STUDIES OF THE CARBON DIOXIDE ABSORPTION CURVE OF HUMAN BLOOD.

I. THE APPARENT VARIATIONS OF $pK_1$ IN THE HENDERSON-HASSELBALCH EQUATION.

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In 1916 Hasselbalch (1916) demonstrated experimentally what L. J. Henderson (1908) had already deduced theoretically, that the hydrogen ion concentration of blood could be calculated from the carbon dioxide tension and the bicarbonate concentration with a mean error no greater than that of the electrometric method, which he estimated to be about ± 0.02 pH. For convenience he transformed Henderson's equation

$$C_H = K \frac{[H_2CO_3]}{[BHCO_3]}$$

(1)

into the logarithmic form

$$pH = pK_1 + \log \frac{[BHCO_3]}{[H_2CO_3]}$$

(2)

Hasselbalch found that in bicarbonate solutions $pK_1$ varied with the concentration of bicarbonate and assumed that it varied in the same manner in blood. Milroy (1917), Parsons (1919–20), and Michaelis (1920) concluded that there were no theoretical grounds for the assumption of such a variation in blood and in their studies assumed a constant value for $pK_1$. Their position has been accepted by most workers.

Warburg (1922) has shown that the views of Hasselbalch and of Parsons are not irreconcilable. He has reviewed and analyzed all the previous work on blood bicarbonate and hydrogen ion
concentration and has added data of his own obtained by methods more accurate than those of previous workers. He points out that the constant, pK1, in the Hasselbalch equation does not vary with the bicarbonate concentration in blood; but that the volume of the blood corpuscles and the partition of CO2 between the corpuscles and the plasma vary according to the pH of the blood and cause corresponding variations in the ratio \( \frac{[\text{BHCO}_3]}{[\text{H}_2\text{CO}_3]} \) which produce apparent changes in pK1. He shows that Parsons' values for pK1, treated statistically, show a consistent variation with varying pH that is outside the limits of error of his methods.

All these studies have depended on a comparison of electrometric measurements of the hydrogen ion concentration and determinations of the carbon dioxide content of blood which has been brought into equilibrium with gas mixtures of known carbon dioxide tension. It is, however, impossible to settle the question satisfactorily by such comparisons. In a complex biological system such as blood, or even plasma, one cannot hope to attain an accuracy greater than ± 0.01 to 0.02 pH by electrometric measurements. This corresponds to a difference of ± 1 to 2 volumes per cent of CO2. But by the latest improved methods of saturation and analysis of gases in the blood this error has been reduced to ± 0.2 to 0.5 volume per cent of CO2 (Austin et al., 1922; Van Slyke and Stadie, 1921). The changes which might be expected to occur in pK1 are hardly beyond the limits of error of the electrometric method, but should be easily demonstrable by gasometric methods.

**EXPERIMENTAL.**

In the course of some studies of electrolyte equilibria in the blood, certain data have become available that permit an evaluation of the variations of pK1 in whole blood. In one series of experiments oxalated whole blood, obtained from patients in the medical wards of the New Haven Hospital and from members of the hospital and laboratory staff, was saturated with known tensions of CO2 in air. One portion of the blood, thus saturated, was analyzed for CO2 and the volume of its cells was determined by hematocrit. From another portion the plasma was separated and analyzed for CO2. The oxygen capacity of the blood was
also determined. 68 determinations were made on 56 specimens of blood. The experiments fall into two groups. In forty-four experiments the blood was studied at 40 mm. CO₂ tension only; in twelve instances determinations were made at both 30 and 60 mm.

Methods.

Saturation with CO₂ was effected by the method described by Austin, Cullen, Hastings, McLean, Peters, and Van Slyke (1922) as "Second saturation method," with only slight variations. The tonometers used held 700 to 800 cc. and the greatest amount of blood used at one time was 25 to 30 cc. Under these conditions it was found unnecessary to correct for the CO₂ given off or taken up by the blood. Each sample was exposed in two successive tonometers to a gas mixture calculated to give the exact CO₂ tension desired after it had come to the temperature of the water bath (38°C.) in which it was rotated. In order to make sure that this method effected complete equilibrium a third saturation was done in a series of experiments. In no case was there any change in the carbon dioxide content of the blood after the second saturation when as much as 30 cc. of blood were exposed to 20 or 40 mm. of CO₂ tension as is shown in Experiment 1.

