their intake of dietary fiber is low, but their milk intake is very high. There are many other epidemiologic puzzles that need study, and it is likely that various combinations of environmental pollutants and dietary patterns will be found to explain these features of a very serious health problem — colonic cancer — and of other less serious, more slowly developing situations, like diverticulosis. Testing these hypotheses will take many years.

It is unlikely that dietary fiber will be regarded as an essential nutrient in the classical sense, but some range of intake — say, 30 to 60 g per day for an adult — may be found to be both feasible and "protective." There is now enough evidence that our present diet — high in animal protein, saturated fat, salt and sugar — is probably not salubrious and is wasteful of economic energetic factors needed to produce it. One could quite readily decrease its unhealthy features by 30 per cent, and replace the calories by increased consumption of whole-grain cereals and bread, potatoes, vegetables and fruits. Children in particular need to be taught to ingest such a diet and reduce their consumption of foods high in sugar, salt and fat, and low in demand for chewing. In the end everyone would be a bit gassier, but might have less trouble coping with crowded schedules inhibiting defecation. "Instant health" will not be the reward of such a change in diet, but if even some fraction of the current burden of chronic illness might be reduced, much will be owed to the pioneers in the field who forced man to look at this problem in a new way.

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CURRENT CONCEPTS

The Anion Gap

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THE anion gap can be readily calculated from routine laboratory data, and although it has its widest application in the diagnosis of various forms of metabolic acidosis,[1,2] it may sometimes provide an important clue to the diagnosis of disorders such as multiple myeloma[3-5] or bromide intoxication.[6] However, the concept of the anion gap is often misunderstood and misapplied. The purpose of this communication is to discuss in some detail the concept of the anion gap, the implications of abnormalities of the anion gap and, finally, its application to the differential diagnosis of metabolic acidosis.

Concept of the Anion Gap

The anion gap is estimated as $Na - (Cl + HCO_3)$ or $(Na + K) - (Cl + HCO_3)$. Since serum potassium concentration is low and fairly constant, the first of the two equations is more commonly used to estimate the anion gap; this equation puts the normal value of the anion gap at about 12 meq per liter* (8 to 16 meq per liter).[1,7] The term "anion gap" is actually a misnomer to the extent that it implies that there is a gap between cation and anion concentration. Neither is the alternative, "unmeasured anion," an accurate description, since it suggests that there is only 12 meq per liter of unmeasured anion in the serum. The fact is that the concentration of total cations in the serum must equal the concentration of total anions. Furthermore, the concentration of unmeasured anion (i.e., all anions other than chloride and bicarbonate) is about 23 rather than 12 meq per liter. The anion gap, $Na - (Cl + HCO_3)$, is only 12 meq per liter because there is about 11 meq per liter of "unmeasured cation" (i.e., all cations other than sodium). The concept of the anion gap may be defined more clearly in the following revised statements: total serum cations = total serum anions. Since total serum cations are made up of Na and unmeasured cations (UC) and total serum anions of Cl, HCO_3 and unmeasured anions (UA), $Na + UC = (Cl + HCO_3) + UA$. Therefore, $Na - (Cl + HCO_3) = UA - UC$. Since $Na - (Cl + HCO_3)$ = the anion gap, $UA - UC$ = the anion gap.

Table 1. Normal Concentrations of "Unmeasured Cations" and "Unmeasured Anions."

Unmeasured Cation	meq/liter	Unmeasured Anion	meq/liter
K	4.5	Protein	15
Ca	5	PO_4	2
Mg	1.5	SO_4	1
		Organic acids	5
Total	11	Total	23

Thus, the anion gap, although it is estimated from the concentrations of Na, Cl and HCO_3, is actually determined by the concentrations of unmeasured anions and unmeasured cations. The constituents of unmeasured anions and unmeasured cations and their normal concentrations in the serum are shown in Table 1.

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*Some authors[8] subtract the normal anion gap from the observed anion gap as we have defined it; calculated thus, the anion gap should be zero.

Abnormalities in the Anion Gap

It is apparent from the above discussion that a change in the anion gap must involve a change in unmeasured anions or unmeasured cations, unless there is a laboratory error involving the measurement of Na, Cl or HCO_3.

Increased Anion Gap

The anion gap can be increased by one of three mechanisms: decreased unmeasured cations, increased unmeasured anions or a laboratory error involving the measurement of Na, Cl or HCO_3 (Table 2).

