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Disorders associated with an altered anion gap

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Case presentations

Patient 1. A 41-year-old man with chronic schizophrenia went to a local hospital stating that he had attempted suicide by drinking lamp oil. At the time of admission, he appeared intoxicated and quickly became unresponsive and severely acidemic. Crystals resembling calcium oxalate monohydrate were noted in the urine. He was treated with an alcohol infusion for suspected ethylene glycol intoxication and was transferred to Denver General Hospital. The systolic blood pressure was palpable at 80 mm Hg; pulse, 140 beats/min; respirations, 24/min; temperature, 35°C. The patient was comatose and no deep-tendon reflexes could be elicited. Initial laboratory data (Table 1) included: sodium, 146 mEq/liter; potassium, 3.1 mEq/liter; chloride, 100 mEq/liter; bicarbonate, <10 mEq/liter; BUN, 13 mg/dl; creatinine, 2.4 mg/dl; calcium, 8.6 mg/dl; phosphorus, 2.4 mg/dl; uric acid, 9.8 mg/dl; glucose, 234 mg/dl; ethylene glycol, 86 mg/dl; measured serum osmolality, 353 mOsm/kg; and a calculated serum osmolality of 332 mOsm/kg.

The patient was treated initially with intravenous normal saline, sodium bicarbonate (132 mEq), ethanol, thiamine, pyridoxine, and pressor drugs; hemodialysis also was begun. His subsequent course was complicated by acute renal failure requiring multiple dialyses. The patient recovered complete neurologic function and had partial return of renal function over one month. The serum creatinine fell to 2.1 mg/dl, and he was returned to the initial hospital for further care and placement.

Patient 2. A 48-year-old male was admitted to Denver General Hospital for severe alkalemia. He had a history of chronic alcohol abuse. One week prior to admission he began drinking heavily. Three days prior to admission he began to experience nausea and vomiting. On the morning of admission severe spasms in his arms and legs caused him to summon an ambulance. He denied ingestion of salicylates, other medication, methanol, antifreeze, or "bootleg" liquor. He denied seizures. The blood pressure was 130/80 mm Hg; pulse, 100 beats/min; respirations, 20/min; and temperature, 38°C rectally. The patient was alert and oriented but was experiencing spontaneous carpopedal spasm. Initial laboratory data (Table 1) included: serum sodium, 141 mEq/liter; potassium, 3.3 mEq/liter; chloride, 74 mEq/liter; bicarbonate, 32 mEq/liter; and anion gap, 35 mEq/liter. The BUN was 37 mg/dl; creatinine, 2.5 mg/dl; calcium, 10.3 mg/dl; phosphorus, 2.6 mg/dl; uric acid, 12.8 mg/dl; a trace of ethanol; and a negative toxin screen for salicylates and methanol. A serum screen for organic acids using gas chromatography and mass spectroscopy revealed a peak for lactate as well as small peaks for β-OH butyrate, α-OH butyrate, α-ketobutyrate, and two unidentified substances.

The patient was treated with normal saline, potassium chloride, magnesium sulfate, and thiamine. After 48 hours, acid-base status was normal, the serum creatinine was 1.1 mg/dl, and the serum uric acid measured 3.6 mg/dl.

Patient 3. A 34-year-old male developed low back pain 13 months before admission. The back pain increased in severity and he experienced a 10-pound weight loss. Multiple myeloma was diagnosed 9 months before admission. Chemotherapy with cyclophosphamide, vincristine, melphalan, and prednisone was initiated. He was admitted to Denver General Hospital for evaluation for further chemotherapy. Laboratory data included: hemoglobin, 10.3 g/dl; sodium, 137 mEq/liter; potassium, 3.9 mEq/liter; chloride, 105 mEq/liter; and bicarbonate, 27 mEq/liter. The anion was gap 5 mEq/liter. Serum protein electrophoresis revealed a monoclonal spike in the gamma region; quantitative analysis revealed 5.1 g/dl of IgG kappa protein. The bone marrow contained 73% plasma cells.

Discussion

DR. PATRICIA A. GABOW (*Director, Medical Services, Denver General Hospital, Denver, Colorado*): The anion gap is a concept based on the electrically neutral state of serum. It is not a single laboratory measurement, and in different clinical conditions it estimates different substances. Nonetheless, an assessment of the magnitude of the gap has remarkable clinical utility. The interpretation of an abnormal anion gap critically depends on the clinical setting in which the deviation is encountered. To clarify the complex concept of the anion gap, I will consider

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Table 1. Serum values

	Na *mEq/liter*	K *mEq/liter*	Cl *mEq/liter*	HCO_3^- *mEq/liter*	Anion gap *mEq/liter*	Arterial pH	$PaCO_2$ *mm Hg*	PaO_2 *mm Hg*	Lactate *mEq/liter*	Pyruvate *mEq/liter*	β-OH butyrate *mEq/liter*	Acetoacetate *mEq/liter*	Citrate *mEq/liter*
Patient 1													
Outside hospital	131	3.6	100	<10	—	6.87	13	—	—	—	—	—	—
On transfer	146	3.1	100	4	42	7.17	16	153[a]	8.6	0.21	0.069	0.103	0.379
At discharge	139	4.5	108	20	11	—	—	—	—	—	—	—	—
Patient 2													
Emergency room	141	3.3	74	32	35	—	—	—	—	—	—	—	—
On admission	135	3.3	76	29	30	7.76	20	70	6.59	0.48	0.80	0.31	—
2 hours later	133	2.4	78	35	20	—	—	—	—	—	—	—	—
At discharge	140	4.4	103	25	12	—	—	—	—	—	—	—	—

[a] Value obtained while patient was breathing supplemental oxygen.

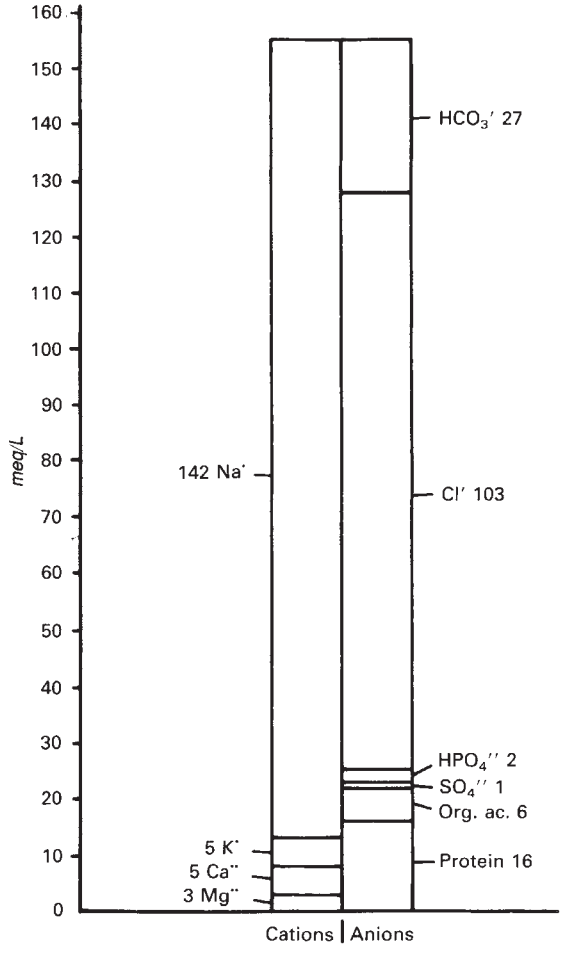

Fig. 1. *The ionic anatomy of serum.* The charge contribution of the serum cations equals that of the serum anions. (Reprinted by permission; from Ref. 1.)

