EDITORIAL

“A Shift to the Left” or “A Shift to the Right” in the Regulation of Erythropoiesis

By Ernest Beutler

The terms “shift to the left” or “shift to the right” have occupied a place in hematologic jargon for decades. The expressions refer, of course, to the degree of maturation of hematopoietic cells. Pulmonary physiologists, however, have assigned a totally different meaning to these expressions; they refer to the position of the oxygen dissociation curve. A virtual explosion of new experimental findings and interpretations now clearly indicates that the hematologist, too, must concern himself with “a shift to the left” or “a shift to the right” of this curve.

The fact that anemia stimulates erythropoiesis has been recognized for a long time and has been a focal point in the search for humoral regulators of red cell formation. Exactly how the body senses the hemoglobin concentration of the blood so that appropriate adjustments in the rate of red cell formation may be made is not yet known. Laboratory measurements of hemoglobin concentration are carried out by measuring light absorption in a diluted sample, but animals are not endowed with spectrophotometric devices to make measurements of the hemoglobin concentration in the blood. Rather, it is likely that an oxygen-sensor serves as the hemoglobinometer of the body. Such an assumption is strengthened by the well-known effect of hypoxia in stimulating erythropoiesis, and of hyperoxia in depressing red cell formation. It is not difficult to visualize how such an oxygen-sensor might function. All that is required is an area in the body in which the rate of the blood flow and the rate of removal of oxygen from the blood is maintained at a constant level (Fig. 1). Under these circumstances the \( pO_2 \) (\( pO_2(F) \), Fig. 1) would be a function of the hemoglobin concentration of the blood, the initial oxygen saturation of the hemoglobin when it entered the sensor, and the shape and position of the oxygen dissociation curve. Since the oxygen content of the plasma is a linear function of the \( pO_2 \), a sensor responding to the amount of oxygen in the plasma could measure alterations in the hemoglobin concentration of the blood.

Until recently most hematologists have given little serious consideration to the effect of the shape and position of this curve on the regulation of red cell formation. Oxygen dissociation curves have, it seems, been of interest primarily to the pulmonary physiologist. Now, however, there has been rapid accumulation of evidence pointing to the fact that the position of the dissociation curve can, and indeed does, influence significantly the steady-state level of the hemoglobin concentration of the blood. Alterations of the oxygen dissociation curve may be responsible for anemia and for polycythemia. Shifts in the position of the oxygen dissociation curve have also become an important consideration in blood storage.
Fig. 1.—The hemoglobinometer of the body, a possible scheme. This device provides a constant rate of blood flow and a constant rate of oxygen removal from the blood. The oxygen tension at the sensor (pO₂(F)) is a fraction of the hemoglobin concentration of the blood and the arterial oxygen tension provided that the oxygen dissociation curve is normal.

Figure 2 illustrates the position of the normal dissociation curve of red cells. Also shown are the positions of curves which have "shifted to the right" or "shifted to the left." When blood is equilibrated with oxygen in the lungs the hemoglobin becomes almost entirely saturated with oxygen. The arterial pO₂ is approximately 100 mm. of Hg, nearly the same as the pO₂ of the air in the alveoli. When a fixed quantity of oxygen is removed from the hemoglobin the resulting pO₂ (and consequently, oxygen content of the plasma) depends on the position of the dissociation curve. If, for example, 50 per cent of the bound oxygen is removed the pO₂ falls to approximately 27 mm. of Hg if the shape and position of the dissociation curve is normal. When the curve has shifted to the right, removing the same amount of oxygen from hemoglobin results in a higher-than-normal partial pressure of oxygen. Consequently the tissues are able to obtain additional oxygen more readily from the blood. The reverse situation obtains when the curve is shifted to the left. Under these circumstances, removal of the same amount of oxygen from hemoglobin results in a lower-than-normal partial pressure of oxygen. The oxygen-tension sensitive hemoglobinometer of the body would interpret a sample of blood with a right-shifted dissociation curve as containing more hemoglobin than a spectrophotometric assay would disclose. A sample of blood with a left-shifted dissociation curve flowing through the hemoglobinometer of the body would be interpreted as containing less hemoglobin than a spectrophotometric assay would disclose. The seemingly appropriate adjustments in the rate of erythropoiesis would result in polycythemia when the curve is shifted to the left and anemia when the shift is to the right.

Structural mutations involving the hemoglobin molecule may produce shifts in the dissociation curve. These mutations, indeed, result in polycythemia when the curve is shifted to the left, as in hemoglobin Chesapeake and hemoglobin Yakima. Presumably, in patients with these abnormal hemoglobins erythropoiesis has been regulated to that point that the pO₂ in the oxygen-sensor reaches a normal level, although, because of the abnormal oxygen dissociation

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Fig. 2.—A schematic representation of the oxygen dissociation curve of whole blood. This curve describes the relationship between the oxygen tension (pO₂) on the one hand and the degree of saturation of hemoglobin with oxygen, on the other. The sigmoid shape of the curve is of considerable physiologic importance in making possible the efficient delivery of oxygen to the tissues. As oxygen is added to normal reduced hemoglobin the configuration of the hemoglobin molecule is altered as each of the four heme groups of hemoglobin binds, in turn, a molecule of oxygen. This results in changes in the affinity of the hemoglobin for additional oxygen, a phenomenon which has been termed the heme-heme interaction. The degree of heme-heme interaction may be calculated from the shape of the dissociation curve.

