Leukocyte Labeling With $^{51}$Chromium. II. Leukocyte Kinetics in Chronic Myelocytic Leukemia

By James L. Scott, Robert McMillan, J. Gary Davidson, and Joseph V. Marino

Sequential or simultaneous leukocyte kinetic studies using radioactive diisopropylfluorophosphate and radiochromate ($^{51}$Cr) yielded similar or identical blood leukocyte disappearance curves in seven patients with chronic myelocytic leukemia (CML). Body surface $^{51}$Cr counting regularly showed a rise in the spleen counting rate during the first hours after infusions of granulocyte populations of mixed maturity. Epinephrine-induced leukocytosis was associated with a fall in the spleen counting rate, lesser decreases over the liver and marrow, rises in the heart and lung counting rates, and an unchanged blood leukocyte disappearance curve. These changes are consistent with the mobilization by epinephrine of a marginal granulocyte pool (MGP), which is largely localized in the spleen and is in equilibrium with the circulating pool. Immature CML granulocyte fractions were cleared from the blood more rapidly than mixed cell populations. The immature cells failed to equilibrate with the splenic MGP, and instead accumulated in the marrow and later recirculated into the blood as mature cells. These findings indicate that the delayed and variably contoured blood granulocyte disappearance curves found in CML are composites resulting from the recirculation of immature granulocytes in the presence of an enlarged total blood pool of mature cells.

Previous studies in chronic myelocytic leukemia (CML) of leukocytes labeled in vitro with radioactive diisopropylfluorophosphate (DF$^{32}$P or $^3$H-DFP) have regularly shown a delay in the disappearance of autologous granulocytes from the blood. The clearance curves differ in contour, both in different patients and in repeated studies of the same patient. When plotted...
against a logarithmic ordinate, three general types of curves are found consistently: single exponentials such as those observed in normal subjects and in conditions associated with mature neutrophilic leukocytosis, curves with two distinct exponential phases, and curvilinear multiexponential curves. A number of explanations for these variations have been proposed.

In the present study, we have investigated the intravascular kinetics of autologous CML leukocytes labeled in vitro with radiochromate ($^{51}$Cr); this technique allows body surface scanning for assessment of the organ distribution of the labeled cells. In most of the subjects a DF$^{32}$P study was also done, for comparison with and validation of the $^{51}$Cr results. The blood disappearance curves of DF$^{32}$P- and $^{51}$Cr-labeled leukocytes were comparable. Body surface scanning curves after the infusion of cells of mixed maturity showed the early pooling of cells in the spleen, described previously by Duvall and Perry. Immature CML blood granulocytes were found to leave the blood more rapidly than mature cells. The young cells were preferentially sequestered in the marrow, and reentered the blood after maturation. This confirms the presence of at least two kinetically different leukocyte populations in the blood in CML.

**Materials and Methods**

The WBC labeling technique is described fully in a preceding report. First, 500 ml of venous blood anticoagulated with ACD-A solution was mixed with 250 ml of 6% dextran in 0.9% saline (Macrodex, Pharmacia Labs.), the RBC allowed to sediment, and the leukocytes in the supernatant concentrated by centrifugation. After resuspension in 50 ml of pH 7.4 dextrose-phosphate buffer containing 500 $\mu$Ci of $^{51}$Cr, the leukocytes were incubated for 30 min at 37°C; in combined labeling studies, 50 $\mu$Ci of DF$^{32}$P were also added during this step. After incubation the excess chromate was reduced by the addition of 30 mg of ascorbic acid. The cells were washed twice with autologous plasma-dextran and resuspended in this for infusion. After the labeled cell infusions, which contained an average of $3 \times 10^{10}$ cells, the leukocytes from serial timed venous blood samples were purified by the method of Athens and co-workers. This method tends to concentrate granulocytes and minimize lymphocyte contamination, but had no effect on the granulocyte differential counts of the CML blood samples. Leukocyte $^{51}$Cr radioactivity was determined in a conventional iodide crystal well, and DF$^{32}$P radioactivity was measured in a thin-window gas flow counter. The nitrogen content of each sample was determined, and leukocyte specific activity was expressed as counts per minute per milligram of leukocyte nitrogen. The results were plotted against time on semilogarithmic graph paper. Body surface counting rates of $^{51}$Cr were determined with a collimated iodide crystal probe over the heart, right upper lung field, liver, spleen, and sacrum as blood samples were obtained. In two studies the granulocytes of whole blood were labeled with DF$^{32}$P, without prior cell separation, by the method of Mauer and co-workers. The number of granulocytes in the TBGP, the CGP, and the MGP were calculated from the formulas of Athens and co-workers.

