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Editorial Views

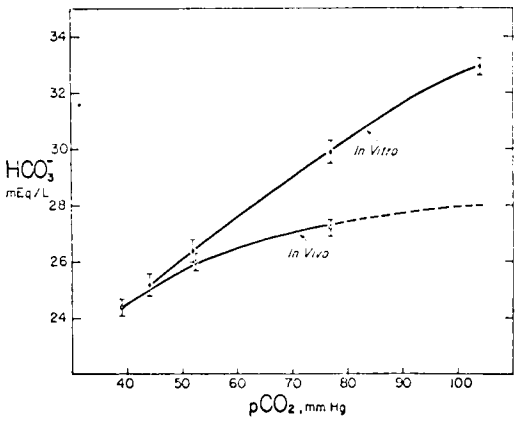
The Great Trans-Atlantic Acid-Base Debate

THE THEORY and technique of acid-base balance have been enriched by recent major advances. These advances have unforunately not been accompanied by clarification of the semantic confusion which continues to plague the interpretation of acid-base disturbances. However, it is at least encouraging to note that the problems of nomenclature and interpretation are receiving widespread publicity—in the form of a running international debate carried forth in the pages of the *Lancet* [1] and *The New England Journal of Medicine*.[2] The challengers (from Boston) have proposed sweeping reforms based on sound theory and experiment; and the defenders (from everywhere else, but most notably from Copenhagen) defend the established position: jargon, nomograms, complexities and all. A brief review of these recent events, together with opinion and evidence in support of the "Boston" position is presented herein.

The recent measurement of whole-body carbon dioxide titration curves by Schwartz and his colleagues [3-5] represents one of the most important experimental advances in acid-base balance since Henderson described the buffer functions of carbonic acid and bicarbonate in 1908. In a series of elegant studies these investigators have described the response to an acutely elevated ambient carbon dioxide tension, carried out in man and in the dog, and the response to chronic elevations in CO_2 in the dog; from their data one can predict the change in bicarbonate to be expected for a given change in carbon dioxide tension—and thus allow a ready separation of the metabolic and the respiratory component of acid-base disturbances. It is particularly encouraging to find that their titration charts are simple and easy to understand, in contrast to the increasingly complex nomograms in general use (see accompanying figure).

Advances in laboratory technique, particularly those of Astrup and of Severinghaus, are well known and impressive.[6, 7] Simple and precise electrodes for the measurement of *p*H and P_{CO_2} are now readily available. Particularly noteworthy has been the demonstration by Astrup and his colleagues that the acid-base balance of blood *in vitro* can be completely defined by the measurement of *p*H of the blood equilibrated at two known levels of P_{CO_2} (one high and one low) and of the *p*H as drawn.[6] The use of the sophisticated Astrup apparatus is facilitated by the nomogram which Astrup and Siggaard-Andersen [6, 8] have constructed for this purpose. But they have retained the difficult terminology of the past and added some not-much-less-difficult new terms of their own. In Astrup's interpretation the metabolic component can be expressed in three ways: as changes in buffer base, which has been retained from Singer and Hastings; [9] as standard bicarbonate,[10] which is roughly equivalent to the outworn but still used CO_2 combining power or alkali reserve; and, it can be expressed as base excess (the latter, in the case of a metabolic acidosis, becomes a "negative base excess"!). None of these expressions offer the advantage of easy or intuitive understanding. All are subject to theoretical criticisms expressed by Schwartz and Relman.[11]

The difficulty, as predicted by Schwartz and Relman in 1963 [11] and confirmed by Schwartz and his colleagues in 1964 and 1965 [3, 4] is that blood *in vivo* does not behave in the same manner as blood *in vitro*. The addition of hydrogen ion (as carbonic acid) generates less



Comparison of the *in vitro* and *in vivo* carbon dioxide titration curves of human blood. The lower curve, representing the *in vivo* response, was drawn by inspection through the average plasma bicarbonate concentrations observed in the 7 subjects during exposure to 7 and 10 per cent carbon dioxide. The dotted extension of this curve is a calculated extrapolation. The upper curve was drawn through the average bicarbonate concentrations observed during *in vitro* titration of blood obtained from 9 additional normal subjects. Ranges shown around each point represent ±1 S.E. (From Brackett, N. C., Jr., Cohen, J. J., and Schwartz, W. B.: Carbon dioxide titration curve of normal man, New Engl. J. Med. 272: 6, 1965.)

