Peripheral Leukocyte Kinetic Studies of Acute Leukemia in Relapse and Remission and Chronic Myelocytic Leukemia in Blastic Crisis

By Herman A. Godwin, Theodore S. Zimmerman and Seymour Perry

It has been only recently that significant progress has been made in the study of leukocyte kinetics and cell proliferation in acute leukemia. This became possible with the introduction of tritiated thymidine (H³TdR), a labeled precursor specific for DNA.¹ With the technic of radioautography, this labeled compound has been employed in vivo to investigate the leukemic cell cycle and cell proliferation in patients with acute leukemia in relapse and in blastic crisis.²-¹¹ In vitro studies to characterize the proliferative capacity of leukemic leukocytes have also been performed.⁵,⁶,¹²-¹⁸

The purpose of this paper is to present data concerning peripheral blood leukocyte kinetics in patients with acute leukemia both in relapse and remission and in patients with chronic myelocytic leukemia in blastic crisis. Liquid scintillation counting of isolated leukocytes and radioautography following single intravenous injections of H³TdR were employed in these studies.

Materials and Methods

Twenty-seven patients with leukemia seen at the National Cancer Institute constituted the study group. Pertinent clinical and hematologic data are summarized in Table 1. Several individuals were evaluated on more than one occasion so that a total of 31 studies is presented. In addition, one hematologically normal individual, a 59-year-old female with metastatic breast carcinoma, was studied. Informed consent was obtained in all studies.

Tritiated thymidine* (H³TdR, sp. act. 1.9 c. per mmole), 75 μc. per kg. body weight, was injected intravenously in a single dose. Peripheral blood samples of 5–20 ml. were drawn just prior to injection of the isotope and at predetermined intervals thereafter. Five percent EDTA was used as the anticoagulant. Leukocytes were isolated by dextran sedimentation and hypotonic lysis as previously described.¹⁹ The cells were washed in normal saline and an aliquot counted in an automatic cell counter.¹ Cell buttons containing a known number of leukocytes (approximately 1 × 10⁹) were prepared by centrifugation at 2100 g for 10 minutes and then hydrolyzed in 0.5–1.0 ml. NCS® reagent.¹ Following the addition of 15...
Fig. 1.—Leukocyte specific activity in the peripheral blood in a hematologically normal individual after the intravenous administration of tritiated thymidine. Vertical scale has been normalized to percent of maximal radioactivity.

ml. toluene phosphor scintillation fluid, radioactivity was determined in a liquid scintillation spectrometer. The efficiency for tritium with this system was 30 percent. Correction for quenching was by means of an external standard.

Radioautographs were prepared from each whole blood sample. Smears were made on clear gelatin-coated microscope slides, air dried, and fixed in absolute methanol. Kodak AR-10 stripping film was applied and the slides were exposed for 4–6 months at 4°C. The radioautographs were then developed, fixed, stained with Giemsa stain, and 400–2000 cell counts performed depending upon the proportion of cells labeled. Background was less than one grain per cell and therefore no correction was applied, but no cell was considered labeled which had less than three grains.

Criteria for designating the status of a patient with acute leukemia were those used by the Acute Leukemia Cooperative Group B.20

RESULTS

Normal Individual

The peripheral blood leukocyte radioactivity curve for a hematologically normal individual is presented in Figure 1 and is similar to those previously reported.21 There was a low level of radioactivity present for 100–120 hours followed by a marked rise with a peak at 170 hours. Decline in activity was rapid thereafter. It has been the experience of this laboratory in 12 studies of hematologically normal individuals that the initial low level of radioactivity does not exceed 20 percent of the major peak.

