Studies of the Production and Life Span of Erythrocytes in Myeloid Metaplasia

By DAVID G. NATHAN AND NATHANIEL I. BERLIN

The pathogenesis of myeloid metaplasia with or without myelofibrosis is obscure. Anemia may be a major cause of disability in this syndrome. The transfusion requirement may become so great due to premature destruction of red cells that splenectomy may be considered, despite the fact that the procedure was once thought to be contraindicated in this disease. Since the spleen and liver may be the only apparent sites of red cell production in myeloid metaplasia, the indications for splenectomy are not well established. Measurement of the rates and sites of red cell production and destruction permits a better evaluation of the hematologic status of such patients. The purpose of this paper is to present the results of studies of four patients with agnogenic myeloid metaplasia and myelofibrosis and one patient with polycythemia vera with myeloid metaplasia. The studies included measurements of plasma and red cell iron turnover with Fe<sup>59</sup>, serial in vivo measurements of Fe<sup>59</sup> in marrow, liver and spleen, the apparent red cell survival with Cr<sup>51</sup>, the rates of accumulation of Cr<sup>51</sup> in spleen and liver in vivo, and the red cell life span with glycine-2-C<sup>14</sup>. The usual peripheral hematology, bone marrow examination and the measurement of fecal urobilinogen excretion were also performed.

Methods and Patients

**Methods**

**Hematology.**—The hematocrit of heparinized venous blood was measured by a microtechnic which obviates the need for correction for trapped plasma. Hemoglobin was measured by the cyanmethemoglobin method. Reticulocytes and platelets were counted by the method of Brecher et al.

The serum iron was measured by the method of Ness. The excretion of fecal urobilinogen was estimated by a modification of the method of Schwartz et al.

**Isotope techniques.**—Plasma and red cell iron turnover were measured by the single dynamic pool method of Huff et al. Analysis of the data in terms of more complex pool systems was not attempted. Twelve to 25 μC of Fe<sup>59</sup> citrate were incubated with 18 ml of fresh frozen AB-plasma which was compatible with each recipient. The quantity of iron was calculated to remain within the iron-binding capacity of the donor plasma; chromatography revealed that all of the Fe<sup>59</sup> was bound to a β-globulin. The total red cell volume was measured by the dilution of red cells labeled with 100 μC of Cr<sup>51</sup>. The excess Cr<sup>51</sup> was reduced with 50 mg of ascorbic acid. The plasma volume was calculated from the measured total red cell volume and the peripheral hematocrit. The apparent red cell survival was estimated by the change in specific activity of Cr<sup>51</sup> per ml of blood. Since some of these patients had deficient red cell production, the count rate was expressed as cpm/ml of whole blood, because it was assumed that in these

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The authors would like to express their appreciation to Mrs. Jeanne G. Waggoner for her excellent technical assistance.

Submitted July 25, 1958; accepted for publication Oct. 12, 1958.
cases the blood volume was more constant than the total red cell volume. The elution rate of Cr" from apparently intact red cells was not measured. An aliquot of the stools collected for four days following administration of the isotope was counted for Fe" and Cr". The plasma, blood and stool levels of Cr" and Fe" were measured in a well-type scintillation counter with a single channel spectrometer to a maximum counting error of 3.5 percent. Correction was made for physical decay. The count rates over the liver and spleen due to Cr" and over the liver, spleen and sacrum due to Fe" were measured by the method of Elmlinger, et al. A single channel gamma ray spectrometer was used to differentiate between Fe" and Cr". The red cell life span was determined by measurement of the specific activity of BaC'4O3 prepared from hemoglobin following the administration of glycine-2-C'4. Urinary hippuric acid specific activity was similarly measured. The BaC'4O3 was suspended in a thixotropic gel and counted in a liquid scintillation spectrometer by a method described elsewhere.

