Granulocyte Kinetic Studies in Patients with Proliferative Disorders of the Bone Marrow

By Alvin M. Mauer and Thomas Jarradi

There is an apparent relationship between chronic myelocytic leukemia, polycythemia vera and essential thrombocythemia which has stimulated the suggestion by Dameshek1 that all three diseases may be the result of a generalized proliferative disorder of the bone marrow. Although overproduction of one blood cell may dominate the clinical picture of these diseases, increased numbers of erythrocytes, platelets and granulocytes may be found in the blood in each of the conditions.

For the study to be reported here, measurements of granulocyte kinetics were made in four patients with chronic myelocytic leukemia, three patients with polycythemia vera and one patient with essential thrombocythemia to determine if the increased concentration of granulocytes in the blood of these patients was indeed the result of increased cell production or possibly related to other factors, such as prolonged survival time. In addition, granulocyte kinetic studies were done in a patient with idiopathic granulocytosis of long standing.

Methods

Granulocyte kinetic studies were done by an in vitro labeling method with $^{32}P$-tagged diisopropylfluorophosphate (DFP$^{32}$) as a cell label.2 The DFP$^{32}$ was obtained from New England Nuclear Corporation and ranged in specific activity from 192 to 380 $\mu$C./mg. of DFP. The patients' own blood was labeled except in three of the studies in the patients with chronic myelocytic leukemia. In these instances, blood was obtained from healthy, type-specific male donors with normal hematologic values.

The blood leukocytes were separated and their radioactivity determined by the method of Athens and coworkers.3 Calculations of the number of granulocytes in the total blood granulocyte pool (TBGP), the circulating granulocyte pool (CGP), the marginating granulocyte pool (MGP), and the granulocyte turnover rate (GTR) were made as described by Athens and coworkers.4,5

Alkaline phosphatase activity of the blood neutrophils was determined by the method...
of Kaplow. The normal score for the method in this laboratory ranges from 12 to 60. The pulmonary function studies done in the patients with polycythemia vera included standard measurements of lung volumes, ventilatory dynamics, functional residual capacities and gas distributions. Arterial blood oxygen saturations were determined by the Van Slyke method.

**Patients**

Patients for this study were from the Cincinnati Veterans Administration Hospital.

**Chronic Myelocytic Leukemia**

*Patient 1.* This 71 year old white farmer was first seen on May 9, 1961, because of complaints of pain in the left upper abdominal area radiating to his left shoulder. He was a thin, well appearing man with a spleen palpable 6 cm. below the left costal margin. His laboratory findings are shown in table 1. The bone marrow was hypercellular with myeloid hyperplasia. Almost complete absence of phosphatase from blood neutrophils was found on alkaline phosphatase staining of blood smears. Busulfan was given from May 12, 1961, to June 8, 1961, with a good response in white blood count and spleen size.

*Patient 2.* This 60 year old white locomotive engineer was admitted on May 31, 1961, because of a painless swelling in the left upper abdomen associated with anorexia, weight loss, and malaise. He was a pale, moderately obese man with a tender liver palpable 4 cm. below the right costal margin and a spleen extending into the pelvis, filling his entire left abdomen. The laboratory findings are shown in table 1. The bone marrow contained increased numbers of megakaryocytes but was otherwise normal. Alkaline phosphatase stains of the blood neutrophils revealed minimal phosphatase activity. Busulfan was given from June 2, 1961, to June 28, 1961, with resulting decrease in spleen size and white blood count.

*Patient 3.* This 33 year old truck driver was admitted on September 26, 1961, because of a dull aching sensation in the left upper abdomen. He was a well appearing man with a spleen palpable 14 cm. below the left costal margin and a liver felt 5 cm. below the right costal margin. A friction rub was felt and heard over the spleen. The laboratory findings are shown in table 1. The bone marrow was hypercellular and alkaline phosphatase staining of blood smears showed no phosphatase content of the neutrophils. Busulfan therapy was started on September 28, 1961, with good response in white blood count and spleen size. The therapy was continued intermittently until July 3, 1962, when he was hospitalized again because of progressive splenomegaly and diffuse bone pain. The bone marrow at that time was markedly hypercellular and the blood neutrophil alkaline phosphatase score was in the low normal range. Laboratory values are shown in table 1.

