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THE MAGNITUDE OF THE BOHR COEFFICIENT: OPTIMAL FOR OXYGEN DELIVERY

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Abstract. This paper examines relationships between the magnitude of the blood Bohr coefficient and arterial–venous changes in blood pH, P_{CO_2} and oxygen affinity during steady-state, aerobic gas exchange. The physical–chemical linkage of the Bohr and Haldane effects is taken into account. It is concluded that for blood in which there is negligible oxygen-linked carbamate formation: (a) arterial–venous pH and P_{CO_2} changes would be minimized if the Bohr coefficient were approximately equal to the respiratory quotient, with opposite sign, and (b) the rightward shift of the oxygen equilibrium curve in the tissues, relative to the curve at arterial pH, would be maximal if the Bohr coefficient were about one half the respiratory quotient (Bohr coefficient −0.35 to −0.5 for RQ 07–1.0). Actual Bohr coefficients in several mammals maximize the right shift of the oxygen equilibrium curve and are therefore optimal for oxygen delivery. Actual Bohr coefficients do not minimize pH or P_{CO_2} changes. These results suggest that the contribution of the Bohr–Haldane effect to oxygen transport is more important than its contribution to pH homeostasis or CO_2 transport.

Bohr effect	Mammal
Carbamino hemoglobin	Oxygen dissociation curve
Haldane effect	P_{50}

The Bohr effect and the Haldane effect are believed to benefit respiratory gas transport and blood acid–base homeostasis. Metabolically produced CO_2 acidifies the blood in the tissue capillaries, causing a rightward shift of the oxygen equilibrium curve (the Bohr shift) that promotes oxygen release. A reverse shift aids oxygen loading in the lung. The magnitude of the Bohr shift is determined by the product of the pH change and the Bohr coefficient. The Haldane effect, which can be defined as hydrogen-ion binding by hemoglobin upon deoxygenation (Siggaard-Andersen, 1974), buffers the increase in blood P_{CO_2} and fall in blood pH during passage through the tissues, and the reverse changes in the lung. By reducing the arterial–venous pH change, the Haldane effect tends to reduce the Bohr shift.

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The Bohr and Haldane effects are linked (Wyman, 1964), such that the Bohr coefficient of hemoglobin is equal to the Haldane coefficient. The properties of blood are more complex than those of hemoglobin solutions because two phases are present, but Siggaard-Andersen (1974) has shown that the Bohr and Haldane coefficients of blood are proportional to the hemoglobin coefficients, and therefore to each other (see Theory). One consequence of this Bohr–Haldane linkage is that an increased blood Bohr coefficient will result in reduced arterial–venous pH change. The net effect could be either a larger or smaller Bohr shift.

The purpose of the present paper is to quantitatively predict the physiological consequences of Bohr–Haldane linkage for the function of whole blood *in vivo*. How would arterial–venous P_{CO_2} and pH changes be affected if the Bohr coefficient were larger or smaller than its actual value? How would the Bohr shift be affected? It was initially evident that no single value of the Bohr coefficient can be most favorable for both buffering and oxygen delivery – a very large coefficient could completely eliminate the arterial–venous pH change, but in the absence of pH change there would be no Bohr shift. Do Bohr coefficients in animals have values that are best for buffering pH and P_{CO_2} changes, or for oxygen delivery, or do they reflect a compromise between these functions? The answer could indicate whether the Bohr effect or the Haldane effect is more important. Several authors have concluded that the Haldane effect is more important than the Bohr effect (Hill *et al.*, 1973; Klocke, 1980; Grant, 1982), while Bartels (1972) emphasized the importance of the Bohr effect in oxygen delivery to the tissues. The following analysis applies to blood which does not have a specific CO_2 effect on oxygen affinity.

Theory

This section describes a method for predicting the *in vivo* consequences of a change in the Bohr coefficient.

Linkage of Bohr and Haldane effects

The Bohr effect of a hemoglobin solution is characterized by the Bohr coefficient, B:

$$B = d \log P_S / dpH \quad (1)$$

where P_S is the P_{O_2} that produces a particular fractional oxygen saturation, S. In hemoglobins from almost all animals the value of B is negative (P_S increases as pH decreases). The Bohr coefficient of a given hemoglobin is typically the same at all pH values within the physiological range (i.e., log P_S is a linear function of pH). It is therefore easy to predict P_S at any pH if its value at a one pH is known.