first the chemistry that underlies the definition of the anion gap, then the clinical disorders in which the anion gap is increased,

Table 2. Conversion of laboratory values for serum constituents to mEq/liter[a]

Ion	Units of concentration reported	Formula for conversion to mEq/liter
Ca^{++}	mg/dl	× [10 ÷ 40] × 2
Mg^{++}	mg/dl	× [10 ÷ 24] × 2
$PO_4^=$ (mgP)	mg/dl	× [10 ÷ 31] × 1.8
$SO_4^=$ (mmol)	mmol/liter	× 2

[a] Conversion from milligrams per deciliter to mEq/liter is performed by multiplying by 10 to convert to milligrams per liter, dividing by the molecular weight, and finally multiplying by the valency.

and finally, I will examine the disorders associated with a decreased anion gap.

Chemistry and definition

The concept of the anion gap arose from the "Gamblegram" described in 1939 [1]. The Gamblegram, illustrated in Figure 1, is a graphic representation of the law of electroneutrality as applied to the charged constituents of serum. This law dictates that the number of net positive charges contributed by serum cations must equal the number of net negative charges contributed by serum anions.

Figure 1 illustrates the charge balance: sodium $[Na^+]$ + potassium $[K^+]$ + calcium $[Ca^{++}]$ + magnesium $[Mg^{++}]$ = bicarbonate $[HCO_3^-]$ + chloride $[Cl^-]$ + phosphate $[PO_4^-]$ + sulfate $[SO_4^=]$ + protein $[Pr^-]$ + organic acid anions $[OA^-]$. (I should note that the phosphate and protein have multiple charges). The units used are milliequivalents per liter because the equation deals with the concentrations of charges (Table 2). Assigning numerical values for the charges of these serum constituents is accomplished easily for sodium, potassium, bicarbonate, and chloride, but with more difficulty for many other serum constituents. Although calcium and magnesium are measured with relative ease, it is important to understand why the total concentration of serum calcium and magnesium rather than just the ionized fraction is used in the calculation of the contribution of calcium to the so-called "unmeasured cations."

The rationale for this is straightforward: the calcium bound to protein (for example, albumin, which is a polyanion) or complexed with bicarbonate, phosphate, sulfate, lactate, or citrate, "covers" an equivalent number of negative charges on these anions, that is, it is balanced electrically by those negative charges. Thus, like ionized calcium, protein-bound calcium and complexed calcium contribute to charge balance in the serum. The same rationale also applies to serum magnesium.

The difficulty in establishing the precise charge contributions of sulfate and organic acid anions arises because clinical laboratories do not measure these serum constituents on a routine basis. The normal fasting serum sulfate level is 0.297 ± 0.038 mmol/liter (mean ± SD); thus sulfate contributes about 0.6 mEq/liter to total serum anions [2]. Van Slyke estimated that organic acids contribute 6 mEq/liter to serum unmeasured anions [3], whereas Van Leeuwen estimated this contribution to be only 3.2 mEq/liter [4]. Van Slyke, however, did not estimate the contribution of specific organic acid anions, and Van Leeuwen considered only lactate. Recent information indicates that at least 29 acid anions are detectable in plasma [5]. In normal individuals the aggregate contribution to the serum anions by lactate, pyruvate, acetoacetate, 3-hydroxybutyrate, and citrate is approximately 1.8 to 2.6 mEq/liter [6].

Although the concentration of serum phosphate is readily obtainable through the clinical laboratory, it is not a simple matter to derive the charge of phosphate; the latter is a function not only of concentration but also of the serum pH. Serum phosphorus concentration in mg/dl is converted to mmol/liter by multiplying by 10 and dividing by 31, the atomic weight of phosphorus. The value is converted to mEq/liter of inorganic phosphate by taking into account the pKa_2' of the phosphate buffer system, which is 6.8. Two negative charges are exposed per molecule of basic phosphate, $HPO_4^=$, and one per molecule of acid phosphate, $H_2PO_4^-$. The negligible amounts of H_3PO_4 and $PO_4^{\equiv}$ in serum are ignored. The ratio of $H_2PO_4^-$ to $H_2PO_4^-$ equals $10^{(pH-6.8)}$. At a pH of 7.4, this ratio is approximately 4 to 1. Thus four-fifths or 80% of the phosphate contributes two negative charges as $HPO_4^=$, and one-fifth or 20% contributes one charge as $H_2PO_4^-$. Thus, the charge contribution of phosphate in mEq/liter at pH 7.4 is obtained by multiplying the molar concentration of phsophate by the sum of 0.8 times 2 and 0.2 times 1, that is, 1.8.

Example: Given a serum phosphorus of 4.0 mg/dl and a serum pH of 7.40:

$$4.0 \text{ mg/dl} \div 3.1 = 1.29 \text{ mmol/liter}$$
$$[HPO_4^=]/[H_2PO_4^-] = 10^{(7.4-6.8)} \cong 4$$
$$\% [HPO_4^=] = 100 \times 4 \div (4 + 1) = 80\%$$
$$[HPO_4^=] = 0.80 \times 1.29 = 1.03 \text{ mmol/liter}$$

Therefore: $[HPO_4^=] = 1.03 \text{ mmol/liter} \times 2 \text{ mEq/mmol} = 2.06 \text{ mEq/liter}$

$[H_2PO_4^-] = 0.26 \text{ mmol/liter} \times 1 \text{ mEq/mmol} = 0.26 \text{ mEq/liter}$

$[HPO_4^=] + [H_2PO_4^-] = 2.06 + 0.26 = 2.32 \text{ mEq/liter}$

Simply: $[H_2PO_4^=] + [H_2PO_4^-] = 1.8 \text{ mEq/mmol} \times 1.29 \text{ mmol/liter} = 2.32 \text{ mEq/liter}$

Normal serum proteins are polyanions. Although their net contribution to overall charge balance is difficult to assess exactly, a normal mixture of serum proteins contributes 1.8 to 2.4 mEq/liter per gram of protein at pH 7.40. This charge reflects a number of variables: the type of protein, the concentration of protein, and serum pH. The number of negative charges on a protein molecule may not correspond to the contribution to charge balance in the serum because a cation on the protein surface may bind to more or less than one negative charge. Thus Van Leeuwen uses the term net cation equivalency (NCE) [4], and Van Slyke speaks of the base bound by protein (BBP) [3] to represent the charge balance contribution of protein.

