

BUFFERING OF BLOOD PLASMA**

Buffering of the blood plasma in man depends upon the red blood cells, chemical buffers of the blood and tissue cells, respiratory system, and the kidneys. It is the purpose of this paper to give some quantitative estimates of the role of these factors in maintaining the pH of blood plasma.

Addition of nonvolatile acids or alkalies. Within the physiological range, the changes in the bicarbonate concentration of true plasma (plasma in contact with red blood cells) as caused by altering the $p\text{CO}_2$ appears to be proportional to the pH change[†] and can be expressed as:

$$\text{HCO}_3^- = -a \text{pH} + b \quad (1)$$

where a and b are constants. If a nonvolatile acid is added, it is possible to maintain the same pH by reducing the $p\text{CO}_2$. When this occurs, all of the added acid (if it is completely dissociated) is buffered by the HCO_3^- system and the reaction can be written as:



As used here, the symbol H_2CO_3 refers to the sum of the hydrated and nonhydrated forms of physically dissolved carbon dioxide. Other buffer systems have no net participation. This can be shown by one form of the Henderson-Hasselbalch equation:

$$\text{pH} = \text{pK}' + \log \frac{\text{Total conc.} - \text{Acid conc.}}{\text{Acid conc.}} \quad (3)$$

where pK' is the pK' of the weak acid, Acid conc. is the concentration of the weak acid, and Total conc. is the concentration of the anion of the weak acid not only in the free dissociated form but also in the undissociated form as the acid. This equation contains the three variables, pH, Total conc., and Acid conc. If the Total conc. remains the same, and if the pH is held constant by adjustments of $p\text{CO}_2$, then the Acid conc. is also not changed and there is no net participation of the buffer system. The millimoles of HCO_3^- must

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** This work was supported by the U.S. Public Health Service, Grant No. A-2669.
 Received for publication September 9, 1959.

therefore be reduced by the milliequivalents of acid added. The new relationship between the HCO_3^- concentration and pH can be represented as:

$$\text{HCO}_3^- = -a \text{ pH} + b - A \quad (4)$$

where A is the concentration (in mEq/L) of the added acid (assuming the acid is completely dissociated). The concentration of the acid should be in terms of mEq/L blood water. (The Donnan equilibrium causes a slight unequal distribution of diffusible ions across the red cell membrane and for this purpose can be neglected.) Blood is composed of approximately equal volumes of red cells and plasma.² Therefore the amount of protein in the blood is equal to the average of the amount of protein in the red cells and in plasma. Since the protein in the red cells and plasma is respectively 35 per cent² and 6 per cent,² the protein or solid phase in the blood is 20 per cent. The remainder or 80 per cent of the blood is essentially water and therefore there are 0.8 liters of blood water per liter of blood. The buffer value " β "²² can then be obtained by differentiating equation (4) with respect to pH:

$$\beta = -\frac{dA}{d \text{ pH}} = a + \frac{d \text{ HCO}_3^-}{d \text{ pH}} \quad (5)$$

The value of $\frac{d \text{ HCO}_3^-}{d \text{ pH}}$ can be obtained by the use of the Henderson-Hasselbalch equation:

$$\text{pH} = \text{pK}' + \log \frac{\text{HCO}_3^-}{\text{H}_2\text{CO}_3} = \text{pK}' + \frac{1}{2.3} \ln \frac{\text{HCO}_3^-}{\text{Total CO}_2 - \text{HCO}_3^-} \quad (6)$$

where the $\text{Total CO}_2 = \text{H}_2\text{CO}_3 + \text{HCO}_3^-$. By substitution, the following are obtained:

$$\beta = a + \frac{2.3 (\text{H}_2\text{CO}_3) (\text{HCO}_3^-)}{\text{Total CO}_2} + \frac{\text{HCO}_3^-}{\text{Total CO}_2} \frac{d \text{ Total CO}_2}{d \text{ pH}} \quad (7)$$

$$\beta = a + 2.3 (\text{HCO}_3^-) + \frac{\text{HCO}_3^-}{\text{H}_2\text{CO}_3} \frac{d \text{ H}_2\text{CO}_3}{d \text{ pH}} \quad (8)$$