Two types of Bohr coefficient can be distinguished. The fixed-acid Bohr coefficient describes the effect of changing pH by adding fixed (non-CO_2) acid or base at constant P_{CO_2}. The CO_2 Bohr coefficient describes the effect of changing pH by

varying P_{CO_2}. Inequality between the fixed-acid and CO_2 coefficients indicates the presence of a 'specific' effect of CO_2 on oxygen affinity, associated with oxygen-linked binding of CO_2 to hemoglobin as carbamate. Human blood has a specific CO_2 effect (Garby *et al.*, 1972), while bloods of the two species considered in detail in this paper (dog and gray seal) have little or none (Reeves *et al.*, 1982; Lapennas and Reeves, 1982). The present method for predicting the consequences of altering the Bohr coefficient is applicable only in the absence of a significant specific CO_2 effect, i.e., when the two Bohr coefficients are equal. Therefore, it is not necessary to specify the type of Bohr coefficient or the agent causing pH change in the following discussion.

The Haldane effect of a hemoglobin solution is characterized by the Haldane coefficient, H, where

$$H = d[HbH^+]/d[HbO_2] \tag{2}$$

at constant pH and P_{CO_2}. The symbol HbH^+ represents hemoglobin-bound hydrogen ion and HbO_2 is hemoglobin-bound oxygen. Hemoglobins from most animals bind H^+ upon deoxygenation. According to the theory of linked functions (Wyman, 1964), the Haldane coefficient equals the fixed-acid Bohr coefficient in a hemoglobin solution. Increased pH-sensitivity of oxygen affinity is therefore accompanied by increased hydrogen ion binding by hemoglobin upon deoxygenation.

Analogous expressions that take into account the presence of erythrocyte and plasma phases have been derived for blood (Siggaard-Andersen, 1974), as follows: The Bohr coefficient of blood, Bb, is expressed relative to plasma pH, pHp, rather than to intra-erythrocytic pH, pHe. The blood and hemoglobin Bohr coefficients are proportional, according to the relation

$$Bb = B \cdot dpHe/dpHp \tag{3}$$

where dpHe/dpHp is a constant that is less than 1. The base-excess coefficient of blood, BEC, is analogous to the Haldane coefficient of a hemoglobin solution. It expresses the change in blood base excess per change in hemoglobin-bound oxygen concentration. The base-excess coefficient is proportional to the Haldane coefficient of hemoglobin, *i.e.*,

$$BEC = H \cdot F \tag{4}$$

where F is a constant. The base-excess coefficient refers to a given plasma pH, while the Haldane coefficient of hemoglobin refers to the corresponding intracellular pH. If eq. 3 is solved for B, the result can be substituted for H in eq. 4 (using the equality of B and H), yielding

$$BEC = Bb \cdot F/(dpHe/dpHp) \tag{5}$$

Thus, the base-excess change accompanying a change in blood oxygenation, expressed by the BEC, is directly proportional to the blood Bohr coefficient. (The relation between Bb and BEC is more complex if Bb varies with the level of oxygen

saturation (Siggaard-Andersen, 1974). The Bohr coefficient is nearly the same at all levels of oxygen saturation in blood of dog and gray seal (Reeves *et al.*, 1982; Lapennas and Reeves, 1982)).

The base-excess change when blood is deoxygenated at constant P_{CO_2} raises pH and total CO_2 concentration, C_{CO_2}. This accounts for the differences between the CO_2 absorption curves, and pH–log P_{CO_2} buffer lines, of oxygenated and deoxygenated blood. In the absence of carbamate formation, the increase in C_{CO_2} is entirely in the form of bicarbonate. At constant P_{CO_2}, pH and C_{CO_2} are nearly linear functions of base excess (pH, Siggaard-Andersen, 1974; C_{CO_2}, calculated by eq. 14 of Loeppky *et al.*, 1983, using pH as a function of base excess from Siggaard-Andersen). Therefore, the oxy–deoxy differences in blood pH and total CO_2 concentration, at any P_{CO_2}, are proportional to the base-excess coefficient, and hence to the blood Bohr coefficient. If the Bohr coefficient were altered, the oxy–deoxy shifts of the CO_2 absorption curve and buffer line would change proportionally. This fact will be used in predicting *in vivo* consequences of an altered Bohr coefficient, as described below.

