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# This Week's Citation Classic®

**Lichtman M A, Miller D R, Cohen J & Waterhouse C.** Reduced red cell glycolysis, 2, 3-diphosphoglycerate and adenosine triphosphate concentration, and increased hemoglobin-oxygen affinity caused by hypophosphatemia. *Ann. Intern. Med.* 74:562-8, 1971. [Depts. Med., Radiation Biol. and Biophys., and Pediat., Univ. Rochester Sch. Med. and Dentistry, NY]

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 adenosine triphosphate threatened red-cell survival. Both effects decrease oxygen transport. [The *SCI*® indicates that this paper has been cited in over 165 publications since 1971.]

**Marshall A. Lichtman**
**Hematology Unit**
**Department of Medicine**
**University of Rochester Medical Center**
**Rochester, NY 14642**

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**In 1968, while studying phosphate metabolism in the red cells of subjects with severe chronic renal disease, we were measuring red-cell adenosine triphosphate (ATP) using a scintillation counter to detect the light emission produced by the luciferin-luciferase-ATP interaction. The source of ATP was an extract of normal or abnormal red cells. In the patients' samples, the emitted light translated into very high ATP concentrations, characteristic of red cells from patients with severe chronic renal disease. In the samples from one patient, the light emission was extremely low. In prior studies of this patient two months earlier, red-cell ATP had been increased.**

**We thought a pipetting error had been made or that an electrical surge from heavy equipment on the same circuit had led to a malfunction of the detector and hence the unusually low photons detected. Replicate samples were thawed and restudied, and the results again indicated a very low red-cell ATP. Another sample of the patient's blood was obtained, and the red-cell ATP was restudied on this fresh material. The repeat measurement confirmed that the red-cell ATP was very low.**

**In reviewing the record of the patient in question, we learned that he had been given large quantities of aluminum hydroxide gel during the prior two months because of severe hyperphosphatemia, and re-examination of his plasma phosphate indicated a markedly decreased concentration as a result of the aluminum hydroxide ingestion. We went on to establish a strong correlation between red-cell ATP concentration and plasma inorganic phosphate concentration in this patient,[1] and this 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 $pO_2$ is below that at which curve position produces its greatest effects. Favorably and unfavorably positioned curves converge at very low $pO_2$.**

**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.[2] A practical method for doing so has *not* been accomplished at the time of this writing.**

1. **Lichtman M A, Miller D R & Freeman R B.** Erythrocyte adenosine triphosphate depletion during hypophosphatemia in a uremic subject. *N. Engl. J. Med.* 280:240-4, 1969. (Cited 90 times.)
2. **Lichtman M A.** Therapeutic manipulation of hemoglobin function: possible role in the management of acute hypoxia. (Chaplin H. Jr., Jaffé E R, Lenfant C & Valeri C R, eds.) *Preservation of red blood cells.* Washington, DC: National Academy of Sciences, 1973. p. 149-60.

 