Written consent of the patient for the study was obtained after a thorough description and discussion of the experimental nature of the procedure by a member of the research team not involved in the care of the patient. The consent of the physician responsible for the care of the patient was also obtained.

Kinetic studies were performed in eight patients. The pertinent clinical and laboratory findings in these cases are summarized in Table 1. The patients ranged in age from 27 to 79 yr. Palpable splenomegaly was present in six. Their total blood leukocyte counts at the time of the study ranged from 25,000 to 270,000/cu mm. The differential blood leukocyte counts in each case were characteristic of CML. Leukocyte alkaline phosphatase activity was determined in each case by the method of Kaplow, and was decreased in all but one
Table 1.—Clinical and Laboratory Characteristics

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)</th>
<th>Spleen (cm below LCM)</th>
<th>Total WBC (per cu mm)</th>
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<th>Myelo</th>
<th>Meta</th>
<th>PMN</th>
<th>Mono</th>
<th>Lymph</th>
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<td>4</td>
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B1/promy, myeloblasts and promyelocytes; myelo, myelocytes; meta, metamyelocytes; PMN, mature neutrophils; mono, monocytes; lymph, lymphocytes; LAP, leukocyte alkaline phosphatase; Ph¹, Philadelphia chromosome; ND, not done.

(Case 5). Karyotype studies of this patient's blood and marrow granulocytes also failed to demonstrate the Philadelphia chromosome. This abnormality was present in all four of the other cases studied. We gratefully acknowledge the help of Dr. George J. Anday, in whose laboratory the karyotyping was performed.

RESULTS

Comparison of the DF²⁺⁻ and ⁵¹Cr Techniques

In seven patients, leukocyte kinetic studies using both the DF²⁺⁻ and the ⁵¹Cr techniques were made. In Cases 1 to 3, DF²⁺⁻ and ⁵¹Cr studies were performed sequentially. In Cases 1 and 2 the granulocytes were labeled with...
DF\(^{32}\)P by the whole blood method of Mauer and co-workers\(^8\) and in Case 3 the leukocytes were separated before labeling with DF\(^{32}\)P. The blood leukocyte disappearance curves are shown in Fig. 1. In Case 1, circumstances resulted in a 2-wk delay between the DF\(^{32}\)P and the \(^{51}\)Cr studies. There was no significant clinical change in the interim, but the disappearance curves differ in contour. The DF\(^{32}\)P curve is a single exponential during the first day, whereas the \(^{51}\)Cr curve has a more rapid, multiexponential first phase. In Cases 2 and 3 the DF\(^{32}\)P and \(^{51}\)Cr studies were made 2 and 6 days apart, respectively. In both cases the DF\(^{32}\)P and the \(^{51}\)Cr curves are approximately parallel single exponential curves during the first 24 hr. Differences between these curves during the second day of the study are of doubtful significance because in each case the slope is determined by a single measurement of leukocyte specific activity.

In Cases 4 to 7 the separated blood leukocytes were labeled simultaneously with DF\(^{32}\)P and \(^{51}\)Cr (Fig. 2). In all four cases the DF\(^{32}\)P and \(^{51}\)Cr curves are approximately parallel. In Cases 4 and 5 both curves show a rapid exponential fall during the first few hours and for the next 48 hr approximate a single exponential. In Case 6 the curves have two distinct exponential components, whereas in Case 7 the parallel DF\(^{32}\)P and \(^{51}\)Cr curves are multiphasic.

Estimates of the clearance half-time (T\(_{1/2}\)) of these sequential and combined studies are shown in Table 2. The line best fitting a logarithmic plot of the data was approximated visually; because of the early rapid fall in leukocyte specific activity.

**Fig. 2.—**Leukocyte specific activity curves in combined \(^{32}\)DFP and \(^{51}\)Cr studies. Symbols as in Fig. 1.
Table 2.—Comparison of Data Calculated From $^{32}$DFP and $^{51}$Cr Leukocyte Kinetic Studies

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Total WBC (per cu mm)</th>
<th>$T_{1/2}$ (hr) $^{32}$DFP</th>
<th>$T_{1/2}$ (hr) $^{51}$Cr</th>
<th>CBGP $\times 10^3$ Granulocytes/kg</th>
<th>TBGP $\times 10^3$ Gran./kg $^{51}$Cr</th>
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* Multieponential blood WBC disappearance curve.

CBGP, circulating blood granulocyte pool; TBGP, total blood granulocyte pool.

