Fig. 9.1. Basic concepts for electrolyte and H_2O movements into and out of plasma. Electrolytes and H_2O enter plasma from the alimentary tract, from cells, and by injections or infusions. In vitro lysis of blood cells and platelet activation may add K^+ to the plasma or serum. Electrolytes and H_2O may leave the plasma and the body via kidneys, alimentary tract, respiratory tract, or skin, and they may enter extravascular sites within the body in the form of third-space loss (e.g., to pleural and peritoneal cavities). In some pathologic states involving muscle, H_2O or electrolytes shift between the ICF and ECF spaces (see the text for details). Fluids (e.g., plasma or urine) can enter pleural or peritoneal cavities and, if not removed via centesis, electrolytes and H_2O will be absorbed (see the text for details). Plt, platelet; and RBC, erythrocyte.

Fig. 9.2. H^+ and K^+ shift in acid-base disorders.

- In an inorganic acidosis, there is an accumulation of H^+ in ECF. As H^+ shifts into cells to equilibrate concentrations, K^+ shifts out of cells to maintain electrical neutrality and enters plasma (hyperkalemia occurs).[33] In an organic acidosis, hyperkalemia is not expected because additional factors influence plasma $[K^+]$(see the text).

- In an alkalosis, $[H^+]$ in ECF is reduced. As H^+ shifts out of cells to equilibrate concentrations, K^+ enters cells (leaves the plasma; hypokalemia occurs). The illustration shows the alkalotic state beginning with H^+ loss; the H^+ depletion may be due to other processes.

- Conversely, if K^+ depletion causes hypokalemia, K^+ shifts out of the cells and H^+ enters and thus lowers blood $[H^+]$ (alkalemia). The illustration shows the alkalotic state beginning with K^+ loss; the K^+ depletion may be due to other processes.

Fig. 9.3. Actions of aldosterone on principal epithelial cells in cortical collecting tubules. Aldosterone enters the principal cells and binds to receptor proteins. The aldosterone-receptor complex (Aldo-Rcptr) stimulates the synthesis of aldosterone-induced proteins (AIP), which may include components of the Na^+-K^+-ATPase pump and membrane channels for Na^+ and K^+. Through the actions on the pump or channels, aldosterone promotes the following:

1. Na^+ is pumped from the cell to the peritubular fluid, and the resulting luminal cell gradient promotes the resorption of Na^+ through an opened Na^+ channel.
2. K^+ is pumped into the cell from the peritubular fluid and typically exits to the tubular fluid through an opened K^+ channel. When hypokalemia is present, K^+ may return to the peritubular fluid via an opened basolateral membrane channel (K^+ is recycled).
3. Typically, the Na^+-K^+-ATPase pump results in a net negative charge in the tubular fluid (3 Na^+ resorbed and two K^+ secreted). The negative charge promotes the resorption of Cl^- through a paracellular route. When there is less Cl^- available (as occurs with hypochloremia), the negative charge promotes the retention of H^+ in the tubular fluid (the H^+ that passively leaves and reenters the principal cells) and thus increases renal secretion of H^+.

The net result of aldosterone actions in health is the resorption of Na^+ and Cl^- and secretion of K^+. In the presence of hypochloremia, there is increased secretion of H^+, which can promote aciduria or a metabolic alkalosis. ⊗, ATPase pump; and aa, amino acids.

Fig. 9.4. Secretion of H^+ by type A intercalated cells of the distal nephron. Aldosterone enters the type A intercalated cells and binds to receptor proteins. The aldosterone-receptor complex (Aldo-Rcptr) stimulates the synthesis of aldosterone-induced proteins (AIP) that may include components of H^+-ATPase pump. Through the actions of the pump, which is more active during systemic acidemia, aldosterone causes the secretion of H^+ and formation of HCO_3^- through the following processes:

1. H^+ released from the dissociation of H_2O is pumped into the tubular lumen.
2. OH^- released from the dissociation of H_2O combines with CO_2 in the presence of carbonic anhydrase (*CA*) to form HCO_3^-, which is exchanged for Cl^- in the peritubular fluid.
3. Cl^- that enters the cell in the Cl^--HCO_3^- exchanger is secreted into the tubular lumen to maintain electrical neutrality (balance the H^+ secretion).

