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PERSPECTIVES IN BASIC SCIENCE

Stewart and beyond: New models of acid-base balance

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Stewart and beyond: New models of acid-base balance. The Henderson-Hasselbalch equation and the base excess have been used traditionally to describe the acid-base balance of the blood. In 1981, Stewart proposed a new model of acid-base balance based upon three variables, the "strong ion difference" (SID), the total weak acids (A_{Tot}), and the partial pressure of carbon dioxide (P_{CO_2}). Over 20 years later, Stewart's physiochemical model still remains largely unknown. In this review, we will present both the traditional and the Stewart models of acid-base balance and then derive each using an "ion equilibrium method." Modern theories of acid-base balance may be useful toward the understanding of complex acid-base disorders.

Almost a century ago, Henderson [1] used an equilibrium theory of carbonate species to suggest a physiochemical approach to acid-base balance in human blood. Later, Hasselbalch provided a simple formula (the Henderson-Hasselbalch Equation) to describe those equilibria. Thereafter, Van Slyke realized the importance of noncarbonate buffers, principally hemoglobin and proteins, in the regulation of acid-base behavior [2].

From these early observations, Siggaard-Anderson and others have developed the standard (base excess) model of acid-base balance in common use today [2]. This model has enjoyed much success and is used widely. The model is relatively easy to understand, is simple mathematically, and relies on easy-to-measure variables.

However, the standard approach to acid-base balance is not without its detractors. Base excess is derived by titration of the blood with acid or base in vitro. Since base excess is measured in a "closed" apparatus, some investigators have criticized base excess as artificially derived, physiologically unregulated, and otherwise irrelevant to an "open" in vivo system. Others have criticized base excess for merely *quantifying* rather than truly *explaining* acid-base disturbances.

Key words: acid-base, Stewart theory, ion equilibrium, base excess, strong ion difference.

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In 1981, Stewart [3, 4], a Canadian physiologist, proposed a radically different approach to acid-base balance. He started by discarding many of the features of the traditional model, including the standard notions of acids and bases. Based upon the laws of mass action, the conservation of mass and the conservation of charge, he derived relatively complex mathematical formulas to describe acid-base balance, while introducing two new variables, the strong ion difference (SID) and the total weak acids (A_{Tot}).

The reaction from defenders of the "standard model" was vitriolic. To Siggaard-Andersen and Fogh-Andersen [5] and their followers, the "Stewart approach is absurd and anachronistic." Partly as a result of this criticism, Stewart's equations are largely unknown outside a small circle of anesthesiologists and intensivists. In the intensive care unit, however, new models of acid-base behavior have become important to describe complex acid-base derangements.

Using standard quantitative chemistry, Wooten [6] has derived both the traditional and the Stewart equations from a common "master equation." When nonbicarbonate buffers are held constant, the Stewart equations simplify so that ΔSID is equal to the more familiar base excess. When nonbicarbonate buffers vary, as is often the case in the critically ill, the two models potentially differ. The main features of each of these models (standard, Stewart and ion equilibrium) are summarized in Table 1.

Although differing conceptually, the primary goals of each of these three models are similar: (*1*) the measurement of the magnitude of an acid-base disturbance; (*2*) the elucidation of the mechanism of the disturbance; (*3*) the classification of the disturbance as "metabolic" or "respiratory"; and (*4*) the enumeration of the independent variables that govern the disturbance.

The importance of these goals is (*1*) medical education, to frame the paradigm of acid-base balance taught in the medical school curriculum; (*2*) patient care, to unravel the mechanism(s) of complex acid-base disturbances and enable more rationale treatment of those disorders; and (*3*) research, to advance our understanding of ac-

Table 1. Comparison of the base excess, Stewart, and ion equilibrium models of acid-base balance

	Base excess	Stewart	Ion equilibrium
Acids and bases	Bronsted-Lowry	Arrhenius-like	Bronsted-Lowry
Measures magnitude	Yes	Yes	Yes
Explains mechanism	No[a]	Yes	No[a]
Classifies disorder	Yes	Yes	Yes
Independent variables	Base excess, $[HCO_3^-]$, P_{CO_2}	[SID], $[A_{Tot}]$, P_{CO_2}	Any[b]
Intracellular buffers	Yes	No	Not as currently developed
Noncarbonate buffers	No[c]	Yes	Yes
Advantages	Familiar and relatively simple	Comprehensive	Comprehensive and flexible
Disadvantages	Requires "plug-ins" such as anion gap and β	Nonstandard definition of acids and bases	No new mechanistic information

[a]Unless anion-gap is used
[b]May use traditional or Stewart set of variables
[c]Unless Van Slyke's β (Δbase/ΔpH) is used or base excess measured by titration

quired or genetically inherited disorders of the renal tubule or other ion-transporting epithelia.

To determine how well each of these models meets these objectives, we will first briefly describe the traditional model. Then, we will review the salient features of Stewart's work. Finally, we will show that an "ion equilibrium theory" may provide a broad foundation from which both approaches to acid-base balance may be understood.

Historical perspective

Although aware of the buffering power of noncarbonate species, Henderson [1] emphasized the significance of bicarbonate as a reserve of alkali in excess of acids other than carbonic acid. In his now famous monograph, he wrote the law of mass action for carbonate species (the "Henderson equation") as:

$$[H^+] = K_1' \times [CO_2]/[HCO_3^-] \qquad \text{(Eq. 1)}$$

where $[CO_2]$ is the total concentration of dissolved CO_2 gas and aqueous H_2CO_3 in plasma, $[H^+]$ and $[HCO_3^-]$ are the concentrations of hydronium and bicarbonate in plasma, and K_1' is the equilibrium constant for the associated reaction.

Subsequently, Hasselbalch and Gammeltoft [7] and Hasselbalch [8] adopted the Sorensen convention (where $[H^+]$ is expressed by pH), and rewrote equation 1 ("the Henderson-Hasselbalch equation") as:

$$pH = pK_1' + \log[HCO_3^-]/(S_{CO_2} \times P_{CO_2}) \qquad \text{(Eq. 2)}$$

where the total CO_2 concentration in expressed in terms of S_{CO_2} (the solubility coefficient of CO_2 in plasma) and P_{CO_2} (the partial pressure of CO_2 in plasma).

