Coexistent Chronic Lymphatic Leukemia
and Polycythemia Vera
Morphologic and Clinical Studies with Particular Reference to
Unusual Iron Metabolism

By W. F. Bethard, M.D., M. H. Block, M.D.,
and M. Robson, B.S.

SINCE the original description of polycythemia vera by Vaquez in 1892,1 instances of its coexistence with chronic myelogenous leukemia have been recorded.2 The subsequent appearance of one during the course of the other is thought to be sufficiently commonplace to raise the question of whether or not they might be different manifestations of the same disease. Polycythemia, presumably primary, is not unknown as an intercurrent development in multiple myeloma,3 but this is rare enough to have allayed speculation about mutual etiology. A single case is on record of polycythemia occurring with Hodgkin's disease.4 Only one instance has been documented of true polycythemia accompanying a primary tumor of the lymphopoietic system, particularly a tumor constituted predominantly of small lymphocytes.5 As with many diseases, however, the paucity of formal reports may not accurately represent the experience of capable yet literarily diffident practitioners.

The basic structure of hematopoietic tissue in the normal human adult is a reticular cell network with supporting fibers. Both bone marrow, which consists of the precursors of granulocytes, erythrocytes, and platelets, and lymphatic tissue, which is the source of lymphocytes and monocytes, are derived from this ubiquitous reticular tissue. Lymphatic leukemia, even in early stages, is characterized by replacement of normal hematopoietic tissue by lymphatic tissue; this occurs as well in areas of potential hematopoiesis, such as the liver. As a result, myeloid cells are largely replaced, in the marrow, by leukemic lymphatic tissue, thus reducing the production of granulocytes, erythrocytes, and platelets. Compensatory myeloid metaplasia never occurs.

In polycythemia vera the major abnormality is extreme hyperplasia of all marrow elements, except lymphocytes. A small amount of extramedullary blood formation may be present, but there is no increase in lymphatic tissue. The production of excess circulating myeloid derivatives (erythrocytes, granulocytes, and platelets) is dependent upon this pancytopenia of the marrow, and it may be completely inhibited by an adequate dose of radiophosphorus which decreases the marrow cellularity without affecting directly any elements in the peripheral blood. In secondary polycythemia also there is hyperplasia of myeloid tissue, in particular of the erythroblastic elements. Consequently it would seem ex-
W. F. BETHARD, M. H. BLOCK AND M. ROBSON

Extremely improbable that the two processes, i.e., lymphatic leukemia involving hyperplasia of lymphatic tissue and polycythemia with hyperplasia of myeloid tissue, would coexist in the same patient. This has been borne out by clinical experience.

Case Report*

Clinical History and Physical Examination

The patient was an 81 year old white female who had enjoyed exceptionally good health for most of her life. About two months prior to the first clinic visit she noticed gradual diminution of her usual vigor and occasional unsteadiness when walking. Twelve days before the first examination intransigent insomnia appeared, and she denied sleep during this time, except for infrequent "catnaps". There had been no headaches, visual disturbances, or evidences of gross neurologic abnormality. She had not had cardiac angina, symptoms of peripheral vascular disorder, nor signs of congestive failure. There was no bleeding or thrombotic diathesis, and she had never had symptoms suggestive of peptic ulcer.

Past history was significant only in that she had had a single episode of asthma at the age of 44, and malaria at the age of 19. There was no history of cyanosis. She had weighed 190 lbs. from the ages of 29 to 44, but had lost to 125 during two years of marital discord soon thereafter and had never regained the lost weight. Family history was noncontributory.

Physical examination on February 28, 1952 revealed a gaunt but unusually alert woman who had neither overt cervical masses nor turgid facies. The skin was normal for her age and nail beds were pink. Conjunctivae were slightly congested. Moderate bilateral lenticular opacities made fundal examination difficult, but no gross abnormalities were apparent. ENT examination was negative, except for partial dentures. The neck was slender and the thyroid was palpably smooth, firm, and nontender. Thorax was thin and expansile with respiration. Lungs were clear. Breasts were atrophic. The heart was slightly enlarged in that the left cardiac border measured 9.5 cm. from the midsternal line in the fifth left intercostal space. (MCL 9.0 cm.) Pulse rate was 84 and regular, and the blood pressure was 138/78. Peripheral arteries were tortuous and thickened, but those in the extremities were easily palpable and bilaterally equal. The abdomen was quite scaphoid and devoid of excess subcutaneous fat. The liver edge could be palpated at the costal margin on the right, and on the left the spleen extended 3 cm. below the costal margin. It was firm, smooth, and nontender. Just above and to the left of the umbilicus was a pulsatile mass over which auscultation revealed a systolic bruit. The mass was small and ill-defined. Speculation arose as to whether this represented aneurysmal dilation of the abdominal aorta or a normal aorta in an extremely thin patient. There was no evidence to indicate an arteriovenous shunt. Extremities were normal and without signs of osteoarthropathy or cyanosis. There was no significant lymphadenopathy. Pelvic examination was negative, as was the neurologic examination.

