To the Editor,

In Blood, 5:233, 1950,1 William H. Crosby described a patient and his family who were diagnosed as having hereditary nonspherocytic hemolytic anemia. The patient was born in 1923 of mixed English and French antecedents and raised in Southern Louisiana. He had entered military service in 1943. The extensive erythrocyte studies performed at that time (Brooke General Hospital, 1946-48) had failed to reveal an etiologic mechanism for the hereditary hemolytic process. Splenectomy in April, 1948, had not significantly improved his anemia. We wish to present a brief follow-up.

The patient, at age 43, was seen again at Brooke General Hospital during October 1967 because of additional medical problems. In January 1967, a right nephrectomy had been performed for renal cell carcinoma. Irradiation therapy was given to the affected area, and subsequently to many other areas for recurrent metastases. His admission on October 12, 1967, was prompted by severe dyspnea and chest pain, related to a pleural effusion and a pericardial tamponade.

His on-going hemolytic process was manifested by a hematocrit of 30%, a hemoglobin of 8.8 g/100 ml, persistently elevated reticulocyte counts, and indirect bilirubinemia of 1.3 mg/100 ml. His peripheral blood smear demonstrated marked polychromasia, no spherocytes, numerous Howell-Jolly bodies, leukocytosis, and thrombocytosis. The patient was not transfused.

About 2 weeks after his discharge on November 1, 1967, he expired suddenly at home. Permission for a postmortem examination was not obtained.

On two occasions during his hospitalization, a blood sample along with a control specimen was sent to K. R. Tanaka at Harbor General Hospital, Torrance, Calif., for red cell enzyme determinations. The heparinized blood samples of October 16, 1967 had a reticulocyte count of 24.9%, that of October 25, 1967 in ACD, 22.9%.

All red cell enzymes studies (hexokinase to lactate dehydrogenase in the Embden-Meyerhof pathway, and glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase, glutathione reductase, glutathione peroxidase, and ATPase) were found to be normal or increased in activity, except for puruvate kinase (PK), which was decreased in activity. The patient's red cell PK activity was 2.54 units (Table 1) in the presence of marked reticulocytosis. The leukocyte PK activity of the patient was normal. The red cell content of reduced glutathione was normal. Specifically, triose phosphate isomerase activity was normal in view of his part-French ancestry and Louisiana background. The red cell PK value of 2.54 is somewhat higher than that generally found in the homozygous patient with the usual type of PK deficiency. However, assays at various substrate concentrations (0.03 mM to 6.0 mM phosphoenolpyruvate) did not reveal a kinetically aberrant isozyme of PK. In addition, 0.3 mM fructose-1,6-diphosphate did not activate the PK activity of the patient's red cells.

Subsequent studies on the proband's brother and sister demonstrated very low red cell PK activity characteristic of homozygosity (Table 1); both had evidence of active hemolysis. The three daughters of the proband had intermediate PK values typical of heterozygotes (Table 1); their hemograms were normal. Kinetic studies and experiments with fructose-1,6-diphosphate failed to disclose a kinetically aberrant isozyme of PK in any of these individuals. The wife of the proband had a normal PK value and a normal hemogram.

The studies summarized above indicate that the patient described by Crosby in 1950 had PK-deficiency hemolytic anemia. Although the anemia in this patient and his family was previously reported to be transmitted as a Mendelian dominant character-
istic, our data are consistent with the well established autosomal recessive mode of transmission for pyruvate kinase deficiency.