*Patient 4.* This 46 year old white railroad trainman was admitted on July 5, 1962, because of symptomatic anemia. A diagnosis of chronic myelocytic leukemia had been first established in 1958 and a good response to splenic irradiation had been obtained. During the following 3 years he had received intermittent busulfan therapy. Moderate hepatosplenomegaly and pallor were the notable physical findings on this admission. The laboratory findings are given in table 1. The bone marrow specimen was hypercellular but with decreased numbers of megakaryocytes. The blood neutrophil alkaline phosphatase score was below the normal range of values.

**Polycythemia Vera**

*Patient 5.* This 69 year old white man was found to have polycythemia vera in 1953 at another hospital. Treatment for this disease had been intermittent courses of busulfan and radioactive phosphorus. In August, 1960, a supracondylar amputation of his right leg was done because of arteriosclerotic obliterative disease. A painful ulceration of the left ankle necessitated admission to the Cincinnati Veterans Hospital on January 18, 1961. He was a markedly pelloronic man with a spleen palpable 3 cm. below the costal margin and ab-
Table 1.—Laboratory Findings: Chronic Myelocytic Leukemia

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Date</th>
<th>Hematocrit (%)</th>
<th>Reticulocytes (%)</th>
<th>Platelets (No./mm.³ x 10⁶)</th>
<th>WBC (No./mm.³)</th>
<th>PMN</th>
<th>MMy</th>
<th>My</th>
<th>MyB</th>
<th>Eo</th>
<th>Ba</th>
<th>Ly</th>
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<td>0</td>
<td>0</td>
<td>14</td>
<td>20</td>
</tr>
</tbody>
</table>

PMN = mature neutrophil; MMy = metamyelocyte; My = myelocyte; MyB = myeloblast; Eo = eosinophil; Ba = basophil; Ly = lymphocyte; Mo = monocyte; NRBC = nucleated red blood cell.
sent pulses in the left foot. Laboratory findings are given in table 2. The bone marrow was hypercellular and alkaline phosphatase stains of the blood showed increased neutrophil phosphatase with a score of 238. The arterial oxygen saturation was 97 per cent and pulmonary function studies were normal. Busulfan was given from March 30, 1961, to May 2, 1961, with decrease in spleen size and blood counts. The alkaline phosphatase score remained elevated, however.

**Patient 6.** This 71 year old white man was admitted to the Cincinnati Veterans Administration Hospital in February, 1960, with the diagnosis of polycythemia vera and generalized arteriosclerosis. He had been treated during the previous 8 years with radioactive phosphorus, the last treatment being given in July, 1959. He was obese and plethoric with a spleen palpable 2 cm. below the left costal margin. There was a partial left hemiplegia. Pulses were absent in both lower extremities and dry gangrene was present in the right great toe. Laboratory findings are shown in table 2. The bone marrow was hypercellular and alkaline phosphatase staining of blood smears showed an increased phosphatase content of the neutrophils, with a score of 208. He was given 3.5 mc. of radioactive phosphorus on February 16, 1960, and 4.0 mc. on March 25, 1960, without any noticeable effect. Busulfan therapy from June 20, 1960, to August 1, 1960 produced a hematologic remission. However, by February, 1961, a relapse was evident.

**Patient 7.** This 48 year old white salesman was admitted on May 26, 1961, because of a 3-month history of progressive fatigue, weight loss and mild exertional dyspnea. He was a plethoric, moderately obese man who appeared well. The liver and spleen were both palpable 3 cm. below the costal margins. Laboratory findings are shown in table 2. The bone marrow was hypercellular and the alkaline phosphatase stain of the blood neutrophils revealed increased phosphatase activity, with a score of 160. Arterial oxygen saturation was 91.42 per cent at rest, 91.7 per cent after exercise, and 95.3 per cent on breathing 100 per cent oxygen. Chest x-rays, intravenous pyelograms, renal and pulmonary function studies were all normal. He was given no therapy and discharged on June 21, 1961.

