Special Report

Further Light on the Acid-Base Debate

THE FOLLOWING report is the result of arduous and lengthy efforts among many workers in the field of acid-base equilibrium including several anesthesiologists, and it represents a fair appraisal of the state of the art at the present time. This report does not present the clear cut, simplified picture which many might have expected from the New York Academy of Sciences Conference on Acid-Base Measurements held in November 1964. While this meeting resulted in very significant areas of agreement, it was unable to settle a major issue: the most suitable measure for characterizing the metabolic component of acid-base equilibrium. However, in this debate, differences of opinion were by no means determined by geographical location. This report also points out a major pitfall in acid-base chemistry today, which was echoed in the editorial recently published in ANESTHESIOLOGY,* namely, a confusion between methodology and interpretation.

Indeed, as stressed throughout this report, a clear distinction should be made between the measurements which are performed in the laboratory and their clinical interpretation for diagnosis and therapy. It is, therefore, an error to state that certain of these measurements, such as: "buffer base, standard bicarbonate and base excess have no quantitative validity." None of the investigators referred to by Dr. Bunker, on either side of the Atlantic (or the Pacific), would make this statement which is, in effect, a negation of analytical chemistry.

At present, emphasis should be placed on the proper performance of the techniques, whatever they are, which are used to measure acid-base factors. If properly performed, these techniques will yield valid quantitative data. How all of this data can be best used for patient care is still open to debate, but everyone agrees that proper interpretation of laboratory data depends upon the clinical assessment of each individual case. Considerable more work will have to be done in order to determine which measure of the "metabolic component" is more useful for diagnosis or therapy in each of the many clinical disturbances of acid-base equilibrium.

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* Bunker, J. P.: The great trans-Atlantic acid-base debate, ANESTHESIOLOGY 26: 591, 1965.

Statement on Acid-Base Terminology
Report of ad hoc committee of New York Academy of Sciences Conference (November 23 and 24, 1964)

On the occasion of a symposium on "Current Concepts of Acid-Base Measurements" held under the auspices of the New York Academy of Sciences (November 23 and 24, 1964) a number of investigators discussed proposals designed to reduce semantic confusion in the field.* It was hoped that teaching by and communication among workers in various fields would be helped if the basis and application of the subject were described according to a common usage. The meeting revealed a measure of agreement on many topics and clarified the basis of the disagreement on others. In deference to these conflicting views the committee simply reports below definitions and terminology which appeared to be acceptable to most participants and indicates where disagreement occurred and where problems may arise in the future. Recommendations are not made, but the weight of agreement on many topics may encourage others to adopt the same usage and terminology.

Definitions and Principles

1. *Acid-Base Terminology.* In the Brønsted-Lowry system an acid is a proton donor and a base is a proton acceptor. Acid-base reactions can be described as follows:

$$A_1 + B_2 \rightleftharpoons A_2 + B_1$$

where A_1, B_1 represent one conjugate acid-base pair and A_2, B_2 represent a second conjugate acid-base pair. Thus, for the dissociation of acetic acid in water:

$$CH_3COOH + H_2O \rightleftharpoons H_3O^+ + CH_3COO^-$$

CH_3COOH (acetic acid) and CH_3COO^- (acetate ion) represent one conjugate acid-base pair and H_3O^+ and H_2O represent the second conjugate acid-base pair. The Brønsted-Lowry concepts have been shown to have many advantages over those of the older electrolytic dissociation theory based on the work of Ostwald and Arrhenius. In particular, the older definitions do not take into account the central role of water in acid-base reactions in aqueous systems. The current trend in undergraduate chemistry courses is to use the Brønsted-Lowry system to the exclusion of the older terminology.[1]

2. *Buffers.* As defined by Van Slyke[2] "These are substances which by their presence in solution increase the amount of acid or alkali that must be added to cause unit change in *p*H." Weak acids with their conjugate bases act as buffers. In biological fluids, such acids include carbonic, phosphoric, organic acids and the acid (proton donor) groups of protein molecules. Van Slyke has defined the buffer value, β, as a differential ratio:

$$\beta = \frac{db}{dp\mathrm{H}}$$

where *db* is an increment of strong base in equivalents. In these terms, a solution has unit buffer value when a liter will take up 1 equivalent of strong base per unit increase of *p*H on the assumption that there is no volume change. An increment of strong acid is equivalent to a decrement, $-db$, of strong base and will produce a decrement of *p*H, $-dp\mathrm{H}$. Thus β is always positive. (For further details see Van Slyke[2] and Bates.[2]) Anions and cations such as chloride, sodium, potassium, magnesium and calcium do not functions as buffers, *i.e.*, are neither acids nor bases. They are "aprotes."

