Clinical Consequences of Enzyme Deficiencies in the Erythrocyte

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ABSTRACT

The anucleate mature erythrocyte also lacks ribosomes and mitochondria and thus cannot synthesize enzymes or derive energy from the Krebs citric acid cycle. Nevertheless, the red blood cell is metabolically active and contains numerous residual enzymes and their products which are essential for its survival and normal functioning. Enzyme deficiencies in the Embden-Myerhoff glycolytic pathway can result in nonspherocytic hemolytic anemia (NSHA), and some are also associated with neuromuscular or neurologic disorders. Glucose-6-phosphate dehydrogenase deficiency in the hexose monophosphate shunt also results in hemolytic anemia, especially following exposure to various drugs. Defects in glutathione synthesis and pyrimidine 5'-nucleotidase deficiency also cause NSHA, as does increased adenosine deaminase activity. Glutathione synthetase deficiency which is not limited to the red cell also presents as oxoprolinuria with neurologic signs. All red cell enzyme defects appear as single gene errors, in most cases recessive in inheritance, either autosomal or X-linked.

Clinical Consequences of Enzyme Deficiencies in the Erythrocyte

Prior to maturity, the nucleated red blood cell (rbc) can perform a variety of metabolic functions, including active enzyme synthesis. The mature erythrocyte has no nucleus or ribosomal apparatus, and thus cannot synthesize protein. However, it is not metabolically inert and contains over 40 different enzymes, many of which are essential for its survival or normal functioning. The purpose of this report is to review some inherited enzyme deficiencies of the erythrocyte which compromise its viability in the circulation or its capacity to transport oxygen, resulting in clinical disease.

Red Blood Cell Metabolism

In addition to the metabolic restrictions on the mature erythrocyte previously noted, its energy sources are also some-
what limited by the loss of its mitochondria. Without these organelles, the rbc cannot metabolize pyruvate through the Krebs citric acid cycle. Other energy substrates can be used by the red cell, but the major source is normally glucose through either the Embden-Meyerhoff or hexose monophosphate pathways. The energy thus derived has several essential uses:\textsuperscript{3,24}

(1) the maintenance of sodium and potassium gradients across the cell membrane;
(2) the prevention of calcium accumulation in the red cell membrane;
(3) maintenance of the integrity and shape of the rbc membrane;
(4) reduction of methemoglobin and oxidized glutathione;
(5) inactivation of peroxides and other oxidants which denature hemoglobin; and
(6) maintenance of levels of organic phosphates, e.g., 2,3 diphosphoglycerate (2,3-DPG) and adenosine triphosphate (ATP), affecting hemoglobin-oxygen affinity.

The energy derived from the Embden-Meyerhoff glycolytic pathway is primarily stored in the high energy phosphate of ATP. The latter is used to drive the sodium and potassium pumping systems which oppose the passive diffusion of these ions and water across the cell membrane. If unopposed, these natural processes would result in eventual hemolysis. Anaerobic glycolysis also generates reducing power by converting nicotinamide adenine dinucleotide (NAD\textsuperscript{+}) to NADH, which reduces methemoglobin to hemoglobin. Synthesis of 2,3-DPG also occurs in the glycolytic pathway.

Normally, the hexose monophosphate pathway (HMP) accounts for only 10 percent of the glucose metabolism of the red cell.\textsuperscript{3} This percentage is greatly increased during oxidative stress with the production of NADP\textsuperscript{+} from NADPH. The HMP maintains this conversion in favor of NADPH, which keeps glutathione in its reduced form, in turn protecting the rbc from peroxidation. Pentose formed in the HMP may be used in the synthesis of nucleotides or rearranged to the 3-and 6-carbon sugars used in glycolysis for production of additional 2,3-DPG and ATP.

Some common hereditary diseases of the rbc which involve alterations in shape (e.g., spherocytosis, elliptocytosis, etc.) are likely membrane defects and may involve enzyme deficiencies not yet identified.\textsuperscript{24} This review will be limited to known enzyme deficiency states, many of which cause nonspherocytic hemolytic anemia.

