Acta Anaesthesiol Scand 1995: 39: Supplementum 106, 123-128

Base excess or buffer base (strong ion difference) as measure of a non-respiratory acid-base disturbance

O. SIGGAARD-ANDERSEN AND N. FOGH-ANDERSEN

Department of Clinical Biochemistry, Herlev Hospital, University of Copenhagen, Denmark

Stewart in 1983 (*Can J Physiol Pharmacol* 1983: 61: 1444) reintroduced plasma buffer base under the name "strong ion difference" (SID). Buffer base was originally introduced by Singer and Hastings in 1948 (*Medicine (Baltimore)* 1948: 27: 223). Plasma buffer base, which is practically equal to the sum of bicarbonate and albuminate anions, may be increased due to an excess of base or due to an increased albumin concentration. Singer and Hastings did not consider changes in albumin as acid-base disorders and therefore used the base excess, *i. e.* the actual buffer base minus the buffer base at normal pH and pCO_2, as measure of a non-respiratory acid-base disturbance. Stewart and followers, however, consider changes in albumin concentration to be acid-base disturbances: a patient with normal pH, pCO_2, and base excess but with increased plasma buffer base due to increased plasma albumin concentration get the diagnoses metabolic (strong ion) alkalosis (because plasma buffer base is increased) combined with metabolic hyperalbuminaemic acidosis. Extrapolating to whole blood, anaemia and polycytaemia should represent types of metabolic alkalosis and acidosis, respectively. This reveals that the Stewart approach is absurd and anachronistic in the sense that an increase or decrease in any anion is interpreted as indicating an excess or deficit of a specific acid. In other words: a return to the archaic definitions of acids and bases as being the same as anions and cations.

We conclude that the acid-base status (the hydrogen ion status) of blood and extracellular fluid is described in terms of the arterial pH, the arterial pCO_2, and the extracellular base excess. It is measured with a modern pH-blood gas analyzer. The electrolyte status of the plasma is a description of the most important electrolytes, usually measured in venous blood with a dedicated electrolyte analyzer, i.e. Na^+, Cl^-, HCO_3^-, and K^+. Albumin anions contribute significantly to the anions, but calculation requires measurement of pH in addition to albumin and is usually irrelevant. The bicarbonate concentration may be used as a screening parameter of a non-respiratory acid-base disturbance when respiratory disturbances are taken into account. A disturbance in the hydrogen ion status automatically involves a disturbance in the electrolyte status, whereas the opposite need not be the case.

Key words: Albumin anion; bicarbonate; blood; chloride; electrolytes; hydrogen ion.

There is general agreement that plasma pH is the target of neutrality regulation of the body fluids and the overall measure of a clinical acid-base disturbance. There is also agreement that the arterial pCO_2 is an independent variable and measure of a respiratory acid-base disturbance. However, there is still discussion about the most relevant measure of a non-respiratory also called metabolic acid-base disturbance, i.e. a change in pH not caused by a change in pCO_2.

Among suggested measures of a non-respiratory acid-base disturbance are: total CO_2, actual bicarbonate, standard bicarbonate, standard pH, buffer base, whole blood base excess, and extracellular base excess. The most recent parameter, suggested by Stewart in 1981 (1, 2), is SID, acronym for strong ion difference, which is, however, apart from the name, exactly identical with the buffer base suggested by Singer and Hastings in 1948 (3).

Several authors have adopted SID (5-11) and we have been asked why we do not accept this "approach to acid-base which revolutionizes our ability to understand, predict, and control what happens to hydrogen ions in living systems" (2). In the following we will discuss each of the suggested parameters and explain why we prefer the extracellular base excess. But first it seems necessary to rehearse the definitions of acids and bases.

Before year 1923 acids and bases were synonyms for anions and cations. A sodium ion for example, was a base which could be neutralized by acid, chloride ion for example, to form a salt: sodium chloride (12, p. 7-10). In 1923-24 Brønsted and Lowry set focus on the hydrogen ion (the protons) (13, 14). The chemical potential of hydrogen ions determines the acidity of a solution. The pH value is directly proportional to the negative value of the chemical

potential. An acid is defined as a substance which is able to give off a hydrogen ion at the given pH, a base a substance which is able to bind a hydrogen ion. A buffer pair is a week acid, which enters equilibrium with its corresponding week base at the given pH. According to these definitions chloride and sodium ions are neither acid nor base but aprotes (without protons).