A noteworthy increase in the anion gap due to a decrease in unmeasured cations, K, Ca, Mg, is rarely seen clinically, because their concentrations are normally low in relation to that of sodium and an extreme decrease in any of them is incompatible with life. If, however, all three unmeasured cations decreased simultaneously, as in magnesium deficiency, the anion gap might increase substantially.

Increased anion gap is most commonly due to increased concentration of unmeasured anions. The cause of increased unmeasured anions may be accumulation of organic acids, as in lactic acidosis or ketoacidosis, or accumulation of the anions of inorganic acids such as sulfate or phosphate, as in uremic acidosis. In uremic acidosis, however, the accumulation of sulfate or phosphate accounts for only a small fraction of the total increase in unmeasured anions; the remainder comprises numerous other anions, including many organic anions in low concentrations.[9] An increase in the anion gap due to increased serum albumin concentration is theoretically possible, but hyperalbuminemia does not occur clinically except for the transient elevation that follows albumin infusion or acute dehydration. In acidosis caused by ingestion of ethylene glycol, methanol, paraldehyde or salicylate, the anions responsible for increased anion gap have not been fully identified, although lactate and the anions of ketoacids may be increased. Accumulation of exogenous anions can also lead to increased anion gap. In methanol intoxication, the greatest part of unmeasured anions may be formate,[10] whereas in salicylate intoxication, accumulation of salicylate is partly responsible for increased anion gap. Other exogenous anions that may accumulate to cause increased anion gap include penicillin, carbenicillin[1] and, in the context of clinical experiment, nitrate.[11]

An increase in the anion gap due to laboratory error can be seen with falsely increased serum sodium or falsely decreased serum chloride or bicarbonate.

Table 2. Causes of Increased Anion Gap.

Decreased unmeasured cation:
Hypokalemia, hypocalcemia, hypomagnesemia.
Increased unmeasured anion:
Organic anions: lactate, ketone acids.
Inorganic anions: phosphate, sulfate.
Proteins: hyperalbuminemia (transient).
Exogenous anions: salicylate, formate, nitrate, penicillin, carbenicillin, etc.
Incompletely identified: anion accumulating in paraldehyde, ethylene glycol, methanol and salicylate poisoning, uremia, hyperosmolar hyperglycemic nonketotic coma.
Laboratory error:
Falsely increased serum sodium.
Falsely decreased serum chloride or bicarbonate.

Table 3. Causes of Decreased Anion Gap.

Increased unmeasured cation:
Increased concentration of normally present cation: hyperkalemia, hypercalcemia, hypermagnesemia.
Retention of abnormal cation: IgG globulin, tromethamine (TRIS buffer), lithium.
Decreased unmeasured anion:
Hypoalbuminemia.
Laboratory error:
Systematic error: hyponatremia due to viscous serum, hyperchloremia in bromide intoxication.
Random error: falsely decreased serum sodium, falsely increased serum chloride or bicarbonate.

Decreased Anion Gap

The anion gap can be decreased by one of three mechanisms: increased unmeasured cations; decreased unmeasured anions; or laboratory error involving the measurement of serum sodium, chloride or bicarbonate (Table 3).

Decreased anion gap attributable to increased concentration of unmeasured cations may occur when the concentration of cations normally present is increased — e.g., hyperkalemia, hypermagnesemia or hypercalcemia — or when abnormal cations accumulate, such as gamma globulin in multiple myeloma, lithium or tromethamine (TRIS buffer, THAM). A decrease in anion gap has recently been shown to occur only in patients with IgG myeloma; patients with IgA myeloma have normal anion gap.[5] The isoelectric points of the IgG paraproteins are such that at physiologic pH these proteins act as cations. Another recent study, however, failed to find a correlation between the extent of decrease in anion gap and the type of monoclonal immunoglobulin in patients with asymptomatic plasma-cell dyscrasias.[12]

Decreased anion gap resulting from decreased concentration of unmeasured anions is seen in hypoalbuminemia; this is probably the most common cause of decreased anion gap. Serum albumin provides approximately 11 meq per liter of serum anion*; a decrease in serum albumin from 4 to 2 g per 100 ml, for example, should reduce the anion gap by 5.5 meq per liter.