Patients
The diagnosis of agnogenic myeloid metaplasia was established by bone marrow biopsy and in some cases (S. P., M. B. and J. G.) by spleen biopsy. The diagnosis of polycythemia vera was based upon peripheral hematologic, bone marrow and blood volume findings. The patients remained on the wards of the Metabolism Service during the initial phases of the study. The details of their clinical courses are summarized in the appendix.

RESULTS
The results of the blood volume, iron turnover and fecal urobilinogen studies are shown in table 1. The four patients with myeloid metaplasia and myelofibrosis (J. G., M. E. G., S. P. and M. B.) were clearly anemic by both blood volume and peripheral blood count standards. Three had elevation of the plasma volume above 46 ml./Kg. The serum iron was low in one patient (S. P.) and slightly elevated in another (M. B.). The plasma iron turnover was increased in all four patients. The red cell iron turnover was increased in three patients and was very low in one patient (M. B.) who had an increased plasma iron turnover. The latter finding indicates that the plasma iron turn-

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**Table 1.—Blood Volume, Iron Turnover and Fecal Urobilinogen Data in Five Patients with Myeloid Metaplasia**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Red Cell Volume (cc./Kg.)</th>
<th>Plasma Volume (cc./Kg.)</th>
<th>Serum iron (micrograms %)</th>
<th>Plasma iron turnover (mg./Kg./A.)</th>
<th>Red Cell iron turnover (mg./Kg./A.)</th>
<th>Fecal urobilinogen (mg./A.)</th>
<th>Hemoglobin index (%), excluding HbA</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.G.</td>
<td>18</td>
<td>41</td>
<td>97</td>
<td>1.0</td>
<td>0.50</td>
<td>42</td>
<td>12.5</td>
</tr>
<tr>
<td>M.E.G.</td>
<td>16</td>
<td>55</td>
<td>99</td>
<td>2.6</td>
<td>0.75</td>
<td>166</td>
<td>70</td>
</tr>
<tr>
<td>S.P.</td>
<td>18</td>
<td>64</td>
<td>40</td>
<td>2.0</td>
<td>1.4</td>
<td>178</td>
<td>42</td>
</tr>
<tr>
<td>M.B.</td>
<td>23</td>
<td>63</td>
<td>180</td>
<td>0.55</td>
<td>0.04</td>
<td>101</td>
<td>12.5</td>
</tr>
<tr>
<td>M.G.</td>
<td>43</td>
<td>38</td>
<td>82</td>
<td>0.48</td>
<td>0.47</td>
<td>150</td>
<td>13.2</td>
</tr>
<tr>
<td>Reference</td>
<td>males</td>
<td>29</td>
<td>13</td>
<td>15</td>
<td>15</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>Normal</td>
<td>males</td>
<td>29.9</td>
<td>38.7</td>
<td>50–150</td>
<td>0.4–0.45</td>
<td>0.22–0.28</td>
<td>100–300</td>
</tr>
<tr>
<td></td>
<td>females</td>
<td>24.9</td>
<td>36.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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over may be an unreliable index of red cell production. In the presence of
large numbers of nucleated red cells and reticulocytes in the peripheral blood,
overestimation of the rate of organ erythropoiesis due to initial uptake of the
injected Fe\(^{59}\) by the circulating immature cells may occur.*

The patient with polycythemia vera (M. G.) had an elevated total red cell
volume and an increased red cell iron turnover.

The fecal urobilinogen excretion and the hemolytic indexes\(^{25}\) were in good
agreement with the isotopic red cell life span data except in the case of M. B.

The calculated specific activity of newly formed hemoglobin derived from
the \(\text{C}^{14}\) specific activity of urinary hippuric acid\(^{1}\) is plotted in open circles
on the \(\text{C}^{14}\) life span graphs (see DISCUSSION).

None of the stool samples contained significant levels of Cr\(^{51}\) or Fe\(^{59}\).

The clinical and isotopic data for each patient are plotted separately in
figures 1 to 10.