ACTUAL BICARBONATE

Bicarbonate is the most important buffer in a biological system at constant pCO_2. Therefore, as a first approximation, a pure sodium bicarbonate solution with added salts may serve as a model of the body fluids. In this model, a decrease or increase in bicarbonate concentration directly reflects the amount of added non-carbonic acid or base, while the bicarbonate concentration is independent of changes in pCO_2. Furthermore, the Henderson-Hasselbalch equation provides a simple relationship among the respiratory parameter, pCO_2, the non-respiratory parameter, $cHCO_3^-$, and the overall acidity parameter, pH.

The plasma total CO_2 concentration, also called CO_2 content, is only slightly higher than the bicarbonate concentration. It has been much employed as a routine measure of a metabolic acid-base disturbance, simply because it was easy to measure with the Van Slyke apparatus (15). The bicarbonate concentration or the CO_2 content, measured on a modern chemical analyzer, is still fully adequate as a routine screening parameter for metabolic acidosis or alkalosis in patients with normal respiration.

However, a pure bicarbonate solution is too simple as a model of blood and extracellular fluid. Due to non-bicarbonate buffers, especially albumin and haemoglobin, a change in bicarbonate concentration does not reflect the total amount of accumulated non-carbonic acid or base, but more importantly: the bicarbonate concentration is not independent of variations in pCO_2. As pCO_2 increases, carbonic acid is buffered by non-bicarbonate buffers and the bicarbonate concentration increases. An elevated bicarbonate concentration may therefore erroneously be interpreted as a metabolic alkalosis when respiratory acidosis is the cause. There are reports of this misinterpretation in the literature (16). One approach to solve this problem was to measure the bicarbonate concentration at a standard pCO_2: standard bicarbonate. Another approach was to use the sum of bicarbonate and non-bicarbonate buffer anions: buffer base

STANDARD BICARBONATE

As early as 1916 Hasselbalch suggested measuring the "reduced" pH after equilibrating the blood with a pCO_2 of 5.33 kPa (40 Torr). The year after, Van Slyke and Cullen suggested measuring the CO_2 combining power that is the CO_2 content after the technician had blown expiratory air into the serum for a while. In 1954 Astrup designed an apparatus with a pH electrode and tonometer for measuring the standard bicarbonate, that is the bicarbonate concentration of the plasma phase of whole blood equilibrated with a CO_2-O_2 gas mixture of pCO_2 5.33 kPa (for references see 12, p. 92-96).

None of these parameters quantitatively express the amount of non-carbonic acid or base accumulated in the blood. However, such a quantitative measure had previously been suggested by Van Slyke in terms of the pH corrected bicarbonate, which is the bicarbonate concentration of serum or whole blood after equilibrating the sample with different gas mixtures and interpolating to a pH of 7.40. A change in Van Slyke corrected bicarbonate directly indicates the amount of accumulated non-carbonic acid or base (17).

BUFFER BASE (STRONG ION DIFFERENCE)

Singer and Hastings used the second approach to quantify a metabolic acid-base disturbance (3). They employed the old definitions of acids and bases being anions and cations, respectively. Their starting point was the Gamble diagram with the two columns of cations and anions of equal height, illustrating the law of electro-neutrality (18). They defined buffer base as the sum of strong "bases" (aprote or non-buffer cations) minus the sum of strong "acids" (aprote or non-buffer anions). In other words they focus on all other ions than the hydrogen ion. They used the symbol (B_B^+). Today aprote anions and cations are neither acids nor bases. In modern terminology, the concentration of "buffer base" is defined as the sum of the products of substance concentration and charge number of aprote ions ($c\mathrm{AI} \cdot z\mathrm{AI}$). According to the law of electro-neutrality this must equal the negative sum of the products of substance concentration and charge number of buffer ions ($c\mathrm{BI} \cdot z\mathrm{BI}$):

$$(B_B^+) \stackrel{\text{def}}{=} \Sigma(c\mathrm{AI} \cdot z\mathrm{AI}) = -\Sigma(c\mathrm{BI} \cdot z\mathrm{BI}).$$

Unfortunately the distinction between aprote ions and buffer ions is somewhat arbitrary, depending upon the actual pH interval. A lactate ion is a buffer ion when the pH is around 3.6 but is considered an aprote anion at a pH around 7.4. One of the anion groups of HPO_4^{2-} is a buffer anion at a pH around 6.8 where the anion $H_2PO_4^-$ may be considered an aprote.