Physiological oxygen equilibrium curve

The 'physiological' oxygen equilibrium curve is the relation between oxygen saturation and P_{O_2} that pertains *in vivo*, where blood pH is not constant but changes as oxygen is exchanged for CO_2. The pH normally falls as oxygen is released to the tissues because enough CO_2 enters the blood to counteract the tendency of the Haldane effect to raise pH. If metabolism is entirely aerobic (CO_2 is the only acid entering the blood) and gas exchange is in steady state (tissue CO_2 and O_2 stores are constant), then the physiological oxygen equilibrium curve can be constructed as follows: When oxygen saturation has declined from its arterial value, Sa, to a particular value, S, C_{CO_2} will exceed arterial C_{CO_2}, Ca_{CO_2}, by an amount equal to the product of the O_2 released and the tissue respiratory quotient, RQ

$$C_{CO_2} = Ca_{CO_2} + Cb_{Hb} \cdot RQ \cdot (Sa - S) \tag{6}$$

where Cb_{Hb} is blood hemoglobin concentration. Blood pH will then have a new value, pH_S, which differs from arterial pH, pHa, by an amount ΔpH_S.

Blood pH at a given saturation level, pH_S, can be predicted using the CO_2 absorption curves and buffer lines of oxygenated and deoxygenated blood, as shown in fig. 1. It is assumed that blood CO_2 content and pH at a given P_{CO_2} vary in direct proportion to oxygen saturation between the curves for oxygenated and deoxygenated blood (Peters and Van Slyke, 1931; Scheipers *et al.*, 1975). Figure 1 illustrates prediction of blood pH when half the arterial oxygen has been released. The process can be repeated to obtain pH_S at other levels of oxygen saturation.

The Bohr shift of the physiological oxygen equilibrium curve is described by $\Delta \log P_S$, the difference between the logarithms of P_S at pHa and pH_S. The Bohr shift is equal to the product of ΔpH_S and the Bohr coefficient.

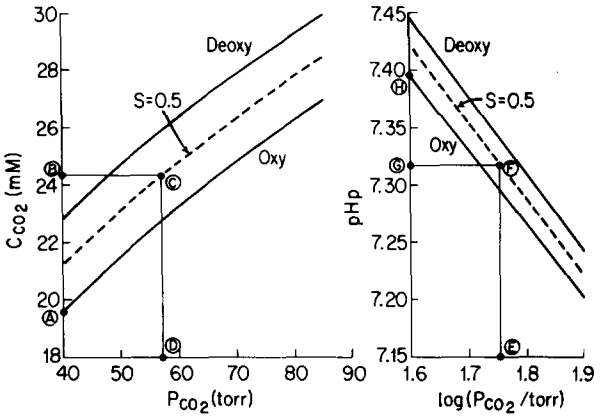

Fig. 1. Method for predicting *in vivo* change in blood pH when one half of arterial oxygen is exchanged for CO_2. Arterial blood is assumed to be fully saturated and to have P_{CO_2} of 40 torr, yielding the arterial CO_2 concentration indicated by point A. The C_{CO_2} at half saturation, B, was calculated by eq. 6. This C_{CO_2} is located on the dashed CO_2 absorption curve midway between the oxy and deoxy curves, point C, yielding the corresponding P_{CO_2}, D. The logarithm of this P_{CO_2}, E, corresponds to point F on the dashed buffer line midway between the oxy and deoxy lines, and thus to the predicted pH at half saturation, G, which is lower than the pH of arterial blood, H. (Data on C_{CO_2} and pH of oxygenated and deoxygenated dog blood as functions of P_{CO_2} from Rodkey *et al.*, 1971; hemoglobin concentration 9.5 mM.)

Results

Effect of altered Bohr coefficient

Figure 2 shows CO_2 absorption curves and buffer lines that would result if the Bohr coefficient of dog blood were reduced to half its actual value. The oxy–deoxy shifts of CO_2 concentration and pH are also reduced by half. The process illustrated in fig. 1 can be used to predict P_{CO_2} and pH of this hypothetical blood after release of a specified amount of oxygen. At any level of oxygen saturation, P_{CO_2} is higher, and pH lower, than for actual blood. Figure 3 shows predicted ΔpH_S at half saturation for a range of assumed Bohr coefficients, and for RQ values spanning the normal physiological range (0.7 and 1.0). The value of ΔpH_S would be greatest if the Bohr coefficient were zero. Both ΔpH_S and the change of P_{CO_2} from the arterial value would decline to zero if the Bohr coefficient were about equal to the respiratory quotient, with opposite sign.

