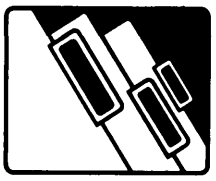
Case Report



The Urine Anion Gap: The Critical Clue to Resolve a Diagnostic Dilemma in a Patient with Ketoacidosis

JACK G. HILTON, M.D., ARTHUR C. VANDENBROUCKE, Ph.D., ROBERT G. JOSSE, M.D., GLORIA C. BUCKLEY, B.A., AND MITCHELL L. HALPERIN, M.D.

Usually, ketoacidosis presents few if any diagnostic or therapeutic problems; in this article, we report a case where ketoacidosis was clinically occult and biochemically obscure. The patient presented with acute pancreatitis associated with a modest antecedent alcohol intake. Metabolic acidosis with a normal anion gap (10 meq/L) was observed together with moderate hyperglycemia and a 2+ (but not 4+) test for serum ketones. None of the usual causes of metabolic acidosis with a normal anion gap was identified nor was there an obvious explanation for a reduction in unmeasured anion gap (e.g., hypoalbuminemia, dysproteinemia, or the presence of abnormal halides). Despite the initial normal anion gap, ketoacidosis was suspected clinically and this was confirmed by the elevated serum B-hydroxybutyrate of 8 mmol/L. We deduced that the serum unmeasured anions, which should have been increased by at least 8 meq/L, were being underestimated because of the effect of hypertriglyceridemia on the serum chloride determination. When the serum chloride was reestimated by a method not influenced by hyperlipidemia, the value was 102 mmol/L not 112 mmol/L and, when reevaluated, the anion gap was indeed appropriately elevated. In addition, the urine anion gap (Na + K − Cl) was 103 meq/L in the absence of renal disease. This indicated that the expected large quantity of urinary ammonium must have been masked by an even greater quantity of unmeasured anion; in this case proven by direct measurement to be B-hydroxybutyrate. Finally, metabolism of the alcohol ingested, which yields hepatic NADH, could explain, in part, the modest hyperglycemia and the absence of a 4+ test for serum ketones. With this information, appropriate treatment for ketoacidosis was instituted and within 36–48 h the bicarbonate (23 mmol/L) and the anion gap (11 meq/L) returned to normal. Thus, knowledge of how the determination of the serum chloride can be influenced by hypertriglyceridemia and, at the same time, our utilization of the urine anion gap permitted us to make the diagnosis and effect the treatment of an obscure case of metabolic acidosis due to ketoacidosis. DIABETES CARE 1984; 7:486–90.

In diabetic ketoacidosis (DKA), the low insulin levels lead to increased glucose production, accelerated fat metabolism, and the accumulation of B-hydroxybutyric and acetoacetic acids (for review, see refs. 1 and 2). Patients with this disorder usually develop hyperglycemia, metabolic acidosis with a wide anion gap, and a strongly positive test for serum ketones. Generally, the increase in the anion gap is proportional to the decrease in serum bicarbonate concentration.[3–6]

Hyperchloremic metabolic acidosis (HCMA) is diagnosed when there is a fall in blood bicarbonate concentration without a concomitant increase in the anion gap; in this disorder, there is a relative increase in the serum chloride concentration. HCMA commonly occurs in patients who have gastrointestinal or urine bicarbonate loss; it can be seen in patients who have ingested ammonium chloride or its equivalent, but this is a very rare occurrence. However, there is also an "indirect loss of bicarbonate" resulting in a non-anion gap type metabolic acidosis.[6,7] In some patients with DKA, the loss of B-hydroxybutyrate in the urine may be extremely large so that HCMA develops during the course of DKA.[6–8] The mechanisms responsible for this combined acidosis are summarized in Figure 1.