bicarbonate in the intact human than in whole blood in a test tube. This should not have been unexpected, since hemoglobin is the major nonrespiratory buffer of the body. Thus, as carbon dioxide tension (and carbonic acid) rise, (H^+) combines with anionic sites within the red cell, releasing bicarbonate which diffuses into the plasma *and* into the rest of the extracellular compartment.

The implications of this are several. First, clearly, the titration curve for bicarbonate and P_{CO_2} *in vivo* differs from that obtained *in vitro*. Secondly, any calculation of metabolic parameters based upon *in vitro* titrations does not apply to the *in vivo* situation. *Buffer base, standard bicarbonate*, and *base excess* accordingly have no quantitative validity.* These calculated parameters do not apply to the whole patient; and *they do not apply to the whole blood as it circulates within the patient.*

The foregoing may be distressing to accept, in as much as most of the recent acid-base literature has been expressed in these terms, but this is no reason to perpetuate fundamental errors. Furthermore, the Schwartz concepts are extremely useful in the solution of at least one paradox which has puzzled anesthesiologists, namely, does a respiratory acidosis cause a metabolic acidosis? Beecher and Murphy suggested that it might.[12] Frumin and Holaday and their associates [13, 14] reported a moderate to marked fall in "buffer base" during anesthesia complicated by respiratory acidosis, and they concluded that the respiratory acidosis had caused a metabolic acidosis. The author of this editorial also noted that an increase in P_{CO_2} was accompanied by an increase in bicarbonate which was considerably less than expected (and thus there was a fall in calculated "buffer base"); but, failing to find evidence of accumulation of nonvolatile acids, he concluded that no metabolic acidosis occurred [15, 16] and that there might be something wrong with the calculations. Schwartz has shown us what was wrong.

Our own data [15] and that of Frumin [13] and of Holaday [14] do, in fact, provide strong confirmation for Schwartz's observations and for his interpretation. The calculated bicarbonate values, which accompanied the acute severe elevations in partial pressure of carbon dioxide reported in these 3 studies fall very closely on Schwartz's *in vivo* P_{CO_2}–bicarbonate titration curve. Complete data from a single representative case are presented in the accompanying table. Although the fall in calculated "buffer base" suggests a severe metabolic acidosis, the serum bicarbonate concentration is precisely that predicted from Schwartz's data, and the measurement of electrolytes and organic acids show no evidence of metabolic acidosis. On the contrary, the metabolic response was in the direction of a metabolic alkalosis, and was consistent with the extrarenal response to an acute respiratory acidosis described in the nephrectomized dog by Giebisch, Berger and Pitts.[17] †

* Nor does the *corrected bicarbonate*, the use of which this author has recommended.[16]

† The redistribution of electrolytes which occurs during respiratory acidosis is, of course, little more than the well-known chloride shift, but including other anions. The observed fall in other anions must occur in the presence of the rising serum bicarbonate of respiratory acidosis in order to maintain electrical neutrality. Similarly, the fall in serum bicarbonate during respiratory alkalosis must

Metabolic Response to Acute Respiratory Acidosis During Ether Anesthesia

Duration of Anesthesia (minutes)	*p*H	P_{CO_2}* mm. Hg	(HCO_3^-)* mEq./liter	B_B† mEq./liter	Serum Na^+ mEq./liter	Serum K^+ mEq./liter	Serum Cl^- mEq./liter	Plasma Lact. mEq./liter	Plasma Pyruv. mEq./liter	Plasma Cit. mEq./liter	Serum‡ PO_4 mg.%
0	7.43	39	25.1	49.6	141	3.9	102	0.3	0.13	0.33	2.7
60	7.47	31	22.2	48.0	140	4.5	102	1.0	0.17	0.35	2.8
130	6.96	140	32.1	39.5	144	4.1	104	0.7	0.12	0.27	5.5
205	7.40	43	24.3	50.0	143	4.0	100	0.4	0.13	0.30	6.6

* Calculated from *p*H and total CO_2 with the Singer and Hastings nomogram.[9]

† Buffer base (B_B) calculated from *p*H, total CO_2, and hematocrit with the Singer and Hastings nomogram.[9]

‡ Equivalence varies with *p*H. Mg. per cent × 0.6 is approximately equal to mEq./liter.