While a mathematical description of the equilibrium of carbonate species was interesting theoretically, the practical importance of this equation was not immediately apparent. In 1914, Van Slyke [9] was studying the acidosis of diabetic coma while working in the Rockefeller Institute. In order to make the Henderson-Hasselbalch equation useful clinically, he realized that he would need to devise methods to measure each of the equation's three variables, pH, $[HCO_3^-]$ and P_{CO_2}. Within 3 years, he developed a volumetric blood gas apparatus to measure plasma CO_2. As the pH electrode was introduced in 1923, Van Slyke was soon able to measure CO_2 tension, total CO_2, and pH at the bedside [10, 11].

Using the new measuring devices, Van Slyke was able to determine the relative contribution of "volatile" and "nonvolatile" buffers" to overall body buffering capacity. After injecting sulfuric acid into dogs, he found that 40% of the acid was neutralized by tissue cells, 30% was neutralized by hemoglobin, and the remaining 30% was buffered in the extracellular fluids [9]. He concluded that the pH of the blood was maintained, albeit at the expense of an alkali deficit. This concept proved to be useful clinically because he could now calculate the amount of bicarbonate to administer to his diabetic patients to partially correct their acidosis.

In order to present his data graphically, Van Slyke, in 1921, rearranged the terms of equation [2] to obtain "the buffer curve" [12–15]:

$$\log P_{CO_2} = -pH + \log [HCO_3^-]/K_1' \times S_{CO_2} \qquad \text{(Eq. 3)}$$

The buffer curve equation indicates that the plot of pH vs. log P_{CO_2} should be linear with an intercept equal to log $[HCO_3^-]/K_1' \times S_{CO_2}$.

In the ensuing years, investigators have proposed a wide assortment of parameters to describe the blood buffers. For example, some investigators have measured the *change* in buffering capacity with pH. The buffer value (β) of a solution is defined as the quantity or amount of hydrogen ion that can be either added to or removed from a solution with a resultant change of one pH unit (Δbase/ΔpH). For example, β is ~5.4 mmol/L/pH for bicarbonate and ~0.1 mmol/g/pH for serum proteins [12–15]. As erythrocytes are permeable to protons, the slope of the buffer curve varies with the hemoglobin concentration. As a result, whole blood is a better buffer than separated plasma [16].

Other investigators have measured the total buffer

capacity of blood. In the 1920s, Van Slyke defined standard bicarbonate (VSSB) as the concentration of serum bicarbonate after equilibration of the blood to pH 7.4 [17–20]. VSSB quantifies the concentration of bicarbonate corrected for respiratory effects. In 1948, Singer and Hastings [21] introduced buffer base to determine blood buffering capacity from a complex nomogram [21]. They defined buffer base as the difference between the sum of the cations and the sum of the anions present in plasma or in whole blood. By the principle of electroneutrality, this difference is equal to sum of the buffer anions (HCO_3^-) and the protein anions (P^-).

Finally, Siggaard-Andersen proposed measuring the difference in buffering capacity from normal. To do this, he refined Van Slykes' alkaki deficit and introduced base excess (22–24). Base excess specifies the number of milliequivalents (meq) of acid or base that are needed to titrate 1 liter of blood to pH 7.40 at 37°C while the P_{CO_2} is held constant at 40 mm Hg. Base excess corrected for hemoglobin, the major intracellular buffer of erythrocytes, is called the "standard base excess" (SBE). Assuming that the nonvolatile buffers remain constant, SBE measures the "metabolic" component of acid-base disorders independent of the "respiratory" component, P_{CO_2}.

Buffer value, standard bicarbonate, and buffer base are all useful to describe the acid-base behavior of plasma. Although the single best or clinically most useful parameter has not been determined, base excess has conquered its rivals to form the cornerstone of standard clinical acid-base chemistry [25].

The standard model: Base excess and P_{CO_2}

The standard theory has the following features: (*1*) an acid is a H^+ donor and a base is a H^+ acceptor, after Brønsted-Lowry; (*2*) the quantity of H^+ added to or removed from the blood is considered to determine the final pH; (*3*) plasma membranes may be permeable to H^+, and thus intracellular as well as extracellular chemical reactions influence the pH; (*4*) an analysis of nonvolatile buffer equilibrium is not necessary to describe acid-base balance; and (*5*) an estimate of the magnitude of an acid-base disturbance even when the underlying cause remains unknown.

According to the Henderson-Hasselbalch equation, the pH of serum depends upon only two variables, P_{CO_2} and $[HCO_3^-]$. This pair is unique among body buffers because P_{CO_2} is rapidly eliminated by respiration ("open system"). Pitts [26] stated that the "regulation of the concentration of this one buffer pair fixes the hydrogen ion concentration and thereby determines the ratios of all the other buffer pairs." Therefore, there is no reason to describe mathematically noncarbonic or intracellular buffers.

However, Siggaard-Andersen [27] realized that P_{CO_2} and $[HCO_3^-]$ are not independent variables and in fact do not in general vary independently of one another. Therefore, the Hendersen-Hasselbalch equation alone cannot separate the respiratory from the metabolic components of an acid-base disorder. Siggaard-Anderson [27] suggested that the CO_2 equilibration curve (which he called the "Van Slyke formula") can describe the relationship between the pH and $[HCO_3^-]$:

$$[HCO_3^-] - 24.4 \text{ mmol/L} = -(2.3 \times [\text{Hgb}] + 7.7) \times (\text{pH} - 7.40) + \text{BE}/(1 - 0.023 \times [\text{Hgb}]) \qquad \text{(Eq. 4)}$$

where BE is the base excess of whole blood and [Hgb] is the concentration of hemoglobin (in mmol/L) in whole blood. To obtain standard base excess, measured [Hgb] may divided by the factor 3 or assumed to have a value of 6 g/dL [5, 27]. The numerical values 2.3 and 7.7 depend upon the concentrations and molar buffer values of the intra- and extracellular buffers, respectively. Base excess for plasma can, of course, be obtained by setting [Hgb] = 0 mmol/L.