**Essential Thrombocytethmia**

**Patient 8.** This 55 year old white farmer was admitted on October 16, 1961. He had had intermittent easy bruising, epistaxis and hematuria for many years. In addition he had been admitted in June, 1957, because of a large hematoma of the left thigh and again in November, 1960, following a spontaneous retroperitoneal hemorrhage. He was a thin, well appearing man with a liver palpable 2 cm. below the right costal margin and a spleen felt 1 cm. below the left costal margin. Laboratory findings are shown in table 3. The bone marrow was hypercellular, and alkaline phosphatase stains of blood neutrophils revealed increased phosphatase activity with a score of 203. Busulfan was given from November, 1960, to February, 1961, and from June, 1961, to October, 1961.

**Idiopathic Leukocytosis**

**Patient 9.** This 47 year old white salesman was admitted to the psychiatric service in August, 1959, with a diagnosis of chronic paranoid schizophrenia. Until discharge in Octo-

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**Table 2.—Laboratory Findings: Polycythemia Vera**

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Date</th>
<th>Red Blood Count (No./mm. $^3$)</th>
<th>Hemoglobin (Gm. %)</th>
<th>Hematocrit (%)</th>
<th>Reticulocytes (%)</th>
<th>Platelets (No./mm. $^3$ x 10$^9$)</th>
<th>White Blood Count (No./mm. $^3$)</th>
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<td>1.07</td>
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GRANULOCYTE KINETIC STUDIES

Table 3.—Laboratory Findings: Essential Thrombocytosis

<table>
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<tr>
<th>Patient Number</th>
<th>Date</th>
<th>Red Blood Count (No./mm.$^3$ x 10$^6$)</th>
<th>Hemoglobin (Gm. %)</th>
<th>Reticulocytes (%)</th>
<th>Platelets (No./mm.$^3$ x 10$^6$)</th>
<th>White Blood Count (No./mm.$^3$)</th>
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<td>8</td>
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<td>1.07</td>
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<td>11-6-60</td>
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Table 4.—Laboratory Findings: Idiopathic Leukocytosis

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<th>Patient Number</th>
<th>Date</th>
<th>Hematocrit (%)</th>
<th>Reticulocytes (%)</th>
<th>Platelets (No./mm.$^3$ x 10$^6$)</th>
<th>White Blood Count (No./mm.$^3$)</th>
<th>Differential White Cell Count (%)</th>
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<tr>
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<tr>
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<td>0.39</td>
<td>15,900</td>
<td>66 1 2 21 10</td>
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</tr>
<tr>
<td>6-8-61</td>
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<td>—</td>
<td>—</td>
<td>16,650</td>
<td>63 2 1 26 8</td>
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</tr>
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</table>

Her, 1961, he was otherwise asymptomatic and afebrile. During this prolonged period, however, a persistent leukocytosis was present which was unexplained by any evidence of infection. Physical examinations were repeatedly normal. Laboratory findings are shown in table 4. The bone marrow was hypercellular with decreased fat content. The myeloid series was hyperplastic but maturation was normal. The myeloid:erythroid ratio was 10:1. Megakaryocytes were present in normal numbers. A small axillary node was biopsied in May, 1960, and showed mild non-specific reactive hyperplasia. The erythrocyte sedimentation rate ranged from 25 to 30 mm. during the 26 months of observation. Liver and renal function studies, serum proteins, serum electrolytes and chest and bone x-rays were all normal. Serial alkaline phosphatase stains showed increased phosphatase content of the blood neutrophils.

