Disorders of Acid-base Balance

Mitchell L. Halperin, Shih-Hua Lin, Manjula Gowrishankar and Kamel S. Kamel

Overview of Hydrogen Ions

Hydrogen ions (H^+) play a central role in cellular physiology [1, 2]. Their most important function is in the regeneration of adenosine triphosphate (ATP) that permits cells to perform biological work. To regenerate ATP, H^+ are first actively pumped out of mitochondria using energy derived from a redox pump; this creates an electrochemical driving force for H^+ to enter mitochondria. This proton motive force across the inner mitochondrial membrane is largely due to voltage (inside negative) and also to a pH difference (inside alkaline). When H^+ diffuse into the mitochondrial compartment, the entry system has two components, a special H^+-ATP synthetase that is linked to a system to convert ADP plus inorganic phosphate to ATP. This system of linking H^+ transport and ATP turnover is a fundamental one in acid-base homeostasis. For example, the reverse of this reaction causes H^+ to be transported out of cells of the collecting duct with the driving force being the hydrolysis of ATP – the H^+ pump is now an H^+-ATPase using energy trapped in ATP to move H^+ against its electrochemical gradient [3].

The H^+ concentration in all body compartments is maintained at a very low level because H^+ bind very avidly to histidine residues in proteins. Binding of H^+ to proteins changes their charge (more positive) – this might alter their configuration, and possibly their function [4]. Since most proteins are enzymes, transporters, contractile elements, and structural compounds, a change in their function could pose a major threat to survival. Notwithstanding, not all H^+ binding to proteins results in a diminished function; for example, H^+ binding to hemoglobin promotes the release of O_2 at the tissue level and the converse applies in the alveoli of the lung [5].

Two quantitative aspects illustrate this delicate homeostasis for H^+. First, the concentration of H^+ in plasma is exceedingly tiny as compared to the concentrations of ions like bicarbonate (HCO_3^-) (P_{HCO3}), sodium (Na^+) (P_{Na}), potassium (K^+) (P_K), or chloride (Cl^-) (P_{Cl}). Moreover, the concentration of H^+ is maintained within a very narrow range in the extracellular fluid (ECF) (40 2 nM) or in cells (close to 80 nM in many cell types) [6]. This is even more impressive because an enormous number of H^+ are produced and removed by metabolism each day [7]. In more detail, acids are obligatory intermediates of carbohydrate, fat, and protein metabolism. For example, since adults typically consume (and oxidize) 1,500 mmol of glucose per day, at least 3,000 mmol or 3,000,000,000 nmol of H^+ are produced (as pyruvic and/or L-lactic acids) and removed daily. In an adult eating a typical Western diet, 70 mmol or 70,000,000 nmol of these H^+ are added to the body. This implies that there are very effective control mechanisms that minimize fluctuations in the concentration of H^+, thereby avoiding large changes in the net valence on body proteins.

Table 1. Major concepts in acid-base balance. For details, see text. Reproduced with permission [187].

Concept	Comment
1. Net H^+ production is revealed by finding new anions.	The rate of turnover of ATP sets an upper limit on the rate of ketoacid and L-lactic acid production and removal. Diminished metabolic removal of ketoacids is critical for ketoacid accumulation.
2. Buffering of H^+ is good if H^+ are removed by HCO_3^- and not proteins.	A low tissue PCO_2 is needed for the BBS. Tissue PCO_2 depends on the arterial PCO_2, CO_2 production and blood flow rates.
3. Kidneys add new HCO_3^- to the body by excreting NH_4^+.	NH_4^+ production is stimulated by a low PCT cell pH, and is limited by PCT ATP turnover and the presence of an alternate fuel.
4. Eliminate dietary alkali with endogenous H^+ production.	Alkali is eliminated by organic acid production and the excretion of organic anions in the urine as their Na^+ and K^+ salts.
5. Excrete urine at a pH of 6.0.	Arguably, this is the most important renal function in acid-base balance because a urine pH of 6 minimizes the risk of uric acid and $CaHPO_4$ stone formation.

BBS = Bicarbonate Buffer System.

Overview of Acid-base Balance

An analysis of acid-base balance must consider not only acid balance but also the balance for bases or alkali.

Acid-balance

There are 3 major components to consider in the physiology of acid balance (Figure 1). First, during the metabolism of certain dietary constituents, H^+ are produced. This production of H^+ is recognized by finding of the appearance of new anions (Table 1) [2, 7]. Second, H^+ are ultimately removed from the body largely because they react with HCO_3^-, forming CO_2 + water; the CO_2 so-formed is eliminated via the lungs. The net result of these reactions is a deficit of HCO_3^- in the body that is equal to the net H^+ load. Third, generate new HCO_3^- (without H^+) to replace that lost in titrating these H^+ [8]. This is accomplished by excreting ammonium ions (NH_4^+) in the urine.

Base-balance

The diet also provides alkaline salts [9]; the best example is the ingestion of fruits that contain K^+ citrate salts. Metabolism of these citrate anions occurs rapidly in the liver and

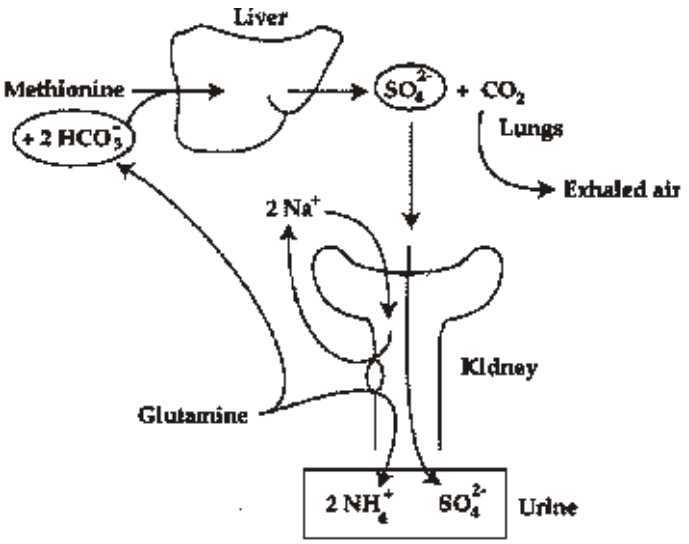

Figure 1. Acid balance. The portion of new H^+ produced in metabolism that requires renal actions for its elimination come from the oxidation of sulfur-containing amino acids depicted as methionine oxidation in the liver. This process removes HCO_3^- from the body and adds SO_4^{2-} anions. The kidney excretes these extra SO_4^{2-} anions while adding an equal quantity of HCO_3^- to the body. This is achieved as equivalent amounts of $NH_4^+ + SO_4^{2-}$ are excreted in the urine. Reproduced with permission [187].

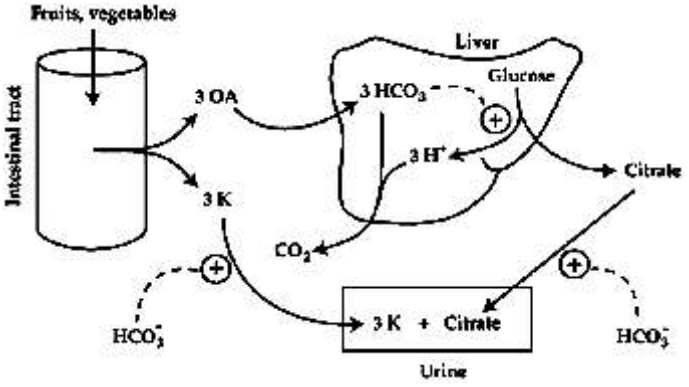

Figure 2. Disposal of an alkali load. The alkali load of the diet is derived from ingested K^+ salts of organic anions for the most part. This spectrum of organic anions is converted to HCO_3^- in the liver. Organic acids (citric acid in this example) are then produced by hepatocytes and its conjugate base (citrate anion) will be excreted in the urine as a K^+ salt. Reproduced with permission [187].

the net result in acid-base terms is the production of HCO_3^- [7]. Removal of this HCO_3^- load is achieved via production of new endogenous organic acids including citric acid [9]. The H^+ of these acids titrate HCO_3^- and base balance is maintained by excreting the conjugate base of these acids (e.g., $citrate^{3-}$) in the urine as their Na^+, K^+, and/or calcium (Ca^{2+}) salts [2, 9 – 12] (Figure 2). This disposal of alkali with the excretion of organic anions minimizes the risk for kidney stone formation. It avoids the excretion of HCO_3^- which, by alkalinizing the urine, could lead to calcium phosphate precipitation [13]. Further, in response to a load of alkali, renal reabsorption of citrate declines [14], citrate chelates Ca^{2+} in the urine and therapy reduces the risk of stone formation.

H^+ Production

CONCEPT 1: H^+ production is revealed by finding of new anions.

Metabolic analysis of net production of acids: A metabolic process can span more than one organ (Figure 3). In general, the starting

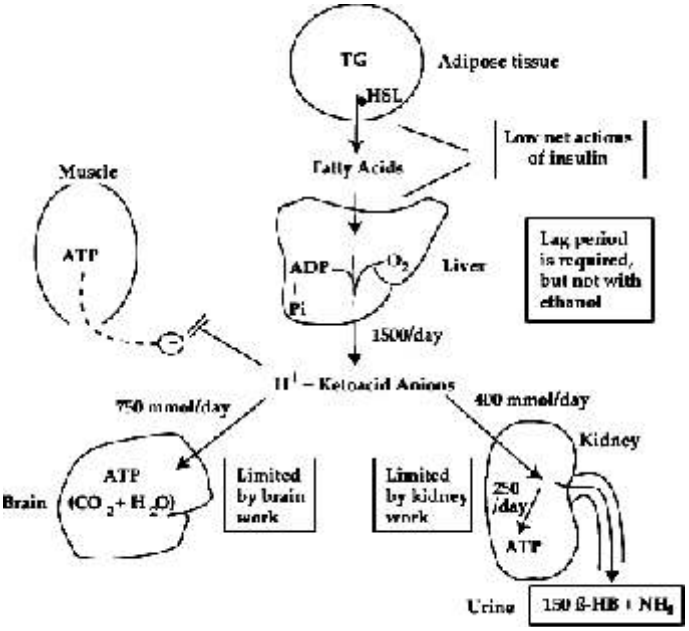

Figure 3. The metabolic process involved in ketoacid metabolism. The metabolic process of ketoacid metabolism begins with activation of hormone sensitive lipase (HSL) in adipose tissue. After a lack of insulin for several days, the production of ketoacids in the liver rises to about 1500 mmol/day. The main sites of removal of ketoacids are the brain (750 mmol/day) and the kidneys (400 mmol/day). Reproduced with permission [187].

points are dietary or stored fuels (glycogen or triglycerides) and the final products are ATP or storage forms of fuels [2]. From an acid-base perspective, one can determine if H^+ are produced or consumed in a metabolic process by a quantitative examination of the net charge or valence of its substrates and end products [7]. H^+ are formed if the net charge of the compounds produced is more anionic than that of substrates; the converse is also true. In this analysis, the net charge on adenine nucleotides (ADP, AMP, ATP) or NAD(P) does not need to be considered as the conversion of ATP to ADP to do biological work initiates the regeneration of ATP and NAD(P).

Acid balance is maintained if the new anions are metabolized to neutral end products, or if they are excreted in the urine along with H^+ or NH_4^+. On the other hand, there is a net gain of H^+ in the body if these anions are retained in the body or are excreted as their Na^+ or K^+ salts. Therefore every new anionic valence retained in the body or excreted with Na^+ or K^+, one new H^+ was added (Figure 4). Using the above analysis, the net addition of H^+ to the body can be classified into 2 categories:

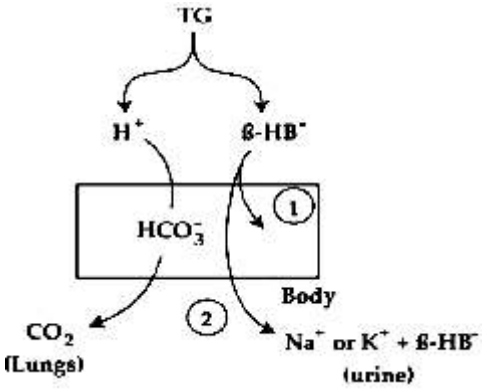

Figure 4. Metabolic analysis of net production of acids. The partial oxidation of storage triglyceride (TG) yields H^+ plus -hydroxybutyrate anions (--HB^-). The H^+ are titrated in the body by HCO_3^-, generating water and CO_2 – the latter is exhaled and the body has a deficit of HCO_3^- and a gain of -HB^-. If the -HB^- are retained in the body (point 1) or are excreted as Na^+ (or K^+) salts (point 2), there is a deficit of HCO_3^- that is equivalent to a net gain of H^+. Reproduced with permission [187].

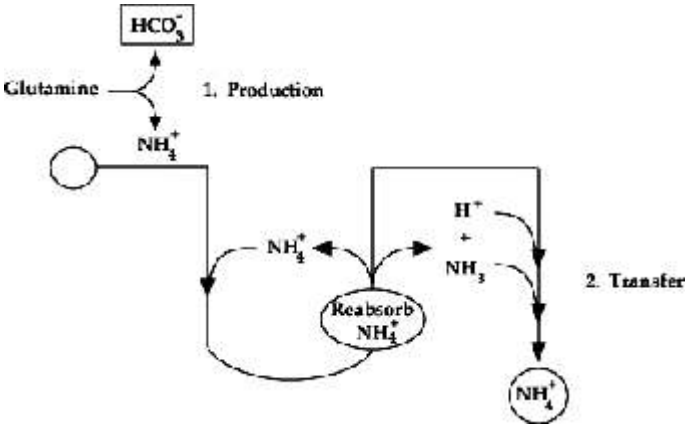

Figure 5. Physiology of NH_4^+ excretion. There are 2 major steps. First, NH_4^+ and HCO_3^- are produced when glutamine is metabolized in cells of the PCT. Second, NH_4^+ is transferred via the medullary interstitial compartment to the lumen of the MCD because of a high medullary interstitial concentration of NH_3 and NH_4^+.

– *H^+ production during normal metabolism:* In effect, this means the production of sulfuric acid (SO_4^{2-} anion + 2 H^+) from the oxidation of sulfur-containing amino acids and the production of phosphoric acid from the oxidation of monovalent phosphate diesters. These latter H^+ are removed when they are excreted bound to phosphate in the urine as $H_2PO_4^-$ (titratable acid excretion). On the other hand, H^+ that are produced with sulfate (SO_4^{2-}) anions during metabolism of sulfur-containing amino acids cannot be removed via metabolism or by excreting SO_4^{2-} in the urine because the affinity of SO_4^{2-} for H^+ is too low at typical urine pH values. In this case, maintenance of acid balance requires a mechanism for the generation of new HCO_3^- *without* adding H^+ to the body. This is accomplished by metabolizing a neutral amino acid, glutamine, to a cation (NH_4^+) and an organic anion (-ketoglutarate). This anion is metabolized in the kidney to a neutral end product (CO_2 and/or glucose), yielding new HCO_3^- that are added to the body. For a net gain of HCO_3^-, NH_4^+ must be made into an end product of metabolism by being excreted in the urine (Figure 5) [15].

– *H^+ production during incomplete or abnormal metabolism:* We cite 3 major examples here. First, the fastest rate of production of H^+ is from carbohydrate metabolism when the supply of oxygen is inadequate to meet demands. Now L-lactic acid is generated by anaerobic glycolysis (Table 2). Although metabolism of the L-lactate$^-$ anion to a neutral end product (e.g., glucose, glycogen or CO_2) removes H^+, this occurs at a much slower rate. Second, H^+ production occurs during fat metabolism if there is a relative lack of insulin. In this case, ketoacids (-hydroxybutyric acid and acetoacetic acid) are formed [16]. The degree of ketoacidosis depends on how quickly the brain and the kidneys remove these acids. Third, at times, compounds are ingested (usually alcohols or precursors of alcohols) that can be metabolized to anions at a much faster rate than these anions can be converted to neutral end products to remove these H^+.

Endogenous net production of acids, a physiological analysis: We can identify 2 major categories of endogenous acid production. One type of H^+ production requires renal net acid excretion to eliminate these H^+ (e.g.,

Table 2. Rates of production of H^+ and its removal. The rate of L-lactic acid production listed in this table is that occur during anaerobic metabolism, assuming an O_2 consumption rate of 12 mmol/min and that the rate of turnover of ATP is unchanged. This rate is much greater than in all other causes of net H^+ addition. H^+ removal by metabolism of L-lactate anions is depicted for gluconeogenesis and oxidation in the liver and kidneys.

	Rate (mmol/min)
Production of H^+	
– L-lactic acid during anoxia	72
– ketoacids during a lack of insulin	(up to) 1.5
– methanol/ethylene glycol	(up to) 1.0
Removal of H^+	
– *renal generation of new HCO_3^-*	
– normal	0.03
– chronic acidosis	0.15
– *metabolism (maximum in vivo rates in mmol/min)*	
– L-lactic acid	4 – 8
– ketoacids in brain and kidneys	1.0

monovalent diester phosphates and sulfur-containing amino acids described above). H^+ produced in metabolism of sulfur-containing amino acids are eliminated by the excretion of an equivalent amount of NH_4^+ in the urine. The second type of dietary-driven H^+ production is part of the physiological response to eliminate the dietary alkali (part of base balance, Figure 2, [9, 11]). This process yields H^+ plus organic anions – H^+ titrate HCO_3^-, while the organic anions are made into end products of metabolism by being excreted in the urine as their Na^+ and/or K^+ salts. Hence although both types represent endogenous H^+ production, they have very different functions.

Basis for metabolic acidosis: There are 3 ways to raise the concentration of H^+ in the body – the addition of acids that yield H^+ (one form of metabolic acidosis), failure to eliminate CO_2 normally (called respiratory acidosis), and failure to add new HCO_3^- to the body by excreting enough NH_4^+ (another form of metabolic acidosis). In yet another condition, H^+ may redistribute from the ECF to the intracellular fluid (ICF) compartments without requiring an overall change in the total number of H^+ in the body. An example of such a shift of H^+ into cells occurs in patients with a large deficit of K^+. In this case one develops an intracellular gain of H^+ together with a gain of HCO_3^- in the ECF compartment [17, 18]; from the perspective of the ECF, this is called metabolic alkalosis, but from the perspective of the ICF compartment, it would be called metabolic acidosis and a deficit of K^+ (see Chapter on K^+ where metabolic alkalosis is considered in more detail).

Tools to HelpIdentify Net Production of Acids

Metabolic acidosis that is due to an overproduction of acids can be recognized by finding the "footprints" of the added acids,

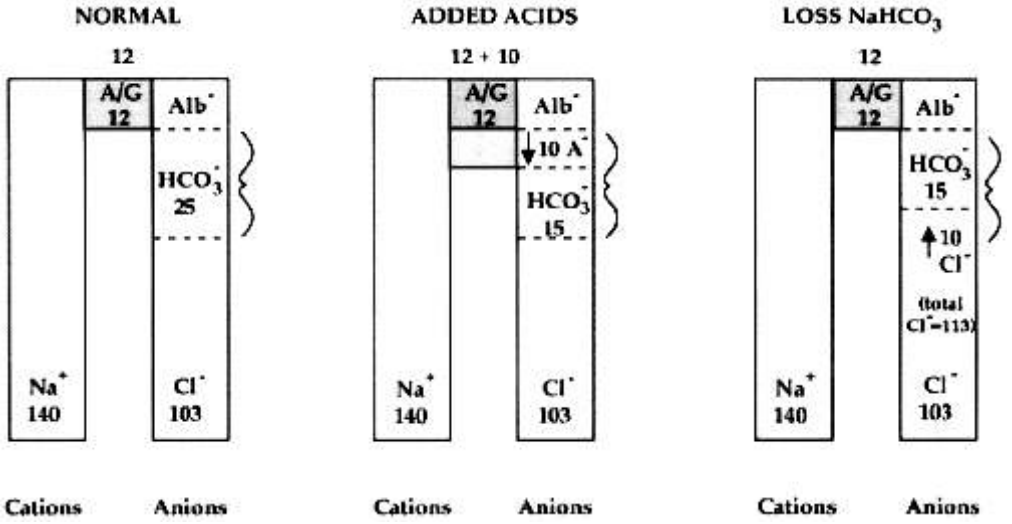

Figure 6. Plasma anion gap. The anion gap is a calculation for "diagnostic convenience"; it reveals the "footprints" of added acids. One measures only the major cation Na^+ and subtracts the major anions Cl^- and HCO_3^-. The usual value is 12 mEq/l (140 – 103 – 25); the anion that is not measured as such is primarily albumin. When acids are added and their anions are retained in the ECF compartment, the P_{HCO3} falls and the extra anions are revealed by the larger value for the plasma anion gap. When $NaHCO_3$ is lost, the P_{HCO3} falls and there are no extra anions; rather, the P_{Cl} rises.

their conjugate bases (or new anions) in the body (Figure 6) or in excreted fluids (usually the urine). At times one can gain a helpful hint about the nature of the added acids from examining the renal handling of their anions.

New anions in the body: New anions in the body are detected by calculating the anion gap in plasma (Figure 6). The concentration of unmeasured anions in plasma (the plasma anion gap) is the difference between the concentrations of the measured cation (Na^+) and the measured anions (Cl^- and HCO_3^-) in plasma (Equation 1). K^+ is not commonly included in this anion gap calculation because its concentration is low relative to that of Na^+. The usual normal range for the plasma anion gap is 12 2 mEq/l and this reflects for the most part, the net anionic valence of albumin in plasma. In some laboratories, this value may be closer to 6 or 8 mEq/l due to higher reported values for Cl^- because of different analytical techniques for measurement of Cl^-.

$$\text{Plasma anion gap} = P_{Na} - (P_{Cl} + P_{HCO3}) = 12 \quad 2\,\text{mEq/l} \qquad (1)$$

If the value for the plasma anion gap is higher than expected for the anionic valence on albumin, this suggests that acids have accumulated (Figure 6, middle panel). There are, however, some potential pitfalls to consider when evaluating the plasma anion gap. The net anionic charge on albumin accounts for most of this "gap". At a plasma pH of 7.4 and a concentration of albumin is 40 g/l or 4 g/dl, its valence is close to 12 mEq/l (when the valence on K^+ is ignored) [19]. Therefore a low concentration of albumin in plasma will cause the "baseline" value for the anion gap in plasma to be lower; as a clinical short cut, for

every 10 g/l decline in albumin concentration, one should anticipate a 3 – 4 mEq/l fall in the "baseline" value for the plasma anion gap.

Another cause for a low anion gap in plasma is the presence of unusual cations in plasma such as myeloma proteins. Although hypercalcemia or hypermagnesemia will in theory lower the value for the plasma anion gap, the change in their concentrations is rarely high enough to make a significant change in the plasma anion gap; the same is true for other cations such as lithium. A low plasma anion gap can be due to overestimation of Cl^- (e.g., bromism).

Renal handling of new anions: The renal handling of anions produced in association with H^+ has an important effect on the magnitude of the rise in the plasma anion gap as compared to the decrease in the P_{HCO3} [20]. One can utilize the renal handling of these anions to help recognize which acid was produced. For example, if the new anions are retained in plasma, this implies that there was little excretion of these anions in the urine. For the most part, this means either a low rate of filtration (low GFR), protein binding, and/or avid reabsorption of these new anions by the kidney (L-lactate anions, ketoacid anions, and to a lesser extent, D-lactate anions). On the other hand, metabolic acidosis due to a high rate of production of acids can be associated with a near-normal anion gap in plasma if the accompanying anion is largely excreted in the urine; an example is the production of hippuric acid and excretion of the anion, hippurate as its Na^+ or K^+ salt (e.g., in glue sniffers [21]).

Plasma osmolal gap: This tool is used primarily to detect uncharged, low molecular weight precursors of acids. In practice, the calculation of the plasma osmolal gap is used to detect toxic alcohols (methanol and ethylene glycol). The plasma osmolal gap is defined as the difference between the measured and the calculated plasma osmolality (P_{Osm}). The calculated P_{Osm} is the sum of twice the plasma P_{Na} plus the concentration of glucose (P_{Glu}) and of urea (P_{Urea}) in plasma, all in mM terms (Equation 2). To convert to mM terms, divide the BUN in mg/dl by 2.8 and the P_{Glu} in mg/dl by 18.

$$\text{Plasma osmolal gap} = \text{Measured } P_{Osm} - ((2 \times P_{Na}) + P_{Urea} + P_{Glu}) \quad (2)$$

To use this calculation, one must presume that there is no error in measurement of P_{Na} (e.g., due to hyperlipidemia). Ethanol will also be detected by the calculation of the plasma osmolal gap. Therefore one should not think that methanol or ethylene glycol is absent simply because there is a history of consumption of ethanol. At times, compounds such as mannitol, or very high concentrations of ions such as Mg^{2+} may cause a high value for the plasma osmolal gap. When there is methanol or ethylene glycol toxicity, the value for the plasma osmolal gap is usually considerably greater than 25 mOsm/kg H_2O.

Buffering of H^+

CONCEPT 2: In physiological buffering, H^+ are to be removed by the bicarbonate buffer system and not by proteins.

In the traditional view, the role of buffering is to minimize the change in the concentration of H^+ when an acid or alkali is added to a solution. From a physiological perspective, however, the main role of buffering is to force H^+ to bind to HCO_3^- rather than to proteins [4]. Binding of H^+ to intracellular proteins could be detrimental to cellular function because this changes the charge on these proteins which could alter their tertiary structure and may thereby affect their function. Therefore, while it is customary to rely on measurements

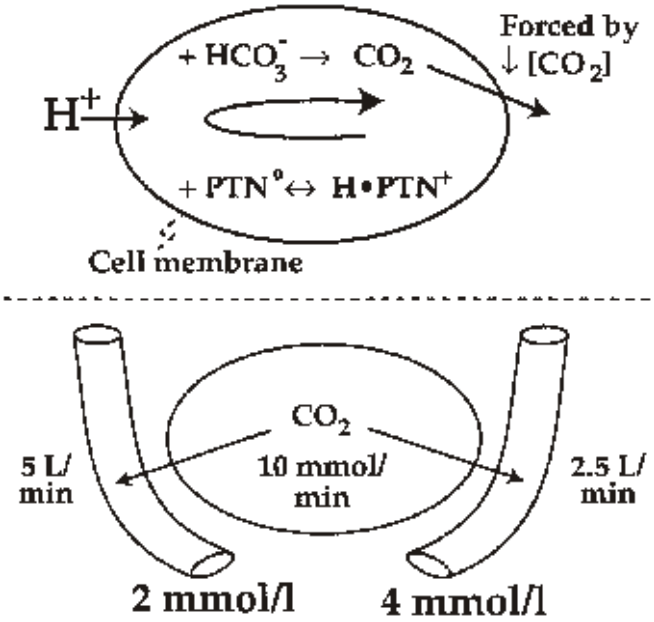

Figure 7. Role of the tissue PCO_2 in the selection of ICF buffers. As shown in the top portion of the figure, when the tissue PCO_2 falls, the H^+ concentration in cells will decrease and these H^+ will be removed by HCO_3^-. This will reduce the quantity of H^+ bound to intracellular proteins ($H\bullet PTN^+$). As shown in the bottom portion of the figure, there will be a rise in the cell and venous PCO_2 when the blood flow rate is slower (2.5 vs 5 l/min), as may be the case in a patient with a contracted ECF volume. This higher cell PCO_2 forces H^+ to bind to proteins. The converse occurs when the ECF volume is re-expanded.

in plasma (pH, PCO_2, P_{HCO3}^-) to assess the acid-base disturbance, it is also important to recognize that events in the ECF, and especially in arterial blood, may not reflect the acid-base status in the ICF compartment.

Several factors determine the degree of binding of H^+ to intracellular proteins (Figure 7). The first step for buffering of H^+ in cells is that they must cross cell membranes. Buffering by intracellular HCO_3^- can only occur if the tissue PCO_2 falls (Equation 3).

$$H^+ + HCO_3^- \quad H_2CO_3 \quad H_2O + CO_2 \qquad (3)$$

Distribution of H^+ Between the ECF and ICF

This issue will be considered in some detail because it also provides the basis to understand why hyperkalemia develops in patients with certain types of metabolic acidosis [22]. To shift K^+ out of cells, the mechanism of entry of H^+ into cells should cause a less negative voltage in cells. H^+ move across cell membranes by passive entry of electroneutral free acids or by carrier-mediated transporters for monocarboxylate acids. With regard to the former, diffusion must be very slow because the concentration of free acids with pK values in the 2 – 4 range are very low at the pH of body fluids. Hence specific transport systems that permit H^+ to cross cell membranes are the most important pathways to understand (Figure 8).