Patient J. G. (figs. 1 and 2)

The plasma Fe\(^{59}\) disappearance rate was greater than normal with sub-
stantial uptake and release of the isotope by the liver and slight uptake and
release of Fe\(^{59}\) by the kidney and sacrum. The latter curves may have been
due to scattering of radiation from the massive liver, although the left kidney
was shown to contain red cell precursors by biopsy. The Fe\(^{59}\) uptake by the
red cells was fifty per cent. The Cr\(^{51}\) survival was slightly shortened (normal,
28 to 32 days), and there was no significant localization of the isotope in the
liver. The \(\text{C}^{14}\) curve reached a peak at a normal rate but of a specific activity
of about one half of the normal. The curve then declined steadily and curvi-
linearly until transfusions caused it to fall almost to zero. The mean survival
time as estimated by the method of Neuberger and Niven was 85 days.\(^{26}\)

Although the calculated red cell iron turnover was greater than normal,
some of this turnover may have been due to uptake of the circulating Fe\(^{59}\)
by the peripheral immature red cells, and further overestimation may have
resulted from the patient's recent weight loss. In favor of over-all decreased
red cell production were the low specific activities of both Fe\(^{59}\) and \(\text{C}^{14}\) in the
red cells. An expanded body pool of iron and glycine may also have accounted
for this low activity.

In summary this patient appeared to produce an insufficient number of red
cells with a somewhat shortened life span. The \(\text{C}^{14}\) curve reflected slow ran-
dom destruction of red cells as well as a finite life span. The enlarged kidneys
may have produced a significant number of red cells.

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*This possibility was suggested to us by Dr. L. R. Wasserman.

\(^{1}\)If the specific activity of glycine is assumed to be uniform throughout the liver and
bone marrow, then the specific activity of newly formed hemoglobin may be calculated
from the urinary hippuric acid specific activities of the same time period by multiplying
the latter by \((9 \times 8 \div 6.28)\), where 9 is the number of carbon atoms in hippuric acid,
\(34\)\(^{1}\)

\(^{2}\)is the fraction of heme carbon atoms derived from glycine and 6.28 is the ratio of the
\(34\)\(^{1}\) specific activity of heme to hemoglobin.
Figs. 1 (top) and 2 (bottom).—Isotopic and clinical data in patient J.G. The peripheral blood counts and transfusions are charted in their time relationships to the Fe59 uptake, Cr51 survival and C14 life span. The open circles on the C14 life span section represent the specific activity of newly formed hemoglobin calculated from the hippuric acid specific activity.
Patient M. E. G. (figs. 3 and 4)

The plasma iron disappearance rate was markedly increased and the bulk of the isotope was taken up by the spleen and liver. The spleen discharged the isotope incompletely. The liver discharged about one-third of its maximum amount and stored the remainder. The marrow was largely inactive. The Cr51 life span was distinctly short with premature destruction of labeled cells in the spleen. The Fe59 uptake was 35 per cent; this peak value was achieved more slowly than normal. The curve was transiently depressed by the second group of transfusions, indicating expansion of the blood volume, and then declined slowly, commensurate with 30 per cent utilization of the Fe59 made available by the destruction of labeled cells. The C14 curve was initially depressed by transfusions, and therefore the time that the curve may have reached its peak is not known. It declined linearly from 40 to 117 days, indicating slow random destruction of red cells. Transfusions tended to produce a small overestimation of the rate of decline. The mean red cell survival26 was 66 days.

The very rapid plasma Fe59 disappearance and apparent slow release of Fe59 from the spleen together with the low red cell uptake of Fe59 and random destruction of circulating red cells may indicate that the spleen was actively producing red cells in this patient, but that some of the cells which were produced were destroyed before their release from the spleen and others were destroyed by the spleen shortly after their release.