We have preferred the "Second saturation method" to the "First," because it is simpler and permits the production of the exact CO₂ tension desired, and because we have not been able to convince ourselves by theory or experiment that the "First" is more accurate. To be sure there is no possibility of checking the gas mixture in the "Second method" and the gas mixture must be prepared with great accuracy. In only one experiment of a much longer series than that here presented, is there any internal evidence of an error in the preparation of the original gas mixture. On repeated occasions duplicate blood samples exposed in different tonometers have shown no greater variation than duplicate samples from the same tonometer, an indication that no significant errors enter in the preparation of gas mixtures. (See Experiment 2.) Attempts to analyze the gas mixtures disclosed certain unforeseen difficulties. In the manifold described (Austin et al., 1922) the CO₂ is introduced from a carefully calibrated and water-jacketed burette at known temperature, and saturated with water vapor at atmospheric pressure. The diluent, air, is allowed to enter from the room at a different and variable temperature through a small amount of water. When the gases are analyzed in the Haldane burette it is assumed that both CO₂ and diluent were introduced, saturated with water vapor, at the same temperature and pressure. In testing out the method the fact that such an assumption was involved at first escaped recognition, and unaccountable differences were found between the calculated and observed CO₂ tensions in the tonometers. When precautions were taken to ascertain the pressure and temperature of the diluent air and to insure its saturation with water vapor these differences at once disappeared. (See
Experiment 3.) The total pressure in the system is not important in these experiments provided the final oxygen tension is sufficient to insure complete oxygen saturation and this is amply provided for in either method. The "First saturation method" attempts to overcome these difficulties by opening the tonometers to the air in the course of saturation and thus assuring equilibrium with atmospheric pressure. This renders it impossible to obtain the exact CO₂ tension desired. The method which we have chosen is not as well adapted to experiments that demand the establishment of exact pressure conditions for more than one gas because it presupposes that all the gases under investigation are pure. That this assumption is justified when CO₂ is obtained from a Kipp generator with a water trap to remove acid, as it was in our experiments, we have proved by analysis; but it is not justified when one is dealing with gases obtained from commercial cylinders.

It was shown by Christiansen, Douglas, and Haldane (1914) and has since been emphasized by Dale and Evans (1922) that the CO₂ capacity of blood diminishes progressively if it is permitted to stand. Austin et al. (1922) found that this change was very slow in horse blood and could be eliminated by chilling the blood. We have determined the rate of change in human blood and have found that, if blood is kept chilled (standing in water drawn from an ice cooler), its CO₂ capacity remains unchanged for at least 3 hours. This is true even when it is left with a considerable surface exposed to the air, in a thin layer in the bottom of a Pyrex glass beaker. (See Experiment 4.) All specimens of blood used in these experiments were kept chilled in narrow tubes. The blood, however, was saturated as soon as possible (15 to 60 minutes) after it was drawn.

Experiment 1.—30 cc. of blood were exposed in two successive tonometers to CO₂-air mixtures containing the proper amount of CO₂ to give the desired tension at 38°C. 5 cc. were then removed for analysis and the remaining 25 cc. exposed in a third tonometer to the same tension of CO₂. This blood was then analyzed for CO₂.

<table>
<thead>
<tr>
<th>CO₂ tension.</th>
<th>CO₂ content.</th>
<th>Difference.</th>
</tr>
</thead>
<tbody>
<tr>
<td>mm.</td>
<td>vol. per cent</td>
<td>vol. per cent</td>
</tr>
<tr>
<td>20</td>
<td>42.3</td>
<td>42.5</td>
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<td>20</td>
<td>24.5</td>
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<tr>
<td>40</td>
<td>60.1</td>
<td>60.0</td>
</tr>
<tr>
<td>40</td>
<td>61.9</td>
<td>62.1</td>
</tr>
</tbody>
</table>

Experiment 2.—Duplicate samples of blood were saturated in separate tonometers, delivered over mercury, and then analyzed for CO₂ in duplicate.
Experiment No.  CO₂ tension.  CO₂ content.