If the system is not in contact with a gas phase, then the Total CO_2 does not change, and equation (7) becomes:

$$\beta_{\text{tc}} = a + \frac{2.3 (\text{H}_2\text{CO}_3) (\text{HCO}_3^-)}{\text{Total CO}_2} \quad (9)$$

where β_{tc} is the buffer value due to the total chemical buffers. For a bicarbonate solution, the value of "a" is equal to zero within the physiological range and so:

$$\beta_b = \frac{2.3 (\text{HCO}_3^-) (\text{H}_2\text{CO}_3)}{\text{Total CO}_2} \quad (10)$$

where β_b is the buffer value due to bicarbonate. The value of "a" therefore represents the buffer value of the chemical buffers excluding HCO_3^- and so $a = \beta_c =$ buffer value of chemical buffers excluding bicarbonate.

For a phosphate solution, it can be similarly shown by differentiating the Henderson-Hasselbalch equation that the buffer value is:

$$\beta_p = \frac{2.3 (\text{H}_2\text{PO}_4^-) (\text{HPO}_4^-)}{\text{H}_2\text{PO}_4^- + \text{HPO}_4^-} \quad (11)$$

where β_p is the buffer value due to phosphate.

If the system is equilibrated in contact with a gas phase, then the value of $\frac{d \text{ Total CO}_2}{d \text{ pH}}$ will depend upon the $p\text{CO}_2$, since H_2CO_3 is proportional to the $p\text{CO}_2$ (Henry's Law). The buffer value due to the presence of a gas phase, β_g , can be obtained by subtracting equation (9) from equation (7):

$$\beta_g = \frac{\text{HCO}_3^-}{\text{Total CO}_2} \frac{d \text{ Total CO}_2}{d \text{ pH}} \quad (12)$$

Thus, the total buffer value is equal to the sum of the individual components:

$$\beta = \beta_c + \beta_b + \beta_g = \beta_{tc} + \beta_g \quad (13)$$

For average arterial true plasma,² $a = 21.6 \text{ mM/pH}$, $\text{HCO}_3^- = 24.0 \text{ mM}$, $\text{H}_2\text{CO}_3 = 1.2 \text{ mM}$, $\text{Total CO}_2 = 25.2 \text{ mM}$, $\text{pH} = 7.40$, and $p\text{CO}_2 = 40 \text{ mm Hg}$. The value of β_c is therefore equal to 21.6 mEq/L-pH (mEq/L per pH unit). For separated arterial plasma (plasma not in contact with red cells), $a = 5.4 \text{ mM/pH}^2$, and so the value of β_c for the plasma is 5.4 mEq/L-pH , and the remainder, 16.2 mEq/L-pH , is the β_c for the red cells. It can be estimated from normal plasma ranges²⁸ that $\text{H}_2\text{PO}_4^- = 0.24 \text{ mM}$ and $\text{HPO}_4^- = 0.96 \text{ mM}$, and so β_p only amounts to 0.4 mEq/L-pH . The buffer value of plasma protein is determined by difference and amounts to 5.0 mEq/L-pH . The value of β_b is only 2.6 mEq/L-pH . These values of β_c and β_b agree with those originally obtained by Van Slyke,²¹ and point out that most of the chemical buffering in whole blood is due to the red blood cells.⁹