H^+ do not appear to enter cells by ion channels because if H^+ or HCO_3^- ion channels were present and open in cell membranes, the ratio of the concentration of H^+ in the ICF and ECF compartments would be similar to that of K^+. Therefore the concentration of H^+ in the ICF compartment would be 30 – 40 times higher than that in the ECF compartment – i.e., the pH of the ICF compartment would be close to 1.5 pH units lower than the ECF while measured values are close to 0.3 pH unit [6]. Three pathways are available for electroneutral H^+ movement.

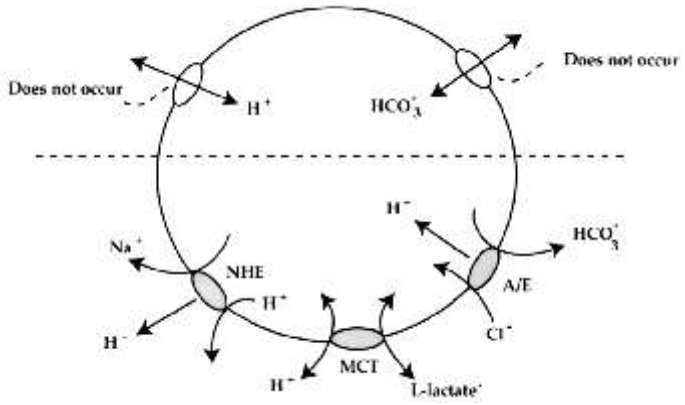

Figure 8. Pathways for net H^+ transport across cell membranes. The circle represents a cell. Given the large net ICF negative voltage across cell membranes and the 2-fold H^+ concentration difference, H^+ or HCO_3^- ion channels could not be in an open configuration (open ovals above the dashed line). Rather, there are 3 possible transport systems, as shown by the shaded ovals, which could lead to the net transport of H^+. Abbreviations: NHE = Na^+/H^+ exchanger; MCT = monocarboxylic acid transporter; AE = Cl^-/HCO_3^- anion exchanger.

(i) The monocarboxylic acid transporter (MCT): The MCT catalyzes, for example, the cotransport of L-lactate$^-$ or -HB$^-$ anions plus H^+ across cell membranes [23]. Because flux through this cotransporter is electroneutral, it does not cause a change in the resting membrane potential. Therefore this form of transport of H^+ does not lead directly to a shift of K^+ across cell membranes.

(ii) The Na^+/H^+ exchanger (NHE): A simple examination of existing concentrations of Na^+ and H^+ in the ECF and ICF compartments indicates that the NHE must be largely inactive in vivo because it is appreciably displaced from its electrochemical equilibrium (Na^+ concentration in the ECF compartment is higher (140 vs ~ 14 mM) and lower H^+ concentration is lower (40 vs 80 nM) in the ECF compartment). When NHE does become active, the only direction for net movement of H^+ is from the ICF to the ECF compartment [24]. Hence NHE is *not* directly involved in buffering of an ECF H^+ load.

(iii) The chloride (Cl^-)/HCO_3^- anion exchanger (AE): This AE catalyzes an electroneutral exchange of anions [25]. Exit of HCO_3^- leads to the accumulation of Cl^- in the ICF compartment. Since all cells have Cl^- channels in their membrane [26], the rise in the ICF Cl^- concentration in conjunction with the usual negative voltage forces Cl^- to exit from cells (Figure 9). This export of negative voltage when Cl^- ions exit causes a less negative voltage in cells. As a result, K^+ will exit from cells if K^+ channels are open. The net effect of this flux through the AE is the export of K^+ and HCO_3^- from cells. Thus a shift of K^+ out of cells would occur in response to an inorganic acid load or a non-monocarboxylic organic acid load such as citric acid [27].

Buffering of H^+ by Intracellular Proteins

P_{HCO3}: When the P_{HCO3} is very low, there is little HCO_3^- in the ECF compartment to buffer newly added H^+ so most of these H^+ will now be bound to intracellular proteins. Hence when the P_{HCO3} is *very* low and if there is a possibility that it may decline even further, this may be an indication to administer $NaHCO_3$. In this regard, it is also important to note the impact of very small absolute changes in the P_{HCO3} when this concentration is very low to begin with. For instance, if the fall in the P_{HCO3} is only 2 mM, but it fell from 4 mM to 2 mM, there is a doubling (100% rise) of the plasma H^+ concentration and a fall

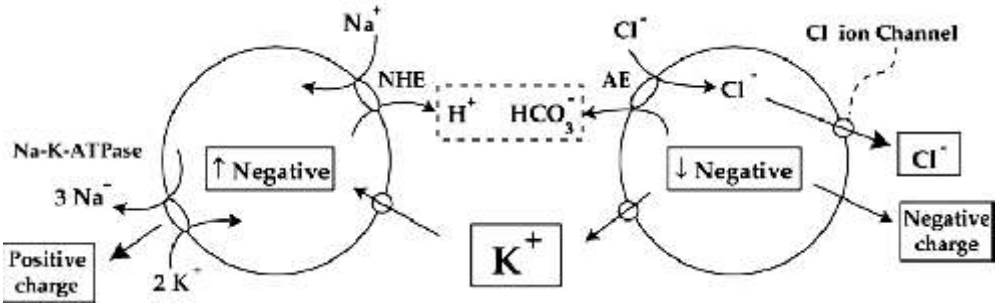

Figure 9. NHE and NE adjust the cell voltage and the P_K. The circles represent cells with their usual net negative ICF voltage. Because of the higher Na^+ concentration outside cells and the higher H^+ concentration in cells, the NHE catalyzes H^+ exit and Na^+ ion entry into cells in an electroneutral fashion (left portion). This transport requires activation by insulin or intracellular acidosis. When Na^+ ions are exported by the Na-K-ATPase, the voltage in cells becomes more negative. The net effect is to shift K^+ ions into cells. As shown on the right, because of the much higher Cl^- ion concentration outside cells, the AE catalyzes HCO_3^- exit and Cl^- ion entry into cells in an electroneutral fashion. The combination of flux through the AE and the Cl^- ion channel tends to decrease the negative ICF voltage and cause intracellular acidification and ECF alkalinization. This transporter required activation but the mechanism is not clear. The net effect is to shift K^+ ions into cells.

in plasma pH of 0.3 units if the arterial PCO_2 remains unchanged (which is likely to be the case as hyperventilation is probably already maximal). In contrast, a fall in the P_{HCO3} of 2 mM from 25 mM to 23 mM will cause only a 10% rise in the plasma H^+ concentration.

Arterial PCO_2: A high value for the arterial PCO_2 can have profound effects on the ICF pH in a patient with metabolic acidosis. For CO_2 to diffuse out of cells, intracellular PCO_2 will have to be somewhat higher than in the capillaries. The arterial PCO_2 depends on the balance between CO_2 production and its removal from the body by ventilation (Figure 7). Thus the arterial PCO_2 will be higher in a patient who cannot increase ventilation appropriately. In this case, mechanical ventilation is the most effective means to lower the intracellular pH and thereby minimize the binding of H^+ to intracellular proteins. There are several ways to assess this ventilatory response to the presence of metabolic acidosis (Table 4). Use the approximately 1 : 1 ratio between the fall in P_{HCO3} from the normal value of 25 mM and the fall in arterial PCO_2 from 40 mmHg [28]. We emphasize that these are not meant to be exact values.

CO_2 production: As an isolated event, a rise in CO_2 production rate will increase the capillary PCO_2. Similarly, a low arterial PCO_2 may also reflect a lower rate of production of CO_2 in patients who have a fixed degree of ventilation [29].

Venous PCO_2: The impact of a higher venous PCO_2 on the degree of buffering of H^+ by intracellular proteins is illustrated in Figure 7. If the venous PCO_2 is high, the intracellular PCO_2 will be even higher, which shifts the equilibrium of Equation 3 to the left, raising the H^+ concentration in the ICF so that more H^+ will bind to proteins. Three factors could lead to an elevated venous PCO_2; first, a high PCO_2 of arterial blood; second, a higher rate of metabolic production of CO_2; third, the quantity and the concentration of CO_2 that each liter of blood must carry will rise if there is a reduced rate of blood flow to an organ. It follows that in the setting of metabolic acidosis associated with reduction in ECF volume (Table 3), a very important mea-

Table 3. Metabolic acidosis classified according to extracellular fluid volume status.

Metabolic acidosis with a reduced "effective" circulating volume
– type A L-lactic acidosis (*venous* volume may not be reduced)
– diabetic or alcoholic ketoacidosis
– gastrointestinal loss of $NaHCO_3$
– metabolic acidosis and excessive loss of Na^+ in the urine
  – e.g. overproduction of hippuric acid in glue-sniffers

Metabolic acidosis with a near-normal or expanded ECF volume
Increased anion gap
– ketoacidosis of fasting or due to hypoglycemia
– toxic alcohol ingestions (methanol, ethylene glycol)
– overproduction of D-lactic acid
– renal failure

Normal anion gap
– low NH_4^+ excretion (e.g. distal RTA)
– proximal RTA

Table 4. Expected responses to primary acid-base disorders.

Disorder	Response
Metabolic acidosis	For every mM fall in P_{HCO3} from 25 mM, the arterial PCO_2 should fall by 1 mmHg from 40 mmHg.
Metabolic alkalosis	For every mM rise in P_{HCO3} from 25 mM, the arterial PCO_2 should rise by 0.7 mmHg from 40 mmHg.
Respiratory acidosis	
Acute	For every mmHg rise in arterial PCO_2 from 40 mmHg, the plasma H^+ concentration should rise by 0.77 nM from 40 nM. Alternatively, for every 2-fold increase in arterial PCO_2, the P_{HCO3} should increase by 2.5 mM.
Chronic	For every mmHg rise in arterial PCO_2 from 40 mmHg, the plasma H^+ concentration should rise by 0.32 nM, or the P_{HCO3} should rise by 0.3 mM from 25 mM.
Respiratory alkalosis	
Acute	For every mmHg fall in the arterial PCO_2 from 40 mmHg, the plasma H^+ concentration should fall by 0.74 nM from 40 nM.
Chronic	For every mmHg fall in arterial PCO_2 from 40 mmHg, the plasma H^+ concentration should fall by 0.17 mM, or the P_{HCO3} should fall by 0.4 mM from 25 mM.

sure to correct the intracellular acidosis may in fact be the aggressive restoration of the effective circulating volume.

Hypokalemia: Hypokalemia may be present in some patients with metabolic acidosis (e.g., patients with distal renal tubular acidosis (RTA) or those with diarrhea or glue sniffing). As K^+ shift from the ICF into the ECF compartment, electroneutrality must be maintained. This could be achieved if the K^+ are lost from the ICF along with intracellular anions (phosphate), or if K^+ enter and extracellular cations (Na^+ and/or H^+) exit. To the extent that there is a net exit of K^+ and entry of H^+, the degree of intracellular acidosis will become more severe and now more H^+ should be titrated by intracellular proteins. Hypokalemia may also affect the intracellular H^+ concentration by causing respiratory muscle weakness; the hypoventilation could cause a rise in arterial and thereby the tissue PCO_2.

Excretion of NH_4^+

CONCEPT 3: Generation of new HCO_3^- without H^+ occurs when NH_4^+ is excreted.

To generate new HCO_3^-, glutamine, must be metabolized in the cells of the proximal convoluted tubule (PCT) to yield NH_4^+ and the -ketoglutarate (-KG) anion [15]. Metabolism of -KG to neutral end products (CO_2 or glucose) yields HCO_3^- that are added to the body. Nevertheless, for a net gain of HCO_3^-, NH_4^+ must be made into an end product of metabolism by being excreted in the urine (Figure 5). The rate of excretion of NH_4^+ can be influenced by 2 major factors, its rate of production in the PCT and its rate of transfer to the final urine.

Production of NH_4^+: Several factors influence the rate of production of NH_4^+. It is important to recognize that there is a 1- to 2-day lag period before acidosis augments renal ammoniagenesis. In response to chronic metabolic acidosis, the rate of excretion of NH_4^+ can increase to more than 200 mmol/day [30, 31]. Hypokalemia also stimulates ammoniagenesis as it causes intracellular acidosis [32]. The converse is true for hyperkalemia. There is an upper limit on the rate of NH_4^+ production in cells of the PCT set by the rate of regeneration of ATP in these cells [33]. ATP is utilized in PCT cells primarily to provide the energy for the reabsorption of filtered Na^+ [34]. Hence patients with a low GFR filter less Na^+ and they have a lower rate of reabsorption of Na^+ in the PCT. This lessens the need to regenerate as much ATP so the rate of production of NH_4^+ is lower in these patients. Rarer causes of a low rate of production of NH_4^+ are low levels of glutamine in plasma (malnutrition) [35] or if another fuel is oxidized by the cells of the PCT for regeneration of ATP (e.g., an excessive supply of ketoacids or fatty acids as in patients receiving total parenteral nutrition) [36]. Patients with isolated proximal RTA may have a lower rate of NH_4^+ production due to an alkalinized PCT cell pH, the underlying pathophysiology in this condition [37].

Transfer of NH_3 into the urine: NH_4^+ produced in cells of the PCT is secreted into its lumen, at least in part, by replacing H^+ on the Na^+/H^+ exchanger (NHE-3), making it a Na^+/NH_4^+ exchanger [38]. Reabsorption of NH_4^+ in the medullary thick ascending limb (mTAL) of the loop of Henle (LOH) occurs when NH_4^+ replaces K^+ on the Na^+, K^+, 2 Cl^-cotransporter [39]. This provides the "single effect" for the medullary recycling of NH_4^+ required for the establishment of a high concentration of NH_4^+ and NH_3 in the medullary interstitium (Figure 5). The function of this medullary interstitial NH_4^+/NH_3 system in our opinion is to prevent the excretion of urine with too low a pH [40]. An important factor that influences the transfer of

NH_4 from the medullary interstitial compartment to the urine is the secretion of H^+ in the distal nephron. This H^+ secretion provides the luminal substrate for an NH_4^+/H^+ ion exchanger [41]. This NH_4^+/H^+ exchanger results in the net addition of NH_3 into the lumen.

H^+ secretion in the distal nephron is mediated primarily by an H^+-ATPase, but it may also occur by an H^+/K^+-ATPase. Distal H^+ secretion by the H^+-ATPase is an electrogenic process that tends to create a lumen positive voltage [42]. Because the lumen of the MCD can only maintain a small positive voltage [43], for H^+ secretion to continue, either an anion (like Cl^-) must be secreted along with H^+ or a cation like Na^+ or K^+ must be reabsorbed.

H^+ secretion also occurs by an H^+/K^+-ATPase, but only if H^+ acceptors are available in the lumen of the distal nephron. These luminal H^+ acceptors are HCO_3^- and NH_3. Luminal HCO_3^- can be high if its reabsorption by upstream nephron segments was diminished or if HCO_3^- was secreted into the lumen of the MCD by a Cl^-/HCO_3^- anion exchanger [25]. In this latter circumstance, there is a net reabsorption of K^+ and Cl^-; hence this combination of ion exchangers may be important for K^+ homeostasis under conditions of K^+ depletion [44]. If both the H^+/K^+-ATPase and the Cl^-/HCO_3^- anion exchanger were active simultaneously, the urine PCO_2 should be very high. When NH_3 is available to accept H^+ secreted by the H^+/K^+-ATPase, its overall function could be to reabsorb K^+ and/or excrete NH_4^+.

Importance of the Urine pH to Avoid Kidney Stone Formation

All the water-soluble waste products and all the ions and water ingested in excess of needs must be excreted in the urine without forming precipitates. One of the most important renal physiological functions is to excrete urine with a composition that makes ions and organic materials sufficiently soluble to avoid kidney stone formation. Key to this aim is to have independent regulation of the urine pH – select a value that is close to 6.0 to achieve this aim [45] (Figure 10). Excreting urine at

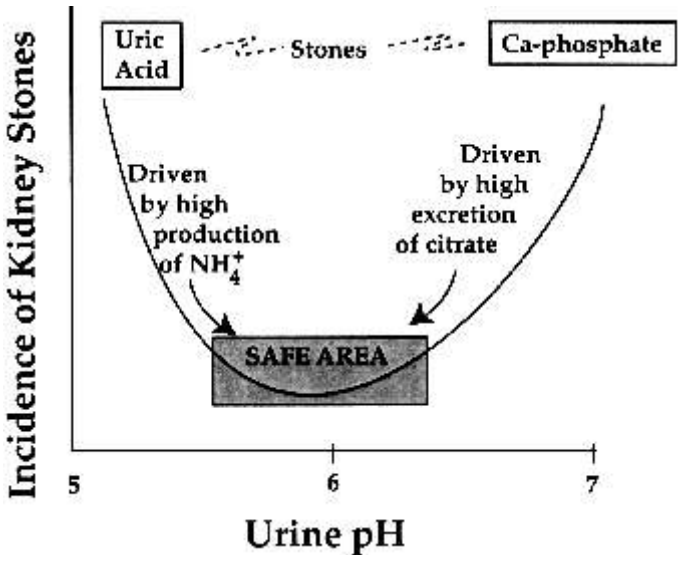

Figure 10. Urine pH and kidney stones. The safest urine pH to avoid kidney stones is close to 6. Below this value, uric acid stones are most likely to form. Ca-phosphate stones precipitate in alkaline urine. By driving NH_4^+ excretion with a high distal H^+ secretion, a considerable quantity of H^+ can be eliminated at a urine pH close to 6.0. By excreting organic anions rather than HCO_3^-, a considerable quantity of HCO_3^- can also be eliminated at a urine pH close to 6.0 (see Figure 2).

this pH must not sacrifice acid-base balance. This in turn means that with a large, chronic acid load, the excretion of NH_4^+ should be maximally high at a urine pH of close to 6 (see reference Kamel et al. 1998 [46] for more discussion). Similarly, when an alkali load is ingested, it must be excreted without obligating a large excretion of HCO_3^- and thereby a high urine pH [9, 11] – this latter topic will be discussed in more detail when $CaHPO_4$ stones are considered below.

Avoiding uric acid kidney stones: Uric acid is the waste product of purine metabolism [47]. The free acid form, uric acid, rather than total urates is the critical component for kidney stone formation because uric acid is sparingly soluble in water (Equation 4). Because the pK of uric acid in the urine at 37ºC is close to 5.3 [47], precipitation of uric acid can be avoided without increasing the urine volume by raising the urine pH to 6 at the same total urate excretion rate [48].

$$Urate^- + H^+ \quad \text{Uric acid (pK 5.3)} \qquad (4)$$

Avoiding $CaHPO_4$ kidney stones: All the ionized Ca^{2+} absorbed from the GI tract of an adult is excreted in the urine in steady state [49]. The chemistry of Ca^{2+} and HPO_4^{2-} in the urine is the same as in the body [50], but with one exception. A metabolic equivalent of HCO_3^- in acid-base terms, citrate [14], can chelate ionized Ca^{2+} in the urine, forming a soluble ion complex and thereby minimize the risk of $CaHPO_4$ kidney stone formation. This excretion of citrate rises with an alkali load [14], a time when urine $H_2PO_4^-$ is converted to HPO_4^{2-} – i.e., when the urine pH rises towards the pK of the phosphate buffer system (pH 6.8). In this context, the body disposes of the usual alkali load of the diet by forming an organic acid such as citric acid [9, 11]. The H^+ of citric acid titrate HCO_3^-. The citrate anions rather than an appreciable amount of HCO_3^- are excreted in the urine so that the urine pH remains close to 6.0 without sacrificing acid-base balance [48] (Figure 10). Excreting citrate rather than HCO_3^- when there is a dietary alkali load chelates Ca^{2+} in the urine, lessening the risk of Ca-containing kidney stones in alkaline urine [51].

Tests Used at the Bedside to Estimate NH_4^+ in the Urine

The first step to evaluate the renal response to chronic metabolic acidosis in a patient is to examine the rate of excretion of NH_4^+. Since most routine biochemical laboratories do not provide a direct assay for the concentration of NH_4^+ in the urine (U_{NH4}), clinicians usually employ the following indirect tests to *estimate* U_{NH4}. To convert the U_{NH4} to an excretion rate, one needs to know the urine flow rate or divide the U_{NH4} by the urine creatinine concentration. Normal adults excrete close to 20 mg of 200 mol of creatinine per kg body weight [52].

The urine net charge: The sum of the concentrations of urinary cations and anions must be equal. The major urine cations are Na^+, K^+, and NH_4^+, and the major urine anion is Cl^- (although there are also modest concentrations of SO_4^{2-}, phosphate, HCO_3^- and organic anions). The urine net charge provides a qualitative *estimate* of the U_{NH4} providing that the major anion excreted with NH_4^+ is Cl^- (Equation 5, Figure 11). Hence if the U_{NH4} is appropriately high, the U_{Cl} should be appreciably greater than the sum of the $U_{Na} + U_K$, and the urine net charge is said to be *negative*. On the other hand, with a low U_{NH4}, the U_{Cl} is less than the sum of the $U_{Na} + U_K$. In this case, the urine net charge is said to be *positive*, suggesting that a defect in NH_4^+ excretion is at least contributing to the pathogenesis of metabolic acidosis. Be careful. This will not be true if an

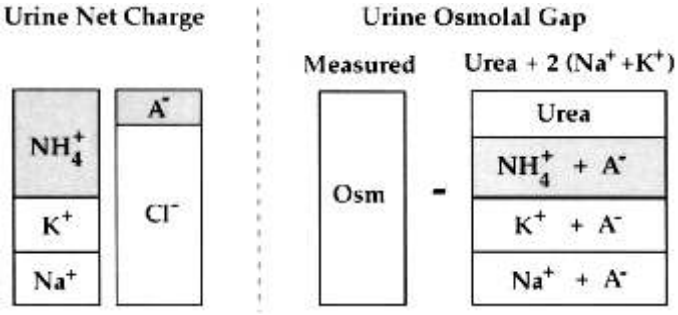

Figure 11. Use of the urine net charge and urine osmolal gap to reflect the concentration of NH_4^+ in the urine. The urine net charge is shown in the left portion of the figure and the urine osmolal gap is shown in the right portion of the figure. The components needed to calculate the U_{NH4} are depicted by the clear areas. Reproduced with permission [187].

anion other than Cl^- accompanied U_{NH4}. Some examples of these non-Cl^- urine anions are hippurate, -HB, salicylate, organic anions, and anions of drugs such as penicillin-type antibiotics given in high dosage. In such cases, one must use the urine osmolal gap to estimate U_{NH4}.

$$\text{Urine net charge} = U_{Na} + U_K - U_{Cl} \quad (5)$$

The urine osmolal gap: The urine osmolal gap is the best indirect test to estimate the U_{NH4}. The rationale for the urine osmolal gap is also depicted in Figure 11. The major osmoles in the urine are urea and electrolytes; occasionally, glucose may be present in the urine in high concentrations. The contribution of electrolytes is approximately equal to twice the sum of the concentrations of the major cations, Na^+, K^+ (since each cation is accompanied by an anion). Therefore, the total urine osmolality (U_{osm}) can be approximated as shown in Equation 6 in which the concentration of all the substances in the urine is given in mM terms as described earlier. A significant difference between the measured and calculated U_{osm} indicates the presence of an NH_4^+ salt in the urine. The U_{NH4} is half the urine osmolal gap. The rate of excretion of NH_4^+ is then obtained by multiplying this approximate concentration by the urine flow rate or estimated from the urine creatinine concentration and its excretion rate [52]. If this is substantially less than 3 mmol NH_4^+/kg/day, then the kidneys are at least a contributing factor to the degree of metabolic acidosis because there is a lower than expected rate of excretion of NH_4^+.

$$\text{Calculated } U_{osm} = U_{Urea} + U_{Glu} + 2\,U_{Na} + 2\,U_K$$
$$U_{NH4} = 0.5 \times$$
$$(\text{measured } U_{osm} - \text{calculated } U_{osm}) \quad (6)$$

Tests to Detect the Basis for the Low Rate of Excretion of NH_4^+

Use of the urine pH: In patients with chronic metabolic acidosis, a low rate of excretion of NH_4^+ could be due to decreased availability of NH_3 in the medullary interstitium or decreased H^+ secretion in the distal nephron (Figure 12). The basis for low NH_4^+ excretion can be deduced from the urine pH (Figure 13). A low value for the urine pH (< 5.3) suggests a defect in NH_4^+/NH_3 availability in the renal medullary interstitium whereas a high urine pH (> 7) suggests that the limiting step is H^+ secretion in the distal nephron (Equation 7) [53 – 57].

$$H^+ + NH_3 \quad NH_4^+ \quad (7)$$

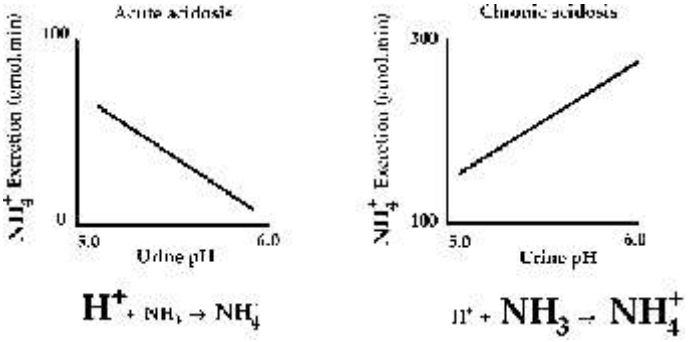

Figure 12. Use of the urine pH to detect U_{NH4}. As shown on the left, during acute metabolic acidosis, the rate of excretion of NH_4^+ is only modestly higher while the urine pH is low. This is because there is enhanced distal H^+ secretion, but a time lag before the rate of renal production of NH_4^+ is augmented. In contrast, during chronic metabolic acidosis shown on the right, the rate of renal production of NH_4^+ is so high that the availability of NH_3 in the medullary interstitial compartment provides more NH_3 in the lumen of the MCD than H^+ secretion in this nephron segment. Therefore note the much higher NH_4^+ excretion rate at a urine pH of 6. Reproduced with permission [187].

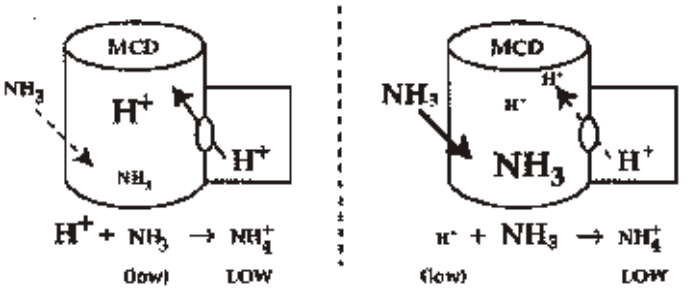

Figure 13. The urine pH reveals the basis for the low U_{NH4}. A decreased availability of NH_4^+/NH_3 in the medullary interstitial compartment is the defect shown on the left side of the figure by the dashed arrow. Its main features are a low excretion of NH_4^+ and a high urine H^+ concentration (low urine pH). A defect in distal H^+ secretion is shown by the dashed arrow in the right side of the figure. Its main features are a low excretion of NH_4^+ and a low urine H^+ concentration (high urine pH). Reproduced with permission [187].

Test for the Capacity to Synthesize NH_4^+ in the PCT

Once one knows that the rate of excretion of NH_4^+ is low in a patient who has a low urine pH, one can assess the rate of production of NH_4^+ in vivo by measuring the rate of excretion of NH_4^+ following the administration of a loop diuretic [58]. At peak diuresis, the rate of NH_4^+ excretion in a normal adult is close to 60 mol/min and this reflects the capacity for renal ammoniagenesis. A lower peak rate of NH_4^+ excretion would imply a low rate of production of NH_4^+ in PCT cells [37, 59].

Tests to Evaluate H^+ Secretion

A low rate of excretion of NH_4^+ in a patient with metabolic acidosis could be due to a defect in H^+ secretion in the PCT and/or the distal nephron.

Tests to Evaluate the Secretion of H^+ in the PCT

Some patients have metabolic acidosis associated with a lower than normal capacity to reabsorb filtered HCO_3^- [60]. Usually the site of the defect in renal H^+ secretion is in the PCT, but at times, it may also involve the distal nephron. Notwithstanding, these patients also have a reduced rate of excretion of NH_4^+ and this is a very important cause of their metabolic acidosis. To detect a defect in H^+ secretion in the PCT, one generally measures the rate of excretion of HCO_3^- and/or its reabsorption after an infusion of $NaHCO_3$. Another test that helps in this assessment is the rate of excretion of citrate at a given pH of plasma.