RESULTS

Chronic Megalytic Leukemia (Table 5)

Three patients were infused at a time of disease relapse with labeled blood from hematologically normal male donors. The leukocyte radioactivity in the patients decreased in a single exponential fashion with $T_{1/2}$'s ranging from 6.5 to 12.0 hours. If the assumption is made that the infused normal granulocytes equilibrated with the leukemic granulocytes, the total blood granulocyte pools of each of the patients was quite large. In patients 2 and 3, both the circulating and marginating pools were increased in size, but in patient 1 all of the infused leukocyte radioactivity was in the circulating granulocyte pool. If for the purposes of calculation the further assumption is made that the normal and leukemic mature granulocytes disappear at the same rate, the number of granulocytes turned over per day in these patients was markedly increased.

Three patients were also infused with their own labeled blood. None of them was in complete remission and two of the patients had myelocytes in the blood at the time of study. The leukocyte radioactivity curves obtained in these patients are shown in figure 1. Within the error of this method, the
Table 5.—Granulocyte Kinetics in Patients with Chronic Myelocytic Leukemia

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Date of Study</th>
<th>Total WBC (No./mm.³)</th>
<th>Granulocytes (%)</th>
<th>Total WBC (No./mm.³)</th>
<th>Granulocytes (%)</th>
<th>Pool Sizes (No. cells/Kg × 10^9)</th>
<th>T-½ (hrs.)</th>
<th>GTR (No. cells/Kg × 10^9)</th>
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<td>—</td>
<td>—</td>
<td>213</td>
<td>16.5</td>
<td>215</td>
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</table>

*Obtained with an extrapolated value for blood leukocyte radioactivity at t₀ (see text).
leukocyte radioactivity curves of patients 1 and 3 cannot be distinguished from a single exponential curve but in patient 4 at least a two-component curve was found. The T-½'s of these curves ranged from 11.0 to 17.5 hours. The calculations derived from these studies are shown in table 5. Calculations in patient 4 were made with both the blood leukocyte radioactivity at 0 time and the value obtained by extrapolation.

Polycythemia Vera (Table 6)

The total blood granulocyte pools in all of these patients were also large on the initial studies. Both the circulating and marginating pools were increased in size, but the marginating pool was the larger compartment in each patient. A second study was done on patient 5 after response to busulfan therapy and the blood granulocyte pools had decreased in size.

The T-½'s of blood leukocyte radioactivity ranged from 7.5 to 9.5 hours. The calculated granulocyte turnover rates were large on each initial study, but in patient 5 the turnover rate had decreased after therapy.
Table 6.—Granulocyte Kinetics in Patients with Polycythemia Vera

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Date of Study</th>
<th>Total WBC (No./mm³)</th>
<th>Granulocytes (%)</th>
<th>Pool Sizes (No. cells/Kg. x 10⁹)</th>
<th>T-½ (hrs.)</th>
<th>GTR (No. cells/Kg. x 10⁹)</th>
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Table 7.—Granulocyte Kinetics in a Patient with Essential Thrombocythemia

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<th>Total WBC (No./mm³)</th>
<th>Granulocytes (%)</th>
<th>Pool Sizes (No. cells/Kg. x 10⁹)</th>
<th>T-½ (hrs.)</th>
<th>GTR (No. cells/Kg. x 10⁹)</th>
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<td>75</td>
<td>290</td>
<td>8.0</td>
<td>482</td>
</tr>
</tbody>
</table>

Table 8.—Granulocyte Kinetics in a Patient with Idiopathic Granulocytosis

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Date of Study</th>
<th>Total WBC (No./mm³)</th>
<th>Granulocytes (%)</th>
<th>Pool Sizes (No. cells/Kg. x 10⁹)</th>
<th>T-½ (hrs.)</th>
<th>GTR (No. cells/Kg. x 10⁹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>11-20-60</td>
<td>17,060</td>
<td>71</td>
<td>216</td>
<td>7.5</td>
<td>546</td>
</tr>
<tr>
<td></td>
<td>6-5-61</td>
<td>16,550</td>
<td>65</td>
<td>246</td>
<td>7.5</td>
<td>546</td>
</tr>
</tbody>
</table>

Essential Thrombocythemia (Table 7)

The total blood granulocyte pool was found to be large in this patient, comparable to the results in the patients with polycythemia vera. Both the circulating and marginating pools were increased in size. The T-½ of blood leukocyte radioactivity was 8.0 hours and the calculated granulocyte turnover rate was 480 x 10⁷ cells/Kg./day.

