$$\bar{i}_{pq} = \bar{x}\text{-}\bar{w}, \text{ etc.},$$
$$\sigma^2_{i_{pq}} = [(\Sigma(w^2) + \Sigma(x^2) - 2\Sigma(wx))]/N - \bar{i}^2_{pq},$$

and similarly for $\sigma_{i_{qr}}$, $\sigma_{i_{rs}} \cdots$.

The product moment for any two growth increments, say i_{pq} and i_{rs}, is

$$\Sigma(i_{pq}i_{rs}) = \Sigma(wy) - \Sigma(wz) - \Sigma(xy) + \Sigma(xz).$$

In the special case in which three *consecutive* stages, say w, x, y, are involved we write

$$\Sigma(i_{pq}i_{qr}) = \Sigma(wx) - \Sigma(wy) + \Sigma(xy) - \Sigma(x^2).$$

Problem 3.—To determine the correlation between the size of the organism at any stage and any growth increment.

The notation of problem (2) may be used. The physical constants for the growth stages and growth increments have been given. The product moments are

$$\Sigma(wi_{pq}) = \Sigma(wx) - \Sigma(w^2), \Sigma(xi_{qr}) = \Sigma(xy) - \Sigma(x^2),$$
$$\cdots, \Sigma(wi_{qr}) = \Sigma(wy) - \Sigma(wx), \Sigma(wi_{rs}) = \Sigma(wz) - \Sigma(wy), \text{ etc.}$$

Illustrations of applicability will be given elsewhere.

3 (1585)

The carbon dioxid dissociation curve and the arterial and venous carbon dioxid tension of human blood in health and in disease.

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A method for the direct determination of the carbon dioxid tension of human arterial and venous blood has been applied to a series of normal and pathological subjects. The method is similar to one recently described by Means, Bock and Woodwell[1] for the determination of arterial carbon dioxid tension, but was developed and applied by us independently before the appearance of Means' paper. It is a development of the work of Henderson and Haggard[2] on the "Hemato-Respiratory Func-

[1] Means, Bock and Woodwell, *Transactions Am. Assn. Physicians*, 1920.

[2] Henderson and Haggard, *Journ. Biol. Chem.*, 1919, xxxix, 163.

tion" and consists in the simultaneous determination of the carbon dioxid dissociation curve of the blood at body temperature and the carbon dioxid content of both the arterial and venous blood as they occur in the body.

This method has been applied in whole or in part to twenty-three subjects, on whom thirty-eight observations have been made. The group studied consisted of three normal persons, seven patients with decompensated cardiac disease, six patients with severe anemia, four with diabetes, two with emphysema, one with polycythemia and one with chronic nephritis. Whenever it was found practicable the alveolar carbon dioxid tension was also determined by the Haldane[1] method.

The normal limits of variation in height of the carbon dioxid dissociation curve at 37.5° C. were found to agree with those established by previous observers. At 42 mm. CO_2-tension the limits of variation of the carbon dioxid combining power of whole blood are 43 and 56 volumes per cent. The height of the normal resting dissociation curve is as Christiansen, Douglas and Haldane [2] previously found, characteristic for each individual.

In three of the seven patients with cardiac decompensation the dissociation curve lay below the normal limits, indicating a real reduction of the available alkali of the blood. The carbon dioxid capacity of the venous plasma was, however, normal in these cases. The difference between the CO_2-capacity of whole blood and that of venous plasma found in these cases may be explained by the fact that the carbon dioxid capacity of the venous plasma as determined by the Van Slyke[3] method is dependent upon the carbon dioxid content of the blood as it exists in the veins. Therefore, in conditions like cardiac decompensation, in which there is a retention of carbon dioxid in the venous blood, the carbon dioxid combining capacity of the venous plasma is inapplicable as a measure of the available alkali of the blood. For this reason whole blood should be used or else the whole blood should be equilibrated with a standard CO_2-air mixture before the plasma is removed.

[1] Haldane and Priestley, *Journ. Physiol.*, 1904–5, xxxii, 225.

[2] Christiansen, Douglas and Haldane, *Journ. Physiol.*, 1914, xliii, 244.

[3] Van Slyke, *Journ. Biol. Chem.*, 1917, xxx, 347.

The dissociation curve in severe anemia is more nearly horizontal and lies at a higher level than does the normal dissociation curve at carbon dioxid tensions that exist in the body. This is due to the diminution of the hemoglobin, which has the power, according to Parsons[1] and Henderson[2], of combining with a part of the alkali of the blood. The diminution of hemoglobin renders a larger proportion of the alkali of the blood available for combination with carbon dioxid at low tensions of CO_2. This reduces the "buffer" action of the blood against carbon dioxid so that for a given change of CO_2-tension the corresponding change in hydrogen-ion concentration is greater than normal. This is offered as a partial explanation of the exertional dyspnea found in these cases.

The P_H of blood exposed to a carbon dioxid-air mixture of the same CO_2-tension as that existing in the alveolar air obtained by the Haldane method was calculated from the $H_2CO_3/BHCO_3$ ratio and found to vary between 7.42 and 7.29, with an average of 7.35. In general the alveolar carbon dioxid, dissociation curve and alveolar P_H during rest vary in different individuals but are constant and characteristic for any given individual.