<table>
<thead>
<tr>
<th></th>
<th>Tonometer 1.</th>
<th>Tonometer 2.</th>
<th>Difference</th>
</tr>
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<tr>
<td></td>
<td>vol. per cent</td>
<td>vol. per cent</td>
<td>vol. per cent</td>
</tr>
<tr>
<td>1</td>
<td>58.6</td>
<td>58.6</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>55.0</td>
<td>55.0</td>
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</tr>
<tr>
<td>3</td>
<td>60.0</td>
<td>59.9</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Experiment 3.—CO₂-air mixtures were introduced into tonometers containing a small amount of water, in the manner described in the "Second saturation method." Samples of the gas were then analyzed in a Haldane gas burette and the CO₂ tension was obtained by analysis compared with that calculated by formula from the size of the tonometer, the amount of CO₂ introduced, the amount of air introduced, and the temperature and pressure of both CO₂ and air.

<table>
<thead>
<tr>
<th></th>
<th>Calculated</th>
<th>Observed</th>
<th>Difference</th>
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<tr>
<td></td>
<td>vol. per cent</td>
<td>vol. per cent</td>
<td>vol. per cent</td>
</tr>
<tr>
<td>CO₂</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4.92</td>
<td>4.99</td>
<td>0.07</td>
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<tr>
<td>4.32</td>
<td>4.27</td>
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</tr>
<tr>
<td>4.93</td>
<td>4.83</td>
<td>0.10</td>
<td></td>
</tr>
</tbody>
</table>

Experiment 4.—Blood was withdrawn from the arm vein of J.P. at 10.30 a.m. into a tube containing potassium oxalate. It was then divided into two equal portions. One was kept over mercury, without contact with air, in the tube into which it was originally drawn. The other half was placed in an open beaker. Both samples were chilled at once. The sample in the open beaker was stirred thoroughly.

A sample from each specimen was saturated at once at 38° with 40 mm. CO₂. (Saturation complete at 11.20 a.m.) The remainder of each was allowed to stand chilled until 2 p.m. when samples were again taken and analyzed.

<table>
<thead>
<tr>
<th>Determination No.</th>
<th>Results of analysis:</th>
<th>CO₂ vol. per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Saturated at once, without contact with air ..........</td>
<td>63.0</td>
</tr>
<tr>
<td>2</td>
<td>&quot; &quot; &quot; after preliminary exposure and shaking,</td>
<td>63.3</td>
</tr>
<tr>
<td>1a</td>
<td>&quot; &quot; 2 p.m. without contact with air,</td>
<td>63.1</td>
</tr>
<tr>
<td>2a</td>
<td>&quot; &quot; 2 &quot; after exposure to air in beaker,</td>
<td>63.5</td>
</tr>
</tbody>
</table>
CO₂ Absorption Curve. I

The time of exposure in the 38° water bath was 15 minutes for each saturation. Experiments indicated that 10 minutes were sufficient to effect equilibrium and that 15 minutes were not enough to produce any alteration in the CO₂ capacity of the blood.

After saturation the blood was transferred to sampling tubes over mercury and was centrifugated in completely filled stoppered tubes, from which the plasma was removed to similar sampling tubes with all the precautions to avoid loss of CO₂ described by Austin et al. (1922).

The analyses of blood and plasma for CO₂ were performed in the manner described by Van Slyke and Stadie (1921) in a Van Slyke burette, of the long stem type, graduated in 0.01 cc., water-jacketed and provided with a mechanical shaker (Stadie, 1921). The burettes were calibrated by weight of mercury delivered as suggested by Y. Henderson (1918) for the calibration of Haldane burettes. The calibration was further verified by the analysis of freshly prepared solutions of anhydrous sodium carbonate.

Van Slyke and Stadie (1921) have pointed out that there is a slight reabsorption of CO₂ by the small amount of fluid left in the Van Slyke burette when atmospheric pressure is restored to permit measurement of the gas. Van Slyke obtained only 98.2 per cent of theory in the analysis of carbonate solutions and has introduced a corresponding correction into his last equation for the calculation of CO₂. We have determined this error in a number of Van Slyke burettes and have found that it is constant for any one apparatus, but varies in different instruments. We have, therefore, determined the extent of the error empirically for each instrument and introduced a corresponding correction. Two burettes have been employed in this series of experiments: one has a correction factor of \( \frac{1}{0.986} \), the other of \( \frac{1}{0.977} \). These factors have been verified by three observers to eliminate the possibility of personal variations.

