This paper described the curtailment of red-cell glycolysis, decreased red-cell organic phosphates, and increased hemoglobin-oxygen affinity that resulted from severe hypophosphatemia, which occurred during the use of parenteral nutrition. The observations suggested that decreased concentrations of red-cell 2,3-diphosphoglycerate impaired red-cell function and that decreased red-cell adenine triphosphate threatened red-cell survival. Decreased red-cell ATP concentration and plasma inorganic phosphate concentration in this patient,


resulted from severe hypophosphatemia, which led to studies of other types of hypophosphatemia such as that induced by parenteral nutrition with hypertonic glucose and protein hydrolysate. In those studies, we examined the effect of decreased red-cell ATP on cell viability and function and looked for decreases in other intracellular organic phosphates, especially 2,3-diphosphoglycerate, which had recently been shown to play a key role in modulating hemoglobin-oxygen affinity.

Our publication has by the standard of the Science Citation Index achieved some attention; yet it is less important than we originally believed. Hypophosphatemia has to be extreme to have an effect on the red cell, and it is likely that compensating mechanisms protect oxygen transport. Perhaps of greater importance was the implication that hemoglobin-oxygen affinity could be manipulated, hopefully to the benefit of the patient who has impaired oxygen transport. However, if oxygen extraction is high, as it is in most cases of poor oxygen delivery, the affinity of hemoglobin for oxygen is a less important variable since the capillary PO2 is below that at which curve position produces its greatest effects. Favorably and unfavorably positioned curves converge at very low PO2.

Interest in this work derived, in part, from the cross-disciplinary implications of the relationship of hypophosphatemia to red-cell organic phosphate concentrations. Interest groups included students of red-cell metabolism and viability, abnormalities of phosphate metabolism and abnormalities of cells as a result of renal failure, the effects of phosphate depletion, the use of parenteral nutrition, and the modulation of hemoglobin-oxygen affinity to improve oxygen delivery. The military biomedical research program also had interest in devising ways to manipulate the affinity of hemoglobin for oxygen in order to ameliorate acute mountain sickness in troops recently placed at high altitude and to enhance their combat readiness. We and others spent considerable time trying to capitalize on these observations to develop methods to modulate oxygen-hemoglobin affinity in vivo and improve oxygen transport by pharmacologic agents. A practical method for doing so has not been accomplished at the time of this writing.

This Week's Citation Classic