Studies on Human Erythrocyte Nucleotide Metabolism.

II. Nonspherocytic Hemolytic Anemia, High Red Cell ATP, and Ribosephosphate Pyrophosphokinase (RPK, E.C. 2.7.6.1) Deficiency

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With the technical assistance of Klaus K. Kürschner

A 29-yr-old black woman was found to have a long-standing, nonspherocytic hemolytic disorder associated with a marked reduction in the activity of erythrocyte ribosephosphate pyrophosphokinase (RPK, PRPP synthetase, E.C. 2.7.6.1). Although the patient's erythrocytes had about 50% of the average RPK activity of normal mature human erythrocytes, this level represented only about 20–30% of the activity in comparable reticulocyte-rich blood samples from patients with other types of hemolytic anemias. The concentrations of adenosine triphosphate, adenosine diphosphate, adenosine monophosphate and, therefore, of total adenine nucleotides in her erythrocytes were markedly increased, even well above the levels in extracts of comparable reticulocyte-rich blood samples. ATPase activity was increased three- to fourfold, consistent with the reticulocytosis. Adenylate kinase and adenine phosphoribosyltransferase activities were normal. The activities of all enzymes of the Embden-Meyerhof and hexose monophosphate shunt pathways and enzymes related to glutathione metabolism were normal or increased, consistent with the reticulocytosis. The concentrations of glycolytic intermediates, other than adenine nucleotides, were normal. The conversion of glucose, adenosine, and inosine to lactate was normal or increased. Autohemolysis was of the Dacie Type II. The concentrations of erythrocyte-reduced glutathione were high normal or elevated. The stained blood film showed a striking degree of basophilic stippling of the erythrocytes. Studies of the erythrocytes of the patient's only known relative, a son, have failed to reveal any hematologic or enzymatic abnormalities. A direct causal relationship between RPK deficiency, high ATP concentrations, and nonspherocytic hemolytic anemia could not be derived from data now available. The final decision as to whether the deficiency is primary and causative or is an epiphenomenon requires investigation of additional cases.
HEREDITARY NONSPHEROCYTIC HEMOLYTIC ANEMIA has been demonstrated in association with a variety of genetically determined erythrocyte enzyme deficiencies. In addition, there are now five reported syndromes (two of which may be identical) characterized by marked elevation in red cell ATP and total adenine nucleotides. In the first and most extensively studied, high ATP levels were not associated with hemolysis or definable metabolic abnormalities but were clearly hereditary. In the second, hereditary increases in erythrocyte PK activity to about twice normal were believed related to the high ATP. Red cell 2,3-diphosphoglycerate (2,3-DPG) was greatly decreased below normal levels, but hemolysis was not present. The third syndrome was observed in two infants only. Both were reported to have erythrocyte 2,3-DPG phosphatase deficiency, a hemolytic disorder, and a multiplicity of congenital anomalies. The complexities were such that cause and effect relationships were essentially impossible to ascertain with any assurance. Busch and Heimpel have described a fourth entity—hereditary non-spherocytic hemolytic anemia with high red cell ATP, normal PK, and a suspected but undefined enzymatic or other metabolic defect. We have recently reported in abstract form a fifth, clinically similar syndrome in which a marked reduction in activity of erythrocyte RPK (ribosephosphate pyrophosphokinase or PRPP synthetase, E.C. 2.7.6.1) was observed. Identity with the case reported by Busch is, of course, uncertain. RPK catalyzes the production of AMP and PRPP from ATP and R-5-P. PRPP is an important metabolite in purine, pyrimidine, and pyridine nucleotide metabolism.

MATERIALS AND METHODS

Hematologic data and routine blood chemistries were obtained by the usual standard procedures. Erythrocyte reduced glutathione (GSH) was measured as described by Beutler et al., employing 5,5'-dithiobis-(2-nitrobenzoic acid). Fetal hemoglobin was measured according to Singer et al. Hemoglobin was tested for heat stability by the method of Dacie et al. Autohemolysis tests were performed according to the method of Selwyn and Dacie as modified by Rudolph and Gross. Studies relating to methemoglobin content and to erythrocyte capacity for methemoglobin reduction in nitrite-treated cells were conducted as described previously. Hemoglobin electrophoresis was in starch gel.