Laboratory Data

The weight was 41.3 Kg. Urinalysis was normal on two occasions. The hemogram at the first visit was as follows: hemoglobin 19.1 gm., RBC 7.64 million, hematocrit 75 per cent, platelets 246,000, WBC 28,300. Differential—Polys. 22 per cent, small lymphs, 78 per cent. Subsequent hemoglobin, red count, and hematocrit values were somewhat lower, but they were done after 500 ml. of whole blood had been removed by phlebotomy (table 1).

Serum Kahn was negative. Two three day stool collections yielded average daily fecal urobilinogen excretions of 119 and 106 mg./day respectively, and these stools were negative for occult blood (benzidine test). Two electrocardiograms were normal. NPN was 28 mg. per cent. Plasma proteins were as follows: Alb. 4.40, Glob. 1.90, Total 6.30 Gm. per cent. Roentgenograms of the upper gastrointestinal tract revealed normal esophagus, stomach, and duodenum. No lesion was demonstrated by intravenous pyelography, but an old compression fracture of the centrum of L-4 was incidentally seen. Chest film was normal, except

* The patient was kindly referred by Dr. Samuel Roebuck.
CHRONIC LYMPHATIC LEUKEMIA AND POLYCYTHEMIA VERA

for the fact that the anterior-posterior cardiac silhouette measured 38 per cent oversize. Arterial oxygen saturation was 97 per cent. Measurements of blood oxygen saturation by means of a photelectric oximeter attached to an ear lobe showed a prompt drop after inhalation of carbogen,* followed by a prompt return to normal when oxygen was used.†

Morphology

Needle biopsies of bone marrow, liver, and spleen were obtained and representative sections of each are shown in figures 1, 2, and 3 respectively. The marrow was about 80 per cent cellular and 20 per cent fat. This hypercellularity was due to the presence of both nodular and diffuse areas of dense lymphatic tissue, the predominant cells being small lymphocytes. Occasional residual small areas of normal myeloid tissue could be found but these were reduced in number. Liver architecture was well preserved and there was no excess bile nor stainable iron. Hepatic parenchyma appeared normal (fig. 2-B). Portal tissue was quantitatively increased, however, and although this seemed to be mostly collagen, small lymphocytes were seen in increased numbers (fig. 2-A). The basic architecture of the spleen was preserved, but this was the result of abnormal distension of the sinusoids of the red pulp by erythrocytes. Thus the simultaneous extreme increase in small lymphocytes in the cords of the red pulp was rendered less spectacular (fig. 3-B). White pulp was present in two to three times the normal amount and consisted of densely packed small lymphocytes without germinal nodules or follicular pattern (fig. 3-A). The marrow, liver, and spleen sections were stained for iron by the prussian blue technic, but no iron could be demonstrated.‡

Experimental Studies

Since a diagnosis of polycythemia is supported by the presence of an elevated blood volume as well as increased erythropoiesis, these measurements were undertaken. Blood volume was determined with radioactive phosphorus.§ Phlebotomy (500 ml.) had been done one month previously, so homeostasis had presumably been re-established. Total blood volume was 4200 ml. (100.2 ml./Kg.), red cell volume 2560 ml. (62 ml./Kg.), and plasma volume 1640 ml. (39.8 ml./Kg.). These values agreed well with those found in polycythemia by Berlin et al.,† in