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Table 1. Pyruvate Kinase Assay Results in Family

<table>
<thead>
<tr>
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<th>Red Cell Pyruvate Kinase*</th>
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<tbody>
<tr>
<td>Propositus (12)†</td>
<td>2.54</td>
</tr>
<tr>
<td>Brother L.S. (10)†</td>
<td>0.13</td>
</tr>
<tr>
<td>Sister E.S. (13)†</td>
<td>0</td>
</tr>
<tr>
<td>Wife</td>
<td>6.82</td>
</tr>
<tr>
<td>Daughter R.S.</td>
<td>3.46</td>
</tr>
<tr>
<td>Daughter L.S.</td>
<td>2.90</td>
</tr>
<tr>
<td>Daughter J.S.</td>
<td>3.46</td>
</tr>
<tr>
<td>Normal range</td>
<td>4.03–6.93</td>
</tr>
<tr>
<td>Mean ± S.D.</td>
<td>5.46±0.82</td>
</tr>
</tbody>
</table>

†Corresponding to designation in Fig. 1 of 1950 paper.
*One enzyme unit of PK activity is equivalent to one μmole of NADH oxidized per minute by $10^{10}$ erythrocytes at 37°C under our assay conditions.

To the Editor,

The prognostic value of total fetal hemoglobin in acquired aplastic anemia in children has been forwarded by Bloom and Diamond. According to these authors, when total fetal hemoglobin is less than 400 mg/100 ml, the prognosis of aplastic anemia is unfavorable. This conclusion prompted us to assess the value of total fetal hemoglobin as a prognostic criterion in acquired aplastic anemia in adults. Hemoglobin F was determined by the method of Singer et al. The results of the study in 27 patients with aplastic anemia, either idiopathic or of various etiology including benzene, were presented at the Fifth Congress of the Asian-Pacific Society of Haematology held in Istanbul, September 1969. Sixteen of these patients had a marked hypoplastic bone marrow. In these patients, mean fetal hemoglobin percentage was 4.6% (SD ± 3.316), mean total fetal hemoglobin value was 202.8 mg/100 (SD ± 146.1). In 14 of these patients, the total fetal hemoglobin value was less than 400 mg/100 ml. Six of them recovered. Six had a fatal outcome and two showed no improvement. In the remaining two patients with aplastic anemia associated with hypoplastic bone marrow, the total fetal hemoglobin value was higher than 400 mg/100. One of them has recovered, and the other one has died. Considering these facts, we concluded that, in our series of acquired aplastic anemia, there was no exact correlation between the amounts of fetal hemoglobin and the prognosis of aplastic anemia in adults. This conclusion was emphasized in another study. Twelve out of 32 patients with pancytopenia associated with long-term exposure to benzene had hypocellular or acellular bone marrows. Mean fetal hemoglobin in seven of them in whom hemoglobin analyses were performed was 5.4% (SD ± 2.09), and the mean total fetal hemoglobin value was 365 mg/100 ml (SD ± 175.2). Three out of these seven pancytopenic patients with long-term exposure to benzene associated with hypocellular bone marrow, in whom the total fetal hemoglobin
value was less than 400 mg/100 ml have recovered. Contrary to this, the remaining four patients had a total fetal hemoglobin value higher than 400 mg/100 ml. Three of them also recovered. Only one patient is still under treatment, and only a mild improvement in his hematological and clinical condition has been noted. Thus, we suggested again in our above mentioned papers that in pancytopenic patients exposed to benzene, associated with hypoplastic bone marrow, the total fetal hemoglobin value does not have the same prognostic value, as forwarded by Bloom and Diamond in acquired aplastic anemia in children. On the other hand, we had similar results concerning the total fetal hemoglobin value in pancytopenic refractory anemias with normocellular or hypercellular bone marrows.

REFERENCES

3. Aksoy M, Dinçol K, Erdem S, Akgün, T: The results obtained from a triple treatment with androgens, steroids and phytohemagglutinin of aplastic anemia of various etiology with emphasis on the prognostic value of total fetal hemoglobin content and bone marrow cellularity. Fifth Congress of the Asian and Pacific Society of Haematology, September 1–6, 1969, Istanbul, p 31

NEWS AND VIEWS

NATIONAL LEUKEMIA ASSOCIATION

The National Leukemia Association is presently accepting applications for grant support from physicians doing leukemia and lymphoma research. The deadline for submitting applications October 15th. Please address all questions to: Mr. Arthur M. Blau, President, National Leukemia Association, Roosevelt Field, Garden City, N.Y. 11530.