Red Blood Cells Enzyme Deficiencies in the Embden-Meyerhoff Pathway

**PYRUVATE KINASE DEFICIENCY**

Although the recognition of nonspherocytic hemolytic anemia (NSHA) was made as recently as 1953, it was not until 1961 that Valentine et al.\textsuperscript{32} discovered pyruvate kinase (PK) deficiency, the most common cause of NSHA. PK deficiency is second to glucose-6-phosphate dehydrogenase (G-6-PD) deficiency as the most common inherited rbc enzyme defect and is an autosomal recessive disorder. Although it has been suggested that heterozygotes may infrequently have clinical findings, most of these examples are confounded by the simultaneous occurrence of other hemolytic disorders.\textsuperscript{3} Large numbers of heterozygotes have been found to have no hemolytic disease, and it is doubtful that the heterozygous condition itself causes hemolysis.\textsuperscript{3}

Considerable heterogeneity in biochemical properties of mutant PK enzymes has been observed and may explain the marked variation in hemolysis and anemia in affected patients. Disease occurs in true homozygotes who have inherited two identical mutant alleles, as well as in double heterozygotes, or genetic compounds, with two different mutant alleles affecting different parts of the PK enzyme. The latter condition could give
rise to two different abnormal amino acid substitutions with the formation of two variant enzymes or their hybrid enzyme. Since PK is known to be an allosteric enzyme affected by fructose diphosphate with marked pH dependency, a mutant allele might result in enzyme products with modifications of either the catalytic or the allosteric site. Gherardi et al. has recently reported data on a family suggesting an alteration of the PK allosteric site.

In addition to the hereditary PK deficiency, the enzyme defect can be caused by a wide variety of hematologic disorders. These include, most commonly, acute leukemia, as well as cytopenias, anemias, and aplasias. The acquired vs. hereditary forms of PK deficiency can be differentiated by observing the return of enzyme activity to normal once the underlying disorder is treated, or by family studies. The latter rely on the facts that parents of patients with hereditary PK deficiency are obligate heterozygotes with diminished enzyme levels intermediate between normal and affected, and siblings of patients with hereditary PK deficiency may also have demonstrable PK disorders.

Since some investigators have reported no relationship between in vitro properties of variant PK enzymes and the severity of hemolysis, the hypothesis has been advanced that hemolysis in PK deficient red cells is caused by another defect in the cell membrane. However, interpretation of biochemical results is hampered by several factors. First, inheritance of two different mutant alleles allows formation of five different types of the tetramer enzyme. Also, studies utilizing crude hemolysates are hampered by the actions of other enzymes, and purification of PK itself can change its kinetic properties. Failure to remove contaminating leukocytes results in the measurement of their PK enzymes, which are neither deficient nor of the same type as the red cell enzyme in PK deficiency.

Earlier studies and those recently reported by Bowman and Oski have suggested that the spleen is the first organ to trap and destroy susceptible PK deficient red cells, principally reticulocytes. These observations help to explain the reticulocytosis which occurs in all red cell PK-deficient patients after splenectomy. When the spleen is present, its low oxygen tensions prevent mitochondrial ATP production in reticulocytes both in normal and PK-deficient patients. The later would also suffer from impaired glycolysis, with further reduction of available ATP. The ATP-dependent cation pump appears defective in red cells from such patients, and this might affect the external calcium pump and cause intermembrane calcium concentration, inducing membrane rigidity. This sequence could be the pathogenesis of the abnormal cell morphology and deformability reported in erythrocyte populations in PK-deficiency anemia following splenectomy.

Because of the biochemical heterogeneity of PK-deficiency, variability of clinical expression is expected. Anemia may be so severe that multiple transfusions or splenectomy is life-saving, or the patient may remain asymptomatic for years. Other signs are also not distinctive for PK-deficiency disease. Patients may have jaundice, bilirubinuria, splenomegaly, and sometimes gallstones. Jaundice usually presents in the neonatal period and kernicterus has been reported and can be fatal. Hemolysis increases during intercurrent infection and following use of oral contraceptives. PK-deficiency is a cause of failure to thrive in severely affected children. Radiographs show the changes secondary to a hypertrophic bone marrow seen during any severe anemia.