Table 1.—Clinical Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Race</th>
<th>Diagnosis</th>
<th>Disease Status and Treatment at Time of Study</th>
<th>Hgb (gms.)</th>
<th>WBC (mm.(^3))</th>
<th>Blasts (%)</th>
<th>Bone Marrow Blast Cells (%)</th>
<th>Remarks</th>
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<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>F</td>
<td>W</td>
<td>ALL</td>
<td>(a) Untreated</td>
<td>8.1</td>
<td>9,800</td>
<td>60</td>
<td>100</td>
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<tr>
<td>2</td>
<td>34</td>
<td>M</td>
<td>W</td>
<td>ALL</td>
<td>(b) Remission following vincristine and prednisone</td>
<td>4.0</td>
<td>8,400</td>
<td>0</td>
<td>100</td>
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<tr>
<td>5</td>
<td>63</td>
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<td>ALL</td>
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<td>7.3</td>
<td>87,700</td>
<td>70</td>
<td>100 (Auer rod -)</td>
<td>100 (Auer rod -)</td>
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<td>6</td>
<td>63</td>
<td>M</td>
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<td>AML</td>
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<td>7</td>
<td>13</td>
<td>F</td>
<td>W</td>
<td>AML</td>
<td>Untreated</td>
<td>8.6</td>
<td>7,900</td>
<td>48</td>
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<tr>
<td>8</td>
<td>50</td>
<td>M</td>
<td>W</td>
<td>AML</td>
<td>Untreated</td>
<td>8.4</td>
<td>81,600</td>
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<td>W</td>
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<td>F</td>
<td>W</td>
<td>AML</td>
<td>Untreated</td>
<td>8.8</td>
<td>7,600</td>
<td>85</td>
<td>&gt;95 (Auer rod +)</td>
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<td>11</td>
<td>10</td>
<td>F</td>
<td>N</td>
<td>AML</td>
<td>Untreated</td>
<td>8.8</td>
<td>5,600</td>
<td>19</td>
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<td>12</td>
<td>10</td>
<td>F</td>
<td>W</td>
<td>AML</td>
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<td>9.6</td>
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<td>(a) Early relapse</td>
<td>10.2</td>
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<td>&lt;5 (Auer rod -)</td>
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<td></td>
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<td>(b) Remission following cytosine arabinoside</td>
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<td>ALL</td>
<td>Remission</td>
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<td>16</td>
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<td>Remission</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>(b) Bone marrow remission, ovarian masses with leukemia infiltrates</td>
<td>9.8</td>
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<td>(b) Spleen, 2 cm.</td>
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<td>18</td>
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<tr>
<td>19</td>
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<td>7,100</td>
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<td>20</td>
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<tr>
<td>21</td>
<td>48</td>
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<td>N</td>
<td>CML, BC</td>
<td>Untreated for BC</td>
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<tr>
<td>22</td>
<td>65</td>
<td>M</td>
<td>W</td>
<td>CML, BC</td>
<td>Relapse of BC, receiving dibromomannitol</td>
<td>9.0</td>
<td>6,000</td>
<td>25</td>
<td>50 (Ph +)</td>
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<tr>
<td>23</td>
<td>41</td>
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<td>W</td>
<td>CML, BC</td>
<td>Relapse of BC, receiving dibromomannitol</td>
<td>7.4</td>
<td>40,000</td>
<td>64</td>
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<tr>
<td>24</td>
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<td>CML, BC</td>
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<td>W</td>
<td>CML, BC</td>
<td>Untreated for BC</td>
<td>9.6</td>
<td>56,000</td>
<td>92</td>
<td>100 (Ph +)</td>
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<td>W</td>
<td>CML, BC</td>
<td>Untreated for BC</td>
<td>9.9</td>
<td>6,900</td>
<td>56</td>
<td>90 (Ph +)</td>
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<tr>
<td>27</td>
<td>42</td>
<td>F</td>
<td>W</td>
<td>CML, BC</td>
<td>BC on combination chemotherapy — prednisone, vincristine, 6-MP, and methotrexate</td>
<td>8.5</td>
<td>4,200</td>
<td>52</td>
<td>&gt;90 (Ph +)</td>
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*ALL = Acute Lymphocytic Leukemia.
AML = Acute Myelocytic Leukemia.
CML = Chronic Myelocytic Leukemia.
BC = Blastic Crisis.

**Ph + = Philadelphia chromosome positive.
**Distance below costal margin.
Fig. 2.—Peripheral blood leukocyte specific activity in patients with untreated acute lymphocytic leukemia.

Radioautographic analysis revealed that the early radioactivity was due predominantly to labeled large lymphocytes and occasional monocytes and small lymphocytes. The lymphocyte labeling index (LI) during this period varied from 4.3–6.3 percent. The rapid increase in activity was due to the appearance of labeled neutrophils with the neutrophil LI at the peak being 30.8 percent. Only rare labeled lymphocytes were identified at this time.

Acute Lymphocytic Leukemia, Untreated

Two of the patterns (patient Nos. 1 and 2) obtained in patients with untreated acute lymphocytic leukemia are presented in Figure 2. As can be seen, there was an early appearance of leukocyte radioactivity with initial peaking at 40–50 hours. A second peak was present in patient No. 1 at 115 hours and a questionable peak at 95 hours in patient No. 2. Peripheral blood radioactivity was still present when the studies terminated.

