The American Journal of Medicine

VOL. XXIII AUGUST, 1957 NO. 2

Editorial

Anions Versus Cations?

A COMMENDABLE trend, discussed here a few years ago [*1*], urges us to stop calling anions *acids* and cations *bases*. Perhaps it is in this spirit that several writers now refer to acid-base balance as *anion-cation* balance. The result, however, is just opposite to the one presumably intended: more clearly than ever anions are equated with acidity, cations with basicity, and acid-base balance as a war between the opposed anions and cations.

The present-day student [*2*] finds the unitarian approach to hydrogen-ion control far more satisfactory. Communication must, however, be preserved between the two viewpoints; our students still need to understand how it is possible to discuss the subject in terms of fixed ions, and some of their seniors should perhaps note that the subject can, if necessary, be discussed without reference to fixed ions! With this need in mind, I would like to add to my earlier discussion [*3*] this hypothetic dialogue:

ANTAGONIST: If the concept of anion-cation balance is defective, why does it work out as well as it does?

REPLY: Because fixed anions and cations are carefully defined so that in conjunction their concentrations reflect the level of the real actors, namely the buffer anions and through them the hydrogen ion. Under these conditions one gets the impression that the fixed ions are producing or combating disturbances of the acid-base balance.

ANTAGONIST: But do not serum analyses show metabolic acidosis to be caused either by a high chloride level (that is, a hyperchloremic acidosis) or by some other fixed anion?

REPLY: On the contrary I would view the elevated anion concentrations as a *result*, not a *cause* of the acidosis. An acid HX, is the cause. The H^+ which it provides is the real hazard. At the moment of analysis this H^+ has mainly disappeared by reacting with buffer anions, whereas X^- is still present. Therefore, we tend to blame X^-.

ANTAGONIST: Consider then that 0.9 per cent NaCl is an acidifying body fluid because of its high chloride content. To permit it to become neutral, we need to create a gap between the Na^+ and Cl^- concentrations, for example by removing chloride. Such a gap automatically will be filled with bicarbonate ion in the biologic environment. Does not this show that chloride is acidifying?

REPLY: True, at the high CO_2 pressure of our internal environment, "physiological" saline solution becomes quite acid. Such a solution cannot form a single bicarbonate ion without also forming a H^+. It is these hydrogen ions which must be extracted from it before it can be neutral. The removal of HCl (but not merely of Cl^-) would accomplish this purpose. But note that this limitation does not arise from the chloride ion level.

ANTAGONIST: Consider also that the ultimate correction of metabolic acidosis is renal, not respiratory, because only the kidneys can excrete the acidifying fixed anions.

REPLY: The respiratory correction is non-ultimate because it cannot actually excrete hydrogen ions; it merely renders most of them

[1] RELMAN, A. S. What are acids and bases? *Am. J. Med.*, 17: 435, 1954.

[2] KAUFMAN, H. E. and ROSEN, S. W. Clinical acid-base regulation—the Bronsted schema. *Surg., Gynec. & Obst.*, 103: 101, 1956.

[3] CHRISTENSEN, H. N. Control of the hydrogen ion. *New England J. Med.*, 247: 174–175, 1952.

innocuous by the reactions, $H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons CO_2\uparrow + H_2O$. These two reactions must, however, be reversed to restore the normal bicarbonate level; hence the hydrogen ion ultimately reappears. It is for this reason that the kidney must excrete all the H^+ of the invading acid.

ANTAGONIST: But is it not by excreting the excess anion that the kidney corrects the acidosis? As the urine is acidified, the doubly-charged phosphate ion is converted to the singly-charged form, so that more fixed anion can be excreted or, what amounts to the same thing, more fixed cation conserved.

REPLY: Instead I prefer to say that as the H^+ concentration is increased in the renal tubular lumen by secretory activity, $HPO_4^=$ is converted to $H_2PO_4^-$. In this way more H^+ is excreted to help correct the acidosis. The adjustment in Cl^- and B^+ excretion seems to me incidental.

ANTAGONIST: How then would you explain the place of ammonia synthesis in combating acidosis? Does this not operate by substituting NH_4^+ ions to conserve fixed cations?