Patient S. P. (figs. 5 and 6)

The plasma Fe59 disappearance was very rapid with rapid uptake and virtually complete release of the isotope by the spleen and liver. The marrow stored a small amount of Fe59. The Cr51 survival was short, with equivocal evidence of premature splenic destruction of cells. The observed rate of accumulation of Cr51 in this massive spleen may lead to underestimation of the degree of hypersplenism, since the scintillation detector measured a smaller than usual fraction of the Cr51 distributed throughout the spleen. The red cell Fe59 uptake was normal. An initial dip in the curve occurred between 28 and 54 days, which may indicate the ranges of the cell lives around a mean of approximately 42 days. There was reutilization of the Fe59 followed by a second dip associated with transfusions which probably produced expansion of the blood volume. The C14 curve rapidly reached a peak of higher than normal specific activity. It then declined sharply indicating rapid random destruction of erythrocytes with a mean life span of 44 days.

This patient probably produced an increased number of red cells but became anemic because of marked shortening of the red cell life span. The major site of red cell destruction was not definitely determined, although the spleen was suspected. Gastrointestinal bleeding was not detected until the C14 curve had reached low levels.

*The size of the spleen is of importance in comparing the rate of accumulation of Cr51 in that organ from one patient to another since the cpm/μC. injected depend as much upon the fraction of spleen encompassed by the detector as upon the degree of hypersplenism. A more dependable comparative measurement might be (cpm/μC. injected) × (volume of spleen). The latter parameter might be estimated by radiographic means.
MYELOID METAPLASIA: PRODUCTION AND LIFE SPAN OF RED CELLS

Figs. 3 (top) and 4 (bottom).—Isotopic and clinical data in patient M.E.G.
Figs. 5 (top) and 6 (bottom).—Isotopic and clinical data in patient S.P.
Patient M. B. (figs. 7 and 8)

The patient maintained a fairly high transfusion requirement. The plasma radioiron disappearance rate was slow, and most of the isotope was stored in the liver. The spleen curve was consistent with some erythropoietic activity as well as storage. The sacral curve was similar in shape to, but far less active, than that of the spleen. The uptake of Fe59 by the red cells was extremely low despite a high reticulocyte and nucleated cell count, indicating grossly deficient production of red cells. The uptake declined to zero commensurate with low reutilization. The Cr51 survival curve was shortened and there was significant localization of Cr51 in the spleen as well as in the liver.

The C14 life span curve was of low specific activity and decreased in a gently curvilinear manner, suggesting random destruction of newly formed red cells. The mean life span26 was 64 days. The large number of transfusions may have contributed significantly to the decline of the curve.*

Erythropoiesis was markedly deficient in this patient, and the red cell life span was shortened with apparent premature destruction of red cells by the spleen and to a lesser extent by the liver.

Patient M. G. (figs. 9 and 10)

This patient presented with an elevated total red cell volume, which remained constant during the study. The plasma Fe59 disappearance was normal, in contrast to the very rapid disappearance usually seen in polycythemia vera.15 There was evidence of hepatic, splenic and marrow erythropoiesis. The Cr51 survival was normal and there was insignificant localization of Cr51 in the spleen. The red cells took up 100 per cent of the administered Fe59 and the C14 curve reached its maximum peak somewhat earlier than normal, maintained a plateau and then decreased. The mean life span26 was 127 days.

This patient produced more red cells than normal in the spleen, liver and marrow. The red cell life span was normal. The result was a new steady state with an increased total red cell volume.

Discussion

The precise evaluation of red cell production and life span depends upon a constant total red cell volume due to adequate production during the period of measurement. Some of these patients had deficient erythropoiesis and/or a short red cell life span, so that periodic blood transfusions were required. Transfusions will not affect the apparent uptake of Fe59 nor the Cr51 specific activity in whole blood if the blood volume remains constant. However, the specific activity of Fe59 or Cr51 in red cells and of C14 in hemoglobin may often be significantly altered by transfusions. Although the transfusions administered to the above group of patients complicate the studies, certain interpretations may be made.

