Studies of the Rate of Production and Life Span of Erythrocytes in Acute Leukemia

By David G. Nathan and Nathaniel I. Berlin

The pathogenesis of anemia in malignant disease has been defined more clearly in recent years, but the anemia of acute leukemia remains poorly understood. Boiron, Schapira and their co-workers measured the iron turnover with Fe$^{59}$ and the red cell life span with either the glycine-2-C$^{14}$ or the Ashby technic in 17 patients with acute leukemia. Elmlinger et al., Bothwell et al. and Huff et al. have each studied two or three patients with acute leukemia with Fe$^{59}$. Wetherly-Mein et al. have studied five patients with Fe$^{59}$ and Cr$^{51}$.

The purpose of this paper is to report the results of studies performed on six adult patients with acute myelogenous leukemia and one adult patient with acute monocytic leukemia. Six of these studies included the measurement of plasma and red cell iron turnover with Fe$^{59}$, serial in vivo measurements of Fe$^{59}$ in the spleen, liver and bone marrow, the blood volume and apparent red cell survival with Cr$^{51}$-labeled cells, the rate of accumulation of Cr$^{51}$ in spleen and liver in vivo, and the red cell life span with glycine-2-C$^{14}$. One study included only the measurement of plasma and red cell iron turnover.

METHODS

The hematologic, chemical and isotopic methods have been described previously in this Journal.

PATIENTS

The patients were admitted to the wards of the National Cancer Institute, and diagnosis of acute leukemia was established. Six cases of acute myelogenous and one case of acute monocytic leukemia were studied. The Appendix contains a summary of the clinical findings of each patient. Antimetabolite therapy and blood transfusions were administered at the direction of the Chemotherapy Service of the National Cancer Institute. None of the patients exhibited hemorrhagic blood loss during the initial phases of the study. B. D. had intermittent hemorrhage during the final 30 days of her illness. Intermittent infection or fever of unknown origin was common, but the patients were afebrile during the initial phases of the studies.

RESULTS

The results of the blood volume, iron turnover and fecal urobilinogen studies are shown in table 1. In all the patients, the total red cell volume was either at or below the lower limits of normal, while the plasma volume was elevated in four of the seven patients. The serum iron concentration was elevated in one patient (C. R.) and normal in the others. One patient (G. G.)
TABLE 1.—Blood Volume, Iron Turnover and Fecal Urobilinogen Data in 7 Patients with Acute Leukemia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Plasma Vol. ml./Kg.</th>
<th>RBC Vol. ml./Kg.</th>
<th>Serum Fe. Micromg.</th>
<th>Plasma Fe turnover mg./Kg./day</th>
<th>RBC Fe turnover mg./Kg./day</th>
<th>Fecal Urobilinogen mg./day</th>
<th>Hemolytic Index mg./f.u./100 Gm. circulating hematogobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. A.</td>
<td>60</td>
<td>20.2</td>
<td>87</td>
<td>1.4</td>
<td>0.61</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td>F. G.</td>
<td>37</td>
<td>24</td>
<td>116</td>
<td>0.07</td>
<td>0</td>
<td>100</td>
<td>21</td>
</tr>
<tr>
<td>C. R.</td>
<td>55</td>
<td>22</td>
<td>238</td>
<td>1.3</td>
<td>0.06</td>
<td>81</td>
<td>18</td>
</tr>
<tr>
<td>W. R.</td>
<td>55</td>
<td>14</td>
<td>127</td>
<td>0.31</td>
<td>0.03</td>
<td>81</td>
<td>18</td>
</tr>
<tr>
<td>G. C.</td>
<td>46</td>
<td>24</td>
<td>110</td>
<td>0.74</td>
<td>0.37</td>
<td>107</td>
<td>19</td>
</tr>
<tr>
<td>B. D.</td>
<td>36</td>
<td>12</td>
<td>143</td>
<td>0.43</td>
<td>0.13</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>H. W.</td>
<td>42</td>
<td>19</td>
<td>148</td>
<td>0.51</td>
<td>0.16</td>
<td>276</td>
<td>14</td>
</tr>
</tbody>
</table>