Glycolytic Intermediates

Five milliliters of freshly drawn whole blood were immediately dispersed in 10 ml of 0.6 N perchloric acid (PCA). The PCA-precipitated blood was shipped in ice, always with simultaneously processed normal blood, to the Los Angeles laboratory. Glycolytic intermediates were determined as described by Minakami et al., except for 2,3-DPG which was measured by a modification of the method of Krimsky. In incubation studies employing the patient's intact cells, phosphate buffers, and substrate additives, the determinations of glucose utilized, lactate and pyruvate produced, total and fractionated adenine nucleotides, and 2,3-DPG were identical to those employed in the measurement of these compounds in whole blood.

Separation of Erythrocytes According to Density and Cell Age

Erythrocytes, in a limited number of experiments, were fractionated by discontinuous, buoyant density gradients essentially as described by Bishop and Prentice and by Leif and Vinograd. However, only two fractions—a bottom layer comprising 25–30% of cells and a top layer consisting of the remaining 70–75%—were employed in these studies. The adequacy of separation was monitored by reticulocyte counts and by pyruvate kinase
(PK) (and sometimes glucose-6-phosphate dehydrogenase [G6PD]) determinations on top and bottom cells. PK and G6PD activities are characteristically increased in younger erythrocytes.

Enzyme Studies

The activities of red cell glycolytic and nonglycolytic enzymes were measured by methods previously reported. All of the enzymatic activities of the Embden-Meyerhof pathway, the two dehydrogenases of the hexose monophosphate (HMP) shunt, as well as glutathione peroxidase and reductase and glyoxalase I and II, were assayed individually. The distal pentose shunt, transketolase, and transaldolase activities were screened in terms of fructose-6-phosphate (F-6-P) production from ribose-5-phosphate (R-5-P).

The assays for RPK (PRPP synthetase) and adenine phosphoribosyltransferase (APRT, E.C. 2.4.2.7) were performed employing nonisotopic reactants as described elsewhere in this issue. ATPase was assayed according to Brewer et al.30 Adenylate kinase (AK) activity was measured essentially as described by Haslam and Mills.31

Intact, washed red cell incubations employed isotonic NaCl-KH₂PO₄ buffer, pH 8.0, and additives of glucose, inosine, adenosine, and adenine alone or in combination.

CASE REPORT

L.T. is a black female born in 1942. Her parents are unknown, and she has no known siblings. In 1946 at the time of a minor respiratory illness, a stained blood film revealed basophilic stippling of many of the erythrocytes. In 1949, she was hospitalized for mild poliomyelitis. The hemoglobin was 10 g/100 ml, and increased basophilic stippling was again noted. In 1953, the spleen was found to be enlarged 2–4 cm below the costal margin. The following studies at that time were all normal or negative: total and differential leucocyte count, urinalysis, serum bilirubin, Coombs' antiglobulin test, hemoglobin electrophoresis on paper, sickle cell preparation, and osmotic fragility test. The hemoglobin was 9 g/100 ml, reticulocytosis of 10% was noted, and marked basophilic stippling of erythrocytes was present.

In 1958, she was hospitalized for splenectomy. During the previous 5 yr the hemoglobin usually ranged from 8 to 10 g/100 ml, and she had been occasionally transfused when values below 8 g/100 ml were reported. A preoperative oral cholecystogram was normal, as was the appearance of the gall bladder and liver at surgery. The spleen was normal on microscopic examination. The Coombs' test, direct and indirect, was again negative. Since splenectomy, the hemoglobin has usually ranged from 9–12 g/100 ml, marked reticulocytosis of 10–40% has been present, and the expected post-splenectomy findings of Howell-Jolly bodies, Pappenheimer bodies, and a few circulating normoblasts have been consistently noted. The patient was first seen at St. Vincent's Hospital and Medical Center in New York in 1970. The described hematologic abnormalities were confirmed, including the unusual degree of basophilic stippling. The concentration of methemoglobin was normal, 1%. Hemoglobin electrophoresis (starch gel) showed only hemoglobin A with normal amounts of A₂. The hemoglobin was stable on heating to 50°C. The incubated osmotic fragility test revealed a small population of cells more fragile than normal, but the pattern was not characteristic of hereditary spherocytosis.

