A Fable of Our Time:  
Oxygen Transport, or Does the Emperor Have New Clothes?

REGULATION of the interaction between hemoglobin and oxygen has been the subject of numerous papers and several symposia since the last Editorial on the subject. Although a host of genetic, environmental and extraerythrocytic metabolic or hormonal influences modulate this relationship, data to substantiate the physiologic import of acute shifts in the oxyhemoglobin dissociation curve (O₂HbDC) secondary to altered 2,3-diphosphoglyceric acid (2,3-DPC) concentrations are remarkably meager. The pattern of interest and its relevance to clinical medicine are reminiscent of the emperor and how he displayed his new clothes. Fear of challenging authority has caused us to treat implication as functional truth, while excluding the option that the physiologic import of such phenomena may be minor. According to the great physiologist, Joseph Barcroft, “the art of successful advertising consisted in making some statement about the commodity advertised which was in fact perfectly true but which was quite irrelevant.”

Are we faced here with the same problem? Will no one admit that the emperor is naked, or does it take a child’s uncluttered mind to recognize it? Are the changes in O₂HbDC relevant and, if so, how much of a shift is necessary to elicit a recognizable response in blood flow, oxygen uptake, or organ function? If irrelevant in normal man, are these changes important in the sick?

A pH change (i.e., the Bohr shift) has long been recognized as the principal modulator of hemoglobin–oxygen affinity. Although altering plasma pH from 7.35 to 7.45 will lower F₅₀ (P₅₀ at 50 per cent saturation) of the “standard dissociation curve” 3 torr, equivalent to a 20 per cent decrease in 2,3-DPC, little excitement has been generated by this shift, and few have tried to endow it with major physiologic significance. Is the 2,3-DPC effect not another “laboratory game,” possibly a vestige of evolution that no longer matters for whole-body economy? The constancy of the milieu interieur is characterized by its enormous ability to undergo wide fluctuations consistent with the vagaries of everyday stress. Dare we not admit that some fluctuations are of little practical consequence? After all, lack of a response to 2,3-DPG is known to exist in other animal species without obvious effects on well-being.

Addressing ourselves to the clinical problem, are the changes seen after massive blood transfusions physiologically significant, enough to warrant prevention or correction? In this issue of ANESTHESIOLOGY, McConn and Derrick describe in detail the natural history of erythrocytic 2,3-DPG during storage in ACD solution, in the frozen, glycerolized state, and after transfusion into man. Although they describe very nicely a “storage lesion” and how it is correctable by appropriate additives, we must temper our enthusiasm for activism until physiologic relevance has been demonstrated.

The full story is complex and far from clear. Fluctuations in thyroid activity cause similar variations in 2,3-DPG, and these have been attributed to compensation necessary for abnormal O₂ consumption. Intravenous hyperalimentation and the associated hypophosphatemia reduce the erythrocyte 2,3-DPC concentration and increase the affinity of hemoglobin for oxygen (i.e., O₂HbDC shifts further to the left despite constant plasma pH); conversely, in chronic renal failure the elevated serum inorganic phosphorus level is associated with a high level of 2,3-DPG in the erythrocyte. It has been suggested that intraerythrocytic pH is the principal modality regulating the synthesis or breakdown of 2,3-DPG in the glycolytic cycle. However, it is likely that the pH-dependent transfer of inorganic phosphate across the erythrocyte membrane, fluctuations in plasma precursor levels (e.g., glucose, pyruvate), and states of hormonal activity (e.g., thyroid, parathyroid) are equally important in vivo. Finally, hypoxemia is assumed to be the initiating and sustaining impetus for increased 2,3-DPG levels found in congenital heart disease.
though equivalent hypoxemia at high altitude or in chronic pulmonary disease appears to be, at best, a mild stimulus.

Logic leads us to suggest that a shift in the O$_2$HbDC is most likely to have physiologic consequences in organs that have high arteriovenous O$_2$ content differences, such as the heart and brain. According to preliminary experiments in the heart–lung preparation, when myocardial oxygen consumption is fixed, coronary blood flow increases or decreases depending on the hemoglobin affinity for O$_2$, while the effluent venous P$_a$O$_2$ remains constant within a narrow range (i.e., mid-20’s). If this is indeed an important regulatory factor in the intact animal, then its significance for the critically ill patient with impaired myocardial activity becomes apparent. Current work in our laboratory (Trichet et al., in preparation) suggests that transfusion of whole blood deficient in 2,3-DPG may act as a feedback stimulus to increase thyroid activity intended to restore 2,3-DPG to normal. The price paid is an associated increase in whole-body O$_2$ consumption, with a need for greater blood flow, a compensation not always available to the critically ill patient.

Finally, do erythrocytes retain their ability to respond to an appropriate metabolic stimulus once transfused? Although additives may keep 2,3-DPG at control levels during storage, as indicated by McConn and Derrick, this does not exclude the possibility that metabolic insufficiencies may persist after transfusion, nor does it eliminate the likelihood that membrane transport mechanisms continue to be abnormal (e.g., restoration of erythrocytic K+ to normal takes several days) and intra-extraerythrocytic inhibitors may play a significant role in the persistence of metabolic aberrations. These are burning questions, in need of analysis before we can decide how to interfere therapeutically. They are particularly relevant to the scholarly clinician, because the only adequate experimental model is the sick patient.

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References
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