Hematologic Studies on Erythropoietic Porphyria: A New Case with Severe Hemolysis, Chronic Thrombocytopenia, and Folic Acid Deficiency

By SAMUEL GROSS

With the technical assistance of Vicki Keefer

ERYTHROPOIETIC porphyria is a rare inborn error of porphyrin metabolism; forty-two well documented cases have been described to date. Among the features common to this disorder is a hemolytic component of varying degree and severity. The precise nature of the hemolytic defect and its relationship to changes in other organs such as the liver and the spleen is not clear. The case reported here is that of an 8-year-old white male with a severe hemolytic anemia and thrombocytopenia who developed a folic acid deficiency during the course of investigation. Also emphasized in this report is the diffuse involvement in this disorder and the intracorpuscular nature of the red cell defect.

MATERIALS AND METHODS

Hematologic Studies

Hemoglobin, hematocrit and cell counts were determined by standard methods as were the direct antiglobulin test, sickle cell preparation, peripheral smear, Heinz body and bone marrow stains.1 Marrow hemosiderin preparations were carried out according to the method of Rath and Finch.2

Red cell benzidine stains were performed according to a modification of the technic of Garcia-Blanco and Forteza-Bover.3 Marrow and peripheral blood films were dyed initially with Wright’s stain, cleared with buffer and distilled water and blotted dry. They were then immersed in acetone-free absolute methyl alcohol containing 200 mg. per cent each of benzidine and sodium nitroprusside, 0.05 ml. of glacial acetic acid, and 0.15 ml. of 30 per cent hydrogen peroxide per 100 ml. of solvent. The films were stained for 1–2 minutes, sufficient time to produce a blue color in the hemoglobin moiety without overly decolorizing the Wright’s stain of the normoblastic nuclei.

Biochemical Studies

Serum bilirubin was determined by the method of Hsia, Hsia and Gellis, using pure bilirubin as a standard.4 The bromsulfalein excretion test was performed as described by Ham.1 Serum folic acid levels were determined according to the method of Waters and Mollin.5 Normal: > 5.0 mcg./ml. Urinary formiminoglutamic acid (FIGLU) excretions were done by the method of Zalusky and Herbert.6 Normal (without histidine loading): 0–5 mg./12 hours. Hemoglobin type was determined by paper7 and gel8 electrophoresis.
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Plasma acid phosphatase determinations were carried out as described by Shinowara et al. Normal: 2-4 units. Plasma-bound iron and binding capacity was determined by the method of Schade et al. Normal: 80-120 µg per cent with 20-30 per cent saturation. Glucose-6-phosphate dehydrogenase (G-6-P-D) activity was assayed according to the technic of Zinkham et al. Normal: 180-240 units/100 ml of RBC's at 25 C. Urinary porphobilinogen was sought by the method of Watson and Schwartz. The qualitative urinary excretion of coproporphyrin and uroporphyrin involved the method of Waldenström, and the quantitative assay was performed by Dr. Rudi Schmid.

Autohemolysis Tests

The rate of red cell hemolysis in autologous and homologous plasma was determined by a modification of the technic of de Gruchy et al. Sterile defibrinatel blood was collected in conical flasks from both the patient and an homologous control. Under sterile technic, both sets of cells were mixed with homologous plasma as well as with their respective plasmas. The hematocrits were adjusted to 20 per cent. Two ml. of appropriately mixed blood were then transferred into each of 24 sterile 5 ml. bottles. In the first eight bottles, blood alone was placed; to each of the second eight bottles had previously been placed 0.10 ml. of 10 per cent glucose in 0.85 per cent sodium chloride; to each of the third eight bottles had previously been added 0.10 ml. of adenosine triphosphate to produce a final concentration of 0.02 M in whole blood. All of the tubes were then subdivided into 1 ml. portions, half of which were incubated at 37 C. for 24 and 48 hours in the dark and the remainder incubated for 24 and 48 hours at 37 C. under a U.V. light source provided by U.V. light, Mil 2F-C, C. W. Gates and Co. The hemolysis was measured as described by Dacie. Normals after 48 hours: blood alone 1.0-3.5 per cent, blood with added glucose 0.0-0.8 per cent, blood with added adenosine triphosphate 0.0-0.8 per cent.