The Siggaard-Andersen nomogram [22–24] solves the simultaneous equations [2] and [4] for base excess. Thus, acid-base disorders can be completely described and characterized by the two variables, base excess and P_{CO_2}.

Whole-body acid-base balance. Hasselbalch [7], in 1915, had coined the term "compensation" to describe homeostasis in acid-base disturbances. For example, the lungs may balance a primary disorder of alkali deficit due to diabetic ketoacidosis by removing CO_2. The kidneys may balance primary retention of CO_2 due to respiratory disease by excreting an acid load in the form of titratable acid, ammonium and free H^+. Eventually, the kidneys restore buffering capacity by generating new bicarbonate though cellular metabolism.

The Stewart model: SID, A_{Tot}, and P_{CO_2}

The traditional approach is often successful in clinical practice. However, the model appears to break down at physiologic extremes. For example, the buffer curve (equation 3) indicates that the plot of pH vs. log P_{CO_2} should be linear with an intercept equal to log $[HCO_3^-]/K_1' \times S_{CO_2}$. However, experimental data cannot be fitted to the equation [28]. The plot of pH vs. log P_{CO_2} is in fact displaced by changes in protein concentration or the addition of sodium or chloride and becomes nonlinear in markedly acid plasma (Fig. 1).

Although Koppel and Spiro described the effect of nonvolatile buffers on the buffer curve as early as 1914 [29], the Siggaard-Anderson model offers no explanation for these findings.

For example, consider a critically ill patient with septic shock and multiple organ failure. The management has consisted of cardiopressors, mechanical ventilation, antibiotics, and large volumes of normal saline solution. Laboratories reveal Na^+ 130 mmol/L, K^+ 3.0 mmol/L, Cl^-

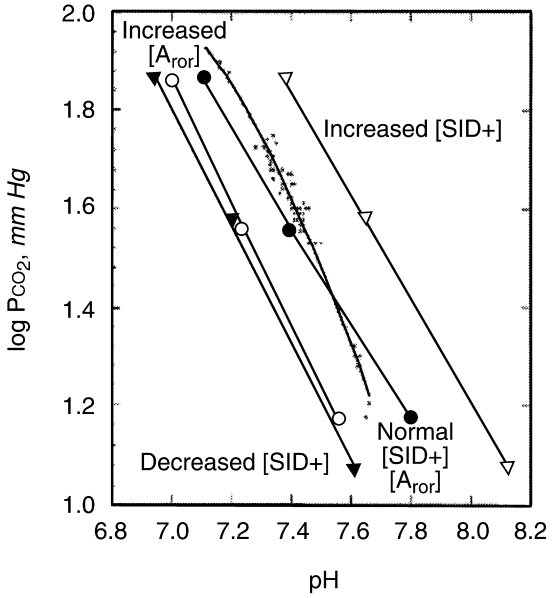

Fig. 1. The buffer curve. The line plots of linear in vitro and curvilinear in vivo log P_{CO_2}–pH relationship with plasma. Symbols are (○), plasma with a protein concentration of 13 g/dL (high [A_{Tot}]); (▽), plasma with a high [SID] of 50 mEq/L; (●), plasma with a normal [A_{Tot}] and [SID]; (▼), plasma with a low [SID] of 25 mEq/L; (dots), curvilinear in vivo log P_{CO_2}–pH relationship. Adapted from reference [28]; used with permission.

111 mmol/L, albumin 1.5 g/dL, phosphate 2.0 mg/dL, $[HCO_3^-]$ = 9.25 mmol/L, and P_{CO_2} = 30 mm Hg. The patient is acidotic, with a pH = 7.10. The base excess = −15 meq/L. The anion gap ((AG) = $[Na^+] + [K^+] - [Cl^-] - [HCO_3^-]$) is 12.8 meq/L. Although the base excess provides the *magnitude* of the acid-base disturbance, the traditional model offers no further insight into the *mechanism* of the acid-base disorder.

These and similar observations prompted Stewart, a Canadian physiologist, to put forward a novel approach of acid-base balance [3, 4].

Stewart's theory has the following features: (*1*) an acid is any species that raises the H^+ concentration of a solution, approximating the Arrhenius definition; (*2*) the quantity of H^+ added or removed from a physiologic system is not relevant to the final pH, since $[H^+]$ is a "dependent" variable; (*3*) human plasma consists of fully dissociated ions ("strong ions" such as sodium, potassium, chloride, and lactate), partially dissociated "weak" acids (such as albumin and phosphate), and volatile buffers (carbonate species); (*4*) an evaluation of nonvolatile buffer equilibrium is important to the description of acid-base balance; (*5*) the weak acids of plasma can be described as a pseudomonoprotic acid, HA; and (*6*) plasma membranes may be permeable to strong ions, which constitute the "independent" variable SID. Thus, transport of strong ions across cell membranes may influence $[H^+]$.

With these assumptions, Stewart wrote six equations (equations 5 to 10) based upon the laws of mass action, the conservation of mass, and the conservation of charge:

Water Dissociation Equilibrium

$$[H^+] \times [OH^-] = K'_w \quad \text{(Eq. 5)}$$

where K'_w is the autoionization constant for water.

Electrical Neutrality Equation

$$[SID] + [H^+] = [HCO_3^-] + [A^-] + [CO_3^{-2}] + [OH^-] \quad \text{(Eq. 6)}$$

where SID is the "strong difference" ($Na^+ + K^+ - Cl^-$ − lactate) and $[A^-]$ is the concentration of dissociated weak acids.

Weak Acid Dissociation Equilibrium

$$[H^+] \times [A^-] = K_a \times [HA] \quad \text{(Eq. 7)}$$

where K_a is the weak acid dissociation constant for HA.

Conservation of Mass for "A"

$$[A_{Tot}] = [HA] + [A^-] \quad \text{(Eq. 8)}$$

where $[A_{Tot}]$ is the total concentration of weak acids.

Bicarbonate Ion Formation Equilibrium

$$[H^+] \times [HCO_3^-] = K'_1 \times S \times P_{CO_2} \quad \text{(Eq. 9)}$$

where K'_1 is apparent equilibrium constant for the Henderson-Hasselbalch equation and S is the solubility of CO_2 in plasma.