Decreased anion gap may be due to random or systematic error in measurement resulting in underestimation of sodium concentration or overestimation of

*This calculation is based on a normal albumin concentration of 4 g per 100 ml, a molecular weight of albumin of 69,000 and the average negative charge per millimol of albumin of 18 meq.

chloride or bicarbonate concentration. Systematic error in the measurement of serum sodium may occur if the serum is viscous and an automatic diluter is used. Increased viscosity causes delivery of a decreased volume of the sample and hence results in falsely low serum sodium concentration. A viscosity-independent diluter will prevent this problem.[13] If bromide is present in the serum, it will be measured as chloride by most chloride-measuring technics. If chloride determination is carried out with a colorimetric technic, the tendency of such technics to give erroneously high levels for bromide will result in an apparent serum chloride level that is higher than the true total halide (chloride + bromide) concentration, resulting in a decrease in anion gap. Such a spurious decrease in the anion gap can be avoided by the use of potentiometric technics for chloride determination, which measure both halides accurately.[6]

Clinical Application of the Anion Gap

Table 4 lists the causes of acidosis with increased anion gap.

Metabolic acidosis is frequently associated with an increased anion gap. The main reason is that most of the anions responsible for the increase in the anion gap in metabolic acidosis originate from acids, which titrate bicarbonate and cause acidosis. When the decrease in bicarbonate concentration is made up by the retention of the anions of acids that titrated bicarbonate, chloride concentration will remain normal while the anion gap increases (normochloremic acidosis with increased anion gap). It is important to realize that metabolic acidosis in this situation is not due to the retention of those anions but rather to decreased bicarbonate concentration. The removal of the abnormal anions by renal excretion without regeneration or administration of bicarbonate will not correct acidosis but will merely restore the anion gap to normal. Furthermore, the increase in the anion gap may be much greater than the decrease in bicarbonate concentration, if bicarbonate is regenerated or administered while abnormal anions are retained. A larger increase in anion gap than would have been anticipated from bicarbonate concentration can be found in patients with lactic acidosis who have been treated with sodium bicarbonate.

When a decrease in bicarbonate concentration is not accompanied by increased anion gap, the law of electroneutrality demands either that chloride concentration be higher or that sodium concentration be lower than normal. In either case, the acidosis is hyperchloremic, absolutely or relatively, since chloride concentration is judged in relation to sodium concentration. Table 5 lists causes of hyperchloremic acidosis. In all these conditions, hyperchloremic acidosis develops through one of four mechanisms described below.

First of all, it can occur if the extracellular volume is increased with isotonic sodium chloride solution. Bicarbonate concentration decreases by dilution, and chloride concentration increases reciprocally while sodium concentration remains unchanged. A clinical example of this situation is dilutional acidosis. Secondly, hyperchloremic acidosis can result from a gain of chloride-containing acids such as HCl, NH_4Cl, arginine chloride or lysine chloride. In this situation, as bicarbonate is titrated by acid, it is replaced by chloride. Thirdly, hyperchloremic acidosis can occur by loss of bicarbonate. When bicarbonate is lost with sodium, normal serum osmolality is maintained by concomitant loss of water. Serum sodium remains normal while chloride concentration increases by contraction of the extracellular volume. If loss of water does not accompany the loss of sodium bicarbonate, hyponatremia will result, and the normal chloride concentration will represent relative hyperchloremia. Subsequent retention of sodium chloride will restore serum sodium concentration to normal and will produce absolute hyperchloremia. Clinical examples include renal tubular acidosis and acidosis due to diarrhea. Fourthly, hyperchloremic acidosis can result from the gain of acid with anion other than chloride if the anion is rapidly cleared from the body, usually by renal excretion. When bicarbonate is first titrated by such acids, their anions will replace bicarbonate, chloride concentration will be normal, and the anion gap will increase. Subsequently, renal excretion of the sodium salts of the retained anions together with water will raise serum chloride concentration by contraction. Hypovolemia will then cause sodium chloride to be retained, resulting in a slight further increase in the

Table 4. Metabolic Acidosis with Increased Anion Gap (Normochloremic Acidosis).

Ketoacidosis
Lactic acidosis
Uremic acidosis
Hyperosmolar hyperglycemic nonketotic coma
Ingestion of toxins:
Salicylate
Methanol
Ethylene glycol
Paraldehyde

Table 5. Metabolic Acidosis with Normal Anion Gap (Hyperchloremic Acidosis).