Histologic and Cytological Studies

Following decalcification, the deciduous incisors were sectioned and stained with hematoylin and eosin according to standard methods. Sections of spleen and liver were similarly stained. Iron pigmentation in the latter two organs was sought with a prussian blue stain. Unstained specimens were examined for fluorescence under a Zeiss ultraphot microscope with a Zeiss No. 44 filter. Chromosome counts on peripheral blood were performed according to the technic of Moorehead et al.

CASE REPORT

J. R., an 8-year-old white male of Irish, Scotch and Slovenian extraction was first seen at Babies and Childrens Hospital at 7 years of age with an admitting diagnosis of a non-spherocytic hemolytic anemia. He was the third youngest of five siblings, the others, in addition to his parents and known relatives, being in excellent health.

His initial hospitalization in another city occurred at 7 months of age with an admitting complaint of pallor since birth. At that time his pertinent physical findings, in addition to pallor, included frontal bossing and hepatosplenomegaly of moderate degree. Laboratory studies revealed a hemoglobin of 5.5 Gm. per cent, red blood count of 2 x 106/mm.3, white count of 11,400/mm.3, platelet count of 102,000/mm.3, nucleated red cell count of 850/mm.3 and 6 per cent reticulocytes. The red cell morphology was described as showing hypochromia, microcytosis, anisocytosis, poikilocytosis, with occasional spherocytes. Additional laboratory studies were negative for sickle cell preparations, abnormal osmotic fragilities, direct antiglobulin, acid hemolysis and Donath-Landsteiner tests. He received a short course of oral iron therapy without benefit, following which a blood transfusion temporarily restored his hemoglobin to normal. Because of the need for additional transfusions and the presumptive evidence that this patient had a hemolytic anemia...
of undetermined origin, a splenectomy was performed at 8½ months of age with the thought that such a procedure would alleviate the hemolytic process. However, he continued to require transfusions every 5 to 7 weeks, and in addition his platelet counts showed a persistent, insidious decline. Shortly after the splenectomy, his diapers were noted to be pink stained. Furthermore, following his initial exposure to sunlight, he developed varying numbers of vesicular lesions on the exposed parts of his body (fig. 1). Occasionally these bullous lesions became filled with sanguinous fluid, presumably due to the thrombocytopenia, which not infrequently led to rather marked epistaxes. In the course of his development, hypertrichosis, in the form of fine downy hair, was noted over his face and extremities; his teeth exhibited a brownish discoloration, and the frontal bossing and hepatomegaly persisted. Because of the outspoken hemolytic anemia, his need for transfusions continued unabated, and on occasion was hastened due to superimposed bleeding diatheses. Yet his growth and development remained normal (50th percentile for both height and weight); and at the time of his first admission to this hospital, he was essentially as described. Following the diagnostic evaluation of this patient, studies on the remaining members of the immediate family failed to reveal even remote evidence of a similar disorder.

**RESULTS OF LABORATORY STUDIES**

**Hematologic Data**

The initial hematological studies, detailed in table 1, were as follows: hemoglobin 6.0 Gm. per cent, hematocrit 17 per cent, corrected white cell count 11,200/mm³, 80 nucleated red cells/100 white cells, platelets 60,000/mm³, and reticulocytes 5.0 per cent. Sickle cell preparations and direct and indirect antiglobulin tests were negative. The Wright’s stained film of peripheral blood was characterized by hypochromia, poikilocytosis, anisocytosis, polychromasia and targeting. In addition, as shown in figure 2, many of the normoblasts contained both single and multiple nuclear inclusions. When stained with Wright’s stain and counterstained with benzidine-
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Table 1.—Hematologic Data*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (Gm. %)</td>
<td>4.2–7.0</td>
</tr>
<tr>
<td>Platelets (mm.³)</td>
<td>35,000–65,000</td>
</tr>
<tr>
<td>Reticulocytes (%)</td>
<td>3.8–11.0</td>
</tr>
<tr>
<td>Nucleated red cells (~/100 WBC)</td>
<td>35–130</td>
</tr>
<tr>
<td>Peripheral smear</td>
<td>hypochromia, anisocytosis, poikilocytosis, targets, stippling, polychromasia</td>
</tr>
<tr>
<td>Heinz body test</td>
<td>negative</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>normoblastic with nuclear inclusions and decreased megakaryocytes</td>
</tr>
<tr>
<td>Fluorescence</td>
<td>positive in &gt;80% of developing nucleated red cells</td>
</tr>
<tr>
<td>Bone marrow hemosiderin</td>
<td>markedly increased</td>
</tr>
<tr>
<td>Chromosomes</td>
<td>normal</td>
</tr>
</tbody>
</table>