Mean

| Normal | Males 38.7 | 29.9 | Females 37 | 24.9 | 50–170 | 0.31–0.40 | 0.22–0.28 | 100–300 | 11–21 |

had a moderately increased plasma and red cell iron turnover, and one (R. A.) a greatly increased plasma and red cell iron turnover. Four patients demonstrated decreased red cell iron turnover, and one (F. G.) had failure of red cell production as evidenced by failure of uptake both of Fe$^{59}$ and C$^{14}$ in red cells. In four patients with decreased red cell iron turnover, the plasma iron turnover was increased. This precludes the use by itself of the plasma iron turnover as an estimate of red cell production in these cases. The fecal urobilinogen excretions and calculated hemolytic indexes were in poor agreement with the red cell life span data (vide infra). None of the patients demonstrated significant levels of Fe$^{59}$ or C$^{14}$ in the stool collections.

The hippuric acid specific activities are presented in table 2.

The relationship between the peak uptake of Fe$^{59}$ by the sacrum and the maximum uptake of Fe$^{59}$ and C$^{14}$ by the red cells and the relationship between the maximum uptake of Fe$^{59}$ and C$^{14}$ by the red cells are presented in figure 14 (see Discussion).

The clinical and isotopic data for each patient are presented in graphic form and are grouped under accelerated or diminished erythropoiesis.

**Accelerated Erythropoiesis**

**Patient G. G. (figs. 1 and 2).—**The hemoglobin was normal at the onset of the study and slowly declined. Antimetabolite therapy was followed by, but not necessarily related to, a marked increase in transfusion requirement, presumptive shortening of the life span of transfused cells and a sharp decrease
in the reticulocyte count. The in vivo count rate due to Fe\(^{59}\) demonstrated possible hepatic erythrogenesis in addition to active marrow erythropoiesis. There was otherwise normal localization of Fe\(^{59}\) and Cr\(^{51}\) in the spleen and liver. The red cell life span by the Cr\(^{51}\) technic was normal. The C\(^{14}\) curve rose rapidly to maximum specific activity and maintained a plateau until the onset of the transfusion requirement. Despite a normal Cr\(^{51}\) red cell survival up to 40 days, a shortened but finite red cell life span—possibly due to the development of extracorpuscular abnormalities after 40 days accompanied by failure of the marrow to reutilize the Fe\(^{59}\)—is suspected, since the specific activity of Fe\(^{59}\) in the blood decreased more than could be predicted on the basis of blood volume expansion.\(^a\) The decrease in the C\(^{14}\) specific activity is probably due to transfusions as well as to premature red cell destruction. The increase in specific activity of Fe\(^{59}\) in the red cells between days 10 and 33 may indicate a progressive decrease in the rate of erythropoiesis and is compatible with the decrease in reticulocyte count observed at the same time. Since a small fraction of the red cells is labeled initially and since these have a finite life span, a decrease in the production of non-labeled cells will result in a relative concentration of labeled cells. This effect on erythropoiesis might be explained by the action of antimetabolite therapy, increasing severity of disease, or both.

Despite initially accelerated erythropoiesis, a marked increase in transfusion requirement occurred, due to the development of deficient production of red cells and a short red cell life span.

**Patient R. A. (figs. 3 and 4).—**This patient had a moderate transfusion requirement throughout the study. The plasma radioiron disappearance was rapid. Body surface counting revealed prompt uptake and release of iron by the marrow and secondary localization of Fe\(^{59}\) in the spleen and liver, which indicated premature red cell destruction and/or rapid storage of iron. The Cr\(^{51}\)-labeled cells disappeared at two rates, one with a half time of 2.5 days and

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\(^a\) The per cent uptake of Fe\(^{59}\) by the red cells is calculated by multiplying the counts/min./ml. of whole blood by the ratio of the blood volume to the total administered Fe\(^{59}\). Therefore, no change in the observed per cent uptake of Fe\(^{59}\) will occur if the blood volume remains constant unless the body iron stores are significantly expanded or there is failure of the marrow to reutilize iron. Similarly, the slope of the Cr\(^{51}\) survival curve will be unaffected by transfusion if no change in the blood volume occurs. Since the C\(^{14}\) curve is a function of the specific activity of hemoglobin, it will be significantly depressed by transfusion despite stability of the blood volume.