The autohemolysis test exhibited a pattern designated as Type II by Selwyn and Dacie.14 In duplicate samples, autohemolysis after 48 hr was 12.4% and 11.2%, respectively. Additions of glucose not only failed to correct, but appeared to accentuate autohemolysis to 21.8% and 43.5%. Neutralized ATP, however, nearly corrected the autohemolysis to normal.

Between 1965 and 1969, the patient lived in the Virgin Islands. She had an uneventful pregnancy and in November, 1965 delivered spontaneously a full-term, normal infant. She was transfused postpartum and, by history, had a rather severe reaction with chills, fever, and back pain, but no known oliguria. In this connection, the indirect (but not direct) Coombs' test, although negative when the patient was 15 yr old, is at present
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positive. This is believed to be a consequence of the incompatible blood transfusion received postpartum at age 22.

In 1966, the patient noted ease of fatigue and inconstant upper abdominal discomfort. Jaundice was present, and a diagnosis of hepatitis was entertained. Symptoms and jaundice subsided and recurred, and in 1969 a liver biopsy was interpreted as showing an atypical chronic hepatitis. At the time of her first visit to St. Vincent's Hospital in 1970, she continued to have intermittent jaundice and upper abdominal pain. The liver was palpable 5 cm below the right costal margin. Total serum bilirubin was 5.7 mg/100 ml, with 2.3 mg/100 ml direct reacting. Serum alkaline phosphatase was 17.4 King-Armstrong Units, SGOT 40 IU lactic dehydrogenase (LDH) 565 IU, cholesterol 151 mg/100 ml, BUN 9.0 mg/100 ml, and serum uric acid 5.6 mg/100 ml. An intravenous cholangiogram showed only faint visualization of the common bile duct, without obvious dilatation or obstruction. During several months of observation, symptoms and jaundice waxed and waned but persisted. In June of 1971, she underwent laparotomy with cholecystectomy, an operative cholangiogram, and liver biopsy. The gall bladder showed chronic cholecystitis and cholesterosis. The liver biopsy demonstrated persistent hepatitis with portal fibrosis, hemosiderosis, and numerous areas of hepatic regeneration. Since operation, she has remained pain free, though slightly icteric. The hemolytic process has continued, with reticulocytosis of 20–25% the rule.

RESULTS

Hematologic

The essential findings in patient L.T. are given in the Case Report, and only salient features will be summarized here. Anemia has been moderate, marked reticulocytosis has been consistently noted, and a very unusual degree of basophilic stippling of erythrocytes on stained blood films has been repeatedly observed since age 4 yr. No hemoglobinopathy was demonstrable. The Type II autohemolysis pattern is nonspecific but in our experience is unusual, except in pyruvate kinase (?K) deficiency which this patient clearly does not have.

Reduced Glutathione (GSH)

Distinctly high erythrocyte GSH was observed in the Los Angeles laboratory, and suggestively high (though somewhat lower) values were obtained in New York. In the former, erythrocyte GSH was 1225 μg/10ⁱ⁰ erythrocytes, with normal being 700 ± 80. In the latter, expressed in different terms, GSH was 91.0 mg/100 ml erythrocytes. This value is in the high normal to slightly elevated range for this laboratory.

Phospholipids

Red cell phospholipids, generously studied by Dr. Eugene L. Gottfried, showed a quite normal pattern, except for slight elevations in cholesterol and total phospholipid content consistent with young and large erythrocytes. The relative phospholipid distribution by a densitometric screening procedure was normal.