<table>
<thead>
<tr>
<th>Date</th>
<th>Hgb. Gm.</th>
<th>RBC</th>
<th>Hct %</th>
<th>Retics. %</th>
<th>Platelets</th>
<th>WBC</th>
<th>Small Lymphs. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-28-52</td>
<td>19.1</td>
<td>7.64</td>
<td>75</td>
<td>246,000</td>
<td>28,300</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>3-1-52</td>
<td>15.5</td>
<td>5.94</td>
<td>60</td>
<td>27,200</td>
<td>77</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>3-13-52</td>
<td>15.0</td>
<td>6.05</td>
<td>55</td>
<td>39,900</td>
<td>77</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>3-31-52</td>
<td>16.5</td>
<td>6.48</td>
<td>58</td>
<td>22,800</td>
<td>77</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>4-1-52</td>
<td>16.4</td>
<td>6.54</td>
<td>60</td>
<td>275,000</td>
<td>18,300</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>4-4-52</td>
<td>16.3</td>
<td>6.41</td>
<td>61</td>
<td>246,000</td>
<td>58</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>5-15-52</td>
<td>15.2</td>
<td>6.13</td>
<td>58</td>
<td>37,400</td>
<td>57</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>5-21-52</td>
<td>15.4</td>
<td>5.43</td>
<td>58</td>
<td>16,600</td>
<td>57</td>
<td>57</td>
<td></td>
</tr>
</tbody>
</table>

* 10 per cent carbon dioxide and 90 per cent oxygen.
† This work was done by Drs. W. E. Adams and M. Newman of the Department of Surgery, University of Chicago.
‡ Special iron stains were done by Dr. Ernest Beutler of the Department of Medicine.
§ Phosphate.
that the increase in total blood volume represented chiefly a raised red cell volume, and the plasma volume remained within normal limits.

Four serum iron determinations were done by the method of Barkan and Walker (table 2). Each was inordinately low, but multiple control determina-
TABLE 2.—Serum Iron Values

<table>
<thead>
<tr>
<th>Patient serum (γ per cent)</th>
<th>Prepared standard (γ per cent)</th>
<th>Pooled rat sera (γ per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>200</td>
<td>150</td>
</tr>
<tr>
<td>10</td>
<td>200</td>
<td>150</td>
</tr>
<tr>
<td>7</td>
<td>190</td>
<td>150</td>
</tr>
<tr>
<td>7</td>
<td>190</td>
<td>150</td>
</tr>
</tbody>
</table>

Fig. 4.—This is a semilogarithmic plot of radioiron in plasma, as a function of time in hours after intravenous injection.

Tensions performed simultaneously failed to indicate technical error. Values are given in table 2. To confirm the extremely low serum iron, the iron binding capacity of the patient's plasma protein was measured according to the method of Rath and Finch.* A proportionately high quantity of 348 γ per cent was obtained.

* This work was done through the courtesy of Dr. A. R. Feinstein.
Plasma iron turnover rate as well as erythrocyte radioiron utilization was determined by the method of Huff et al.\textsuperscript{19} Approximately 2.0 \( \mu \)c of \( \text{Fe}^{59}\) in a solution containing 2.5 \( \mu \)g of iron as ferric chloride were incubated for 20 minutes under sterile conditions with 15 ml of the patient's plasma. An aliquot was taken as a standard, and the remainder was reinjected intravenously. Samples of plasma were obtained for radioiron determination at 18, 31, 59, 120, and 180 minutes after injection. From these values and from the plasma volume the total amount of radio iron within plasma could easily be calculated. These quantities were plotted semilogarithmically as a function of time as demonstrated in figure 4.

From inspection of the curve it was apparent that its slope changed abruptly just after two hours. Although only two points were known from there on, all points were best satisfied by resolving the curve into two distinct components. A third, early component, due to mixing, could probably also have been found had plasma samples been obtained at appropriate intervals within fifteen minutes after injection of the tracer. It is recognized that the slow component would be more solidly delineated by an appropriate five hour value, but unfortunately

\* Supplied by Oak Ridge Laboratory and produced by neutron bombardment of enriched \( \text{Fe}^{58}\).
this circumstance was not foreseen and further samples were not obtained. When
the curve was considered as having two components (fig. 4), it was seen that
the first, or rapid one, possessed a half-time of 0.2 hours, and that the second
had a half-time of 10.2 hours.

Further blood samples were taken at approximately daily intervals (first and
sixth days were omitted) for the next eleven days. Red cells were separated from
plasma and the radioiron concentration within red cells was determined. From
this, as well as from the red cell volume, the total erythrocyte radioiron in the
peripheral circulation could be found. These values, expressed as per cent of
the injected tracer dose, were plotted as a function of time as shown in figure 5.
It can be seen that 99 per cent of the injected tracer appeared in erythrocytes
by the ninth day after injection. Normally, a maximum of 75 per cent can be
found at this time.