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**Table 2.—Urinary Hippuric Acid Specific Activity**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Component I</th>
<th>Component II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N_0)^a</td>
<td>(t_{1/2})</td>
</tr>
<tr>
<td>B. D.</td>
<td>65 cpm/mg. BaCO(_3)</td>
<td>2 days</td>
</tr>
<tr>
<td>G. G.</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>H. W.</td>
<td>6.7</td>
<td>(1/2)</td>
</tr>
<tr>
<td>C. R.</td>
<td>30</td>
<td>(1/2)</td>
</tr>
</tbody>
</table>

^\(N_0\) is the extrapolated initial value.
\(t_{1/2} = \) half time.
Figs. 1 (top) and 2 (bottom).—Clinical and isotopic data in patient G. G. The peripheral blood counts and treatment are charted in their time relationships to the Fe59 uptake, Cr51 survival and C14 life span. The plasma Fe59 disappearance curves are plotted on time scales of hours and days.

the other 15 days. The biphasic curve may have been due to cell damage during the labeling process. There was very rapid localization of Cr51 in the spleen and liver. The uptake of Fe59 into red cells was less than 50 per cent despite accelerated erythropoiesis presumably due to premature destruction of labeled cells. The specific activity continued to decrease, probably as a result of the blood volume expansion produced by transfusions. Peripheral
edema was noted at this time. The specific activity of $^{14}$C in hemoglobin decreased as a result of transfusions. The patient expired before the actual red cell life span could be measured. The shape of the $^{14}$C curve and the $^{59}$Fe and $^{51}$Cr data indicate that this patient produced more red cells than normal, that these cells had a short and possibly finite life span, and were destroyed in the spleen and liver.

**Deficient Erythropoiesis**

*Patient F. G. (figs. 5 and 6).—This patient maintained a large transfusion requirement and a very low reticulocyte count.*

The plasma iron disappearance was slow with no incorporation of radioiron into circulating red cells. The greater part of the plasma iron was removed by the liver (*vide infra*). No $^{14}$C appeared in hemoglobin. There was an associated shortening of the life span of transfused red cells as measured by the $^{51}$Cr technic with rapid splenic and hepatic localization of $^{51}$Cr-labeled cells.

Absent red cell production and short life span of donor cells produced a marked transfusion requirement.

*Patient H. W. (figs. 7 and 8).—The hemoglobin fell slowly and the patient’s course was terminated by a blastic crisis.*

The plasma radioiron disappearance was slightly prolonged. The in vivo scanning demonstrated prompt marrow uptake and decreased release of iron from the marrow. Thirty per cent of the $^{59}$Fe was incorporated into red cells.

The liver and spleen initially cleared the greater part of the plasma iron. Subsequently, the liver apparently discharged iron to the extracellular fluid.
which was then taken up by the spleen and possibly by the marrow. The red cell survival as measured with Cr$^{51}$ was normal, and there was minimal splenic and hepatic localization of Cr$^{51}$. The C$^{14}$ curve shows a rapid rise to a plateau of moderately low specific activity.

Despite high nucleated red cell and reticulocyte counts, deficient erythropoiesis was the sole demonstrable cause of anemia in this case. Red cell production by the marrow is likely exaggerated in these data, since the cir-
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Figs. 7 (at left) and 8 (at right).—Clinical and isotopic data in patient H. W.

culating nucleated red cells and reticulocytes probably utilized a significant fraction of the administered Fe$^{59}$. *

Patient B. D. (figs. 9 and 10).—Following the initial transfusions, the hemoglobin values declined until the final month when episodes of moderate gastrointestinal and urinary tract hemorrhage occurred. Initial reticulocyte counts were normal.

The plasma radioiron disappearance rate was normal. The Fe$^{59}$ red cell uptake was 30 per cent, and the specific activity fell when premature cell destruction, hemorrhage and presumable failure to reutilize iron occurred. The in vivo studies revealed incomplete release of iron from the marrow and increased liver uptake. Secondary localization of Fe$^{59}$ occurred in the spleen. The Cr$^{51}$ survival curve was shortened, with accelerated localization of Cr$^{51}$ in the spleen and liver. The C$^{14}$ curve shows an initial dip caused by transfusions, followed by a steady rise which may indicate either progressive bone marrow failure to produce red cells or that the initially transfused cells left the circulation more rapidly than the cells labeled with C$^{14}$. The fall in C$^{14}$ specific activity beginning at day 50 is considered to be due to premature red cell destruction and in part to hemorrhage and transfusions.