The initial radioactivity peak in both patients was related to labeled blast cells with maximum labeling indices of 5 percent (patient No. 1) and 2.3 percent (patient No. 2). It should be noted that on the routine differential count in patient No. 2 no blasts were observed. However, on radioautographic analysis of 4000 cells, the blasts were seen. The questionable small second peak in patient No. 2 was comprised of labeled blast cells, neutrophils, and lymphocytes while the larger second peak in patient No. 1 consisted predominantly of labeled neutrophils (LI 9 percent) with the persistence of small numbers of labeled blast cells (LI 0.5 percent). The radioactivity after 150 hours was found in neutrophils and no labeled blast cells were seen even when 2000 cells were examined.

Acute Myelocytic Leukemia, Untreated

The eight untreated cases of acute myelocytic leukemia (AML) demonstrated early appearance of peripheral blood leukocyte radioactivity with ini-
Fig. 3.—Leukocyte kinetic curve in a patient with acute myelocytic leukemia.

Initial peaks between 25 and 50 hours post-injection of H³TdR. Second peaks were observed at 65–120 hours. In Figures 3 and 4, the results of two studies in which frequent peripheral blood determinations were obtained during the early period of investigation are shown. In these patients, definite primary and secondary peaks were seen separated by 50 (Figure 3) and 40 (Figure 4) hours, respectively. The initial peaks in all cases were composed of labeled blast cells. The secondary peaks were also predominantly due to labeled blasts although small numbers of labeled neutrophils and lymphocytes were present. Blast cell labeling indices were variable but usually did not exceed 10 percent at the peak. However, patient No. 5 (Figure 3) had a blast cell LI of 31.6 percent associated with the initial radioactivity peak. Blast cell labeling indices were always smaller in association with the second peaks although mean grain counts did not change significantly. Small numbers of labeled circulating blasts were identified at 200 hours in four cases studied for that period of time.

Acute Myelocytic Leukemia, Relapse

Patient No. 13 (Figure 5) was studied on three occasions during various phases of her disease. At the initiation of the first study, the patient was considered to be in remission by bone marrow examination (<5 percent blast cells) and by the absence of circulating abnormal cells. However, her leukocyte radioactivity curve was abnormal with the presence of an early peak at 25 hours. Simultaneously, small numbers of leukemic blast cells (4 percent of the total white cell count) appeared in the peripheral blood, and it was the labeling of these cells and small numbers of lymphocytes which accounted for
Fig. 4.—Peripheral blood leukocyte kinetic curve in a patient with untreated acute myelocytic leukemia.

the abnormal peak. The second, and major, peak was composed primarily of labeled polymorphonuclear neutrophils although small numbers of labeled blast cells were also present.

The second investigation was performed after antileukemic therapy had induced a complete remission. The kinetic pattern and radioautographic analysis were normal.

On the occasion of the third study, the patient was in relapse. A major peak of radioactivity correlating with labeled blast cells was present at 48 hours. Secondary peaks at 140 and 190 hours were associated with a predominance of labeled neutrophils although labeled blast cells were also present. Leukocyte radioactivity at the termination of this study (240 hours) was confined to neutrophils.

Acute Leukemia, Remission

Eight individuals with ALL and one with AML were in bone marrow remission (<5 percent blast cells) at the time of study. In six of these cases,
there was no evidence of disease by the usual criteria, so that remission was considered complete. Illustrative peripheral leukocyte kinetic patterns are presented in Figure 5 and in the composite Figure 6.

Patient No. 20 with hepatosplenomegaly and biopsy-proven leukemic infiltration of the liver but with bone marrow remission demonstrated a predominant peak of leukocyte radioactivity at 20 hours. This marked early radioactivity was due to the presence of labeled lymphocytes and neutrophils. Patient No. 19 although considered to be in a complete remission had an early peak at 24 hours with maintenance of the radioactivity level above that normally expected for the early time period. Lymphocyte labeling accounted for the major activity (lymphocyte LI 3.1 percent) with occasional labeled blast cells, monocytes, and neutrophils also present. This patient relapsed less than two months following study. The early peak in patient No. 18 was related to an unexplained but transient monocytosis (15 percent monocytes with a monocyte LI of 16 percent).

Patient No. 17 was of special interest. When first studied, she was in complete remission and had a normal leukokinetic pattern. At the time of her second study, she had developed bilateral ovarian masses shown at laparotomy to be leukemic infiltrates while maintaining a remission bone marrow and peripheral blood status. Her peripheral leukocyte radioactivity pattern and radioautographic analysis showed no change.