The arterial CO_2-tension, as determined in three normals, is also a characteristic of the individual, as is the arterial P_H. The limits of variation of the arterial P_H are, however, greater than those of the alveolar P_H, being 7.23 to 7.45. As a natural corollary to this it is found that, contrary to general opinion, the alveolar tension is not always the same as that of the arterial blood. The arterial tension may be as much as 10 or 11 mm. Hg. higher than the alveolar even in normal resting persons.

An empirical equation to correct the carbon dioxid tension of the arterial and venous blood for oxygen-unsaturation is proposed. It assumes that the action of oxygen on the carbon dioxid combining capacity of whole blood is a function of the concentration of hemoglobin in the blood and the ratio of reduced to oxy-hemoglobin. The equation employed was:

$$\frac{6.38}{18.5} \times \begin{pmatrix} O_2 \text{ capacity of blood} \\ \text{in vol. per cent.} \end{pmatrix} \times \frac{\begin{pmatrix} \text{Per cent. } O_2 \text{ unsaturation} \\ \text{of blood} \end{pmatrix}}{100} =$$

[1] Parsons, *Journ. Physiol.*, 1917, li, 440, 1920, liii, 340.

[2] Henderson, L. J., *Journ. Biol. Chem.*, 1920, li, 401.

D vol. per cent. (Amount by which the carbon-dioxido combining capacity of blood is increased as a result of the effect oxygen unsaturation).

As applied to the figures given by Haldane[1] and by Joffe[2] it shows an error of only 10 per cent. between CO_2-tensions of 30 and 70 mm. inclusive. This equation has been employed in the calculation of arterial and venous carbon dioxid tension. Although the differences in CO_2 tension between arterial and venous blood are greater and more variable than the results of indirect methods have led us to believe, the slope of the dissociation curve and the effect of oxygen combined prevent any change in the hydrogen-ion concentration. The P_H of venous blood as calculated from the $H_2CO_3/BHCO_3$ ratio is practically the same as that of arterial blood.

In cardiac dyspnea the difference between alveolar and arterial CO_2-tension was always much greater than normal, varying from 13 to 19 mm. Hg. This indicates some impairment of the mechanism for the elimination of carbon dioxid in the lungs: either that parts of the lungs are unaerated or that they are imperfectly ventilated. The arterial P_H was once absolutely diminished and once relatively diminished, indicating the presence of a true carbon dioxid retention. Most of the patients studied did not recover compensation, but in one case the carbon dioxid retention disappeared completely and the arterial P_H and the relation of arterial to alveolar carbon dioxid tension, returned to normal. The difference between arterial and venous carbon dioxid content and arterial and venous carbon dioxid tension was only occasionally greater than normal. A retarded circulation rate is therefore not a necessary concomitant of cardiac decompensation with dyspnea. The venous and arterial P_H were practically identical even in those cases with an increased difference between arterial and venous carbon dioxid tension because of the greater oxygen-unsaturation of the venous blood.

In severe anemia not only is the dissociation curve higher and more nearly horizontal than normal at CO_2-tensions that exist in the body, but the compensating effect of oxygen is greatly

[1] Christiansen, Douglas and Haldane, *Journ. Physiol.*, 1914, xliii, 244.

[2] Joffe, Poulton, Poulton and Poulton, *Journ. Physiol.*, 1920, liv, 129.

diminished because of the diminution of hemoglobin. In spite of the fact that the difference in carbon dioxid content and tension between arterial and venous blood is comparatively small, there is a very definite difference in P_H. The arterial P_H lies well to the alkaline side of the 7.35 line in those cases where there is a difference, while the venous point lies practically on the 7.35 line.

It is suggested tentatively as an explanation of this phenomenon, that the tissue CO_2-tension and P_H must lie at or above that of the venous blood and not in equilibrium with the arterial blood. As it is presumably the tissue CO_2-tension or hydrogen-ion concentration in the respiratory center which controls the respiratory mechanism, the tendency of the repsirations will be to maintain this constant rather than the hydrogen-ion concentration of the arterial blood. In normal persons arterial and venous P_H are practically identical because of the slope of the dissociation curve and the effect of oxygen. In anemia the effect of these compensating reactions is diminished so that true relations become more evident. It has already been demonstrated by Michaelis,[1] and others that the hydrogen-ion concentration of the venous blood is maintained constant at $P_H = 7.35$ with a variation of ± 0.08, which agrees well with our values for both arterial and venous P_H.

4 (1586)

Precipitin response in the blood of rabbits, following subarachnoid injections of horse serum.

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During the treatment of cases of cerebrospinal meningitis with antimeningococcic serum in a large Army hospital,[2] a curious reaction was repeatedly observed. This appeared in patients who, after having received several intraspinous treatments with serum, were given serum intravenously. While such injec-

[1] Michaelis, Wasserstoffionenkonzentration, Berlin, 1914.

[2] Hospital of the American Embarkation Center, LeMans, France.