A 37-yr-old man presented with diabetes mellitus, pan-

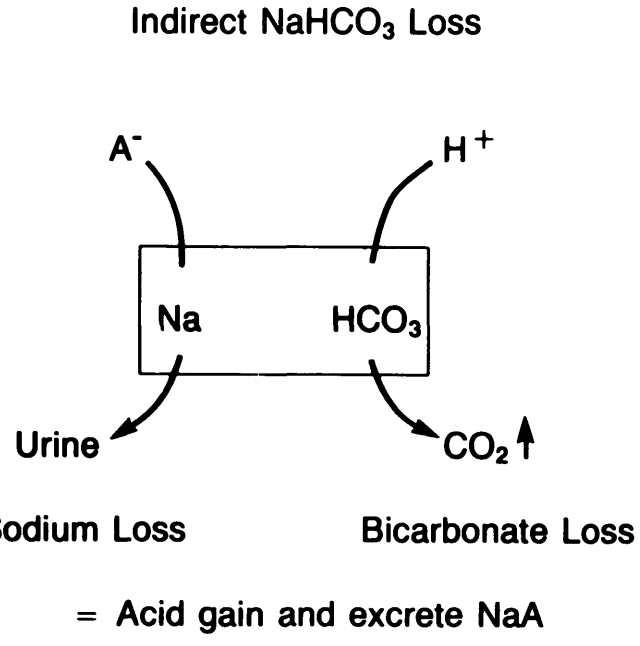


FIG. 1. The indirect loss of sodium bicarbonate from the extracellular fluid. For this loss to occur, the acid, B-hydroxybutyrate, is added to the extracellular fluid. The hydrogen ions react with bicarbonate in the ECF and the resulting CO_2 is blown off via the lungs. The anion (A^-), B-hydroxybutyrate, is filtered by the kidney and some is excreted in the urine; should the quantity excreted exceed the excretion of ammonium, then sodium (or potassium) would be excreted for electrical neutrality. With respect to the ECF, note that the hydrogen ion and B-hydroxybutyrate produced are both lost, and in so doing, sodium bicarbonate is lost indirectly from the ECF (enclosed rectangle).

creatitis, and hypertriglyceridemia. The metabolic acidosis was of the normal anion gap type (HCMA). None of the usual causes of HCMA could be identified. Both our understanding of how hypertriglyceridemia may affect the serum chloride determination (and hence the anion gap) and our utilization of the urine anion gap independently permitted us to diagnose DKA in a very atypical case.

CASE REPORT

A 37-yr-old Caucasian man presented to hospital complaining of severe epigastric pain that radiated to the back. Three days before his admission, he developed anorexia and discontinued his usual alcohol intake except for a single glass of wine just before presentation. One day before admission, he became nauseated and developed the acute onset of severe epigastric pain. There was no history of polyuria, polydypsia, diarrhea, vomiting, or the ingestion of exogenous acids or halides. Past history revealed chronic alcohol abuse since his late teens. An elevated "random" blood sugar had been noted by his family physician 3 wk previously. There was no family history of hypertriglyceridemia. His son had developed diabetes mellitus at age 3.

Physical examination revealed a very flushed man in moderate distress; body weight was 55 kg. Vital signs recorded on admission revealed a regular pulse rate of 102/min, blood pressure 110/70 mm Hg with a postural drop of 10 mm Hg, respiratory rate of 28/min, and a temperature of 37.8°C. His eyes were sunken, mucous membranes were dry, and his skin turgor was decreased. Eruptive xanthomata were noted over both lower extremities. The abdomen was diffusely tender but there were no localizing signs; the bowel sounds were hyperactive and there was no organomegaly.

