A NEW EQUATION FOR THE OXYGEN DISSOCIATION CURVE OF BLOOD

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OXYGEN dissociation curves of blood have attracted the attention of many physiologists and physical chemists for well over forty years. It is well known that in case of pure dialysed hæmoglobin, the curve assumes the shape of a simple Langmuir adsorption isotherm, while in the case of blood, a number of S-shaped curves are obtained under various conditions. The percentage oxygen absorption by blood decreases with (*a*) a decrease in the pH (*i.e.*, an increase in eH[1]), (*b*) an increase in the mineral salt concentration, or (*c*) an increase in the carbon dioxide tension.[2] Many attempts have so far been made to explain this phenomenon and also to derive a suitable equation for these curves, epecially by Hill,[3] Adair[4] and by L. Pauling[5] besides several others. Hill's equation was discarded as empirical and unsatisfactory.[6] Many of the other equations are based on assumptions and hypotheses of very advanced nature and are rather complicated, involving a number of constants. Further, these equations govern only one or two aspects of the problem and are not very satisfactory at the extreme oxygen tensions. Thus, a simple and comprehensive equation, covering all the influencing factors, does not seem to have been worked out yet.

A reinvestigation of the problem, based on elementary physico-chemical principles, has therefore been taken up by the present author. This investigation is based on two postulates, evidence in support of which can be cited from the more recent work on hæmoglobin.

(*i*) It is the hæmoglobinate *ion* that takes up oxygen and not the unionised hæmoglobin *molecule* as was assumed by the previous investigators. This is supported by the fact that about 65% of the hæmoglobin in blood exists as the potassium salt and only 35% as free hæmoglobin. Instances can be cited where such organic ions (though less complex ones) take up oxygen in alkaline media. Further, this postulate explains the increased oxygen absorption with increased alkalinity (pH) of blood, as also the influence of mineral salts.

(*ii*) Osmotic pressure determinations of hæmoglobin by Gutfreund[7] show evidence in favour of its dissociation, though only to a slight extent. It is therefore postulated that in blood, Hb_4 exists in a dissociation equilibrium with Hb and that it is the Hb that actually combines with oxygen giving HbO_2 and not Hb_4. A number of molecules of this HbO_2 may then combine (or associate) with a suitable number of Hb molecules to give the various "intermediate compounds" of Pauling, Roughton and others, *viz.*, Hb_4O_2, Hb_4O_4, Hb_4O_6 and Hb_4O_8. This can be schematically represented as follows:

$$Hb_4 \rightleftharpoons 4\,Hb \overset{O_2}{\rightleftharpoons} \underbrace{3\,Hb + HbO_2} \rightleftharpoons Hb_4O_2$$

$$\downarrow\uparrow O_2$$

$$\underbrace{2\,Hb + 2\,HbO_2} \rightleftharpoons Hb_4O_4$$

$$\downarrow\uparrow O_2$$

$$\underbrace{Hb + 3\,HbO_2} \rightleftharpoons Hb_4O_6$$

$$\downarrow\uparrow O_2$$

$$4\,HbO_2 \rightleftharpoons Hb_4O_8.$$

Thus, the intermediate compound hypothesis of oxyhæmoglobin fits well into the above scheme.

Starting from these postulates and applying the Law of Mass Action to the hæmoglobin-oxygen reaction under various conditions, the following equations have been derived for the various curves.

i) $Y = 100K_1p/(1+K_1p)$

for pure dialysed hæmoglobin, which is identical with the Hill's first equation.

ii) $Y = (100-S)\,e^h \cdot \dfrac{K_1p}{1+K_1p}$

for blood under the influence of pH and in presence of mineral salts.

iii) $Y = \dfrac{100\,K_1p}{(1+K_1p)} \cdot \dfrac{(1+p)}{(1+p+K_2p')}$

for blood at a carbon dioxide tension p'.