3. *pH, Hydrogen Ion Concentration and Hydrogen Ion Activity.* As defined formally by Sørensen[4,5] *p*H bears a theoretically simple relation to the hydrogen ion concentration

* *Andersen, O. S., Astrup, P.*, Bates, R. G., Brown, E. B., Butler, T. C., *Campbell, E. J. M., Chinard, F. P.*, Christensen, H. N., Darrow, D. C., Engel, K., Eichenholz, A., Elkinton, J. R., Fencl, V., Filley, G. F., Fink, B. R., Gambino, S. R., Hastings, A. B., Holaday, D. A., Huckabee, W., Moore, F. D., *Nahas, G. G.*, Peirce, E. C., Redstone, D., Refsum, H. F., Relman, A. S., Schwartz, W. B., Siesjö, B. K., Simmons, D. H., Singer, R. B., Van Slyke, D. D., Welt, L. G., Whitehead, T. P., *Winters, R. W.*, Robin, E. D., Severinghaus, J. W., Weisberg, H. F. Members of the *ad hoc* committee are shown in italics.

$[H^+]$ or c_{H^+} as follows:

$$pH = \log \frac{1}{[H^+]} = \log \frac{1}{c_{H^+}} \quad (1)$$

In practice, however, it is necessary to use an operational definition of *p*H. Thus, the following is generally accepted:

$$pH = pH_s + \frac{(E - E_s)\,F}{2.3026\,RT} \quad (2)$$

where pH_s is the assigned *p*H value of a standard buffer, E and E_s are the values of the electromotive force of a *p*H cell with the electrodes immersed in the unknown fluid and in the standard (denoted by subscript s), respectively, F is the Faraday, R is the gas constant and T is the absolute temperature.

Practically, *p*H defined in this manner can be related to the activity of hydrogen ion, a_{H^+}, as follows:

$$pH = \log \frac{1}{a_{H^+}} = -\log a_{H^+} \quad (3)$$

Because the activity coefficient of the hydrogen ion is not known accurately, the accuracy of values calculated for hydrogen ion concentration, c_{H^+}, is uncertain. Therefore, expression of measured a_{H^+} as, for example, c_{H^+} in nanomoles per liter (nmol./l.) is at best an approximation. Thus, if expression (1) is used to calculate c_{H^+} from a *p*H value determined experimentally this is equivalent to assigning the value of unity to the hydrogen ion activity coefficient implicit in expression (3). There was a strong belief that where hydrogen ion concentration is reported the activity coefficient used should be explicitly stated.

The distinction between molar and molal concentration units is of importance in biological fluids and the scale used should be clearly indicated. Thus, the *p*H values obtained from (2) and (3) are related to a molal concentration scale.

Whether electrometric or colorimetric procedures are used to measure *p*H, the values obtained depend on the *p*H values assigned to the standards. The *p*H values assigned to the standards are different at different temperatures. In reporting *p*H values, the values assigned to the standards and the temperature at which the determinations are made must be indicated in order to permit comparisons with values obtained by other investigators.

In the case of *p*H determinations carried out on samples of whole blood, the *p*H values obtained reflect the *p*H of the plasma phase slightly modified by the effect of the suspended erythrocytes. Because the *p*H values depend on the temperature at which the determinations are carried out, the temperature of the blood (or patient) as obtained must be given as well. If correction of *p*H values are made because the temperature of the blood sample as obtained differs from its temperature when the *p*H measurement is made, then the procedure used should be given.

4. *The Carbon Dioxide System.* The definitions of the constituents of the carbon dioxide system vary depending on whether a physiological or physico-chemical viewpoint is used. The interrelationships are outlined elsewhere.[6]

a. *Total carbon dioxide concentration.* The carbon dioxide extractable from a biological fluid in the presence of strong acid. This represents the following known chemical species: dissolved carbon dioxide, carbonic acid, bicarbonate ion, carbonate ion, carbamino compounds. Usual units are mmol./l.†

b. *Partial pressure of carbon dioxide, carbon dioxide tension of biological fluids.* The partial pressure of carbon dioxide in a gas phase in equilibrium with the biological fluid. The symbols are P_{CO_2} or pCO_2. The symbol P is used according to "Standardization of Definitions and Symbols in Respiratory Physiology," Fed. Proc. 9: 609, 1950. The symbol p is used by ISO in relation to the gaseous phase. Usual units are millimeters of mercury (Torr).