The pertinent laboratory results are summarized in Table 1. The urine contained 2+ glucose but ketones were absent. There was no proteinuria and the sediment was normal. Urine pH ranged between 5.1 and 5.3. A "lipid cake" formed on top of an arterial blood sample drawn at the time of admission. The plasma cholesterol was 813 mg/dl (21 mmol/L) (normal = 240 mg/dl or 6.2 mmol/L) and triglyceride was 4430 mg/dl (50 mmol/L) (normal = 195 mg/dl or 2.2 mmol/L) in this blood sample. Lipoprotein electrophoresis and ultracentrifugation showed a pattern consistent with type 5 hyperlipidemia. On admission, the plasma amylase activity was 62 U/L (N = 10–70 U/L); when the serum was treated to remove the lipid, the subsequent serum amylase level in this blood sample was 259 U/L. The plasma calcium was 8.0 mg/dl (2.0 mmol/L) (normal = 8.8–10.4 mg/dl or 2.2–2.6 mmol/L) with a total protein of 6.1 g/dl (61 g/L) and an albumin of 3.25 g/dl (32.5 g/L). The undiluted plasma showed only 1+ ketones with Ketostix (Ames Division, Miles Laboratories, Elkhart, Indiana).

TABLE 1
Blood and serum parameters during the course of therapy

Parameter	Before insulin	Postinsulin therapy	
		24 h	48 h
Blood gases			
pH	7.29	7.43	7.40
PCO_2 (mm Hg)	18	29	38
PO_2 (mm Hg)	110	89	92
Serum electrolytes			
NA^+ (mmol/L)	133	138	140
K^+ (mmol/L)	4.1	3.7	3.9
Cl^- (mmol/L)	114	111	106
Total CO_2 (mmol/L)	9	17	23
Anion gap (meq/L)	10	10	11
Blood metabolites			
Glucose (mg/dl)	198	270	234
BHB (mmol/L)	8	1	ND
Lactate (mmol/L)	1.2	0.5	ND
Creatinine (mg/dl)	2		
BUN (mg/dl)	6.7	9.8	14.3
Phosphate (mg/dl)	4.7	2.5	ND
Hgb (g/dl)	12.1	12.4	ND

Values given are those taken immediately preceding insulin administration. However, on admission, the bicarbonate concentration was 16 mmol/L and fell to close to 10 mmol/L despite the administration of 150 mmol of sodium bicarbonate.

TABLE 2
Repeat blood values during the 12-h pretreatment period*

Parameter	Sample					
	1	2	3	4	5	6
Na^+ (mmol/L)	133	131	130	133	133	134
K^+ (mmol/L)	4.1	3.9	3.7	4.0	3.8	4.0
Cl^- (mmol/L)	114	113	111	111	111	110
HCO_3^- (mmol/L)	9	7	10	10	12	12
Anion gap (meq/L)	10	11	9	12	12	12

*For details, see text.

TABLE 3
Urine parameters during the course of therapy

Parameter	Before insulin	24 h after insulin
Na^+ (mmol/L)	94	159
K^+ (mmol/L)	55	35
Cl^- (mmol/L)	46	257
Anion gap (meq/L)	103	−63
NH_4^+ (mmol/L)	30*	103*
BHB^- (mmol/L)	108*	

*NH_4^+ and BHB^- levels were also calculated per g of creatinine as this provides an index of excretion per unit time.

Over the first 12 h (before insulin therapy), the plasma bicarbonate concentration fell from 16 to 11 mmol/L despite the fact that sodium bicarbonate was administered (150 mmol in 12 h). The values for serum electrolytes in seven consecutive samples during this interval are shown in Table 2. The serum bicarbonate concentration remained close to 11 mmol/L, and the anion gap ranged from 9 to 12 meq/L. Initially, therapy was started with normal saline supplemented with potassium chloride. Ten units of regular insulin was administered subcutaneously 12 h after admission. Serum electrolytes and blood gases returned to normal within 48 h (Table 1). Lipid values fell toward normal after 72 h of therapy. The urine acid base and electrolyte values before and after insulin therapy are summarized in Table 3.