If the system is in contact with a gas phase of infinite volume, then the value of H_2CO_3 must be constant according to Henry's Law at equilibrium and by definition, $\beta_{gA} =$ buffer value due to a gas phase at a constant $p\text{CO}_2$. Another buffer value, β_{gR} can be defined as:

$$\beta_{gR} = \beta_g - \beta_{gA} = \beta - \beta_A \quad (14)$$

where β_A is the total buffer value of the system at a constant $p\text{CO}_2$. Since $\frac{d \text{H}_2\text{CO}_3}{d \text{pH}}$ is zero under this condition, equation (8) reduces to:

$$\beta_A = a + 2.3 (\text{HCO}_3^-) \quad (15)$$

Substitution of equation (7), equation (12), and equation (15) into equation (14) leads to:

$$\beta_{gA} = 2.3 \frac{(\text{HCO}_3^-)^2}{\text{Total CO}_2} \quad (16)$$

Similarly, substitution of equation (8) and equation (15) into equation (14) results in:

$$\beta_{gR} = \frac{\text{HCO}_3^- \frac{d \text{H}_2\text{CO}_3}{d \text{pH}}}{\text{H}_2\text{CO}_3} \quad (17)$$

For arterial true plasma, β_A is equal to 76.8 mEq./L-pH and β_{gA} is equal to 52.6 mEq./L-pH. *In vivo*, the respiratory system controlling alveolar ventilation (and thus the $p\text{CO}_2$) represents β_g . Essentially the respiratory system acts by liberating H_2CO_3 when an acid is added and by accumulating H_2CO_3 when an alkali is added. Thus, if alveolar ventilation is not changed, β_A represents the total blood buffer value and occurs when the respiratory system does not respond to changes in pH.

If the alveolar ventilation is controlled so that there is no change in pH, then the values of $\frac{d \text{Total CO}_2}{d \text{pH}}$, $\frac{d \text{H}_2\text{CO}_3}{d \text{pH}}$, β_{gR} , β_g , and β become infinite.

This would occur if the respiratory system is sensitive to changes only in pH and not in $p\text{CO}_2$. The value of β_{gR} represents the ventilation adjustment *in vivo* and actually depends upon the sensitivity of the respiratory system to pH and $p\text{CO}_2$. In order to determine β_{gR} , it is necessary to know the *in vivo* relationship between H_2CO_3 and pH. This relationship (produced by a nonrespiratory disturbance) has been determined by Gray¹⁴ and, expressed in units appropriate to this development, is:

$$\text{pH} = 9 - \log \frac{5.48 + 82 (\text{H}_2\text{CO}_3) - 39.5 (\text{H}_2\text{CO}_3)^2}{\text{H}_2\text{CO}_3} \quad (18)$$

By differentiation, $\frac{d \text{H}_2\text{CO}_3}{d \text{pH}}$ can be obtained and then the value of β_{gR} can be found by substitution into equation (17):

$$\beta_{gR} = \frac{2.3 (\text{HCO}_3^-) [5.48 + 82 (\text{H}_2\text{CO}_3) - 39.5 (\text{H}_2\text{CO}_3)^2]}{5.48 + 39.5 (\text{H}_2\text{CO}_3)^2} \quad (19)$$

The value of β_{gR} is equal to 41.6 mEq./L-pH. Table 1 summarizes the

various components of the buffer value in blood and illustrates that most of the buffering is done by the respiratory system.

Addition or removal of H₂CO₃. The H₂CO₃ can be increased by a decreased alveolar ventilation or by an increase in carbon dioxide production by the cells or a combination of both. (Or of course, by an increase of

TABLE 1. COMPONENTS OF THE BUFFER VALUE OF HUMAN BLOOD

System	β in mEq/L-pH	% of total	
		No vent. adjust.	With vent. adjust.
Total chemical buffers of			
plasma in whole blood (β_{tc})	24.2	31	20
Plasma bicarbonate (β_b)	2.6	3	2
Excluding bicarbonate (β_c)	21.6	28	18
Red blood cell phase	16.2	21	14
Plasma phase	5.4	7	4
Plasma protein	5.0	6	4
Plasma phosphate (β_p)	0.4	1	0
Respiratory system (β_r)	94.2	...	80
No ventilation adjustment (β_{rA})	52.6	69	45
Change in ventilation (β_{rR})	41.6	...	35
Blood buffer value with no ventilation adjustment (β_A)	76.8	100	65
Total blood buffer value with ventilation adjustment (β)	118.4	...	100