Carbonate Ion Formation Equilibrium

$$[H^+] \times [CO_3^{-2}] = K_3 \times [HCO_3^-] \quad \text{(Eq. 10)}$$

where K_3 is the apparent equilibrium dissociation constant for bicarbonate.

Combining the above equations, we obtain "the Stewart Equation":

$$a[H^+]^4 + b[H^+]^3 + c[H^+]^2 + d[H^+] + e = 0 \quad \text{(Eq. 11)}$$

where $a = 1$; $b = [SID] + K_a$; $c = \{K_a \times ([SID] - [A_{Tot}]) - K'_w - K'_1 \times S \times P_{CO_2}\}$; $d = -\{K_a \times (K'_w + K'_1 \times S \times P_{CO_2}) - K_3 \times K'_1 \times S \times P_{CO_2}\}$; and $e = -K_a K_3 K'_1 S P_{CO_2}$.

The solutions to equation 11 are plotted using published values for the rate constants (Fig. 2).

If we ignore the contribution of the smaller terms in the electrical neutrality equation (equation 6), then equation 6 becomes:

$$[SID] = [HCO_3^-] + [A^-] \quad \text{(Eq. 12)}$$

where $[A^-]$ is the concentration of dissociated weak noncarbonic acid, principally albumin and phosphate. The

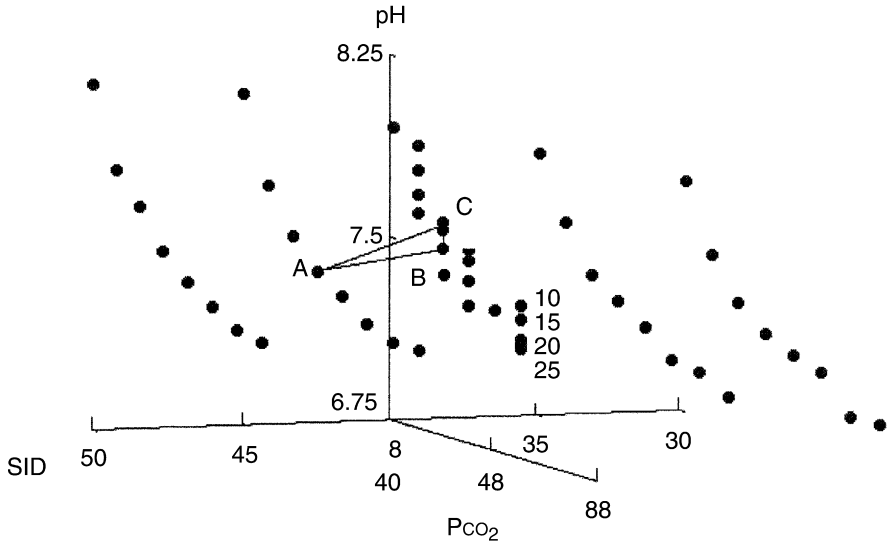

Fig. 2. Graph of independent variables (P_{CO_2}, SID, and A_{Tot}) vs. pH. Values were used for the rate constants K_a, K'_w, K'_1, K_3, and S_{CO_2}. Point A represents [SID] = 45 mEq/L and $[A_{Tot}]$ = 20 mEq/L and point B represents [SID] = 40 mEq/L and $[A_{Tot}]$ = 20 mEq/L. In moving from point A to point B, $\Delta SID = \overline{AB} = BE$. However, if $[A_{Tot}]$ decreases from 20 mEq/L to 10 mEq/L (point C), then $AC \neq \Delta SID \neq BE$. Data plotted from references [3, 4].

Stewart equation 11 may then be simplified to read as follows:

$$pH = pK'_i + \log \frac{[SID] - K_a[A_{tot}]/K_a + 10^{-pH}}{SP_{CO_2}} \quad \text{(Eq. 13)}$$

This "simplified" Stewart equation has the same form as equations 2 and 3 ("the buffer curve") [28]. However, pH is now a function of the noncarbonate buffers, $[A_{Tot}]$. The redrawn buffer curve now fits the experimental data that are presented in Figure 1. In addition, when $[A_{Tot}]$ is set to zero, equation 13 simplifies to the more familiar Henderson-Hasselbalch equation (equation 2).

The independent variables. By combining equations for the conservation of charge, conservation of mass balance and four equilibrium reactions (the dissociation of water, the CO_2 hydration reaction of carbonic acid to bicarbonate, bicarbonate to carbonate, and undissociated to dissociated weak acids), Stewart developed a fourth-order polynomial equation relating H^+ to three independent variables (SID, $[A_{Tot}]$ and P_{CO_2}) and five rate constants (K_a, K'_w, K'_1, K_3, and S_{CO_2}) (equation 11). All other variables, such as $[H^+]$ and $[HCO_3^-]$ are dependent variables. He further asserted that equation 11 not only quantifies the acid-base status, but also provides the only mechanisms through which acid-base regulation and homeostasis may occur [3, 4, 30–36]. Changes in SID, for example, cause shifts the position of water equilibrium (equation 5) to cause changes in $[H^+]$.

Apart from thermodynamic equilibrium equations, there is evidence to support this claim. Ionic charge may disrupt hydrogen bonds and thereby affect water's dissociation constant (K'_w), clathrate structure, and hydrogen ion conductance (by the "Grotthuss mechanism") [37–43].

For example, K'_w is 1×10^{-14} at room temperature and increases to $\sim 2 \times 10^{-14}$ in 0.25 mol/L tetramethylammonium chloride. The large K'_w favors the "autodeprotonation" of water. In this case, the dissociation of water is strongly influenced by the charged species in the milieu.

Chaplin [44, 45] has suggested that water is highly organized and forms an icosahedral cluster structure. Various ions may stabilize ("kosmotropes") or disrupt ("chaotropes") the "structure" of water. For example, small or multiply charged ions with high charge density (e.g., SO_4^{2-}, HPO_4^{2-}, Mg^{2+}, Ca^{2+}, Li^+, Na^+, H^+, OH^-, and HPO_4^{2-}) are kosmotropes, whereas large, singly charged ions with low charge density (e.g., $H_2PO_4^-$, HSO_4^-, HCO_3^-, I^-, Cl^-, NO_3^-, NH_4^+, Cs^+, K^+, and tetramethylammonium ions) behave as chaotropes [41, 45]. Charged species may affect the integrity of the lattice and may in turn affect the ordering of the hydrogen bonding.