Figure 4 shows values of the Bohr shift at half saturation, corresponding to the pH changes in fig. 3. For a given RQ, the Bohr shift is greatest when the Bohr coefficient is about $-0.5 \cdot RQ$. Higher RQ produces a larger Bohr shift for a given Bohr coefficient. The dashed curves in fig. 4 show that the same Bohr coefficient maximizes the Bohr shift at other levels of oxygen saturation. The actual Bohr coefficient in dog blood is between the values that would give maximal Bohr shifts for $RQ = 0.7$ and $RQ = 1.0$.

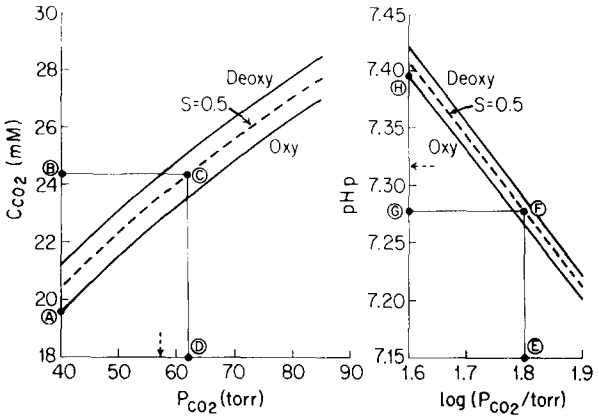

Fig. 2. Prediction of *in vivo* pH at half saturation if the Bohr coefficient had one half the actual value. Other conditions are as in fig. 1. The CO_2 absorption curve and buffer line of oxygenated blood are assumed to be unchanged, while changes of C_{CO_2} and pH upon deoxygenation at each P_{CO_2} are reduced to one-half the actual values. The P_{CO_2} at half saturation (D) is higher and the pH (G) is lower than in actual dog blood (dashed arrows).

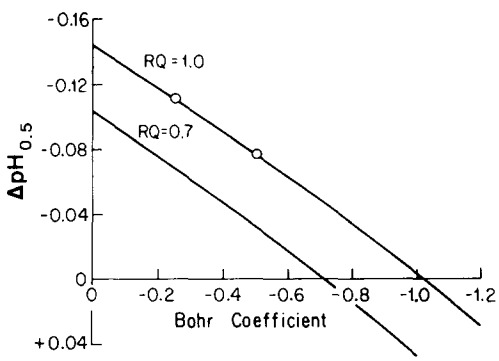

Fig. 3. Predicted *in vivo* changes of plasma pH upon release of one half of arterial oxygen, $\Delta pH_{0.5}$, for dog bloods having varying assumed Bohr coefficients. The points on the line for RQ = 1 are taken from figs. 1 and 2. Predicted $\Delta pH_{0.5}$ is greatest when the Bohr coefficient is zero, and declines to zero when the Bohr coefficient is approximately equal to the RQ, with opposite sign.

This analysis was repeated using blood of the gray seal. Again, the greatest Bohr shift is predicted when the Bohr coefficient is about half the RQ (fig. 5), and this corresponds closely to the actual Bohr coefficient in this species.

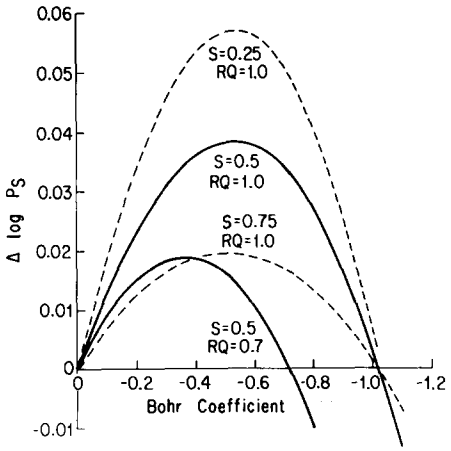

Fig. 4. Bohr shifts, $\Delta \log P_S$, between dog blood at arterial pH and blood at predicted *in vivo* pH for various values of the Bohr coefficient. The Bohr shifts at half saturation (solid curves) were calculated from the data in fig. 3. The maximal Bohr shift occurs at the same Bohr coefficient for S = 0.75 and 0.25 (dashed curves) as at S = 0.5. The actual Bohr coefficient is −0.49.