Clinical Course

The total period of observation of this patient was unfortunately limited to
three months. During that time there was no addition to the history or physical
findings, except for subsidence of her intractable insomnia. This followed
promptly after phlebotomy, but causal relationship is vague. Blood counts have
already been summarized (table 1). On the last clinic visit, two and a half months
after the experimental studies cited, blood was drawn for repeat serum iron
determination. This value was 80 γ per cent, and control determinations were
normal. The serum iron-binding capacity was measured this time by two methods,
that of Rath and Finch, and a new process, using radioiron, which was developed
in this laboratory. Values were 280 and 272 γ per cent respectively. Additional
blood volume and radioiron studies were contemplated but the patient declined.

Discussion

In this patient the diagnosis of chronic lymphatic leukemia can be made with
certainty in view of the typical morphology of the blood, bone marrow, liver,
and spleen. Absence of significant lymphadenopathy is not contradictory, but
rather indicative of a clinically benign process which not infrequently attends
old age. Polycythemia was strongly suggested by the initial blood count. Con-
firmation was provided by the normal plasma volume, elevated red cell volume,
and elevated total blood volume. Ordinarily, in untreated cases of polycythemia
vera, the decrement in peripheral erythrocyte concentration is not so remarkable
after a single 500 ml phlebotomy. It is often the case, however, after earlier
phlebotomies have depleted iron stores and thus rendered the erythrocytes hemo-
globin deficient. Although there is no history of previous treatment by phlebot-
omy, red cell hypochromia and microcythemia, as well as the extremely low
plasma iron level and absence of stainable tissue iron, speak for an iron-deficient
state in this patient. No evidence of chronic blood loss was found. The fact that,
after reduction by phlebotomy, and without use of marrow inhibiting agents,
the red blood count failed to rise for at least three months is indicative of the
mildness of the polycythemia. It does not vitiate the diagnosis.

Differentiation of primary and secondary types of polycythemia may be diffi-
cult. The latter presupposes some initiating defect which prevents adequate
tissue oxygenation. Most often this takes the form of cardiorespiratory or vascular dysfunction in which arterial blood cannot be fully saturated with oxygen. Other initiating conditions, such as endocrine disturbances, arteriovenous anastomoses, and subtentorial tumors, are known, but the mechanisms by which these produce polycythemia are vague. In this patient the diagnosis of primary polycythemia is favored by the normal arterial oxygen saturation, the normal oximeter studies, and the absence of any clinical condition to which polycythemia is a known sequela. There was no evidence to suggest either pulmonary or cardiac insufficiency. The question might arise as to whether or not aneurysmal dilatation of the aorta were present, and, if so, might not this cause polycythemia. If dilatation were conceded, there was nothing to indicate shunting of arterial blood into the venous return, and this is considered prerequisite to secondary polycythemia.

Histologically the bone marrow was typical of chronic lymphatic leukemia. Sections of the liver and spleen were compatible with such a diagnosis, but they were not pathognomonic. There was no evidence of extramedullary hematopoiesis in the tissues examined. Cells of the erythroid series could easily be found in the bone marrow specimen, but they were numerically reduced as compared to normal. Comparison with the usual polycythemia vera bone marrow emphasized this reduction. A problem arises as to the source and site of production of sufficient erythrocytes to result spontaneously in a blood volume of polycythemic proportions. It is possible that none of the needle biopsies was representative of the total volume of organ sampled. In the marrow, myeloid tissue consisting of hemocytoblasts, erythroblasts, reticulum cells, and myelocytes was interspersed among dense areas of small lymphocytes but this was never in normal amounts. It would have been desirable to repeat the biopsies at other sites, but the patient understandably declined. A theoretic possibility that erythrocytes can arise directly from lymphocytes must be considered, but there is little or no evidence to support this. The source of erythropoiesis has not been adequately demonstrated.

Huff postulated that plasma concentration of intravenously injected radioiron would decrease logarithmically with time until a constant value was reached. This would occur when the tracer had attained equilibrium within the total iron pool, at that time its concentration in plasma would be too small for measurement by the usual methods. The simple exponential curve presumably represented exit of radioiron from plasma for utilization in various biologic compartments at essentially equal rates. Its negative slope has been purported to be an index of the rate of erythropoiesis. In general this is probably true in that all plasma iron clearance curves reported by Huff, and all previously obtained by the authors, have been resolvable into components of single negative slope if early deviations due to mixing were ignored. Depots other than marrow remove iron from the plasma, and the assumption that all processes occur at equal rates is not necessarily valid. A priori they occur simultaneously; comparatively, however, amounts from plasma to tissues other than marrow are quite small so that they may be masked when plasma iron content and total iron stores are normal. In this patient, probably by virtue of the extremely low plasma iron, the disappearance curve for radioiron from plasma displayed two distinct components.
The data support the premise that plasma beta-1 globulin is not cleared of conjugated iron entirely by erythropoietic tissue, and that removal for erythropoiesis is probably represented by the rapid component having a half-time of 0.2 hours. This corresponds well with half-times found in cases of polycythemia vera or in severe iron-deficiency anemia. The second, slow component has a half-time of 10.2 hours and approximates that seen in cases of primary refractory anemia. It probably represents extrahematopoietic iron utilization. If plasma iron turnover is calculated on the basis of the rapid component, a value of 0.231 mg./Kg./day is obtained. This is below the normal limits for males of 0.30 to 0.40 mg./Kg./day as established by Huff.\(^\text{19}\) Apparently the rapidity of turnover cannot fully compensate for the small amount of iron present in this patient.