Special studies. Abdominal ultrasound was within normal limits as were three views of the abdomen. With sodium bicarbonate loading, the urine pH did not rise above 7.0 until the serum bicarbonate concentration approached 24 mmol/L and the fractional excretion of bicarbonate was 9% indicating that proximal renal tubular acidosis was not present. Furthermore, the initial fractional excretions of B-hydroxybutyrate, inorganic phosphate, and urate were all within the expected normal range when the patient had untreated ketoacidosis,[7] and generalized aminoaciduria was not observed. All of the above tended to rule out proximal tubular defects.

Laboratory methods. The following tests were performed on an IL 508 (Instrumental Laboratory, Inc., Lexington, Massachusetts): sodium and potassium (by ion-selective electrodes), chloride (by a mercuric-thiocynate colorimetric procedure[9]), total carbon dioxide (by an automated procedure based on the manometric method of Van Slyke[10]), and glucose (by the glucose-oxidase method[11]). Amylase was determined on an IL Multistat (Instrumental Laboratory, Inc., Lexington, Massachusetts) using the Panatrak kit (Calbiochem-Behring, La Jolla, California). The KDA (American Monitor Corp., Indianapolis, Indiana) was used to determine cholesterol (enzymatically with the CHOD-PAP kit from Boehringer-Mannheim Canada, Ltd., Dorval, Quebec), calcium (by the O-cresolphthalein complexone method[12]), total protein (by the Biuret procedure[13]), and albumin (with bromcresol green[14]). Triglyceride was determined by thin-layer chromatography.[15] B-hydroxybutyrate and lactate were measured by enzymatic analyses as previously described.[7]

Comparison of the serum chloride concentration using three different instruments. Chloride concentrations were determined using the IL 508, an Auto Analyzer II (Technicon Instrument Corp., Tarrytown, New York), and the Parallel (American Monitor Corp.). The IL 508[9] and the AA II[16] both use the same in-house mercuric-thiocynate reagent; with the AA II, the sample is dialyzed before it enters the colorimeter. The Parallel uses mercuric 2,4,6-tripyridyl-s-triazine (TPTZ)[17] in its determination. The IL 508 and the Parallel rely mainly on high dilution factors and surfactants to reduce interference due to lipemia.

DISCUSSION

As shown in Tables 1 and 2, the initial laboratory results were compatible with metabolic acidosis of the normal anion gap type. This disorder appeared to be ongoing in that the plasma bicarbonate concentration did not rise when sodium bicarbonate was administered. The diagnostic considerations are summarized in Table 4.

Although the intake of hydrochloric acid (or its equivalent) can produce HCMA, there was no evidence to suggest

TABLE 4
Clinical approach to HCMA

- HCl intake
  - Also $CaCl_2$, NH_4Cl, arginine hydrochloride, etc.
- Sodium bicarbonate loss
  - Gastrointestinal, e.g., diarrhea, ileus, drainage
  - Renal
    - Direct bicarbonate loss
      - Proximal RTA, carbonic anhydrase inhibitors
    - Indirect bicarbonate loss
      - Production of an acid and the loss of its sodium salt (see Figure 1 and refs. 6 and 7)
- Anion gap type of metabolic acidosis with a low value for the anion gap
  - Problem with anions, e.g., hypoalbuminemia, chloride detection errors
  - Unusual cations, e.g., multiple myeloma, lithium, etc.

this cause in our patients. In addition, low initial urine pH values ruled out ongoing renal bicarbonate wasting. Although sequestration of bicarbonate-rich fluids in the gut secondary to an ileus may cause HCMA, there was no clinical or radiologic evidence of ileus. In our approach to this patient, we reasoned that if HCMA was due to the nonrenal loss of bicarbonate, the patient should excrete large quantities of ammonium in the urine. To assess ammonium excretion, we examined the urine indirectly (immediately) and directly (later).