Finally, ionic charge may affect the diffusion of $[H^+]$ in water. Using a supercomputer to perform ab initio path integral simulations, Tuckerman et al [42, 43] found that the hydrated proton in liquid water forms a "fluxional" defect in the hydrogen-bonded network. A tricoordinate $H_3O^+(H_2O)_3$ complex is transformed via proton transfer into a $[H_2O–H–OH_2]^+$ complex. The rate of proton diffusion to a new water molecule is determined by the rate of hydrogen bond breaking in the second solvation shell. The SID, as well as Stewart's other independent variables, may affect this rate-limiting step.

Further investigations are required to determine precisely the interactions of ions, proteins, and water in biologic solutions.

Each of Stewart's independent variables will now be examined in turn.

THE SID. The "apparent" strong ion difference $[SID_a]$, is given by:

$$[SID_a] = [Na^+] + [K^+] - [Cl^-] - [\text{lactate}] - [\text{other strong anions}] \quad \text{(Eq. 14)}$$

In normal plasma, $[SID_a]$ is equal to the "effective" strong ion difference $[SID_e]$, which is given by equation 12.

Figge et al [46, 47] have developed an equation relating $[SID_e]$ explicitly to the plasma concentrations of albumin and phosphate:

$$[SID] = (1000 \times 2.46 \times 10^{-11} \times P_{CO_2}/10^{-pH}) + [\text{albumin}] \times (0.123 \times pH - 0.631) + [\text{phosphate}] \times (0.309 \times pH - 0.469) \quad \text{(Eq. 15)}$$

where [albumin] is expressed in g/dL and [phosphate] is expressed in mmol/L. When pH = 7.4, equation 15 yields:

$$[A^-] = 2.8\ [\text{albumin g/dL}] + 0.6\ [\text{phosphate mg/dL}] \quad \text{(Eq. 16)}$$

Mathematically, Stewart's SID is equivalent to the buffer base of plasma of Singer and Hastings [21].

THE $A_{Tot.}$ Although the noncarbonate buffers in blood are polyelectrolytes, Stewart and others have successfully modeled these species as a single monoprotic acid HA with a composite total concentration $[A_{Tot}]$. The normal $[A_{Tot}]$ of human plasma is not well established and measurements have ranged from 12 to 24 mEq/L. In practice, $[A_{Tot}]$ is usually calculated from the concentration of total protein, whereby $[A_{Tot}] = k \times [\text{total protein}]$ (g/dL). K is most commonly reported as 2.43, although some have reported values as high as 3.88 [46–55]. $[A_{Tot}]$ is also equal to $K_t \times [\text{albumin}]$ (g/dL) where reported values for K_t range from 4.76 to 6.47 [46–55].

THE P_{CO_2}. Stewart's third independent variable, P_{CO_2}, is the same as that already encountered in the traditional model.

These observations may prompt reexamination of the role of transepithelial chloride conductance in the regulation of acid-base balance. For example, mutations of the genes encoding the Na^+-HCO_3^- cotransporter (NBC-1), the B1 subunit of the H^+-adenosine triphosphatase (ATPase) and the Cl^--$[HCO_3^-]$ exchanger (AE1) are collectively referred to as renal tubular acidosis (RTA) [56]. In the traditional model, the resulting hyperchloremic metabolic acidosis is attributed to low net acid excretion. In the Stewart model, acidosis is due to hyperchloremia and the retention of chloride by the renal tubule.

For example, mutations in the *WNK1* and *WNK4* genes are associated with pseudohypoaldosteronism type II (PHA II). Recently, Choate et al [57] have linked these mutations with a high transtubular chloride flux. This observation suggests that that the acidosis of PHA II may be due to high reabsorption of chloride, as predicted by the Stewart model.

Patients with cystic fibrosis (CF), a disorder of the cystic fibrosis transmembrane regulator (CFTR) that functions primarily as a chloride channel, may develop a hypochloremic metabolic alkalosis [58]. Bartter syndrome, characterized by alkalosis and a low fractional distal reabsorption of chloride, is caused by a mutation in the gene encoding the Na-K-2 Cl cotransporter (NKCC2), the outwardly rectifying potassium channel (ROMK), or the chloride channel (CLCNKB) [59, 60]. In the traditional model, metabolic alkalosis is these disorders is attributed to "volume contraction." In the Stewart model, alkalosis is due to hypochloremia and loss of chloride through the skin or urine. Additional investigations of renal tubular chloride transport in these disorders are warranted.

Whole-body acid-base balance. In traditional acid-base theory, respiratory disorders are mediated by CO_2 while metabolic derangements are caused by the production or removal of H^+. In Stewart's theory, respiratory disorders are also medicated by CO_2. However, the three independent variables SID, $[A_{Tot}]$ and P_{CO_2} determine $[H^+]$ and explain acid-base disturbances. A change in pH may be brought about only by a change in one or more of these variables and by no other means. The components of buffer base, $[HCO_3^-]$ and $[A^-]$, are merely dependant variables and as such do not and cannot regulate $[H^+]$. Physiologically, the kidney, intestine, and tissue each contribute to SID while the liver mainly determines $[A_{Tot}]$ and the lungs P_{CO_2}.

One may classify acid-base disorders based according to Stewart's three independent variables (Table 2). Acidosis results from an increase in P_{CO_2}, $[A_{Tot}]$, or temperature, or in a decrease in $[SID^+]$. Metabolic acidosis may be due to overproduction of organic acids (e.g., lactic acid, ketoacids, formic acid, salicylate, and sulfate), loss of cations (e.g., diarrhea), mishandling of ions (e.g., RTA) or administration of exogenous anions (e.g., poisoning). These all result in a low SID. Alkalosis results from a decrease in P_{CO_2}, $[A_{Tot}]$, or temperature, or in an increase in $[SID^+]$. For example, metabolic alkalosis (e.g., due to vomiting) may be due to chloride loss resulting in a high SID.