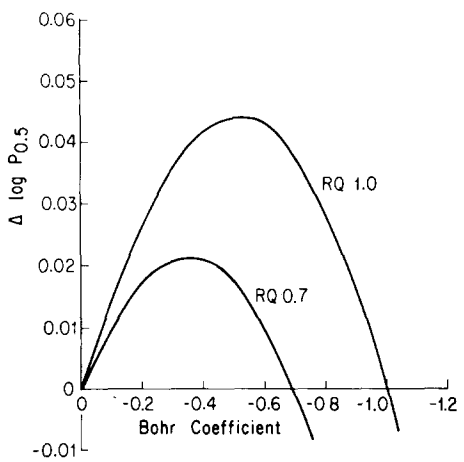

Fig. 5. Bohr shifts for various assumed Bohr coefficients in gray seal blood. The actual coefficient is −0.47. (Based on data from Lapennas and Reeves, 1982.)

Discussion

Bohr coefficients of −0.35 to −0.5, depending on the RQ, should produce the greatest possible rightward shift of the physiological oxygen equilibrium curve, and can therefore be said to be optimal for oxygen delivery. This prediction applies to blood with negligible specific CO_2 effect under steady-state, aerobic conditions. The actual values in dog and gray seal blood are in this range, so natural selection

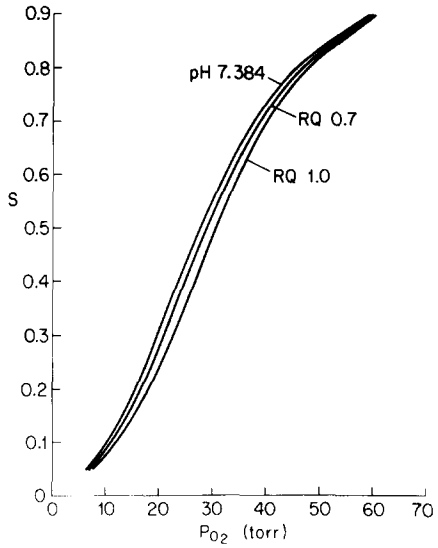

Fig. 6. Predicted physiological oxygen equilibrium curves of gray seal blood for RQ = 0.7 and RQ = 1.0 compared with curve at constant arterial pH.

has apparantly favored such Bohr coefficients. This suggests that the Bohr effect plays a significant role in oxygen delivery despite the fact that Bohr shifts do not seem very large (fig. 6). Reported Bohr coefficients for many other species are similar (Bartels, 1976), but most values in the literature are CO_2 coefficients, and it is often not known whether there is a specific CO_2 effect.

Hill *et al.* (1973) and Klocke (1980) estimated the contributions of the Bohr and Haldane effects to pulmonary oxygen and CO_2 transport, and concluded that the Haldane effect is more important than the Bohr effect. Bartels (1972) pointed out that the Bohr effect would be more important in the tissues, especially the heart and working skeletal muscle, than in the lungs, because of the greater pH changes. However, Grant (1982) analyzed the influence of the Bohr–Haldane effect on both pulmonary and tissue gas exchange, and concluded that its most important function was reducing tissue P_{CO_2} and acidosis, rather than promoting release of oxygen. If the buffering and/or CO_2 transport roles of the Haldane effect were more important than the contribution of the Bohr effect to oxygen delivery, we would expect Bohr coefficients to have values in the range -0.7 to -1.0, which would achieve perfect pH homeostasis and would mediate the most CO_2 transport. Instead, Bohr coefficients have smaller values that are optimal for oxygen delivery, suggesting that it is the contribution of the Bohr effect to oxygen transport that is more important.

What factors could lead to differences between Bohr coefficients of various species? One might be activity level, but Jurgens *et al.* (1982) found that bats, which have high metabolism during flight, have Bohr coefficients no larger than those of similar size non-flying mammals. It has been thought that diving would pose problems in oxygen delivery that would favor a larger Bohr coefficient, but coeffi-

cients in seals are no larger than those of terrestrial mammals (Lapennas and Reeves, 1982). These results are understandable if larger Bohr coefficients would be less, rather than more, favorable for oxygen delivery. The present analysis does not explain the tendency for the Bohr coefficient to be larger in small mammals (Bartels, 1976). Some variation in Bohr coefficient among species might be associated with diet-related differences in respiratory quotient. A carbohydrate diet might favor a larger Bohr coefficient than a protein or lipid diet.