Also shown are the positions of the oxygen dissociation curve when the affinity of hemoglobin for oxygen is increased, “a shift to the left,” or decreased, “a shift to the right.”

curve, the patient is now polycythemic. The lack of severe anemia when it is shifted to the right in hemoglobin Kansas is probably due to the marked abnormality in the shape of the curve, resulting in a greatly lowered arterial oxygen saturation.

It has also been suggested that variations in the degree of compensation in different hemoglobinopathies associated with a moderate decrease in red cell survival could be due to shifts in the dissociation curve. Alteration in the amino acid sequence of the hemoglobins is not the only way in which the position of the dissociation curve may be shifted. A classic means of shifting the dissociation curve is by altering the pH of the blood. Recently, it has been clearly demonstrated that intracellular phosphate compounds, particularly ATP and 2,3-diphosphoglycerate, can produce marked displacement of the oxygen-dissociation curve. Apparently, these compounds are bound to hemoglobin, the binding resulting in a lower affinity of the
hemoglobin molecule for oxygen. Since the levels of ATP and 2,3-DPG within the erythrocyte are subject to alteration by regulation of the rate of metabolism by way of the Rapoport-Luebering cycle, the erythrocyte is provided with an opportunity to adjust its own oxygen dissociation curve. Even relatively brief exposure to high altitudes results in the accumulation of 2,3-DPG within the red cell, and a right shift in the dissociation curve has been observed in patients with erythrocytosis secondary to arterial hypoxemia of chronic pulmonary disease. Although this may make it simpler for the red cells to deliver sufficient quantities of oxygen to the tissue without too severe a drop in tissue Po2, too great a right shift of the dissociation curve could be a handicap, since the red cells would then fail to bind sufficient oxygen in the lungs.

It seems entirely possible that alterations in the concentration of 2,3-diphosphoglycerate in erythrocytes may also affect the steady-state level of hemoglobin by shifting the oxygen dissociation curve. A family with an increase in red cell ATP levels, in which there was marked diminution of erythrocyte 2,3-DPG levels is of particular interest in this respect. Since the sum of ATP and 2,3-DPG levels was considerably lower than normal, one would anticipate a left shift in the dissociation curve. Indeed, although there was modest shortening of red blood cell survival in this family, there was a statistically significant increase in the hemoglobin level of the blood. It would seem very worthwhile to measure the erythrocyte 2,3-DPG and ATP levels and oxygen dissociation curves of other patients with mild, and otherwise unexplained polycythemia.

Conversely, one would predict that elevations of red cell 2,3-DPG levels would result in a right shift of the dissociation curve and anemia. Although pyruvate kinase deficiency produces a marked increase in red cell 2,3-DPG levels, it is difficult to interpret the result of this shift, since marked shortening of red cell survival also occurs. It seems likely, however, that other metabolic disorders of the red cell may exist in which a right shift of the dissociation curve is not accompanied by shortened red cell survival and in which anemia may be ascribed to the change in the oxygen-binding properties of hemoglobin. One may speculate that pharmacologic manipulation of the levels of red cell intermediates may indirectly change the rate of erythropoiesis. Thus, it will be of interest to examine the effects of agents such as cobalt and testosterone on the oxygen dissociation curve.

In 1954 it was demonstrated that the oxygen dissociation curve of blood stored in ACD solution gradually shifted to the left. This observation initially received relatively little attention, and its mechanism remained obscure. The demonstration that 2,3-DPG and ATP levels markedly influenced the position of the dissociation curve have now explained this finding. Stored blood becomes severely depleted of 2,3-DPG in less than 2 weeks. It now becomes apparent that massive blood transfusion with 2,3-DPG depleted blood might be quite hazardous. The transfused red cells would lack the capacity to effectively deliver oxygen to the tissues for some hours. If this is so, why has there not been greater clinical recognition of such hazards? Most individuals who receive blood transfusions have only a fraction of their circulating red cell mass
replaced each day. Patients who are bleeding massively would ordinarily be transfused with units of stored blood of various ages, some of it quite fresh. Occasionally a massively bleeding patient might be transfused with sufficient blood stored for over 2 weeks within a short period of time to cause severe tissue anoxia. But such desperately ill patients often die, and it would not be surprising if in the complex clinical situation surrounding massive hemorrhage the death would not be ascribed to failure of transfused red cells to deliver their load of oxygen to tissues.

It is apparent that during the next few years it will be necessary for the hematologist in the laboratory and in the clinic to show more concern for the position of the oxygen dissociation curve. It is entirely possible that many patients who now have anemia or polycythemia of unknown origin may actually be suffering from a "shift to the left" or a "shift to the right."

REFERENCES

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ERNEST BEUTLER