The rationale behind buffer base is that accumulation of strong acid or base is reflected stoichiometrically in a decrease respectively increase, whereas changes in pCO_2 does not affect the buffer base concentration. The rise in bicarbonate concentration associated with a rise in pCO_2 is

matched by a fall in concentration of other buffer anions

Measurement of buffer base is not easy if it is based on the equation of definition, which requires separate measurement of all the aprote cations and anions. It is easier to calculate buffer base on the basis of the second equality, calculating the bicarbonate concentration and adding the concentration of other buffer ions, e.g. haemoglobin anion. Singer and Hastings used this approach and constructed a nomogram which, among other calculations, allows calculation of plasma and whole blood buffer base from pH, pCO_2, and haematocrit.

The problem with buffer base is that the normal mean value, i.e. the value in blood or plasma at a pH of 7.40 and a pCO_2 of 5.33 kPa, depends on the concentration of buffers, primarily haemoglobin and albumin. Singer and Hastings were fully aware of this and recommended to use delta buffer base $\Delta(B_B^+)$, i.e. the change in buffer base from the value at pH=7.4 and pCO_2 = 5.33 kPa, as the measure of a metabolic acid-base disturbance (see 12, p. 27).

Stewart, who reintroduced buffer base under the name "strong ion difference" with the symbol [SID] (1,2), and his followers Fencl and coworkers from Boston (5-10), do not use delta buffer base ("delta strong ion difference") as measure of a metabolic acid-base disturbance. A decreased [SID] due to decreased albumin concentration, but with normal pH and pCO_2, is interpreted as "hypoalbuminaemic alkalosis" compensated by "strong ion acidosis". All anions, including buffer anions, are thought of as having been added or removed from the plasma as acids. Plasma is thought of as originating from pure water (or a neutral salt solution) by addition of pure albumin, which is titrated to the actual pH at the actual pCO_2 with strong base (strong cation). Hence [SID] is elevated in the case of hyperalbuminaemia. This interpretation of an elevated albumin (or elevated haemoglobin in the case of whole blood) as indicating a type of metabolic acidosis, and similarly a decreased albumin or haemoglobin as indicating a type of metabolic alkalosis, is contrary to all previous rational thinking. Singer and Hastings would never have called a decreased whole blood buffer base due to anaemia a metabolic acidosis with anaemic alkalosis.

BASE EXCESS

The key component in the acid-base status of blood, plasma, or other body fluids is the hydrogen ion. The amount of hydrogen ion added to or removed from the system may be determined by back titration to the original (reference) pH by adding or removing hydrogen ion (with Cl^-) when the pH is above or below the reference pH, respectively.

The two quantities which describe a chemical component in a physico-chemical system are the chemical potential (the intensive quantity) and the stoichiometric amount of substance of the component (the extensive quantity) (19). The former is often expressed as the activity or concentration of free component in the system. The latter is generally divided by the volume of the system and expressed as the stoichiometric concentration or concentration of total component in the system. Examples of these two quantities are: pCO_2 and concentration of total CO_2, pO_2 and concentration of total O_2, concentrations of free and total calcium ion, concentrations of free and total thyroxin. In the case of hydrogen ion the intensive quantity is pH, which is directly proportional to the negative chemical potential. The stoichiometric concentration is represented by the concentration of titratable hydrogen ion.

In blood or plasma, where pCO_2 is an independent variable, the concentration of titratable hydrogen ion is determined by titrating to a pH of 7.4 at a pCO_2 of 5.33 kPa at a temperature of 37 °C. This quantity with opposite sign is called the base excess, understanding that a negative value indicates a base deficit, which is equivalent with a non-carbonic acid excess (12, p. 12). It is numerically identical with the $\Delta(B_B^+)$ of Singer and Hastings. In view of the ambiguity of the words acid and base it might be preferable to use the name (net) titrimetric (or stoichiometric) concentration of hydrogen ion or (net) concentration of titratable hydrogen ion (symbol ΔctH^+, or Δc_tH^+). This would emphasize that the quantity refers to hydrogen ions, not cations or anions, and indicate that the quantity may be either positive or negative.