Erythrocyte Enzymes

Assays of all of the glycolytic enzymes of the Embden-Meyerhof and hexose monophosphate (HMP) shunt pathways were entirely normal or increased, as
expected for reticulocyte-rich blood. Glutathione reductase, glutathione peroxidase, and glyoxalases I and II activities also were normal. Pyruvate kinase activity was not only quantitatively normal, but the kinetics of the enzyme's reactions were demonstrated to be entirely normal in detailed additional studies.

Adenine Nucleotide Metabolism

ATPase activity, in two separate blood samples each containing approximately 20% reticulocytes, resulted in the hydrolysis from ATP of 13.7 and 11.7 μmoles of inorganic phosphorus (Pi)/hr per 10¹⁰ red cells at 44°C. Fifty to 60% of activity was ouabain inhibitable. These values are three to four times our normal mean but within the range observed in samples with reticulocytosis of this magnitude. The electrolyte composition of the patient's erythrocytes was normal (Na⁺ 10.0 and K⁺ 92.0 meq/liter). Lactate was very actively produced by the patient's red cells in isotonic NaCl/KH₂PO₄ buffer (pH 8), employing intact cells and both glucose and adenosine substrates. The results with adenosine as additive indicated the integrity of the enzymatic sequence from nucleoside phosphorylase to lactate. Since adenosine must be deaminated to inosine in order to serve as a substrate for nucleoside phosphorylase, an active adenosine deaminase could also be inferred. With additions of adenosine, total red cell adenine nucleotides almost doubled during a 3-hr incubation at 37°C, clearly indicating that adenosine kinase was also active in the patient's erythrocytes. In other incubations, 2,3-diphosphoglycerate (2,3-DPG) disappeared rapidly in the absence of glycolytic substrates, and conversely 2,3-DPG levels were restored in depleted cells when substrate was added. 2,3-DPG phosphatase and mutase were present. Assays of adenylate kinase and of adenine phosphoribosyltransferase (APRT), the latter measured as previously described, likewise gave values normal for our laboratory. Activity of APRT was higher than that of simultaneously shipped control cells, though not as high as sometimes seen in the presence of reticulocytosis. It may be added that serum uric acid levels were normal, 5.6 mg/100 ml.

When the activity of RPK (PRPP synthetase) was assayed in terms of the production of both reaction products, PRPP and AMP, very low values were repeatedly observed with multiple blood samples studied over a 1-yr

| Table 1. RPK Activity in Patient, Normal Subjects, and Reticulocyte-Rich Blood |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|
| Assay* | Normals | Retics. 7-25% | Patient L. T. |
| A | 30.5 ± 3.78 | 59.5 | 16.5 |
| B | 30.6 ± 3.82 | 57.6 | 16.2 |

*Assay A measures reaction product PRPP, and B reaction product AMP. RPK activity is expressed as μmoles of reaction product (PRPP or AMP) produced/hr per 10¹⁰ erythrocytes at 37°C and under our assay conditions. Values for patient L.T. are means of repeated blood samples obtained over 1-yr period. Patient's reticulocyte count averaged 19.6% and ranged from approximately 11-25% during this period.

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Fig. 1. Mean adenine nucleotide concentrations in peripheral blood. Assay values in two separate specimens from the proband are shown by open and closed circles. Cross-hatched bars were derived from 79 normal control specimens. Their numbers on abscissa indicate an interval between sampling and assay of less than 24 hr (1), 24-48 hr (2), 48-72 hr (3), and more than 72 hr (4). Solid bars designated "R" were obtained from 15 specimens with reticulocytosis (mean, 7.8%; range, 2.3-22.3%) from causes other than identifiable erythroenzymopathies. Shaded area over total adenine nucleotide bars encompasses 2 SD above each mean.