Albumin contributes about 2.0 to 2.8 mEq/liter for each g/dl in human serum, and globulin provides approximately 1.3 to 1.9 mEq/liter for each g/dl. Van Leeuwen found a negligible NCE for gamma globulin and assumed that the alpha and beta fractions contributed all of the NCE attributable to the globulin [4]. Changes in pH affect the NCE by either associating (lower pH) or dissociating (higher pH) protons from reactive chemical groups and by altering the tertiary structure of the protein. Both Van Slyke and Van Leeuwen reported an increase in BBP or NCE of 0.10 mEq/liter per g/dl of protein for each increment in pH of 0.10 units [3, 4]. A summary of the contributions of total protein, albumin, and globulin to normal serum charge balance is expressed in the following equations:

$$\text{Van Slyke BBP} = 1.04 \times [\text{protein, g/dl}] \times (\text{pH} - 5.08)$$
$$\text{Van Leeuwen NCE} = 1.03 \times [\text{protein, g/dl}] \times (\text{pH} - 5.66)$$

From the foregoing, it obviously is impractical to employ a formula for serum charge balance that demands measurement of all the constituents. In fact, the utility and appeal of the anion gap concept stems partially from the ease with which this complex multivariable equation reliably can be simplified to one in which only readily available determinations are utilized: serum sodium, chloride, and bicarbonate (actually total carbon dioxide content) concentrations. In this simplification, potassium, calcium, and magnesium are considered unmeasured cations (UC) and phosphate, sulfate, protein, and organic acids are considered unmeasured anions (UA). This simplification thus requires neither measurement of all the serum constituents nor calculation of their charge contribution. Nonetheless, the simplification still accurately describes the electrically neutral state of the serum:

$$Na^+ + UC^+ = HCO_3^- + Cl^- + UA^-, \text{ or}$$
$$Na^+ - HCO_3^- - Cl^- = UA^- - UC^+ = \text{anion gap.}$$

Henceforth in this essay I will define the anion gap as follows:

$$\text{anion gap} = [Na - (Cl + TCO_2)]$$

Applying normal values for serum concentrations of sodium, chloride, and bicarbonate yields a predicted normal anion gap of 10 to 12 mEq/liter. Indeed, most published studies report a mean value of 12 mEq/liter and a range of 8 to 16 mEq/liter encompassing two standard deviations [6–8]. Such data are based on flame photometric determinations of sodium and on measurements of Autoanalyzer chloride and total carbon dioxide. Newer laboratory methods may result in slightly lower normal values, but the principles discussed here still apply.

From the equation that I just elucidated, which defines the anion gap, it is clear that a decrease or increase in the gap could result from a number of perturbations. Irrespective of such perturbations, however, electroneutrality is always maintained.

For example, increases in both the chloride and unmeasured cation concentrations decrease the anion gap, as can occur in patients with hyperproteinemia secondary to multiple myeloma. Increases in the anion gap are more common than are decreases. Increases can result from an increase in organic anions and a concomitant decrease in the serum bicarbonate concentration, as in lactic acidosis. Although an increase in unmeasured anions theoretically could result from an increased negative charge contribution by phosphate, protein, sulfate, or organic anions, for practical purposes only increases in organic anions account for large increases in the anion gap.

In the following sections, I will discuss first the acidemic and alkalemic states accompanied by an increased anion gap and the observed constituents of a large gap. Then I will consider the disorders accompanied by a decreased anion gap.

Increased anion gap in acidemic states

Historically, the recognition that an overproduction of organic acids increases the anion gap but that an isolated loss of bicarbonate does not has been responsible for the popularity of the anion gap concept. Thus, assessment of the gap is helpful in differentiating metabolic acidosis into its two major types: acidosis with an increased anion gap, in most of which organic acids cause the acidosis, and acidosis with a normal anion gap (hyperchloremic), in which loss of bicarbonate occurs with a concomitant increase in serum chloride.

Patient 1 is an instructive example of the diagnostic utility of the anion gap. He had profound hypobicarbonatemia and an increased anion gap almost certainly caused by an increased production of organic acids (Table 1). Why does an increase in organic acids result in an increased anion gap, as calculated from the serum sodium, chloride, and bicarbonate concentrations? The organic acids generated are buffered in substantial part by extracellular bicarbonate with the resultant consumption of bicarbonate and the appearance of an unmeasured organic anion (OA^-), in accordance with the following equation:

$$H^+OA^- \text{ (organic acid)} + Na^+ + HCO_3^- \rightleftarrows Na^+ OA^- + H_2O + CO_2.$$

Thus, in this setting, the increase in the anion gap results from the buffering of generated organic acids. However, it is not true that an increase in endogenously generated organic acids and the subsequent buffering of these acids *always* leads to an increase in anion gap. In diabetic ketoacidosis, for example, the end result of increased ketoacid production can be either hyperchloremic acidosis or acidosis with an increased anion gap [9]. The explanation for this variability is not straighforward. Ketoacids are excreted in the urine at very low serum levels. If the patient maintains an adequate salt intake and preserves normal or nearly normal extracellular fluid volume, renal perfusion, and glomerular filtration rate, ketoanions may be excreted nearly as fast as they are generated. Under these circumstances, chloride is retained by the kidney in place of ketones, a rise in the serum chloride balances the fall in the serum bicarbonate concentration, and the serum anion gap remains normal. If extracellular fluid volume is not preserved, however, as is usually the case, renal function declines and the excretion of ketoanions is retarded. An acidosis with an increased anion gap results. In other varieties of organic acidosis, less potential exists for the development of hyperchloremic acidosis because the other organic acids have higher renal thresholds even in the presence of normal renal function [10].

Table 3. Characteristics of anion gap acidosis[a]