An increase in net titratable hydrogen ion reflects addition of hydrogen ion, whether added from the outside or generated within the system. For example, oxygenation of haemoglobin causes an increase in net titratable hydrogen ion because hydrogen ions are liberated from the so-called oxygen linked buffer groups, an effect, which is traditionally called the Haldane effect (see 12 p. 71). Hydrogen ions cannot be added without simultaneously adding some anion or removing some cation. The Haldane effect results in addition of hydrogen ions with the simultaneous disappearance of $=NH^+$, $=NH_2^+$, or $-NH_3^+$ ions of the oxygen linked buffer groups..

In actual practise net titratable hydrogen ion is not determined by titration but rather by calculation as Singer and Hastings did from pH, pCO_2, and the buffer concentration. A curve nomogram was constructed for this purpose, later transformed into an alignment nomogram similar to the Singer and Hastings nomogram (see 12, p. 51-70). An equation for calculating net titratable hydrogen of whole blood was also developed (12, p. 51, Eqn 15), later named the Van Slyke equation (20, 21) to honour Donald D. Van Slyke's contributions to our understanding of acid-base equilibria (although he used the old definitions of acids and bases as being equivalent to anions and cations). An updated version of the Van Slyke equation is given in

Table 1.

While base excess is defined as titratable base, titrating to an end point pH of 7.40 at a pCO_2 of 5.33 kPa, plasma buffer base (SID) may be determined (in principle at least) by titrating to an end point pH equal to the isoionic pH of albumin at a pCO_2 of zero (12, p. 27). The titration would not include all the phosphate ions, but this would cause a very minor discrepancy. This point of view clearly shows the analogy between base excess and buffer base, but also shows that the end point of titration is much more physiological in the case of base excess than in the case of buffer base.

Table 1.
The Van Slyke equation (21) updated. For calculation of the extracellular concentration of net titratable hydrogen ion, ΔctH^+_{Ecf}, divide the haemoglobin concentration of the blood by 3: $cHb_{Ecf} = cHb_B/3$.

ΔctH^+_B	$= - (1 - cHb_B/cHb^-) \cdot (\Delta cHCO_3^-{}_P + \beta H^+_B \cdot \Delta pH_P)$,
cHb_B	haemoglobin concentration of the blood,
cHb^-	= 43 mmol/L, an empirical parameter accounting for erythrocyte plasma distributions,
$\Delta cHCO_3^-{}_P$	$= cHCO_3^-{}_P - cHCO_3^-{}^-$,
$cHCO_3^-{}_P$	actual bicarbonate concentration of the plasma, calculated from pH and pCO_2 using the Henderson-Hasselbalch equation,
$cHCO_3^-{}^-$	= 24.5 mmol/L, bicarbonate concentration in standard plasma at $pH^- = 7.4$ and $pCO_2^- = 5.33$ kPa,
βH^+_B	$= \beta_m Hb^- \cdot cHb_B + \beta_P$, buffer value of non-bicarbonate buffers in blood,
$\beta_m Hb^-$	= 2.3, *apparent* molar buffer capacity of haemoglobin (monomer) in whole blood (11, p. 47),
β_P	$= \beta_m Alb^- \cdot cAlb_P + \beta_w Glb^- \cdot \rho Glb_P + \beta_m PO_4 \cdot cPO_4$, $\approx \beta_w Pr^- \cdot \rho Pr_P$, buffer value of non-bicarbonate buffers in plasma, default value = 7.7 mmol/L,
$\beta_m Alb^-$	= 8.0, molar buffer capacity of albumin,
$cAlb_P$	substance concentration of albumin in plasma, (default value 0.65 mmol/L),
$\beta_w Glb^-$	= 0.075 mol/kg, apparent specific buffer capacity of plasma globulins,
ρGlb_P	mass concentration of globulins in plasma,
$\beta_m PO_4$	= 0.309 (at pH = 7.4), molar buffer capacity of phosphate ion,
cPO_4	concentration of inorganic phosphate in plasma,
$\beta_w Pr^-$	= 0.11 mol/kg, apparent specific buffer capacity of total protein in plasma,
ρPr	mass concentration of total protein in plasma,
$\Delta pH_P = pH_P - pH^-$.	