Normal subjects who are given a chronic acid load excrete as much as 400 mmol of ammonium each day.[18] Such high concentrations of ammonium can be detected indirectly by examining the urine "anion gap" ($Na^+ + K^+ - Cl$).* During chronic metabolic acidosis due to the nonrenal loss of sodium bicarbonate, this anion gap will be negative (i.e., more Cl^- than $Na^+ + K^+$) due to the excretion of ammonium (NH_4^+). In our patient, the initial value for the urine anion gap was 103 meq/L (i.e., *less* Cl^- than $Na^+ + K^+$), indicating that there was the excretion of at least 103 meq of an anion other than chloride and bicarbonate, which would be even more if the urine contained ammonium. Thus, we concluded that the simple loss of sodium bicarbonate in an ileus could not completely describe the pathophysiology of the clinical events.

Because the patient had past history of hyperglycemia and modest hyperglycemia on admission (Table 1), the plasma and urine were tested for ketones. Both tests were only mildly positive, suggesting, along with the anion gap determination, that ketoacidosis was not the main acid-base diagnosis. However, since a high NADH/NAD ratio (due to ECF volume contraction, localized hypoxia, and the small ethanol intake) can make these tests underestimate the degree of ketoacidosis,[19] the blood B-hydroxybutyrate concentration was measured directly and the value was markedly elevated at 8 mmol/L (Table 1). We reasoned that the elevated urine anion gap (Na + K greater than Cl) was due to the excess of B-hydroxybutyrate, and this was also confirmed by direct measurements. Hence the basis of the metabolic acidosis (i.e, ketoacidosis) became clear although the reason for the normal plasma anion gap in the presence of 8 mmol/L B-hydroxybutyrate was obscure. Accordingly, treatment with insulin, saline, and potassium was instituted and the patient recovered dramatically—the serum electrolytes and blood acid-base values returning to normal within 36–48 h (without additional bicarbonate therapy). Once the ketonemia had returned to normal and the patient was still acidemic, the urine anion gap was −63 meq/L (i.e., more Cl than $Na^+ + K^+$) indicating that excess ammonium was being excreted; direct urinary measurements confirmed this (Table 3). The reason for the low urine anion gap in early samples was that the ammonium was excreted but its quantity was less than that of B-hydroxybutyrate (Table 3).

The reason for the normal serum anion gap in the face of an elevated blood B-hydroxybutyrate concentration in early blood samples was not immediately clear to us. The anion gap can be low in a patient if the serum albumin concentration is reduced, if halides such as bromide are ingested, or if an unusual cationic protein is present in the circulation, for example, multiple myeloma.[20] However, none of the above was present in this case. Accordingly, we wondered, as suggested by Graber et al.,[21] if the hyperlipidemia had influenced

TABLE 5
Effect of triglycerides on the serum chloride concentration*

Chloride method (mmol/L)				Lipids (mg/dl)	
Patient	508	AA	Parallel	Chylomicrons	Triglycerides
1	90	90	86	Neg	1373
2	117	100	103	Pos	1630
3	101	103	102	Neg	6323
4	108	90	94	Pos	3987
5	118	90	96	Pos	5662
6	104	101	100	Trace	1108
7	105	101	98	Pos	377
8	103	98	95	Neg	3260
9	100	101	99	Pos	2614
10	95	92	91	Neg	3216
Mean	104	97	96		

*For details, see text. Patients 8 and 9 are the exceptions to the rule that chylomicron triglycerides are the critical factor causing a falsely high chloride value on the 508 instrument.