It can also be shown that these three equations are only the particular solutions of a more general equation given below, governing all the influencing factors, *viz.*, the presence of mineral salts, pH and the presence of carbon dioxide.

iv) $Y = (100-S)\,e^h \cdot \dfrac{K_1p}{(1+K_1p)} \cdot \dfrac{(1+p)}{(1+p+K_2p')}$

where Y is the observed oxygen absorption by blood or by pure dialysed Hb, S is a factor proportional to the mineral salt concentration, $h = (pH - pK)$ or $(eK - eH)$, p is the oxygen tension at equilibrium with blood, p' is the carbon dioxide tension at equilibrium with blood, and K_1 and K_2 are constants.

This equation has the unique advantage of governing all the factors influencing the absorption of oxygen by blood. It involves only two constants and is much simpler than some of the previous equations containing as many as four constants. It is significant, as has been found, that most of the observed data for the oxygen absorption by blood under various physiological conditions fit into this equation in a very satisfactory manner.

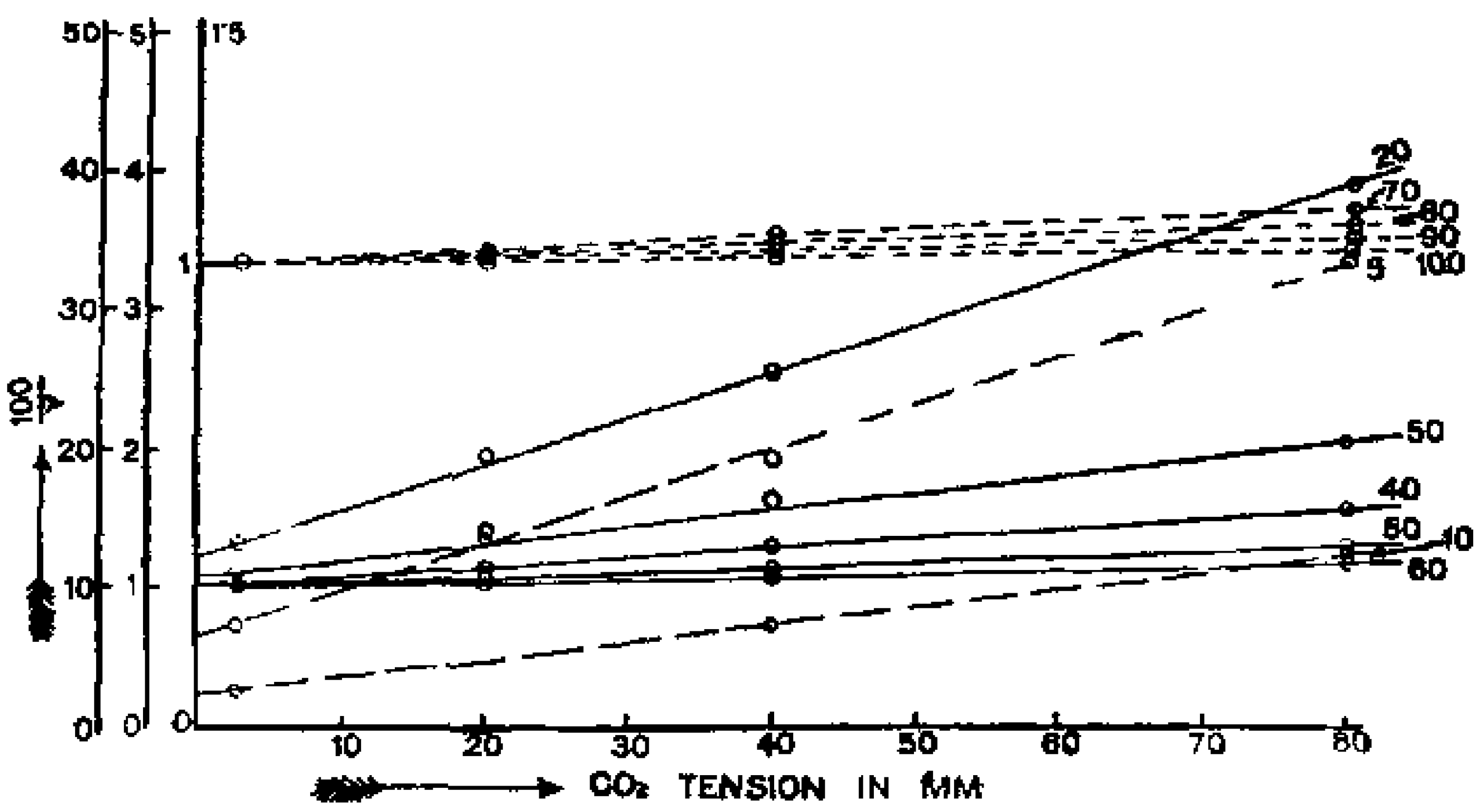

FIG. 1. The oxygen tension for each curve is marked at the end of the curve. The scale for 100/Y for tensions between 0 and 10 mm. is reduced 10 times to bring the curves within the size of the figure. The scale for 100/Y for tensions 70 mm. to 100 mm. is increased 10/3 times, to show them clearly without overlapping.

Thus, for instance, for a particular specimen of blood (*i.e.*, $h =$ constant and $S =$ constant in the above equation) and at a definite oxygen tension (*i.e.*, $p =$ constant), equation (iv) can be directly transposed into the following equation, giving a linear relation between the carbon dioxide tension and the reciprocal of the oxygen absorption :

$$100/Y = \alpha + \beta p'$$

where, α and β are constants for a given oxygen tension, *i.e.*, Equation (*iv*) predicts that if 100/Y be plotted as ordinate against the corresponding p' as abscissæ at any constant oxygen tension, a straight line should be obtained for each oxygen tension. When the reciprocals of Y/100 (*i.e.*, of percentage oxygen absorption) from Henderson's *et al.