The net result if stimulated by acidemia or aldosterone is increased H^+ and Cl^- secretion and increased HCO_3^- in plasma. In an independent process but in the same cells, a H^+-K^+-ATPase promotes the resorption of K^+ and secretion of H^+; this pump is more active when hypokalemia is present. Thus, hypokalemia promotes increased H^+ secretion, HCO_3^- production, and thus alkalosis.
⊗, ATPase pump; ◯, cotransporter or counter transporter (antiporter); and aa, amino acids.

Fig. 9.5. Gastric or abomasal secretion of H^+ and Cl^-. H^+ and HCO_3^- are formed from the combination of OH^- (from H_2O) and CO_2 in a reaction catalyzed by carbonic anhydrase. H^+ (from H_2O) is secreted into the lumen via a H^+—K^+-ATPase pump. The generated HCO_3^- is transported to the ECF via a Cl^--HCO_3^- exchanger. Cl^- is actively pumped into the lumen with Na^+ and K^+, but most Na^+ and K^+ ions are resorbed, thus leaving H^+ and Cl^- in the lumen. The major results of the process are gastric secretion of H^+ and Cl^-, a lesser plasma $[Cl^-]$, and greater plasma $[HCO_3^-]$.
⊗, ATPase pump; and ◯, cotransporter or counter transporter (antiporter).

Fig. 9.6. Excretion of H^+ via NH_4^+.

- Proximal renal tubular epithelial cells: Acidemia results in the increased uptake and degradation of glutamine. Energy for electrolyte transport is provided by the $3Na^+$-$2K^+$-ATPase and involves the increased activity of glutaminase (*Glnase*) and glutamate dehydrogenase (*GMD*). These processes reduce the severity of acidemia by (1) H^+ combining with NH_3 to form NH_4^+ and (2) the generation of HCO_3^-, which can buffer ECF H^+. The increased renal excretion of NH_4^+ obligates the excretion of anions (primarily Cl^-) to maintain electrical neutrality.

- Collecting tubular epithelial cells: In the collecting tubules, NH_3 diffuses into the tubular fluid and combines with H^+ that is secreted with Cl^-. This renal compensation for an acidemia increases the renal excretion of H^+ (in NH_4^+), increases the renal excretion of Cl^-, generates HCO_3^-, and thus produces a compensatory hypochloremic metabolic alkalosis.

⊗, ATPase pump; and ◯, cotransporter or counter transporter (antiporter).

Fig. 9.7. Proximal tubular conservation of HCO_3^-. H^+ secreted by a luminal border Na^+-H^+ exchanger combines with filtrate HCO_3^- to form H_2CO_3. Dissociation of H_2CO_3 into CO_2 and H_2O is facilitated by luminal carbonic anhydrase. After passive absorption, cellular carbonic anhydrase helps CO_2 and OH^- (from H_2O) combine to form HCO_3^-, which is transported to the peritubular fluid via a Na^+-$3HCO_3^-$ cotransporter. The H^+ released from the H_2O is available for secretion in the next cycle. The energy for the HCO_3^- conservation is provided by a Na^+-K^+-ATPase pump in the basolateral membrane. The electrolyte movement in the figure is not balanced; movement of other electrolytes (K^+, Cl^-, and NH_4^+) are involved to maintain electrical neutrality. The net result of the process is HCO_3^- conservation and Na^+ resorption, but the HCO_3^- that enters the peritubular fluid is not the same HCO_3^- molecule that entered the ultrafiltrate. Thus HCO_3^- is not directly resorbed (HCO_3^- is a not a resorbable anion). ⊗, ATPase pump; and ◯, cotransporter or counter transporter (antiporter).

Fig. 9.8. Secretion of HCO_3^- by type B intercalated cells of the distal nephron. When there is metabolic alkalosis (increased plasma $[HCO_3^-]$ and alkalemia), type B intercalated cells can secrete HCO_3^- into the tubular lumen and concurrently generate H^+. In respect to HCO_3^- and H^+, type B intercalated cells essentially have the opposite function of type A intercalated cells. The net result is increased renal excretion of HCO_3^- and increased H^+ and Cl^- in plasma. ⊗, ATPase pump; and ◯, cotransporter or counter transporter (antiporter).