REPLY: Instead I prefer to say that every time an ammonium ion is substituted for a urinary urea N atom, one extra H^+ is eliminated. Again excretion of the anion excess may be considered incidental.

ANTAGONIST: But when we come to balance studies, must we not discuss acid-base regulation in terms of fixed anions and cations? The organism has an almost unlimited ability to synthesize hydrogen ions, for example by converting palmitic acid into 8 moles of acetic acid, or glucose into 2 moles of lactic acid. Surely one cannot construct a balance of H^+!

REPLY: True, the organism can form huge quantities of H^+, whether we choose to say glucose has formed lactic acid or lactate ions plus hydrogen ions. But let us complete these metabolic reactions: In order to oxidize lactate or acetate to CO_2 and water we must again take up the H^+ from the environment:

$$CH_3COO^- + H^+ + 2O_2 \rightarrow 2H_2O + 2CO_2\uparrow.$$

(The course of the reaction is of course more complex than this but the net effect is the same.) Metabolic reactions are constantly forming and removing H^+, but for such substrates the balance will be precisely zero. Only when intermediates accumulate will hydrogen ions accumulate. Subsequent catabolism of the intermediates will correct the acidosis unless, of course, the intermediates meanwhile are lost from the body, as in ketonuria, leaving a deserted hydrogen ion. Similarly, the hydrogen ions arising from metabolic CO_2 are again removed as the CO_2 is expired. Only the hydrogen ions deserted by HCO_3^- escaping into excreta will cause net acidification.

Furthermore, valuable information has already been gained by the technic of hydrogen-ion balance. For example, a negative hydrogen-ion balance (increased urinary titratable acidity and NH_4^+ excretion, decreased HCO_3^- excretion) during recovery from hypokalemic acidosis has shown that the apparently alkalotic cat actually contained *more* than a normal supply of H^+, presumably in the cells [*4*].

ANTAGONIST: How can you explain the acidosis caused by phosphate and sulfate retention, for example in uremia, except by bicarbonate displacement? Does not acetoacetate cause acidosis by displacing bicarbonate?

REPLY: How can bicarbonate be displaced unless H^+ is supplied to convert it to H_2CO_3? I question whether the mere retention of sulfate or phosphate actually is acidifying! Here, too, the hydrogen ion must cause the acidosis. In ketosis, for each acetoacetate one H^+ is formed; surely this produces the acidosis.

We must keep distinct from this problem the separate question of how acid is produced when protein is catabolized. The oxidation of a "neutral" S of cysteine or methionine to sulfate inevitably produces 2 H^+, in the test tube or in the body. It is not likely that phosphate residues release hydrogen ions upon the catabolism of phosphoproteins or other phosphomonoesters, although catabolism of such phospho*diesters* as the nucleic acids and phospholipids should lead to H^+ release. But this is a separate problem.

ANTAGONIST: You say that Na^+ and K^+ and Cl^- do not enter into reactions to produce H^+ or OH^-. Yet when Na^+ replaces cellular K^+ in potassium deficiency, is there not evidence that H^+ also accumulates in the cells? Is the Na^+ really as inert as you say?

REPLY: There must indeed be at least one exception to the biologic inertness of sodium and potassium and probably of chloride also. A carrier substance must bind Na^+ specifically to

[4] COOKE, R. E., SEGAR, W. E., REED, C., ETZWILER, D. D., VITA, M., BRUSILOW, S. and DARROW, D. C. The role of potassium in the prevention of alkalosis. *Am. J. Med.*, 17: 180, 1954.

ferry it out of the cells; the Na^+ may very well displace a H^+ in combining with the carrier. The amount of Na^+ so bound at any instant must be very small. Probably we have a valuable clue to the nature of this reaction in the curious H^+ distribution of potassium deficiency.

Note, however, that the existence of such reactions by no means justifies our considering the various fixed cations as equivalent alkalinizing agents.

HALVOR N. CHRISTENSEN, PH.D.
Department of Biological Chemistry,
University of Michigan Medical School,
Ann Arbor, Mich.