Fractional excretion of HCO_3^- (FE_{HCO3}): The bulk of filtered HCO_3^- is reclaimed (reabsorbed indirectly) in the PCT [61], but an appreciable portion (close to 15%) is normally reclaimed by H^+ secretion downstream in the nephron. To perform this test, enough $NaHCO_3$ is infused to raise the P_{HCO3} to 25 mM. At this point, if the FE_{HCO3} exceeds 15%, there is a defect in H^+ secretion [61, 62]. A high FE_{HCO3} could be expected if there is a very large defect in H^+ secretion in the PCT or a smaller defect in PCT H^+ secretion plus a reduced distal capacity for H^+ secretion.

Citrate excretion: The rate of excretion of citrate seems to reflect the pH in PCT cells with a higher rate of citrate excretion if these cells have a more alkaline pH in PCT cells. The rate of excretion of citrate is very low during all forms of metabolic acidosis except in patients with the isolated form of proximal RTA where there is an appreciable degree of citraturia despite metabolic acidosis [63]. This led to the speculation that an alkaline PCT cell is the underlying lesion causing low HCO_3^- reabsorption, low NH_4^+ production, and citraturia in these patients [37]. The rate of excretion of citrate in children and adults consuming their usual diet is close to 400 mg/g creatinine [14, 64]. To ensure that citraturia reflects an alkaline PCT cell rather than a component of a more generalized PCT dysfunction (Fanconi syndrome), citraturia should disappear following a small additional acid load [65].

Tests to Evaluate the Secretion of H^+ in the Distal Tubule

If the PCO_2 in alkaline urine is 70 mmHg or higher, a major defect in distal H^+ secretion is unlikely [66] (Figure 14). Nevertheless, there

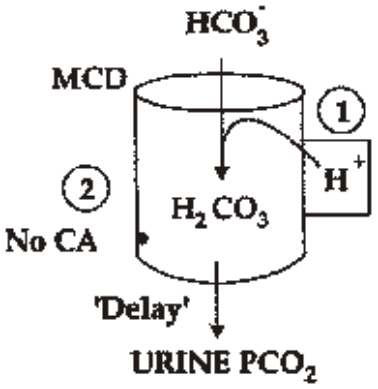

Figure 14. The urine PCO_2. When $NaHCO_3$ is given, there is a large delivery of HCO_3^- to the distal nephron so this HCO_3^- is virtually the only H^+ acceptor in its lumen. Because there is no luminal carbonic anhydrase (CA), the H_2CO_3 formed will be delivered downstream and form CO_2 plus water. Thus if the U_{PCO2} is appreciably higher than the plasma PCO_2, this provides evidence for distal H^+ secretion. Reproduced with permission [187].

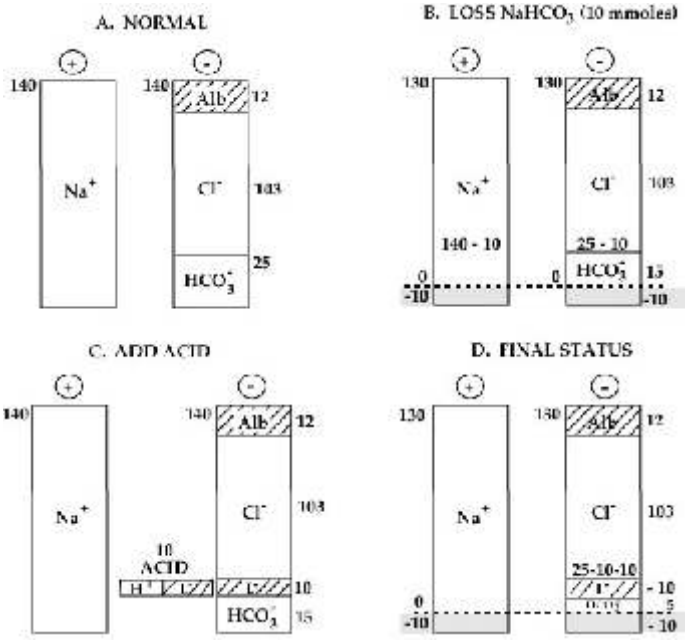

Figure 15. Mixed acid-base disturbance: Recognizing 2 types of metabolic acidosis. The sum of the valences on cations and anions in plasma are always equal. In this example, the missing anions (due largely to the anionic charge on albumin shown by the hatched symbol) are constant at 12 mEq/l; this value is 16 mEq/l if K^+ is included in the sum of cations in plasma. When Na^+ and HCO_3^- are lost (shaded area in panels B and D), there is no change in the plasma anion gap. When L-lactic acid is added, there is a fall in the concentration of HCO_3^- together with an equal rise in the plasma anion gap (panel C). The combination of both types of metabolic acidosis is shown in panel D.

are other factors such as a poor renal concentrating ability (low medullary interstitial PCO_2) that may cause the urine PCO_2 to be lower despite an intact distal H^+ secretion [67].

Detecting Mixed Acid-base Disorders

More than one acid-base disturbance can be present at one time. We shall illustrate how to identify the simultaneous presence of several acid-base disturbances from the history, physical examination, and laboratory results (Figure 15).

Clinical example: A 24-year-old person had severe diarrhea that resulted in a deficit of $NaHCO_3$ (Figure 15B). Because of the continuing loss of Na^+, his ECF volume became markedly contracted. As a result of the very low circulating volume, there was not enough oxygen delivery to tissues to meet their demand so anaerobic production of ATP was stimulated. This results in a net production of L-lactic acid. This accumulation of 10 mmol of L-lactate anion per liter of plasma should raise the plasma anion gap by 10 mEq/l (Table 4, Figure 15C). Simultaneously, the 10 mmol of H^+ added per liter will lower the P_{HCO3} by 10 mmol/l (Equation 8).

$$10\,\text{L-lactate}^- + 10\,H^+ + 15\,HCO_3^- \quad 10\,CO_2 + 10\,H_2O + 10\,\text{L-lactate}^- + 5\,HCO_3^- \qquad (8)$$

Continuing with this scenario, the release of aldosterone (due to a contracted ECF volume) stimulates the excretion of K^+ [68]. As a result, a deficit of K^+ occurs and this could lead to muscular weakness. If the respiratory muscles are involved, there may be an inability to lower the arterial PCO_2 to the expected degree. In summary, by working backwards beginning at the far right of Table 5, each of the 3 acid-base disorders can be identified.

– Respiratory acidosis: The PCO_2 in blood should be as low as possible (less than 20

Table 5. Identification of a mixed acid-base disorder. For details, see text. The value for albumin in plasma is 4 g/dl (40 g/l), a normal level which does not change throughout the course of illness in this patient. Hypoventilation in this case is due to a deficit of K^+. H●L = L-lactic acid.

Plasma		Normal	Loss $NaHCO_3$ (10 mM)	Gain H●L (10 mM)	Effect of hypoventilation
pH		7.40	7.30	7.13	6.83
HCO_3^-	mM	25	15	5	5
Anion gap	mEq/l	12	12	22	22
PCO_2	mmHg	40	30	15	30

mmHg) with such a low value for the P_{HCO3} (5 mM). Hence the arterial PCO_2 is too high for this clinical setting.

– Metabolic acidosis due to a gain of acid: The elevated value for the anion gap of 10 mEq/l with a normal concentration of albumin in plasma suggests that 10 of the 20 mM fall in P_{HCO3} was due to the added L-lactic acid.

– Metabolic acidosis due to loss of $NaHCO_3$: The fact that the fall in the P_{HCO3} is much greater than the rise in the plasma anion gap suggests a deficit of $NaHCO_3$. This deficit of $NaHCO_3$ is even larger than what is apparent from this calculation because of the significant ECF volume contraction (HCO_3^- concentration vs HCO_3^- content, Table 10).

Clinical Disorders

Metabolic Acidosis

Definition: In metabolic acidosis, there is a fall in the plasma pH and P_{HCO3}. Because other primary acid-base abnormalities may coexist, the plasma pH and/or P_{HCO3} may not be low. For example, if respiratory alkalosis is also present, the pH will be higher; if metabolic alkalosis is also present, the P_{HCO3} and plasma pH may not be low. Therefore clues from the history and physical examination together with additional laboratory data (plasma anion gap) must be integrated to know whether metabolic acidosis is present.

Clinical Classification

We divide the causes of metabolic acidosis into two subgroups, those with overproduction of acids and/or those in which there is a loss of $NaHCO_3$ (Table 6).

Overproduction of acids: When an acid (HA) is added to the body, the vast majority of H^+ are buffered by the bicarbonate buffer system (BBS) [4] and this leads to the loss of HCO_3^- together with a gain of new anions (A^-) (Figure 4). Quantitatively, for every mEq of HCO_3^- lost, there will be an equivalent net gain of A^-. Factors such as the volume of distribution of anions versus H^+, a change in the ECF volume, and the renal handling of these anions will affect the 1 : 1 ratio between the fall in the P_{HCO3} and the rise in plasma anion gap (Table 7). With a decrease in the ECF volume, the concentration of both new anions

Table 6. Mechanisms responsible for the development of metabolic acidosis.

A) Acid gain
- **(i) With retention of anions in plasma:**
  - L-lactic acidosis (hypoxia, problems with pyruvate metabolism)
  - Ketoacidosis (relative insulin lack and low GFR or CNS function)
  - Toxic alcohol ingestion (e.g., methanol, ethylene glycol)
  - D-lactic acidosis (and other organic acids produced by gastrointestinal bacteria)
  - Ingested acids
  - Pyroglutamic acidosis
- **(ii) With a high rate of excretion of anions in urine:**
  - Glue-sniffing (hippuric acid overproduction)
  - Diabetic ketoacidosis with excessive ketonuria

B) $NaHCO_3$ loss
- **(i) Direct**
  - Loss via the GI tract (e.g., diarrhea, ileus, fistula)
  - Loss in the urine (proximal RTA or low carbonic anhydrase II or IV activity)*
- **(ii) Low urinary excretion of NH_4^+ (look at urine pH to categorize further)**
  - **(a) Low urine NH_3 (urine pH ~ 5) = Problem with PCT ammoniagenesis:**
    Decreased GFR, hyperkalemia, alkaline pH in PCT cells, decreased glutamine availability, fuel competition (e.g., TPN)
  - **(b) Defect in net distal H^+ secretion (urine pH often ~ 7):**
    H^+ ATPase defect or alkaline -intercalated cells (e.g., carbonic anhydrase II deficiency)
    H^+ back-leak (e.g., amphotericin B)
    HCO_3^- secretion in the collecting ducts (anion exchanger trafficking disorder)
  - **(c) Problem with both distal H^+ secretion and NH_3 availability (urine pH ~ 6):**
    Diseases involving the renal interstitial compartment

*These patients also have a low rate of excretion of NH_4^+.

Table 7. Content vs concentration of $HC0_3^-$ in the ECF compartment. An 8-year-old 20 kg female presented with an extremely high P_{Glu} (2,000 mg/dl, 110 mM), a venous plasma pH of 7.19, a P_{HCO3} of 25 mM, and a severely contracted ECF volume (2 vs her normal 4 l) [69]. Metabolic acidosis is present because of the reduced content of HCO_3^- in her ECF compartment (H^+ + -HB^- + HCO_3^- anion gap + CO_2 + H_2O). Reproduced with permission [187].

	ECF (l)	P_{HCO3} (mM)	ECF HCO_3^- content (mmol)	Plasma anion gap (mEq/l)
Normal state	4	25	100	12
Hyperglycemia	2	25	50	24

and HCO_3^- will rise. Thus there will be a larger increase in the unmeasured anion gap and a smaller fall in the P_{HCO3} [69], disturbing the expected 1 : 1 ratio in these parameters.

In most cases where metabolic acidosis is associated with an increased value for the anion gap in plasma, there is an overproduction of acids where many of the anions produced

along with H^+ are retained in the ECF. The major exception to this rule is renal failure because in this setting, metabolic acidosis is present with an increase in the plasma anion gap, but there is no excess production of acids. On the other hand, metabolic acidosis caused by an excessive production of acids need not be accompanied by a significant rise in the anion gap in plasma if the accompanying anion is rapidly excreted in the urine (e.g., hippurate anion in glue sniffing [21]).

There are many different causes for the development of metabolic acidosis, each having a specific implication for therapy. In most cases, the rise in the concentration of H^+ per se is not the major threat to survival; those causes associated with acute potentially life-threatening consequences are listed in Table 8. Many of the causes of metabolic acidosis and an increased plasma anion gap are associated with a reduced "effective" ECF volume (diabetic ketoacidosis (DKA), alcoholic ketoacidosis, and most cases of type A L-lactic acidosis, Table 3). Should one find a relatively normal ECF volume, the basis for the metabolic acidosis is usually renal failure, toxic alcohol ingestion (methanol or ethylene glycol), or possibly excessive production of acids such as D-lactic acid by bacteria in the gastrointestinal (GI) tract.

Loss of $NaHCO_3$

In this type of metabolic acidosis, almost no new anions are present in plasma. There are 2 major groups for this type of metabolic acidosis, one is the direct loss of $NaHCO_3$ and the other is an indirect loss of $NaHCO_3$ due to a low rate of excretion of NH_4^+ (Figure 4).

Loss of $NaHCO_3$ via the GI tract: The most common site for the loss of $NaHCO_3$ is via the GI tract. While $NaHCO_3$ may be lost in diarrhea fluid, for an appreciable degree of chronic metabolic acidosis to be sustained, there is usually a simultaneous defect in NH_4^+ excretion by the kidney. In more detail, in a 70 kg adult with chronic metabolic acidosis and normal kidneys, the rate of excretion of NH_4^+ would be close to 200 mmol per day. If 1 liter of diarrhea solution contains 50 mmol of HCO_3^-, this GI loss would have to be about 4 liters per day to cause a continuing fall in the P_{HCO3}. The deficit of Na^+ would be enormous and life-threatening without a large input of NaCl. Hence it follows that chronic acidosis in this setting implies either a very large or an acute GI losses, a renal problem with NH_4^+ excretion (e.g., due to low GFR), and/or overproduction of organic acids via the GI tract (Equation 9) [70, 71].

$$Na^+ + HCO_3^- + H^+ + \text{D-lactate}^- \quad Na^+ + \text{D-lactate}^- + CO_2 + H_2O \qquad (9)$$

Indirect loss of $NaHCO_3$: A low rate of excretion of NH_4^+ is the key finding in patients with distal RTA [56]; it is also a prominent feature in certain patients with proximal RTA [37]. In a patient with metabolic acidosis, with no increase in the plasma anion gap, and a low rate of excretion of NH_4^+ (Figure 15, left-hand side), the basis for low NH_4^+ excretion can be deduced from the urine pH. If the urine pH is greater than 7, one should suspect a defect in H^+ secretion. The PCO_2 in alkaline urine can be used to assess distal H^+ secretion (Figure 14) [66] and the FE_{HCO3} can be used to assess proximal H^+ secretion. A high rate of excretion of citrate in a patient with metabolic acidosis suggests that an alkaline PCT cell could be the cause of diminished PCT H^+ secretion [37]. In contrast, if a patient had similar findings to the above, but had a low value for the urine pH (e.g., < 5.3), this would suggest that there is a defect in NH_3 availability in the renal medullary interstitial compartment

Table 8. Threats to life in association with metabolic acidosis.

Setting of acidosis	Threat to life	Clinical clues
L-lactic acidosis due to low cardiac output (shock)	"Energy crisis", H^+ load	Low plasma pH, high plasma anion gap, high $P_{Lactate}$
Renal failure	Hyperkalemia	Low GFR, high plasma anion gap
Distal RTA, diarrhea, treatment of DKA	Hypokalemia	Normal plasma anion gap, arrhythmias, muscle weakness
Methanol or ethylene glycol intake	Toxic products	History, high plasma anion gap, high plasma osmolal gap
DKA or, alcoholic ketoacidosis	Low ECF volume, rarely acidosis per se	Type 1 diabetes mellitus, ethanol, P_{Glu}, ketoacid screen

(Figure 13). The usual causes for the low NH_4^+/NH_3 are a low GFR and/or hyperkalemia. In their absence, we would look for low levels of glutamine in blood and/or a high level of fat-derived fuels (e.g., patients on total parental nutrition) because these fuels compete with glutamine as the source for regeneration of ATP in the cells of the PCT. If none of these is present, we would suspect an alkaline proximal cell pH. This entity of an alkaline proximal ICF pH remains speculative because there are no hard data in humans and suitable experimental models in animals are lacking.

Loss of "Potential" HCO_3^-

In some patients, there is excessive loss of the conjugate base of the acid in the urine (or in stool). While overproduction of acids is the major basis for the acidosis in these patients, yet the loss of these anions in the urine represents the loss of potential HCO_3^- as their metabolism could have resulted in the removal of H^+ (Figure 4, [72]).

Likelihood of a Major Threat to Life

Disorders that cause metabolic acidosis can harm patients through a variety of mechanisms (Table 8). We shall consider 4 major categories:

Very Fast Rate of Production of H^+

In essence, the only condition associated with extremely rapid net production of acid is L-lactic acidosis due to hypoxia (Table 2). The threat here is that ATP may not be regenerated quickly enough. Quantitatively, the rate of acid addition can be approximated by

Table 9. Causes of metabolic acidosis associated with hyperkalemia. Specific disorders causing hyperkalemia in patients with metabolic acidosis are described. In addition, if tissue necrosis has occurred in a patient with metabolic acidosis, hyperkalemia may also be present.

Cause	Pathophysiology	Total K^+ content
Renal failure	Low renal excretion of K^+ (and NH_4^+)	High
Low aldosterone bioactivity	Low renal excretion of K^+ (and NH_4^+)	High
DKA	Insulin deficiency leads to shift of K^+ out of the ICF	Low

noting the rate of increase in the plasma anion gap and the rate of excretion of anions in the urine.

H^+ Binding to Intracellular Proteins

The important factors here are not only the magnitude of H^+ load, but also the tissue PCO_2 as this determines the distribution of buffering of H^+ load between the BBS and intracellular proteins. A high venous PCO_2 implies that the tissue PCO_2 is also high and that more H^+ are buffered by intracellular proteins. Hence it follows that in the setting of metabolic acidosis associated with a low cardiac output, a very important measure to correct the intracellular acidosis is aggressive restoration of the cardiac output (Figure 7). In addition, if the arterial PCO_2 is not low enough, mechanical ventilation is essential.

Coexisting Problems of K^+ Balance

Many of the risks associated with metabolic acidosis may come about through associated disturbances of K^+ balance. Both hyperkalemia and hypokalemia may occur (Table 9). We shall be succinct here because issues concerning K^+ are discussed in the accompanying Chapter on K^+.

Hyperkalemia may be involved in the etiology of metabolic acidosis, because hyperkalemia impairs NH_4^+ excretion [32]. In contrast, if metabolic acidosis is seen in the setting of renal failure, a low excretion of K^+ and hyperkalemia may be present. Hyperkalemia is commonly seen in the setting of DKA despite the total body K^+ deficit, because K^+ tend to shift out of cells during insulin deficiency [73]. Finally, tissue necrosis or ischemia can lead to both L-lactic acidosis and release of K^+ from cells. Regardless of the pathophysiology, hyperkalemia can be life-threatening due to cardiac arrhythmias, and must be aggressively treated. Fortunately, one of the measures employed in the therapy of DKA, insulin, enhances K^+ entry into cells, and therefore reduces the degree of hyperkalemia.

Hypokalemia may occur either in association with the chronic metabolic acidosis of distal RTA, diarrhea, or metabolic acidosis caused by toluene (e.g., glue sniffing). Hypokalemia may also occur as a complication of insulin therapy in patients with DKA. Because insulin causes K^+ to enter cells (Figure 9), it may unmask the total body K^+ deficit and lead to the life-threatening complications

Table 10. Factors to consider in the use of $NaHCO_3$.

A. Factors favoring the use of $NaHCO_3$
- Hyperkalemia.
- P_{HCO3} less than 5 mM.
- Absence of an anion that can be metabolized into HCO_3^- (longer term consideration).
- Low likelihood that kidneys will be able to excrete NH_4^+ at a high rate (longer term issue).
- Independent benefit likely to arise (e.g., in salicylate overdose to limit entry of salicylate into brain cells and to favor its urinary excretion).
- High net rate of H^+ production (e.g., inability to rapidly reverse hypoxic L-lactic acidosis).

B. Factors that suggest a danger for the use of $NaHCO_3$
- Hypokalemia.
- Coincident use of insulin in a patient with a large K^+ deficit.
- Elevated ECF volume.
- Hypernatremia (minor).

of acute hypokalemia, particularly cardiac arrhythmias.

Specific problems related to the cause of the acidosis: In fact, in some of the causes of metabolic acidosis, the acidosis serves as a marker or a "symptom" of a serious underlying disease (e.g., methanol or ethylene glycol toxicity, Table 8). Clearly, these underlying processes must be addressed with specific therapy to avoid the adverse consequences that are independent of the acidosis.

Management

The management of a patient with metabolic acidosis requires a consideration of both general measures that are applicable to most patients as well as attention to specific issues relative to the cause of the disorder. We shall focus initially on the use of alkali because the use of mechanical ventilation was considered earlier, and treatments to deal with hyperkalemia or hypokalemia will be considered in the Chapter on K^+.

One cannot draw a definitive conclusion as to whether $NaHCO_3$ should or should not be used to treat a patient with metabolic acidosis because there are no firm data upon which to base this conclusion. Suggestions for and against the use of $NaHCO_3$ are summarized in Table 10.

Arguments Favoring the Use of $NaHCO_3$

It seems intuitively obvious that at some point, too many H^+ may become bound to proteins and compromise cellular functions. For example, myocardial contractility in vitro [74] and binding of adrenaline to its receptors are decreased when the fall in pH is large [75]; these effects may be reversed by lowering the concentration of H^+. Notwithstanding, the administration of $NaHCO_3$ does not seem to enhance the contractility of the ischemic myocardium in vivo [76].

There are data in experimental animals that might help. The administration of a large dose of $NaHCO_3$ appeared to be beneficial in the setting of hypoxic L-lactic acidosis in rats induced by ventilation with a hypoxic gas mixture. The survival period in these rats was extended even though $NaHCO_3$ led to an enhanced rate of production of L-lactic acid [77]. If these data apply to humans with hypoxia-induced L-lactic acidosis, the admin-

istration of $NaHCO_3$ might be viewed as a temporary measure that "buys time" to allow for more direct interventions to deal with the underlying cause(s) for the metabolic acidosis to be employed. Nevertheless, one must not administer too much $NaHCO_3$ because it may lead to the development of pulmonary edema unless very high rates of Na^+ removal could be achieved.

In a patient who has metabolic acidosis due to a low rate of excretion of NH_4^+, metabolic acidosis will persist unless $NaHCO_3$ is given. In this case, one must give enough $NaHCO_3$ to titrate H^+ that have accumulated, then maintain that person on enough alkali to match the net positive H^+ balance (usually 20 – 40 mmol/day in an adult).

Arguments Against the Use of $NaHCO_3$

Increased production of CO_2

When $NaHCO_3$ is administered, HCO_3^- reacts with H^+ and CO_2 is produced. Some have argued that this represents an important deleterious effect of HCO_3^- therapy because this CO_2 can enter cells and cause a paradoxical acidification of the ICF. This is a circular argument because if the source of the H^+ that titrate the administered HCO_3^- is H^+ bound to intracellular proteins (Figure 7), the ICF should have been alkalinized and not acidified. In contrast, if the source of these H^+ was due to the production of ATP in the process of anaerobic glycolysis, stimulation of L-lactic acid production by alkali could also be beneficial because it was accompanied by the conversion of ADP to ATP [77]. A possible acute danger in this latter case could occur if some of the CO_2 produced was retained because pulmonary function was not adequate or mechanical ventilation was not appropriately adjusted.

Concern about the possible adverse effects of enhanced production of CO_2 following therapy with $NaHCO_3$ in the acidotic patient prompted the development of carb-bicarb ($Na_2CO_3 \bullet 2(NaHCO_3)$). The titration of 4 mmol of H^+ by $NaHCO_3$ leads to the production of 4 mmol of CO_2, whereas similar buffering with carb-bicarb leads to the production of 3 mmol of CO_2. Since metabolic production of CO_2 is normally close to 10 mmol/min, and the rate of alkali administration might be close to 4 mmol/min during very aggressive alkali therapy, the difference in CO_2 production rate in fact will only be from 14 to 13 mmol/min with $NaHCO_2$ versus carb-bicarb, a trivial difference. There has been only limited clinical experience with this agent in patients with a severe degree of metabolic acidosis, the only setting in which it is rational to test it.

Failure to Detect Back-titration of Non-bicarbonate Buffers

Another argument against the use of $NaHCO_3$ or carb-bicarb to treat patients with a severe degree of metabolic acidosis comes from experiments in rats. The administered alkali to rats pretreated with HCl failed to yield an acute and significant back-titration of non-bicarbonate buffers [78]. This, however, could have been because of a rise in tissue PCO_2.

Fall in Concentration of Ionized Ca^{2+}

This occurs because addition of HCO_3^- leads to very rapid production of carbonate and precipitation of $CaCO_3$. It has been suggested that a fall in concentration of ionized Ca^{2+} in the interstitial fluid compartment might depress myocardial contractility [79]. Never-

theless, this might be more apparent than real if the HCO_3^- administered does not raise the P_{HCO3} markedly. If this were to be a problem, it should have been very obvious in situations where carb-bicarb was used because with carb-bicarb, carbonate is added directly.

Hypokalemia

Hypokalemia could be a problem when $NaHCO_3$ is given, especially if there is total body K^+ depletion as seen in patients with DKA [80 – 82], glue sniffers [21], or certain patients with distal RTA. The presence of a low P_K should prompt one to avoid the use of $NaHCO_3$, at least until the P_K has returned toward the normal range, or only to use it along with an appropriate amount of K^+ to avoid a cardiac arrhythmia (see accompanying Chapter on K^+).

ECF Volume Overload and Hypernatremia

This is only a problem in patients with metabolic acidosis who have an expanded ECF volume (patients with renal failure), in patients with a compromised circulation (cardiogenic shock), or those where enormous amounts of alkali might be used (e.g., hypoxic lactic acidosis). Hypernatremia may be produced and/or exacerbated if hypertonic $NaHCO_3$ is given.

Enhanced Production of L-lactic Acid

When $NaHCO_3$ is given to patients with L-lactic acidosis, the rate of production of L-lactic acid increases. This however may be considered beneficial if it reflects an increased rate of regeneration of ATP in vital organs [77], and if the H^+ so-produced are titrated by the BBS and not by intracellular proteins.

Rebound Metabolic Alkalosis

In metabolic acidosis due to overproduction of H^+ and anions (L- or D-lactate, or -hydroxybutyrate and acetoacetate), the acidosis will be improved when these anions are metabolized to HCO_3^-. If all the anions are converted to HCO_3^- and the patient also received $NaHCO_3$, the final plasma P_{HCO3} could be higher than normal if renal excretion of HCO_3^- did not occur [83]. The main clinical significance of rebound metabolic alkalosis is primarily when patients are being weaned from a mechanical ventilator, and the impact of HCO_3^- on the renal excretion of K^+, which can further exacerbate hypokalemia [84].

Recommendations

One must individualize the decision for each patient, balancing potential benefits versus adverse effects. None of these factors is an absolute indication or contraindication, but by examining each of them, it should be possible to make a reasonable decision. If the decision is made to administer $NaHCO_3$, an equally difficult issue is how much to give and how fast it should be given. It is important to recognize that as the baseline P_{HCO3} falls, a progressively greater amount of added H^+ are buffered on intracellular proteins. Therefore, when $NaHCO_3$ is given, the hope is that much of it will titrate these intracellular H^+, and will effectively disappear as CO_2 and water, and therefore the increment in the P_{HCO3} will be small. Moreover, CO_2 removal by the lungs

Table 11. Ketoacid turnover during chronic fasting. Values are presented as mmol/day.

Ketoacid metabolism	Organ	Turnover
Net production	Liver	1500
Oxidation	Brain	750
	Kidney	250
	Muscle, etc.	200
Conversion to acetone	?	150
Excretion	Kidney	150

Table 12. Causes of ketoacidosis.