Activity in some studies and the biphasic or multiphasic character of the curves in others, calculations of the slope of the curves by the method of least squares was not considered to be justified. The $^{51}$Cr curve in Case 1 is insufficiently linear to allow a reasonable approximation of the $T_{1/2}$; in Case 6 the $T_{1/2}$ value of the first portion of the biphasic curve is given in Table 2. In every case the $T_{1/2}$ values are greater than normal. There is no correlation between the $T_{1/2}$ values, which are within a narrow range of 19 to 30 hr, and the blood leukocyte counts, which range between 28,000 and 270,000/cu mm.

TBGP size was calculated from the percentage of the labeled cells recovered in the circulation at zero time. In Cases 1, 2, and 7 there is reasonable agreement between the TBGP size estimates calculated from the DF$^{32}$P and the $^{51}$Cr data, but in Cases 3 through 6 the $^{51}$Cr data gave TBGP size estimates substantially greater than those calculated from the DF$^{32}$P results.

Fig. 3.—Representative $^{51}$Cr body surface counting rate curves. Closed circles, Case 1; open circles, Case 2; triangles, Case 4; X Case 5; +, Case 7.
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Body Surface Counting of $^{51}$Cr

Representative body surface counting rate curves are shown in Fig. 3. The usual results are represented by the curves of Cases 4, 5, and 7. The curves of Cases 1 and 2 are depicted because the results were somewhat unusual.

The heart counting rate curves varied in contour from one case to another and, with the exceptions of Cases 2 and 7, do not resemble the blood leukocyte specific activity curves. The failure of the precordial counting rate curve to reflect the decrease in the radioactivity of blood flowing through the heart in these cases was probably the result of accumulations of radioactivity in the spleen. Slight differences in the axis of the body counting device were found to cause significant changes in both the heart and spleen counting rate determinations. Lung counting rates were monitored in Cases 1, 2, 3, and 6 and in each case were parallel to the heart curves.

The spleen curves vary in contour, but early accumulation of radioactivity over the spleen was observed in every study. In Cases 1 and 2, splenic accumulation of radioactivity was exceptionally great and prolonged. In each case, splenic radioactivity reached peak levels within the first 12 hr of the study and then declined. Except for Case 1, the hepatic curves fell off in a fashion resembling the blood leukocyte specific activity curves during the first 6 hr of study. Later slight increases in hepatic radioactivity were seen in Cases 4 and 5. The exceptional accumulations of radioactivity in the spleen in Case 1, and in both the spleen and liver in Case 2, were associated with greater enlargement of these organs and higher blood leukocyte counts. Sacral marrow counting rates were monitored in Cases 3, 4, 5, and 7. Case 3 was studied twice with
similar results, except for the transient changes associated with epinephrine infusion in the second study (Fig. 4). In both studies the sacral curve rose by about 50% during the first 8 hr and fell to about half of the initial value at 24 hr. In case 4 the sacral curve was parallel to the heart curve, which approximated the blood leukocyte specific activity curve. The sacral curve of Case 5 was essentially flat. In Case 7 the sacral curve fell in parallel with the blood curve during the first 2 hr of the study and then rose to reach a plateau at 10 hr. The latter curves are not illustrated because of their complexity and variability.

Kinetic Effects of Epinephrine

In the second study of Case 3 the kinetic effects of epinephrine were determined. Between the two studies the blood leukocyte count had risen from 28,000 to over 50,000/cu mm. An intravenous infusion of 0.5 mg of epinephrine was given over a 10-min period, 3 hr after the labeled leukocyte infusion, and during the increase in splenic radioactivity. The body counter was placed over the spleen just before the epinephrine infusion, and changes in the counting rate were monitored with a recording ratemeter (Fig. 4, insert). During the epinephrine infusion there was a decrease in the spleen counting rate, and a rise in the blood leukocyte count from about 50,000 to slightly more than 90,000/cu mm. The blood leukocyte differential count and the hematocrit were unchanged. After completion of the infusion there was a gradual increase in the splenic counting rate curve and a decrease in the blood leukocyte count to preepinephrine levels. The blood granulocyte disappearance curve was not substantially altered during the epinephrine infusion.

Monitoring of the spleen counting rate was interrupted immediately before and after completion of the epinephrine infusion and again after the spleen counting rate had returned to its preinfusion level, to determine body surface counting rates over the heart, lung, liver, and sacrum. Epinephrine infusion was associated with a sharp fall in the accumulating sacral radioactivity. During the epinephrine infusion the liver counting rate, which was already decreasing, fell somewhat more sharply. The heart counting rate and the counting rate over the lung, not shown in the figure, increased during the infusion. Within an hour after beginning the infusion, each of these curves had either returned to preinfusion levels or had resumed their previous trends. The sacral counting rate reached a maximum 8 hr after the labeled cell infusion, and began to fall at 12 hr. The liver counting rate returned to a level slightly below the preepinephrine level, and fell gradually thereafter. The heart counting rate fell slightly at 8 hr and, 24 hr after beginning the study, fell sharply and in parallel with a fall in the spleen curve.