the environmental carbon dioxide.) Equation (1) must still be valid even after addition of H₂CO₃. The net addition of H₂CO₃ (represented by d G) will result in an actual change in the H₂CO₃ and HCO₃⁻, so that, neglecting carbamino formation (which is very small at a constant partial pressure of oxygen²), the following must hold:

$$d G = d H_2CO_3 + d HCO_3^- \tag{20}$$

Differentiation of equation (20) with respect to pH, results in:

$$\beta_{ha} = - \frac{d G}{d pH} = - \frac{d H_2CO_3}{d pH} - \frac{d HCO_3^-}{d pH} \tag{21}$$

where β_{ha} is the buffer value when the acid involved is H₂CO₃. Equation (4) can be rewritten as:

$$\text{HCO}_3^- = -a \text{ pH} + b - X \quad (22)$$

where X is the concentration of a nonvolatile acid added. The value of $\frac{d \text{HCO}_3^-}{d \text{pH}}$ can be obtained by differentiating equation (22) with respect to pH :

$$\frac{d \text{HCO}_3^-}{d \text{pH}} = -a - \frac{d X}{d \text{pH}} \quad (23)$$

Differentiation of the Henderson-Hasselbalch equation (6) with respect to pH gives:

$$\frac{d \text{H}_2\text{CO}_3}{d \text{pH}} = \frac{\text{H}_2\text{CO}_3}{\text{HCO}_3^-} \frac{d \text{HCO}_3^-}{d \text{pH}} - 2.3 \text{H}_2\text{CO}_3 \quad (24)$$

The resulting equations obtained by substitution of equation (23) into equations (21) and (24) can be combined to yield:

$$\beta_{\text{na}} = \left(1 + \frac{\text{H}_2\text{CO}_3}{\text{HCO}_3^-} \right) \left(a + \frac{d X}{d \text{pH}} \right) + 2.3 (\text{H}_2\text{CO}_3) \quad (25)$$

Equation (25) can be simplified to:

$$\beta_{\text{na}} = \left(a + \frac{d X}{d \text{pH}} \right) \frac{\text{Total CO}_2}{\text{HCO}_3^-} + 2.3 (\text{H}_2\text{CO}_3) \quad (26)$$

If a pH increase due to a decrease in H_2CO_3 is greater than a pH decrease due to an addition of a nonvolatile acid, then there will be a net increase in pH ; and thus the value of $\frac{d X}{d \text{pH}}$ will be positive and add to the buffer value. The value of $\frac{d X}{d \text{pH}}$ will be positive when there is either a net removal of a nonvolatile acid in the presence of a decreased pH or a net addition of a nonvolatile acid in the presence of an increased pH .

For the situations in which no nonvolatile acids (or alkalis) are added, then $\frac{d X}{d \text{pH}} = 0$ and equation (26) becomes:

$$\beta_{\text{h}} = a \frac{\text{Total CO}_2}{\text{HCO}_3^-} + 2.3 (\text{H}_2\text{CO}_3) \quad (27)$$

where β_{h} is the buffer value when the acid involved is H_2CO_3 and no nonvolatile acids (or alkalis) are added. For average arterial true plasma,³ $a = 21.6 \text{ mM/pH}$, $\text{HCO}_3^- = 24.0 \text{ mM}$, $\text{H}_2\text{CO}_3 = 1.2 \text{ mM}$, and $\text{Total CO}_2 = 25.2 \text{ mM}$. Thus, $\beta_{\text{h}} = 25.4 \text{ mEq/L-pH}$. For a bicarbonate solution, containing the same CO_2 concentrations, the value of a is zero, and thus the value of β_{h} is then equal to only 2.8 mEq/L-pH . Again the importance

of α , which represents the buffer value of chemical buffers excluding bicarbonate, is demonstrated in buffering.