Glycolytic Intermediates

Figure 1 depicts the striking elevations in ATP and total adenine nucleotide content in the erythrocytes of patient L.T. As indicated in the figure and defined in the legend, adenine nucleotide concentrations in perchloric acid (PCA) extracts of blood assayed immediately after collection or subjected to shipment and storage in ice for up to 3 days or more are recorded. It is clear that some nonenzymatic hydrolysis of ATP phosphorus occurred during shipment and storage. Measurable ATP declined modestly, ADP increased proportionately, and very slight increase in AMP accompanied these changes. The total adenine nucleotides, however, remained remarkably constant over period (Table 1). In the presence of reticulocytosis, RPK activity is characteristic increased to a marked degree (Table 1). The reticulocyte-rich erythrocyte population of L.T. can be meaningfully compared only with young red cell populations of similar mean age. While they possess approximately 50% of the RPK activity of cells of normal blood, the patient's cells have but 15-30% of that observed in patients with 7-26% reticulocytosis associated with other hemolytic syndromes. For example, in three subjects with reticulocytosis of 19-26% (the patient's reticulocytes averaged 19.6% in our studies), RPK activities ranged from 51 to 81 U. The K_m (R-5-P), pH optimum, and storage stability of RPK in hemolysates of the patient's cells did not differ from normal. In density gradient studies, RPK activity in the top, less dense fraction containing 12.2% reticulocytes was 17.3-18.3, as compared to but 5.7-9.6 U in the lower, denser fraction containing 2.4% reticulocytes. The less dense, reticulocyte-rich cells also assayed substantially higher than the denser, bottom fraction in terms of G-6-PD and PK activities, corroborating the effectiveness of separation in these studies.
a period of several days. Table 2 records assays of adenine nucleotides in extracts prepared from locally collected blood maintained at 4°C and studied at intervals. The features apparent in shipped specimens were confirmed. In patient L.T., the total adenine nucleotides were increased well above 2 SD of the mean of reticulocyte-rich blood. The fractionated nucleotide values were also greatly increased individually. In fact, the observed values in the patient are the highest thus far encountered in our laboratory. High ATP and strikingly elevated concentrations of total adenine nucleotides clearly characterize the patient’s hemolytic process.

In addition to adenine nucleotides, the following glycolytic intermediates were assayed on shipped extracts of blood from the patient and control subjects: glucose and fructose-6-phosphates, fructose-1,6-diphosphate, dihydroxyacetonephosphate, 3-phosphoglyceraldehyde, 2,3-diphosphoglycerate, 3- and 2-glycerophosphates, phosphoenolpyruvate, pyruvate, and lactate. While certain of these have a reputation for lability even in cold PCA, we have repeatedly assayed extracts collected and shipped refrigerated and find little departure from values assayed immediately. The same experience applies to extracts prepared locally and assayed in duplicate after storage at 4°C for intervals of 1–8 days. While some caution in interpretation must clearly be exercised, characteristic patterns of intermediate accumulation in other deficiencies, such as those of pyruvate kinase and triosephosphate isomerase, have not in our experience been dampened or obscured in blood extracts obtained and shipped as described. In the patient’s blood, no significant departure from our norms was encountered. In particular, 2,3-DPG was neither increased nor decreased, ranging between 2860–5760 μmoles/10ⁱ⁰ cells in blood collected at widely separated intervals. Simultaneous controls (two different subjects) assayed 2920 and 3130 μmoles/10ⁱ⁰ erythrocytes.

**Family Studies**

The patient’s only known living relative is a son, age 6, who was placed in a foster home shortly after birth. Limited studies have been performed on the son’s erythrocytes. The hemogram is normal, except for some eosinophilia.

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<th>Table 2. Adenine Nucleotide Stability in Perchloric Acid-Precipitated Peripheral Blood Specimens Stored at 4°C</th>
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<td><strong>Specimen</strong></td>
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*Specimens No. 1 and 2 are duplicates.  
†Duration of storage.
noted in the leukocyte differential formula. The reticulocyte count is 1.1%. Red cell methemoglobin and GSH are normal. Alkali-resistant fetal Hb is 1.94% (normal), the Hb possesses normal heat stability, and the electrophoretic pattern on starch gel at pH 8.6 shows a normal Hb A + A₂ pattern. The activity of red cell enzymes hexokinase, PK, and G6PD are entirely normal and are not increased as is seen in young erythrocyte populations. The crucial RPK assay revealed normal activity (28.6 U by method A and 26.3 U by method B). The son’s erythrocytes cannot be shown to share the abnormalities of his mother’s cells.