Decreased erythropoiesis and short but finite red cell life span produced an

*From unpublished data of Dr. L. R. Wasserman.
anemia which was slowly progressive. The sudden onset of red cell loss owing to intermittent hemorrhage coupled with a further decrease in red cell production increased the transfusion requirement.

**Patient C. R. (figs. 11 and 12).**—This patient was on antimetabolite therapy when the study was started. Nucleated red cells were observed in the peripheral blood.
The red cell iron turnover was decreased with a decreased uptake and release of iron from the marrow. The liver cleared most of the plasma iron and there was secondary localization of Fe59-labeled red cells in the spleen and liver together with apparent transfer of iron from the spleen to the liver. The initial Cr51 survival curve was considerably shortened, perhaps in part as a result of damage of red cells during the labeling process, since there was a rapid accumulation of the Cr51 noted in the spleen and liver one day after the isotope was administered. The C14 red cell life span showed rapid
and random destruction of red cells as well as a low specific activity. The low C¹⁴ and Fe⁵⁹ specific activities were probably the result of premature red cell destruction as well as of deficient erythropoiesis. A repeat determination of the Cr⁵¹ survival performed 20 days later showed an increase in the apparent red cell life span.

This patient was initially studied during a phase of bone marrow depression and with a short red cell life span, compatible with random destruction of circulating red cells. The repeat Cr⁵¹ survival data indicate that the rate of red cell destruction decreased.

Patient W. R.—This patient was studied with Fe⁵⁹ only and without body surface scanning. The results indicate markedly decreased erythropoiesis (see figure 13).

**DISCUSSION**

The measurement of red cell iron turnover and particularly the measurement of the red cell life span with either Cr⁵¹ or C¹⁴ is best carried out when the patient has a constant total red cell volume as a result of production of an adequate number of red cells and not as a result of transfusions. In fact, in the absence of erythropoiesis, the rate of decrease of Cr⁵¹ per ml. red cells will be only a measure of the rate of elution of Cr⁵¹ from intact red cells. The life span of the red cell can only be determined under these conditions if the total circulating Cr⁵¹ is known. This would require frequent blood volume determinations. However, these measurements require a minimum of 20 to 30 days for the Cr⁵¹ technic, and if the red cell life span is normal, a minimum of 120 to 140 days for the C¹⁴ method.

The clinical course of most patients with acute leukemia is such that
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either antimitabolite therapy or transfusions will be necessary in any given four month period. In six of these studies, the iron turnover measurements were virtually completed before antimitabolite therapy was begun, and the effect of these drugs on the initial red cell survival cannot be clearly determined from these cases. If the transfusions do not alter the total blood volume, they will not affect the content of $^{51}Cr$ and $^{59}Fe$ in the whole blood, but the $^{14}C$ specific activity in hemoglobin will be decreased. Nevertheless, it was thought that despite these difficulties, a study of this type would be helpful in understanding the nature of the anemia of acute leukemia.

One of these patients (R. A.) demonstrated increased red cell production with an increased rate of destruction as suggested by Jaffe. Another (G. G.) initially had moderately accelerated erythropoiesis as described in acute leukemia by Boiron and Schapira and in chronic leukemia by Huff et al. The remainder of the patients demonstrated decreased red cell production, a finding in agreement with the conclusions reached with the use of a modified Ashby technic by Stats.

Figure 14 shows a correlation between the percentage uptake of $^{59}Fe$ by red cells and the count rate due to $^{59}Fe$ over the sacrum. It also demonstrates the relationships between the uptake of $^{14}C$ in red cells (as hemoglobin specific activity) and the peak observed $^{59}Fe$ activity in the sacrum, and between the uptakes of both $^{14}C$ and $^{59}Fe$ in the red cells.