Disorder	Organic acid responsible (% of ↑ AG)	Level of anion gap *mEq/liter* Range / Mean	Systemic pH
Non-toxin related			
Diabetic ketoacidosis [9, 75][b]	β-OH butyric acid	18–44	6.95–7.36
	Acetoacetic acid (26%–143%)	33	7.17
		18% > 35	0% > 7.40
Lactic acidosis [54, 55, 76, 77]	Lactic acid	18–67	6.75–7.54
	Pyruvic acid	32	7.14 ± 0.22
		30% > 35	20% > 7.40
Renal failure, acute[c] [50]	SO_4, PO_4, a variety of organic acids (% ?)	16–29	—
		22 ± 5	—
		0% > 35	—
Renal failure, chronic [78, 79]		17–23	7.19–7.42
			7.35 ± 0.06
Hyperglycemic, hyperosmolar nonketotic coma [33]	Unknown	18–36	6.81–7.43
		29	7.30 ± 0.17
		10% > 35	25% > 7.40
Rhabdomyolysis[c] [50]	Unknown	16–55	6.69–7.90
		27	7.33 ± 0.26
		16% > 35	42% > 7.40
Heat stroke without hypotension Classic[c] [51, 52]	Lactic acid (17%–68%)	21–27	7.26–7.44
		23 ± 2	7.34 ± 0.12
		0% > 35	33% > 7.40
Heat stroke without hypotension Exertional [80]	Lactic acid and others	18–34	—
		24 ± 6	—
		0% > 35	—
Toxin related			
Alcohol [6, 35, 36, 47–49]	Ketoacids	19–37	6.96–7.76
	BHB > AcAc[d]	26 ± 6	7.28 ± 0.18
	Lactic acid (19%–98%)	8% > 35	56% > 7.40
		12% < 20	
Methanol[c] [31, 38, 40, 81]	Formic acid	17–65	6.7–7.58
	Lactic acid (% ?)	32	7.17 ± 0.22
		35% > 35	17% > 7.40
Ethylene glycol [32, 40, 45, 46]	Lactic acid	11–58	6.72–7.37
	Glycolic acid	37 ± 11	6.98 ± 0.2
	Oxalic acid	42% > 35	0% > 7.40
Salicylates [29, 30, 37]	Variety of organic acids (% ?)	10–34	7.32–7.61
		0% > 35	7.43 ± 0.1
		60% < 20	50% > 7.40
Toluene [26–28][c]	Unknown	17–39	6.88–7.35
		14% > 35	7.13 ± 0.15
		32% < 20	0% > 7.40

[a] Data utilized available on request to author.
[b] Numbers in brackets refer to references.
[c] Subjects included only if anion gap > 16 mEq/liter.
[d] BHB refers to β-OH butyric acid; AcAc refers to acetoacetic acid.

Another issue exemplified by the first patient is the identification of the specific cause of the increased anion gap and acidemia. Table 3 lists the disorders associated with increased anion gaps. Among these disorders, renal failure is unique in that a decrease in renal function rather than an increase in organic acid production accounts for the increase in the anion gap. In addition to the more common disorders listed in Table 3, occasional cases of acidosis with an increased anion gap have been reported after intoxication with iron [11, 12], hydrogen

sulfide (by inhalation) [13], nalidixic acid [14], papaverine [15], paraldehyde [16–21], strychnine [22], isoniazid [23, 24], and with outdated tetracycline [25]. In keeping with the diminished therapeutic use of paraldehyde, no cases of intoxication with this agent have been reported in more than a decade.

The differential diagnosis of acidosis with an increased anion gap is extensive, and one must utilize the history, physical examination, and supporting laboratory data to identify the specific cause when it is not apparent. As in the first patient, the history provides the most critical information. Patients should be questioned specifically about a history of diabetes, renal disease, and alcohol or other drug ingestions. For example, alcoholic ketoacidosis, one of the most common causes of this type of metabolic acidosis, most often is diagnosed from the history. Patients with this condition typically abuse alcohol chronically and admit recent heavy alcohol consumption, usually accompanied by inadequate caloric intake and vomiting.

The physical examination provides important information regarding tissue perfusion, a characteristic exhaled odor, and mental status. The presence of acidosis with an increased anion gap in a patient in shock most often is due to lactic acidosis. In less dramatic clinical settings, however, the diagnosis of lactic acidosis is verifiable less often. In our study, lactic acidosis was confirmed biochemically in only 43% of the patients in whom it was suspected on clinical grounds [6]. As in this patient with ethylene glycol intoxication, lactic acidosis can be superimposed on another disorder.

In a patient with unexplained metabolic acidosis with an increased anion gap, the degree to which the anion gap is elevated can be helpful in identifying the cause. Among the disorders listed in Table 3, patients who have sniffed solvents [26–28] or who are intoxicated with salicylates [29, 30] commonly have anion gaps of 17 to 19 mEq/liter. Patients with the other disorders listed usually have anion gaps between 20 and 30 mEq/liter. Patients with anion gaps greater than 35 mEq/liter usually have ethylene glycol or methanol intoxication or lactic acidosis. Rarely, patients with methanol [31] or ethylene glycol intoxication [32], hyperglycemic hyperosmolar coma [33], and lactic acidosis [34] can have anion gaps greater than 50 mEq/liter. Therefore, intoxication with methanol or ethylene glycol was considered in this patient on the basis of the markedly increased anion gap alone. Severe acidemia (pH < 7.00) occurs most commonly in diabetic ketoacidosis, lactic acidosis, and methanol or ethylene glycol intoxication. Hyperglycemia suggests diabetic ketoacidosis or hyperglycemic hyperosmolar coma, although modestly elevated serum glucose levels, <250 mg/dl, can occur in alcoholic ketoacidosis. Hyperglycemia and glycosuria also can occur in salicylate intoxication [30]. Conversely, hypoglycemia should suggest alcoholic ketoacidosis because serum glucose levels are lower than 50 mg/dl in about 13% of patients with this disorder [35, 36]. Ketonuria occurs almost invariably in diabetic ketoacidosis, commonly in alcoholic ketoacidosis, and in approximately 25% of patients with salicylate intoxication [37]. Ketonuria has been reported in patients with methanol intoxication [38], but these patients were also consuming ethanol and may have had alcoholic acidosis as well. Assessment of renal function is valuable, although it is unusual for metabolic acidosis with an increased anion gap to be the major manifestation of either acute or chronic renal failure. In patients with ethylene glycol intoxication, the urine sediment can contain many calcium oxalate crystals. Testing blood and urine for the toxins listed in Table 3 may be diagnostic when ingestion of a toxin is suspected or when there is no other apparent cause for acidosis with an increased anion gap.

Calculation of the osmolal gap may be helpful, particularly if methanol and ethylene glycol levels cannot be determined rapidly. The utility of the osmolal gap is illustrated by Patient 1. The osmolal gap is defined as the difference between the measured and the calculated plasma osmolality. The plasma osmolality can be measured quickly in most clinical laboratories and also can be calculated by the application of one of a variety of equations developed for this purpose [39]. A sophisticated version recently has been used in studies of methanol and ethylene glycol intoxication [40]:

$$P_{OSM} = [1.86\ Na(mEq/liter) + \text{serum glucose (mg/dl)}/18 + \text{BUN (mg/dl)}/2.8 + \text{ETOH (mg/dl)}/4.6] \div 0.93$$

The sodium is multiplied by 1.86 to account for the effect of ionic activity; the serum glucose, urea, and ethanol are divided by their molecular weight to convert the units to mOsm/kg H_2O. Division by 0.93 simply corrects for the percentage of plasma water. In subjects in whom methanol or ethylene glycol intoxication is suspected, ethanol should be included in the calculation because it is the most commonly encountered exogenous substance with osmolar activity sufficient to influence the results. A discrepancy of 10 mOsm or more between measured and calculated osmolality, as occurred in Patient 1, suggests the presence of an osmotically active substance in the plasma that is not measured and thus not included in the calculation. Such an elevation of the osmolar gap occurs in methanol and ethylene glycol intoxication, chronic renal failure [41], shock with lactic acidosis [42], and diabetic ketoacidosis [40].