Ordinarily about 75 per cent of intravenously administered radioiron appears in the red cell mass within two weeks, and this is dependent upon three factors, namely: (1) Size of iron stores, (2) adequacy of plasma transport, and (3) rate of erythropoiesis.\(^\text{14}\) Admixture of tracer with reduced amount of storage iron may result in higher specific activity within red cells in the presence of a normal production rate. This is observed in iron deficiency anemia. Increased erythropoiesis may also heighten the per cent of injected radioiron appearing in erythrocytes even though iron stores are normal. This is found in polycythemia. Specific activity of red cell iron remains normal. In this patient 99 per cent of the tracer appeared in the red cell mass by the ninth day (fig. 5). This decided elevation could represent low iron stores, increased erythropoiesis, or both. At present there is no convenient way to distinguish between the two conditions, but the extremely low plasma iron, the high serum iron-binding capacity, and the absence of stainable tissue iron would favor the former.

**SUMMARY**

1. A case of coexistent chronic lymphatic leukemia and polycythemia vera is described.

2. The source of the erythrocytosis was not apparent. Erythroid hypoplasia was seen in the bone marrow, and there was no apparent extramedullary hematopoiesis in specimens of liver or spleen.

3. Plasma iron content was inordinately low, and this was confirmed by a correspondingly high plasma iron-binding capacity. No stainable iron could be demonstrated in the tissues examined.

4. The curve for plasma iron clearance was best satisfied by two components of different negative slopes. The more rapid had a half-time of 0.2 hours and probably represented removal of iron for erythropoiesis. The slower had a half-time of 10.2 and probably represented extrahematopoietic iron utilization.

5. Erythrocyte radioiron utilization was greater than normal and approximated 100 per cent within nine days. This could have been a manifestation of depleted iron stores, accelerated erythropoiesis, or both.

**ADDENDUM**

In March, 1953, eleven months after discharge from the hospital, the patient unexpectedly appeared in the OPD for medical care. She was hospitalized and all previously performed studies were repeated. With the exceptions to be mentioned, results were unchanged. The hemoglobin was 17.9 Gm., RBC 6.93
million, hematocrit 69 per cent, platelets 138,000, WBC 23,250, differential—polys 12 per cent, small lymphocytes 87 per cent, and monocytes 1 per cent. Physical examination was as previously recorded. Microscopic sections of bone marrow and liver revealed the same alterations as before. Spleen biopsy was technically unsatisfactory even though the spleen remained large. Blood volume was elevated to polycythemic proportions. An electrocardiogram gave evidence of anterior wall myocardial infarction which had occurred since previous hospital discharge. Its age was indeterminant, and there had been no suggestive symptoms.

Radioiron plasma clearance and erythrocyte uptake determinations were repeated. Plasma radioiron clearance, plotted semilogarithmically as a function of time, described a straight line having a half-time of 0.34 hours. There was no second component as found previously. Plasma iron turnover was 0.527 mg./Kg./day—or somewhat greater than twice the value found before. Serum iron was 34 γ per cent, and the serum iron-binding capacity was 375 γ per cent. Absence of a so-called extrahematopoietic component in the second plasma iron clearance could be explained by either masking by the increased amount of iron cleared from plasma or by a technical error in the first determination. This point should be re-examined in animals rendered markedly iron-deficient. Erythrocytes contained 95.5 per cent of the injected tracer on the 72nd day after injection.

REFERENCES

Coexistent Chronic Lymphatic Leukemia and Polycythemia Vera: Morphologic and Clinical Studies with Particular Reference to Unusual Iron Metabolism

W. F. BETHARD, M. H. BLOCK and M. ROBSON