Fig. 9.9. Bar diagrams of anion gap concepts. In all cases, total cation charge concentration equals total anion charge concentration. The uC^+ is due mostly to charges from fCa^{2+}, fMg^{2+}, and some globulins, whereas the uA^- is due mostly to charges from PO_4, SO_4, and anions of organic acids and proteins (Pr^-). Proteins are separated in the diagrams to illustrate their relative contributions to total anionic charge. Cations and anions that contribute to the anion gap are within the *grey-shaded areas*. In these examples, the uC^+ concentrations remain constant but may not be in pathologic states.

A. In healthy animals, the anion gap is almost equivalent to the combined physiologic concentrations of anions of organic acids and proteins, PO_4, and SO_4.

B. In a normochloremic metabolic acidosis (therefore low $[HCO_3^-]$), the increased anion gap represents increased concentrations of uA^- (organic acid anions, PO_4, SO_4, or other anions of the acids). These acidoses may be organic (e.g., lactic acidosis) or inorganic (e.g., renal failure).

C. In a hypochloremic metabolic acidosis (therefore low $[HCO_3^-]$ and low $[Cl^-]$), the increased anion gap represents increased concentrations of uA^-

(organic acid anions, PO_4, SO_4, or anions other than Cl^- or HCO_3^-). These acidoses may be organic (e.g., lactic acidosis) or inorganic (e.g., renal failure).

D. In a hypochloremic metabolic alkalosis (therefore high $[HCO_3^-]$), the anion gap is not increased because the sum of $[Cl^-]$ and $[HCO_3^-]$ and the sum of $[Na^+]$ and $[K^+]$ have not changed. These alkaloses may occur with vomiting or gastrointestinal sequestration of H^+ and Cl^-.

E. With concurrent hyponatremia and hypochloremia, the anion gap has not changed because the $[Na^+]$ and $[Cl^-]$ decreased proportionally and other concentrations did not change. These findings are more common when there is concurrent loss of Na^+ and Cl^-; for example, intestinal loss via diarrhea or renal loss in hypoadrenocorticism.

F. With hypoproteinemia, the anion gap is decreased because there is a lower concentration of proteins, an increased sum of $[Cl^-] + [HCO_3^-]$, and no change in the sum of $[Na^+] + [K^+]$. These findings occur in hypoproteinemic disorders when there are not concurrent acid-base disorders (e.g., hepatic failure).

Fig. 9.10. Products of aerobic and anaerobic glycolysis. Catabolism of each glucose molecule results in two pyruvate molecules, two H^+ ions, and a net production of two ATP molecules. When there is adequate oxygenation of cells and after pyruvate enters mitochondria, pyruvate enters the Krebs citric acid cycle (tricarboxylic acid cycle) with pyruvate dehydrogenase (PDH) promoting the breakdown of pyruvate to form CO_2, GTP, NADH, and $FADH_2$. GTP, NADH, and $FADH_2$ are used to generate 36 molecules of ATP in other reactions (therefore a net 38 molecules of ATP). However, if tissue hypoxia is present, pyruvate is instead converted to L-lactate in a reaction promoted by LD. This reaction uses H^+ and thus increases the pH in the cells (or uses the H^+ produced by catabolism of glucose). The pK_a of lactic acid is 3.1, so nearly all of the lactate produced remains in the anionic form; very little buffers H^+ to form lactic acid at physiologic pH values. As explained in the text, the acidemia in lactic acidosis caused by anaerobic conditions comes from the use of ATP (which produces H^+) for energy because ATP production (which consumes H^+; reactions not shown) is not efficient in anaerobic conditions. ADP, adenosine diphosphate; AMP, adenosine monophosphate; CoA, coenzyme A; $FADH_2$, reduced flavin adenine dinucleotide; GTP, guanosine triphosphate; NAD^+, nicotinamide adenine dinucleotide; and NADH, reduced nicotinamide adenine dinucleotide.