1. Diabetic ketoacidosis
– usually Type 1 or IDDM; rarely Type 2 or NIDDM
– damage to -cells of the pancreas
– pancreatic destruction as in hemochromatosis

2. Alcoholic ketoacidosis
– low insulin due to low ECF volume (-adrenergic effect)
– metabolism of ethanol to ketoacids
– lower oxidation of ketoacids in brain (sedative effect of ethanol), and kidneys (low GFR)

3. Low stimulus to pancreatic -cells because of hypoglycemia
– starvation
– low production of glucose in the liver (e.g. glycogen storage disease or inhibition of gluconeogenesis)

4. High production of acetic and butyric acid by GI bacteria together with inhibition of hepatic acetyl-CoA carboxylase.

must keep up with the increment in CO_2 production.

A decision needs to be made on the initial target P_{HCO3} when a patient has an extremely low baseline P_{HCO3}. A reasonable target is either to double the P_{HCO3} or to aim for an absolute value of 5 – 6 mM. If the P_{HCO3} rises from 2 to 4 mM and the PCO_2 remains unchanged, the pH will rise by 0.3 units. Nevertheless, one cannot make an accurate assessment of the amount of $NaHCO_3$ to give because the volume of distribution HCO_3^- is unknown.

Specific Causes for Metabolic Acidosis

The list of causes of metabolic acidosis is provided in Table 6.

Ketoacidosis

Ketoacids are a fat-derived fuel destined for oxidation in the brain. The main signal for their formation is a relative lack of insulin (Figure 3). There are 3 major causes of ketoacidosis (Table 12). In biochemical terms,

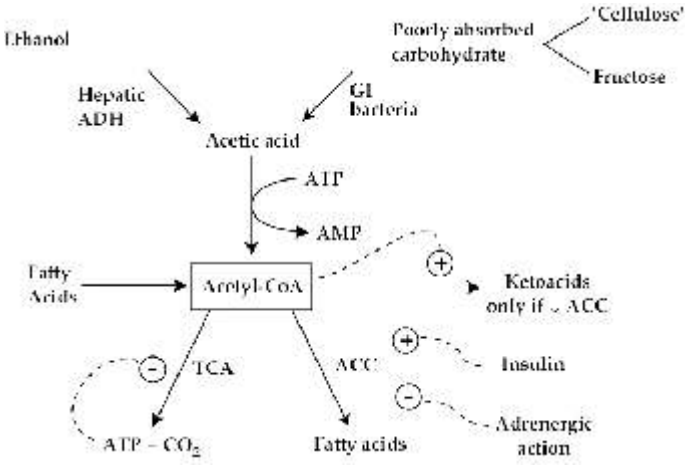

Figure 16. Metabolism of acetyl-CoA in the liver. There are two major sources of acetic acid and thereby hepatic acetyl-CoA, ethanol and acetic acid produced during the bacterial fermentation of poorly absorbed carbohydrates. Production of acetyl-CoA from these precursors bypasses the usual regulatory steps that involve fatty acid oxidation. Hence a high supply of these precursors and inhibition of acetyl-CoA carboxylase (ACC) by hormones such as adrenaline lead to the unregulated formation of ketoacids.

one must appreciate why there was a relative lack of insulin to favor ketoacid production and why the rate of removal of ketoacids was diminished. Production occurs in the liver whereas removal is largely the result of oxidation in the brain and kidneys (Table 11). The time course of events in patients with diabetic ketoacidosis (DKA) has an interesting feature. Towards the end-stage, the degree of ketoacidosis becomes more severe, and very quickly. Because there is little leverage to increase the rate of ketogenesis appreciably due to the control exerted by the limited rate of turnover of ATP in hepatocytes [85, 86], for ketoacidosis to worsen rapidly, there must be a major decline in the rate of utilization of ketoacids.

Brain: A decrease in the rate of turnover of ATP in the brain will lead to a decreased rate of oxidation of ketoacids. Should general anesthetics or sedatives be administered, or if coma be present, the degree of ketoacidosis will be more severe.

Kidney: If the GFR is very low, less Na^+ will be of filtered and this will decrease the reabsorption of Na^+ and thereby the renal need for regeneration of ATP. In quantitative terms, a low GFR can lead to the failure to remove several hundred mmoles of ketoacids per day.

Summary: One can appreciate why the natural history of DKA has a steep deterioration late in its course because of coma and prerenal failure.

Diabetic Ketoacidosis

DKA is the metabolic consequence of a lack of actions of insulin and it is characterized by the accumulation of glucose and ketoacids in the body [16]. The precipitating illness and the complications of this metabolic disturbance can be life-threatening. The changes in the hepatic metabolism that lead to overproduction of ketoacids are depicted in Figures 3 and 16.

Clinical Presentation

DKA may be the first indication of undiagnosed type 1 diabetes mellitus in children. The precipitating causes include an intercurrent illness (gastroenteritis, pancreatitis, infections), and situations where counter-regulatory hormones may be present in

excess (e.g., thyrotoxicosis, surgery, stress, pregnancy, and hyperadrenocorticism). With repeat episodes of DKA, failure to take insulin can be an important etiologic factor. Rarely, DKA occurs in older patients with type 2 diabetes mellitus when there is an unusually large decrease in the rate of oxidation of ketoacids due to impaired level of consciousness and a very low GFR.

The clinical manifestations are the expected consequences of the major biochemical changes, hyperglycemia, glucosuria, and ketoacidosis.

Hyperglycemia: Early signs and symptoms represent exacerbations of the classic features of diabetes mellitus in poor control – thirst, polydipsia, polyuria, weakness, lethargy, and malaise.

Glucosuria: Hyperglycemia causes an osmotic diuresis with loss of Na^+ and water, resulting in ECF volume contraction, low blood pressure, postural hypotension, and tachycardia.

Ketoacidosis: Metabolic acidosis results in an increased rate and depth of breathing (air hunger, Kussmaul respiration). The conversion of acetoacetic acid to acetone imparts the characteristic fruity odor to the breath.

Other findings: Not all the clinical findings, however, are completely explained in terms of biochemical aberrations. The state of consciousness does not correlate well with the concentration of ketoacids in blood. A much better correlation was found between the level of stupor and coma and the P_{osm} that in turn reflect the low circulating volume (and possibly, the higher PCO_2 in cells of the brain, Figure 7).

Another feature of DKA that remains unexplained is hypothermia, even in the presence of infection. This together with the fact that leukocytosis is a common finding in these patients may at times obscure an underlying infection.

Anorexia, nausea, vomiting, and abdominal pain are frequent nonspecific gastrointestinal complaints, especially in children. These symptoms, together with abdominal tenderness, decreased bowel sounds, guarding, and leukocytosis, may be severe, mimicking an acute abdominal emergency. Rebound tenderness is usually (but not universally) absent – the presence of hyperglycemia and ketonemia should signal the correct diagnosis. The cause for the abdominal pain is not entirely clear, but in some cases it may be related to hypertriglyceridemia and pancreatitis.

Signs and symptoms of the disorder that precipitated DKA should be appreciated – in fact, these may dominate the clinical picture.

Laboratory Evaluation

Hyperglycemia, ketonemia, glucosuria, and ketonuria are the 4 hallmarks of the laboratory diagnosis of DKA.

Hyperglycemia: The degree of hyperglycemia varies markedly – the P_{Glu} usually exceeds 250 mg/dl (14 mM). Higher P_{Glu} values are seen if there is a marked reduction in the GFR (usually with oliguria) or if the patient has consumed a large quantity of carbohydrate, for example, in the form of sweetened soft drinks to quench thirst (usually with polyuria) [87]. If the ECF volume is markedly contracted, not only will there be an exaggerated degree of hyperglycemia, but glucosuria may be reduced considerably because the filtered load of glucose may not exceed the tubular capacity for its reabsorption. In rare cases, hyperglycemia may be less marked for other reasons (e.g., a reduced rate of gluconeogenesis secondary to the intake of ethanol or biguanides or exaggerated renal glucosuria).

Ketoacids: In DKA, serum ketones are usually strongly positive in a dilution of 1 in

Table 13. Typical deficits in a patient with DKA.

	Quantity	Comment	Danger
Na^+	3 – 9 mmol/kg	Restore Na deficit, but not too quickly	Cerebral edema if early and too rapid
K^+	4 – 6 mmol/kg	Must await insulin action to shift K^+ into cells Examine P_K	Initial hyperkalemia > 1.5 h, hypokalemia
Water	Usually many liters	Half ICF, half ECF	Do not repair water deficit too early
Bicarbonate	Can be > 500 mmol of H^+ buffered	If increased anion gap, need not give $NaHCO_3$ unless very severe acidosis	Strong opinions held, but not backed up with clean data

8. However, only acetoacetate and acetone yield a positive reaction with the nitroprusside test (Acetest) used for clinical screening for ketoacids. If there is an increase in the $NADH^+$: NAD ratio, as occurs with hypoxia or ethanol oxidation, ketoacids will be predominantly in the form of -hydroxybutyric acid which is not detected by these clinical tests; a specific enzymatic analysis will be necessary to measure -hydroxybutyric acid. If the urinary excretion of ketoacid anions is larger than expected, as may occur with the intake of acetylsalicylic acid, or if there is a defect in reabsorption of ketoacid anions by the PCT, a hyperchloremic type of metabolic acidosis will be present [88].

Sodium: In patients with DKA, there is a large deficit of Na^+ (3 – 9 mmol/kg body weight, Table 13). This is the result of the osmotic diuresis.

Plasma Na^+ concentration: Much attention is given to the possibility that glucose will draw water out of cells and thereby, lower the P_{Na}. This occurs only when the addition of glucose is hyperosmolar to plasma. In contrast, when glucose is added as a solution that has an osmolality similar to or lower than the P_{osm}, there is no shift of water from cells. In this circumstance, the P_{Na} will be lower than seen with hypertonic glucose addition for an identical rise in P_{Glu} [89]. Therefore calculations based on the expected shift of water and thereby an expected fall in P_{Na} for a given P_{Glu} should not be done because the assumptions made are not valid [90 – 92]. Therefore we calculate the effective P_{osm} (Equation 10) to help clinical decision-making with regard to the appropriate tonicity of fluid therapy [93]. Corrections should be made for major changes in the P_K.

$$\text{Effective } P_{osm} = 2 \times P_{Na} + P_{Glu} \quad \text{(in mM terms)} \qquad (10)$$

Potassium: In patients with DKA and good renal function, there is always a decrease in the total body content of K^+, usually in the range of 4 – 6 mmol/kg body weight (Table 13). Despite this deficit of K^+, the P_K is usually increased to the mid-5 range [94] because K^+ has shifted from the ICF to the ECF

Table 14. Content of HCo_3^- in the ECF compartment in a patient with DKA. The example given is a 70-kg person who has an ECF volume of 15 L when normal (top line) and 12 L while in DKA (bottom line). The content of HCO_3^- is decreased by 75 mmol in DKA. Despite this loss, there is a 1:1 relationship between the fall in P_{HCO3} and rise in P_{-HB} because of an equivalent loss of -HB with Na^+ and/or K^+ in the urine. This represents the indirect loss of $NaHCO_3$.

	Plasma		ECF volume	ECF content		
	P_{HCO3} mmol/l	P_{-HB} mmol/l	liters	HCO_3^- mmol	Ketoacids mmol	$HC0_3^-$ + Ketoacids mmol
normal	25	0	15	375	0	375
DKA	10	15	12	120	180	300

compartment due to the lack of insulin (Figure 9) [73].

P_{HCO3}: In patients with DKA, the P_{HCO3} is low because H^+ were added to the ECF along with -hydroxybutyrate and acetoacetate anions. Nevertheless, there is also an indirect loss of Na^+ and HCO_3^- – this loss occurs early in the course of DKA because there is a lag period before there is a large increase in the rate of excretion of NH_4^+ [15]. As a result, ketoacid anions are excreted in the urine with Na^+ or K^+ and hence the indirect loss of $NaHCO_3$ (Figure 4). This component of the metabolic acidosis may not be appreciated because there is often a 1 : 1 relationship between the fall in P_{HCO3} and the rise in the plasma anion gap. This quantitative relationship occurs because *concentrations* rather than the *content* of HCO_3^- in the ECF compartment are considered (Table 14). This component of the HCO_3^- deficit becomes evident during therapy as the ECF volume is expanded [69, 95, 96].

PCO_2: There should also be a predictable degree of hypocapnia depending on the degree of metabolic acidosis (Table 4). Since hypothermia may occur in patients with DKA, one must take this into consideration when interpreting the PCO_2 and PO_2 values reported by the laboratory because the measurements are made at 37ºC.

GFR: Since patients with DKA often have a very low ECF volume, their GFR will be reduced whereas the concentrations of urea (P_{urea}) and creatinine (P_{creat}) will be elevated in plasma. The P_{urea} (BUN) is less reliable as an index of the GFR because it is also influenced by protein intake, tissue catabolism, rate of gluconeogenesis, catabolic drugs, and urine flow rate. Notwithstanding, there may also be errors in the measurement of creatinine depending on the method used. Higher P_{creat} values are reported with the picric acid method if the level of AcAc is elevated [97] whereas lower P_{creat} values are reported with severe hyperglycemia if the enzymatic assay for creatinine is performed on the Kodak analyzer [98].

Treatment of the Patient with DKA

DKA is a medical emergency that demands urgent treatment. Mortality is influenced by a number of factors that include its precipitating cause, the age of the patient, the level of

consciousness, and the severity of the biochemical abnormalities. In children, the leading cause of morbidity and mortality is the development of cerebral edema (discussed later) [99, 100]. Other causes of death are infection, vascular thrombosis, and shock. Early diagnosis, a better design of therapy, and dealing with the underlying causes of DKA may reduce the mortality rate. Our emphasis will be on the threats to the patient's life during therapy of DKA (Table 15). Treatment will be discussed under the following headings: body fluid compartments, insulin, bicarbonate, predisposing factors and how to avoid complications of therapy.

Table 15. Complications to avoid during therapy.

On admission
Shock
Aspiration pneumonitis
Thrombotic episodes
Hyperkalemia with cardiac arrhythmias
From 1.5 h onwards
Hypokalemia with cardiac arrhythmias
From 6 h onwards
Neuroglucopenia
From 5 – 15 h
Cerebral edema
Anytime
Complications of the underlying illness
Lack of insulin actions

Body Fluid Compartments

Focus on the ECF volume: The ECF volume should be re-expanded quickly only if there is a hemodynamic emergency. It is very difficult to assess the degree of ECF volume contraction on clinical grounds [101 – 103]. The following laboratory findings can help to provide a quantitative assessment of the patients' ECF volume [69]. The hematocrit (ratio of red blood cells (RBC) volume/blood volume) is particularly useful if the patient is not anemic. For example, if the initial hematocrit were 60%, this would suggest that the plasma volume is contracted by more than 50% (Equation 11). Moreover, the ECF volume is contracted to a greater degree than the plasma volume because the volume of RBC should remain constant (in the absence of a severely abnormal P_{Na}) and Starling forces should expand the plasma volume at the expense of the interstitial volume [69].

Normal: 0.40 = 2 l RBC volume/5 l blood volume (3 l plasma + 2 l RBC)

Patient: 0.60 = 2 l RBC volume/3.3 l blood volume (1.3 l plasma + 2 l RBC) (11)

We also find 2 other indices helpful to monitor changes in the effective vascular volume [69]. First, if the venous PCO_2 is appreciably higher than the arterial PCO_2 (> 10 mmHg), it suggests a slower blood flow rate past cells drained by that venous system (same CO_2 production, but CO_2 is carried away in fewer liters of blood, Figure 7). Second, a rise in urine output usually signals an increase in the GFR and thereby a higher filtered load of glucose and a larger osmotic diuresis. With the initial urine output rise, the rate of intravenous infusion should be increased by a similar volume to maintain the slow and steady re-expansion of the ECF volume.

The next decision concerns the composition of the infusate. There is still some dispute about which is the most appropriate intravenous solution to use. We strongly favor the initial administration of 0.9% saline (154 mM NaCl) to avoid a large fall in the effective P_{osm} (Equation 10). When the P_{Glu} falls below 250 mg/dl (15 mM), glucose should be added to the infusate. Further fluid therapy is determined by the clinical assessment, biochemical measurements, and calculated and/or expected losses.

Focus on the ICF volume: The deficit of ICF water should be replaced much more slowly. Once the hemodynamic emergency is dealt with, one can now safely switch to half isotonic saline in adults with DKA because cerebral edema is not common in these patients. The goals for ICF therapy differ in children with DKA as discussed later in the section on complications of therapy.

Insulin: Insulin plays a central role in arresting ketogenesis, but this is rarely an urgent aspect of therapy because the maximum possible rate of ketogenesis is only ~ 1 mmol/min [86]. In our view, the only emergency action of insulin needed is its effect to decrease the P_K by accelerating a shift of K^+ into cells in a patient with a significantly abnormal EKG due to hyperkalemia. While insulin will help lower the P_{Glu}, its hypoglycemic effects are minimal early in therapy. Rather, the P_{Glu} will fall initially as a result of re-expansion of the ECF volume (dilution) and glucosuria (decrease the glucose pool size) [104]. 6 – 8 hours after therapy began, insulin will increase the rate of oxidation of glucose (because competing fat fuels are no longer available) and by promoting the synthesis of glycogen [87].

Low-dose, short-acting insulin regimens are now commonly used. Given the uncertainty of absorption by other routes, the intravenous route is advisable. A typical dose in adults is 0.1 Units/kg as an intravenous bolus, followed by a constant infusion of 0.1 Units/kg/h. A bolus of insulin should not be used in children because it may lead to brain cell swelling [93]. The putative mechanism involves activation of the Na^+/H^+ exchanger in brain cell membrane with a resultant gain of ICF solutes (Na^+) [105].

Insulin therapy has potentially detrimental effects that should be anticipated and avoided. The major ones are hypokalemia (at 1 – 3 h) and hypoglycemia (at 6 – 10 h). The former risk is discussed below and the latter one is minimized by infusing glucose when the P_{Glu} falls to 250 mg/dl (~ 15 mM).

Potassium: Typically, the P_K on presentation in patients with DKA is in the mid-5 range [94]. A lower P_K indicates that a rather severe K^+ deficit exists and patients are at higher risk for cardiac arrhythmias, paralytic ileus, and muscle weakness that may also involve respiratory muscles after insulin is given. Once therapy has commenced, the P_K falls rapidly, often within the first hour. This is due primarily to the uptake of K^+ into the ICF (replacing Na^+ and H^+). Minor contributing factors are the loss of K^+ in the urine, correction of the acidosis, and dilution from re-expansion of the ECF volume.

The initial aim of therapy is to ensure a normal P_K during the acute stages of therapy. Replenishing the total deficit of K^+ in the body will take time because it requires the re-accumulation of intracellular anions (primarily organic phosphates). K^+ should be given as intravenous KCl, but only when the P_K is < 5.0 mM. Typical regimens are: give 20 mmol K^+/hour if the P_K is 4 – 5 mM; give 40 mmol K^+/hour if the P_K is 3.0 – 4.0 mM, and 40 – 60 mmol K^+/hour if the P_K is < 3.0 mM. The EKG as well as the P_K can be used to monitor the rate of replacement of K^+.

While it is prudent to consider the urine output, patients with oliguria may still need a supplement of K^+ if their P_K is distinctly low. When DKA has been corrected, oral supplementation of K^+ (and phosphate, usually from diet) should be continued over several days to replenish the deficits in the intracellular compartments.

Because hypokalemia is also a complication of therapy with $NaHCO_3$, if a patient presents with a low P_K and acidosis that is severe enough to require treatment with $NaHCO_3$, one could make a case for withholding insulin for an hour or so until suffi-

cient K^+ and HCO_3^- have been administered. Since the rate of net ketoacid production is ~ 1 mmol/min [86], withholding insulin for that hour will not have a major impact on the degree of acidosis because more HCO_3^- than this can be given.

$NaHCO_3$

Early therapy: $NaHCO_3$ is rarely needed. Nevertheless, it is difficult to resist giving $NaHCO_3$ when the P_{HCO3} is < 5 mM especially if there is a source of loss of $NaHCO_3^-$. A severe degree of hyperkalemia is also a possible indication for the use of $NaHCO_3$.

Later therapy: After the ketoacidosis has been largely reversed, some patients may have a lingering hyperchloremic type of metabolic acidosis due in part to a low rate of excretion of NH_4^+. These patients may need to ingest $NaHCO_3$ to raise their P_{HCO3}.

Phosphate

The usual deficit of phosphate is 1.5 – 2.5 mmol/kg body weight (Table 13). While only close to 10% of patients have hypophosphatemia at presentation, once therapy is instituted virtually every patient becomes profoundly hypophosphatemic. There are no controlled studies documenting the absolute benefits of the acute replacement of phosphate. A number of theoretical considerations, however, suggest that it may be beneficial to replace some of the deficit of phosphate early in therapy. The rate of infusion of phosphate should not exceed 50 mmol/8 h.

Complications Observed During Therapy

While hypokalemia, hypoglycemia, relapse of ketoacidosis, and thrombotic events may occur, we shall focus on cerebral edema in this section.

Cerebral edema: Typically, DKA is first diagnosed in childhood. Cerebral edema is more common during therapy in the first episode of DKA, possibly because there was a delay in suspecting that this may be the diagnosis by family members. Cerebral edema occurs in ~ 1% of cases and it is the major cause of mortality in this setting [99, 100]. Even though most children with cerebral edema survive, many are left with significant neurological deficits. Even those who seem to be neurologically intact may have subtle cognitive and behavioral deficits.

Cerebral edema is the result of a rise in brain water and hence intracranial pressure because of the fixed volume of the skull. At the clinical level, typically, the child who develops cerebral edema appears to be recovering normally from DKA, but takes a rapid turn for the worse close to 5 – 15 h after the onset of therapy. Nevertheless, 1/20 children developed cerebral edema prior to receiving therapy – a possible reason for this was discussed in reference [89]. The warning signs of impending cerebral edema are often subtle, including new onset of drowsiness and/or irritability that can progress rapidly to a disordered state of consciousness that may terminate with respiratory arrest and death.

While CT or MRI imaging will confirm this diagnosis, we are very reluctant to send patients suspected of having cerebral edema for these studies because they need extremely urgent medical treatment that cannot wait for even a few minutes. Moreover, they need to be observed very carefully and the imaging department does not have the facilities to do

Table 16. Anticipated results of therapy of DKA.

Glucose:	Will fall 5.5 mmol/l (100 mg/dl) over each of the first 6 hours. Reasons for fall are dilution (early), glucosuria (mid-time) and metabolism (late).
Sodium:	Rise in the P_{Na} of 1.6 mmol/l per 100 mg/dl (5.5 mmol/l) decline in P_{Glu} owing to a shift of water into the ECF.
Potassium:	Sudden fall over 1 – 2 hours owing to shift of K^+ into cells when insulin acts. This is the best early indicator of the biological actions of insulin.
Bicarbonate:	Will not rise for several hours. The P_{HCO3} will be close to 16 – 18 mmol/l once ketoacidosis largely disappears (6 – 8 hours later).
Ketoacids:	Slow steady decline over 8 hours to 1 mmol/l range. Serum quick test for ketones will be positive much longer. The Quick test may actually become more positive, despite less ketoacidosis owing to conversion of H● -HB to H●AcAc.
Anion gap:	Fall in parallel with ketoacids, will return to normal in 8 – 12 hours.
Complications:	See Table 15.

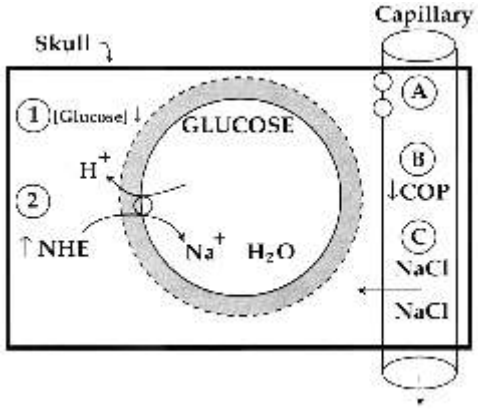

Figure 17. Risk factors for cerebral edema. The solid rectangle represents the skull. The 2 risk factors for swelling of brain cells are shown on the left and include a higher concentration of glucose and/or its metabolites in the brain due to rapid lowering of the P_{Glu} (site 1) and activation of the $Na^+ : H^+$ exchanger (NHE) by insulin (site 2). The factors causing expansion of the ECF volume are shown on the right and could be the result of a less restrictive blood brain barrier (site A), a fall in the colloid osmotic pressure (COP) in plasma (site B), and/or the excessive administration of saline (site C). Reproduced with permission [187].

this. Even when one has the results of the imaging studies, changes in the clinical state can occur so rapidly that this result may not mirror the current status in a timely fashion.

Pathophysiology of Cerebral Edema

A more detailed view of the pathophysiology of cerebral edema will be considered under the following headings (Figure 17).

Factors related to an expansion of the ECF compartment of the brain: One can think of these as early or later events. The early factors might include a less restrictive blood brain barrier (BBB), the use of an initial bolus of saline, especially if there is not a hemodynamic reason to give it, and an initial decline in the colloid osmotic pressure of plasma. In more detail, although somewhat controversial, there is evidence of subclinical cerebral edema before therapy is instituted when CT scans of the brain were examined [106 – 108]. This may be the result of a less restrictive BBB that permits the intracranial

ECF volume to increase, effectively bypassing the protective mechanisms that normally exist to prevent a rise in intracranial pressure. The initial bolus of saline will be distributed on first pass in the blood volume and cause a sudden rise in hydrostatic pressure and a fall in the colloid osmotic pressure of arterial blood. In addition to the fall in albumin concentration, the colloid osmotic pressure could decrease due to a fall in the Donnan force in plasma, possibly the result of a less anionic charge on albumin associated with rapid re-expansion of the ECF volume [109]. Hence Starling forces together with a less restrictive BBB could act in concert to expand the volume of the intracerebral ECF compartment further. The message we derive from these analyses is: a large bolus of saline should **not** be given unless there is frank hemodynamic collapse in children with DKA.

Factors associated with a rise in brain cell volume: There are two factors to consider, a fall in the effective P_{osm} and a rise in intracellular osmoles. Firts treatment regimens that have been associated with cerebral edema usually cause a significant fall in the effective P_{osm} (Equation 10). A rapid fall in the P_{Glu} may predispose to cerebral edema by allowing the shift of water into brain cells (a compartment with an osmolality that decreases less rapidly than the effective P_{osm}). As partial compensation for the high effective P_{osm} in a patient with DKA, the brain seems to accumulate osmoles such as sorbitol, fructose, taurine and glutamine that minimize the degree of water shift out of brain cells. Once the P_{osm} falls, however, these organic osmoles cannot be removed rapidly from brain cells and they will attract water, contributing to the development of cerebral edema [110]. Second, one should avoid an initial bolus of insulin because it may cause an increase in the number of particles in cells of the brain [105]. In more detail, insulin activates the Na^+-H^+ exchanger in the cell membrane (Figure 9). By causing an increase in the entry of Na^+ into brain cells along with the exit of H^+ that were bound to intracellular proteins, there will be a net increase in the number of particles in the ICF, and this will draw water into these cells.

The P_{Na} is typically much higher in children for a given degree of hyperglycemia (i.e., with a P_{Glu} of 50 mM (900 mg/dl), the P_{Na} is usually in the 125 – 130 mM range in adults [81, 104] but closer to 140 mM in children [93, 111]. We speculate that this could reflect the higher GFR early in type 1 diabetes mellitus leading to a higher rate of glucosuria for the same degree of hyperglycemia. Moreover, the $U_{Na} + U_K$ in this urine is close to $^1/_3 - ^1/_2$ isotonic saline (plus glucosuria). Hence there would be a larger excretion of electrolyte-free water in children.

Issues for Therapy

The best strategy is to prevent cerebral edema from developing. This can probably be achieved by avoiding therapies that will over-expand the ICF and ECF volumes of the brain. We would not administer a bolus of insulin to treat DKA in children. The initial saline infusion should be targeted to avoid circulatory collapse – we would not otherwise give a bolus of saline. Once the patient is hemodynamically stable, the Na^+ deficit should be replaced slowly, with an upper limit of 6 – 9 mmol/kg depending on the initial impression of the degree of ECF volume contraction (use the hematocrit if possible) [69].