If there is also a net removal (or gain) of nonvolatile acid caused by either the tissue cells or kidney or both, then the value of $\frac{dX}{d\text{pH}}$ does not equal zero, and can approach infinity (when there is no change in pH). Although, the kidney cannot remove acid rapidly enough to overcome an effect due to an acute respiratory disturbance (producing a H_2CO_3 change), it is to be pointed out that given a sufficient period of time, the buffer value due to the kidney can approach infinity (as evidenced by a normal pH in spite of a sustained respiratory disturbance). Such a situation occurs in the response to high altitude when the alveolar ventilation is increased, but the kidneys have eliminated sufficient bicarbonate until essentially the pH is returned to about normal.⁸ Also in chronic pulmonary insufficiency, the data indicate that the pH is within a normal range in spite of high partial pressure of carbon dioxide.¹⁸

Factors concerned in the in vivo regulation of the pH of blood plasma. The relationship between the alveolar ventilation and the pCO_2 is given by¹⁹:

$$\dot{V}_A = \frac{863 R \dot{V}_{\text{O}_2\text{S}}}{P_{\text{ACO}_2}} \quad (28)$$

where \dot{V}_A is the (expired) alveolar ventilation in ml/min, $\dot{V}_{\text{O}_2\text{S}}$ is the oxygen uptake in ml/min (corrected to standard condition, i.e., temperature = 0° C. and pressure = 1 atm), P_{ACO_2} is the alveolar partial pressure of CO_2 , and R is the ratio of the carbon dioxide output in ml/min to the oxygen uptake in the same units. This equation assumes that the pCO_2 of the environment is equal to zero. If the carbon dioxide output is constant, then the product (R) ($\dot{V}_{\text{O}_2\text{S}}$) is constant, and thus the alveolar ventilation is inversely proportional to the P_{ACO_2} . Factors which tend to prevent equilibrium between arterial blood and the gas alveolar phase¹⁸ are (i) diffusion, (ii) venous arterial shunts, and (iii) unequal ventilation-blood flow ratios in the various alveoli. These factors will tend to increase the concentration of the physically dissolved carbon dioxide in the arterial blood assuming equilibrium with the alveolar tension. Actual measurements do not demonstrate any carbon dioxide change,¹⁸ but the reason for this is that the method for detecting such a change is not sensitive enough. (The actual concentration of the physically dissolved gas is many times recorded as the partial pressure of the gas in a gas phase which would be in equilibrium with the liquid phase.) Thus, within experimental error, the P_{ACO_2} can be

assumed to be in equilibrium with the arterial blood, and thus the H_2CO_3 (in the arterial plasma) will be proportional to the $P_{\text{A}\text{CO}_2}$.

During the unsteady state in which the carbon dioxide output is not constant, then the simple reciprocal relationship between the $P_{\text{A}\text{CO}_2}$ and \dot{V}_{A} will not be valid. The actual concentration of H_2CO_3 in the plasma will depend upon the rate of release of the H_2CO_3 from the large body carbon dioxide reservoir⁷ and the rate of removal of the H_2CO_3 , mainly by the respiratory system. If the respiration is stopped for a short time (breath holding), then the arterial concentration of H_2CO_3 will increase exponentially to the venous concentration of H_2CO_3 .⁸ Under physiological conditions, steady states of carbon dioxide occur relatively rapidly due to the rapidity of the respiratory adjustments and the easily available tissue carbon dioxide stores.⁷