*Usually obtained at time of admission for transfusions.
†Level obtained at time of folate deficiency.

nitroprusside solution, the nuclear inclusions stained a deep blue consistent in color and intensity with the cytoplasmic hemoglobin and in contrast with the pink-violet nucleus. By this technic there was no confusion in discriminating between target cells and nuclear inclusions. A bone marrow preparation, consistent in appearance with the marrow obtained at 7 months of age, was normoblastic and showed a striking decrease in megakaryocytes. The marrow hemosiderin stain was markedly positive. Fluorescence, as shown in figure 3, was present in 60–70 per cent of the developing erythroid precursors and in some of the reticulocytes.

Biochemical Data

The results of the biochemical studies are presented in table 2. A summation of the more significant data includes elevated levels of hemoglobins A₆ and F, high normal plasma acid phosphatase values, and significantly elevated uroporphyrin and coproporphyrin levels. Serum iron and percent saturation were consistently elevated. The low folic acid and elevated FIGLU levels will be discussed under therapy.

Hemolysis Tests

The results of the red cell hemolysis tests in both autologous and homologous plasma, as shown in table 3, indicate quite conclusively that the patient's red cells, whether in autologous plasma or in that of an homologous donor, behaved abnormally. Furthermore, neither glucose nor ATP corrected the defects. Conversely, the donor red cells behaved in a characteristically normal fashion regardless of the vehicle. In addition, there was no disparity between these tests run in the dark and under direct ultraviolet light.

Histologic Data

Teeth, liver, spleen: Following the initial substantiation of the diagnosis of erythropoietic porphyria, an unusual point of dental interest was noted.
Figs. 2–3.—See legend, facing page.
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Table 2.—Biochemical Data

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
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<tr>
<td>Direct and indirect antiglobulin test</td>
<td>negative</td>
</tr>
<tr>
<td>Bound iron/total binding capacity (μg. %)</td>
<td>317/325</td>
</tr>
<tr>
<td>Hemoglobin partition (%)</td>
<td></td>
</tr>
<tr>
<td>Hb A</td>
<td>80-85</td>
</tr>
<tr>
<td>Hb A2</td>
<td>3.8</td>
</tr>
<tr>
<td>Hb F</td>
<td>10-18</td>
</tr>
<tr>
<td>Porphobilinogen (mg./24 hr.)</td>
<td>negative</td>
</tr>
<tr>
<td>Uroporphyrin (μg./24 hr.)</td>
<td>7500</td>
</tr>
<tr>
<td>Coproporphyrin (μg./24 hr.)*</td>
<td>&gt;700</td>
</tr>
<tr>
<td>Acid phosphatase (units)</td>
<td>4.0</td>
</tr>
<tr>
<td>Folic acid (mμg./ml.)</td>
<td>2.9</td>
</tr>
<tr>
<td>Urinary FIGLU (mg./24 hr.)*</td>
<td>901, 14§</td>
</tr>
<tr>
<td>Bilirubin (direct/total mg. %)</td>
<td>0.8/1.3</td>
</tr>
<tr>
<td>Glucose-6-phosphate dehydrogenase (units/100 cc, RBC)</td>
<td>300</td>
</tr>
<tr>
<td>BSP retention (%)</td>
<td>4</td>
</tr>
<tr>
<td>Blood lead level (μg. %)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Often inaccurate when present with increased levels of uroporphyrin.
†Without histidine loading.
‡Before therapy.
§After therapy.
∥Normal = <0.06 μg. per cent.