BASE EXCESS OF THE EXTRACELLULAR FLUID

Whole blood base excess remains constant when pCO_2 is varied in a blood sample *in vitro*. However, when the pCO_2 is varied *in vivo*, by CO_2 inhalation or hyperventilation, not only blood but all extracellular fluid is equilibrated with the new pCO_2. When pCO_2 increases pH tends to decrease more in the poorly buffered interstitial fluid than in the well buffered blood. Hydrogen ions therefore tend to diffuse from the interstitial fluid into the blood where they are buffered in the erythrocytes. This addition of H^+ to the blood is registered as a fall in whole blood base excess while the plasma base excess rises slightly (see 12, p. 96 and p. 115-119). The actual ionic movements involve a diffusion of bicarbonate ions from the erythrocytes to the plasma and interstitial fluid in exchange for chloride ions. Standard bicarbonate, CO_2 combining power, whole blood buffer base, and plasma buffer base (SID) all display changes similar to the changes in plasma and whole blood base excess during acute pCO_2 changes *in vivo*. However, the base excess of the total extracellular fluid remains constant.

It is not possible to obtain a sample of average extracellular fluid (including erythrocytes). However, a blood sample diluted three fold (1 + 2) with its own plasma may serve as a model of the extracellular fluid. Base excess of such a model of the extracellular fluid may be calculated using the Van Slyke equation and it now represents the most relevant measure of a metabolic acid-base disturbance. Modern pH-blood gas analyzers calculate the extracellular base excess and present the result with the same ease as they present the actual bicarbonate concentration.

Bill Schwartz and Arnold Relman in Boston in 1967 continued to advocate the use of the actual bicarbonate concentration (22) and a discussion in letters to the editors of several journals was called “the great trans-Atlantic acid-base debate” by John Bunker (23). It may now be called “the great trans-American acid-base debate” because John Severinghaus in San Francisco is one of the strongest advocates of the extracellular base excess (24-29).

TYPES OF METABOLIC ACIDOSIS AND ALKALOSIS

Metabolic acidosis or alkalosis may have many different etiologies: vomiting, diarrhoea, renal failure, anaerobic metabolism, to name a few, resulting in complex acid-base and electrolyte disturbances. As a consequence of the electro-neutrality principle, hydrogen ions cannot be added or removed without simultaneous addition or removal of an anion or exchange with a cation. Analysis of the other ions (the electrolyte status) may give some clue to the cause of a base excess or deficit, especially when elevated levels of an organic anion such as lactate or 3-hydroxy-butyrate are found. But an increased blood lactate, for example, does not necessarily indicate lactic acidosis. It could be due to

infusion of sodium lactate as a therapeutic measure in a case of metabolic acidosis due to gastrointestinal loss of sodium bicarbonate. The diagnosis hyperchloraemic acidosis, a relic from the time when chloride was considered an acid, does not reveal anything about the etiology of the acidosis. It could be due to dehydration and loss of sodium bicarbonate. The same applies to hypochloraemic alkalosis and hypernatriaemic alkalosis, which merely indicate an increased base excess associated with decreased chloride or increased sodium, respectively.

Jabor and Kazda in their application of the Stewart approach (11, present volume) describe a set of equations, to classify metabolic acid-base disturbances on the basis of concomitant changes in other electrolytes. They diagnose hyperchloraemic acidosis, hypochloraemic alkalosis, hyperphosphataemic acidosis, hypophosphataemic alkalosis, and hyperalbuminaemic acidosis and hypoalbuminaemic alkalosis, and acidosis and alkalosis "caused by" increases or decreases in undetermined anions. They emphasize that in patients with a normal extracellular base excess many hidden acid-base disorders may be present. In our terminology we would say that many hidden water and electrolyte disorders may be present. Three examples suffice to illustrate the unfamiliar and inept terminology resulting from the Stewart approach:

1)A patient has normal pH, pCO_2, and extracellular base excess. Plasma sodium is 149 mmol/l, chloride 110 mmol/L, albumin 0.9 mmol/L. Plasma buffer base (SID) is 45 mmol/L (normal 40 mmol/l). Potassium, calcium, magnesium, and phosphate are normal. In our terminology the patient has a normal acid-base status but a marked hyperalbuminaemia and a moderate hypernatraemia. In the Stewart terminology the elevated plasma buffer base indicates a metabolic alkalosis and classifying the disturbance according to Jabor and Kazda the patient has hypochloraemic (!) alkalosis combined with hyperalbuminaemic acidosis.