c. *Carbonic acid concentration.* The concentration of the chemical species H_2CO_3. In biological fluids, the concentration of this species is quantitatively negligible in comparison with dissolved carbon dioxide concentration. Usual units are mmol./l.

d. *Dissolved carbon dioxide concentration.* Strictly, the concentration of the physically dissolved CO_2 gas. However, carbonic acid, H_2CO_3, is usually included. The sum is designated as $S \times P_{CO_2}$ where S is the coefficient

† Abbreviation recommended by the International Standardization Organization (ISO).

relating the sum of the concentrations of dissolved CO_2 and H_2CO_3 in mmol./l. to pCO_2 in millimeters of mercury. The value of S is temperature dependent.

e. *Bicarbonate ion concentration.* The strict chemical definition is the concentration of the HCO_3^- ion in a biological fluid. However, in physiological studies, bicarbonate ion concentration is calculated as total carbon dioxide concentration minus $S \times P_{CO_2}$. Thus, the physiological usage includes carbamino compounds, and carbonate plus bicarbonate while the chemical definition does not. In the definitions which follow, the term "bicarbonate" is used in the physiological sense. The error introduced by this approximation is small in plasma and extracellular fluid but large in intracellular fluid. Units are mmol./l. or mEq./l.

f. *Standard bicarbonate concentration.*‡ The bicarbonate ion concentration in the plasma from whole blood that has been equilibrated to a P_{CO_2} of 40 mm. of mercury at 37° C. (As defined originally of Jørgensen and Astrup,[7] the temperature of equilibration was 38° C.) Units are mEq./l.

g. *Bicarbonate concentration at standard pH (7.40).*‡ Similar to standard bicarbonate concentration except that P_{CO_2} is variable and *p*H is fixed at 7.40.

h. *Carbon dioxide combining power.* The total carbon dioxide concentration of anaerobically separated plasma equilibrated to a P_{CO_2} of 40 mm. of mercury at room temperature. (This determination is no longer generally used because it is too dependent upon the conditions in the blood when plasma is separated.) Usual units are mmol./l.

5. *Buffer Base.* In Brønsted terminology the sum of concentrations in mEq./l. of the buffer anions of whole blood bicarbonate, plasma proteins, hemoglobin. This definition does not include the small amounts (at constant *p*H) of other buffers such as organic phosphates of the red cells. (See Singer and Hastings.[8,9] Units are mEq./l.)

6. *Base Excess.*‡ The formal definition given by Siggaard-Andersen and Engel[10] is as follows: the base concentration in mEq./l. of whole blood as measured by titration with strong acid to *p*H 7.40 at a P_{CO_2} of 40 mm. of mercury at 37° C. (originally *p*H 7.38 and 38° C.). For negative values of base excess the titration is carried out with strong base. Such negative values can be denoted by the term "base deficit."

7. *The Henderson-Hasselbalch Equation.* This equation relates the different forms of carbon dioxide in plasma:

$$pH = pk'_1 + \log \frac{[\text{total } CO_2] - S \times P_{CO_2}}{S \times P_{CO_2}}$$

$$= pk'_1 + \log \frac{[HCO_3^-]}{S \times P_{CO_2}}$$

where pk'_1 is the negative logarithm of the apparent first ionization constant of H_2CO_3 and S is the factor relating the partial pressure of carbon dioxide and the sum of the dissolved carbon dioxide and carbonic acid in plasma. Calculation of one of the three variables, *p*H, $[HCO_3^-]$, P_{CO_2} from the other two is valid only for a single phase such as the plasma or serum sample as separated from whole blood. There is no simple procedure for applying the Henderson-Hasselbalch equation to whole blood.

Characterization of the Acid-Base Status of Blood

It was in this area that disagreements were most evident between conferees. The problem is how best to determine and describe the metabolic component of acid base equilibrium *for clinical purposes.* Everyone agreed that P_{CO_2} is the only adequate measure of the respiratory component. The last half century of effort to characterize the metabolic (non-respiratory) component has left a trail of techniques and terms, some of which have been abandoned. But the conferees disagreed on which should be retained. In view of this disagreement, the two most widely held opinions on this unsettled matter are presented below.

