation as the universal basic mechanism of the leukemias. This in turn has led to the therapeutic avalanche upon the specious excessive proliferative mechanism. Obviously a considerable number of patients with granulocytic leukemia are not benefited significantly by this approach and our attention should once again be turned to reconsideration of other mechanisms underlying this and possibly other types of leukemia.23 This decrease in cell production previously reported22-24 has recently been confirmed by isotope studies of Craddock et al. in man as lengthening the individual cell generation time.2

Based on evidence obtained in man and in dogs,26-28 it has been postulated that the transfer of leukocytes from the tissues into the blood of normal subjects was determined by the leukocyte concentration in the circulation. This mechanism may be impaired in the leukemic subject,23 in whom an increased non-readily available reservoir may encroach upon and thereby restrict the capacity and function of the RAR (fig. 4). In the three instances of marrow hypocellularity, the extramedullary hematopoietic sites may have compensated for the apparent reduction of the NRAR of the marrow.

Studies of these marrows indicated no change in proliferation during or following leukapheresis; this was particularly striking when compared with normal subjects.1-4 The predominant cell removed during leukapheresis in the normal subjects was the PMN. Granulocytopoiesis was subsequently stimulated 24 to 48 hours later.2,8 In the leukemic patients the dominant cell removed was the cell which characterized the leukemia, yet no excess proliferation was observed in the marrow or blood studied for 10 days later.

The continued fall in the peripheral leukocyte concentration following the procedure, and the slow return over 1 to 22 days later to the initial level suggests that proliferation of the dominant cell type is variable but slower than anticipated. Certainly the prompt response characteristic of the normal subject was lacking. Indeed, in some instances it appeared that the necessary stimulus for leukopoiesis had been removed.

If the mature PMN inhibits leukopoiesis,7,29,30 its removal from patients with chronic granulocytic leukemia should result in increased proliferation. Conversely, removal of large numbers of immature granulocytes from patients with acute granulocytic leukemia should cause no stimulation of the marrow if they lack this inhibitory property. It is significant, therefore, that we found no marked difference in the response to leukapheresis between acute and chronic granulocytic leukemia, although predominantly immature
Fig. 4.—Schematic representation of the total leukocyte reservoir of hematologically normal subjects (left) and leukemic subjects (right). A = total number of circulating leukocytes; B = total number of extracirculatory leukocytes; T = leukocyte withdrawal from the blood; C = container in which the number of leukocytes removed (N) is collected; No = the original level of leukocytes; and N, = the level attained following leukapheresis.

and both immature and mature granulocytes were removed, respectively. The number of PMN’s removed in the patients with chronic granulocytic leukemia were equal to, greater than, or less than the number removed from normal subjects.

The rate of replenishment of the PMN in granulocytic leukemia was similar to the rate of normals in four of nine instances (table 4). The rate of replenishment of immature granulocytes exceeded that of the PMN’s on three occasions, although more immature granulocytes than PMN’s were removed in 12 studies.

A comparison of the rates of replenishment of the immature granulocytes (myeloblasts, promyelocytes, myelocytes, and metamyelocytes) with the PMN’s was possible in Studies #2, 3, 4, 5, 7 and 8 (table 4). These were patients with chronic granulocytic leukemia converting to a more fulminant state. The ratio of the replenishment rate of immature granulocytes to PMN’s ranged from 1.5 to 16.5 and was apparently independent of the various types of leukocytes removed.

The rate of replenishment of small lymphocytes in chronic lymphocytic leukemia based on a single study was 0.38 x 10⁶ per Kg. per day. Data for the comparison of lymphocyte replenishment in leukemias and normal subjects are not available but in this instance the replenishment required 21 days, attesting to a slow rate of cell production. Prolonged life span of the lymphocytes in this disease must be given consideration as one of the primary causes of hypercellularity.

Ingram produced leukopenia in a lymphomatous dog with a lymphocytic
leukemic blood picture. Initially in poor condition, the dog developed a “blastic” crisis 17 days after leukocytapheresis. This change was not attributed to the procedure although it was considered. Exacerbation of the leukemic state was not seen in our series. In fact, most of the patients appeared temporarily improved.

In one patient (PAL), the peripheral blood leukocyte concentration was replenished more rapidly after splenectomy than on two occasions prior to splenectomy. Splenectomy in granulocytic leukemia is often followed by a myeloblastic crisis within 6 months.26 The change in performance of circulating leukocytes following splenectomy and leukapheresis suggests that the spleen exerts considerable influence upon leukopoiesis in chronic granulocytic leukemia, perhaps as a removal organ or by some mechanism of growth control.

In selected cases the leukocyte number may be materially reduced by leukocyte withdrawal without endangering the patient. The continued slow removal of leukocytes may serve to deplete saturated reservoirs of leukocytes and also to remove the products of excessive leukocyte destruction. This may permit the marrow, spleen, and liver to regain their normal functions without injury to normal hematopoietic tissues, as is often unavoidable in effective radiation or chemotherapy.