*Transfusions may be expected to alter C14 red cell life span curves since the curves are based upon the specific activity of hemoglobin. If, however, the donor cells have a far shorter life span than those of the recipient, little of the effects of transfusion will be observed if samples are taken as far in time from transfusions as is consistent with over-all accuracy.
Figs. 7 (top) and 8 (bottom).—Isotopic and clinical data in patient M.B.
Red cell production in agnogenic myeloid metaplasia may be markedly increased, as in S. P., or decreased, as in M. B. It is of interest to note that these two patients had massive spleens of somewhat similar size. Nucleated red cells and reticulocytes may be abundant in the peripheral blood without any rela-
tionship to the degree of erythropoiesis. Furthermore, red cells may be produced in the spleen at a rapid rate but fail to be discharged into the peripheral blood, as suspected in M. E. G. The case of J. G. illustrates that splenectomy may be followed by massive erythropoietic hepatomegaly. The kidney may also become massively enlarged as a result of myeloid, erythroid and megakaryocytic infiltration. Of interest is the fact that J. G. showed no signs of renal insufficiency despite marked cortical and medullary infiltration with precursors of formed blood elements. The pathophysiology of deficient erythropoiesis, as occurred in M. B., is not clear. Splenic fibrosis may have occurred with resultant diminution of the total number of red cell precursors.

The patients with agnogenic myeloid metaplasia all had shortened red cell life spans, and the spleen itself may be clearly demonstrated to be a site of premature red cell destruction (M. B., M. E. G.). The C14 curves indicate that the characteristic poikilocytic, anisocytic red cell in this disease meets its end primarily by a process of random destruction, however. The probability that a given cell may be randomly destroyed is lower in certain cases (J. G.) than that which has been observed in the hemolytic phases of chronic lymphatic leukemia.21

Excessive continual utilization of labeled glycine did not appear to be of significance in these studies since the calculated specific activities of newly formed hemoglobin derived from the specific activity of urinary hippuric acid declined rapidly.

The patient with polycythemia vera and myeloid metaplasia (M. G.) had a normal C14 life span curve as described by London et al.27 The early peaks described by Berlin et al.28 were not noted in this patient.

The small number of cases studied in this series precludes general statements regarding therapy. It would appear, however, that a patient such as M. B. who produces very few red cells in his spleen, but whose red cell life span is shortened due to intrinsic cellular abnormalities and apparent hypersplenism, would benefit by splenectomy. The decision is certainly not clear from the data in the cases of M. E. G. and S. P., in whom splenic red cell production is apparently active. In these cases anemia results from splenic destruction in excess of production. Since the liver is demonstrably erythropoietic, splenectomy might be safely undertaken if no general medical contraindications to surgery existed.

**Summary**

1. Four patients with agnogenic myeloid metaplasia and one patient with polycythemia vera and myeloid metaplasia were studied with Fe59, Cr51 and glycine-2-C14.
2. Three of the patients with agnogenic myeloid metaplasia had active splenic, hepatic or renal erythropoiesis. One had deficient erythropoiesis.
3. The red cell life span was short in all of the patients with agnogenic myeloid metaplasia, definite splenic sequestration occurring in two patients. The red cell life span was normal in the patient with polycythemia vera and myeloid metaplasia.
4. The possible indications for splenectomy were discussed.
SUMMARIO IN INTERLINGUA

1. Esseva utilisate Fe59, Cr51, e glycina-2-C14 in le studio de quatro patientes con agnogenic metaplasia myeloide e de un patiente con polycythemia ver e metaplasia myeloide.

2. Tres del quatro patientes con agnogenic metaplasia myeloide habeva active erythropoiese splenic, hepatic, o renal. Le erythropoiese del quarte esseva deficieniente.

3. Le durata vital del erythrocytos esseva breve in omne le patientes con agnogenic metaplasia myeloide. In duo de illes, definite sequestration splenic esseva constatate. Le durata vital del erythrocytos esseva normal in le patiente con polycythemia ver e metaplasia myeloide.