Although this patient exhibited the classical uroporphyrin and coproporphyrin excretion in accompaniment with the red cell fluorescence, his deciduous teeth failed to fluoresce. Because of a retardation in the parturition of his lower deciduous incisors and the subsequent malocclusive eruption of his permanent teeth, dental extractions were performed. The sections of the deciduous incisors failed to show evidence of fluorescence. However, they did exhibit a minimal degree of cementum hypercellularity. Following the eruption of the permanent teeth, fluorescence was readily demonstrable and in sharp contrast to the remaining deciduous teeth.

Sections of the spleen and liver obtained at the time of splenectomy 7 years ago were available for study. The spleen and liver (figs. 4 and 5) demonstrated a marked accumulation of hematopoietic precursors in the sinusoids. Myeloid precursors and rare megakaryocytes were also present. In figure 5, a megakaryocyte is clearly visible. Only minimal fluorescence was present in these organs. Nor was it possible to ascertain with certainty whether fluorescence was evident in the hematopoietic precursors. Both of these organs contained variable but large amounts of iron within the cytoplasm of the

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Fig. 2. (top)—Peripheral smear stained with Wright’s, benzidine and nitroprusside (x910). Normoblastic nuclei stain pink-violet, and the inclusions stain purple (center). The target cells are clearly distinguished from the cells containing nuclear inclusions. The hemoglobin generally stains dark except in areas where greater destaining has occurred.

Fig. 3. (bottom)—Unstained marrow smear photographed in fluorescence microscope (x910). The red fluorescence is particularly impressive in the nuclei, but is also present to a lesser degree in the reticulocytes.
Fig. 4.—Spleen (H. & E. x300). The sinusoids of the red pulp are filled with numerous hematopoietic elements. These cell forms are mainly erythroid precursors, but occasional megakaryocytes and myeloid forms are also present. There is a considerable amount of iron deposited within the cytoplasm of cells in the sinusoids.

Fig. 5.—Liver (H. & E. x300). Within the hepatic sinusoids are groups of hematopoietic elements. These are mainly erythroid precursors, and a megakaryocyte is present in the field. There is no evidence of hepatocellular disease. Moderate amounts of iron are present in association with these intrasinusoidal cells.
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Fig. 6.—The response to oral folic acid, 15 mg./day, following the development of a folate deficiency.

sinusoidal cells, most marked in the spleen. Furthermore, there was no evidence of hepatocellular disease.

Therapeutic Studies

Pyridoxine, adenosine monophosphate and folic acid: Neither pyridoxine administered in an oral dose of 250 mg. twice daily during a 4-week period, nor adenosine monophosphate, 100 mg. per day I.M. for 2 weeks, altered the clinical course of the disease. In fact, during the course of the investigations, it became obvious that the frequency of transfusions was steadily increasing and was associated with an early decline in hemoglobin, a relative reticulocytopenia and decreased numbers of nucleated red cells. As shown in table 2, the evidence of a folate deficiency was substantiated by a low serum folic acid level and increased urinary formiminoglutamic acid excretion. Of interest was the fact that there was no marrow evidence of a megaloblastic change. Following the administration of oral folic acid, 15 mg. per day, the patient's course, as seen in figure 6, showed a dramatic improvement. The transfusion frequency decreased to an 8–9 week interval concomitant with a rise in reticulocytes and nucleated red cells and a decline in FIGLU excretion to a normal level of 14 mg./24 hours. The thrombocytopenia, however, did not improve.

COMMENT

Increased hemolysis has been a common finding in most of the reported cases of erythropoietic porphyria. However, in only a few patients has it been severe, and in many it has been intermittent. In the majority of these patients the hemolysis has been either mild and/or well compensated. Furthermore, measurements of red cell survival have shown a marked varia-
tion and, not infrequently, a poor clinical correlation. Splenectomy, in several of these patients, produced variable results. In three of the more severe cases with blatant anemia (de Marval and Pons, Varadi, Aldrich et al.), splenectomy reduced the hemolysis greatly, yet was essentially ineffective in Gray and Neuberger's patient. In the present case, the hemolytic process had been severe, requiring multiple transfusions beginning at 7 months of age with a frequency of every 4-6 weeks. Splenectomy, performed at 8.5 months of age, was ineffective.