The data herein indicate that current beliefs of leukocyte proliferation, tissue saturation, and leukocyte transfer in the leukemic states in man, as derived from the classical concepts of leukemia, are in need of serious revision and must be subjected to experimental test in man. These studies are further support of a dynamic equilibrium between cell production and destruction which is disturbed in the leukemic states. Furthermore, the transfer of leukocytes from the tissues into the blood is impaired, a fact not previously recognized within the confines of the classical concept of leukemia. All leukemias are not necessarily manifested by an excessive rate of proliferation of the dominant leukocyte. Indeed, many leukemias have demonstrated rates of leukocyte replenishment and proliferation that are less than normal.22,24,25 In these leukemias the elevated leukocyte levels in the blood and tissues may be more attributable to an excessively prolonged leukocyte life span and accumulation than to an increased rate of leukocyte production.

Since, in theory, chemotherapy of the leukemias is aimed at the most vulnerable site of the leukocyte, the definition of the defect in each type of leukemia as primarily proliferative, accumulative, or both, is crucial. Leukapheresis in man is a safe and feasible technic for investigating hematodynamic mechanisms in normal and abnormal hematopoietic states. Prolonged leukocyte withdrawal should be explored for possible therapeutic application.

**Summary**

Eleven patients with leukemia and one patient with myeloid metaplasia underwent leukapheresis on 18 occasions for 94 to 275 minutes during which 93 to $1668 \times 10^9$ leukocytes were removed. All patients exhibited a significant and continued decline of peripheral leukocyte concentration during or after the procedure. In 12 of the 18 instances, the leukocyte concentration returned
slowly to the initial leukocyte level within 1 hour to 22 days. The number
of leukocytes withdrawn represented 16 to 247 per cent of the initial circulating
volume removed at a rate of 0.13 to 1.14 leukocyte blood volumes per hour.
The RAR was 1:1 to 12:1 to the circulating leukocyte number. Rate of re-
plenishment of the circulating immature leukocyte numbers were $4.0 \times 10^7$
to $52.2 \times 10^9$/Kg./day. The PMN's were replaced at rates of $10 \times 10^9$ to $7.05$
$x 10^9$/Kg./day which were equal to or slower than in normal subjects. Changes
in number occurred in the dominant leukemic cell types without significant
shifts in the differential counts. No changes in marrow population other than
a slight decrease in cellularity were observed.

The data indicate that in the leukemic patient the peripheral leukocyte con-
centration was not maintained or replenished promptly following the with-
drawal of sizeable quantities of leukocytes, demonstrating a block in transfer
of leukocytes from the tissues to the blood. This is in marked contrast to the
leukocytosis and marrow stimulation observed in hematopoietically normal
subjects following leukaphereses.

The platelet counts fell promptly during leukapheresis, returning toward
type levels in eight studies within 7 hours following the procedure. In four
studies the platelet counts returned to control levels in 3 to 9 days. The
changes in platelet concentrations were similar to those observed with
hematologically normal subjects. The size of the platelet reservoir in these
leukemic patients is about twice that of the circulating blood.

**SUMMARIO IN INTERLINGUA**

Dece-un patieute con leucemia e un patieute con metaplasia myeloide
esseva subjicite a leucapherese in 18 occasiones durante inter 94 e 275 minutas. Le
quantitate de leucocytos eliminate esseva inter $93 e 1668 \times 10^9$. Omne Ic
patieutes exhibiva un significative e continue declino del concentration periph-
eric de leucocytos durante o post le intervention. In 12 del 18 occasiones, le
concentration de leucocytos retornava lentemente al nivello initial in le curso
de inter 1 hora e 22 dies. Le numero del leucocytos eliminate representava
inter 16 e 247 pro cento del circulante volumine initial. Le elimination progre-
deva a un rapiditate de inter 0,13 e 1,14 volumines leucocytic total per hora.
Le proportion del prestemente disponibile reservoir de leucocytos al circulante
leucocytos esseva inter 1:1 e 12:1. Le rapiditate del re-supplementation del
numero de immatur leucocytos in le circulation esseva inter $4.0 \times 10^7$ e $52.2 \times 10^9$
per kg per die. Le polymorphonucleares esseva reimplaciate a cadentias
de inter $10 \times 10^9$ e $7.05 \times 10^9$ per kg per die, lo que esseva equal o inferior al
correspondente cifras in subjectos normal. Le alterationes occurreva in le
dominante typos leucemic de cellula, sin significative modification del numerations
differential. Esseva observate nulle alteration in le population medullari,
excepte un leve declino del cellularitate.

Le datos indica que in le patieute con leucemia le concentration peripherc
de leucocytos non esseva mantenite o promptemente reconstituite post le
elimination de considerabile quantitates de leucocytos, lo que indica le presentia de un bloco in le transferimento de leucocytos ab le tissus ad in le
sanguine. Isto es un marcae contrasto con le leukocytosis e le stimulation
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del medulla que es observate post leukaphereses in hematopoieticamente normal subjectos.

Le numeration del plachettas declinava promptemente durante le leukapheresese e retornava in octo studios al nivellos de controlo intra septe horas post le intervention. In quatro studios le numeration del plachettas retornava al nivellos de controlo in inter 3 e 9 dies. Le alterationes del numeration plachettal esseva simile a illos observate in hematologicamente normal subjectos. Le magnitude del reservoir de plachettas in iste patientes con leucemia es circa duo vices le total de plachettas in le sanguine circulante.

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