*The urine anion gap is useful in two major clinical settings—the differential diagnosis of HCMA and to assess the causes of renal potassium wasting. In the former circumstance, the clinician attempts to quantitate the urinary excretion of ammonium. The prerequisites for its use are first that the urine does not contain abundant unusual anions (e.g., bicarbonate, ketone bodies, carbenicillen, etc.). To assess this, a urine pH below the mid-6 range indicates that there is little bicarbonate excretion; a negative test for ketones (plus clinical suspicion) provides the clinician with information concerning ketone body anions; this together with an evaluation of drug intake and drug metabolism should provide the required screening information in most instances. We have recently compared the rate of ammonium excretion to the urine anion gap in 96 otherwise normal subjects with HCMA produced by ammonium chloride ingestion;[23] there was a direct linear relationship between these two parameters with the rate of ammonium excretion exceeding the urine anion gap by 80 meq/day. In practical terms a negative value for the urine anion gap (Cl exceeds Na + K) indicates that the urine contains appreciable quantities of ammonium (at least 80 mM). Expressing these results per creatinine excretion permits the clinician to evaluate the ammonium excretion rate (concentrations will vary depending on the degree of water diuresis). The second major use for the urine anion gap is to reflect the excretion of a nonreabsorbed anion that may have played an important role in renal potassium wasting. To maintain electrical neutrality when anions are lost in the urine, they must be accompanied by major urinary cations such as sodium or potassium. In this case, a stimulus for aldosterone release (e.g., ECF volume contraction) together with a high filtered load of nonreabsorbed anions could help to explain the inappropriate renal potassium loss.

the electrolyte results making the initial value for the anion gap artificially low. The serum chloride determination by the chloride analyzer, which was in use for "stat" samples, can yield falsely elevated values due to the turbidity of the sample. Thus, hypertriglyceridemic samples from this patient could have led to a falsely high serum chloride value on all samples except those measured with direct potentiometric chloridometers; it appears that the chylomicron triglycerides cause this problem. Hence, we suspect that the serum chloride concentrations were spuriously elevated and the anion gap artifactually reduced because of the effect of hypertriglyceridemia on these laboratory tests (Table 5).

Thus, in retrospect, several features acting in concert tended to obscure the clinical diagnosis of diabetic (and possibly alcoholic) ketoacidosis, and the urine anion gap was very helpful in such a diagnostic dilemma by revealing the excretion of an organic anion. First, the hyperglycemia was only modest in this patient—this could be related to the small amount of ethanol ingested (for review, see ref. 22). Second, ketoacidosis was hard to detect because the serum test for ketones was not strongly positive and the anion gap was not elevated. However, the alternate diagnosis of gastrointestinal bicarbonate loss was also not convincing for the reasons described. Accordingly, the clinical diagnosis depended on clinical suspicion and the interpretation of the urine anion gap, which was confirmed by a retrospective analysis of the blood, and urine B-hydroxybutyrate as well as urine ammonium concentrations. Once the correct diagnosis was suspected, appropriate therapy was begun and the recovery was rapid and uneventful.

From the Departments of Medicine and Clinical Biochemistry, St. Michael's Hospital, Toronto, Ontario, Canada.

Address reprint requests to Dr. M. L. Halperin, Lab #1, Research Wing, St. Michael's Hospital, 38 Shuter Street, Toronto, Ontario, Canada M5B 1A6.

REFERENCES

[1] Kreisberg, R. A.: Diabetic ketoacidosis: new concepts and trends in pathogenesis and treatment. Ann. Intern. Med. 1978; 88:681–95.

[2] Foster, D. W., and McGarry, J. D.: The metabolic derangements and treatment of diabetic ketoacidosis. N. Engl. J. Med. 1983; 309:159–69.

[3] Emmett, M., and Narins, R. G.: Clinical use of the anion gap. Medicine 1977; 56:38–54.

[4] Oh, M. S., and Carroll, H. J.: The anion gap. N. Engl. J. Med. 1977; 297:814–17.

[5] Adrogue, H. J., Wilson, H., Boyd, A. E., Suki, W. N., and Eknoyan, G.: Plasma acid-base patterns in diabetic ketoacidosis. N. Engl. J. Med. 1982; 307:1603–10.

[6] Halperin, M. L., Bear, R. A., Hannaford, M. C., and Goldstein, M. B.: Selected aspects of the pathophysiology of metabolic acidosis in diabetes mellitus. Diabetes 1981; 30:781–87.