2)A patient has normal pH, pCO_2, and extracellular base excess with normal plasma sodium, potassium, calcium, magnesium, and phosphate, but slightly increased chloride (111 mmol/l) and decreased albumin (0.38 mmol/L). Plasma buffer base (SID) is 34 mmol/L. In our terminology the patient has a normal acid-base status with slight hyperchloraemia and hypoalbuminaemia. In Jabor and Kazda's terminology the patient has hyperchloraemic acidosis and hypoalbuminaemic alkalosis. This example clearly shows that they use the terms acidosis and alkalosis to refer to changes in the concentration of anions (*in casu* chloride and albuminate) not to refer to added or removed hydrogen ion.

3)A patient has pH=7.00, pCO_2=16.5 kPa, and extracellular base excess = 0.0 mmol/L. The plasma base excess is 3.0 mmol/L, plasma buffer base (SID) is 43 mmol/L. Plasma sodium, potassium, calcium, magnesium, phosphate are normal, but chloride is slightly decreased to 102 mmol/l. Plasma albumin is normal, but the concentration of plasma albumin anion is decreased to 9.0 mmol/L due to the low pH. In our terminology the patient has a pure respiratory acidosis with no metabolic component. In the Stewart terminology the patient has a slight metabolic alkalosis (reduced plasma buffer base), and in the Jabor/Kazda terminology the patient has a slight hypoalbuminaemic and hypochloraemic alkalosis. This example illustrates that plasma buffer base (SID) does not remain constant in a pure respiratory acid-base disturbance *in vivo*, and it also reveals some inconsistency between the original Stewart terminology and the terminology suggested by Jabor and Kazda since Stewart would not have diagnosed the hypoalbuminaemic alkalosis.

CONCLUSION

The Stewart approach was proclaimed a revolutionary new approach and it was stated that "many current models for ion movements through membranes will require modification on the basis of this quantitative analysis" (2). Several publications on SID were praised in editorials in the respective journals (4, 30) and we do acknowledge that the study by Figge, Mydosh, and Fencl on the isoionic pH and buffer value of human albumin (9) has provided valuable reference data.

We have shown, however, that the approach is anachronistic and the terminology misleading, confusing anions and cations with acids and bases. The acid-base status of blood and extracellular fluid is equivalent to the hydrogen ion status, not equivalent to the electrolyte status of the plasma. Due to the electro-neutrality principle changes in the hydrogen ion status automatically involve changes in the electrolyte status but the opposite need not be the case. The three relevant acid-base quantities are the arterial pH, the arterial pCO_2, and the extracellular base excess. Determination requires an arterial blood sample and a modern pH-blood gas analyzer. Total CO_2 (bicarbonate) measured in venous plasma using an electrolyte analyzer or multi-purpose chemical analyzer may be used as screening parameter in patients without respiratory disorders. All other parameters suggested as measures of a metabolic acid-base disturbance are obsolete.

ACKNOWLEDGEMENT

Robert Schlichtig, M.D., Department of Anesthesiology, V.A. Medical Center, University of Pittsburgh, provided help and stimulation (31).