Ether anesthesia was administered for ligation and stripping of varicose veins. Patient was allowed to accumulate carbon dioxide by rebreathing between 60 and 130 minutes. The elevation in bicarbonate falls on Schwartz's CO_2 titration curve for acute respiratory acidosis in man[4]; the directly measured electrolytes show no evidence of metabolic acidosis.

It may be readily agreed there is great need for clarification, for simplication, and for agreement. This plea has been made repeatedly in the past in the *Lancet*.[1] It has been made again by Schwartz, Relman and their colleagues, with specific proposals and butressed with new data. But the reluctance to give up old and familiar medical terminology (no matter how difficult to understand) is great.

What can be done? It had been hoped that the recent conference held by the New York Academy of Sciences[19] attended by Astrup and Schwartz and their associates, by Hastings, and by other distinguished contributors to acid-base lore, would allow for the needed reform, but it is apparent that limited progress was made. I believe that it is particularly appropriate that the anesthesiologist devote special attention to these unresolved problems of acid-base balance. The anesthesiologist produces, in the course of his operating room duties, more and bigger disturbances in acid-base balance in a week than other physicians are apt to see in a year. Accordingly the anesthesiologist has found the need to become proficient in the measurement of blood gases, and his is often the only laboratory in the hospital prepared to make a definitive assessment of the acid-base balance. As the expert in the technique and the interpretation of such disturbances, which he should be, the anesthesiologist should raise a major voice in the great debate.

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be accompanied by an equivalent rise in other serum anions, again to maintain electrical neutrality. This latter response has unfortunately—and erroneously—been called the metabolic acidosis of hyperventilation.[18]

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PROLONGED NITROUS OXIDE Twenty mice were under anesthesia for six days with 50 per cent nitrous oxide and oxygen. All animals survived prolonged inhalation of this oxygen-gas mixture. Towards the third day of the experiment the peripheral blood picture showed a moderate, reversible granulocytopenia. No changes of the karyotype of the bone marrow cells were noted. (*Efuni, S. N., Federmesser, K. M., and Smertenko, I. I.: Examination of the Peripheral Blood and Karyotype Under Prolonged Anaesthesia With Nitrous Oxide Under Experimental Conditions (Russian) Eksp. Khir. Anest. 3: 72, 1964.*)

SPINAL ANESTHESIA Headache following spinal anesthesia occurred most often on the third day, next on the second or fourth day; in 88 per cent within four days. This complication was noted in 18 of 152 cases, in 8 per cent of male and 19 per cent of female patients. Neither the type of agent nor the level of injection was an essential factor in determining the incidence, but speed of injection seemed to be a factor since 12 per cent of those receiving slow injection and 20 per cent of those receiving rapid injection developed headache. The direction of the oblique section of the needle point was also important, headache occurring more often when the section was perpendicular to the spinal cord than when it was parallel. Spinal fluid pressure was often lower in those complaining of headache. Nevertheless, adjustment of the pressure relieved the headache in only 2 of 15 cases. Cortisone (5 mg. to 25 mg.) given immediately before or simultaneously with the spinal anesthesia reduced the incidence of headache. Autonomic nervous system examination of 16 patients with headache showed 11 to have autonomic instability. The postspinal headache is considered to result from loss of spinal fluid. The fall in spinal fluid pressure causes intracranial venous stagnation, dilatation of venous sinuses and vasospasm of intracranial arteries. The use of as small a needle as possible and simultaneous administration of steroid hormones is recommended to prevent it. Steroid hormones are also effective in its treatment. (*Shiraha, Y.: Headache Following Spinal Anesthesia; Pathogenesis and Treatment (Japanese), J. Ther. (Tokyo) 46: 725, 1964.*)