Immature Granulocyte Kinetics

The kinetics of immature CML granulocytes were evaluated in two patients. In one (Case 6) this was done by fractionating the blood leukocytes after the infusion of labeled whole blood granulocytes. The whole blood granulocytes were labeled with DF32P and 51Cr in the usual way. A portion of each post-infusion blood sample was freed of mature granulocytes by passage through a
nylon column (Fenwal Leukofilter), which resulted in the removal of more than 95% of the polymorphonuclear and metamyelocyte forms. The specific activity of the remaining immature granulocytes was compared with that of the unfractonated leukocytes. The immature fraction was about two-thirds myelocytes and one-third promyelocytes and myeloblasts, and comprised about 30% of the total blood leukocytes. The young cells were cleared from the circulation more rapidly than the mixed leukocyte population (Fig. 5). The curve is multiphasic; the T½ of the rapid first phase is about 5 hr. The disappearance curve of the unfractonated leukocyte population is a biphasic exponential; the T½ of the shorter first phase is about 20 hr. The paired DF32P and 51Cr curves of both the mixed and the immature cell fractions are practically parallel.

To assess further the kinetics of the immature cells, this fraction was isolated with the nylon column technique and labeled with 51Cr prior to infusion in Case 8. Two consecutive 500-ml blood samples were processed to yield 1.2 × 10^10 immature forms, which made up 16% of the blood leukocyte count of 49,000/cu mm. The red cells were recovered, suspended in saline, and returned to the circulation before infusion of the labeled granulocytes. After the first study day the leukocytes were fractionated with the nylon column technique; the mature granulocytes were recovered by eluting the adsorbed cells with 0.02% EDTA solution. The specific activities of the immature and mature fractions were compared with the specific activity of unfractonated leukocytes (Fig. 6). The T½ of the disappearance curve immediately after injection of the labeled immature cell fraction was about 4 hr (Fig. 6 insert). After the first 24 hr the specific activity of the immature fraction approximated a biphasic exponential curve and fell more rapidly than the approximately triphasic exponential curve of the unfractonated leukocytes. The
specific activity of the mature cell fraction was greater than that of the unfractionated cells after the third day of the study. The curve is biphasic.

The disappearance of the immature leukocyte fraction from the blood was associated with an initially rapid and later gradual rise in radioactivity over the sacral marrow area. This reached a peak on the sixth day, and thereafter fell approximately in parallel with the heart counting rate curve. The heart curve paralleled the specific activity curve of the unfractionated leukocytes during the entire study, unlike the results found in studies of labeled CML leukocytes of mixed maturity. This probably reflects the absence, in the immature cell kinetic study, of the early and sometimes sustained increase in splenic radioactivity that influenced the heart counting rate curve in the studies of labeled cells of mixed maturity. Infusion of the labeled immature granulocyte fraction was followed by a small and transient early increase in splenic radioactivity of a few hours’ duration (Fig. 6, insert), but thereafter the spleen curve fell in parallel with the heart and the mixed blood leukocyte specific activity curves. This continued for the first 10 days of the study. During the next 7–10 days the spleen curve approximated a plateau. The slight rise in spleen counts between the 10th and 17th days and the fall on day 20 are exaggerated by the logarithmic ordinate, and the absolute changes are too small to justify interpretation.

**DISCUSSION**

Previous studies in normal subjects showed that the blood disappearance curves of DF32P and 51Cr-labeled leukocytes were similar but not always
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identical. The calculated recovery of labeled whole blood leukocytes in the circulation, on which estimates of the size of the MGP and the TBGP are based,⁸ was for ⁵¹Cr-tagged cells regularly less than half that found for granulocytes labeled with DF³²P.⁶ Subsequent studies indicate that the lower estimates of ⁵¹Cr-tagged cell recovery resulted from our failure to take into account the early and rapid disappearance of lymphocytes¹¹ from the labeled normal leukocyte population.