1. *Use of Whole Blood Base Excess (or change of buffer base "ΔBb").* One group holds that the metabolic component of acid-base equilibrium is most precisely characterized by the base excess (*i.e.*, change in whole blood buffer base at constant homoglobin concentration), a quantity which being independent of P_{CO_2} in a physicochemical sense pre-

‡ Values for standard bicarbonate and base excess may refer either to blood as drawn or to the blood oxygenated *in vitro*.[11] In both cases methods used should be stated.

cisely expresses the number of milliequivalents of acid or base lost or gained by one liter of *whole blood.* This quantity can be accurately derived or measured by any of several methods, one of which involves the "titration" of blood samples with CO_2 *in vitro.* This group recognizes further: (1) that base excess is not independent of P_{CO_2} *in vivo* (*i.e.,* that the CO_2 "titration" curve of blood *in vitro* differs slightly from that of blood *in vivo*); (2) that such a fact is not a relevant argument against the validity of the analytical method for its determination, but is, however, a relevant argument in the interpretation of any given value for base excess of whole blood; (3) that a physiological assessment of the patient is essential for the proper interpretation of the base excess as it is for interpretation of all acid-base data.

In summary therefore, this group believes that the most suitable measures for characterizing the acid-base status of blood are:

(1) Whole blood base excess or change of buffer base.
(2) Blood or plasma P_{CO_2}.
(3) Plasma *p*H.

2. *Use of the Plasma Bicarbonate.* The second group holds that the traditional method of characterizing acid-base status of the blood in terms of the CO_2-bicarbonate buffer system of the plasma is more meaningful. This group recognizes that plasma bicarbonate as a measure of the metabolic component is not independent of P_{CO_2} in either a physicochemical sense (because of the effects of CO_2 upon the non-bicarbonate buffers) nor in a physiological sense. This group also believes: (1) that most of the advantages claimed for base excess are lost since base excess is not independent of P_{CO_2} physiologically; (2) that the datum provided by base excess (*i.e.,* the number of mEq. of acid/or base gained or lost per *liter* of *whole blood*) is not required for clinical purposes, since it cannot be acted upon directly in any sound theoretical manner in the formulation of therapeutic programs; (3) that each datum must be interpreted physiologically to be useful diagnostically. Thus, for clinical purposes, base excess offers no advantages over the plasma bicarbonate as a measure of the metabolic component.

In summary, therefore, this group believes that the most suitable measures for characterizing the acid-base status of blood are:

I. Plasma bicarbonate.
II. Blood or plasma P_{CO_2}.
III. Plasma *p*H.

Interconversion (most conveniently by graph) enables both views to be taken of any situation provided the hemoglobin concentration and the O_2 saturation of blood samples are recorded.

Description of Clinical Disturbances of Acid-Base Equilibrium

The following represents the consensus but by no means the unanimous opinion of the conferees with respect to description of clinical disturbances of acid-base equilibrium. While use of a uniform terminology to describe disturbances is obviously desirable, this does not appear possible at this time. It would, however, seem desirable that the details of any system of terminology substantially different from the one described below be fully stated so that confusion of terms may be avoided.

1. *Definitions of "Acidosis" and "Alkalosis."* Although a usage based upon some change in the chemical composition of the blood is widespread, the majority of the conferees preferred to use the terms in a physiological sense: the terms "acidosis" and "alkalosis" describe abnormal processes or conditions which would cause a deviation of *p*H if there were no secondary changes in response to the primary etiologic factor. The compartment of the body fluids (*i.e.,* extracellular or intracellular) in which these changes are occurring should be specified, but when not specified, it is assumed that the extracellular compartment is being referred to.

In this usage, "acidosis" and "alkalosis" either unmodified or modified either by such general adjectives as "respiratory" or "metabolic" or more specific adjectives (*e.g.,* "renal," "diabetic," "lactic," "diarrheal," etc.) describe the overall process or condition without making such usage dependent upon deviation of *p*H *per se.*

2. *Definitions of "Simple" and "Mixed" Disturbances of Acid-Base Equilibrium.* Simple

disturbances of acid-base equilibrium are those in which there is a single primary etiologic factor known to produce a disturbance in acid-base equilibrium. Mixed disturbances of acid-base equilibrium are those in which two or more primary etiological factors are present simultaneously.

3. *Designation of Secondary or Compensatory Phenomena.* According to the above definitions the usual secondary physiologic (*i.e.*, compensatory) responses to a primary disturbance are not designated as "acidosis" or "alkalosis." The adjectives "secondary" or "compensatory" may be applied to describe a change in composition of the blood (*e.g.*, P_{CO_2}, bicarbonate concentration) or to describe a process (ventilation, renal excretion of acid) but are not used to modify the nouns "acidosis" or "alkalosis." For example, the secondary hyperventilation occurring in simple metabolic acidosis would not be described as "secondary or compensatory respiratory alkalosis." By the same token, the renal production of bicarbonate occurring in simple respiratory acidosis is not a "secondary or compensatory metabolic alkalosis."