To examine the relationship between [SID] and $[A_{Tot}]$, Wilkes et al [53] obtained 219 arterial blood samples from 91 critically ill patients in an intensive care unit. In this population, a low $[A_{Tot}]$ was balanced by hyperchloremia, resulting in a low [SID]. Although the pH remains normal initially, such patients easily develop acidemia when stressed because of the steepness of the pH vs. SID plot at low $[SID^+]$ (Fig. 2).

In addition, Wilkes et al [53] found a strong correlation between [SID] and P_{CO_2}. Together, these observations suggest that disturbances of [SID] are compensated by changes in P_{CO_2} while disturbance of $[A_{Tot}]$ are balanced by changes in [SID].

The clinical usefulness of the Stewart equations may

Table 2. Classification of metabolic acid-base disorders based upon the Stewart model

Metabolic alkalosis	Metabolic acidosis
Low serum albumin	Low SID and high SIG[b]
Nephrotic syndrome, hepatic cirrhosis	Ketoacids, lactic acid, salicylate, formate, methanol
High SID[a]	Low SID and low SIG[b]
Chloride loss	RTA, TPN, saline, anion exchange resins, diarrhea, pancreatic losses
Vomiting, gastric drainage, diuretics, posthypercapnea, chloride wasting diarrhea due to villous adenoma, mineralcorticoid excess, hyperaldosteronism, Cushing syndrome, Liddle syndrome, Bartter syndrome, exogenous cortocosteroids, licorice	
Na load (as acetate, citrate, lactate)	
Ringer's solution, TPN, blood transfusion	

Abbreviations are: SID, strong ion difference; SIG, strong ion gap; RTA, renal tubular acidosis; TPN, total parentoral nutrition.
[a] The "normal" value of SID is generally taken as ~40 mEq/L. However, SID varies as a function of A_{Tot}.
[b] Theoretically, the "normal" SIG should be zero. However, the normal range of SIG has not been established.

be facilitated by the use of computers. Watson [54, 61] has created a powerful computer program with a graphic user interface that calculates the dependent variables (including bicarbonate and pH) based upon the entry of the three independent variables (SID, P_{CO_2}, and A_{Tot}). In addition, one may vary the temperature and any of the rate constants. The results are presented numerically and in the form of a "Gamblegram."

Strong Ion Gap (SIG)

One of the most useful approaches to come out of the Stewart Theory is the evaluation of acid-base disturbances using the strong ion gap (SIG). The SIG is an estimate of unmeasured ions similar to the more familiar anion gap (equation 17) [62–65].

$$AG = [Na^+] + [K^+] - [Cl^-] - [HCO_3^-] \qquad \text{(Eq. 17)}$$

where AG is the anion gap.

Combining equations 12, 14, and 17,

$$SIG = AG - [A^-] \qquad \text{(Eq. 18)}$$

where $[A^-]$ = 2.8 (albumin g/dL) + 0.6 (phosphate mg/dL) at pH 7.4.

Unlike the anion gap, the SIG is normally close to zero. Analogous to conventional interpretation of the anion gap, however, metabolic acidosis with a high SIG is due to unmeasured anions while metabolic acidosis with SIG ~0 mEq/L is usually due to retention of chloride. It has been suggested that the SIG may be especially useful for the detection of "unmeasured" anions in critically ill, hypoalbuminemic patients with normal pH, base excess, and anion gap [62–64].

If we now reexamine our critically ill patient, the cause of the acidosis becomes readily apparent. From equation 15, we find that $[SID_e]$ = 14 mEq/L. By inspection, the $[SID_a]$ = 22 mEq/L and the difference ($SIG = SID_a - SID_e$) is 8 mEq/L. From Table 2, we find that the patient's acidosis is due to a combination of low SID and a high SIG. The low SID is due to hyperchloremia, which may result from massive fluid resuscitation with normal saline solution. The high SIG is due to an unexplained anion, in this case most likely lactic acid due secondary to sepsis. From equation 18, we learn that a normal anion gap does not preclude a high SIG in the face of low serum albumin. The alkalinizing effect of a low A_{Tot} (Fig. 2) confounds the usual interpretation of base excess and anion gap. The acidosis may improve with the administration of fluids with a high SID and with better treatment of the underlying sepsis. In the context of renal failure, both of these goals may potentially be achieved by the use of continuous venovenous hemofiltration (CVVH) [66, 67].

Toward a unified theory of acid-base behavior: Ion equilibrium theory

The interdependence of the traditional and Stewart variables (base excess, $[HCO_3^-]$, P_{CO_2}, and pH vs. [SID], $[A_{Tot}]$, $[HCO_3^-]$, P_{CO_2}, and pH, respectively) arise as a consequence of their underlying assumptions and are important in applying the models to clinical problems. In contrast, thermodynamic state functions do not depend upon the path or mechanism of the process under study. Precisely because a detailed mechanism is not required, equilibrium thermodynamics provides a powerful way to calculate the response of a system to a perturbation.

In an equilibrium theory, one enumerates some property of a system, such as proton number or charge, and then distributes the property among the various species comprising the system according to the energetics of that particular system [6, 68, 69]. One may chose any convenient path or set of variables to describe the equilibrium state, not just the one(s) normally used in nature. The link between the plasma base excess and the Stewart methods may be obtained by applying this notion to different sets of variables, but in the same general form [6].

Unlike the traditional and Stewart models, ion equilibrium theory makes no assumption about the dependence or independence of any parameter. As a consequence, the model provides no new insight into the mechanism of acid-base disorders.

However, one may derive from a single "master equation": (*1*) a general form of the Van Slyke equation (equation 4); (*2*) base excess, as the change in Van Slyke's

standard bicarbonate (ΔVSSB) "corrected" for noncarbonate buffers; (*3*) Van Slyke's buffer base, β; and (*4*) a mathematical link between base excess and SID.