The mean variation in duplicate determinations by this method is less than 0.2 volume per cent and the agreement between specimens exposed in different tonometers has been equally good.

The effect of oxalate on the CO₂ capacity of blood has been a continual source of controversy. Austin et al. demonstrated that in concentrations of less than 0.5 per cent it did not alter the CO₂ capacity of blood. Warburg (1922) agrees with this but adduces evidence that oxalate alters the distribution of CO₂ between the plasma and cells. In the same experiments by Austin et al., however, the CO₂ capacities of plasma from both defibrinated and oxalated blood also were found to be identical.¹ These experiments were carried out with the utmost care with the express purpose of determining the effect of oxalate. In a concentration of 1 per cent, potassium oxalate does alter the CO₂ capacity, but it also produces hemolysis in most specimens of blood. In concentrations of less than 0.5 per cent we are convinced that no such changes occur. In all our experiments

¹ Unpublished data.
the blood was drawn into tubes containing just enough neutral potassium oxalate, crystallized on the walls of the tubes, to give a final oxalate concentration of not less than 0.2 per cent and not more than 0.4 per cent.

The oxygen capacity was determined by a modification of the method of Van Slyke and Stadie devised by Dr. C. Lundsgaard, in which both saturation and analysis are performed in the Van Slyke burette. The method gives results identical with those obtained by the older methods.

Hematocrit determinations were made by means of the ordinary Daland hematocrit fitted to a No. 1 International Equipment Company centrifuge. Duplicate determinations were made on each blood sample and only two pairs of hematocrit tubes were used throughout. Centrifugation at high speed was continued until the cells were transparent. Duplicates varied by less than 1 per cent. Although the absolute values obtained by any hematocrit method are open to question, the relative values here reported are sufficiently accurate for our purposes.

Parsons (1919–20) has pointed out that whether blood or plasma is used for electrometric determination of pH, the value obtained represents the hydrogen ion concentration of the plasma only. In this view Warburg (1922) concurs. It follows naturally that, if proper values for pK₁ are assumed, the pH values calculated from plasma and blood by the Hasselbalch equation, should agree. Van Slyke (1922) estimated the value of pK₁ in plasma and blood as 6.100 and 6.150, respectively. However, when the pH of plasma and that of whole blood are calculated with these pK₁ values no agreement is obtained, as is shown by Columns 11 to 13 of Table III. If there were a constant difference between pK₁ of blood and plasma of 0.05, the values in Column 13 should be constant. On analysis, however, the values are seen to increase with the hemoglobin or cell content of the blood. More careful study reveals the fact that there is a lesser tendency for the difference to vary with pH. These variations are of the same kind as those obtained by Warburg. That there is a valid basis for such an apparent variation of pK₁, Warburg has shown in a careful theoretical and mathematical analysis of the various factors involved in the determination of pH by the Henderson-Hasselbalch equation. There is, according to Warburg, no change in pK₁, itself, for such a change would involve a variation in the dissociation constants of carbonic acid and bicarbonate. There is, however, a change in the factors that go to make up the ratio

2 Personal communication.
If the equation is written in logarithmic form it is clear why such corrections cause an apparent change in $pK_1$. If we assume a correction factor for $[BHCO_3]$, $m$, and one for $[H_2CO_3]$, $n$, this equation will read:

$$pH = pK_1 + \log [BHCO_3] + \log m - (\log [H_2CO_3] + \log n)$$

These two corrections can be combined with $pK_1$.