Six individuals with acute leukemia in complete remission [patient Nos. 1 (second study), 13 (second study), 14, 15, 16, and 17 (first study)] had nor-
Fig. 6.—Leukocyte kinetic patterns in patients with acute lymphocytic leukemia in bone marrow remission.
Fig. 7.—Peripheral blood leukocyte kinetics in patients with chronic myelocytic leukemia in relapse and in blastic crisis.

The leukocyte kinetic curve typical of patients with chronic myelocytic leukemia (CML) is shown in Figure 7 (patient No. 21). Two major peaks of leukocyte radioactivity are characteristic in this disease with the presence of an early, sharp peak at 31–40 hours and a second broader peak between 100 and 165 hours. There is no difference between the two with respect to differential counts, types of cells labeled, and total grain counts. The predominant cell labeled in both peaks is the myelocyte. When patient No. 21 developed the blastic phase, he was studied again with H3TdR. The initial early peak observed in the first study was still present, but the second broad peak was no longer present. Radioautographic analysis now revealed that labeled cells were predominantly blast cells.

The typical pattern observed in six cases of blastic crisis (BC) is shown in Figure 8 (patient No. 23). There was an early peak of radioactivity similar to that found in untreated acute leukemia. The most striking difference between this pattern and that in typical CML was the absence of the second broad peak which was replaced by smaller, more discrete peaks occurring at 95–140 hours. The predominant labeled cell throughout was the blast although during the later time periods; small numbers of labeled neutrophils were present. Labeled blasts could be identified in small numbers at 200 hours in cases which were studied for that length of time.

Patient No. 22 (Figure 7) previously studied in a typical CML phase had the usual leukocyte radioactivity pattern with labeled myelocytes predominating in both peaks. There were no circulating blasts in the peripheral blood and the bone marrow contained 15–25 percent blast cells. Later when his bone marrow was consistent with BC (50 percent blast forms), he was restudied and found to have a radioactivity pattern similar to that obtained in the
initital study. At this time, there were 25 percent blast cells in the circulating blood. The initial peak was now composed of labeled blast cells (LI 11 percent) while the second broad peak was related to both blasts and neutrophils with no other elements labeled. The early portion of the broad second peak was due primarily to blasts (LI 31.7 percent) while the later, more sustained portion of the peak was primarily related to neutrophils (maximum LI 29.8 percent) with decreasing numbers of labeled blasts.

DISCUSSION

Peripheral blood leukocyte dynamics are considerably altered from normal in patients with acute leukemia in relapse and chronic myelocytic leukemia in blastic crisis. Following intravenous injection of H3Tdr, peripheral blood leukocyte radioactivity was detected by liquid scintillation counting almost immediately and was found to be in blast cells on radioautographic analysis. There was then a progressive increase in radioactivity representing the appearance of increasing numbers of labeled blast cells with peak activity in 1–2 days. The early, gradual rise in labeled blasts was probably due to influx from the bone marrow and possibly other sites as has been previously suggested.4,5,21 In contrast, in hematologically normal individuals and patients with acute leukemia in complete remission, there was only a low level of activity present at this time related to labeled large lymphocytes and occasional monocytes and small lymphocytes.
There were secondary peaks of peripheral blood leukocyte radioactivity in all patients with acute leukemia in relapse and CML in BC, which usually were composed primarily of labeled blasts although small numbers of neutrophils were present in addition. The LI of blast cells always diminished between the initial peak and the secondary peak. These peaks were most clearly discernible in the patients whose leukokinetic patterns are shown in Figures 3 and 4. Since the two peaks were separated by 40-70 hour intervals, one might consider that the peripheral leukocyte radioactivity curves represented the release of successive waves of leukemic blast cells from the bone marrow with generation times between 40 and 70 hours. Such values for generation times would be similar to previous estimates although considerably longer and shorter generation times have also been suggested. Alternatively, recirculation of labeled blasts might account for secondary peaks of activity.

There are certain features of the peripheral blood leukocyte specific activity pattern which are distinctive in CML. As noted earlier, two peaks consisting primarily of labeled myelocytes are present. In the present studies, patient No. 22 when in blastic crisis had a peripheral leukokinetic pattern which was similar to that obtained when he was in a typical CML phase of disease. However, the initial peak obtained by liquid scintillation counting on this occasion was comprised of labeled blasts while the second broad peak represented labeling of both blasts and neutrophils. The neutrophils predominated later in the peak and at the usual time observed in normal individuals. Once the disease became well established, the second broad peak disappeared and was replaced by discrete, smaller peaks. The loss of the broad peak was correlated with increasing bone marrow involvement with leukemic blast cells and with the appearance of fewer labeled neutrophils suggesting that the release of normal neutrophils was not greatly affected until normal precursors were replaced by the abnormal blast cells. It is of interest that the leukocyte specific activity patterns obtained in patients with CML in BC resembled some of the patterns in patients with acute leukemia in relapse (patient Nos. 2, 5, 6).