REFERENCES

1. Stewart PA. How to understand acid-base: a quantitative acid-base primer for biology and medicine. New York: Elsevier/North-Holland, 1981.
2. Stewart PA. Modern quantitative acid-base chemistry. *Can J Physiol Pharmacol* 1983: **61**: 1444-1461.
5. Rossing TH, Maffeo N, Fencl V. Acid-base effects of altering plasma protein concentration in human blood in vitro. *J Appl Physiol* 1986: **61**: 2260-2265.
6. McAuliffe JJ, Lind LJ, Leith DE, Fencl V. Hypoproteinemic alkalosis. *Amer J Med* 1986: **81**: 86-90.
7. Fencl V, Rossing TH. Acid-base disorders in critical care medicine. *Annu Rev Med* 1989: **40**: 17-29.
8. Figge J, Rossing TH, Fencl V. The role of serum proteins in acid-base equilibria. *J Lab Clin Med* 1991: **117**: 453-467.
9. Figge J, Mydosh T, Fencl V. Serum proteins and acid-base equilibria: a follow-up. *J Lab Clin Med* 1992: **120**: 713-719.
10. Fencl V, Leith DE. Stewart's quantitative acid-base chemistry: Applications in biology and medicine. *Resp Physiol* 1993: **91**: 1-16.
11. Jabor A, Kazda A. Modelling of acid-base equilibria. *Acta Anaesth Scand* 1995: **39**: Supplementum 106, 000-000.
12. Siggaard-Andersen O. The acid-base status of the blood, 4. revised ed. Copenhagen: Munksgaard, 1976, and Baltimore: Williams & Wilkins Company, 1976.
13. Brønsted JN. Einige Bemerkungen über den Begriff der Säuren und Basen. *Rec Trav Chim Pays-Bas* 1923: **42**: 718-728.
14. Lowry TM. The electronic theory of valency. IV. The origin of acidity. *Trans Faraday Soc* 1924: **20**: 13-15.
15. Van Slyke DD, Neill JM. The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. *J Biol Chem* 1924: **61**: 523-575.
16. Astrup P, Severinghaus JW. The history of blood gases, acids and bases. Copenhagen: Munksgaard, 1986: 1-332.
17. Van Slyke DD, Austin IH, Cullen GE. The effect of ether anesthesia on the acid-base balance of the blood. *J Biol Chem* 1922: **53**: 277-292.
18. Gamble JL. Chemical anatomy, physiology and pathology of extracellular fluid, 5. ed. Cambridge (Mass.): Harvard Univ Press, 1947.
19. Siggaard-Andersen O, Durst RA, Maas AHJ (IFCC, Expert Panel on pH and Blood Gases, IUPAC, Commission on Quantities and Units in Clinical Chemistry). Approved recommendation (1984) on physico-chemical quantities and units in clinical chemistry with special emphasis on activities and activity coefficients. *J Clin Chem Clin Biochem* 1987: **25**: 369-399. *Ann Biol Clin* 1987: **45**: 89-109.
20. Siggaard-Andersen O. Acid-base algorithms. *NBS Special Publication* 1977: **450**: 21-26.
21. Siggaard-Andersen O. The Van Slyke equation. *Scand J Clin Lab Invest* 1977: **37**, Suppl 146: 15-20.
22. Schwartz WB, Relman AS. A critique of the parameters used in the evaluation of acid-base disorders. *N Engl J Med* 1963: **268**: 1382-1388.
23. Bunker J. Great trans-Atlantic acid-base debate. *Anesthesiol* 1965: **25**: 591-594.
24. Severinghaus JW. Acid base balance nomogram. A Boston - Copenhagen detente? *Anesthesiol* 1976: **45**: 539-41.
25. Levesque PR, Severinghaus JW. The Boston-Copenhagen detente, correspondence. *Anesthesiol* 1977: **47**: 232-234.
26. Severinghaus JW, Astrup P. History of blood gas analysis. *Int Anesth Clinics* 1987: **25**: 47-59.
27. Severinghaus JW, Levesque PR. Acid-base balance controversy. *J Clin Monitor* 1991: **7**: 274-279.
28. Severinghaus JW. More RIpH, letter. *JAMA* 1992: **267**: 2035-2036.
29. Severinghaus JW. Siggaard-Andersen and the "great trans-Atlantic acid-base debate". *Scand J Clin Lab Invest* 1993: **53**, Suppl 214: 99-104.
30. Reeves RB. Error proved and corrected: net anionic charge on serum albumin. *J Lab Clin Med* 1991: **117**: 437-437.
31. Schlichtig R. Validity of [base excess] and determination of critical tissue PCO_2 in humans *in vivo*. (Under preparation).
3. Singer RB, Hastings AB. An improved clinical method for the estimation of disturbances of the acid-base balance of human blood. *Medicine (Baltimore)* 1948: **27**: 223-242.
4. Reeves RB. Commentary on review article by Dr. Peter Stewart. *Can J Physiol Pharmacol* 1983: **61**: 1442-1443.

Address:
Ole Siggaard-Andersen, MD, PhD
University of Copenhagen
Dept. of Clinical Biochemistry
Herlev Hospital
DK-2730 Herlev, Denmark

Siggaard-Andersen O. Hydrogen-ions and blood gases. In. Brown SS, Mitchell FL, Young DS (eds). Chemical diagnosis of disease. Amsterdam: Elsevier/North-Holland: 1979: 181-245.

Siggaard-Andersen O. Bibliography. Scand J Clin Lab Invest 1993: 53, Suppl 214: 11-21.