4. *Designation of Mixed Disturbances.* Mixed disturbances of acid-base equilibrium are designated by names describing the effects of each etiologic factor separately, *e.g.*, metabolic acidosis and respiratory alkalosis. All "double-named" disturbances are mixed disturbances and such double-names do not represent simple disturbances with secondary or compensatory changes. To be absolutely clear it may be preferable to preface these "double-names" with the term "mixed disturbance," *e.g.*, "mixed disturbance with metabolic acidosis and respiratory alkalosis." Criteria for diagnosis of a mixed disturbance require that there be evidence of more than one primary disturbance occurring simultaneously and such evidence should be presented.

5. *Terms to Describe the State of Acid-Base Variables in Blood.* The *most* desirable practice is to report the actual numerical data (*e.g.*, $pH = 7.40$, $P_{CO_2} = 40$ mm. of mercury, etc.). The *second* most desirable practice is to use the terms "high," "low" and "normal" to qualify these variables, the normal range to be defined. While there should be no necessity for any other terms to describe the deviations of the acid-base parameters in the blood, it appears that the lack of such terms and the consequent use of other terms (such as "acidosis" or "alkalosis," "metabolic" or "respiratory") has been one important cause of confusion of nomenclature. Therefore, if there is need for such terms, the following words might be used as the third but least desirable practice: "acidemia" and "alkalemia" to indicate *p*H deviation; "hypercapnia" and "hypocapnia" to indicate deviation of P_{CO_2}; and "hyperbasemia" and "hypobasemia" to indicate deviations of the metabolic component. Since different investigators use different parameters to measure the metabolic component, the one used should be specified (*i.e.*, "bicarbonate," "standard bicarbonate," "base excess" or "buffer base"). This practice avoids the use of the terms "acidosis" and "alkalosis" to describe *p*H deviations of blood *per se;* it would also avoid the use of the terms "metabolic or respiratory acidosis or alkalosis" to indicate deviation of the respiratory or metabolic component of blood *per se.*

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AUTONOMIC NERVOUS SYSTEM Information regarding the maturation of the autonomic nervous system control mechanisms in human infants during normal development has led to difficulty in interpreting abnormal autonomic nervous system function. Familial dysautonomia results in aberrant catecholamine metabolism, malfunctioning visceral sensing mechanisms (baroreceptors and chemoreceptors) and deficiencies in other afferent systems (taste and pain). In view of current knowledge, infants and young children cannot be identified in terms of a predominance of a parasympathetic or sympathetic function. (*Lipton, E. L., Steinschneider, A., and Richmond, J. B.: Autonomic Nervous System in Early Life, New Eng. J. Med. 273: 201 (July 22) 1965.*)

POSTOPERATIVE BLEEDING Blood is lost into the gastrointestinal tract during and after operations upon it. The amount so lost was studied by injecting chromium labeled red cells before operation, doing blood volume studies before and daily after surgery, and collecting and analyzing all gastrointestinal aspirate and feces for six days. When tagged red blood cells are instilled into the gastrointestinal tract, 80 to 85 per cent is recovered in the stool. If there was no gross evidence of bleeding, the blood loss in the postoperative period was less than 100 ml. Postoperative anemia cannot be explained by seepage into the gastrointestinal tract. (*Rustad, H., and Vinje, O. L.: Intestinal Blood Loss in Surgery of the Gastrointestinal Tract, Acta Chir. Scand. 129: 192 (Feb.) 1965.*)

BARBITURATE POISONING Barbiturates are the commonest drugs involved in poisoning cases, and patients who have taken them may be comatose for years. The decision as to whether or not to use prophylactic antibiotics to ward off respiratory infection is debatable. In order to study the problem, 144 poisoned patients were studied. They were treated with endotracheal intubation, gastric aspiration and lavage, 4 with assisted respiration, and 15 with peritoneal dialysis. The 144 patients were divided into a control and a treated group. The treated patients were given penicillin twice daily until they had been conscious for 24 hours. The remaining group did not receive antibiotics. Five of the control group developed respiratory infections, and three of the treated group developed similar infections. None was serious. Prophylactic antibiotics should only be given to patients in whom a respiratory infection exists or potentially exists. (*Mackintosh, T. F., and Matthew, H.: Do Unconscious Poisoned Patients Need Prophylactic Penicillin? Lancet 1: 1252 (June 12) 1965.*)