Idiopathic Granulocytosis (Table 8)

In this patient in whom a persistent, unexplained granulocytosis had been present, the total blood granulocyte pool was found to be large on two occasions, with both blood granulocyte compartments sharing in the enlargement. Although a measurement of the T-½ of blood leukocyte radioactivity was impossible on the first study, a T-½ of 7.5 hours was found on the second study. The calculated granulocyte turnover rate at this time was 546 x 10⁷ cells/Kg./day.

Discussion

An increased blood granulocyte concentration is not necessarily indicative of increased cell production but might also result from increased cell survival time in blood or from a shift of granulocytes from the marginating to the circulating compartment. Therefore, to establish the mechanism for granulocytosis in patients with chronic myelocytic leukemia, polycythemia vera and essential thrombocythemia, measurements of compartment sizes and turnover rates were needed. For this purpose, the DFP₂ in vitro labeling method was chosen.

The results of granulocyte kinetic studies in normal male subjects have
been published by Athens and coworkers. The mean value and standard
deviation for the sizes of the normal blood granulocyte compartments ex-
pressed as the number of cells x 10⁷/Kg. of body weight are as follows:
TBGP = 65 ± 22; CGP = 32 ± 11; and MGP = 33 ± 16. The mean half-
time of leukocyte radioactivity with one standard deviation was 6.6 ± 1.2
hours and the mean GTR was 180 ± 74 x 10⁷ cells/Kg./day.

There were particular problems, however, in the use of this method in
the study of patients with chronic myelocytic leukemia. Labeling of the
myeloid series with DFP³² is not uniform and immature myeloid cells present
in the blood of these patients would be expected to label more heavily than
the mature neutrophils. Furthermore, Monti and coworkers found a time
course after in vivo labeling with tritiated thymidine in patients with chronic
myelocytic leukemia that suggested that the disappearance of myeloid cells
from the blood of these patients depended not on random factors but rather
on cell maturation. Thus, the lack of uniform labeling and the influence of
cell maturation would be expected to affect seriously the interpretation of
the decrease in blood leukocyte radioactivity after DFP³² labeling. Eosino-
phils, basophils, and normoblasts would have taken up only small amounts
of the label, therefore the presence of these cells in the leukocyte samples
would not significantly influence the leukocyte radioactivity curves in these
patients.

To study the problem as well as possible with this label, therefore, infusion
of the labeled normal granulocytes in addition to infusion of the patient’s
own labeled cells was done. In the three instances in which labeled normal
blood was infused, the leukocyte radioactivity decreased in a single ex-
ponential fashion with T-½’s ranging from 6.5 to 12.0 hours. In two of the
patients (1 and 3) the labeled normal granulocytes disappeared from the
blood at a rate within the range expected for the disappearance of granulo-
cytes from the blood of a normal subject. In these two patients there was
no evidence that environmental factors retarding turnover of granulocytes
contributed significantly to the increase in blood granulocyte concentra-
tion as is the case in steroid-induced granulocytosis. In patient 2, the T-½ of
leukocyte radioactivity was increased somewhat, indicative perhaps that in
this patient a retardation of granulocyte removal may have contributed to the
increased blood granulocyte concentration. If the assumption is made that
the normal labeled granulocytes equilibrate with the leukemic granulocytes
and subsequently act in a similar manner, granulocyte pool sizes and cell
turnover were markedly increased. However, no evidence for the similar
behavior of leukemic and normal granulocytes can be derived from this
study. Furthermore, differences from normal cells in the leukemic granulo-
cytes such as alkaline phosphatase content and chromosome constituency
would invalidate any conclusions drawn from these kinetic calculations.