In children, we use isotonic saline to avoid a fall in the effective P_{osm} (Equation 10). The target value for the P_{Na} in the first 5 – 15 hours is that which keeps a constant effective P_{osm}. Adding KCl, to isotonic saline is a good choice when the patient is undergoing a rapid

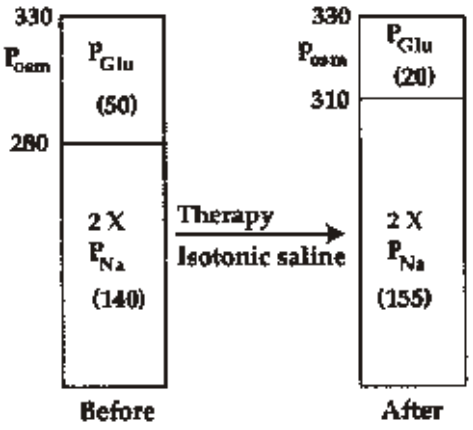

Figure 18. Fall in the effective plasma osmolality and the development of cerebral edema. For details, see text. A rise in the P_{Na} is needed to prevent a fall in the effective P_{osm} when there is a fall in the P_{Glu}. The P_{Na} must rise by $^1/_2$ the fall in the P_{Glu} to maintain a constant P_{osm} of 330 mOsm/kg H_2O.

glucose-induced osmotic diuresis because this will defend the effective P_{Osm} when the P_{Glu} falls. There is evidence to suggest that maintaining a constant "effective" P_{osm} at the expense of hypernatremia may protect against cerebral edema [93]. This can be accomplished by permitting the P_{Na} to rise by half the fall in P_{Glu} in mM terms (Equation 10), thereby keeping the effective P_{osm} constant (Figure 18). As mentioned earlier, the P_{Na} in children with DKA who have a P_{Glu} of 50 mM (900 mg/dl) is usually close to 140 mM [93, 111]. When this P_{Glu} falls by 30 mM (540 mg/dl), the P_{Na} would have to rise by 15 mM to 155 mM to keep the effective P_{osm} constant (Equation 10). To achieve this aim, the intravenous solutions must have the same effective osmolality as the P_{osm} in an oliguric patient or as the urine when the patient has a large urine output.

If signs of cerebral edema did develop, hypertonic saline or mannitol should be infused rapidly to reverse cerebral edema by drawing water out of the brain [112]. Our aim would be to give enough hypertonic solutes to see a prompt clinical response. Usually, this would require an increase in the effective P_{osm} of 10 mOsm/kg H_2O (administer 10 mmol of mannitol or 5 mmol of hypertonic NaCl/l body water using the clinical response as your guide).

Precipitating Events

During therapy for DKA, it is also necessary to treat any precipitating event or accompanying illness. Although clinical rhabdomyolysis is uncommon, enzymes of muscle origin (CPK, AST, and LDH) are often elevated in plasma. Thrombotic events in veins due to a slow blood flow rate should also be anticipated.

Alcoholic Ketoacidosis

Alcoholic ketoacidosis is seen following binge drinking of large amounts of ethanol complicated by poor food intake and vomiting (usually due to alcohol-induced gastritis) [113, 114]. The lack of food intake and the ECF volume depletion lead to suppression of insulin secretion via an -adrenergic effect [115]. This combination of hormonal changes both increases lipolysis in adipose tissue (stimulation of hormone-sensitive lipase) and diminishes hepatic lipogenesis (inhibition of hepatic acetyl-CoA carboxylase (ACC)) (Figure 16).

Ethanol, the principal carbon source for the formation of ketoacids, is metabolized in the liver to produce acetyl-CoA. Constraints set by the rate of turnover of ATP in hepatocytes limits the rate of oxidation of acetyl-CoA to

produce ATP [85, 86]. This, together with the inhibition of the synthesis of fatty acids in liver (inhibition of ACC by the low insulin and high circulating counter-insulin hormones such as adrenaline and glucagon), leads to the rapid formation of ketoacids. The acidosis may be quite severe and have a relatively rapid onset, with ketoacid anion levels of up to 20 mM; it is associated with an increase in the anion gap in plasma. Establishing the diagnosis of alcoholic ketoacidosis may not be straightforward. One reason is that there are frequently coexisting acid-base disturbances that result in the blood pH being normal or even alkalemic in up to 50% of patients. Metabolic alkalosis commonly occurs as a result of the vomiting, and respiratory alkalosis may occur due to stimulation of ventilation by alcohol withdrawal or aspiration pneumonia.

The second difficulty in diagnosis is that there is occasionally a falsely low or perhaps negative screening test for ketones [116]. The nitroprusside reagent reacts with acetoacetate and acetone. Acetoacetate is in equilibrium with -HB in a reaction catalyzed by the enzyme -hydroxybutyrate dehydrogenase (Equation 12). This is an NAD^+-NADH linked reaction and the ratio of end products depends on the NAD^+/NADH ratio which in turn reflects the redox state in liver cells. In alcoholic ketoacidosis, the NAD^+/NADH ratio in the liver is often more reduced than usual due in part to the metabolism of ethanol (which generates NADH) or to tissue hypoperfusion as a result of the marked degree of ECF volume contraction. In this setting, the more reduced NAD^+/NADH ratio increases the amount of -hydroxybutyrate relative to that of acetoacetate so that the screening test for ketones may be falsely low.

$$AcAc^- + NADH + H^+ \qquad -HB^- + NAD^+ \quad (12)$$

The diagnosis of alcoholic ketoacidosis is therefore suspected in light of the clinical situation and laboratory abnormalities noted above. A key finding is that the P_{Glu} is not very elevated as it would be in DKA. At times it is difficult to distinguish alcoholic ketoacidosis from methanol or ethylene glycol poisoning as the primary cause of acidosis. This diagnosis is very important to make because therapy differs. Both can cause metabolic acidosis, a high anion gap in plasma, an elevated value for the plasma osmolal gap, and a near-normal P_{Glu}. Nevertheless, there is one clinical clue that can help – if the ECF volume is not very contracted, one would suspect methanol or ethylene glycol overdose. A direct assay for methanol and ethylene glycol is needed to establish the diagnosis.

Treatment of Alcoholic Ketoacidosis

The treatment of alcoholic ketoacidosis is usually straightforward. Isotonic saline is required to correct the marked degree of ECF volume depletion [113]; if the P_{Glu} is definitely low, a small quantity of glucose should be added to raise the P_{Glu} to the high-normal range. The higher P_{Glu} should now stimulate insulin secretion and thereby, diminish the rate of ketoacid production. Attention must be paid both to K^+ and phosphate depletion, which are common in this disorder. Treatment with $NaHCO_3$ is rarely required because the degree of acidemia is usually mild and the net production of ketoacids can be reversed quickly with appropriate intravenous fluid therapy. One must bear in mind that a deficiency of thiamin might be present in a patient who is malnourished so this vitamin must be given with the initial therapy in this setting.

The prognosis is usually excellent; in one case series only about 50% of the patients required hospital admission, and the mortality

Table 17. Causes of L-lactic acidosis.

Type A (hypoxic)
- circulatory failure (cardiogenic shock or secondary to sepsis)
- severe hypoxemia (lung problem or high altitude)
- severe anemia
- excessive demand for oxygen (e.g. generalized seizure, vigorous exercise)

Type B (compromised metabolism of L-lactate)
- a variety of diseases that severely affect the liver
- inhibition of gluconeogenesis (e.g. by ethanol)
- inborn error of metabolism affecting pyruvate dehydrogenase, the tricarboxylic acid
- cycle, or the electron transport system
- thiamine deficiency
- riboflavin deficiency or low bioactivity
- isoniazide (vitamin B_6 deficiency)

rate was only 1% including problems related to underlying lesions such as pneumonia and pancreatitis [114].

Ketoacidosis of Prolonged Fasting

Ketoacidosis of fasting is usually a mild disorder with a P_{HCO3} that is characteristically close to 18 mM and an anion gap that is less than 19 mEq/l (suggesting that the accumulation of ketoacid anions is not more than 7 mM). The rate of production of ketoacids is close to that in DKA, but the rate of production is matched by the removal of ketoacids by oxidation in the brain and kidneys plus their excretion with NH_4^+ in the urine [46]. The P_{Glu} is usually close to 60 mg/dl (3 mM). Specific treatment for this form of ketoacidosis other than re-feeding is not required because it is rapidly cured by intake of carbohydrate.

L-lactic Acidosis

L-Lactic acidosis may be classified into two major categories depending on whether or not the supply of oxygen is matched to tissue demands for energy metabolism. In type A L-lactic acidosis, the production of L-lactic acid is increased and its removal impaired because of tissue hypoxia (Figure 19). In contrast, in type B L-lactic acidosis, hepatic removal of L-lactate is impaired for reasons other than hypoxia [117] (Table 17).

Type A Lactic Acidosis

Type A L-lactic acidosis is particularly frustrating to treat because its underlying cause

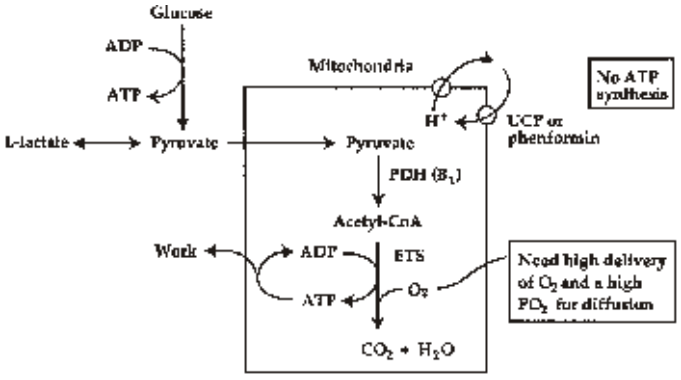

Figure 19. Biochemistry of L-lactic acidosis. The major production of L-lactic acid occurs when the supply of O_2 is inadequate to meet demand to support metabolic and physical work and/or uncoupling of oxidative phosphorylation due to open H^+ channels (UCP). Vitamin B_1 (thiamin), is a cofactor in the reaction catalyzed by pyruvate dehydrogenase (PDH). L-lactic acid can also accumulate when the ability to metabolize L-lactate is compromised.

may be extremely difficult to reverse. Examples include cardiogenic shock, septic shock, and multiple organ failure. It is also important to recognize that the rate of net L-lactate production may be extremely rapid, resulting in severe acidosis very quickly. It is widely believed that the accumulation of the L-lactate anion per se is not harmful and is important only as a sign of serious metabolic dysfunctions. Nevertheless, the L-lactate anion can chelate ionized Ca^{2+} [118 – 120], an ion that is critical for myocardial contraction [121]. In addition, Veech and Fowler [122] have suggested that a higher $NADH/NAD^+$ ratio can impair metabolism. Therefore there are theoretical reasons to suspect a primary role for the L-lactate anion in the poor outcome.

Hypovolemic shock: L-lactic acidosis caused by hemorrhage or extensive loss of Na^+-rich fluid (diarrhea, etc.) is the easiest of the causes to treat. Infusion of isotonic saline is the most appropriate initial therapy for most patients. In patients with severe hypoalbuminemia, colloids, such as albumin or plasma, may also be given. Whether one should add $NaHCO_3$ to the initial intravenous fluid depends on the factors discussed earlier – the severity of the acidosis, the respiratory compensation, the P_K, and probably most important, the likelihood of rapid reversal of the underlying cause of the hypovolemia. Usually, correction of hypovolemia will correct tissue hypoxia and rapid reversal of the L-lactic acidosis due to metabolic conversion of the accumulated L-lactate anions to HCO_3^- should be anticipated (~ 4 – 8 mmol of L-lactate may be removed per minute via oxidation or gluconeogenesis [2]).

Cardiogenic shock: This is much more difficult to manage, because the underlying cause of the tissue hypoxia – low cardiac output – is often difficult to reverse rapidly. Key issues to consider in patients with this diagnosis are ensuring that left ventricular filling pressure is adequate (which usually requires pulmonary capillary wedge pressure measurement) and that readily treatable causes of cardiogenic shock such as pericardial tamponade are not overlooked. The use of inotropes, afterload reducing agents, and/or an intraaortic balloon pump may be required. The administration of $NaHCO_3$ is often of limited use because of constraints imposed by ECF volume expansion and pulmonary edema.

Septic shock: L-lactic acidosis in a patient with sepsis is a grave prognostic finding. Treatment of the underlying infection with appropriate antibiotics, surgical drainage of an abscess if present, optimization of intravascular volume, and the use of inotropic agents are all essential, but often futile once multiple organ failure is present.

Use of dichloroacetate: One approach to treatment of patients with L-lactic acidosis is to use dichloroacetate (DCA) [123]. DCA activates the pyruvate PDH and thereby facilitates pyruvate (and therefore L-lactate) removal via metabolic conversion to acetyl-CoA and then to CO_2 and water. This may allow for more regeneration of ATP per molecular of O_2 consumed because now glucose or L-lactate rather than fatty acids are selected as the fuel to be oxidized [124]. DCA may have beneficial effects on myocardial function via a similar mechanism.

Early reports on the use of DCA in critically ill patients with L-lactic acidosis were somewhat encouraging. Notwithstanding, a prospective, randomized controlled trial of 252 patients with L-lactic acidosis, the majority of whom had sepsis and multi-organ failure, failed to show clinically significant benefit of DCA [125]. The results are not surprising considering that 18 mmol of H^+ are produced when 18 mmol of ATP are regenerated by anaerobic glycolysis, but only 1 mmol of H^+ is removed when the same amount of ATP is re-

generated by the aerobic oxidation of L-lactate [2]. Therefore one cannot overcome a rapid rate of production of L-lactic acid by enhancing its rate of removal unless anaerobic glycolysis is inhibited. Furthermore, as pointed out before, L-lactic acidosis per se maybe an epiphenomenon that reflects the presence of serious metabolic dysfunctions.

Type B L-lactic Acidosis

Hepatic disease: L-lactic acidosis is frequently seen in patients with acute hepatic necrosis with liver failure, such as that caused by viral hepatitis. It may also be seen as a more stable, chronic L-lactic acidosis where L-lactate removal is impaired in patients, for example, with malignancy that have liver metastases or infiltration with or without a large tumor burden outside the liver. The mechanisms that contribute to the L-lactic acidosis in these patients include replacement of a sufficient number of liver cells with tumor cells to impair L-lactate removal, production of metabolites by tumor cells such as the amino acid tryptophan that may lead to inhibition of hepatic gluconeogenesis, and/or the fact that tumor cells produce a quantity of L-lactic acid that exceeds the hepatic capacity to remove it in this setting.

Administration of $NaHCO_3$ to patients with type B L-lactic acidosis due to liver disease may have negative effects. First, the $NaHCO_3$ may increase L-lactate production (from glucose) by de-inhibiting phosphofructokinase-1 in malignant cells. Thus if the source of this glucose is ultimately from gluconeogenesis, a considerable amount of lean body mass may be lost [126]. Second, if for instance 150 mmol of $NaHCO_3$ were given along with 1 l of D_5W, the 276 mmol of glucose provided could be converted to 552 mmol of H^+ (2 L-lactate- and 2 H^+ per glucose), a quantity that exceeds the 150 mmol of HCO_3^- given.

Thiamin deficiency: Thiamin (vitamin B_1) deficiency is a specific example of type B L-lactic acidosis that merits emphasis. Thiamin is an essential cofactor of the PDH complex, an enzyme required for the regeneration of ATP from glucose [2, 127]. A special circumstance where the effect of thiamin deficiency can be very acute occurs when ketoacids were the main brain fuel (alcoholic ketoacidosis), but ketoacids disappeared when insulin levels rise (restoration of ECF volume, especially if hyperglycemia is also present). The target organ for a deficit of thiamin is the brain for two reasons: first, the brain is dependent on glucose as its energy fuel, and therefore flux through the PDH must occur in order to have ATP regeneration (unless ketoacids are present); second, there are very high rates of ATP turnover in certain areas of the brain. Hence, one can anticipate two hazards from a deficiency of thiamin, a local deficit of ATP, and a consequent local H^+ accumulation in an organ with limited buffer capacity. This may help explain why Wernicke-Korsakoff syndrome develops in these patients. Treatment is obviously thiamin replacement *before* the ketoacid concentration in plasma falls to very low levels.

Thiamin deficiency is most often seen in alcoholics who are poorly nourished, but it has also been described in patients receiving total parenteral nutrition when thiamin was not supplemented. The clinical manifestations of the L-lactic acidosis due to thiamin deficiency are confusion, hypotension, tachycardia, tachypnea and signs of congestive heart failure.

Ethanol: The acidosis observed in patients who have consumed large quantities of ethanol is frequently multifactorial. One component that may be observed in addition to ketoacidosis is L-lactic acidosis. The degree

of L-lactic acidosis is usually mild (< 5 mM) because it reflects the more reduced $NADH/NAD^+$ ratio due to ethanol metabolism that is largely restricted to the liver. A more severe degree of L-lactic acidosis suggests that there is L-lactic acid overproduction caused by hypoxia (resulting from shock due to gastrointestinal bleeding, for example), thiamin deficiency, seizures (alcohol withdrawal, delirium tremens, and/or a CNS lesion), or L-lactic acid underutilization due to severe liver disease. The management of this situation is mainly supportive, including normalization of the ECF volume and provision of thiamin. Once ethanol is completely metabolized, NADH levels will fall, L-lactate will be converted to pyruvate, and thereby to either glucose and/or CO_2 and water. This will lead to the regeneration of HCO_3^-, and the resolution of the L-lactic acidosis.

Biguanides: Biguanides are frequently used for patients with type 2 diabetes to lower the P_{Glu}. Initially, phenformin was the drug that was used, but because it led to the development of L-lactic acidosis [128], its use was curtailed. Currently, metformin is the drug of choice in this class – it does not seem to be a single cause of L-lactic acidosis [128b]. Biguanides, are lipophylic weak acids that can cross the mitochondrial membranes and cause uncoupling of oxidative phosphorylation in a fashion similar to dinitrophenol. The reason for the higher likelihood of L-lactic acidosis with phenformin than metformin is that phenformin has a larger hydrophobic end. Certain conditions lead to higher blood levels of these drugs, including renal insufficiency, reduced liver function or alcohol abuse, and heart failure and therefore, patients with these conditions are more predisposed to serious L-lactic acidosis with this class of drugs.

Antiretroviral drugs: L-lactic acidosis has been reported in patients with HIV infection treated with various antiretroviral agents. The agent most frequently associated with L-lactic acidosis is zidovudine [129], but didanosine, stavudine, lamivudine, and indinavir have also been implicated. Antiretroviral drug therapy is associated with mitochondrial myopathy as well as hepatic steatosis. Either muscle or liver involvement could, in theory, explain the L-lactic acidosis. Initially, mitochondrial myopathy, as manifested by ragged-red fibers and mitochondrial DNA depletion, was thought to be the main mechanism of L-lactic acidosis. Because the L-lactic acidosis did not become much more severe with exercise [129], we suspect that a more likely mechanism of the lactic acidosis might be the massive hepatomegaly and steatosis (Figure 20). This view was supported by the fact that a small dose of ethanol markedly increased the degree of L-lactic acidosis [129].

Riboflavin deficiency and/or tricyclic antidepressants: The active metabolites formed from vitamin B_2 (riboflavin), flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), are components of the mitochondrial electron transport system, the principal pathway to regenerate ATP, and for the enzyme, glutathione reductance. Riboflavin must be activated via an ATP-dependent kinase to produce FMN and FAD (Figure 21). This kinase is inhibited by tricyclic antidepressant drugs, such as amitriptyline and imipramine [130]. The activity of the kinase is decreased in hypothyroidism. Decreased activity of this kinase in a patient with myxedema crisis was associated with pyroglutamic acidosis [131]. Patients who consume a diet that is poor in B vitamins and take this class of antidepressants, can develop a chronic form of L-lactic acidosis. The reason that this is a chronic steady state L-lactic acidosis is still not clear.

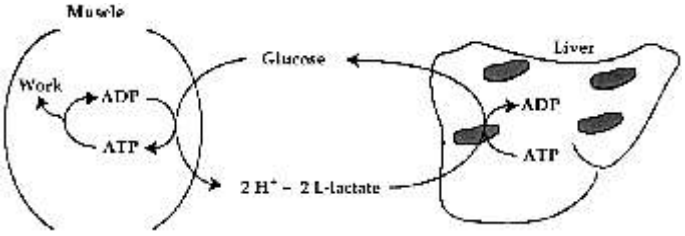

Figure 20. L-lactic acidosis and anti-retroviral drugs. The major basis for L-lactic acidosis is due to a problemwith L-lactic metabolism in the liver. While a lower activity of the mitochondrial electron transport system is possible, we favor the hypothesis that a large replacement of liver parenchyma by triglyderides (hepatic steatosis, depicted by the gray ovals) could explain why there is a reduced rate of L-lactic acid removal and a sensitivity to ethanol-induced L-lacitc acidosis.

The diagnosis is suspected by the history, and riboflavin deficiency is supported by finding a low activity of glutathione reductase in erythrocytes (a flavoprotein-dependent enzyme). Riboflavin supplementation leads to a prompt reversal of the metabolic acidosis in these patients suggesting that the defect is via competitive inhibition that is overcome by high riboflavin levels [132, 133].

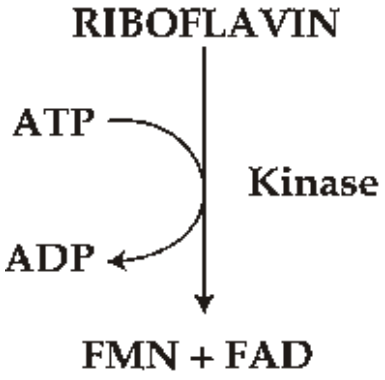

Figure 21. L-lactic acidosis and riboflavin deficiency. Riboflavin (vitamin B_2) must be activated to FMN or FAD to become an active component in the electron transport system, the mitochondrial pathway to regenerate ATP. Either a deficiency of riboflavin or inhibition of its kinase by tricyclic antidepressant drugs can lead to low levels of FMN and/or FAD.

Isoniazide: Prolonged convulsive seizure, regardless of cause, can lead to L-lactic acidosis. The seizure disorder induced by isoniazide is interesting because of its mechanism and clinical importance (Figure 22). Of note, the incidence of tuberculosis is rising worldwide and isoniazide is frequently used for its therapy.

The mechanism of the seizure and L-lactic acidosis may be the result of the formation of an isoniazide-vitamin B_6 complex, pyridoxal--isonicotinoyl-hydrazone, via a non-enzymatic reaction. This results in a rapid development of vitamin B_6 (pyridoxine) deficiency state [134]. Pyridoxal phosphate is a cofactor for the enzymatic reaction of glutamic acid decarboxylase in which glutamate is converted to gamma amino butyric acid (GABA). GABA is an inhibitory neurotransmitter. Therefore a deficiency of GABA could result in increased excitability and thereby lead to a seizure [135].

Patients on chronic hemodialysis are at increased risk of isoniazide-induced toxicity because they tend to be deficient in vitamin B_6 due to the efficient removal of this vitamin by hemodialysis. Vitamin B_6 deficiency can be suspected by finding a low activity of alanine aminotransferase in erythrocytes.

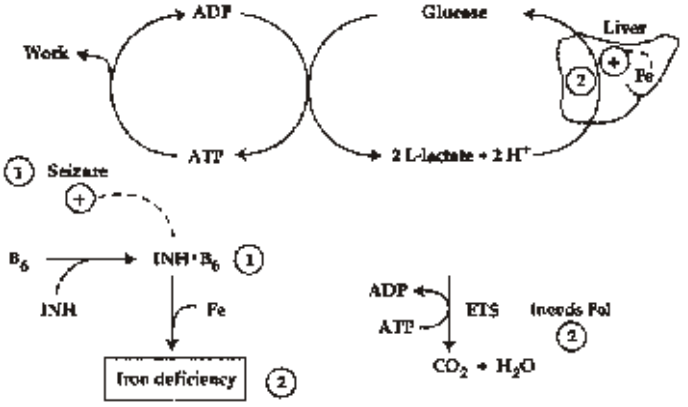

Figure 22. L-lactic acidosis due to the metabolism of isoniazide. For details, see text. The major cause of L-lactic acidosis is a seizure due to vitamin B_6 deficiency (site 1). A minor contributor to the development of lactic acidosis could be the chelation of iron (site 2) that diminishes the L-lactic acid removal rate, ETS electron transport system.

There are two factors that contribute to the degree of L-lactic acidosis (Figure 22). First, the deficiency of vitamin B_6 is responsible for isoniazide-associated seizure and thereby L-lactic acidosis. This is supported by the fact that there is a rapid and almost invariable cessation of seizure and recovery from L-lactic acidosis in response to a large dose of intravenous vitamin B_6 [136 – 138]. The recommended dose of vitamin B_6 for treatment of isoniazide toxicity is the same gram amount as the isoniazide dose ingested. If the amount of isoniazide is unknown, the recommended approach is to give 5 g of pyridoxine in 500 ml of fluid over 2 hours [138]. The second factor that could contribute to the degree of L-lactic acidosis is iron deficiency caused by chelation of iron by the isoniazide-vitamin B_6 complex. This could result in an electron transport defect and hence higher production of L-lactic and also a slower rate of its removal via gluconeogenesis because of the need for iron as a cofactor in both processes.

Methanol Poisoning

Methanol is metabolized by hepatic alcohol dehydrogenase. It is, however, a poor substrate for this enzyme and therefore high levels of methanol are needed for an appreciable rate of methanol metabolism. The molecular weight of methanol is only 32, so subjects do not need to ingest a large number of grams of methanol to produce an appreciable quantity of toxic metabolites. One can suspect that methanol is present from the history and the laboratory findings of a large plasma osmolal gap or metabolic acidosis accompanied by a large increase in the anion gap in plasma [139]. Note that the osmolal gap in plasma is due to methanol whereas the anion gap in plasma is due to formate anions. Therefore, later in the disorder when methanol has been largely oxidized, the plasma osmolal gap will not be elevated, but a high anion gap type of metabolic acidosis may be present.

The consequences of methanol ingestion may be classified as those arising from the effects of methanol itself and those of its metabolites. Methanol causes inebriation like ethanol. The serious toxicity of methanol arises from its metabolism to yield formaldehyde. Further metabolism of formaldehyde yields formic acid; however, acidosis is not usually the major concern. Formaldehyde is highly toxic to the central nervous system resulting in progressive coma and thalamic hemorrhage. The enzyme retinol dehydrogenase is located in the retina and it can catalyze the

conversion of methanol to formaldehyde and this leads to optic neuritis and blindness.

There may be difficulties in diagnosing methanol poisoning. In many cases, the origin of the ingested methanol is not recognized (e.g., substitution of methanol for ethanol in a recreational setting), so that clinical suspicion of the diagnosis may be lacking. Because methanol has such a low affinity for alcohol dehydrogenase, methanol toxicity can be delayed if ethanol is also ingested. Consequently, if one relies on finding metabolic acidosis, the diagnosis may be missed early on, even though plasma methanol levels are high. Accordingly, if there is the slightest suspicion that methanol may have been consumed and the plasma osmolal gap is significantly elevated, specific assays in blood for methanol should be undertaken. Another clue is that metabolic acidosis is present when the ECF volume is not appreciably contracted.

Treatment of Methanol Poisoning

First and foremost, the rate of metabolism of methanol to toxic end products should be slowed by giving ethanol or an inhibitor of alcohol dehydrogenase, 4-methylpyrazole (fomepizole, Antizol). The methods for administering Antizol and ethanol are described in the section on ethylene glycol.

Prognosis: The prognosis in methanol poisoning is closely related to the pH at presentation, with almost 100% mortality seen when the pH is less than 6.80. It is likely that the mortality is not caused directly by acidemia itself, but that the severity of acidosis reflects the generation of formaldehyde that causes the central nervous system toxicity. Therefore, although acidosis should be aggressively treated, the removal of methanol and its metabolites is the key to successful treatment.

Ethylene Glycol Poisoning

Ethylene glycol (automobile antifreeze, molecular weight 62) is readily available and is highly toxic. Like methanol, ethylene glycol is metabolized by the liver alcohol dehydrogenase to a variety of toxic end products. Patients with ethylene glycol poisoning have similar findings to those with methanol poisoning – CNS depression, increased anion gap metabolic acidosis and increased plasma osmolar gap. They differ in that they will often develop acute renal failure and pulmonary edema. The diagnosis may be suspected with the above findings plus abundant oxalate crystals in the urine, and confirmed by an assay that quantitates ethylene glycol in blood.

Treatment of Methanol and Ethylene Glycol Poisoning

The principles of treatment of ethylene glycol poisoning are virtually identical to that for methanol. They include administration of ethanol to achieve blood concentrations of about 20 mM (100 mg/dl) in order to reduce ethylene glycol metabolism, and removal of ethylene glycol and its metabolites by hemodialysis. One could administer fomepizole, an inhibitor of hepatic alcohol dehydrogenase, instead of ethanol. The major difference in treating ethylene glycol poisoning is that when acute oliguric renal failure is present, ECF volume overload or pulmonary edema may limit the amount of $NaHCO_3$ that can be administered so early dialysis is critically important.