The anemia in this disorder, with few exceptions, has generally been described as normochromic with increased numbers of circulating reticulocytes and nucleated red cells. In several cases, however, a detailed description of the red cell morphology has been lacking. The observations by Schmid et al. regarding the unusual nuclear inclusions in the fluorescing normoblasts seen in their patients casts some light on the nature of the hemolytic process. These inclusions were readily demonstrated in the present patient by a routine Romanowsky stain and by special contrasting technics with the use of a Wright's, benzidine-nitroprusside stain. However, the overall bizarre nature of the peripheral morphology, viz., hypochromia, poikilocytosis, etc., was so striking as to suggest one of the thalassemic syndromes. The possibility that these intranuclear inclusions were heme or heme-like substances was strongly supported not only by the special staining technics but by their appearance under the electron microscope, a study soon to be reported. With the cumulative data suggesting that coexistence of two red cell lines, the likelihood that the hemolytic defect was intracorpuscular is highly tenable. The work of Rosenthal showing a decrease in survival of porphyric red cells in a non-porphyric recipient lends further support to this concept. Yet other studies have suggested that hematoporphyins in the presence of light give rise to hemolysis of normal cells in vitro. In the present case, seasonal differences in hemolytic activity were not apparent. Indeed, with the exception of the vesicular eruptions, the patient was generally better during the summer months. In addition, the in vitro hemolysis studies, as shown in table 3, support the evidence of an intracorpuscular defect. Normal plasma did not alter the per cent hemolysis of porphyric red cells, nor did porphyric plasma exert an untoward effect on normal cells; and in no instance did ultraviolet light enhance the hemolytic activity. Furthermore, glucose was only partially effective in restoring the per cent hemolysis of the porphyric cells to normal, and both AMP and ATP exerted no effect. Indeed, the data suggests a paradoxical action with AMP and ATP.

Recent electron microscopic studies by Bessis and Breton-Gorius have demonstrated a defect in cellular iron utilization in the hypochromic hypersideremic anemias, some of which are associated with increased hemolytic activity. The precise nature of this defect is unknown, but it is suspected that the metabolism of hemoglobin is blocked at various sites, according to the disease in question; and the immobilized iron accumulates in the mitochondria and in the cytoplasm, thereby producing the typical hypochromic appearance. In congenital porphyria, the preponderant evidence indicates an
intracorpuscular defect, viz., a hypochromic cell line with heme-like accumulations in the fluorescing normoblastic nuclei and an abormal degree of red cell lysis. As for pathogenic considerations, the possibility is present that the type I porphyrins, or the defect responsible for porphyrin I overproduction, may interfere with normal heme biosynthesis.

The persistence of fetal hemoglobin in this patient was probably based upon its continued synthesis. Although evidence of persistent high Hb F has not been mentioned previously in erythropoietic porphyria, it is well recognized that Hb F may persist in certain anemic states, particularly if the disorder begins at an age when it is still being produced. This phenomenon, seen in thalassemia and sickle cell disease, also occurs in some cases of congenital spherocytosis as well as in certain of the congenital regenerative anemias. Many of these disorders, interestingly, are intracorpuscular in nature. The slight elevation in Hb A2, characteristically seen in some of the thalassemic syndromes, is less readily explainable.

The additional finding of a moderate to severe thrombocytopenia deserves mention because of its rarity. The presumptive evidence of its presence at birth (post-circumcisional bleeding) and unequivocal evidence by 7 months of age appears to be related to a defect in megakaryocyte production. The recent work of Oski et al. demonstrating an elevation in plasma acid phosphatase levels in patients with thrombocytopenia associated with megakaryocyte proliferation has been explained on the basis of a release of this substance secondary to excessive platelet destruction. The presence of a
normal plasma acid phosphatase level in this patient is perhaps consistent with a defect in megakaryocyte production. However, the relationship between the porphyria and the megakaryocytic hypoplasia at present defies explanation.

The findings in the liver and spleen are noteworthy from several points of view. The failure to demonstrate marked accumulations of porphyrins by fluorescent microscopy in either organ most likely is due to the time lapse between preparation and visualization of these substances (7 years), and probably reflects the continuous decay in fluorescence by the action of light. There is, furthermore, no evidence that the fixative removes porphyrins. However the evidence of rather marked extramedullary hematopoiesis and iron pigment deposition in the liver and spleen supports the severity and chronicity of the anemic process.