$$pH = (pK_1 + \log m - \log n) + \log [BHCO_3] - \log [H_2CO_3]$$

or

$$pH = pK_1' + \log [BHCO_3] - \log [H_2CO_3]$$

If $pK_1$ in plasma is constant, the pH of plasma can be determined from the CO$_2$ content of whole blood at known tension if some means can be devised to calculate the $[BHCO_3] : [H_2CO_3]$ ratio in plasma from that in whole blood. By the mathematical treatment of data collected from the literature and from experiments of his own, Warburg derived an equation by which he believed the $[BHCO_3] : [H_2CO_3]$ ratio and therefore the pH of plasma could be calculated from the CO$_2$ content, CO$_2$ tension, and hemoglobin concentration of whole blood. He also presents a graphic chart to facilitate the calculation. Warburg's correction factors were developed largely from the results of experiments on horse blood at room temperature. On the basis of a few experiments on human blood at 38°C, and the data of Joffe (1920–21) he concluded that horse blood at room temperature was very similar to human blood at body temperature in its reaction to CO$_2$. When Warburg's correction factors were applied to our experiments the results were highly unsatisfactory. Furthermore, an attempt to derive a new set of correction factors by means of Warburg's equation proved unsuccessful. A graphic chart (Chart 4) has, however, been constructed which permits the calculation of plasma pH from blood CO$_2$. Our inability to utilize Warburg's equation for the development of correction factors does not necessarily imply any error in the principles on which this equation was developed. The mathematical develop-
ment of the equation is unquestionably logical; but certain assump-
tions which Warburg has made with regard to the variables in the
equation are not in agreement with the experimental values here
presented. In order to make this clear it is necessary to consider
certain aspects of Warburg's theory, but it is not necessary, for
our purposes, to follow all the steps of his mathematical treatment.

In brief the problem which presents itself is to predict the
$[\text{BHC}_3]:[\text{HLJOS}]$ ratio of plasma from that of blood. In this
ratio $[\text{H}_2\text{CO}_3]$ is calculated as dissolved CO$_2$ by the equation

$$\frac{p_{\text{CO}_2}}{760} = [\text{H}_2\text{CO}_3]$$

(7)

in which $\alpha$ is the solubility coefficient, and

$$[\text{BHC}_3] = \text{Total CO}_2 - [\text{H}_2\text{CO}_3]$$

(8)

Bohr (1905) found the relative solubility coefficient for CO$_2$
in plasma to be 0.975, so that $\alpha_{\text{plasma}} = 0.975 \times \alpha_{\text{water}}$. The
relative solubility coefficient for CO$_2$ in whole blood was somewhat
lower and has been fixed by most workers at 0.91 to 0.92. War-
burg points out that it is not proper to use a mean solubility
coefficient for the calculation of the dissolved CO$_2$ in blood. Blood
is a mixture of cells and plasma and the solubility coefficient in
blood will depend on the relative amounts of plasma and cells
present.

According to Bohr, the relative solubility coefficient for CO$_2$
in red blood cells is 0.81. By applying this value and using
hematocrit determinations to measure the relative amounts of
cells and plasma one should obtain a more exact solubility coeffi-
cient for whole blood. For our purposes, in which all work is
done at constant temperature, a simple equation has been devised.

$$\begin{align*}
\alpha_{\text{CO}_2 (\text{water})} \text{ at } 38^\circ\text{C.} &= 0.555 \text{ (Bohr)} \\
\alpha_{\text{CO}_2 (\text{plasma})} \text{ at } 38^\circ\text{C.} &= 0.975 \times 0.555 \\
\alpha_{\text{CO}_2 (\text{cells})} \text{ at } 38^\circ\text{C.} &= 0.810 \times 0.555
\end{align*}$$

The amount of CO$_2$ dissolved in a unit of blood is

$$0.555 \frac{p_{\text{CO}_2}}{760} \left[0.975 \text{ (volume of plasma)} + 0.81 \text{ (volume of cells)}\right] = [\text{H}_2\text{CO}_3]$$

(9)
If we call the volume of cells, c, the volume of plasma = 1-c and we get
\[
\frac{0.555}{760} (0.975 (1 - c) + 0.81 c) \rho_{CO_2} = [H_2CO_3]
\]
This can be simplified to
\[
(0.7118 - 0.1205 c) \rho_{CO_2} = [H_2CO_3]
\]
By means of Chart 1 the CO₂ dissolved in blood with different proportions of cells can be obtained at sight.

**CHART 1.** For the determination of CO₂ dissolved in blood with varying cell volume. Oxygen capacity divided by 0.45 may be used instead of cell volume.

Warburg estimates the average ratio of oxygen capacity to cell volume in human blood at 0.48. Our own determinations fix this ratio at 0.465 at an average pH of 7.3. Our values agree better
than Warburg's with other estimates found in the literature. By dividing the oxygen capacity by 0.465 one can obtain the corresponding value for cell volume and this value can be used to derive the dissolved CO₂ from Chart 1 or equation (10).