Jacobsen et al found that the osmolal gap ranged from 37 to 125 mOsm/kg H_2O in methanol intoxication and from 21 to 49 mOsm/kg H_2O in ethylene glycol intoxication [40]. In methanol and ethylene glycol intoxication, there is a significant correlation between the serum level of the intoxicant and the osmolal gap [40]. An osmolal gap also is present when the percentage of plasma water is reduced, as in hyperlipemic states. Acetonemia and reduction of plasma water can account for the osmolal gap that sometimes occurs in diabetic ketoacidosis [40]. The nature of the unmeasured osmotically active substances found in chronic renal failure and in lactic acidosis is not known. An increased osmolal gap in the absence of severe diabetic ketoacidosis, chronic renal failure, or lactic acidosis is suggestive of methanol or ethylene glycol intoxication and, as in Patient 1, can provide additional support for the diagnosis.

Increased anion gap in alkalemic states

As the second patient under discussion today demonstrates, an increased anion gap can occur in alkalemic as well as in acidemic states. For example, alkalemia can exist despite an increase in organic acid production if a concomitant and overriding metabolic or respiratory alkalosis is present. Moreover, alkalemia itself can induce an increase in organic acid production [43]. In addition, an increased anion gap and alkalemia can coexist even in the absence of an increase in organic acid production; first, as mentioned earlier, alkalemia tends to

increase the net negative charge of serum proteins and second, certain exogenously administered anions can, via metabolism or effects on renal function, generate metabolic alkalosis and, by partial persistence in the circulation, elevate the anion gap. I will elaborate on these points in a moment. In our study of patients with an increased anion gap, 10 of the 42 subjects were alkalemic, and 9 had a normal serum pH [6].

Admittedly, increased organic acid production, as in diabetic ketoacidosis, lactic acidosis, and intoxication with ethylene glycol or methanol, typically is associated with acidemia, but even in these disorders exceptions do occur [44–46]. Patients with certain other disorders associated with an increased anion gap quite frequently are alkalemic. For example, alkalemia occurs in as many as 50% of patients with either alcoholic ketoacidosis [6, 35, 36, 47–49] or salicylate intoxication [30]. Similarly, in one study 42% of 52 patients with rhabdomyolysis and an increased anion gap were alkalemic [50]. Four of 7 patients with classic heat stroke and an increased anion gap in the absence of hypotension had systemic pH values greater than 7.39 [51, 52].

Alkalemia in alcoholic ketoacidosis, salicylate intoxication, rhabdomyolysis, and classic heat stroke usually is accounted for by the coexistence of either respiratory or metabolic alkalosis or both, present to a degree sufficient to counteract the acidifying effect of organic acid overproduction. This mixed acid-base disturbance is illustrated well by the second patient. He had respiratory alkalosis with a $PaCO_2$ of 16 mm Hg. Respiratory alkalosis frequently occurs in patients, such as the one under discussion, who are undergoing alcohol withdrawal. He also had hyperbicarbonatemia and thus metabolic alkalosis. Metabolic alkalosis is a frequent occurrence under these circumstances because profuse vomiting is often a prominent feature of the clinical picture [49]. Quite commonly, again as in this patient, the increase in the anion gap is the only evidence signifying the presence of metabolic acidosis. As a corollary, the degree of hyperbicarbonatemia would be even more marked were it not for the coexisting organic acidosis. Indeed, the anion gap can be used to estimate the "potential" bicarbonate concentration in such cases of mixed metabolic acidosis and alkalosis; if one adds the *increment* in the anion gap to the actual serum bicarbonate concentration, a measure of the true extent of the metabolic alkalosis can be obtained. In Patient 2 for example, this calculation yields a "potential" bicarbonate concentration of 57 mEq/liter. One can think of this value as the level of serum bicarbonate concentration that would have been present had the newly formed organic acids not titrated away a portion of the bicarbonate. During recovery, however, the serum bicarbonate concentration rarely if ever rises to the anticipated level. As in Patient 2, repair of the metabolic acidosis usually is accompanied by only a modest rise in the serum bicarbonate concentration. The reason for this apparent discrepancy is not clear. However, the attenuated increment in serum bicarbonate may reflect in part the bicarbonaturia that accompanies the restoration of extracellular volume and the provision of an adequate amount of chloride. The urine pH of 7.5 in this patient is consistent with this phenomenon.

The interpretation of an increased anion gap in patients with alkalemia is complicated because alkalemia per se can affect the anion gap. Alkalemia can increase both organic acid generation and the contribution of protein negative charge to the anion gap.

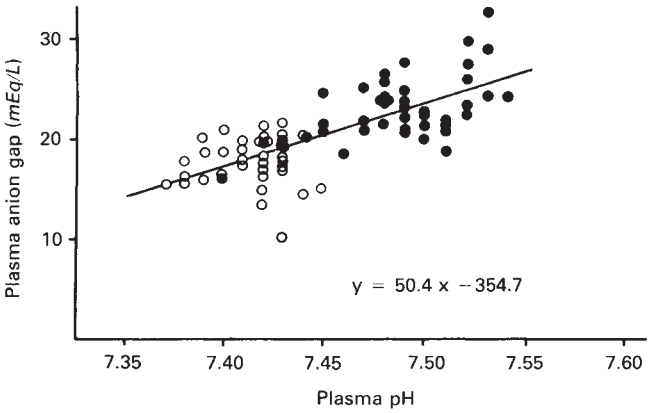

Fig. 2. *Relationship between plasma anion gap and plasma pH during chronic, diuretic-induced metabolic alkalosis in dogs.* Open symbols denote values obtained during control period; closed symbols denote values obtained during metabolic alkalosis period. Equations for least-squares regression lines are shown in respective panels; value for slope of each line was significantly different from zero ($P > 0.01$). (From Ref. 57.)

In acute respiratory alkalosis, lactic acid production can increase modestly and elevate plasma lactate by 2 to 3 mEq/liter. The increase in lactic acid production appears to result from an increased activity of phosphofructokinase which, in turn, enhances glycolysis via the Embden-Meyerhof pathway, and increases the conversion of glucose to lactate [43].

The effect of metabolic alkalosis on organic acid production has not been fully evaluated. Sodium bicarbonate administration does increase lactic acid production in experimental lactic acidosis [53]. Similarly, 2 patients with tumor-related lactic acidosis treated with sodium bicarbonate reportedly had increased lactic acid production following such therapy [54, 55]. Finally, Hood et al demonstrated that bicarbonate administration increases ketoacid excretion during starvation in obese human subjects [56]. The authors did not, however, determine whether the increase in ketoacid excretion resulted from an increase in ketoacid production or from decreased utilization. The elevated levels of organic acid anions evident in Patient 2 might reflect the influence of alkalemia on organic acid production.

In addition to the putative stimulating effect of bicarbonate administration and alkalemia on organic acid production, alkalemia increases unmeasured anion concentration increasing the net negative charge on serum proteins. Two interrelated factors are responsible. First, alkalemic states often are associated with a reduction in extracellular fluid volume, hemoconcentration, and a rise in the serum protein concentration. In Patient 2, for example, serum protein concentration rose from 6.3 g/dl to 8.7 g/dl. Second, proteins surrender protons when titrated in an alkaline direction, thereby uncovering additional negative charges.