Diagnosis of frank decreases of PK activity can be made biochemically using a coupled reaction in which the product, pyruvate, oxidizes NADH to NAD$^+$ in the lactate dehydrogenase reaction. Trials
with various therapies such as steroids, AMP, magnesium, and riboflavin have been disappointing; blood transfusions and splenectomy are the currently effective modes of therapy.3

GLUCOSE PHOSPHATE ISOMERASE DEFICIENCY

The conversion of glucose-6-phosphate to fructose-6-phosphate via glucose phosphate isomerase (GPI) is the second step of the Embden-Meyerhoff pathway. Deficiency of GPI is one of the more common identifiable causes of NSHA, probably third in frequency to G-6-PD-and PK-deficiencies. Like PK deficiency, GPI-deficiency anemia is an autosomal recessive disorder and was not reported until relatively recently, (1968).1 Since that time numerous examples have been reported in diverse population groups. The enzyme appears to occur in dimer form and, unlike PK, GPI isozymes from different tissues have similar electrophoretic properties and are also deficient when the red cell enzyme is decreased. Diminished deformability of GPI-deficient red cells has recently been reported, and the suggestion made that this predisposes them to splenic sequestration.26

The diversity of deficient and nondeficient variants of GPI isozymes among people may explain the continuum of severity of clinical disease. Anemia may be mild, or may require frequent transfusions and splenectomy. Symptoms and signs referable to NSHA are commonly observed; only rarely have other features such as mental retardation, increased blood viscosity, and increased liver glycogen been reported.3 None of these features are characteristic of GPI-deficiency, and diagnosis requires assay of enzyme activity. Effective management of these patients is limited to splenectomy, and results have been almost universally helpful.3

HEXOKINASE DEFICIENCY

Hexokinase deficiency is a rare cause of NSHA and is inherited as an autosomal recessive disorder. Although heterozygotes have approximately half the normal enzyme activity, similar levels are frequently seen in hexokinase-deficient patients. This observation can be explained by the marked decrease in levels of this enzyme with aging of the normal red cell. With reticulocytosis, the larger population of younger cells containing more enzyme in the deficient variants masks the true extent of the enzyme reduction. This finding also complicates the chemical demonstration of hexokinase deficiency, but the diagnosis can be made if hexokinase is compared to other age-dependent enzymes such as PK and G-6-PD.3

Clinical manifestations of hexokinase deficiency are those of NSHA. Symptoms of anemia may be more severe than the anemia alone would suggest because of the associated low 2,3-DPG levels, which further compromise oxygen delivery. In addition, easy fatigability upon physical exertion and muscle hypertrophy in the distal extremities with glycogen deposition has been reported in two sisters with hexokinase deficiency.12

Experience with treatment is limited to the few patients discovered to date, but splenectomy has been effective.

PHOSPHOFRUCTOKINASE DEFICIENCY

The third step of the Embden-Meyerhoff pathway is the phosphorylation of fructose-6-phosphate to fructose-1,6-disphosphate catalyzed by phosphofructokinase (PFK). This reaction proceeds in the forward direction almost exclusively and is a key point of regulation of glycolysis. PFK deficiency shows autosomal recessive inheritance.

Muscle PFK is deficient in type VII glycogen storage disease, a metabolic
myopathy characterized by easy fatigability during childhood and subsequent severe muscle weakness and wasting, resembling type V (McArdle’s) disease. Patients with muscle PFK-deficiency disease have shortened red cell survival and may have clinical manifestations of NSHA. The latter has been observed in patients with red cell PFK-deficiency without muscle disease. These differences in clinical expression may be explained by the additional rbc isozyme on electrophoresis compared to the pattern for muscle, and differing biochemical properties of red cell vs. muscle enzymes. Non-nucleated red cells may be more sensitive than nucleated muscle cells to the effects of mutational enzyme alterations.