The true value of [BHC0₃] in blood is obtained by subtracting from the total CO₂ found the [H₂CO₃] value indicated by Chart 1. It remains to find the relation between the [BHC0₃] of whole blood and that of plasma. This relation is defined by Warburg's equation

\[
[BHC0₃]_{\text{plasma}} = [BHC0₃]_{\text{blood}} \times \frac{100}{100 - Q (1 - D)}
\]  

(11)

where \(Q\) = the cell volume in volumes per cent and \(D\) = the ratio \([BHC0₃]_{\text{cells}}/[BHC0₃]_{\text{plasma}}\). In this equation \(D\) is unknown and it remains to determine it or to see how closely it can be predicted. Warburg considers that the pH of the blood is the chief determinant of the value of \(D\) and he has determined the relation of \(D\) to pH. That \(D\) varies with pH in our experiments, also, is evident from Chart 2 in which the abscissa represents the pH of plasma and the ordinate the reciprocal of \(D\). (We have used the reciprocal of \(D\) instead of \(D\) because it gives a better distribution of points and brings the relation out more clearly.) The deviations from the mean line, AB, are, however, considerable and suggest that there are variable factors other than the pH which influence the value of \(D\).

Many of the experiments of this series were done on blood from patients with diseases which produced obvious changes in other substances in the blood than CO₂. It seemed possible that the scattering was due to such pathological changes. One or two of the extreme deviations seemed to support this view, but the remainder showed little more scattering among pathological bloods than among normal bloods. A comparison of the experiments in which only one point of the absorption curve was determined and those in which two points were determined revealed an interesting anomaly. The change in \(D\) observed in the two point experiments was always less than would have been expected if \(D\) varied according to the statistical average AB, derived from the mean of the whole group of the experiments. This is shown in Chart 2.
where the changes in the two point experiments are represented by the fine lines. In no case is the slope of one of these lines as great as the slope of the line AB.

In studies of the respiratory function and gaseous equilibrium of the blood it is often more useful to know the oxygen capacity than the cell volume. If the oxygen capacity is to be used for the calculation of the difference between the [BHCO₃] of blood and that of plasma, instead of the hematocrit value, Q in equation (11) also becomes a variable. Hamburger (1902) demonstrated that the cell volume of blood was not a constant, but varied with changes in pH. This observation has been repeatedly confirmed and is evidenced in the two point experiments of this series. Warburg has studied the relation of cell volume to pH in horse blood and has substituted the values thus derived for Q in equation (11). These values he admits are not exactly applicable to human blood; but the error thus introduced he considers negligible.
Chart 3 shows the relation of hematocrit values to pH in our series of experiments. In this chart the abscissa represents pH, the ordinate the ratio of oxygen capacity to cell volume. Although statistical treatment shows a slight tendency for the cell volume to increase as the pH falls, the scattering is so great that no mean curve drawn from these data would be of any value. It seems hardly possible to ascribe these variations to errors in hematocrit determinations alone, because in the two point curves the change in cell volume was consistently obtained.

If neither D nor Q in equation (11) can be predicted with certainty it is clear that Warburg's equation, though in itself correct, cannot be used for the calculation of the apparent difference between pK₁ of blood and that of plasma. It may be added that Warburg's correction factors gave a greater error than did his equa-
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tion with mean values of Q and D derived from our data. This was to be expected because our values for Q and D are entirely different from his. It remained to devise empirical correction factors. The observed differences between log \([\text{BHCO}_3^-] \) in whole blood and in plasma, which we have called \(\Delta \text{pK}_1 \), do, as we have said, show a definite tendency to increase as the oxygen capacity increases and a lesser tendency to increase with increasing pH.