Ethanol administration: Maintenance of a plasma ethanol level of about 20 mM (100 mg/dl) nearly completely inhibits methanol and ethylene glycol metabolism. Since ethanol distributes throughout total body water, administer a bolus of 0.6 g of ethanol per kg of body weight to increase its plasma level by 1

mg/ml (100 mg/dl). The maintenance dose should be equal to the expected metabolic removal rate for ethanol; at a plasma level in excess of 3 mM (14 mg/dl) – the hourly amount of ethanol removal is about 0.11 g per kg body weight [140]. In an alcoholic patient, the amount of ethanol metabolized is expected to be about 50% higher, and hence about 0.16 g of ethanol per kg body weight should be infused hourly. In a patient on hemodialysis, one can increase the rate of infusion of ethanol or add ethanol to the dialysis bath to achieve a concentration of 20 mM. The only way to ensure an optimal ethanol plasma level is to measure ethanol levels frequently and adjust its rate of infusion.

Administration of fomepizole (4-methylpyrazole): The target level of fomepizole in humans is 100 – 300 mol/l (8.6 – 24.6 mg/l) to assure near-complete inhibition of hepatic alcohol dehydrogenase. Its plasma half-life varies with the dose, even in patients with normal renal function. Fomepizole distributes rapidly in total body water. With multiple doses, fomepizole augments its own metabolism by inducing the cytochrome P450 mixed-function oxidase system; this effect increases the elimination rate by about 50% after about 30 – 40 hours. The side effects of fomepizole include headache, nausea, dizziness, and allergic reactions (rash and eosinophilia). Venous irritation and phlebosclerosis occur if the drug given is undiluted; therefore it should be diluted with at least 100 ml of 0.9% sodium chloride or D_5W.

The loading dose is 15 mg/kg, followed by 10 mg/kg q2h for four doses, then 15 mg/kg q12h (because of the P-450 enzyme induction) thereafter until the toxic alcohol level is less than 20 mg/dl. All doses should be administered as a slow intravenous infusion over 30 minutes. Fomepizole is dialyzable and the frequency of dosing should be increased to q4h during hemodialysis.

Salicylate Intoxication

The most common acid-base disturbance associated with salicylate intoxication is respiratory alkalosis due to central respiratory stimulation [141]. Metabolic acidosis may complicate the picture, however, especially in children. Because toxic levels of salicylate are considerably less than 10 mM (140 mg/dl), the elevation of the plasma anion gap in salicylate-associated metabolic acidosis is caused by the accumulation -HB, sometimes L-lactate anions, and other unidentified organic anions in addition to a small contribution by salicylates. Acidemia is uncommon because of coexisting respiratory alkalosis.

Treatment of Salicylate Intoxication

Treatment of salicylate intoxication is aimed at increasing urine salicylate excretion and preventing the accumulation of salicylates in brain cells. Salicylate is a weak organic acid that is transported across cells and renal epithelia, in its undissociated form. Alkalinizing the urine reduces salicylate reabsorption by the kidney and this may enhance its excretion; similarly, alkalinizing the ECF tends to prevent salicylate accumulation in cells, so acidemia should be avoided.

Alkalinizing the urine can be achieved with $NaHCO_3$ administration. The major risk of this therapy is excessive elevation of blood pH because of coexistent respiratory alkalosis and the risk of worsening pulmonary or cerebral edema. If the blood pH exceeds 7.55 as a result of this therapy, one dose of acetazolamide (250 mg) should be given to induce bicarbonaturia. Although acetazolamide causes an acid disequilibrium pH in the lumen of the PCT, it still promotes salicylate excretion [142]. One must avoid larger doses of acetazolamide as this may induce significant meta-

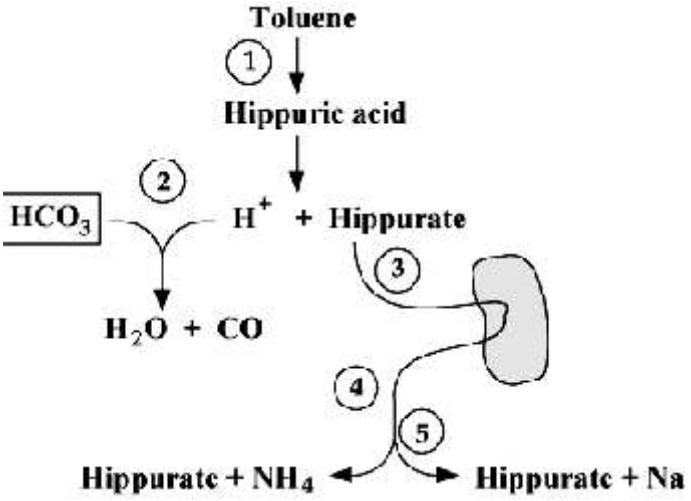

Figure 23. Metabolic acidosis due to the metabolism of toluene. The metabolism of toluene occurs in the liver. It is initiated by cytochrome P450, and then benzoic acid is produced via alcohol and aldehyde dehydrogenases. Hippuric acid is produced due to conjugation with glycine (all represented as site 1 for simplicity). The H^+ are titrated by HCO_3^- for the most part (site 2). The hippurate anion is secreted by the PCT and excreted in the urine, initially with NH_4^+ (site 4) and then with Na^+ and K^+ when the capacity to excrete NH_4^+ is exceeded (site 5). The excretion of hippurate anions with Na^+ and/or K^+ (and not NH_4^+) is the main reason for the metabolic acidosis.

bolic acidosis. Of more importance, acetazolamide will bind to albumin and displace bound salicylates thereby increasing its toxicity [143]. Acetazolamide also causes excessive losses of K^+ in the urine due to inducing bicarbonaturia.

In severe intoxications complicated by the adult respiratory distress syndrome, cardiovascular instability, evidence of cerebral edema, and possibly with severe elevations in salicylate level per se (greater than 6 mM), hemodialysis is the treatment of choice; if hemodialysis is not available, peritoneal dialsis may be used.

Metabolic Acidosis due to Glue-sniffing

Patients who sniff glue for its intoxicating properties absorb a significant quantity of toluene (methylbenzene). Toluene is metabolized via a series of reactions in the liver to hippuric acid that provides the load of H^+ (Figure 23). Despite the production of the hippurate anion, the plasma anion gap is generally not significantly elevated because the kidney, both via filtration and more importantly by tubular secretion, very efficiently excretes hippurate. As a result, there is the development of a hyperchloremic type of metabolic acidosis. Together with the anion excretion, variable amounts of urinary excretion of Na^+ and K^+ may be seen, leading to a degree of ECF volume contraction and hypokalemia, both of which aggravate the degree of intracellular acidosis (Figure 7). Even though there is an enhanced rate of excretion of NH_4^+, this does not result in a negative urine net charge (i.e., $U_{Na+K} > U_{Cl}$, Figure 11) because of the very high rate of excretion of the hippurate anion. The presence of NH_4^+ and hippurate in the urine could be detected by the presence of a significant urine osmolal gap (Figure 11). Thus the clinical features of toluene intoxication include metabolic acidosis, near-normal plasma anion gap, normal plasma osmolal gap, ECF volume contraction, hypokalemia, lower than expected BUN and

a high urine osmolal gap. It had formerly been thought that glue-sniffing was a cause of distal RTA [144], but the high rate of excretion of NH_4^+ in response to the metabolic acidosis in many of these patients means that they do not have distal RTA. Some patients may have another reason for a low rate of excretion of NH_4^+ (e.g., a low GFR) so they have two reasons for the metabolic acidosis, excessive overproduction of hippuric acid and a low rate of NH_4^+ excretion. If the GFR is low enough, there may now be a high anion gap in plasma [21].

Treatment of Metabolic Acidosis due to Glue-sniffing

The treatment of toluene inhalation requires that each of these clinical features be addressed. When the inhalation of toluene stops, ultimately the production of hippuric acid will be diminished, but there can be a lag of 1 – 3 days before there is little hippuric acid generation because of the large volume of distribution of toluene [21]. Hypokalemia and ECF volume contraction need to be corrected with the administration of KCl and saline, according to their severity. If metabolic acidosis is particularly severe, consideration should be given to the use of $NaHCO_3$ because there is no anion present in the body that can be metabolized to HCO_3^-. The major caveat to the use of $NaHCO_3$ in this setting is that coexisting K^+ depletion could be severe. Given the risk of a cardiac arrhythmia, the P_K must be raised first to the low 3 range before $NaHCO_3$ is administered because of the concern that $NaHCO_3$ may exacerbate hypokalemia.

Organic Acid Load from the GI Tract (D-lactic Acidosis)

Certain bacteria in the gastrointestinal (GI) tract may convert carbohydrate (cellulose and fructose) into organic acids. The three factors that make this possible are slow GI transit (blind loops, obstruction), change of the normal flora (usually with antibiotic therapy), and the supply of carbohydrate substrate to these bacteria (foods containing fructose or sorbitol [145] (Figure 24, [70]). The most prevalent organic acid is D-lactic acid [71]. Humans metabolize this D-isomer somewhat more slowly than L-lactate, but acidosis per se rarely is life-threatening. Although humans lack the enzyme D-lactate dehydrogenase, metabolism of D-lactate occurs via the enzyme D-2-hydroxy acid dehydrogenase.

There are three additional points that should be noted with respect to D-lactic acidosis. First, the usual clinical laboratory test for lactate is specific for the L-lactate isomer. Hence the usual laboratory measurement for lactate will not be elevated. Second, GI bacteria produce amines, mercaptans, and other compounds that may cause the clinical symptoms related to CNS dysfunction (personality changes, gait changes, confusion, etc.). Third, some of the D-lactate will be lost in the GI tract or in the urine (if the GFR is not too low) [146, 147]. Hence the degree of rise in the plasma anion gap may not be as high as expected for the fall in the P_{HCO3}.

Treatment should be directed at the GI problem. The oral intake of fructose and complex carbohydrates should be decreased. Antacids should be avoided to decrease the rate of fermentation. Insulin may be helpful by lowering the rate of oxidation of fatty acids and hence permit a higher rate of oxidation of organic acids (Figure 25). Antibiotics could be considered to change the bacterial flora.

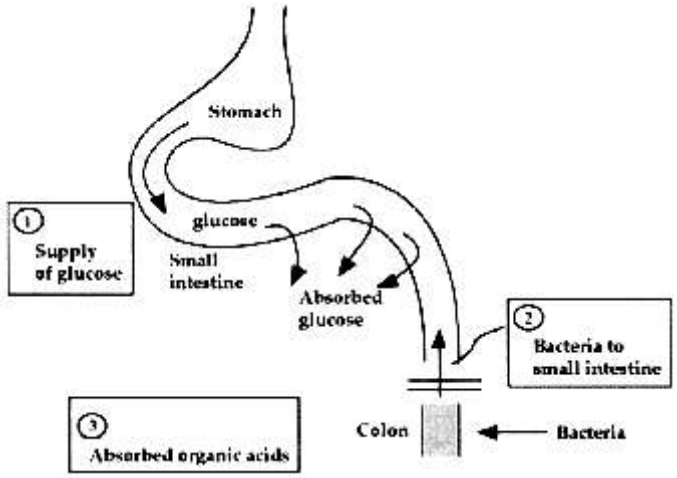

Figure 24. Organic acid production in the GI tract. Bacteria are normally segregated from dietary sugar by GI "geography". For overproduction of D-lactic acid, bacteria in the lower GI tract must mix with sugars. The supply of sugar is critical for organic acid production. Bacteria migrate up to and proliferate in the small intestine. When provided with sugar in this "friendly environment", fermentation produces a variety of organic acids and noxious alcohols, aldehydes and amines; more are produced if more alkali is supplied. There must also be enough mucosal surface area to transport these acids into the body and cause the high plasma anion gap; otherwise the H^+ produced might simply destroy luminal HCO_3^- from the secreted $NaHCO_3$ and lead to the loss of Na^+ plus D-lactate in the stool (a normal anion gap type of metabolic acidosis). The degree of the acidosis also depends on the rate that these organic acids can be oxidized and/or converted to glucose or fat (primarily in the liver).

Pyroglutamic Acidosis

The list of causes of metabolic acidosis with a high anion gap in plasma does not usually include pyroglutamic acidosis (PGA) because it was thought to represent primarily rare inborn errors of metabolism in the glutathione synthesis pathway (defects in 5-oxoprolinase or in glutathione synthetase, Figure 26) [148, 149]. Notwithstanding, there have been an increasing number of case reports where PGA accumulated and caused metabolic acidosis with an increase in the anion gap in plasma [131, 150 – 152]. When plasma levels of PGA rose to the 5 – 10 mM range, the 24-h urine contained 50 – 150 mmol of PGA [131, 150, 151]. The question raised by these observations is, what is responsible for the accumulation of PGA?

Key to the understanding of the accumulation of PGA is the fact that the reduced form of glutathione (GSH) feeds back to inhibit the enzyme (-glutamylcysteine synthetase) that catalyzes the first step in the cycle that leads to the synthesis of glutathione, the conversion of glutamate to -glutamylcysteine (Figure 26) [153].

A major function of reduced glutathione is to detoxify reactive oxygen species (ROS). In this process, the reduced form of GSH is converted to its oxidized form (GS-SG) (Equa-

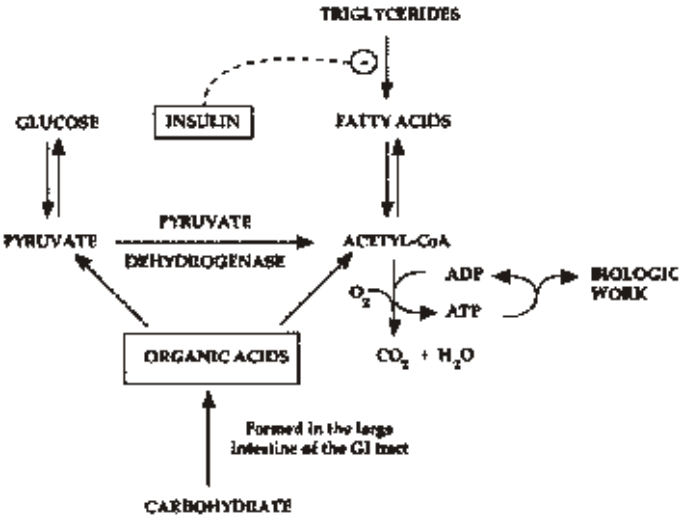

Figure 25. Strategies for therapy in D-lactic acidosis. There are two families of organic acids depending on whether they yield pyruvate or acetyl-CoA, bypassing pyruvate as a metabolic product. Organic anions that cannot be converted to pyruvate can only be oxidized, converted to storage fat, or be converted to ketoacids, but are not substrates for the synthesis of glucose. Fatty acid synthesis only occurs at appreciable rates when insulin levels are high (with meals). If insulin acts and depresses the rate of oxidation of fatty acids, more organic acids may be oxidized [70].

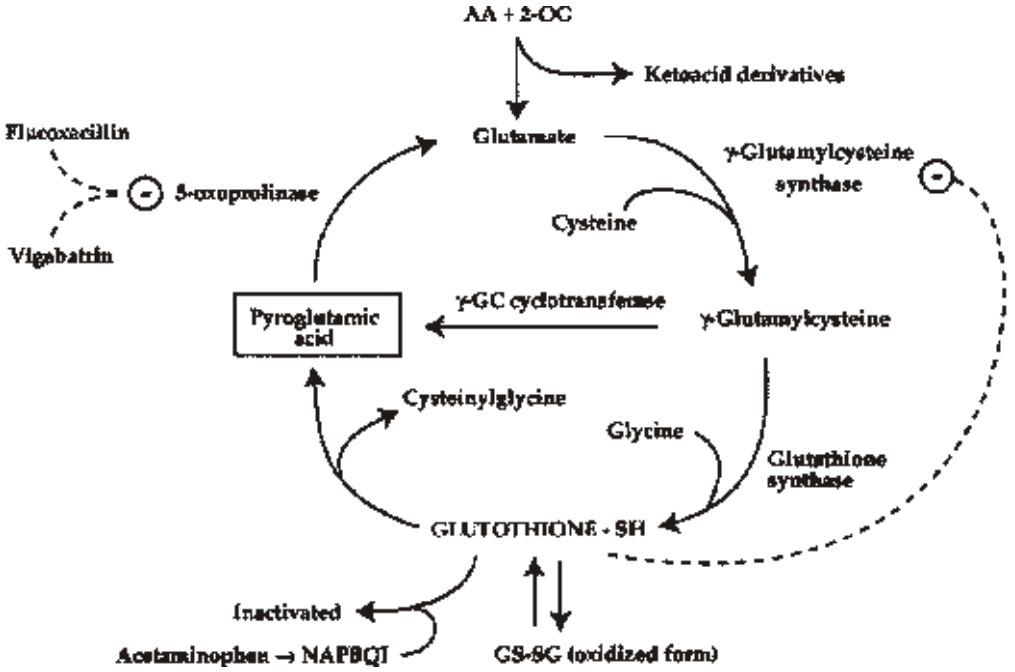

Figure 26. Production of pyroglutamic acid. The pathway begins with glutamate, a key intermediate in transamination reactions. When there are low levels of reduced glutathione (e.g., due to combination with a metabolite of acetaminophen), the production of -glutamylcysteine is stimulated. If the -glutamylcysteine so-formed accumulates, pyroglutamic acid will be formed. In addition, if 5-oxyprolinase is inhibited, pyroglutamic acid will also accumulate. As described in the text, a diminished ability to detoxify ROS is likely to be more important than the acidosis in this setting. Reproduced with permission [187].

tion 13). Hence when ROS accumulate, the concentration of GSH declines and this leads to an accelerated formation of -glutamylcysteine (-GC). This -GC will be converted to PGA by the enzyme -glutamylcysteine cyclotransferase when its concentration rises (Figure 26). Components of the glutathione cycle reside in different compartments of the cell [1]. This adds to the complexity of understanding the regulation of this feedback system.

2 GSH + ROS GS-SG + Inactive ROS (13)

PGA can be synthesized from glutamate when an internal peptide bond forms between its -carboxyl group and the free -amino group (i.e., if glutamate is free or the N-terminal amino acid is a peptide or protein) as long as the latter's -carboxyl group is in an activated state. A number of drugs have been identified as potential causes of PGA acidosis. Some like acetaminophen, after conversion to a metabolite N-acetyl-p-benzoquinonimide (NAPBQI), decrease the concentration of GSH, thereby driving the synthesis of -glutamylcysteine, and thereby PGA (Figure 26). Other drugs (e.g., the antibiotic flucloxacillin [150] and the anticonvulsant, vigabatrin [154]) may inhibit 5-oxoprolinase. A third mode of action could be with drugs or inborn errors of metabolism (e.g., G6PDH deficiency) that result in a diminished concentration of NADPH, the cofactor that reduces GS-SG to GSH [1] (Equation 13).

Acid-base aspects: Applying concept 1 to this pathway, H^+ will only accumulate when the precursor of pyroglutamic acid is glutamine providing that the NH_4^+ so-formed is metabolized to urea in the liver (Equation 14).

Glutamine Glutamate$^-$ + NH_4^+
Pyroglutamate$^-$ + NH_4^+ Urea + H^+ (14)

Renal Acidosis

As described in Table 6, renal disorders may cause metabolic acidosis with either a normal or an increased anion gap in plasma. Most causes have in common a reduced rate of NH_4^+ excretion [56]; in contrast, with a recent onset of proximal RTA, the excretion of HCO_3^- may also contribute to the degree of metabolic acidosis. Whether the plasma anion gap will be elevated or not depends primarily on the GFR. For example, if the GFR is very low, anions such as phosphate and SO_4^{2-} need to have higher concentrations in plasma to be excreted at their usual rate. This in turn leads to a rise in the plasma anion gap (Figure 6), but it does not usually exceed 22 mEq/l or about 10 mEq/l above normal. In this semiquantitative interpretation, it is important to examine the concentration of albumin in plasma because this is the most important constituent of the normal plasma anion gap and hypoalbuminemia is not an uncommon finding in this group of patients. The possible molecular basis for a low rate of excretion of NH_4^+ (Figure 5) or a high rate of excretion of HCO_3^- is shown in Figure 27.

Clinical Approach to a Patient with HCMA

Patients who have HCMA can be divided into three broad categories based on the rate of excretion of components of net acid (Table 18). Our approach to patients with HCMA starts with an assessment of the rate of excretion of NH_4^+ (Figure 28). A low rate of excretion of NH_4^+ is the key finding in patients with distal RTA; it is also expected in patients with proximal RTA and an alkalinized PCT ICF pH. In the latter group, the low rate of excretion of NH_4^+ is usually due to a diminished rate of production of NH_4^+ because of excessive distal delivery of HCO_3^- from the PCT. If an assay of urine NH_4^+ is not available, the

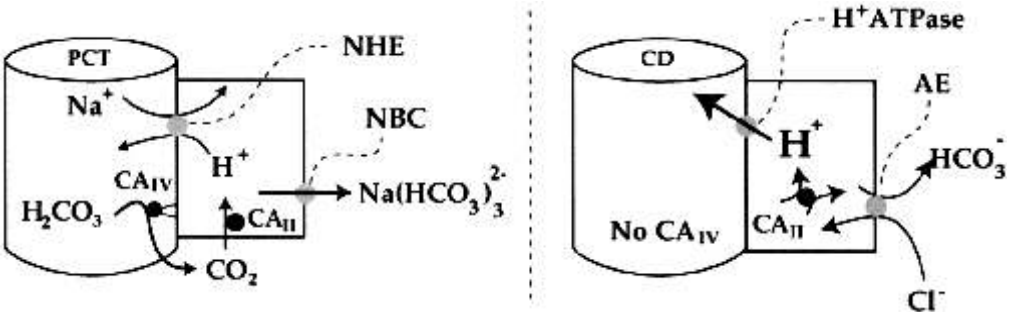

Figure 27. Molecular components for H^+ and HCO_3^- transport in the nephron. The events in the PCT are shown in the left portion of the figure and the events in the collecting duct (CD) are shown in the right portion of the figure. Carbonic anhydrase (CA) is depicted by the small solid circles. Abbreviations: NHE = Na^+/H^+ exchanger in the PCT; NBC = $Na(HCO_3)_3^{2-}$ exit step in the PCT; AE = Cl^-/HCO_3^- anion exchanger.

urine osmolal gap should be used to reflect this excretion rate (Figure 11).

If the rate of excretion of NH_4^+ is high in a patient with HCMA (e.g., overproduction of -hydroxybutyric acid) (Figure 28), a renal component to the acidosis could be present if there is a large loss of the metabolizable -hydroxybutyrate anions in the urine [155]. It should be clear that the main cause of the metabolic acidosis in this patient is overproduction of organic acids; nevertheless, the severity of the acidosis may be aggravated by the presence of a renal lesion that leads to the loss of organic anions (potential HCO_3^-) in the urine. An excessive rate of excretion of organic anions in the urine is suspected if the sum of $Na^+ + K^+ + NH_4^+$ in the urine greatly exceeds that of Cl^- (Figure 11).

In a patient with HCMA and a low rate of excretion of NH_4^+, the basis for low NH_4^+ excretion can be deduced from the urine pH. If the urine pH is greater than 7, one should examine the secretion of H^+ in the PCT (reabsorption of HCO_3^-) and in the distal nephron (Figure 28). We recommend examining the PCO_2 in alkaline urine to detect whether there

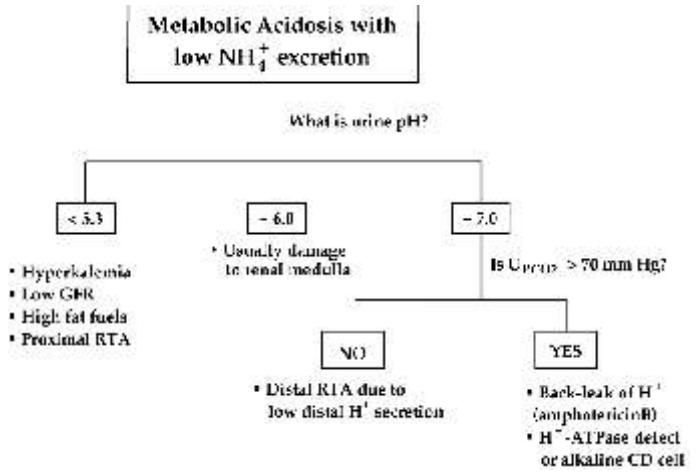

Figure 28. Approach to patients with HCMA. If there is a low rate of excretion of NH_4^+, the urine pH is helpful to determine whether a low distal and/or proximal H^+ secretion or a low NH_3 availability was the cause for the low rate of NH_4^+ excretion.

is a defect in distal H^+ secretion. If urine PCO_2 is < 70 mm Hg, a primary H^+ATPase pump defect or an alkaline -intercalated collecting duct cell pH (e.g., CA_{11} deficiency) should be suspected. This latter lesion also involves the PCT, causing proximal RTA. If urine PCO_2 > 70 mm Hg, suspect a back leak of H^+ from the collecting duct or a defect causing distal HCO_3^- secretion (e.g., a mis-targeted Cl^-/HCO_3^- anion exchange.

HCMA with a low rate of excretion of NH_4^+ and a low value for the urine pH (the actual value is difficult to define precisely, but we consider a low value to be less than 5.3) suggests that there is a reduced availability of NH_4^+/NH_3 in the renal medullary interstitial compartment (Figure 12). The usual causes for the low NH_4^+/NH_3 subgroup are a low GFR or hyperkalemia (Table 18). In their absence, we would look for low levels of glutamine [158], the substrate in plasma for renal ammoniagenesis, and/or a high level of fat-derived fuels (e.g., patients on TPN), because these fuels may compete with glutamine as the source for regeneration of ATP in cells of the PCT [159], and hence lead to a lower rate of production of NH_4^+. Patients with proximal RTA also have a low rate of excretion of NH_4^+. This could be due to an alkaline PCT cell or it could be part of a generalized PCT cell dysfunction (the Panconi syndrome [156, 157]). Both of these groups of patients will have hypercitraturia despite the presence of metabolic acidosis. In the former group, the hypercitraturia is due to an alkaline PCT cell and may disappear if an acid load were administered. In the latter group, the hypercitraturia is part of the generalized PCT cell transport defects.

Loss of $NaHCO_3$ in the Urine

The initial mechanism for the acidosis in patients with proximal RTA is the loss of HCO_3^- in the urine. In contrast, once a steady state supervenes, chronic metabolic acidosis is sustained because the rate of NH_4^+ excretion is much lower than expected in this setting [30, 31]. As mentioned above, these patients will have hypercitraturia despite having metabolic acidosis. The defect in proximal HCO_3^- reabsorption can be demonstrated by finding a FE_{HCO3} that exceeds 10 – 15% during $NaHCO_3$ loading. This, however, need not be performed because the diagnosis is usually evident when large doses of $NaHCO_3$ fail to the P_{HCO3} the normal range. Proximal RTA can occur as an isolated defect [160] or as part of a generalized proximal tubular cell dysfunction (Fanconi's syndrome with a glucosuria, phosphaturia, aminoacidosis, uricosuria and citraturia among others) [156]. The major causes of proximal RTA in adults include increased blood levels of monoclonal immunoglobulins found in patients with multiple myeloma and patients who use the carbonic anhydrase inhibitor, acetazolamide. In contrast, cystinosis [161] and the use of ifosfamide [162] are the most common causes of proximal RTA in children. The hereditary isolated proximal RTA is a rare autosomal recessive disease that can present with ocular abnormalities such as band keratopathy, cataracts and glaucoma [163]. Mutations in the gene encoding for the $Na(HCO_3)_3^{2-}$ cotransporter (NBC1) has been identified in these families. The autosomal dominant form may be caused by mutations in the gene for NHE [164].

Recently, the use of Chinese herbs was described as a cause of the Fanconi's syndrome [165]. Typical Chinese herb nephropathy is associated with acellular interstitial fibrosis and tubular atrophy. Some of these patients

have a profound degree of hypokalemia with muscle paralysis as the presenting feature [166]. Hypokalemia in other causes of the Fanconi's syndrome is usually absent or mild in degree.

The pathological mechanisms of Fanconi's syndrome due to Chinese herb remain unclear. Aristolochic acid found in the Chinese herb has an inhibitory effect on calcium-dependent phospholipase A_2. This may in turn lead to a defect in energy-producing or energy-linked transporting mechanisms and/or have a direct toxic effect on the brush-border membrane of the tubular cells that may cause renal tubule injury with the resultant Fanconi's syndrome.