The present analysis was applied to blood of the bladdernose seal, using the data of Clausen and Ersland (1969). As in dog and gray seal, the predicted Bohr shift would decrease if the Bohr coefficient were larger or smaller than its actual value. However, the measured Bohr coefficient at half-saturation in the bladdernose seal is -0.66 (Clausen and Ersland, 1969), which is greater than half the RQ. Possible causes of this difference as compared to dog and gray seal include: (a) there may be a specific CO_2 effect in bladdernose seal blood or (b) the Bohr coefficient may vary with oxygen saturation.

Anaerobic metabolism supplies additional acid (lactic acid) to blood perfusing the muscles. A Bohr coefficient which was larger than would be optimal under aerobic conditions could take advantage of this additional acid to produce a larger Bohr shift. Hence, we might expect the Bohr coefficient in species that depend heavily on anaerobic metabolism to be higher than in species with little anaerobic metabolism. Seals can use substantial anaerobic metabolism (Scholander, 1940), but their Bohr coefficients appear to be optimal for aerobic conditions. This may reflect the infrequent utilization of anaerobic metabolism during natural diving (Kooyman *et al.*, 1980) and the fact that when anaerobic metabolism does occur, little lactate is released into the circulation until after the dive (Scholander, 1940). However, interpretation of Bohr coefficients in diving animals is complicated by the absence of steady state in gas exchange (see below). Large Bohr coefficients (Root effect) in fishes (*e.g.*, European catfish, Albers *et al.*, 1981; carp, Weber and Lykkeboe, 1978) are related to the mechanism for oxygen secretion into the swimbladder and the eye (Wittenberg and Wittenberg, 1974; Farmer *et al.*, 1979), which involves addition of lactic acid to the blood.

Some other species, in addition to fishes, have conspicuously large Bohr coefficients. The Bohr coefficient is -1.0 in the diving snake *Acrochordus arafurae* (Seymour *et al.*, 1981), and values exceeding the RQ are found in several cephalopods (Lykkeboe *et al.*, 1980; Brix *et al.*, 1981; Houlihan *et al.*, 1982). Lykkeboe *et al.* (1980) described a mechanism in cephalopod blood that prevents pH increase during tissue gas exchange even though the Bohr coefficient exceeds the RQ. More CO_2 is bound to oxygenated than to deoxygenated hemocyanin (opposite to the normal greater binding to deoxygenated pigment). This excess CO_2 is released upon deoxygenation, preventing the pH increase that would otherwise result from the large Bohr coefficient.

In summary, it is possible to predict the consequence of changing the Bohr coefficient in the absence of a specific CO_2 effect. Actual coefficients in several species

are close to the predicted optimum for oxygen delivery and far from the value that would most effectively buffer pH and P_{CO_2} changes. This suggests that the Bohr coefficient has been selected primarily to maximize its contribution to oxygen delivery. Some exceptions to this rule can be explained, but others cannot. The present analysis provides a background against which variations in the Bohr coefficient can be interpreted.

Comments on assumptions

The assumption that changes in C_{CO_2} and pH at constant P_{CO_2} are directly proportional to changes in base excess is not strictly accurate. The rate of change of pH with base excess decreases as pH increases, and this would be reflected in CO_2 absorption curves as well. However, the deviation from proportionality is small over the pH range between oxygenated and deoxygenated blood at constant P_{CO_2}, which was no greater than 0.15 in the cases considered here.

The Bohr coefficient is nearly the same at all saturation levels in dog and gray seal blood, but in other species the Bohr coefficient varies at different levels of oxygenation (man, Garby *et al.*, 1972; marine turtle, Lapennas and Lutz, 1982). If the Bohr coefficient varies with oxygen saturation, then blood base excess (and hence CO_2 concentration and pH) at intermediate levels of oxygen saturation would presumably be related to the integral of the Bohr coefficient with respect to saturation.

The specific CO_2 effect is negligible in blood of dog and gray seal, and also in several birds (muscovy duck, Meyer *et al.*, 1978; chicken, Lapennas and Reeves, 1983) but not in blood of man and some other species. When there is a specific CO_2 effect, the oxy–deoxy shifts in the CO_2 absorption curve and buffer line are due to hemoglobin binding of both CO_2 and H^+, and the present method for predicting the effects of a change in the Bohr coefficient is not applicable.

The assumption that respiratory gases are in a steady state may be appropriate in the dog most of the time, but would not be valid in the seal during diving, when tissue CO_2 stores increase (Scholander, 1940). Analysis of pH changes during diving would have to account for CO_2 partitioning and buffering in the whole body.

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