The relation of \(\Delta \text{pK}_1 \) to cell volume alone was first estimated by the method of group averages. The results are shown in

<table>
<thead>
<tr>
<th>Group No.</th>
<th>No. of points</th>
<th>Range of cell volume variation</th>
<th>Average cell volume</th>
<th>Average pH</th>
<th>Average (\Delta \text{pK}_1 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>4</td>
<td>14.7 to 19 vol. per cent</td>
<td>15.9</td>
<td>7.141</td>
<td>+0.005</td>
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<td>II</td>
<td>7</td>
<td>20 to 29 vol. per cent</td>
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<td>+0.016</td>
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<tr>
<td>III</td>
<td>26</td>
<td>30 to 39 vol. per cent</td>
<td>36.8</td>
<td>7.276</td>
<td>+0.036</td>
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<tr>
<td>IV</td>
<td>31</td>
<td>40 to 49 vol. per cent</td>
<td>43.6</td>
<td>7.308</td>
<td>+0.049</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group No.</th>
<th>pH</th>
<th>No. of points</th>
<th>Average pH</th>
<th>Difference between high and low pH averages</th>
<th>Difference in average (\Delta \text{pK}_1 )</th>
<th>Change in (\Delta \text{pK}_1 ) per 0.1 pH.</th>
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</thead>
<tbody>
<tr>
<td>III</td>
<td>&lt;7.3</td>
<td>11</td>
<td>7.167</td>
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<td>7.356</td>
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<tr>
<td>IV</td>
<td>&lt;7.3</td>
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<td>7.242</td>
<td>0.124</td>
<td>0.008</td>
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<td>7.366</td>
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</table>

Table I. There can be no doubt that \(\Delta \text{pK}_1 \) varies with the cell volume. Groups III and IV were then divided into two subgroups each, according as the pH lay above or below 7.3. The results are shown in Table II. Here again there is an unmistakable relation. The difference is, as far as can be judged from these figures, practically constant between cell volumes of 30 and 50. Below this there are not sufficient points to permit the analysis of the variation with respect to pH.

The mean values obtained for Groups III and IV in Table I were corrected by the corrections from Table II to a pH of 7.3,
and a straight line was drawn through these points from the cell volume line 30 to the cell volume line 50 (Chart 4). Lines parallel to this and 0.006 apart were then drawn to represent pH variations from 7.5 to 7.0. Below 30 volumes per cent of cells the number of observations were so small that any continuation of the lines was open to suspicion. The broken lines in Chart 4 were therefore drawn to conform to the values shown for Groups I and II in Table I and the pH corrections from Table II were continued. This undoubtedly involves an error; but the substitution of another correction value would have been purely arbitrary. (In order to make the upper portion of the curves meet the dotted prolongations it was necessary to curve the former somewhat. The alteration from the straight line form, however, at no point exceeds 0.001 pH.)

**DISCUSSION.**

Comparison of the observed values of ΔpK\(_1\) and those obtained by means of Chart 4 is shown in the last three columns of Table III. The average deviation of all the experiments is ± 0.007. The average deviation of the 57 observations with cell volume of over 30 is the same. In the experiments with high cell volume the deviations are evenly scattered: the total of the negative deviations is 197 against 204 for the positive deviations. The calculated values in the experiments with low cell volume, on the other hand, show a definite tendency to lie too high.

Although the data available are too scanty to warrant an attempt to correct the lower portions of the curves, something of the probable nature of such corrections may be predicted. The [BHCO\(_3\)] concentration in the cells has never been observed to exceed the [BHCO\(_3\)] concentration in the plasma, if we except a few experiments by Haggard and Henderson (1920-21). Furthermore, all observers have agreed that the pH of the cell contents is lower than that of the plasma. That this should be the case is in keeping also with Donnan's (1911) equilibrium theory. But, if the pH and [BHCO\(_3\)] concentration are always lower in the cells than in the plasma, ΔpK\(_1\) must always have a positive value. In order that this may be so, the differentials \(\frac{d\Delta pK_1}{d\Delta pH}\) and \(\frac{d\Delta pK_1}{d (\text{cell volume})}\) must diminish as their denominators approach zero and the pro-
longations of the lines at low oxygen capacity and low pH will
tend to converge and to approach the base line as an asymptote.
The chart is offered not as a final evaluation of the variations
of ΔpK₁ and the determinants of these variations, but as the
closest approximation as yet available. Such an approximation
is essential to the proper interpretation of other data dealing
with blood electrolyte equilibria. The relative accuracy of
different portions of the chart is very variable. The portion
indicated by solid lines is reasonably certain, the remainder is
open to grave doubt, although it can be accepted as an expression
of a general tendency. The material necessary to fill in the gaps
in the chart can be accumulated only slowly, even in an active
medical clinic. Recourse could be had to the artificial production
of anemia and acidosis or alkalosis, either in vitro or in vivo; but
this is not in keeping with the purpose of this work.