The ionic equilibrium model has the following features: (*1*) an acid is a H^+ donor, after Brønsted-Lowry; (*2*) the independent variables are the volumes of acid or base added to solution for titration; (*3*) ions that do not directly participate in $[H^+]$ transfer are "spectator ions" and species which do directly participate in $[H^+]$ transfer are "buffer ions;" (*4*) an analysis of intracellular buffers is omitted similar to the traditional and Stewart models; (*5*) albumin and phosphate are the major contributors to the noncarbonate buffers in plasma; (*6*) the 212 individual amino acid groups of albumin with dissociable protons behave as independent monoprotic acids with dissociation constants K_i; and (*7*) phosphate is a triprotic system with dissociation constants K_{1a}, K_{2a}, and K_{3a}.

Guenther [70], an analytic chemist, has suggested a "master equation" for solving complex acid-base problems. C_B, the total concentration of proton acceptor sites in solution, is given by:

$$C_B = C + \sum_i C_i \bar{e}_i - D \qquad \text{(Eq. 19)}$$

where C is the total concentration of carbonate species proton acceptor sites (in mmol/L), C_i is the concentration of noncarbonate buffer species i (in mmol/L), $\bar{e}_i$ is the average number of proton acceptor sites per molecule of species i, and D is Ricci's difference function:

$$D = [H^+] - [OH^-] \qquad \text{(Eq. 20)}$$

C_B can be reexpressed [6]:

$$C_B = [HCO_3^-] + \left(C_{alb}\frac{\partial \bar{e}_{Alb}}{\partial pH} + C_{phos}\frac{\partial \bar{e}_{phos}}{\partial pH}\right) pH + 52\ C_{alb} - 0.3\ C_{phos} \qquad \text{(Eq. 21)}$$

where β ("buffer value") $= \left(C_{alb}\frac{\partial \bar{e}_{Alb}}{\partial pH} + C_{phos}\frac{\partial \bar{e}_{phos}}{\partial pH}\right)$.

Equation 21 has the same general form as equation 4, "the Van Slyke equation." At pH = 7.4, the derivatives $\partial\bar{e}_{Alb}/\partial$pH and $\partial\bar{e}_{phos}/\partial$pH are equal to 8.3 and 0.29, respectively. The constants 52 and −0.3 depend upon the various pKs and the pH at which the slope of equation 21 is measured [6].

The plot of both the Henderson-Hasselbach equation (equation 2) and the Van Slyke equation (equation 21) has been called "the Davenport diagram" (Fig. 3). An acid-base disturbance may then be characterized by two parameters: (*1*) ΔVSSB, a change in the *position* of the Van Slyke curve; and (*2*) Δβ, a change in the *slope* of the Van Slyke curve.

ΔVSSB measures the magnitude of a metabolic acidosis or alkalosis and is numerically equal to base excess. Δβ measure the change in the plasma's ability to resist perturbations of pH ("buffer strength").

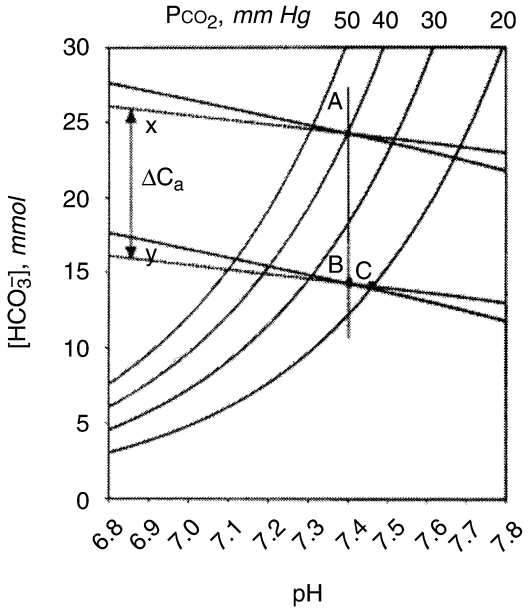

Fig. 3. Davenport diagram ($[HCO_3^-]$ vs. pH) for normal plasma (solid straight line containing point A) metabolic acidosis with ΔVSSB = −10 mmol/L (solid straight line containing point B), plasma with normal values except albumin concentration = 0.33 mmol/L (line x containing point A) and the same corresponding metabolic acidosis with albumin concentration = 0.33 mmol/L (line y containing point C). $\Delta C_B'$ is the change in C_B referenced to a new buffer concentration C_i. Adapted from reference [6], used with permission.

Consider the following example. Normal plasma may be defined by the values pH = 7.40, P_{CO_2} = 40.0 mm Hg, $[HCO_3^-]$ = 24.25 mmol/L, C_{Alb} = 0.66 mmol/L, and C_{Phos} = 1.16 mmol/L.

From equation (21):

$$C_B = [HCO_3] + (8.3\ C_{Alb} + 0.29\ C_{Phos})pH + 52\ C_{Alb} - 0.3\ C_{Phos} = (24.25\ \text{mmol/L}) + \{(0.66\ \text{mmol/L})(8.3) + (1.16\ \text{mmol/L})(0.29)\}(7.40) + (52)(0.66\ \text{mmol/L}) - (0.3)(1.16\ \text{mmol/L}) = 101\ \text{mmol/L}$$

and β = 5.58 mEq/L.

Now reconsider our critically ill patient with lactic acidosis {pH = 7.10, P_{CO_2} = 30.0 mm Hg, $[HCO_3^-]$ = 9.25 mmol/L, base excess = −15 mEq/L, C_{Alb} = 0.24 mmol/L (1.5 g/dL) and C_{Phos} = 0.65 (2 mg/dL)}
ΔC_B (final C_B – initial C_B) is:

$$\Delta C_B = \Delta[HCO_3^-] + (8.3\ C_{Alb} + 0.29\ C_{Phos})pH + 52\ C_{Alb} - 0.3\ C_{Phos} = (9.25 - 24.25\ \text{mmol/L}) + \{(0.24\ \text{mmol/L})(8.3) + (0.65\ \text{mmol/L})(0.29)\}(7.10 - 7.40) = (-15\ \text{mmol/L}) + \{2.2\ \text{mmol/L}\}(-0.30) = -15.66\ \text{mmol/L and} \qquad \text{(Eq. 22)}$$

$$\beta = 2.2\text{mEq/L}$$

In this particular case, use of the traditional Hender-

son-Hasselbalch approach by itself provides only the change due to bicarbonate (15 mmol/L), while ignoring the remaining (0.66 mmol/L) acid load "absorbed" by the noncarbonate buffers. This patient also has a low buffer value so for any given base excess the expected ΔpH is greater than normal.