Travis and Garvin, in a study using the technique of discontinuous density gradient to separate younger from older red cells in neonates, showed increased lability of PFK in older red cells, even when compared to the normal decline of PK activity with age. This suggests that the relative PFK deficiency in neonatal red cells results from instability of an isozyme in newborns, possibly a fetal PFK.

Splenectomy was apparently beneficial in a patient with PFK deficiency.

ALDOLASE DEFICIENCY

Aldolase catalyzes the conversion of fructose-1, 6-diphosphate to two three-carbon compounds, glyceraldehyde-3-phosphate (GAP) and dihydroxyacetone phosphate. A single patient with aldolase deficiency has been reported. The patient was the product of a consanguineous mating, suggesting autosomal recessive inheritance. However, enzyme activity in both parents was normal, suggesting that the normal subunits in the multimeric enzyme may have a stabilizing influence on the entire enzyme complex.

The affected patient had moderate mental retardation, hepatic glycogen storage, and mild NSHA not requiring splenectomy.

TRIOSE PHOSPHATE ISOMERASE DEFICIENCY

The dihydroxyacetone phosphate formed in the aldolase-catalyzed step in glycolysis can undergo no further metabolism in the red cell. Rather, it is converted to GAP via triose phosphate isomerase (TPI).

In addition to NSHA reported in patients with TPI deficiency, most patients manifest a severe neuromuscular dysfunction with onset at age six months and death in childhood. Involved muscles include flexors of the hips, knees and calves, and pronators of the arms. In some, jaundice develops in the neonatal period, prior to death, or may be inapparent but with severe anemia developing at four to five weeks of age. TPI-deficient children appear to be particularly prone to infection, and the leukocyte count is frequently elevated. Phagocytosis by leukocytes is normal when they are suspended in normal serum, and a slight decrease in the number of B-lymphocytes has been reported. The neuromuscular deterioration is progressive; elasticity, hypotonia, opisthotonos, muscle weakness, absent limb reflexes, and hand tremors have been reported. Death in most patients results from respiratory impairment and repeated lower respiratory infections or sudden cardiac arrest. An enzyme assay for TPI deficiency in the red cell hemolysate is diagnostic.

Splenectomy did not benefit the one patient in whom it was done.

GLYCERALDEHYDE PHOSPHATE DEHYDROGENASE DEFICIENCY

The reversible reaction converting GAP to 1,3-diphosphoglycerate (1,3-DPG) is catalyzed by glyceraldehyde phosphate dehydrogenase (GAPD), requires inorganic phosphate, and converts NAD$^+$ to NAHD which is required for methemoglobin reduction. Partial deficiency of GAPD has been reported in several families, but the enzyme defect does
not seem to be related to hemolytic anemia.

**Phosphoglycerate Kinase Deficiency**

Two enzymes compete for 1,3-DPG as a substrate. Phosphoglycerate kinase (PGK) catalyzes its conversion to 3-phosphoglycerate, simultaneously generating ATP from adenosine diphosphate (ADP). Deficiency of PGK is inherited as a sex-linked disorder. Although white cells are affected as well, leukocyte function is normal.

Onset of symptoms is generally early in male hemizygotes and late in heterozygous females. Almost all of the male patients show neurologic deficits. Moderate mental retardation and impaired learning are reported. In males, neonatal jaundice is often present. Anemia is variable, but reticulocytosis is a constant feature. Variable expression of the deficiency in females is explained by the Lyon hypothesis. Krietsch et al have recently reported a large German kindred with PGK deficiency and no overt clinical signs. Diagnosis of male hemizygotes by spectrophotometric assay of the enzyme is possible; heterozygotes have marked variation of enzyme activity, as in other sex-linked disorders, so as to make this unreliable as a means of detecting all carriers.

Three of four patients who underwent splenectomy appeared to benefit from the procedure.