4. Le indicationes possibile pro splenectomia es discutite.

APPENDIX: Case Histories

1. J.G.—This 49 year old white male underwent splenectomy elsewhere eleven years prior to admission because of splenomegaly and mild anemia. Microscopic sections of the spleen revealed myeloid metaplasia. A rib biopsy performed eight years prior to admission revealed myelosclerosis. For five years prior to admission the liver steadily increased in size and the patient complained of epigastric discomfort and fatigue. There was a ten Kg. weight loss during the six months prior to admission. He had frequent epistaxes and gingival bleeding. There was moderate long bone pain. Physical examination revealed a small perivascular hemorrhage in the left fundus. There was rubbery lymphadenopathy. The liver was enlarged to twelve cm. below the costal margin with a smooth edge. The kidneys could not be palpated. The spleen was surgically absent. Initial laboratory data revealed: hematocrit 36 per cent, platelets 587,000/mm.3 with giant forms, white count 40,000/mm.3 with 51 per cent polymorphonuclear leucocytes, 22 per cent lymphocytes, 1 per cent eosinophiles, 7 per cent myeloblasts, 12 per cent myelocytes, 7 per cent metamyelocytes and 9 per cent nucleated red cells. There was marked poikilocytosis and anisocytosis. The white cell alkaline phosphatase was elevated, and the serum vitamin B12 was 800 μg./ml. X-rays revealed a generalized homogeneous increase in bone density. Intravenous pyelograms revealed massive enlargement of both kidneys. A needle biopsy of the left kidney showed myeloid metaplasia. One month after admission the study was begun. The hematocrit had fallen to 31 per cent and continued to fall throughout the study. During this period the liver slowly enlarged to fill approximately three quarters of the abdominal cavity. The patient began to lose weight and required transfusions. A trial of chemotherapy was then instituted with a subsequent fall in the white count and reduction of liver size.

2. M.S.G.—This 61 year old white female noted a left upper quadrant mass six years prior to admission. The spleen and liver were found to be enlarged. The white count and hemoglobin were normal, but there was marked poikilocytosis, and myeloblasts were observed in the peripheral blood. The bone marrow was "hypoplastic." Following these findings the bone marrow gradually became replaced with fibrous tissue. A transfusion requirement of ten units per year developed. The patient began to complain of weakness, weight loss and easy fatigability. The direct Coombs' test was intermittently positive following transfusions. Two years prior to admission she was started on prednisone, 30 mg. per day. Coincident with this she felt somewhat improved, but the transfusion requirement was not altered. The prednisone was stopped three weeks before the study was begun. Physical examination revealed a weak, pale, elderly woman with numerous petechiae and ecchymoses. There was no lymphadenopathy. The spleen extended 18 cm. below the costal margin and across the midline. The liver extended 18 cm. below the right costal margin. Both organs were smooth and not tender. Laboratory data showed: hematocrit 27 per cent, platelets 200,000/mm.3, white count 3,600/mm.3 with 39 per cent polymorphonuclears, 2 per cent bands, 57 per cent lymphocytes, 2 per cent basophils and 2 per
cent monocytes. There were 3 per cent nucleated red cells. The indexes were normal, but the red cells showed anisocytosis and poikilocytosis. The bleeding, clotting and pro-thrombin times were normal as was the serum ascorbic acid. The white cell alkaline phosphatase was normal and the serum 

B_{12} was 400 \mu g/ml. The Coombs' test was initially negative, but following the second set of transfusions the indirect test was transiently positive as a result of the development of an anti-E agglutinin. The study was begun one month after admission. The patient has continued to have a transfusion requirement to maintain the hematocrit above thirty per cent.