Although B. D., H. W. and C. R. utilized a relatively small amount of $^{59}Fe$ and glycine-2-$^{14}C$ for red cell production, maximal utilization occurred more rapidly than normal. Thus, the $^{59}Fe$ and $^{14}C$ curves approached maximal specific activity within four days in each case. This may be interpreted as indicating that a decreased number of erythrocytes were produced in the
marrow, but that they were released from the marrow at a rapid rate as postulated by Castle and Minot. This rapid release of a small number of red cells may have accounted for the reticulocytosis and increased number of nucleated red cells observed in the peripheral blood of some of the patients with over-all decreased red cell production.

Calculation of the specific activity of newly synthesized hemoglobin from the urinary hippuric acid specific activity (table 2) indicates that excessive continual utilization of glycine-2-14C for hemoglobin synthesis did not occur in these studies. Hippuric acid could not be isolated from the urine of one patient (F. G.), and from one (R. A.) the product could be isolated on only three occasions. The other patients demonstrated a rapid initial decrease in hippuric specific activity, followed by a slower decrease similar to the data of Berlin et al. Both components had rate constants greater than those observed by Berlin et al., which may result from rapid glycine turnover in these cases of acute leukemia.

Despite the fact that the liver removed the greater proportion of the plasma iron in cases of deficient erythropoiesis, the marrow does appear to take up significant amounts of iron even when erythropoiesis is entirely absent. In vivo counting in the case of F. G. illustrates this fact. The liver rapidly accumulated the bulk of the radioiron, but the marrow also cleared a significant quantity. From the third to the 19th day, the count rate over the liver due to Fe59 increased as the marrow level fell, but without the appearance of isotope in the red cells. The spleen Fe59 count rate was stable. We conclude therefore, that the marrow released the radioiron, which subsequently was taken up by the liver from the extracellular fluid.

Decreased red cell life span has been described in chronic leukemia and other malignant diseases, and most of the cases described in this report had this abnormality. The 14C curves indicated a shortened but finite life span in four cases and random destruction of cells in one case. The Coombs test and osmotic fragility were normal. The red cells appeared normal morphologically except in the case of H. W., who demonstrated marked poikilocytosis and hypochromia. The hemoglobin electrophoresis and alkali denaturation tests were normal. These findings tend to rule out a red cell defect in these cases and suggest premature destruction of normal red cells by abnormal extrinsic mechanisms.

The bone marrow smears and sections prepared from iliac or sternal aspirations in this series of patients were reviewed by us and by Dr. George Brecher. Although we were able to evaluate erythropoiesis correctly in three of the cases, in the others the histology did not reflect the actual rate of production of red cells. We both overestimated and underestimated the degree of erythropoiesis. The failure of the marrow histology to reflect the actual erythropoietic physiology may have resulted from dilution of the sample with peripheral blood and selective loss of erythrocyte precursors in the aspiration technique. In addition, the small marrow sample may only reflect the number of erythrocyte precursors per unit volume of marrow and not the number of precursors in the total marrow.
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SUMMARY

The rate of red cell formation and the red cell life span were determined in six adult patients with acute myelogenous leukemia by the use of Fe$^{59}$, Cr$^{51}$ and glycine-2-C$^{14}$. One patient with acute monocytic leukemia was studied with Fe$^{59}$ alone.

Erythropoiesis was normal or increased in two patients, deficient in four patients and absent in one. The data indicate that in the cases of deficient erythropoiesis a decreased number of red cells were produced in the marrow, but that they were released at a rapid rate.

The red cell life span appeared to be normal in one patient, short but finite in four patients, and short owing to random destruction in one patient. One study did not include the measurement of red cell life span.

The liver removed an abnormally large proportion of the plasma iron when marrow erythropoiesis was deficient.

The bone marrow examination may be an unreliable indicator of the rate of erythropoiesis.

SUMMARIO IN INTERLINGUA

Le intensitate del formation de erythrocytos e le longevitate del erythrocytos esseva determinate in sex patientes adulte con acute leucemia myelogene, per le uso de Fe$^{59}$, Cr$^{51}$, e glycina-2-C$^{14}$. Un patiente con acute leucemia monocytic esseva studiate solmente con Fe$^{59}$.

Le erythropoiese esseva normal o augmentate in duo del patientes, de-ficiente in quatro, e absente in un. Le datos indica que in le casos de erythropoiese defective, un numero reduceite de erythrocytos esseva producite in le medulla sed que illos esseva liberate de maniera accelerate.