In two instances in which the patient’s own blood was labeled and in-
fused, the blood leukocyte radioactivity decreased apparently in a single
exponential fashion. In the third instance, a double curve was obtained
which most probably was the result of inadequate equilibration of the
labeled cells at the end of the infusion. After the 2-hour sample, the blood leukocyte radioactivity in this patient appeared to decrease in a single exponential fashion also. The $T_{1/2}$'s obtained in these patients ranged from 11.0 to 17.5 hours. It cannot be concluded that the prolonged $T_{1/2}$'s of blood leukocyte radioactivity were solely the result of retarded granulocyte turnover rates. The blood granulocytes of these patients were not uniform with respect to maturation and possibly the slower disappearance of more heavily labeled immature cells might have significantly influenced the blood leukocyte radioactivity curves. Also, from the appearance of the curves it is impossible to be sure that only one or two rate processes were involved in the disappearance of the labeled cells. Evidence has been presented by Craddock that immature normal granulocytes as well as the immature leukemic myeloid cell circulate for longer periods in the blood than the normal mature granulocyte. Thus in these patients the rate of disappearance of the labeled cells very likely was in part a function of cell maturity. In addition, there is no evidence from this study that some equilibration of the labeled immature myeloid cells with extravascular compartments did not take place.

Assuming for purposes of calculations, however, that cell labeling was relatively uniform and the labeled myeloid cells decreased as a result of random factors, the pool sizes and number of cells turned over per day were increased. Even though the stated assumptions are not valid, the error would tend to underestimate the numbers of granulocytes produced per day and therefore the results of all of these studies are consistent with increased granulocyte production in patients with chronic myelocytic leukemia. Precise calculations of pool sizes and turnover rates cannot be made in the disease by this method at present because of the unresolved problems of non-uniform labeling and of factors influencing cell disappearance from the blood.

The presence of the greatly increased numbers of myeloid cells in this disease could result from marked prolongation of cell survival time or production of increased numbers of cells. To accomplish the striking increase in all of the myeloid forms by the former mechanism alone, the time spent in each of the stages of maturation would have to be increased considerably for accumulation of all cell types. The in vitro data of Craddock and the in vivo studies from the laboratories of Patt and Cronkite are more consistent, however, with a generation and maturation cycle in these leukemic cells which is comparable to normal myeloid cells. The production of increased numbers of cells could result from an increase in turnover rate in myeloid precursors—that is, a greater number of cell divisions in myeloid precursors occurring during the usual time required for cell maturation to a non-dividing stage. Once again, from the studies mentioned above there is no evidence that cell division in these leukemic cells occurs more frequently than in normal myeloid precursors. Increased cell production could result from an increase in the number of undifferentiated stem cells converted into myeloid cells, but evidence about this possibility is not available. Maloney, Weber and Patt have found a pattern of ineffective myelopoiesis in the marrows of
normal dogs and have suggested that one method for control of granulocyte production might be through regulating the balance of effective and ineffective cell production. Again no evidence is available concerning the application of this concept to human patients with chronic myelocytic leukemia. Certainly all of the above factors may influence to some degree the formation of the vastly increased number of myeloid cells in this disease but, over-all, an increase in the numbers of cells produced per day evidently results in keeping with the increased excretion of uric acid found in this disease.\textsuperscript{14}

From the studies with DFP\textsuperscript{32} presented here, greater numbers of granulocytes are turned over through blood per day in patients with chronic myelocytic leukemia than in normal subjects. The term granulocyte turnover rate (GTR) has been used in the tables to be consistent with the nomenclature used by Athens and coworkers.\textsuperscript{5} However, this term is a misnomer because the concern is not with rate but with the mass of cells turned over per day. In fact, in none of the patients was the turnover rate found to be increased, but the mass of cells turned over was increased because of the large size of the compartment under study.