Renal tubular acidosis, including the acidosis of aldosterone deficiency.
Uremic acidosis (early).
Acidosis after respiratory alkalosis.
Intestinal loss of bicarbonate or organic acid anions.
Carbonic anhydrase inhibitor: acetazolamide (Diamox), mafenide (Sulfamylon).
Ureterosigmoidostomy.
Dilutional acidosis.
Administration of chloride-containing acid: HCl, NH_4Cl, arginine HCl, lysine HCl.
Administration of nonchloride-containing acid with good renal clearance: sulfuric acid, phosphoric acid, sulfur-containing amino acid.
Use of anion-exchange resin: cholestyramine.
Some ketoacidosis.
Acidosis due to shift of H+ from the cell.

degree of hyperchloremia. If loss of water does not accompany the loss of the sodium salts of the anions, relative hyperchloremia will develop. Titration of sodium bicarbonate by a nonchloride-containing acid and subsequent renal excretion of its sodium salt is tantamount to a loss of sodium bicarbonate in two stages. Similarly, titration of bicarbonate by an organic acid in the gut (e.g., lactic acid from lactulose) and subsequent loss of the organic anion in the diarrheal stool can lead to hyperchloremic acidosis.

It is a common misconception that production or administration of nonchloride-containing acid always leads to normochloremic acidosis with increased anion gap. If the anion of such an acid is retained after titration of bicarbonate, the cause is either low renal clearance or inadequate time for excretion. In ketoacidosis, for example, abrupt production of large amounts of keto acids causes rapid titration of bicarbonate with a large anion gap due to the accumulation of anions of keto acids. However, when the process is protracted and smaller quantities of keto acids are produced, a substantial fraction of ketones can be excreted in the urine, and acidosis will be largely hyperchloremic. This phenomenon will be more pronounced when bicarbonate is not administered and the kidney fails to generate bicarbonate rapidly. Hyperchloremic acidosis is commonly observed in ketoacidosis probably because the renal threshold of beta-hydroxybutyrate is about 2 meq per liter, and hence its clearance is fairly high.[14] Hyperchloremic acidosis is not observed in lactic acidosis, probably because the clearance rate of lactate is much lower than that of the keto acids; the renal threshold of lactate is about 6 meq per liter.[14] The behavior of the body toward sulfuric acid and keto acid is similar. If sulfuric acid is administered acutely, bicarbonate will be titrated, and the anion gap will increase owing to retention of sulfate. However, since the renal clearance of sulfate is very high, sulfate will be excreted very rapidly, and hyperchloremic acidosis will develop. The same concept can be applied to patterns of anion retention in uremic acidosis. Uremic acidosis develops because normal bicarbonate consumption by metabolic acid exceeds the renal capacity to generate bicarbonate. Whether or not "uremic" anions are also retained at this stage is not directly related to the capacity to excrete acid (bicarbonate generation) but depends on individual clearance rates of the anions in question. The majority of patients with uremia show a diminished acid excretion capacity before they manifest a noteworthy retention of unmeasured anions. Thus, in moderate uremia when the serum creatinine is less than 6 to 8 mg per deciliter, hyperchloremic acidosis is a more common finding than acidosis with increased anion gap.

Decreased anion gap is not ordinarily associated with metabolic acidosis, and increased anion gap need not be associated with metabolic acidosis. However, in the diagnosis of metabolic acidosis it is important to be aware of the presence of conditions that independently alter the anion gap. For example, if an organic acidosis developed in a patient with hypoalbuminemia and hence abnormally high serum chloride with decreased anion gap, his serum electrolyte pattern would suggest the presence of hyperchloremic acidosis — i.e., metabolic acidosis with a normal anion gap.

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INDOMETHACIN-RESPONSIVE PANCREATIC CHOLERA

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PANCREATIC cholera, otherwise known as the Verner–Morrison[1] syndrome or the syndrome of watery diarrhea, hypokalemia and achlorhydria,[2] is a rare clinical entity caused by non-β islet-cell tumors. The clinical characteristics, recently reviewed in detail,[3-5] routinely include profuse watery diarrhea, hypokalemia, metabolic acidosis and gastric hyposecretion of acid and pepsin. Other frequent findings include hypercalcemia, glucose intolerance and flush-

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