**Diphosphoglycerate Mutase Deficiency**

The second enzyme which competes for the substrate 1,3-DPG is diphosphoglycerate mutase (DPGM), which transfers the 1-phosphate of 1,3-DPG to 3-phosphoglycerate (3-PGA) forming a molecule each of 2,3-DPG and 3-PGA. This represents the only point in red cell metabolism where a net synthesis of 2,3-DPG occurs. The product 2,3-DPG inhibits DPGM activity, thus decreasing its own synthesis. Both acidosis and increased amounts of ADP also decrease 2,3-DPG synthesis by stimulating the PGK reaction. The enzymes DPGM, diphosphoglycerate phosphatase (DPGP), and monophosphoglycerate mutase (MPGM) appear either to be identical or to share the same enzyme proteins.

Partial deficiencies of DPGM have been described in three unrelated families. Clinical manifestations range from none, to a severe hemolytic anemia with death at age three months. Recently, a clinically healthy 42-year-old man was described with complete deficiency of DPGM, suggesting either marked variability in expression of the deficiency or that another enzyme defect has occurred in affected patients.

Despite sharing the same enzyme proteins, MPGM is normal in most patients with reported DPGM deficiency, which can be detected spectrophotometrically.

**Diphosphoglycerate Phosphatase Deficiency**

Diphosphoglycerate phosphate (DPGP) catalyzes the dephosphorylation of 2,3-DPG to 3-PG. Jacobasch et al studied two infants with retarded development muscle hypertonia, light colored hair, hyperlipidemia, cerebral dysgenesis, and mild, compensated hemolysis. Red cell hemolysates from these infants did not release inorganic phosphate from 2,3-DPG, suggesting DPGP deficiency, although the actual enzyme activity was not measured. Additional patients with this syndrome have not been reported, and confirmation of the postulated enzyme defect may be difficult because of the very low activity of DPGP in normal red cells.

**Enolase Deficiency**

Enolase catalyzes the dehydration reaction which forms phosphoenolpyruvate from 2-phosphoglycerate (2-PGA). A
single case of hemolytic anemia following exposure to nitrofurantoin and attributed to enolase deficiency has been reported.28 No other cases of enolase deficiency appear in the literature, despite frequent assay for this enzyme by reliable spectrophotometric technique.

Red Blood Cell Enzyme Deficiencies in the Hexose Monophosphate Pathway

GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

Glucose-6-phosphate formed in the hexokinase reaction may be oxidized by G-6-PD to 6-phosphogluconolactone, the first step in the hexose monophosphate shunt. NADPH which is converted from NADP+ by the G-6-PD reaction is also a strong inhibitor of the reaction, thus regulating its own synthesis. NADPH is used by the red cell to maintain glutathione in its reduced form, without which the red cells suffers peroxidative damage.

The early recognition that exposure of susceptible individuals to certain drugs such as the antimalarial, plasmoquine, caused hemolytic anemia lead to the discovery of red cell G-6-PD deficiency.7,34 The development of electrophoretic techniques allowed preliminary separation of G-6-PD deficiencies into quite different entities in Mediterranean vs. American black populations.

G-6-PD deficiency is inherited by a sex-linked mode, and it is estimated that approximately 100 million people are enzyme deficient, making it the most common red cell enzyme deficiency.3 Fortunately, the majority of such persons have no clinical findings and are frequently unaware of their biochemical abnormality. An astonishing number of distinct G-6-PD variants has been discovered, and, with a few exceptions noted for G-6-PD Mediterranean, deficient people are not anemic under normal circumstances. Hemolysis may occur following exposure to certain drugs, by infections, by diabetic acidosis, by ingestion of fava beans, and apparently spontaneously during the neonatal period. Heterozygote advantage with regards to resistance to falciparum malaria has been demonstrated and may explain the high gene frequencies noted in some populations.