Shifts of hydrogen ions (either dissociated or nondissociated) can occur across cell membranes and account for a considerable amount of buffering. In order to preserve electrical neutrality, a shift of hydrogen ions into a cell must also be accompanied by a shift of anions out of the cell or a shift of cations into the cell or some combination of these shifts. The hydrogen ion once inside the cell could be removed by buffers, such as protein, which would accept hydrogen ions rapidly. The rate of removal of hydrogen ions by the cells would therefore be limited by the rate of ion transport across the cell membrane. For the red blood cell, the ion shift equilibrates in a couple of seconds and is due to chloride ions⁴; whereas for muscle cell, the ion shift is due mainly to potassium ions.¹⁰ There is also a sodium ion shift from bone and tendon.¹⁵ The following equation can be used to obtain an estimate of the total chemical buffer value of the body:

$$\beta_{\text{B}} = \frac{(\beta_{\text{tc}})(V_{\text{b}}) + (\beta_{\text{t}})(V_{\text{t}})}{V_{\text{b}} + V_{\text{t}}} = \frac{\beta_{\text{tc}} + (\beta_{\text{t}})(S)}{1 + S} = \frac{\beta_{\text{tcb}}}{1 + S} \quad (29)$$

where β_{B} is the total chemical buffer value of the body per unit volume of total body water, β_{t} is the chemical buffer value of tissue (excluding bicarbonate), V_{b} is the blood water volume, V_{t} is the tissue water volume (including interstitial water), S is the ratio of V_{t} to V_{b} , and β_{tcb} is the total chemical buffer value of the body per unit volume of blood water. In obtaining the percentage contributions of the various buffer components, it is important that each buffer value component is calculated using the same volume. Although the total buffer value will depend upon the volume used, the percentage contribution of the buffer components will not depend upon the volume. It has been estimated that the tissue phase contributes about five times as much as the blood phase in buffering.^{17, 22} Thus, the ratio of $(\beta_{\text{t}})(S)$

to β_{tc} is equal to 5. Since about 8 per cent of the body is composed of blood²³ (8 liters blood per 100 kilogram body weight) and since 80 per cent of the blood is water, it follows that 6.4 per cent of the body is blood water (V_b). About 70 per cent of the body is composed of water ($V_b + V_t$),²¹ and so V_t is about 63.4 per cent. The value of S is therefore about 10, and so the ratio of β_t to β_{tc} must be equal to about 0.5. The measured chemical buffer values (excluding bicarbonate) of frog muscle and blood are respectively 6.1 mEq/kg-pH and 17.2 mEq/L-pH,⁹ which would indicate that the ratio of β_t to β_{tc} would be about 0.3. However, as pointed out earlier, other tissues, such as bone, also participate in buffering, and therefore the value of 0.5 seems reasonable. Since β_{tc} is 24.2 mEq/L-pH, the estimated value of β_t is 12.1 mEq/L-pH and β_B is therefore 13.2 mEq/L-pH. The value of β_B is the weighted average of the buffer values of blood and tissue, and shows that the chemical buffering efficiency is much less for the whole body than for the blood. However, the buffer value per unit volume of blood water (β_{tcb}) is greater than either component (β_{tc} or β_t) and equals 6 β_{tc} or 145.2 mEq/L-pH. Thus, these calculations illustrate that although the blood is better buffered than the tissues, the tissues contribute more to the buffering of the body because of their relatively large volume.

The total buffer value of the body must also take into consideration the role played by the respiratory system and kidneys:

$$\beta_T = \frac{\beta_{tcb} + \beta_g + \beta_k}{1 + S} = \beta_B + \frac{\beta_g}{1 + S} + \frac{\beta_k}{1 + S} \quad (30)$$

where β_k is the buffer value of the kidneys per unit volume of blood water and β_T is the total buffer value of the body per unit volume of body water. In calculating the total buffer value of the body per unit volume of body water, it is implied that there is an equal concentration of acids (and alkalies) across the cell membranes of the tissues. If the total buffer value of the body per unit extracellular volume is used, then it is implied that the acids (and alkalies) cannot diffuse into the cells. Actually, neither implication is correct, and the situation will depend upon the actual acid (and alkali) studied. The relation between the total buffer values using the different volumes is:

$$\beta_E = \frac{(V_b + V_t)}{V_E} \beta_T \quad (31)$$

where β_E is the total buffer value of the body per unit extracellular volume and V_E is the extracellular volume (20 per cent of the body²¹). As pointed out before, the buffer value of the kidneys can approach infinity under certain conditions. If the role of the kidneys is neglected (as in nephrectomy)

and if nonvolatile acid is administered, then Table 2 illustrates the components of the total buffer value of the body per unit volume of body water at equilibrium and is compatible with experimental data.^{19, 20} The value of β_E is calculated to be 76.2 mEq/L-pH using the value of 21.8 mEq/L-pH for β_T (Table 2). It is evident that the chemical buffers of the blood only contribute a small percentage to the buffer value of the body, whereas the chemical buffers of the tissues contribute one-half of the total. Again, it should be emphasized, that these calculations assume equilibrium, but that the blood cells react rapidly whereas the tissue cells react much more slowly.

TABLE 2. COMPONENTS OF THE TOTAL BUFFER VALUE OF THE BODY PER LITER BODY WATER (EXCLUDING KIDNEY COMPONENT)

<i>System</i>	<i>β in mEq/L-pH</i>	<i>% of total</i>
Total chemical buffers of body (β_B)	13.2	61
Blood $\left(\frac{\beta_c}{1+S} \right)$	2.2	10
Tissue $\left(\frac{(\beta_t)(S)}{1+S} \right)$	11.0	51
Respiratory system $\left(\frac{\beta_g}{1+S} \right)$	8.6	39
Total buffer value per liter body water (excluding kidney component) (β_T)	21.8	100

Neglecting the role of the kidneys and neglecting chemical absorption of carbon dioxide (carbamino formation), then an estimation of the total buffer value of the body per unit volume of body water (β_{T_h}) to the retention of H_2CO_3 can be obtained using equation (26) :

$$\beta_{T_h} = \frac{\beta_c + (\beta_t)(S)}{1+S} \frac{\text{Total } CO_2}{HCO_3^-} + \frac{2.3 (H_2CO_3)}{1+S} \quad (32)$$

The value of β_{T_h} is calculated to be 13.9 mEq/L-pH, the component due to the tissues is 11.6 mEq/L-pH and the component due to the blood is only 2.3 mEq/L-pH. Thus, again the tissues have a buffer value five times greater than that of blood. *In vivo* experiments have demonstrated the importance of the tissues in buffering.²¹ Actually β_{T_h} represents an average of the blood and tissue buffer values. Due to the unequal distribution of ions across the membranes of cells,² anomalous ion shifts can occur. Thus if the red cell phase is increased, then it is possible that the chloride shift due to addition of H_2CO_3 could increase the plasma HCO_3^- to such an extent

that in spite of an increase of the bicarbonate in the tissue phase (due to addition of H_2CO_3), there will be a net tendency for the bicarbonate to enter the tissues along with some cation. This can explain the observation that when muscle cells are immersed in blood and equilibrated with carbon dioxide, there is a potassium shift from the plasma into the muscle cells.⁹

In summary, the buffering of blood *in vivo* is dependent upon the relatively rapid mechanisms (the first line of defense), involving the respiratory system and the red blood cells, and the relatively slow mechanisms (the second line of defense), involving the kidneys and the tissue cells.

CONCLUSIONS

At a constant pCO_2 , the total blood buffer value is 76.8 mEq/L for a change of one pH unit. Of this total, 3 per cent is due to the plasma bicarbonate, 28 per cent is due to other chemical buffers in the blood, and 69 per cent is due to the presence of a gas phase.

When there is a change in the alveolar ventilation due to the response of the respiratory system to pH and pCO_2 , then there is a substantial increase in the blood buffer value.

The tissues and kidneys have the capacity to contribute substantially to the buffer value of blood, but they react more slowly than the respiratory system and the chemical buffers in the blood.

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