3. S.P.—This 72 year old white male entered with a history of a duodenal ulcer seven years prior to admission. Four years prior to admission refractory anemia was noted. Two years later occult blood was noted in the stool. One year prior to admission splenomegaly was detected and six months later splenic aspiration revealed myeloid metaplasia. Bone marrow biopsy revealed myelosclerosis. During the three months prior to admission he had lost ten pounds, and required fifteen units of blood. Occult blood had been noted in the stools on several occasions. Physical examination revealed increased pigmentation of nipples and palmar lines, coarse rales at both lung bases, the liver palpable 7 cm. below the costal margin, and pitting edema of the legs. The spleen filled the left side of the abdomen. Laboratory examination showed a white count of 7,800 with 44 per cent polymorphonuclear leukocytes, 32 per cent bands, 15 per cent lymphocytes, 2 per cent monocytes and 5 per cent metamyelocytes. The hematocrit was 30 per cent, platelets 505,000/mm.\(^3\), reticulocytes 6.8 per cent, and nucleated red cells 6 per cent. The red cell indexes were normal, although the red cells showed marked poikilocytosis and anisocytosis. The serum uric acid was 6.9 mg. per cent. The white cell alkaline phosphatase was low, and the serum vitamin B_{12} was 12,500 \mu g/ml. X-rays revealed increased bone density. No abnormality of the gastrointestinal tract other than diverticuli was noted. The stools were initially negative for occult blood. One month after admission the study was started. During the initial fifty days of the study the hematocrit remained stable. Then the stools became positive for occult blood. Transfusions became necessary. A second gastrointestinal x-ray examination failed to delineate a bleeding site. He was discharged on a bland diet and has since maintained a transfusion requirement of about one unit per week.

4. M.B.—This sixty year old white male became anemic eight years prior to admission. Splenomegaly was then observed. Two years prior to admission sternal marrow biopsy revealed myelosclerosis, and a splenic aspirate showed myeloid metaplasia. The transfusion requirement was approximately 500 ml. per month. One year prior to admission he began a course of adrenal steroid therapy because the transfusion requirement had risen to 1500 ml. per month. This therapy was discontinued one month before admission. For six months prior to admission there was a thirty pound weight loss, increased sweating and a steady increase in the size of the spleen. There was a two year history of recurrent gout relieved by colchicine. Physical examination revealed that the abdomen was distended by the huge spleen, which extended 3 cm. below the navel and 3 cm. across the midline. The liver extended 5 cm. below the costal margin at the right midclavicular line. There was no lymphadenopathy. Laboratory data were: hematocrit 25 per cent, platelets 330,000/mm.\(^3\), reticulocytes 2.5 per cent, white count 6,300/mm.\(^3\) with 61 per cent polymorphonuclears, 21 per cent lymphocytes, 14 per cent abnormal immature forms, 4 per cent myeloblasts and 15 per cent nucleated red cells. There was poikilocytosis, anisocytosis and basophilic stippling of the red cells. The platelets appeared normal. The osmotic fragility was somewhat increased. The white cell alkaline phosphatase was normal and the serum vitamin B_{12} was 730 \mu g/ml. The serum uric acid was 11 mg. per cent. The study was started three weeks following admission. Transfusions were required throughout.

5. M. G.—This 47 year old white female noted weakness, easy fatigability and weight loss one year prior to admission. A white count was elevated. The hematocrit was 46 per cent. Bib biopsy revealed a richly cellular marrow with a myeloid-erythroid ratio of 5:1. There was neither a bleeding nor a clotting defect. Physical examination indicated that the spleen was palpable 4 cm. below the costal margin. The liver was not palpable.
The face was somewhat ruddy. Laboratory data showed: hematocrit 52 per cent, hemoglobin 16.4 Gm. per cent, platelets 625,000/mm., reticulocytes 0.7 per cent, white count 11,400/mm. with 49 per cent polymorphonuclears, 12 per cent bands, 1 per cent myelocytes, 18 per cent lymphocytes, 4 per cent monocytes and 3 per cent eosinophils. The red cells appeared normal in size and shape. The red cell indexes were normal. The white cell alkaline phosphatase was elevated. The study was begun shortly after admission. The peripheral blood counts remained stable. Five months after admission the total red cell volume was unchanged (2360 ml. or 44 ml./Kg.).

REFERENCES


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