Various nonhematologic diseases have been associated with G-6-PD deficiency. These include increased seizure disorders, cataracts, decreased risk of cancer, exhaustion of renin release stimulated by upright posture, and altered steroid metabolism, all of which remain unconfirmed.3 Mild chronic granulomatous disease has been described in patients with less than one percent of normal G-6-PD activity.

NSHA can occur spontaneously in patients who usually have an unusual variant G-6-PD, which deprives the red cell of virtually all of the enzyme activity.33 Presentation may be in the newborn period with jaundice requiring exchange transfusion. Anemia may be compensated or not, and is markedly increased during intercurrent infection or by inappropriate drug administration. Mild jaundice and splenomegaly is usually present. Heterozygotes for these variants frequently have normal enzyme activity, since the affected cells do not survive long in the circulation, leaving mostly normal cells.3 Diagnosis can be made by the glutathione stability test or by direct measurement of enzyme activity. A fluorescent spot screening test is available.2

Treatment includes avoidance of hemolytic drugs. The list of drugs eliminated should be sensible, and should not include medications such as aspirin, which the patient knows from his own experience is innocuous.3 Nor should the patient be deprived the benefits of therapy with all sulfonamides since Gantrisin, for instance, is not hemolytic. Severe hemolytic episodes may require transfusions. Response to splenectomy in these patients with NSHA has been vari-
able, and genetic counseling may be useful in this group of patients.

6-PHOSPHOGLUCONATE DEHYDROGENASE DEFICIENCY

The enzyme 6-phosphogluconate dehydrogenase (6-PGD) catalyzes the oxidation of 1-carbon from 6-phosphogluconate to carbon dioxide, forming ribulose-5-phosphate. Although hemolytic anemia has been associated with 6-PGD deficiency, it is probably coincidental and red cell survival is shortened little, if at all, in the 6-PGD-deficiency state.3

Defects in Glutathione Synthesis

The two sequential enzyme steps which are potentially involved in hereditary defective-glutathione synthesis are those catalyzed by gammaglutamyl cysteine synthetase (GC-S) and glutathione synthetase (GSH-S). Deficiency of either enzyme can cause hemolytic anemia, and both deficiencies appear to be inherited as autosomal recessive disorders.3 Generalized GSH-S deficiency results in oxoprolinuria, chronic metabolic acidosis usually present in the neonatal period, and in some cases neurologic symptoms.13 Other patients with what may be another type of GSH-S deficiency only manifest symptoms of NSHA. Treatment of the latter includes avoidance of the same compounds which produce hemolysis in G-6-PD deficiency; splenectomy has been beneficial. Vitamin E will prevent oxidant damage to GSH-S-deficient leukocytes and improve their impaired capacity to kill bacteria.6

Glutathione Reductase Deficiency

Glutathione reductase functions during aerobic metabolism in the red cell to maintain reduced glutathione.8 Flavine adenine dinucleotide is the cofactor for the reaction, and it is now apparent that the majority of cases reported as glutathione reductase deficiency are actually due to nutritional riboflavin deficiency,3 resulting in NSHA following exposure to certain drugs or chemicals. These include many, if not all, of the drugs causing hemolysis in G-6-PD deficiency. Rarely, hereditary partial deficiency of glutathione reductase occurs apparently as a dominant disorder,23 but its association with clinical disease is unproven.

Glutathione Peroxidase Deficiency

A variety of environmental influences readily alter glutathione peroxidase (GSHPx) activity, including iron deficiency and selenium deprivation, the latter because GSHPx is a selenium-containing enzyme. GSHPx should protect biological membranes from oxidative damage, but conflicting clinical reports cast doubt on the cause-and-effect relationship between decreased levels of this enzyme and hemolysis. An interesting observation of red cell GSHPx deficiency in patients with multiple sclerosis was recently reported.37 The authors suggested a correlation between the low content of selenium in forage and the high prevalence of multiple sclerosis in certain geographic areas, an association as yet unconfirmed.