From a therapeutic standpoint, the acidosis in these patients is usually mild and complications due to the acidosis are minor. These facts alone argue against alkali therapy in adults. In addition, if exogenous $NaHCO_3$ is given, as the P_{HCO3} rises temporarily, but its excretion will also rise markedly. A large increase in delivery of Na^+ and HCO_3^- to the CCD may augment the secretion of K^+ [84], resulting in hypokalemia and possibly nephrocalcinosis. In contrast, alkali therapy is useful in children to prevent growth retardation [167].

Cause of a Low Rate of Excretion of NH_4^+

Renal failure: As the GFR falls, the synthesis of NH_4^+ declines in the PCT due to ATP turnover constraints [33]. Metabolic acidosis is therefore a common finding with advanced renal insufficiency, although the degree of acidosis is variable. It is rarely severe enough to require urgent therapy with $NaHCO_3$. On the other hand, chronic metabolic acidosis may contribute to fatigue and anorexia, and also skeletal muscle wasting [168] and bone disease [169]. Therefore it is reasonable to give oral $NaHCO_3$ to these patients to maintain the P_{HCO3} close to 20 – 25 mM making certain that the Na^+ load does not lead to hypertension or congestive heart failure. With the onset of dialysis therapy, acid-base balance is maintained by the addition of $NaHCO_3$ or a metabolic precursor of HCO_3^- (e.g., acetate, L-lactate) added to the dialysis fluid.

Distal RTA (classical RTA): The hallmark of distal RTA is a low rate of excretion of NH_4^+ in a patient with chronic metabolic acidosis, a normal value for the anion gap in plasma, and a GFR that is not markedly reduced [56]. Having defined these components, the next step is to find out why the rate of excretion of NH_4^+ is lower than expected in this setting. We rely on the urine pH at this point to separate the patients into 3 categories, those with a primary problem with NH_3 availability (urine pH less than 5.3), those where there is a structural lesion in the renal medulla that compromises both medullary NH_3 availability and distal H^+ secretion (urine pH close to 6), and those with a defect in net distal H^+ secretion (urine pH close to 7). In this latter group, the low rate of excretion of NH_4^+ is due primarily to reduced distal H^+ secretion per se and/or to an excessive amount of HCO_3^- delivered to or secreted in the distal nephron (Figure 29). Generalized medullary damage with a urine pH that is close to 6 is the most common clinical subgroup [53]. Autoimmune disorders (such as Sjögren's syndrome and rheumatoid arthritis, hypergammaglobulinemia) are the most common causes of distal RTA with a very high urine pH in adults [56]. RTA in patients with Sjögren's syndrome seems to be due to a defect in H^+ secretion in the distal nephron. In some of these patients, there was an absence of the H^+-ATPase pump in intercalated cells of the collecting tubule as revealed by an immunocytochemical analysis of tissue obtained by renal biopsy [170]. It is not known how the immune injury leads to the loss of

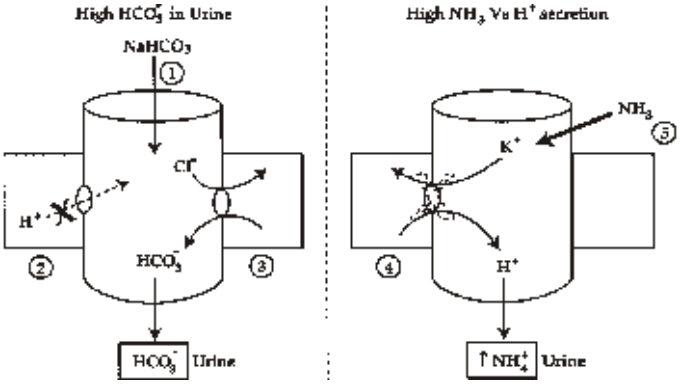

Figure 29. Basis for a high urine pH. There are two subgroups to consider. First, those where the net addition of HCO_3^- by failing to reabsorb $NaHCO_3$ in upstream nephron segments (site 1) or via secretion in the MCD via AE (site 2), exceeds the usual H^+ secretion by the H^+-ATPase in the CCD and MCD (site 2). Second, as shown to the right of the dashed line, those where there is a high medullary NH_3 concentration (due to enhanced PCT production of NH_4^+, site 5) exceeds the secretion of H^+ by the H^+/K^+ ATPase in the MCD (site 4).

H^+-ATPase activity. It has also been suggested that the defect may be due to autoantibodies against carbonic anhydrase II, as high levels of these antibodies were detected in some patients. If these antibodies could enter cells, one would also expect to find a defect in H^+ secretion in the PCT. Ifosfamide, an analog of cyclophosphamide, is also a cause of proximal and distal RTA in both children and adults [162].

Hereditary RTA is most common cause in children [171]. Familial distal RTA is inherited in both dominant and recessive patterns. The autosomal dominant form is associated with mutations in the gene encoding for the AE [172]. Red blood cells of these individuals display normal AE polypeptide abundance. These mutant forms show only a modest reduction in function and do not have a dominant negative effect when expressed in heterologous systems. It is not clear how these mutations lead to the phenotype of distal RTA. In vivo defects in stability, trafficking or sorting of these mutant anion exchangers are possible mechanisms. In Caucasians, AE1 has not been associated with the recessive form of distal RTA; however, AE1 mutations are the major cause of recessive distal RTA in Thailand, Malaysia and Papua New Guinea [173]. In those Southeast Asian patients in whom distal RTA is associated with ovalocytosis, compound heterozygotes of AE1 plus distal RTA mutations with the in-frame deletion ovalocytosis mutation were found [174]. Altered targeting of the mutant AE1 was suggested in one patient with distal RTA and Southeast Asian ovalocytosis because of a high U-B PCO_2 in alkaline urine [175].

Mutations in the gene encoding for the V_1 subunit B1 of the apical membrane vascular H^+-ATPase have been described to cause autosomal recessive distal RTA and bilateral sensorineural hearing loss [176]. Recessive distal RTA without deafness due to mutations in the a V_0 subunit of the H^+-ATPase have also been reported [177]. Mutations in the cytoplasmic carbonic anhydrase II are inherited in autosomal recessive fashion [178]. Patients with this disorder exhibit osteopetrosis, cerebral calcification and defect in H^+ secretion in both the PCT and the distal nephron.

While nephrocalcinosis may be a consequence of distal RTA, hypercalciuria and nephrocalcinosis seem to be the primary events leading to distal RTA in patients with

Dent's disease [179]. Dent's disease is characterized by low molecular weight proteinuria, hyperphosphaturia, hypercalciuria. The ClC-5 chloride channel has been identified as the mutated gene in patients with Dent's disease [180].

RTA with hypokalemia: Distal RTA is often complicated by hypokalemia [181] (the high luminal concentration of HCO_3^- stimulates net secretion of K^+ in the CCD [84], see Chapter on K^+ for more discussion). If distal RTA is present with a severe degree of hypokalemia (P_K < 2 mM), symptoms of muscle weakness or even paralysis might be present [182]. Of greater importance, there is a danger of a cardiac arrhythmia, especially if the EKG is significantly abnormal. Even if the degree of metabolic acidosis is severe, the administration of alkali alone could cause movement of K^+ into cells, worsening the degree of hypokalemia with resultant cardiac effects and/or acute respiratory acidosis. In this circumstance, there is a better strategy for therapy. KCl should be given first; larger amounts can be given safely by the oral or by a nasogastric tube than intravenously providing that the patient can absorb this K^+ load – i.e., that bowel sounds are present. Glucose-containing solutions should be avoided, since they may stimulate insulin release, which may cause an acute shift of K^+ into the cells. Although the addition of K^+-sparing diuretics such as amiloride will reduce the ongoing urine K^+ loss, their quantitative effect is very small and they may provoke hyperkalemia later on; hence we do not recommend their use in this setting. Administration or larger amounts of $NaHCO_3$ should be delayed until the P_K is above 3.0 mM. In the absence of serious hypokalemia, one then asks, how much alkali is required? The answer is not easy to deduce. One must ultimately give enough $NaHCO_3$ to bring the P_{HCO3} to the normal range. Thereafter, the dose of $NaHCO_3$ needed can be deduced. Since the daily normal acid load from the diet is usually about 70 mmol/day [7]. Since urine net acid excretion is usually reduced but not absent, considerably less $NaHCO_3$ is usually required. Supplemental K^+ is often needed as well.

Distal RTA with hyperkalemia: In some classifications, this is called type IV RTA. We do not think that this nomenclature is particularly helpful and prefer a classification that is based on pathophysiology (see reference Kamel et al. 1997 [56] for more discussion). Reduced excretion of NH_4^+ is commonly associated with hyperkalemia [32]. Hyperkalemia leads to reduced excretion of NH_4^+ primarily because it inhibits ammoniagenesis. This subtype of low excretion of NH_4^+ is recognized by finding a low urine pH (usually < 5.3) (Figure 30). A more detailed discussion of hyperkalemia can be found in the Chapter on Potassium in this book.

Therapy depends on the pathogenesis of the hyperkalemia and on the patients' ECF volume status. In patients with hypoaldosteronism due to adrenal disease, ECF volume and blood pressure are usually reduced and al-

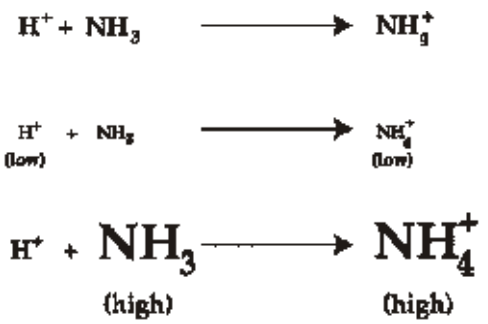

Figure 30. Types of incomplete renal tubular acidosis. The top line depicts the normal state. There are two major causes of a high urine pH. First, there is occult distal RTA due to low distal H^+ secretion in conjunction with the ingestion of a net alkali load (line 2). Second, there is an over-production of NH_4^+ in the PCT due to an acidified PCT cell, the result of a lower activity of the $Na(HCO_3)_3^{2-}$ exit step (see Figure 27).

dosterone replacement with 0.05 – 0.1 mg 9 -fludrocortisone per day plus saline administration is the treatment of choice. Glucocorticoid deficiency, if present, should be corrected. Patients with hyperkalemia due to a faster reabsorption of Cl^- in the CCD are frequently ECF volume expanded and hypertensive (see section on K^+ for more details) [183, 184]. In these patients, 9 -fludrocortisone is of no benefit for the treatment of the hyperkalemia and it may aggravate the degree of Na^+ retention. Additional therapeutic alternatives would include diuretics such as furosemide to increase the excretion of K^+ and Na^+. Correction of hyperkalemia by either mechanism should increase the excretion of NH_4^+ sufficiently to correct the metabolic acidosis.

Incomplete RTA: The cardinal features here are a high urine pH and the absence of acidemia. This persistently alkaline urine pH leads to a high urinary concentration of divalent phosphate and precipitation of Ca phosphate stones (brushite ($CaHPO_4$) stones). There are 3 possible subgroups included in this definition. In the first, a high dietary alkali load is responsible for the high urine pH. The rate of excretion of NH_4^+ is low and citrate excretion is high. The second subgroup of patients may have a high alkali intake plus reduced distal H^+ secretion. This group will have the unique finding of a low urine PCO_2 in alkaline urine. The third subgroup seem to have an acidified PCT pH despite the absence of systemic acidemia [185]. These patients have a high rate of excretion of NH_4^+ relative to their urine pH. Their intracellular acidosis in the PCT should stimulate the production of NH_4^+ and this will lead to a high concentration of NH_3 in the medullary interstitium (Figure 28). Accordingly, this higher delivery of NH_3 as compared the rate of H^+ secretion in the distal nephron will result in a urine pH that is high. Because of an acidified PCT cell pH, these patients have a very low rate of excretion of citrate, which also increases their risk of renal calcium-containing stones.

Respiratory Acid-base Disorders

Control of PCO_2 is important in acid-base physiology. Changes in the arterial PCO_2 result in alterations in the plasma H^+ concentration; far more important, however, is that a change in the venous PCO_2, which reflects the PCO_2 in cells, results in more or less binding of H^+ to intracellular proteins which could change their configuration, and thereby their function (Figure 7). The value for the arterial PCO_2 reflects the concentration of CO_2 in alveolar air required for balance between CO_2 production (metabolism) and CO_2 removal (alveolar ventilation).

CO_2 production: There is a very large production of CO_2 relative to the concentration of CO_2 in the plasma (i.e., 10 mmol of CO_2 are produced per minute, yet the arterial PCO_2 and H_2CO_3 are only 1.2 mmol of CO_2 per liter of blood). The rate of production of CO_2 is determined by the amount of metabolic and mechanical work, and to a lesser extent, the fuels being utilized (oxidation of carbohydrates yields more CO_2 relative to ATP production than does the oxidation of fat-derived fuels [2]).

CO_2 removal (alveolar ventilation): Normal ventilation is mediated by interaction between the central respiratory centers, peripheral chemoreceptors, respiratory muscles, and lung parenchyma. A major clinical task is to consider why ventilation is abnormal; this requires a detailed clinical analysis, but for brevity, it will not be provided here.

Effect of an abnormal PCO_2: With CO_2 accumulation, $H^+ + HCO_3^-$ are produced in equimolar amounts (Equation 3) even though

the P_{HCO3} normally exceeds the concentration of H^+ by close to 10^6-fold. Failure to remove CO_2 at a low enough concentration leads to respiratory acidosis because of the generation of H^+ by displacement of the BBS equilibrium to the left. Excessive ventilation causes a low PCO_2 and this results in respiratory alkalosis via displacement of the equilibrium to the right. In chronic respiratory acidosis, there is an increase in the rate of reabsorption of HCO_3^- by the PCT which results in an elevation in the P_{HCO3} which minimizes the fall in the plasma pH due to the respiratory acidosis; the converse changes occur in chronic respiratory alkalosis. Since these expected values differ in acute and chronic respiratory acid-base disturbances, it is important for the clinician to determine, on clinical grounds, whether the acid-base disturbance is acute or chronic in origin.

Although respiratory acid-base disorders are defined by changes in the arterial PCO_2, important clinical information can also be derived by interpreting the arterial PO_2. The arterial PO_2 is a function of the PO_2 of alveolar air, the diffusion of O_2 across the alveolar capillary membrane, and the degree of unsaturation of venous blood. The alveolar PO_2 is calculated as the inspired PO_2 – 1.25 X the arterial PCO_2. The A-a difference can also clarify whether hypoxemia is due to lung disease or central suppression of ventilation; in the latter case, the A-a difference should be normal. The normal value for the A-a difference depends on age and is up to 15 mmHg, but larger values are seen when more O_2 is extracted from each liter of blood in the capillary.

There are two major types of pulmonary lesions that cause the arterial PO_2 to be substantially lower than that of alveolar air:

– Blood could pass from the pulmonary artery to the pulmonary vein without perfusing alveoli that have a high PO_2 (i.e., a shunt that prevents a good exchange of air). Most lung diseases that cause hypoxemia are numerous small areas of shunting as well as areas of non-ventilated, non-perfused lung; together, these lesions lead to ventilation-perfusion mismatch.
– There might be a barrier to diffusion of O_2 from alveolar air to the capillaries in lungs. The magnitude of the A-a difference is a parameter to be evaluated when trying to decide if a pulmonary condition is improving or worsening.

While the A-a difference is widely used clinically, there are several pitfalls that must be kept in mind:

– For the calculation of the A-a difference, one utilizes the arterial PO_2 that provides a poorer reflection of the content of O_2 than does the O_2 saturation. Thus, the same reduction in O_2 content will have a different impact on the PO_2 at different sites on the oxygen-hemoglobin dissociation curve because this function is sigmoid rather than linear.
– If a fixed volume of venous blood is shunted into arterial blood, the lower its O_2 content, the greater the ultimate fall in arterial PO_2.
– If the cardiac output is lower, but the same volume of blood is shunted from the venous to the arterial side of the circulation as in normal subjects, the decline in arterial PO_2 will now be greater because more O_2 is lost on a per liter of arterial blood basis.
– The PO_2 of inspired air must be known. When patients are receiving O_2 by mask or nasal prongs, the inspired PO_2 may not be known with sufficient accuracy. Therefore, the A-a difference is most useful when patients are breathing room air or are on ventilators with a measured content of inspired PO_2.

– In the calculation of the alveolar PO_2, one must estimate the amount of O_2 removed and replaced by CO_2. To do so, one uses the arterial PCO_2 and assumes an RQ of 0.8. The RQ could be 1 if carbohydrate is the only type of fuel being metabolized and 0.7 with fat as the sole fuel.

Respiratory acidosis, clinical approach: Patients who hypoventilate can be divided into two groups: those who will not breathe appropriately (defective stimulus) and those who cannot breathe appropriately (defective respiratory "equipment"). In addition, patients with a fixed alveolar ventilation (i.e., those on ventilators) develop increased arterial PCO_2 if they have an increased rate of production of CO_2 or an increase in dead space (e.g., pulmonary embolus).

Diagnostic approach: The first step is to decide if the patient has chronic lung disease by the history, physical exam, and available past records. Next, one compares the acid-base status with that expected for that acid-base disorder (Table 4). If a discrepancy exists, a mixed disorder is present. In acute and chronic respiratory acidosis in patients who were previously normal, an empirical linear relationship has been found between the concentration of H^+ and the arterial PCO_2. In essence, there is close to a 3 – 3.5 mM change in the P_{HCO3} for every 10 mmHg parallel change in the arterial PCO_2 and close to a 1 mM change in the P_{HCO3} in acute disorders.

Patients with chronic obstructive pulmonary disease are often on diuretics and may have a coexistent metabolic alkalosis. Because H^+ stimulate ventilation, a lower concentration of H^+ can make the hypoventilation more severe. Interestingly, correction of the metabolic alkalosis in these patients does not result in a large change in their concentration of H^+; instead, there is a significant fall in both the P_{HCO3} and the arterial PCO_2, coupled with an increase in the arterial PO_2. These changes may be associated with a dramatic clinical improvement [186]. It is tempting to speculate that the clinical improvement is due, in part, to the reduction in H^+ buffering on the ICF proteins [4].

Respiratory alkalosis, clinical approach: Respiratory alkalosis is a common abnormality that is often ignored. The mortality rate associated with it in the hospital, which may well be greater than that for respiratory acidosis, reflects the importance of the underlying disease process. One can only be sure that the arterial PCO_2 is low by determining arterial blood gases in most patients. Respiratory alkalosis occurs when the ventilatory removal of CO_2 transiently exceeds its rate of production: thus, both the alveolar and arterial PCO_2 fall. At this lower level of arterial PCO_2, the daily production of CO_2 is then removed by the increased ventilation, which leads to a new steady state. A fall in tissue PCO_2 has an important impact on the concentration of H^+ in the ICF. A decrease in the concentration of H^+ results in back-titration of the protonated ICF proteins which may make these intracellular proteins less positively charged than normal, a change that could lead to altered function. Respiratory alkalosis may result from stimulation of the peripheral chemoreceptors (hypoxia or hypotension), the afferent pulmonary reflexes (intrinsic pulmonary disease), or central stimulation by a host of stimuli. In chronic respiratory alkalosis, there is a temporary small suppression of renal NH_4^+ production and excretion, and the P_{HCO3} falls (H^+ of dietary origin continue to consume HCO_3^- without equivalent renal formation of new HCO_3^-) until the plasma H^+ concentration approaches normal. Chronic respiratory alkalosis is the only acid-base disorder in which a normal plasma concentration of pH might be expected.

References

[1] *Voet D, Voet HG* 1990 Biochemistry. Wiley & Sons, New York

[2] *Halperin ML, Rolleston FS* 1993 Clinical detective stories: a problem-based approach to clinical cases in energy and acid-base metabolism. Portland Press, London

[3] *Steinmetz PR, Andersen OS* 1982 Electrogenic proton transport in epithelial membranes. J Membrane Biol *65:* 155-174

[4] *Vasuvattakul S, Warner LC, Halperin ML* 1992 Quantitative role of the intracellular bicarbonate buffer system in response to an acute acid load. Am J Physiol *262:* R305-R309

[5] *West J* 1989 The 1988 Stevenson Memorial Lecture. Physiological responses to severe hypoxia in man. Can J Physiol Pharmacol *67:* 173-178

[6] *Boron WF* 1992 Cellular buffering and intracellular pH. In: Seldin DW, Giebisch G (eds): The regulation of acid-base balance. Raven Press, New York, pp 33-56

[7] *Halperin ML, Jungas RL* 1983 Metabolic production and renal disposal of hydrogen ions. Kidney Int *24:* 709-713

[8] *Halperin ML* 1989 How much "new" bicarbonate is formed in the distal nephron in the process of net acid excretion? Kidney Int *35:* 1277-1281

[9] *Cheema-Dhadli S, Lin S-H, Halperin ML* 2002 Mechanisms used to dispose of a progressively increasing alkali load in the rat. Am J Physiol *282:* F1049-F1055

[10] *Jungas RL, Halperin ML, Brosnan JT* 1992 Lessons learnt from a quantitative analysis of amino acid oxidation and related gluconeogenesis in man. Physiol Reviews *72:* 419-448

[11] *Lin S-H, Cheema-Dhadli S, Chayaraks S, Chen C-B, Gowrishankar M, Halperin ML* 1998 Physiological role of the potential alkali load in the diet of the rat for acid-base balance. Am J Physiol *274:* F1037-F1044

[12] *Oh MS, Carroll HJ* 1992 Whole body acid-base balance. Contrib Nephrol *100:* 89-104

[13] *Coe FL, Parks JH, Asplin JR* 1992 The pathogenesis and treatment of kidney stones. N Engl J Med *327:* 1141-1152

[14] *Simpson D* 1983 Citrate excretion: a window on renal metabolism. Am J Physiol *244:* F223-F234

[15] *Halperin ML, Kamel KS, Ethier JH, Stinebaugh BJ, Jungas RL* 1992 Biochemistry and physiology of ammonium excretion. In: Seldin D, Giebisch G (eds): The Kidney. Physiology and Pathophysiology. Raven Press, New York, pp 1471-1490

[16] *Halperin ML, Cherney DZI, Kamel KS* 2002 Ketoacidosis. In: DuBose TD Jr, Hamm LL (eds): Acid-base and electrolyte disorders: a companion to brenner and rector's. The Kidney. WB Saunders, Philadelphia, pp 67-82

[17] *Kassirer JP, Schwartz WB* 1966 The response of normal man to selective depletion of hydrochloric acid. Am J Med *40:* 10-18

[18] *Scheich A, Donnelly S, Cheema-Dhadli S, Schweigert M, Vasuvattakul S, Halperin ML* 1994 Does saline "correct" the abnormal mass balance in metabolic alkalosis associated with chloride-depletion in the rat? Clin Invest Med *17:* 448-460

[19] *Van Leeuven A* 1969 Net cation equivalency ("base binding power") of the proteins. Acta Med Scand *422:* 36-57

[20] *Halperin ML, Vasuvattakul S, Bayoumi A* 1992 A modified classification of metabolic acidosis: a pathophysiologic approach. Nephron *60:* 129-133

[21] *Carlisle EJF, Donnelly SM, Vasuvattakul S, Kamel KS, Tobe S, Halperin ML* 1991 Glue-sniffing and distal renal tubular acidosis: sticking to the facts. J Am Soc Nephrol *1:* 1019-1027

[22] *Shafiee MA, Kamel KS, Halperin ML* 2002 A conceptual approach to the patient with metabolic acidosis: application to a patient with diabetic ketoacidosis. Nephron *92S1:* 46-55

[23] *Juel C, Halestrap AP* 1999 Lactate transport in skeletal muscle – role and regulation of the monocarboxylate transporter. J Physiol *517:* 633-642

[24] *Soleimani M, Singh G* 1995 Physiologic and molecular aspects of the Na^+/H^+ exchangers in health and disease processes. J Invest Med *43:* 419-430

[25] *Alper S* 1991 The band 3-related anion exchanger (AE) gene family. Ann Rev Physiol *53:* 549-564

[26] *Nilius B, Droogmans G* 2003 Amazing chloride channels: an overview. Acta Physiol Scand *177:* 119-147

[27] *DeMars C, Hollister K, Tomassoni A, Himmelfarb J, Halperin ML* 2001 Citric acidosis: a life-threatening cause of metabolic acidosis. Ann Emerg Med *38:* 588-591

[28] *Madias NE, Adrogue HJ, Horowitz GL, Cohen JJ, Schwartz WB* 1979 A redefinition of normal acid-base equilibrium in man: carbon dioxide tension as a key determinant of normal plasma bicarbonate concentration. Kidney Int *16:* 612-618

[29] *Kamel KS, Richardson RMA, Goguen JM, Fine A, Levin A, Halperin ML* 1993 Rate of production of carbon dioxide in patients with a severe degree of metabolic acidosis. Nephron *64:* 514-517

[30] *Madison LL, Seldin DW* 1958 Ammonia excretion and renal enzymatic adaptation in human subjects, as disclosed by administration of precursor amino acids. J Clin Invest *37:* 1615-1627

[31] *Simpson D* 1971 Control of hydrogen ion homeostasis and renal acidosis. Medicine *50:* 503-541

[32] *Tannen RL* 1987 Effect of potassium on renal acidification and acid-base homeostasis. Seminars Nephrol *7:* 263-273

[33] *Halperin ML, Jungas RL, Pichette C, Goldstein MB* 1982 A quantitative analysis of renal ammoniagenesis and energy balance: a theoretical approach. Can J Physiol Pharmacol *60:* 1431-1435

[34] *Mandel L, Balaban R* 1981 Stoichiometry and coupling of active transport to oxidative metabolism in epithelial tissues. Am J Physiol *240:* F357-F371

[35] *Marliss EB, Aoki TT, Pozefsky T, Most AS, Cahill GFJ* 1971 Muscle and splanchnic glutamine and glutamate metabolism in post-absorptive and starved man. J Clin Invest *50:* 814-817

[36] *Lemieux G, Vinay P, Robitaille P, Plante G, Lussier Y, Martin P* 1971 The effect of ketone bodies on renal ammoniagenesis. J Clin Invest *50:* 1781-1791

[37] *Halperin ML, Kamel KS, Ethier JH, Magner PO* 1989 What is the underlying defect in patients with isolated, proximal renal tubular acidosis? Am J Nephrol *9:* 265-268

[38] *Nagami GT* 2000 Renal ammonia production and excretion. In: Seldin DW, Giebisch G (eds): The Kidney. Physiology & Pathophysiology. WB Saunders, Philadelphia PA, pp 1995-2014

[39] *Knepper MA, Packer R, Good DW* 1989 Ammonium transport in the kidney. Physiol Rev *69:* 179-249

[40] *Kamel KS, Halperin ML* 2003 Dogmas and controversies in the handling of nitrogenous wastes. J Exp Biol *2:* 2003-2010

[41] *Pitts RF* 1964 Renal production and excretion of ammonia. Am J Med *36:* 720-742

[42] *Al-Awqati Q, Norby LH, Mueller A, Steinmetz PR* 1976 Characteristics of stimulation of H^+ transport by aldosterone in turtle urinary bladder. J Clin Invest *58:* 351-358

[43] *Bengele HH, Schwartz JH, McNamara ER, Alexander EA* 1986 Chronic metabolic acidosis augments acidification along the inner medullary collecting duct. Am J Physiol *250:* F690-F694

[44] *Wingo CS, Armitage FE* 1993 Potassium transport in the kidney: regulation and physiologic relevance of H^+, K^+-ATPase. Semin Nephrol *13:* 213-224

[45] *Coe FL, Parks JH* 2000 Pathogenesis and treatment of nephrolithiasis. In: Seldin DW, Giebisch G (eds): The Kidney. Physiology & Pathophysiology. Lippincott, Philadelphia PA, pp 1841-1867

[46] *Kamel KS, Lin S-H, Cheema-Dhadli S, Marliss EB, Halperin ML* 1998 Prolonged total fasting: a feast for the integrative physiologist. Kidney Int *53:* 531-539

[47] *Asplin JR* 1996 Uric acid stones. Semin Nephrol *16:* 412-424

[48] *Kamel KS, Cheema-Dhadli S, Halperin ML* 2002 Studies on the pathophysiology of the low urine pH in patients with uric acid stones. Kidney Int *61:* 988-994

[49] *Bushinsky DA* 1999 Calcium, magnesium, and phosphorus: renal handling and urinary excretion. In: Favus M (ed): Primer on the metabolic bone diseases and disorders of mineral metabolism. Lippencott, Philadelphia, pp 67-74