Ion equilibrium theory: C_B and SID

One may derive a similar set of equations relating bicarbonate to pH using Stewart's [SID]. While the "conventional equilibria" are calculated from the enumeration of protein binding sites, the "Stewart equilibria" may be calculated from the enumeration of ionic charges.

$$SID = C - \sum_i C_i \overline{Z}_i - D \qquad \text{(Eq. 23)}$$

where $\overline{Z}_i$ is the average charge per molecule of species *i*.

Equation 23 ("ion charge equation") indicates that the difference in charge in the spectator ions is equal to the difference in charge of the buffer ions.

SID may be expressed as [6]:

$$SID = [HCO_3^-] + (8.3\ C_{Alb} + 0.29\ C_{Phos}) \times pH - 42C_{Alb} - 0.3C_{Phos} \qquad \text{(Eq. 24)}$$

where $\beta = (8.3\ C_{Alb} + 0.29\ C_{Phos})$.

Note that equation 24 has the same general form as the Van Slyke equation (equations 4 and 21).

The second part of equation 24 (equation 25) is:

$$[A^-] = (8.3\ C_{Alb} + 0.29\ C_{Phos})pH - 42C_{Alb} - 0.3C_{Phos} \qquad \text{(Eq. 25)}$$

Thus, equation 25 also has the same general form as equation 15. When we convert to more familiar units, equation 25 simplifies to equation 16 at pH 7.4.

Ion equilibrium theory: Linking the traditional and Stewart models

Combining equations yields the additional relationship:

$$C_B = SID + \sum_i C_i \overline{Z}_{\max(i)} \qquad \text{(Eq. 26)}$$

where $\overline{Z}_{\max(i)}$ is the maximum ionic charge for species *i*. For albumin, $\overline{Z}_{\max(i)} = 94$ and for phosphate $\overline{Z}_{\max(i)} = 0$.

Explicitly for plasma,

$$C_B = SID + 94C_{Alb} \qquad \text{(Eq. 27)}$$

Equation 27 indicates that C_B is equal to [SID] plus a constant.

When noncarbonate buffers are held constant,

$$\Delta C_B = \Delta SID = \Delta VSSB = BE \qquad \text{(Eq. 28)}$$

From equation 22, ΔC_B (final C_B – initial C_B) is:

$$\Delta C_B = BE = \Delta [HCO_3^-] + \beta \Delta pH \qquad \text{(Eq. 29)}$$

where $\beta = (8.3C_{Alb} + 0.29C_{Phos})$.

Equation 29 indicates that base excess is a function of ΔVSSB "corrected" for the analytic concentrations of noncarbonate buffers.

When noncarbonate buffers vary, $\Delta C_B \neq \Delta SID \neq \Delta VSSB \neq \Delta BE$. However,

$$\Delta C_B' = \Delta SID' = \Delta VSSB' = \Delta BE' \qquad \text{(Eq. 30)}$$

Equation 30 indicates that for normal plasma, changes in total titratable base, strong ion difference, Van Slyke standard bicarbonate, and base excess are all mathematically equivalent. Equation 30 also indicates that for abnormal noncarbonate buffers, the mathematical equivalence of these terms holds only if each is referenced to the new buffer state.

CONCLUSION

Siggaard-Anderson has made an enormous contribution to the advancement of clinical acid-base chemistry. Out of the chaos of competing definitions, concepts, and terms, he brought an orderly approach to acid-base balance based upon the base excess. To make the model useful clinically, base excess is no longer measured by titration but obtained from a Siggard-Anderson nonogram that assumes normal noncarbonate buffers. With this simplification in mind, acid-base disorders can be described using only two parameters, P_{CO_2} and base excess. However, base excess has been criticized as an artificially derived, physiologically unregulated, and mechanistically unhelpful.

Since Siggaard-Anderson, the medical care of critically ill patients has grown enormously more complex. The extremes of human physiology are confronted routinely and complex problems in acid-base physiology arise frequently.

Stewart has proposed a new description of acid-base balance that is essentially a modern reworking of the buffer base concept of Singer and Hasting. In Stewart's approach, an analysis of noncarbonate buffers is embedded into the foundation of the model. Unlike base excess, Stewart's three independent variables may be used to both quantify and explain acid-base disorders. For example, Stewart's model has been used to explain acid-base disturbances following the massive infusion of normal saline solution, albumin, and blood [71–73].

However, Stewart uses an ad hoc definition of acids and bases that has not been widely adopted. In addition, his claim that [SID] is an "independent variable" while $[HCO_3^-]$ is a "dependent variable" may or may not be justified.

Based upon standard thermodynamic equilibrium equations, the ion equilibrium theory links together the various models of acid-base behavior. One enumerates "proton binding sites" to derive the "traditional" model while one enumerates "ion charge" to derive the Stewart model.

In many situations, both models can be shown to be mathematically equivalent.

As equilibrium equations are independent of path, any convenient set of variables may be used to describe the process under investigation. Therefore, ion equilibrium theory can provide no intrinsic rationale for choosing between the "traditional" and Stewart parameters.

Investigations of the biologic properties of water may lend support to the new models of acid-base balance. The adoption of the Stewart model may provide new insight into the molecular biology and transport physiology of the renal tubule. For example, RTA and Bartter syndrome may be defined primarily as "chloride channelopathies" rather than disorders of net acid excretion. This may have important implications for the treatment of these disorders.

Complex acid-base disorders are easier to understand, explain, and rationalize using Stewart's methods compared with the traditional model. At the very least, Stewart's variables are valid mathematically and may provide more useful clinical information than the older parameters such as base excess and anion gap. For these reasons, the Stewart approach has gained popularity in the intensive care unit setting.

In conclusion, one should not regard acid-base chemistry as a closed chapter in clinical medicine. Advances in basic chemistry, mathematics, and computer science may yet provide new insight into an old problem.

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