*,[8] data are plotted against the corresponding carbon dioxide tensions (p'), it is found that the resulting points strictly lie in one straight line for each oxygen tension The graphs are given in Fig. 1. This striking agreement between the predicted and the observed results not only proves beyond doubt the validity of the present equation, but it also shows that this equation holds good for the whole of the observed range of oxygen and carbon dioxide tensions, while the previous equations were reported to have proved less satisfactory at extreme oxygen tensions [9]

Full details will be published elsewhere. The author thanks Dr. A. A Aiyar of Stanley Medical College, and Prof K. S. Srinivasa Varadan of the Madras Medical College, Madras, for their interest.

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NOBEL PRIZE FOR CHEMISTRY, 1955

THE Nobel Prize for Chemistry has been awarded to Prof. Vincent du Vigneaud, Professor of Biochemistry, Cornell University Medical College, New York. In announcing the award, the Swedish Academy of Sciences mentioned Prof. du Vigneaud's researches on biochemically important sulphur compounds, especially the first synthesis of a hormone which plays a significant role in the regulation of life processes.

Prof. du Vigneaud has carried out extensive research work on the chemistry of a number of complex substances of biological origin. In his book entitled *A Trail of Research in Sulfur Chemistry and Metabolism and Related Fields*, published in 1952, he has presented a very beautiful account of the biochemical research work carried out by him originating from a study of the chemistry of insulin and dealing with the conversion of methionine and homocystine to cystine, the participation of choline, betaine and related compounds in the process of transmethylation and the biosynthesis of 'labile' methyl groups He has also collaborated during World War II with a number of scientists both in U.K. and U.S.A., in the study of the structure and later the synthesis of penicillin. His most important single piece of research, however, has been the working out of the structure of two hormones, produced by the posterior lobe of the pituitary gland, and later their synthesis. These two hormones are built up of the same components, *viz.*, amino acids, as are the proteins. But though the number of these amino acids in these hormones is relatively small in comparison to