Disorders of Nucleotide Metabolism

PYRIMIDINE 5'-NUCLEOTIDASE DEFICIENCY

A hemolytic anemia characterized by marked basophilic stripping of erythrocytes, and thought initially to be caused by ribose phosphate pyrophosphokinase deficiency, was later shown to be due to pyrimidine-5'-nucleotidase (PD-5'-N) deficiency.31 Inheritance is by an autosomal recessive mode, occurrence among populations is widespread, and it is becoming one of the more common known causes of NSHA. PD-5'-N deficiency also occurs as an acquired disease
as a result of lead intoxication, in which it is also the cause of the basophilic stippling.

Anemia due to PD-5'-N deficiency is usually mild and the age of onset is variable. Neonatal hyperbilumbineamia has been observed in this disease, and splenomegaly almost always occurs.

Harley et al have recently shown that the high levels of uridine nucleotides which accumulate in this disorder are derived, at least partially, from biosynthetic pathways, rather than from degradative pathways alone. This suggests the possible effectiveness of treatment with inhibitors of uridine kinase in this disorder. Of the routine therapies, splenectomy has produced variable improvement.

**Increased Adenosine Deaminase Activity**

Decreased adenosine deaminase (ADA) activity, which is associated with combined immunodeficiency syndrome, does not cause red cell abnormalities. On the other hand, increased ADA function, inherited as an autosomal dominant disorder, causes mild anemia which may occasionally be completely compensated. Splenomegaly is present and the reticulocyte count is elevated in affected patients. ATP levels average 60 percent of normal controls and 50 percent of controls with increased reticulocytes. The increased ADA activity may lower red cell ATP levels by effectively shunting adenosine from the adenosine kinase step which normally produces adenine nucleotides.

**Other Enzyme Activities of the Oxidation-Reduction System**

**Catalase Deficiency (Acatalasemia)**

In addition to the protection from oxidative damage of red cells afforded by various elements of the glycolytic and pentose phosphate pathways, other redox enzyme systems are effective. Catalase is one such enzyme whose function is the detoxification of hydrogen peroxide (H₂O₂) produced during normal metabolic processes. In Japanese acatalasemia, addition of excess H₂O₂ to a blood sample results in the formation of methemoglobin. However, patients with this disease have almost normal ratios of methemoglobin to hemoglobin, and only their increase in Heinz body formation suggests susceptibility to the effects of oxidative stress.

One such probable manifestation is a peculiar oral gangrene called Takahara's disease, suffered by about half of acatalasemic children. Other than these occasional and intermittent oral lesions, patients are surprisingly free of symptoms. The presence of residual catalase enzyme in these patients, as well as modestly increased GSHPx levels and significantly increased superoxide dismutase activity, may help explain the comparatively benign clinical manifestations of this seeming biochemical disaster.

**Superoxide Dismutase Deficiency**

The superoxide free radical anion, O₂⁻ is converted by superoxide dismutase into O₂ and H₂O₂. In the absence of superoxide dismutase, O₂ reacts with H₂O₂ to produce hydroxyl radicals and singlet-excited oxygen. All of these free radicals could damage chromosomes, producing increased breaks and rearrangements which exceed the DNA-repair capacity of the cell. Such chromosomal abnormalities occur in patients with Fanconi’s anemia, and Joenje et al. have recently reported decreased red cell superoxide dismutase activity in two unrelated patients with this disease.

**Conclusion**

The deficiency of some red cell enzymes, such as arginase, hypoxanthine-guanine phosphoribosyl transferase,
the virtually complete absence of an isozyme of carbonic anhydrase in red cells produce no obvious hematologic consequences. Enzyme deficiencies involving the anaerobic and aerobic glycolytic pathways frequently produce nonspherocytic hemolytic anemia.

A few of the enzyme deficiencies involved in Embden-Meyerhoff and glutathione synthetic pathways may also produce neurologic disorders.

The erythrocyte uses a complex, interrelated series of reactions to produce ATP and 2,3-DPG, and NADPH and NADH to maintain the normal reduced state of compounds which are being subjected to oxidative stresses. It is probably no coincidence that the red cell utilizes primarily its role of oxygen transport.

References