[7] Hammeke, M., Bear, R., Lee, R., Goldstein, M., and Halperin, M.: Hyperchloremic metabolic acidosis in diabetes mellitus: a case report and discussion of the pathophysiologic mechanisms. Diabetes 1978; 27:16–20.

[8] Oh, M. S., Carroll, H. J., Goldstein, D. A., and Fein, I. A.: Hyperchloremic acidosis during the recovery phase of diabetic ketosis. Ann. Intern. Med. 1978; 89:925–27.

[9] Zall, D. M., Fisher, D., and Garner, M. Q.: Photometric determination of chlorides in water. Anal. Chem. 1956; 28:1665–68.

[10] Van Slyke, P. D., and Neill, J. M.: The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. Int. J. Biol. Chem. 1924; 61:523–84.

[11] Trinder, P.: Determination of glucose in blood using glucose oxidase with an alternate oxygen acceptor. Ann. Clin. Biochem. 1969; 6:24–27.

[12] Baginski, E. S., Marie, S. S., Clarke, W. L., and Zak, B.: Direct microdetermination of serum calcium. Clin. Chim. Acta 1973; 46:49–54.

[13] Cannon, D. C., Olitzky, I., and Inkpen, J. A.: Determination of serum protein by the biuret reaction. *In* Clinical Chemistry Principles and Techniques. Henry, R. J., Cannon, D. C., and Winkelman, J. W., Eds. New York, Harper and Row, 1974:413–16.

[14] Dumas, B. T., and Biggs, H. G.: Determination of serum albumin. *In* Standard Methods of Clinical Chemistry. Cooper, G. R., and King, J. S., Jr., Eds. New York, Academic Press, 1972: 175–88.

[15] Buckley, G. C., Little, J. A., Antar, M. A., and Csima, A.: A comparison of laboratory screening procedures for hyperlipemia. Clin. Chim. Acta 1969; 23:53–62.

[16] Skeggs, L. T., Jr., and Hockstrasser, H.: Multiple automatic sequential analysis. Clin. Chem. 1964; 10:918–36.

[17] deJong, E. B. M., Goldschmidt, H. M. J., van Alpen, A. C. C. M., and Loog, J. A.: An improved automated method for serum chloride. Clin. Chem. 1980; 26:1233–34.

[18] Halperin, M. L., Goldstein, M. B., Jungas, R. L., and Stinebaugh, B. J.: Biochemistry and physiology of ammonium excretion. *In* Clinical Disorders of Fluid and Electrolyte Metabolism. Seldin, D. W., and Giebisch, G., Eds. New York, Raven Press, 1984. In press.

[19] Marliss, E. B., Ohman, J. L., Aoki, T. T., et al.: Altered redox state obscuring ketoacidosis in diabetic patients with lactic acidosis. N. Engl. J. Med. 1970; 18:978–80.

[20] Murray, T., Long, W., and Narins, R. G.: Multiple myeloma and the anion gap. N. Engl. J. Med. 1975; 292:574–75.

[21] Graber, M. L., Quigg, R. J., Stempsey, W. E., and Weis, S.: Spurious hyperchloremia and decreased anion gap in hyperlipidemia. Ann. Intern. Med. 1983; 98:607–609.

[22] Halperin, M. L., Hammeke, M., Josse, R. G., and Jungas, R. L.: Metabolic acidosis in the alcoholic: a pathophysiologic approach. Metabolism 1983; 32:308–15.

[23] Goldstein, M. B., Bear, R., Richardson, R. M. A., Drucker, D., Bendz, O., and Halperin, M. L.: The urine anion gap (UAG)—a valuable diagnostic parameter in hyperchloremic metabolic acidosis (HCMA) and renal potassium (K) wasting. Clin. Invest. Med. 1984. In press.