The relationship between anion gap and pH during one study of experimental metabolic alkalosis is illustrated in Figure 2 [57]. The magnitude of the increment in anion gap with respect to the degree of alkalemia may well reflect both increased acid production and the effect of alkalemia on protein charge. The only organic anion measured in this study was lactate, which increased slightly.

Utilizing Van Leeuwen's formula [4], one would anticipate that alkaline titration alone would have increased the anion gap by 2.3 mEq/liter in Patient 2, whose pH rose from 7.40 to 7.76. Adding the effects of increased serum protein concentration, one can account for an increment in the anion gap of 7.5 mEq/liter in this patient. The observed increment of 23 mEq/liter therefore cannot be ascribed solely to the effects of alkalemia and must imply increased production of organic acids.

Adding to the complexity of interpreting anion gap values in subjects with alkalemia is the recognition that many alkalemic patients have normal or low anion gap values and yet have no evidence of disorders known to be associated with low anion gaps [58–61]. This finding indicates that much remains to be understood about the effect of alkalemia on charge contribution and organic acid production.

Special comment should be made about circumstances in which the anion responsible for elevating the anion gap is itself responsible for the generation of a metabolic alkalosis and alkalemia. When certain organic acid anions (for example, lactate, citrate, acetate) are metabolized by tissues, hydrogen ions are consumed, and bicarbonate ions are generated. The metabolic events involved are summarized in the following equations:

(1) $H_2O \rightarrow H^+ + OH^-$

(2) $C_3H_5O_3^-$ (lactate) $+ H^+ + 3O_2 \rightarrow 3H_2O + 3CO_2$

(3) $OH^- + CO_2 \rightarrow HCO_3^-$

Thus:

(4) $C_3H_5O_3^- + 3O_2 \rightarrow 2H_2O + 2CO_2 + HCO_3^-$

It is evident that oxidation of lactate or any other organic anion generates an equivalent amount of bicarbonate. During brisk administration of these acid anions (usually with sodium or potassium), a minimally increased anion gap and hyperbicarbonatemia can occur before all the exogenous anion is metabolized completely. Following full metabolism, of course, the anion gap returns to normal. This sequence can occur with the administration of lactate, acetate, or citrate, particularly in the setting of decreased renal function [62]. A similar sequence can occur during recovery from an organic acid acidosis, especially lactic acidosis, if exogenous bicarbonate has been administered.

Under some circumstances, the administration of nonmetabolizable salts of organic anions also can result in an increased anion gap and alkalemia. The administration of carbenicillin [63, 64] and high-dose penicillin [65] are possible examples; although alkalemia is well known as a potential complication of using these agents, little information is available about the anion gap in these circumstances. Sodium-deprived rats given carbenicillin do develop metabolic alkalosis associated with an increased anion gap. These effects are accompanied by an initial brisk diuresis with a marked increase in urinary potassium and ammonium excretion [66].

It is clear from the foregoing that a wide variety of pathogenetic processes can affect the anion gap in alkalemic states: *(1)* the coexistence of a metabolic acidosis with an increased anion gap and either a metabolic alkalosis, a respiratory alkalosis, or both; *(2)* an alkalemia-induced increase in organic acid production; *(3)* an increase in protein negative charges that is due to a combination of alkaline titration of protein buffer groups and hyperproteinemia consequent to volume depletion; and *(4)* occasionally, the generation of metabolic alkalosis via the effects of certain anions on metabolism or on renal tubular function.

Table 4. Relationship between level of anion gap and biochemical diagnoses in 51 patients without renal failure[a]

Anion gap *mEq/liter*	Number of patients	Biochemically confirmed organic acidosis	
		Number	*Percentage*
17–19	7	2	29
20–24	20	13	65
25–29	15	12	80
30–45	9	9	100
Total	51	36	71

[a] Adapted from Ref. 6.

Accounting for the increased anion gap

I now would like to turn to the question, can one account for increments in the anion gap by explicit changes in the various serum constitutents that have been discussed? The answer is, not nearly as often as one might imagine. For example, when the anion gap is 17 to 19 mEq/liter, the increment seldom is due to an accumulation of common, identifiable organic acid anions. In our study, only 29% of patients with anion gaps in this range had biochemically confirmed organic acidosis (Table 4) [6]. In many instances, anion gaps in this range reflect alterations in unmeasured cations, proteins, or phosphate.

By contrast, when the anion gap is greater than 30 mEq/liter, an increase in one of the commonly occurring organic acids usually is responsible. Indeed, in our study, an identifiable organic acid anion was found in all patients with such elevations in the anion gap (Table 4). Even under these circumstances, however, the increment in the anion gap often exceeds the measured concentration of organic acid anions. For example, in the first 2 patients under discussion today, the measured levels of organic acid anions respectively accounted for only 25% and 39% of the increment in anion gap observed. A review of 109 patients in whom measurements of organic acid anions were carried out indicates that increases in organic acid levels accounted for 13% to 200% of the elevations in anion gap [6].

In some instances, the failure of organic acids to fully account for the increase in anion gap almost certainly is due to a failure in identifying some or all of the responsible organic acids. In Patient 1 for example, if glycolic acid, the major malefactor in experimental ethylene glycol intoxication [67] had been measured, a more complete accounting of the increase in anion gap might have been possible. In Patient 2, small amounts of several organic acids were demonstrated, but gas chromatographic and mass spectrophotometric techniques were required to do so. This finding demonstrates the technical difficulty encountered when one attempts to identify the majority of plasma organic acids, some of which may increase significantly in metabolic disorders. Indeed, in many disorders, the offending organic acid remains to be identified, as indicated in Table 3. Even in reasonably well-understood disorders such as diabetic ketoacidosis, however, the degree to which identifiable organic acids

Table 5. Causes of a decreased anion gap

Increased unmeasured cation
IgG multiple myeloma
Increased calcium, magnesium, or potassium
Acute lithium intoxication
Polymyxin B administration
Decreased unmeasured anions
Hypoalbuminemia
Dilution
Nonrandom analytical error
Hypernatremia (severe)
Hyperviscosity
Bromide intoxication
Iodide ingestion
Hyperlipidemia

contribute to the observed increase in anion gap ranges widely from 26% to 143% [6]. The possibility that alterations in serum constituents other than organic acids contribute to the discrepancy also must be considered. Changes in the charge contribution of potassium, calcium, phosphorus, and protein can account for as much as a 9 mEq/liter increase in the anion gap. Frequently an unexplained discrepancy exists between the increase in the anion gap and the measurable alterations in the serum constituents. An extensive systematic study of patients with increased anion gaps will be required to clarify this issue.