It is of particular interest that increased granulocyte pool sizes and production rates were found in the patients with polycythemia vera and essential thrombocytthemia. The relationship of these two diseases and chronic myelocytic leukemia has been discussed considerably. Although one cell type may be primarily involved, increased numbers of all three elements may be found in the blood of patients with chronic myelocytic leukemia,\textsuperscript{15} polycythemia vera\textsuperscript{16-18} or essential thrombocytthemia.\textsuperscript{19} Further evidence for a possible relationship has been found in the observation that the clinical picture of acute leukemia may terminate the course of a patient which began as chronic myelocytic leukemia,\textsuperscript{20} polycythemia vera\textsuperscript{21,22} or essential thrombocytthemia.\textsuperscript{23} However, differences in the cellular enzyme concentrations have been demonstrated in the granulocytes of these patients,\textsuperscript{24,25} as well as the finding of an abnormal chromosome in chronic myelocytic leukemia,\textsuperscript{26} which indicate that these diseases are not identical.

There is evidence from the studies reported here, however, that each of these diseases may represent a widespread disorder of marrow proliferation even though the etiologies differ. The increased erythrocyte production in polycythemia vera\textsuperscript{27,29} was accompanied in our patients by an increased granulocyte production as well. Likewise the increased megakaryocyte activity in the patient with essential thrombocytthemia was associated with an increased myeloid response.

The one patient with the prolonged, unexplained granulocytosis was found to have a real increase in the TBGP on two occasions which was the result of an increase in granulocyte production. The etiology of this condition is as yet unknown, but the description by Wintrobe and Hasenbush\textsuperscript{30} of a period of persistent granulocytosis antedating the onset of chronic myelocytic leukemia in some patients indicates the need for careful follow-up evaluation in this patient.
SUMMARY

Granulocyte kinetic studies with DFP\(^{32}\) were done in four patients with chronic myelocytic leukemia, three patients with polycythemia vera, one patient with essential thrombocytopenia, and one patient with persistent, unexplained granulocytosis. The increased blood granulocyte concentration found in the patients with polycythemia vera, essential thrombocytopenia and unexplained granulocytosis was at least in part the result of increased granulocyte production. Precise calculations of granulocyte pool sizes and turnover rates in the patients with chronic myelocytic leukemia were not possible because of unresolved problems related to the non-uniform population of myeloid cells in the blood of these patients. However, within the limitations of the method, a greater number of myeloid cells were turned over per day through blood than in normal subjects. The findings support the concept that a widespread disorder of marrow proliferation exists in chronic myelocytic leukemia, polycythemia vera, and essential thrombocytosis.

SUMMARIO IN INTERLINGUA

Studios kinetic del granulocytos esseva effectuate con le uso de diisopropyl-fluorophosphato a \(^{32}\)F in quatro patientes con chronic leucemia myelocytic, tres patientes con polycythemia ver, un paciente con thrombocytopenia es- tamental, e un paciente con persistente sed inexplicate granulocytosis. Le augmentate concentration de granulocytos in le sanguine, trovate in le patientes con polycythemia ver, thrombocytopenia essential, e inexplicate granulocytosis esseva alminis in parte le effecto de un augmentate production de granulo- cytos. Precise calculationes del magnitude del reservoirs de granulocytos e del intensitate del metabolismo del granulocytos in le patientes con chronic leucemia myelocytic non esseva possibile a causa del non-resolve problemas relationate al non-uniforme population de cellulas myeloid in le sanguine de iste patientes. Tamen, intra le limites del metodo, un plus grande numero de cellulas myeloide esseva metabolisate per die in le sanguine de iste pa- tientes que in subjectos normal. Le constatationes supporta le conception que un extense disordine de proliferation medullari existe in chronic leucemia myelocytic, polycythemia ver, e thrombocytosis essential.

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Thomas Jarrold, M.D., Associate Clinical Professor of Medicine, University of Cincinnati College of Medicine, and Chief, Hematology Research Section, Cincinnati Veterans Administration Hospital, Cincinnati, Ohio.
Granulocyte Kinetic Studies in Patients with Proliferative Disorders of the Bone Marrow

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