This raises the whole question of the propriety of drawing
conclusions with regard to chemical and physiological constants
from pathological blood. The answer to this is clear. Unless
one turns to pathological blood one cannot study the effects of
changes in the cell concentration or the pH of blood. Blood
which has been depleted of its cells or rendered more acid by
experimental methods, either in vivo or in vitro, is no more normal
than the blood from a patient with severe primary or secondary
anemia. Moreover, one of the necessary functions of the clinical
chemist is to determine to what extent the results of normal
control work can be applied to pathological material.

Something must be said about the method of constructing the
correction chart. At first sight the method pursued by Warburg
seems less empirical. Closer analysis shows that this is only an
apparent distinction and Warburg has only obscured his empiri-
cism by mathematics. The importance of Warburg's contri-
bution to the clarification of the mathematical theory of the
Henderson-Hasselbalch equation cannot be belittled; but his
equations involve complicated variable functions, the variations
of which can only be determined by experiment. Warburg's
equation depends upon the proper estimation of the variation of the
distribution of bicarbonate between cells and plasma. The uncer-
tainty of this variation appears from Chart 2. The distribution
coefficient is, in itself, a factor quite as complex as ΔpK₁ and its
variability in these experiments is quite as great. The correlation obtained by comparing $\Delta pK_1$ directly with cell volume and pH is also far better than that obtained by Warburg's more devious method.

**Chart 4.** In Hasselbalch's equation (2) $[\text{BHCO}_3] = \text{Total CO}_2 - \text{dissolved CO}_2$ and $[\text{H}_2\text{CO}_3] = \text{dissolved CO}_2$.

Dissolved CO$_2$ may be derived by equation (9) or obtained from Chart 1, and subtracted from the total CO$_2$ found by analysis, to give $[\text{BHCO}_3]$. Log $[\text{BHCO}_3] - \log$ (dissolved CO$_2$) is then determined and is added to 6.100, the value of $pK_1$ for plasma at 38°C. To the value thus obtained for pH is added the amount indicated in Chart 4 for the corresponding cell volume and pH.

For example, if log $[\text{BHCO}_3] - \log$ (dissolved CO$_2$) = 1.200 and the cell volume of the blood is 40 volumes per cent, the pH uncorrected will be 6.100 + 1.200 = 7.300. The corrected factor for pH = 7.3 and cell volume = 40 is found from Chart 4 to be +0.047. Therefore, the corrected pH will be 7.347.
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<td>61.75</td>
<td>73.60</td>
<td>3.97</td>
<td>4.27</td>
<td>57.48</td>
<td>69.33</td>
<td>7.261</td>
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<tr>
<td>29</td>
<td>30</td>
<td>12.38</td>
<td>30.3</td>
<td>23.75</td>
<td>25.70</td>
<td>2.03</td>
<td>2.14</td>
<td>21.72</td>
<td>23.56</td>
<td>7.129</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>12.38</td>
<td>29.3</td>
<td>33.90</td>
<td>36.50</td>
<td>4.07</td>
<td>4.27</td>
<td>29.83</td>
<td>32.23</td>
<td>6.965</td>
</tr>
</tbody>
</table>

**TABLE III—Concluded.**
Throughout this discussion nothing has been said of the actual value of \( pK_1 \). The value of 6.100 for the \( pK_1 \) of plasma has been accepted as a constant. How far such an assumption is justified can only be determined by electrometric methods.

CONCLUSIONS.

The \( CO_2 \) content of both blood and plasma and the oxygen capacity and cell volume of blood exposed to known mixtures of air and \( CO_2 \) have been determined.

These data support the contention of Warburg that \( pK_1 \) of the Henderson-Hasselbalch equation shows an apparent variation with hemoglobin concentration and with \( pH \).

Warburg's correction factors have, however, proved unsatisfactory when applied to the data of these experiments.

A quantitative estimation of the variations of \( pK_1 \) has been made and a series of curves has been presented by means of which corrections can be made.

By means of these curves the \( pH \) of plasma can be predicted from the \( CO_2 \) content and \( CO_2 \) tension of whole blood with a mean error of less than \( \pm 0.01 \) \( pH \).

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John P. Peters, Harold A. Bulger and Anna J. Eisenman


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