Decreased anion gap

Disorders marked by a decrease in the anion gap have received less attention than have those associated with an increase, because downward deviations occur less often, and disorders associated with such changes are less acutely life threatening. The third patient under discussion today had an anion gap of 5 mEq/liter, a value distinctly below normal. Table 5 lists disorders known to cause a decreased anion gap. This patient clearly had multiple myeloma. The decreased anion gap in this disorder reflects an increase in unmeasured cations; this increase is due to the increased serum concentration of cationic IgG paraproteins [68]. Characteristically IgG paraproteins have isoelectric points higher than 7.40 and therefore are positively charged at normal serum pH. Some investigators speculate that plasma electroneutrality is maintained by an increase in plasma chloride concentration; there are no data confirming this assertion, however. Alterations in sodium, bicarbonate, or other ions may preserve charge balance. Nonetheless, a significant inverse relationship exists between the concentration of the IgG paraproteins in the serum and the level of the anion gap. In addition to the effect of IgG paraproteins, hypercalcemia and hypoalbuminemia also can contribute to a low plasma anion gap in patients with multiple myeloma. A decrease in anion gap also has been reported in patients with asymptomatic plasma cell dyscrasias who demonstrate a paraprotein "spike" [69] and in patients with diffuse polyclonal hypergammaglobulinemia [70]. It is of interest that IgA paraproteins are not associated with a low anion gap because they have isoelectric points slightly below 7.40 and therefore are anionic at normal pH. Indeed, the anion gap potentially could be increased with IgA myeloma, but such an occurrence has not been reported.

Increased levels of certain endogenous cations, namely calcium, magnesium, or potassium, theoretically could decrease the anion gap. But no common disorders typically increase all three, and an increase in any one of magnitude sufficient to decrease the anion gap appreciably would not be compatible with life. Some reduction in the anion gap can result from the administration of cationic drugs; this alteration has been reported in patients with lithium intoxication and in patients receiving the polycationic antibiotic polymyxin B [7].

A reduction in the concentration of one or more unmeasured anions also would be expected to reduce the anion gap. Indeed, hypoalbuminemia is probably the most common cause of a decreased anion gap in hospitalized patients. Each gram-per-deciliter reduction in the serum albumin concentration would be expected to reduce the anion gap by approximately 2.5 mEq/liter. This mechanism is the most likely explanation for the decreased anion gap frequently observed in patients with nephrotic syndrome and in patients with advanced liver disease [7].

Some reduction in the anion gap can occur in hypoosmolar states, presumably as a result of dilution [7]. This change is most apparent in the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). My personal review of case reports reveals that almost 25% of patients with SIADH have an anion gap of less than 6 mEq/liter.

Whenever an abnormally low value for anion gap is obtained, consideration should be given to the possibility of laboratory error. Among the causes of nonrandom laboratory error leading to artifactual reduction in the anion gap, hypernatremia and hyperviscosity are the most important. When serum sodium concentration exceeds 170 mEq/liter, certain flame photometers yield artifactually low values. In the presence of valid measurements for bicarbonate and chloride concentrations, falsely low values for serum sodium result in erroneously low levels for the calculated anion gap. Hyperviscosity also can lead to falsely low values for serum sodium and, hence, anion gap because the flame photometer apparatus may fail to aspirate an aliquot of hyperviscous serum sufficient to yield a valid result.

An artifactually high value for serum chloride concentration of course would also result in a correspondingly low anion gap. Historically, patients with bromide intoxication frequently exemplified this phenomenon. Because bromide reacts very strongly with the reagents utilized to measure chloride by the Autoanalyzer method, artifactually high values for serum chloride concentration were frequently seen in bromide-intoxicated patients [71]. Indeed, this laboratory error may be sufficient not only to lower the value for the anion gap but in some instances to render it negative. Fortunately, bromide intoxication has become much less common in the United States because organic bromides have been removed from virtually all drugs. The pharmaceuticals that do contain bromide have such small amounts that bromism does not occur with usual usage.

Iodide, another halogen capable of accumulating in the serum, also can cause an artifactual increase in serum chloride concentration and hence a decrease in the calculated value for anion gap [72]. Overestimation of serum chloride concentration also can occur, albeit by a different mechanism, in the presence of hyperlipidemia [73]; in this case, lipids scatter light in such a way as to falsely elevate the concentration of chloride when determined by the colorimetric method [73].

Accuracy in the assessment of the anion gap depends, of course, on the accuracy of measurement of the three constitu-

ent substances involved in its calculation. Random errors in measurement of the sodium, chloride, or total carbon dioxide content can invalidate the anion gap calculation by falsely elevating or reducing the value. Indeed, modest deviations in the anion gap from normal frequently may be the consequence of such errors.

Questions and answers

DR. ARNOLD BERNS (*Attending Nephrologist, Michael Reese Hospital*): Does intracellular metabolism break down at the extremes of pH, say below 6.9 or above 7.7, with the result that a variety of different products of intermediary metabolism are produced? And do these products, in the aggregate, contribute to the anion gap?

DR. GABOW: We investigated this question in a preliminary manner using gas chromatographic-mass spectroscopic techniques. If the situation you proposed existed, one would anticipate finding a variety of organic acids at extremes of pH. In fact we occasionally have seen an increase in unusual organic acids (Patient 2), but this does not appear to relate to pH. Additionally, if what you're suggesting actually happens, one would expect that commonly measured organic acids such as lactate, pyruvate, acetoacetate, and β-OH butyrate would account for a lower percentage of the increase in anion gap in severe acidemia. In fact, it appears that in severe acidemia the accountability may be higher. This question has not been well addressed in severe alkalemia and deserves further investigation.

DR. DAVID BUSHINSKY (*Renal Section, Mitchell Hospital, Chicago*): Given that one can find an increased anion gap in each of the four cardinal acid-base disorders, the determination might be regarded as insensitive and nonspecific. In view of this, is it worth even calculating the anion gap, or should one concentrate on actual laboratory measurements such as pH, potassium, and the like in analyzing the patient with an acid-base disorder?

DR. GABOW: The anion gap is simply additional data. Moreover, it is "free" data, calculated from the serum electrolytes. In settings of acidemia and hypobicarbonatemia, an elevated anion gap directs one's thinking toward certain disorders. An anion gap greater than 0.5 (HCO_3^-) + 16, or greater than 30 mEq/liter, almost always indicates an increase of a common organic acid, and this information is helpful. An elevated anion gap is also useful in diagnosing mixed acid-base disorders.

DR. JORDAN J. COHEN: You noted that occasionally patients with diabetic ketoacidosis develop a hyperchloremia rather than an increased anion gap. What is the relationship between this spontaneous hyperchloremia and the hyperchloremia that frequently occurs during treatment and recovery from diabetic ketoacidosis?