It has been suggested that the mean blood transit time for labeled blast cells is approximately 33-43 hours. No attempt was made in this study to estimate blood transit times. However, small numbers of circulating labeled blasts were often identified after 200 or more hours of study. This could represent persistence of cells in the peripheral blood for the entire time period, recirculation of small numbers of labeled cells, or reutilization of label by cells in DNA synthesis. Persistent radioactivity beyond 200 hours was present in neutrophils and lymphocytes.

When a complete remission was obtained in acute leukemia, a normal leukokinetic pattern was restored as has been previously noted in patients with CML in remission. It is of interest that a normal curve was observed in a patient (No. 17) with ALL in bone marrow and peripheral blood remission but with ovarian masses due to leukemic infiltration. If leukemic cells were being released from the infiltrates, they were not detectable in the peripheral blood nor did they affect the leukocyte specific activity curve. In contrast, the curve was abnormal in patient No. 20 who had hepatosplenomegaly and biopsy
proven leukemic infiltration of the liver but was in bone marrow remission. There were also abnormal early peaks in patient Nos. 18 and 19 whose bone marrow examinations were considered to be in remission category. The source of the labeled cells responsible for these abnormal leukokinetic curves is not clear but the important point is that patients who are considered to be in remission by the usual criteria may exhibit abnormal leukocyte kinetic patterns.

Summary

Peripheral blood leukocyte dynamics were investigated in a group of patients with acute leukemia both in relapse and remission and in chronic granulocytic leukemia in blastic crisis. In acute leukemia in relapse and in chronic granulocytic leukemia in blastic crisis, labeled blast cells appeared promptly with a peak at one to two days. Secondary peaks occurred 40-70 hours following the first peaks with labeled blasts usually the predominant labeled cell in both peaks. The time interval between these successive waves of labeled blasts could represent a generation time. The leukocyte specific activity patterns obtained in patients in blastic crisis resembled some of the patterns of patients with acute leukemia.

The leukocyte kinetic patterns in patients with acute leukemia considered to be in complete remission were usually normal. However, in some patients in bone marrow remission only, an abnormal early peak was present usually composed of labeled abnormal cells released early into the peripheral circulation. In the presence of a known leukemic infiltrate, alteration of the normal leukocyte kinetic curve apparently depended upon release of these leukemic cells into the circulating blood.

Summario in Interlingua

Le dynamica de leucocytos in sanguine peripheric esseva investigate in un gruppo de patientes con leucemia acute in recidiva e in remission e in patientes con chronic leucemia granulocytic in crise blastic. In leucemia acute in recidiva e in chronic leucemia granulocytic in crise blastic, marcate blastocytos appareva promptemente con un culmine post inter un e duo dies. Culmines secundari occurreva inter 40 e 70 horas post le prime culmines. In ambe occasiones, marcate blastocytos esseva usualmente le predominante marcate cellulass. Il pare possibile que le intervallo de tempore inter iste successive undas de marcate blastocytos representa un generation. Le configurationes de activitate leucocyto-specific obtenite in patientes in crise blastic resimilava certes del configurationes de patientes con leucemia acute.

Le configurationes de cinetica leucocytic in patientes con leucemia acute in (supponitemente) complete remission esseva usualmente normal. Tamen, in certe patientes in qui le remission esseva restringite al medulla ossee, un precoce culmine anormal esseva presente, composite usualmente de marcate cellulass anormal liberate preccemente ad in le circulation peripheric. In le presentia de un cognoscite infiltrato leucemic, le alteration del normal curva del cinetica leucocytic dependeva apparentemente del liberation de ille cellulass leucemic ad in le sanguine circulante.

Acknowledgment

The authors wish to express their appreciation to Dr. Edward Henderson and Dr. Paul Carbone for allowing us to study their patients and to Miss Ada Brooks for technical assistance.
REFERENCES


Peripheral Leukocyte Kinetic Studies of Acute Leukemia in Relapse and Remission and Chronic Myelocytic Leukemia in Blastic Crisis

HERMAN A. GODWIN, THEODORE S. ZIMMERMAN and SEYMOUR PERRY