Editorial

Environmental Modification of Red Cell Metabolism

By Ernest Beutler

A CASCADE OF REPORTS appearing in the last decade have emphasized the genetic control of red cell metabolism. Deficiencies of most of the glycolytic enzymes have been described and the genetics of these abnormalities have been defined. It has been recognized by most investigators, of course, that the activities of some enzymes are much higher in younger cells than in older cells, and that the same may be true with regard to the concentration of some metabolic intermediates. In general, however, the approach to variability in red cell metabolism has been largely a genetic one.

Recently, it has become more and more apparent that nongenetic factors may greatly influence the levels of both enzymes and intermediates in erythrocytes. In the light of some of the new information which has been developed, it has been necessary to re-examine some data regarding the supposed genetic basis of variability in red cell metabolism. Furthermore, understanding of how to manipulate the metabolism of the red cell by changing its external environment provides us with the potential of modifying the impact of those abnormalities which are clearly genetically inherited.

It has been known for some time that a frank deficiency in thiamine decreases the transketolase activity of human erythrocytes.1 It has also been found that the activity of glutamic-pyruvic transaminase of red cells is diminished in some elderly individuals who appear to be taking a normal diet. However, when they are given pyridoxine supplements, the activity of this enzyme, which uses pyridoxyl phosphate as a coenzyme, increases.2 Most recently it has been found that the activity of red cell glutathione reductase depends upon the dietary intake of riboflavin.3,5 The activity of this enzyme in red cells even of individuals who have an adequate riboflavin intake is increased by the administration of as little as 5 mg. of additional riboflavin daily.

The increase in glutathione reductase activity which occurs when riboflavin is administered depends upon the synthesis of flavin-adenine-dinucleotide (FAD) by the red cell. FAD is a cofactor of glutathione reductase, and inactive enzyme existing within the cell is apparently activated by the newly formed FAD. But FAD is only one of the adenine nucleotide coenzymes which the red cell is able to synthesize. It is known, for example, that the red cell has the capacity to form NAD,6 NADP,6 AMP, ADP, and ATP,7 as well as the biologically important phosphate ester, 2,3-diphosphoglyceric acid (2,3-DPG).

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Phosphate-deficient chicks have decreased red cell ATP levels, and the addition of phosphate to red cell preservative media containing adenine produces a profound increase in the red cell ATP level. Investigations of Syllm-Rapoport et al. suggested that, in vivo, the ATP levels were regulated by factors extrinsic to red cells. When a patient with erythrogenesis imperfecta was transfused with red cells having a normal ATP level, a consistent increase in red cell ATP levels occurred as the transfused cells circulated in their new environment. Adenine was found present in the plasma and it was suggested that this might be the regulator of red cell ATP levels. The possibility that phosphate might be such a regulator was also mentioned but did not receive detailed consideration. However, the important role which phosphate can play in the in vivo regulation of red cell ATP levels in man has recently been demonstrated by the studies of Lichtman et al. A patient with markedly decreased serum phosphate levels due to administration of aluminum hydroxide gel was found to have low red cell ATP levels. When aluminum hydroxide administration was discontinued, the serum phosphate level of the patient, who suffered from severe renal disease, rose to very high levels. Concurrently, the red cell ATP level was observed to increase. Repeated determinations of serum phosphate levels and red cell ATP levels showed that the ATP level showed a remarkable correlation between these two parameters.

The average red cell ATP levels of Negro subjects are slightly, but statistically significantly, lower than the average level of Caucasian subjects. It was suggested that this difference in ATP levels was due to multigenic inheritance and that the lower ATP levels of Negroes might confer some degree of resistance to malaria. The relationship between very high and very low plasma phosphate levels, and red cell ATP levels in the patient of Lichtman et al. prompted us to examine the possible relationship between these parameters in normal subjects, and a weakly positive correlation between serum phosphorus levels and red cell ATP concentration was found. It appears that the serum phosphates levels of Negroes may be slightly lower than that of Caucasians, and this could account, at least in part, for the racial difference in red cell ATP levels. How this would come about is not entirely clear, but it is of interest that the intake of vitamin D appears to influence serum phosphate levels: patients with rickets have hypophosphatemia and hypervitaminosis D tends to increase serum phosphate levels. It has been suggested that the dark skin of people living in tropical climates may have evolved as a necessary defense against the development of hypervitaminosis D in areas where there is a great deal of exposure to the sun. In temperate zones, then, the incidence of rickets in Negroes is higher than whites, since insufficient sunlight reaches the skin to activate adequate quantities of provitamin D. It is interesting to speculate that perhaps the darker skin of Negroes results in slightly lower serum phosphate levels by decreasing the amount of active vitamin D available, and that this in turn influences red cell ATP levels. It is quite remarkable that over 30 years ago Guest and Rapoport demonstrated that red cell ATP levels declined during the development of rickets in rats, and were restored to normal by the administration of vitamin D.

The effect of environmental influences on the levels of red cell 2,3-diphos-
phoglyceric acid have stimulated much interest recently, and has been reviewed in a recent editorial.\textsuperscript{18} The concentration of this regulator of the oxygen affinity of hemoglobin is increased by alkalosis and by exposure to hypoxia.\textsuperscript{19} In acidosis, the amount of 2,3-DPG in the red cells declines.\textsuperscript{12}

The potentialities for manipulating the levels of enzymes and cofactors in red cells is obviously quite large. These afford us an opportunity to help by compensating, at least in part, for genetic defects. A higher level of NADP within the erythrocyte, for example, might help to stabilize unstable mutants of glucose-6-phosphate dehydrogenase, such as are found in patients with nonspherocytic congenital hemolytic anemia. If there are disorders which are the direct results of hereditary glutathione reductase deficiency, these might be ameliorated by the administration of riboflavin. It may be that the use of inhibitors or activators of the critical diphosphoglyceromutase and diphosphoglycerate phosphatase reactions may ultimately make it possible for the clinician to manipulate the level of 2,3-DPG and thus the position of the oxygen dissociation curve for the benefit of the patient.

Recognition of the fact that the activities of red cell enzymes and cofactors are not rigidly fixed may lead to greater understanding of the basis of the variability we observe in populations, and may make it possible to provide rational therapy for some genetic disorders of red cell metabolism for which no therapy has been available previously.

REFERENCES

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