In other patients with congenital porphyria in whom splenectomy was performed, little information is available regarding the nature of the liver and the spleen from the standpoint of extramedullary hematopoiesis and excessive iron pigment deposition. Indeed, the diffuse nature of the involvement may be more than a mere passive response to a hemolytic process and may in fact reflect an active role. Certainly in the present case, splenectomy was without effect and was actually associated with a worsening of the thrombocytopenia.

An additional point of interest includes the lack of fluorescence of the deciduous teeth. The fact that fluorescence was present only in the permanent dentition was probably related to the deposition of excessive porphyrin accumulations following the completion of deciduous teeth development and during the budding stage of the permanent teeth.

The administration of pyridoxine and adenosine monophosphate did not alter the hemolytic process in this patient. Pyridoxine was used because it is a necessary metabolite in the early stages of heme synthesis, namely, the condensation of glycine with succinyl CoA for effective ALA biosynthesis. Although the defect in erythropoietic porphyria occurs at the stage of uroporphyrinogen biosynthesis, the hypochromic hyperferremic features in this patient are not dissimilar to the pyridoxine-dependent anemias in humans or the pantothenate deficiency in certain birds and animals.

Adenosine monophosphate therapy was tried on the basis of evidence presented by Tallman et al. and Lottsfeldt et al. who suggested that the excessive accumulation of porphyrins may possibly interfere with effective purine production as well as heme biosynthesis. The excellent response to this drug noted by this author in one case of acute porphyria and reported by Gajdos et al. in several patients with acute porphyria prompted its use. However, there was failure of response both to pyridoxine and AMP.

The evidence of folic acid deficiency in this patient has been incorporated in more detail in a study of folate deficiency in chronic hemolytic disorders occurring in children and is similar in many respects to previously well documented studies in adults. Its presence was suggested initially by the progressively shorter intervals between transfusions, in association with a steady decline in reticulocyte and nucleated red cell counts. Corroborative
serologic evidence was demonstrated by the low SFA and elevated FIGLU levels. In this instance the severe hemolytic aspects apparently placed an increased demand on marrow activity, thereby producing a relative, but correctible, folate deficiency. However, none of the measures employed to date has altered either the essential nature of the hemolytic process or improved the thrombocytopenic state.

**Summary**

An unusual case of erythropoietic porphyria with a severe hemolytic component and thrombocytopenia has been presented. The relationship between the porphyria and the thrombocytopenia, although unclear, showed definite evidence of persistent megakaryocytic hypoplasia. Additional information emphasizing the severity and chronicity of the anemic process included elevated F and A2 hemoglobins, hyperferremia and extramedullary hematopoiesis. The nature of the hemolytic process appeared to be intracorpuscular and not correctible by normal plasma, glucose or ATP. The abnormal in vitro hemolysis, coupled with the appearance of the abnormal nucleated and mature red cells, are suggestive of the defect in heme synthesis seen in some of the hypochromic hypersideremic anemias. A description of therapeutic attempts as well as the appearance of a folate deficiency are included in the report.

**Summario in Interlingua**

Es presentate un caso inusual de porphyria erythropoietic con un compone nente sever de hemolyse e thrombocytopenia. Le relation inter le porphyria e le thrombocytopenia, benque pauco clar, monstrava definite evidentias de persistente hypoplasia megacaryocytic. Constatazione additional (sublineante le severitate e le chronicitate del processo anemic) includeva elevate nivellos de hemoglobina F e A2, hyperferremia, e hematopoiese extramdullari. Le natura del processo hemolytic pareva esser intracorpuscular e non corrigibile per plasma normal, per glucosa, o per adenosino-triphosphato. Le anormalitate del hemolyse in vitro, insimul con le apparentia del anormal erythrocytos nucleate e matur, rememora le defecto del synthese de hem que es incontrate in certe anemias hypersideremic hypochromic. Le reporto include un description del essayos therapeutic e del apparition de un carentia de acido folic.

**Acknowledgments**

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HEMATOLOGIC STUDIES ON ERYTHROPOIETIC PORPHYRIA


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Hematologic Studies on Erythropoietic Porphyria: A New Case with Severe Hemolysis, Chronic Thrombocytopenia, and Folic Acid Deficiency

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