Fig. 9.11. Chemical structure of pyruvate, lactate, and ketone body molecules. Knowing the chemical composition of molecules can facilitate an understanding of the relationships of those molecules in pathologic states. The reduction of pyruvate by LD increases the formation of L-lactate in lactic acidosis. L-lactate and D-lactate are optical isomers (mirror images). L-lactate is the major form produced by mammalian cells, and D-lactate is produced by bacteria. Of the three ketone bodies, only AcAc and acetone are truly ketones. AcAc can be converted to either acetone or BHB. (Note: *Solid wedges* extend forward, and *dashed wedges* extend backward.)

Fig. 9.12. Schematic comparison of osmotic pressure and colloidal osmotic pressure.

• In the **left** drawing of the renal collecting tubule, under phyisiologic conditions, the peritubular fluid has a much greater osmolality than the tubular fluid. Osmotic pressure can be calculated from osmolality (each 1 mmol/kg of osmolality is equivalent to 19.3 mmHg of osmotic pressure). Therefore, an osmolality of 1000 mmol/kg equates to an osmotic pressure of 19,300 mmHg, and an osmolality of 400 mmol/kg creates 7720 mmHg of osmotic pressure. The large difference in osmolality creates a large osmotic pressure gradient (almost 12,000 mmHg in this example). The peritubular fluid's hypertonicity is mostly due to high concentrations of Na^+, Cl^-, and urea. When ADH is present, it increases the permeability of the tubular epithelium (via aquaporin) to H_2O so that H_2O is resorbed and thus increases the solute concentration in the tubular fluid).

• In the **right** drawing of a capillary wall in skeletal muscle, the colloidal osmotic pressure (synonym: oncotic pressure) is greater in the blood than in the interstitial fluid because the protein concentration is greater in plasma than in interstitial fluid and because of the related Gibbs-Donnan equilibrium. The colloidal osmotic pressure gradient (18 mmHg in this example) tends to cause the movement of H_2O (and small solutes) from interstitial fluid to plasma. The movement of H_2O out of or into the plasma is determined by the hydraulic pressure gradient across the semipermeable membrane (see the Colloidal Osmotic Pressure section in Chapter 7, and General Concepts and Definitions, sect. V, in Chapter 19).

Note: The osmotic pressure gradient in the distal nephron is more than 600 times the colloidal osmotic pressure in the capillary bed. The pressure values are provided to illustrate the magnitude of the differences between the forces of osmotic pressure gradients and colloidal osmotic pressure gradients.

Fig. 9.13. Bar diagrams of serum osmolality concepts. The unmeasured cations (uC) are mostly fCa^{2+} and fMg^{2+}, whereas the unmeasured anions (uA) are mostly PO_4, SO_4, and anions of organic acids. Proteins are not included because they do not contribute significantly to osmolality. Solutes that contribute to the osmo. gap are within the *grey-shaded area*.

A. In healthy animals, nearly all nonprotein solutes are monovalent electrolytes except for urea and glucose (gluc.). The osmo. gap should be near 0 if an appropriate formula for Osm_c is used.

B. In a normochloremic metabolic acidosis (therefore low $[HCO_3^-]$), the osmo. gap is not increased, because the 1.86 $(Na^+ + K^+)$ should account for the sum of all cations and anions. Because electrical neutrality must be maintained, increases in the concentration of unmeasured anions must be accompanied by either increases in cations, decreases in other anions, or both. In any case, the 1.86 $(Na^+ + K^+)$ should account for the sum of all cations and anions.

C. When hyperosmolality is caused by azotemia, the osmo. gap is not increased, because both the Osm_m and the Osm_c are increased proportionately by the higher [urea]. The same concept applies for hyperosmolality caused by hyperglycemia or hypernatremia.

D. When hyperosmolality is caused by an abnormal nonionic solute (e.g., mannitol), the osmo. gap is increased, because the exogenous solute increases the Osm_m but is not included in the Osm_c formula.

E. When hypoosmolality is caused by hyponatremia and hypochloremia, the osmo. gap is not changed, because the Osm_m and the Osm_c are decreased by the same amount.