DR. GABOW: There have been a variety of explanations for the hyperchloremia and hypobicarbonatemia that occur during recovery. The ketoanions represent a potential source of bicarbonate in that during their metabolism they generate bicarbonate. Ketoanions, and thus potential bicarbonate ions, are lost in the urine during the development of diabetic ketoacidosis. Therefore, when keto acid production stops and metabolism of ketoanions begins, total body bicarbonate cannot return to its original level; the anion gap normalizes, hypobicarbonatemia persists, and a hyperchloremic acidosis is observed. Some support for this explanation comes from the observation that hyperchloremic acidosis is more common in the aftermath of diabetic ketoacidosis, in which excretion of potential bicarbonate as ketoanions is substantial, than it is in the aftermath of lactic acidosis, which is accompanied by less renal excretion of the lactate anion and less loss of potential bicabronate. Another possible explanation is that the distribution space of bicarbonate is different than the distribution space of the ketoanions. Therefore, the bicarbonate generated by metabolism is distributed in a larger space than are the ketoanions, and this leads to a rise in the serum bicarbonate that is less than the fall in the anion gap. The spontaneous hyperchloremic hypobicarbonatemia that sometimes occurs during the development of diabetic ketoacidosis probably reflects the former sequence of events. If the keto acid production is low grade and if volume status is well maintained, the keto acids will be buffered and the serum bicarbonate concentration will fall, but the ketoanions will be excreted in the urine. Thus potential bicarbonate is lost, chloride is retained in its place, and a hyperchloremic hypobicarbonatemic state results.

DR. COHEN: I suppose there is yet another possibility, namely that persistent hyperventilation and hypocapnia during recovery from acidosis reduces renal bicarbonate reabsorption and enhances chloride reabsorption. Do you agree?

DR. GABOW: Yes.

DR. SHELDON HIRSCH (*Medical Resident, Michael Reese Hospital*): I have been taught that the decrement in plasma bicarbonate should be roughly equal to the increment in the anion gap in uncomplicated, anion-gap metabolic acidosis and that one should be suspicious of a coexisting acid-base disorder whenever this relationship is disturbed. Do you find this rule to be clinically valid and useful?

DR. GABOW: This is a reasonable "rule of thumb." The anion gap results from the buffering of organic acids by bicarbonate, and therefore the increase in the anion gap should be related to the decrease in bicarbonate. It is probably not an equivalent relationship, however. First, other buffers are involved in addition to bicarbonate. Second, the distribution spaces of bicarbonate and the anion may not be the same. But if the drop in bicarbonate and the increase in anion gap are markedly discrepant, it seems reasonable to consider the possibility of other, coexisting acid-base disorders.

DR. COHEN: You pointed out that there are a number of circumstances in which the anion gap can be enormously elevated, reaching levels of 40 to 50 mEq/liter or higher. Obviously, if a reciprocal relationship exists between the increment in anion gap and the decrement in bicarbonate concentration, such very high values could not occur unless a preexisting or coexisting metabolic alkalosis were present to provide sufficient bicarbonate for buffering. Indeed, as in the second patient presented today, there is often a clear history of an alkalosis-producing process, such as vomiting. But sometimes significant hypochloremia is present in association with metabolic acidosis and there is no obvious explanation for it. Have you observed such patients and, if so, how do you explain this phenomenon?

DR. GABOW: My impression is similar to yours: occasionally no obvious cause for hypochloremia and metabolic alkalosis can be identified. In addition, it appears that the serum bicarbonate concentration never rises as much as one would anticipate from the level of the anion gap. This may reflect volume

expansion and bicarbonaturia with recovery, but I have no explanation for the initial discrepancy.

DR. SERAFINO GARELLA (*Department of Medicine, Michael Reese Hospital*): A potential explanation for such a discrepancy might be derived from results of mineral acid infusion studies. If we assume that organic acids titrate bicarbonate in much the same fashion and to the same degree as do mineral acids, hypochloremia might result. If only approximately 40% of the total acid load is buffered by extracellular bicarbonate, and if most of the offending organic acid anions remain in the extracellular space, the fall in bicarbonate in organic acidosis would be much smaller than the rise in the anion gap, the discrepancy being accounted for by hypochloremia. Indeed, such a possibility has been confirmed by studies in nephrectomized rats [74].

DR. GARY TOBACK (*Renal Section, Mitchell Hospital*): The administration of sodium bicarbonate appears to exacerbate lactic acidosis on occasion. If this observation is valid, how should lactic acidosis be treated?

DR. GABOW: First and foremost, of course, the underlying cause for the lactic acidosis must be addressed, if possible. How to treat the acidemia per se is a difficult question. As I discussed, both alkalemia and bicarbonate administration appear to increase keto acid and lactic acid production in experimental and clinical settings. Arieff's data from an experimental animal model of lactic acidosis suggest that survival is the same in dogs treated with sodium chloride as in dogs treated with sodium bicarbonate. There is, however, no well-established alternative to bicarbonate for the therapy of severe, life-threatening acidosis at this time.

DR. BERNS: Have you had any experience with dichloroacetate in the treatment of lactic acidosis?

DR. GABOW: No, I have not been involved in a clinical trial of dichloroacetate. Dichloroacetate activates pyruvic dehydrogenase and thereby promotes the oxidation of pyruvate in vitro. Thus, it was hypothesized that this agent might lower lactate levels in vivo. In fact, it appears to do so in animal models of lactic acidosis as well as in clinical lactic acidosis. Its utility and, indeed, its precise mechanism of action remains to be demonstrated in a large prospective trial.

DR. CHARLES BENNETT (*Medical Resident, Michael Reese Hospital*): You commented that patients with diabetic acidosis and hypovolemia tend to have an elevated anion gap, whereas those who are normovolemic manifest hyperchloremia. Could a case be made that diabetic patients with hypovolemia and an elevated anion gap might do better if treated with lactated Ringer's solution rather than with sodium chloride? Such an approach to volume repletion might minimize these patients' tendency to develop hyperchloremic acidosis during therapy.

DR. GABOW: Adrogué et al suggest that administration of sodium chloride solutions might contribute to the development of hyperchloremic acidosis by accelerating the loss of ketoanions, that is, potential bicarbonate, in the urine. Whether the transient hyperchloremic acidosis that can occur in this setting contributes to the length of hospitalization or to morbidity is not clear. This possibility must be balanced against the risks of giving bicarbonate or its equivalent in the form of lactated Ringer's solution. As discussed, sodium bicarbonate may increase keto acid production. Perhaps that might prolong the period of ketoacidosis. In addition, the administration of bicarbonate may result in a rebound metabolic alkalosis. Until this is studied in a controlled fashion, it would be difficult to determine which solution or fluid therapy is ideal.

DR. COHEN: You mentioned that patients with hyperglycemic, nonketotic hyperosmolar coma occasionally have very large anion gaps. Such patients usually develop little if any overt acidosis. How do you explain these findings?

DR. GABOW: By traditional teaching, we would conclude that such patients had metabolic alkalosis and a metabolic acidosis based on the anion gap and the calculated potential bicarbonate concentration. It is not unreasonable to assume that these patients in fact have metabolic alkalosis due to the large osmotic diuresis with sodium chloride loss. These patients certainly have volume contraction and large sodium chloride defects. Other factors not yet defined may also be operative.

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