Le longevitate del erythrocytos pareva esser normal in un del patientes, breve sed definite in quatro patientes, e breve in consequentia de destruction erratic in un patiente. Un del studios non includeva le mesuration del longevitate erythrocytic.

Le hepate removeva un anormalmente grande proportion del ferro in le plasma in casos in que le erythropoiese in le medulla esseva defective.

Le examine del medulla ossee es possibilemente un indicator pauco precise del intensitate del erythropoiese.

APPENDIX: CASE SUMMARIES

1. G. G.—This 16 year old white male, with acute myelogenous leukemia, was treated with four units of blood and sustained a complete remission for 2 months. Relapse accompanied by fever and bone pain then occurred, and the study was begun. Physical examination revealed hepatosplenomegaly and generalized lymphadenopathy. He developed a rising white count and serum uric acid, became oliguric, and died of intracerebral hemorrhages, 10 months after the initial diagnosis had been made.

2. R. A.—This 56 year old white male complained of weakness, dyspnea and a 30 pound weight loss for one year prior to admission. Three months prior to admission, a diagnosis of acute myelogenous leukemia was made. The study was begun on admission. Physical examination revealed recent loss of fat and muscle, shotty generalized adenopathy, splenomegaly and hepatomegaly. He received Methotrexate therapy, but failed to remit, became severely pancytopenic, developed fever and bronchopneumonia and died in coma due to intracerebral hemorrhage on the 41st hospital day.
3. F. C.—This 33 year old white female noted fatigue and weight loss two months prior to admission. Anemia was noted two weeks prior to admission, for which she received 2 units of blood. Physical examination on admission revealed gingival hypertrophy, pretibial infiltrates, ecchymoses, lymphadenopathy and hepatosplenomegaly. The bone marrow showed acute myelogenous leukemia. The study was started on admission. She was treated with 6-mercaptopurine and Methotrexate in combination for three months, which produced a transient partial remission, a rise in platelets and subjective improvement. The patient died of cerebral hemorrhages nine months after admission.

4. H. W.—This 73 year old white male noted weakness, dyspnea and weight loss for one month prior to admission. Four days prior to admission, a peripheral blood count revealed pancytopenia, myeloblasts and numerous nucleated red cells. Physical examination revealed pallor, adenopathy, hepatosplenomegaly and ecchymoses. The bone marrow was predominantly promyelocytic and myelocytic with prominent nucleoli. The patient died of intracerebral hemorrhages 32 days after the start of the study.

5. B. D.—This 59 year old white female noted persistent anorexia, nausea, weight loss, low-grade fever and fatigue for six weeks prior to admission. A markedly elevated white count with numerous myeloblasts was noted on the day before admission. Physical examination revealed pallor, retinal hemorrhages, and exudates, sternal tenderness, splenomegaly and numerous ecchymoses. Bone marrow examination revealed acute myelogenous leukemia. The study was begun on admission. She died of a gram-negative bacillus septicemia 70 days after admission.

6. C. R.—This 33 year old white male noted the onset of fatigue, weight loss, easy bruising and intermittent fever seven months prior to admission. Six months prior to admission, the diagnosis of acute myelogenous leukemia was established by bone marrow aspiration. Physical examination on admission revealed multiple petechiae, lymphadenopathy and hepatosplenomegaly. The study was begun on admission. Forty-two days later he was started on Methotrexate, and a complete remission occurred which continued for about 70 days. He then became jaundiced, and died of liver failure secondary to leukemic infiltration.

7. W. R.—This 67 year old Negro male had a persistent anemia which required 30 transfusions in the eight months prior to admission. Therapy with triethylene melamine was carried out for seven months without effect. Physical examination on admission revealed marked wheezes throughout the lungs, hepatosplenomegaly and enlargement of the prostate. The initial bone marrow findings were not diagnostic, but two weeks later, with a coincident fever spike to 40 C., the bone marrow was consistent with acute monocytic leukemia with 58 per cent monocytes in the peripheral blood. One week later the Fe" study was begun. The patient became comatose three months following admission and died with signs of increasing intracranial pressure.

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