[50] *Parks JH, Coward M, Coe FL* 1997 Correspondence between stone composition and urine supersaturation in nephrolithiasis. Kidney Int *51:* 894-900

[51] *Coe FL, Margolis HC, Deutsch LH, Strauss AL* 1980 Urinary macromolecular crystal growth inhibitors in calcium urolithiasis. Miner Electrolyte Metab *3:* 268-275

[52] *Cockcroft DW, Gault MH* 1976 Prediction of creatinine clearance from serum creatinine. Nephron *16:* 31-41

[53] *Wrong O* 1991 Distal renal tubular acidosis: the value of urinary pH, PCO_2 and NH_4^+ measurements. Pediatr Nephrol *5:* 249-255

[54] *Carlisle EJF, Donnelly SM, Halperin ML* 1991 Renal tubular acidosis (RTA): recognize the ammonium defect and pHorget the urine pH. Pediatr Nephrol *5:* 242-248

[55] *Batlle DC, Arruda JAL, Kurtzman NL* 1981 Hyperkalemic distal renal tubular acidosis associated with obstructive uropathy. N Engl J Med *304:* 373-380

[56] *Kamel KS, Briceno LF, Santos MI, Brenes L, Yorgin P, Kooh SW, Balfe JW, Halperin ML* 1997 A new classification for renal defects in net acid excretion. Am J Kidney Dis *29:* 126-136

[57] *Kurtzman NA* 1987 Renal tubular acidosis: a constellation of syndromes. Hosp Prac *22:* 131

[58] *Vasuvattakul S, Gougoux A, Halperin ML* 1993 A method to evaluate renal ammoniagenesis in vivo. Clin Invest Med *16:* 265-273

[59] *Brenes LG, Sanchez MI* 1993 Impaired urinary ammonium excretion in patients with isolated proximal renal tubular acidosis. J Am Soc Nephrol *4:* 1073-1078

[60] *Morris RC Jr* 1969 Renal tubular acidosis. Mechanisms, classification and implications. N Engl J Med *281:* 1405-1413

[61] *Pitts RF, Lotspeich WD* 1946 Bicarbonate and the renal regulation of acid-base balance. Am J Physiol *147:* 138-154

[62] *Edelman C Jr, Soriano J, Boichis H, Gruskin A, Acosta M* 1967 Renal bicarbonate reabsorption and hydrogen ion excretion in normal infants. J Clin Invest *46:* 1309-1317

[63] *Dedmond RE, Wrong O* 1962 The excretion of organic anion in renal tubular acidosis with particular reference to citrate. Clin Sci *22:* 19-32

[64] *Norman ME, Feldman NI, Cohn RM, Roth KS, McCurdy DK* 1978 Urinary citrate excretion in the diagnosis of distal renal tubular acidosis. J Pediatrics *92:* 394-400

[65] *Donnelly S, Brenes L, Halperin ML* 1991 Isolated proximal renal tubular acidosis: dissociation of cellular and systemic pH. J Am Soc Nephrol *2:* 279

[66] *Halperin ML, Goldstein MB, Haig A, Johnson MD, Stinebaugh BJ* 1974 Studies on the pathogenesis of type I (distal) renal tubular acidosis as revealed by the urinary PCO_2 tensions. J Clin Invest *53:* 669-677

[67] *Berliner RW, DuBose TDJ* 1992 Carbon dioxide tension of alkaline urine. In: Seldin DW, Giebisch G (eds): The Kidney. Physiology and Pathophysiology. Raven Press, New York, pp 2681-2694

[68] *Halperin ML, Kamel KS* 2000 Dynamic interactions between integrative physiology and molecular medicine: the key to understand the mechanism of action of aldosterone in the kidney. Can J Physiol Pharmacol *78:* 587-594

[69] *Napolova O, Urbach S, Davids MR, Halperin ML* 2003 How to assess the degree of extracellular fluid volume contraction in a patient with a severe degree of hyperglycemia. Nephrol Dial Trans *18:* 2674-2677

[70] *Halperin ML, Kamel KS* 1996 Turning sugar into acids in the gastrointestinal tract. Kidney Int *49:* 1-8

[71] *Oh MS, Phelps KR, Traube M, Carroll HJ* 1979 D-lactic acidosis in a man with the short bowel syndrome. N Engl J Med *301:* 249-251

[72] *Kamel KS, Ethier JH, Stinebaugh BJ, Schloeder FX, Halperin ML* 1990 The removal of an inorganic acid load in subjects with ketoacidosis of chronic fasting: the role of the kidney. Kidney Int *38:* 507-511

[73] *Zierler K, Rabinowitz D* 1963 Effect of very small concentrations of insulin on forearm metabolism: persistence of its action on potassium and free fatty acids without its effect on glucose. J Clin Invest *43:* 950-962

[74] *Williamson JR, Safer B, Rich T, Schaffer S, Koyabashi K* 1976 Effects of acidosis on myocardial contractility and metabolism. Acta Med Scand *587:* 95-111

[75] *Nahas GG, Zaguy D, Milhard A* 1967 Acidemia and catecholamine output of the isolated canine adrenal gland. Am J Physiol *213:* 1186-1192

[76] *Mazer CD, Naser B, Kamel KS* 1996 Effect of alkali therapy with $NaHCO_3$ or Tham on cardiac contractility. Am J Physiol *270:* R955-R962

[77] *Halperin ML, Halperin FA, Cheema-Dhadli S, Kamel KS* 1994 Rationale for the use of sodium bicarbonate in a patient with lactic acidosis due to a poor cardiac output. Nephron *66:* 258-261

[78] *Kamel KS* 1996 The acute impact of $NaHCO_3$ in treatment of metabolic acidosis on back-titration of non-bicarbonate buffers: a quantitative analysis. Clin Nephrology *45:* 51-55

[79] *Cooper JD, Walley KR, Wiggs BR, Russell JA* 1990 Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. Ann Intern Med *112:* 492-498

[80] *Butler AM, Talbot NB, Burnett CH, Stanbury JB, MacLachlan EA* 1947 Metabolic studies in diabetic coma. Trans Assoc Am Phys *60:* 102-109

[81] *Danowski T, Peters J, Rathbun J, Quashnock J, Greenman L* 1949 Studies in diabetic acidosis and coma, with particular emphasis on the retention of administered potassium. J Clin Invest *28:* 1-9

[82] *Nabarro J, Spencer A, Stowers J* 1952 Metabolic studies in severe diabetic ketosis. Q J Med *82:* 225-243

[83] *Robin ED* 1972 Dynamic aspects of metabolic acid base disturbances: phenformin lactic acidosis with alkaline overshoot. Trans Amer Assoc Physiol *85:* 317-324

[84] *Carlisle E, Donnelly S, Ethier J, Quaggin S, Kaiser U, Kamel K, Halperin ML* 1991 Modulation of the secretion of potassium by accompanying anions in humans. Kidney Int *39:* 1206-1212

[85] *Schreiber M, Kamel KS, Cheema-Dhadli S, Halperin ML* 1994 Ketoacidosis: an integrative view. Diabetes Rev *2:* 98-114

[86] *Flatt JP* 1972 On the maximal possible rate of ketogenesis. Diabetes *21:* 50-53

[87] *Halperin ML, Goguen JM, Scheich AM, Kamel KS* 1993 Clinical consequences of hyperglycemia and its correction. In: Seldin DW, Giebisch G (eds): Clinical disturbances of water metabolism. Raven Press, New York, pp 249-272

[88] *Adrogue HH, Eiknoyan G, Suki WN* 1984 Diabetic ketoacidosis. Role of the kidney in the acid-base homeostasis re-evaluated. Kidney Int *25:* 591-598

[89] *Davids MR, Lin S-H, Edoute Y, Cheema-Dhadli S, Halperin ML* 2002 Hyponatremia and hypergly-

cemia during laparoscopic surgery. Quart J Med *95:* 321-330

[90] *Hillier TA, Abbott RD, Barrett EJ* 1999 Hyponatremia: evaluating the correction factor for hyperglycemia. Am J Med *106:* 399-403

[91] *Katz MA* 1973 Hyperglycemia-induced hyponatremia: calculation of expected serum sodium depression. N Engl J Med *289:* 843-844

[92] *Roscoe JM, Halperin ML, Rolleston FS, Goldstein MB* 1975 Hyperglycemia-induced hyponatremia: metabolic considerations in calculation of serum sodium depression. CMA J *112:* 452-453

[93] *Carlotti A, Bohn D, Halperin ML* 2003 Importance of timing of risk factors for cerebral edema during therapy for diabetic ketoacidosis. Arch Dis Child *88:* 170-173

[94] *Beigelman P* 1973 Potassium in severe diabetic ketoacidosis. Am J Med *54:* 419-420

[95] *Oh MS, Carroll HJ, Uribarri J* 1990 Mechanism of normochloremic and hyperchloremic acidosis in diabetic ketoacidosis. Nephron *54:* 1-6

[96] *Halperin ML, Bear RA, Hannaford MC, Goldstein MB* 1981 Selected aspects of the pathophysiology of metabolic acidosis in diabetes mellitus. Diabetes *30:* 781-787

[97] *Molitch ME, Rodman E, Hirsch CA, Dubinsky E* 1980 Spurious serum creatinine elevations in ketoacidosis. Ann Int Med *93:* 280-281

[98] *Gerrard S, Khayam-Bashi H* 1984 Negative interference with the Ektachem (Kodak) enzymic assay for creatinine by high serum glucose. Clin Chem *30:* 1884 (letter)

[99] *Edge JA* 2000 Cerebral edema during treatment of diabetic ketoacidosis: are we any nearer finding a cause? Diabetes Metab Res Rev *16:* 316-324

[100] *Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, Kaufman F, Quayle K, Roback M, Malley R, Kuppermann N* 2001 Risk factors for cerebral edema in children with diabetic ketoacidosis. N Engl J Med *344:* 264-269

[101] *Chung HM, Kluge R, Schrier RW* 1987 Clinical assessment of extracellular fluid volume in hyponatremia. Am J Med *83:* 905-908

[102] *McCance RA* 1936 Medical problems in mineral metabolism. III. Experimental human salt deficiency. Lancet *230:* 823-830

[103] *McGee S, Abernethy WB, Simel DL* 1999 Is this patient hypovolemic? J Am Med Ass *17:* 1022-1029

[104] *West M, Marsden P, Singer G, Halperin M*L 1986 A quantitative analysis of glucose loss during acute therapy for the hyperglycemia hyperosmolar syndrome. Diabetes Care *9:* 465-471

[105] *Van der Meulen JA, Klip A, Grinstein S* 1987 Possible mechanism for cerebral edema in diabetic ketoacidosis. Lancet *1:* 306-308

[106] *Durr JA, Hoffman WH, Sklar AH, Gammal TE, Steinhart CM* 1992 Correlates of brain edema in uncontrolled IDDM. Diabetes *41:* 627-632

[107] *Hoffman WH, Steinhart CM, Gammal TE, Steele S, Cuadrado AR, Morse PK* 1988 Cranial CT in children and adolescents with diabetic ketoacidosis. Am J Neuroradiol *9:* 733-739

[108] *Hoffman WH, Pluta RM, Fisher AQ, Wagner MB, Yanovski JA* 1995 Transcranial Doppler ultrasound assessment of intracranial hemodynamics in children with diabetic ketoacidosis. J Clin Ultrasound *23:* 517-523

[109] *Kamel KS, Cheema-Dhadli S, Halperin FA, Vasudevan S, Halperin ML* 1996 Anion gap: do the anions restricted to the intravascular space have modifications in their valence? Nephron *73:* 382-389

[110] *Silver SM, Clark EC, Schroeder BM, Sterns RH* 1997 Pathogenesis of cerebral edema after treatment of diabetic ketoacidosis. Kidney Int *51:* 1237-1244

[111] *Mahoney CP, Vlcek BW, DelAguila M* 1999 Risk factors for developing brain herniation during diabetic ketoacidosis. Pediatr Neurol *21:* 721-727

[112] *Porzio P, Halberthal M, Bohn D, Halperin ML* 2000 Design of a treatment for acute symptomatic hyponatremia: ensuring the excretion of a predictable amount of electrolyte-free water. Critical Care Med *28:* 1905-1910

[113] *Halperin ML, Hammeke M, Josse RG, Jungas RL* 1983 Metabolic acidosis in the alcoholic: a pathophysiologic approach. Metabolism *32:* 308-315

[114] *Wrenn KD, Slovis CM, Minion GE, Rutkowski R* 1991 The syndrome of alcoholic ketoacidosis. Am J Med *91:* 119-128

[115] *Porte DJ* 1969 Sympathetic regulation of insulin secretion. Arch Intern Med *123:* 252-260

[116] *Marliss EB, Ohman JL, Aoki TT* 1970 Altered redox state obscuring ketoacidosis in diabetic patients with lactic acidosis. N Engl J Med *283:* 978

[117] *Cohen RD, Woods HF* 1976 Type A lactic acidosis. In: Cohen RD, Woods HF (eds): Clinical and biochemical aspects of lactic acidosis. Blackwell, Oxford, pp 77-91

[118] *Jackson DC* 2002 Hibernating without oxigen: physiological adaptations of the painted turtle. J Physiol *543:* 731-737

[119] *Hallas J* 1987 The association between calcium and acetoacetate, 3-hydroxybutyrate, pyruvate and lactate as determined by potentiometry. Scan J Clin Lab Invest *47:* 581-585

[120] *Urban P, Scheidegger D, Buchmann B, Barth D* 1988 Cardiac arrest and blood ionized calcium levels. Ann Int Med *109:* 110-113

[121] *Marks AR* 2003 Calcium and the heart: a question of life and death. J Clin Invest *111:* 597-600

[122] *Veech R, Fowler R* 1987 Cerebral dysfunction and respiratory alkalosis during peritoneal dialysis with D-lactate-containing dialysis fluids. Am J Med *82:* 572-573

[123] *Stacpoole PW, Harman EM, Curry SH, Baumgartner TG, Misbin RI* 1983 Treatment of lactic acidosis with dichloroacetate. N Engl J Med *309:* 390-396

[124] *Kamel KS, Cheema-Dhadli S, Halperin ML* 1993 Is accelerated oxidation of lactate required for dichloroacetate to lower the level of lactate in blood? Can J Physiol Pharm *71:* 1477-1482

[125] *Stacpoole PW, Wright EC, Baumgartner TG, Bersin RM, Buchalter S, Curry SH, Duncan CA, Harman EM, Henderson GN, Jenkinson S, Lachin JM, Lorenz A, Schneider SH, Siegel JH, Summer WR, Thompson D, Wolfe CL, Zorovich B* 1992 A controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. N Engl J Med *327:* 1564-1569

[126] *Fields ALA, Wolman SL, Halperin ML* 1981 Chronic lactic acidosis in a patient with cancer: therapy and metabolic consequences. Cancer *47:* 2026-2029

[127] *Randle PJ* 1986 Fuel selection in animals. Biochem Soc Trans *14:* 799-806

[128] *Misbin RI* 1977 Phenformin-associated lactic acidosis: pathogenesis and treatment. Ann Intern Med *87:* 591-595

[128b]*Salpeter SR, Greyber E, Pasternak GA, Salpeter EE* 2003 Risk of fatal and nonfatal lactic acidosis with meformin use in type 2 diabetes mellitus: systematic review and meta-analysis. Arch Int Med *163:* 2594-2602

[129] *Gopinath R, Hutcheson M, Cheema-Dhadli S, Halperin ML* 1992 Chronic lactic acidosis in a patient with acquired immunodeficiency syndrome and mitochondrial myopathy: biochemical studies. J Am Soc Nephrol *3:* 1212-1219

[130] *Pinto J, Huang YP, Rivlin RS* 1981 Inhibition of riboflavin metabolism in rat tissues by chlorpromazine, imipramine, and amitriptyline. J Clin Invest *67:* 1500-1506

[131] *Pitt JJ, Hauser S* 1998 Transient 5-oxoprolinuria and high anion gap metabolic acidosis: clinical and biochemical findings in eleven subjects. Clin Chem *44:* 1497-1503

[132] *Fouty B, Frerman F, Reves R* 1998 Riboflavin to treat nucleoside analogue-inducing lactic acidosis. Lancet *352:* 291-292

[133] *Luzzati R, Del Bravo P, Di Perri G, Luzzani A, Concia E* 1999 Riboflavine and severe lactic acidosis. Lancet *353:* 901-902

[134] *Oh MS, Halperin ML* 2003 Toxin-induced metabolic acidosis. In: Madias N, Addrogue H (eds): (in press)

[135] *Chin L, Sievers ML, Herrier RN, Picchioni AL* 1979 Convulsions as the etiology of lactic acidosis in acute isoniazid toxicity dogs. Toxicol Appl Pharmacol *49:* 377-384

[136] *Black LE, Ros SP* 1989 Complete recovery from severe metabolic acidosis associated with isoniazid poisoning in a young boy. Pediatr Emerg Care *5:* 257-258

[137] *Brent J, Vo N, Kulig K, Rumack BH* 1990 Reversal of prolonged isoniazid-induced coma by pyridoxine. Arch Intern Med *150:* 1751-1753

[138] *Alvarez FG, Guntupalli KK* 1995 Isoniazid overdose: four case reports and review of the literature. Intensive Care Med *21:* 641-644

[139] *Jacobsen D, Bredesen JE, Eide I, Ostborg J* 1982 Anion and osmolal gaps in the diagnosis of methanol and ethylene glycol poisoning. Acta Med Scand *212:* 17-23

[140] *Cheema-Dhadli S, Halperin FA, Sonnenberg K, MacMillan V, Halperin ML* 1988 Regulation of ethanol metabolism in the rat. Can J Biochem Cell Biol *65:* 458-466

[141] *Emmett M, Seldin DW* 1989 Overproduction acidosis: salicylate poisoning. In: Seldin DW, Geibisch G (eds): The regulation of acid-base balance. Raven Press, New York, pp 418-420

[142] *Bayoumi A, Campbell P, Schreiber M, Cheema-Dhadli S, Halperin ML* 1993 Towards a more rational treatment of aspirin (ASA) overdose. J Am Soc Nephrol *3:* 293

[143] *Sweeney KR, Chapron DJ, Brandt JL* 1986 Toxic interaction between acetazolamide and salicylate: case reports and a pharmacokinetic explanation. Clin Pharm Ther *40:* 518-524

[144] *Taher SM, Anderson RJ, McCartney R, Popovtzer MM, Schrier RW* 1974 Renal tubular acidosis associated with toluene "sniffing". N Engl J Med *290:* 765-768

[145] *Mishkin B, Mishkin D, Mishkin S* 2002 Natural gas: myths and facts. Canadian J CME *14*: 85-92

[146] *Oh MS, Uribarri J, Alveranga D, Lazar I, Bazilinski N, Carroll HJ* 1985 Metabolic utilization and renal handling of D-lactate in men. Metabolism *34:* 621-625

[147] *Fine A* 1989 Metabolism of D-lactate in the dog and in man. Perit Dial Int *9:* 99

[148] *Al-Jishi E, Meyer BF, Rashed MS, Al-Essa M, Al-Hamed MH, Sakati N, Sanjad S, Ozand PT, Kambouris M* 1999 Clinical, biochemical, and molecular characterization of patients with glutathione synthetase deficiency. Clin Genet *55:* 444-449

[149] *Dahl N, Pigg M, Ristoff E, Gali R, Carisson B, Mannervik B, Larsson A, Board P* 1997 Missense mutations in the human glutathione synthetase gene result in severe metabolic acidosis, 5-oxoprolinuria, hemolytic anemia and neurological dysfunction. Human Molecular Genetics *6:* 1147-1152

[150] *Croal BL, Glen ACA, Kelly CJG, Logan RW* 1998 Transient 5-oxoprolinuria (pyroglutamic aciduria) with systemic acidosis in an adult receiving antibiotic therapy. Clin Chem *44:* 336-340

[151] *Dempsey GA, Lyall HJ, Corke CF, Scheinkestel CD* 2000 Pyroglutamic acidemia: a cause of high anion gap metabolic acidosis. Crit Care Med *28:* 1803-1807

[152] *Yale SH, Mazza JJ* 2000 Anion gap acidosis associated with acetaminophen. Ann Int Med *133:* 752-753

[153] *Richman PG, Meister A* 1975 Regulation of - glutamyl-cysteine snthetase by glutathione. J Biol Chem *250:* 1422-1426

[154] *Bonham JR, Rattenbury JM, Meeks A, Pollitt RJ* 1989 Pyroglutamic aciduria from vigabatrin. Lancet *I:* 1452-1453

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

[156] *Bergeron M, Gougoux A, Vinay P* 1989 The Renal Fanconi Syndrome. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds): Metabolic basis of inherited disease. Raven Press, New York, pp 2569-2580

[157] *Breitschwerdt EB, Ochoa R, Waltman C* 1983 Multiple endocrine abnormalities in Basenji dogs with renal tubular dysfunction. JAMA *182:* 1348-1353

[158] *Halperin ML, Chen CB* 1987 Plasma glutamine and renal ammoniagenesis in dogs with chronic metabolic acidosis. Am J Physiol *252:* F474-F479

[159] *Halperin ML, Ethier JH, Kamel KS* 1989 Ammonium excretion in chronic metabolic acidosis: risks and benefits. Am J Kidney Dis *9:* 265-268

[160] *Brenes LG, Brenes JN, Hernandez MM* 1977 Familial proximal renal tubular acidosis: a distinct clinical entity. Am J Med *63:* 244-252

[161] *Gahl WA, Thoene JG, Schneider JA, O'Regan S, Kaiser-Kupfer MI, Kuwabara T* 1988 NIH conference, cystinosis: progress in a prototypic disease. Ann Intern Med *109:* 557-569

[162] *Skinner R, Pearson AD, English MW, Price L, Wyllie RA, Coulthard MG, Craft AW* 1996 Risk factors for ifosfamide nephrotoxicity in children. Lancet *31:* 578-580

[163] *Igarashi T, Inatomi J, Sekine T, Seki G, Shimadzu M, Tozowa F, Takeshima Y, Takumi T, Takahashi T, Yoshikawa N, Nakamura H, Endou H* 2001 Novel nonsense mutation in the Na^+/HCO_3^- cotransporter gene (SLC4A4) in a patient with permanent isolated proximal renal tubular acidosis and bilateral glaucoma. J Am Soc Nephrol *12:* 713-718

[164] *Igarashi T, Sekine T, Inatomi J, Seki G* 2002 Unraveling the molecular pathogenesis of isolated promixal renal tubular acidosis. J Am Soc Nephrol *13:* 2171-2177

[165] *Vanherweghem JL, Depierreux M, Tielemans C, Abramowicz D, Dratwa M, Jadou M, Richard C, Vandervelde D, Verbeelen D, Vanhaelen-Fastre R* 1993 Rapidly progressive interstitial renal fibrosis in young women: association with slimming regimen including Chinese herbs. Lancet *341:* 387-391

[166] *Lin Y-F, Lin S-H, Tsai W-S, Davids MR, Halperin ML* 2002 Severe hypokalemia in a Chinese male. Q J Med *95:* 695-704

[167] *McSherry E, Morris RCJ* 1978 Attainment and maintenance of normal stature with alkali therapy in infants and children with classic renal tubular acidosis. J Clin Invest *61:* 509-527

[168] *Greiber S, Mitch WE* 1992 Catabolism in uremia: metabolic acidosis and activation of specific pathways. Contrib Nephrol *98:* 20-27

[169] *Bushinsky DA* 1994 Acidosis and bone. Min Electrol Met *20:* 40-52

[170] *Cohen EP, Bastini B, Cohen MR, Kolner S, Hemken P, Gluck S* 1992 Absence of H^+ATPase in cortical collecting tubules of a patient with Sjögren's syndrome and distal renal tubular acidosis. JASN *3:* 264-271

[171] *Alper SL* 2002 Genetic diseases of acid-base transporters. Annu Rev Physiol *64:* 899-923

[172] *Karet FE, Gainza FJ, Gyory AZ, Unwin RJ, Wrong O* 1998 Mutations in the chloride-bicarbonate exchanger gene AE1 cause autosomal dominant but not autosomal recessive distal renal tubular acidosis. Proc Natl Acad Sci USA *95:* 6337-6342

[173] *Bruce LJ, Cope DL, Jones JK, Schoefield AE, Burley M, Povey S, Unwin RJ, Wrong OM* 1997 Familial distal renal tubular acidosis is associated with mutations in the red cell anion exchanger (Band 3, AE1). J Clin Invest *100:* 1693-1707

[174] *Vasuvattakul S, Yenchitsomanus P, Vachuanichsanong P, Thuwajit P, Kaitwatcharachai C,*

Laosombat V, Malasit P, Wilairat P, Nimmannit S 1999 Autosomal recessive distal renal tubular acidosis associated with Southeast Asian ovalocytosis. Kidney Int *56:* 1674-1682

[175] *Kaitwatcharachai C, Vasuvattakul S, Yenchitsomanus P, Thuwajit P, Malasit P, Chuawatana D, Mingkum S, Halperin ML, Nimmannit S* 1999 Distal renal tubular acidosis in a patient with Southeast Asian ovalocytosis: possible interpretations of a high urine PCO_2. Am J Kidney Dis *33:* 1147-1152

[176] *Karet FE, Finberg KE, Nelson RD, Nayir A, Mocan H, Sanjad SA, Rodriguez-Soriano J, Santos F, Cremers CWRJ, Di Pietro A, Hoffbrand BI, Winiarski J, Bakkaloglu A, Ozen S, Dusunsel R, Goodyer P, Hulton SA, Wu DK, Skvorak AB, Morton CC, Cunningham MJ, Jha V, Lifton RP* 1999 Mutations in the gene encoding B1 subunit of H^+-ATPase cause renal tubular acidosis with sensorineural deafness. Nat Genet *21:* 84-90

[177] *Smith AN, Skaug J, Choate KA, Nayir A, Bakkaloglu A* 2000 Mutations in ATP6N1B, encoding a new kidney vacuolar proton pump 116-kD subunit, cause recessive distal renal tubular acidosis with preserved hearing. Nat Genet *26:* 71-75

[178] *Sly WS, Whyte MP, Sundaram V, Tashian RE, Hewett-Emmett D* 1985 Carbonic anhydrase II deficiency identified in 12 families with the autosomal recessive syndrome of osteopetrosis with renal tubular acidosis and cerebral calcification. N Engl J Med *313:* 139-145

[179] *Wrong OM, Norden AGW, Feest TG* 1994 Dent's disease: a familial proximal renal tubular syndrome with low-molecular-weight proteinuria, hypercalciuria, nephrocalcinosis, metabolic bone disease, progressive renal failure and a marked male predominance. Q J Med *87:* 473-493

[180] *Gunther W, Piwon N, Jentsch TJ* 2003 The ClC-5 chloride channel knock-out mouse – an animal model for Dent's disease. Pflüger's Arch *445:* 456-462

[181] *Sebastian A, McSherry E, Morris RCJ* 1971 Renal potassium wasting in renal tubular acidosis (RTA): its occurrence in types 1 and 2 RTA despite sustained correction of systemic acidosis. J Clin Invest *50:* 667-678

[182] *Lin SH, Lin YF, Halperin ML* 2001 Hypokalemia and paralysis. Q J Med *94:* 133-139

[183] *Yang CL, Angell J, Mitchell R, Ellison DH* 2003 WNK kinases regulate thiazide-sensitive Na-Cl cotransport. J Clin Invest *111:* 1039-1045

[184] *Wilson FH, Disse-Nocodeme S, Choate KA, Ishikawa K, Nelson-Williams C, Desitter I, Gunel M, Milford DV, Lipkin GW, Archard J-M, Feely MP, Dussol B, Berland Y, Unwin RJ, Mayan H, Simon DB, Farfel ZJZ, Lifton RP* 2001 Human hypertension caused by mutations in WNK kinases. Science *293:* 1107-1112

[185] *Donnelly SM, Kamel KS, Vasuvattakul S, Narins RG, Halperin ML* 1992 Might distal renal tubular acidosis be a proximal disorder? Am J Kidney Dis *19:* 272-281

[186] *Bear R, Goldstein MB, Phillipson E, Ho M, Hammeke M, Feldman R, Handelsman S, Halperin ML* 1977 The effect of metabolic alkalosis on respiratory function in six patients with chronic obstructive lung disease. Can Med Ass J *117:* 900-903

[187] *Halperin ML* 2004 The ACID truth and BASIC facts – with a Sweet Touch, an enLYTEnment. 5th edition, Toronto ON, Canada