The present studies of CML leukocyte kinetics also show discrepancies between the results of DF³²P and ⁵¹Cr studies. In one case distinctly different disappearance curves were observed. In this instance the cells were isolated prior to labeling with ⁵¹Cr, while the granulocytes were labeled with DF³²P without isolation. In a second case studied in this fashion the curves were comparable. In the first case, the delay of 2 wk between the studies may have been a factor. Substantial variations, ascribed either to inaccuracies of the method or to physiological variations, have been observed between DF³²P studies done a month apart in normal subjects.¹²

We have no satisfying explanation for the poor agreement found between estimates of TBGP size calculated from the ⁵¹Cr and the DF³²P data. Either elution of ⁵¹Cr from the cells or loss of cells from damage by the ⁵¹Cr-labeling procedure could result in the observed overestimates of TBGP size, but neither disadvantage was found to be significant in previous studies.⁵,⁶ In addition, although there is no relationship apparent between the discrepant TBGP estimates and the leukocyte differential counts in these cases, it is conceivable that differences in the distribution of the two isotopes in cells of differing maturity could account for the observed differences. Autoradiographic studies of the distribution of ⁵¹Cr in CML granulocytes of differing maturity are now in progress, for comparison with the ³H-DFP data of Kurth and co-workers¹⁴ and further evaluation of this factor. If these possibilities were important factors, however, it seems likely that the blood leukocyte disappearance curves of cells labeled with the different isotopes would be dissimilar, which was not the case.

The body counting rate curves we observed after infusions of unfractionated ⁵¹Cr-labeled CML blood leukocytes resemble the results previously reported by Duvall and Perry.⁵ The findings are compatible with the interpretations formulated from DF³²P studies by Athens and co-workers.¹ The cells equilibrate within hours with an intravascular MGP, which with ⁵¹Cr-tagged cells is most easily detectable in the spleen. Epinephrine mobilization into the circulation of a splenic MGP, in equilibrium with the circulating granulocyte pool (CGP), is shown by the fall in the splenic counting rate, the coincident rise in the blood leukocyte count, and the lack of change in the blood leukocyte specific activity. The fall in the liver and marrow counting rates during epinephrine infusion indicates that a portion of the MGP also resides in these organs. Enlargement of the MGP of the degree present in CML may be required for the detection of fractions of the MGP residing in organs other than the spleen, because these changes were not detectable in a normal subject.⁶ Previous studies have convincingly shown that a sizable portion of the MGP is extrasplenic; marginated cells can be seen in the blood vessels of other
organs, and stimuli that mobilize the MGP produce granulocytosis in splenectomized individuals.

The finding that immature granulocytes were cleared from the blood more rapidly than mature cells was unexpected, because it has been observed that young granulocytes fail to enter tissue inflammatory exudates and appear to remain in the circulation longer than mature cells. The organ distribution of the 51Cr-tagged immature cell fraction suggests an explanation for these apparently conflicting findings. The rise in the sacral counting rate, concurrent with the fall in blood leukocyte specific activity during the first week of the study, is compatible with the accumulation of young cells in the marrow. The subsequent fall in the sacral counting rate in association with an increase in the proportion of labeled mature cells in the blood suggests that the cells matured during their sojourn in the marrow and then returned to the circulation. The recirculation of immature granulocytes after a period of maturation in the marrow has been demonstrated with other techniques.

These studies confirm the presence in the blood in CML of at least two kinetically different populations of leukocytes, and show that the differences in kinetic behavior are related to cell maturity. The recent studies of Lichtman may be relevant to these behavioral differences. Immature granulocytes are less deformable than mature cells. This has suggested that the egress of granulocytes from the marrow is related to the increase in cell deformability which accompanies maturation. The marrow accumulation of labeled immature CML blood granulocytes observed in our study further suggests that the marrow has some characteristic that facilitates the reentrance of immature cells, which may either have leaked into the blood from the marrow or been formed in other sites. The failure of the immature cells to accumulate initially in the spleen, presumably in the splenic MGP, and to enter the tissues suggests that the surface characteristics of maturity may also be required for cell margination in small vessels and egress into the tissues.

These results also support the suggestion of Galbraith that the blood granulocyte disappearance curve in CML is a composite resulting from the presence of multiple kinetic populations. It seems likely that several interrelated factors influence this curve. Labeled mature granulocytes equilibrate within hours with an enlarged MGP, a major proportion of which resides in the enlarged spleen. The mature CGP is also enlarged in CML. This enlargement of the mature TBGP delays, by dilution of the labeled cells, their clearance from the blood. Concurrently, labeled immature blood granulocytes leave the circulation and enter the marrow. After maturation, they recirculate and equilibrate with other cells in the enlarged mature TBGP. It seems likely that variations in the magnitude of these factors, in different patients and at different stages of the disease, explain the variety of blood granulocyte disappearance curves observed in CML.

REFERENCES

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