DISCUSSION

The salient features of the present case are the following: lifelong non-spherocytic hemolytic anemia characterized by marked increases in the numbers of erythrocytes with basophilic stippling on the stained blood film both before and after splenectomy; abnormally increased autohemolysis, not corrected by glucose additive, but largely corrected by neutralized ATP (Dacie Type II pattern); high normal to substantially increased concentration of erythrocyte GSH; high red cell ATP and total adenine nucleotides; and a marked decrease in the activity of erythrocyte RPK (PRPP synthetase). The latter has hitherto not been reported in association with hemolytic anemia. The findings closely resemble those in a case reported by Busch in which hereditary hemolytic anemia, increased red cell adenine nucleotides, and a Dacie Type II autohemolysis pattern were also associated. In Busch’s case, RPK activity was not determined. In the cells of our RPK-deficient patient, no abnormalities in the pattern of glycolytic intermediates, or in the activities of any enzymes of the Embden-Meyerhof, HMP shunt, or GSH metabolic pathways were demonstrable. ATPase, AK, and APRT activities were likewise normal, as was the Na⁺ and K⁺ concentration in the erythrocytes.

The genetics of RPK deficiency are not defined by data currently available. The erythrocytes of the patient’s son do not share the deficiency, nor does he exhibit any hematologic abnormalities. It is possible that the observed marked reduction in RPK activity is an epiphenomenon and bears no primary relationship to the hemolytic process. For example, the synthesis of RPK in the erythroid precursor cells theoretically could have been repressed secondary to some unmeasured and undetected aberration in red cell metabolism. On the other hand, there is no evidence to support such conjecture, and RPK deficiency may be etiologically related to the hemolytic syndrome. It is of interest in regard to this question that no intermediate level of RPK activity was demonstrable in the patient’s son, an obligate heterozygote if RPK deficiency were inherited as a recessive trait.

The mechanisms by which RPK deficiency might result in premature destruction of erythrocytes characterized by an increased complement of adenine nucleotides are entirely unclear. It may be recalled, however, that ATP is converted to AMP in the reaction catalyzed by RPK. AMP is the only adenine nucleotide at risk in terms of permanent loss from the pool. While it can be converted to other adenine nucleotides via AK and certain reactions of glyco-
lysis, it may also be irreversibly deaminated to inosine monophosphate (IMP), dephosphorylated to adenosine, or, theoretically, in a reversal of the APRT reaction, be converted to free adenine. Deamination is probably the major route of loss, and IMP in the mature human erythrocyte cannot be reconverted to AMP. Any AMP-producing reaction is potentially a source of loss of adenine nucleotides.

On the other hand, the RPK reaction is normally considered as part of a “salvage pathway” rather than a wasteful reaction. Its second product, PRPP, may interact with adenine in the reaction catalyzed by APRT to form AMP. If no AMP is deaminated or otherwise lost, the net result of the sequential reactions of RPK and APRT would be the formation of 2 moles of AMP with expenditure of but 1 mole of ATP. Total adenine nucleotides would thus be increased. The APRT reaction, however, is absolutely dependent on the availability of free adenine, a substance not detectable in plasma, though some indirect evidence exists for an extracorpuscular adenine source. In any event, whether the RPK reaction is potentially wasteful of adenine nucleotides via an AMP leak or is a link in a salvage pathway rests squarely on the degree to which it is followed by the APRT catalyzed reaction. If nicely balanced with adenine availability and APRT activity, a partial, incomplete deficiency of RPK might be envisioned as conserving adenine nucleotides on a net basis. Such admittedly speculative considerations, though of obvious interest to those concerned with erythrocyte metabolism, fail to provide any satisfactory explanation as to how a high ATP syndrome associated with RPK deficiency could mediate a hemolytic process. It remains to be determined if RPK deficiency observed here is an epiphenomenon or is primary and causative, and if the latter is true what delicate disturbance in the metabolic machinery results in shortened erythrocyte life span.

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