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REVIEW

Extracellular Acid-Base Balance and Ion Transport Between Body Fluid Compartments

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Clinical assessment of acid-base disorders depends on measurements made in the blood, part of the extracellular compartment. Yet much of the metabolic importance of these disorders concerns intracellular events. Intracellular and interstitial compartment acid-base balance is complex and heterogeneous. This review considers the determinants of the extracellular fluid pH related to the ion transport processes at the interface of cells and the interstitial fluid, and between epithelial cells lining the transcellular contents of the gastrointestinal and urinary tracts that open to the external environment. The generation of acid-base disorders and the associated disruption of electrolyte balance are considered in the context of these membrane transporters. This review suggests a process of internal and external balance for pH regulation, similar to that of potassium. The role of secretory gastrointestinal epithelia and renal epithelia with respect to normal pH homeostasis and clinical disorders are considered. Electroneutrality of electrolytes in the ECF is discussed in the context of reciprocal changes in Cl^- or non Cl^- anions and HCO_3^-.

Acid-Base Balance Within Body Fluid Compartments

A well-known joke involves a man looking for his lost keys under a street lamp. A passerby, offering to assist him, asks the man where he dropped his keys. The man points down the street. The passerby asks why isn't he looking down the street, and the man answers, "The light is better under the street lamp."

Have we been looking in the wrong—but easier—place to assess clinical acid-base disturbances? Although recent studies suggest important roles of extracellular fluid (ECF) pH and lactate in activation of T cells in immune function, formation of the extracellular matrix, and angiogenesis (28, 34), it is primarily the simplicity of measuring accessible blood that gives it such prominence as a surrogate to determine the health of tissues. Maintenance of intracellular fluid (ICF) pH is critical to processes such as protein synthesis, intermediate metabolism, cell growth, and reproduction. Although much is known concerning mechanisms of its regulation (8, 11), ICF acid-base balance is technically more difficult to assess, is heterogeneous within subcellular compartments, and, since various organs regulate pH with differing degrees of precision, the measure of a single set of blood values cannot accurately reflect the health of all organs. Advances in methods to measure in vivo cell pH (25, 41, 78), as well as pH in various organs under various conditions, will greatly improve our understanding and management of human acid-base disorders.

The ECF usually accounts for one-third of total body water compared with the two-thirds of body water that constitutes the ICF (54, 65). The ECF is further compartmentalized to the intravascular plasma volume, the interstitial fluid (ISF), and the transcellular fluids. A transcellular space is part of the ECF lined by epithelial cells. Examples are the gastrointestinal tract, the renal tubular lumen (urinary space), and sweat gland ducts. These particular spaces are open to the external environment, and, as such, their contents, to variable extents, are lost from the body in health and disease. Other transcellular fluids, or spaces, include the cerebrospinal fluid, and pleural and peritoneal spaces, but because these are not open to the outside environment, they more often reflect ECF acid-base status rather than determine it.

Clinical practice provides many examples in which treatment of an acid-base disturbance of the ECF may have damaging, unobserved effects within the ICF. For example, central nervous system interstitial fluid (ISF) may acidify as a result of an intracranial hemorrhage. The ISF acidosis

signals the respiratory control center to cause hyperventilation, a necessary compensation protecting neuronal pH from acidifying, but at the expense of peripheral respiratory alkalosis (13, 48, 68). An intervention that normalizes peripheral blood pH may result in removing a necessary component of brain pH regulation.

Plasma Membrane Ion Transport and Acid-Base Homeostasis

One concept proposed in this review is that overall acid-base homeostasis in the body can be thought of as functioning in a dynamic similar to many electrolytes. K^+ homeostasis illustrates the concept. External K^+ balance refers to the matching of dietary intake (and absorption) to renal excretion while maintaining a nearly constant plasma [K^+]. Since over 98% of body K^+ resides within the ICF at concentrations ~35-fold higher than that in the ECF (72), a meal containing large quantities of K^+ could severely and dangerously increase the relatively low [K^+] in the ECF, if retained there. Internal balance of K^+ refers to the movement of K^+ from ECF to the large capacity ICF, a redistribution that causes minimal concentration changes in both ICF and ECF. The redistribution maintains K^+ gradients and membrane electrochemical potential differences critical for all cells, notably for cardiac muscle. Internal balance is rapidly regulated by insulin and catecholamines through stimulation of Na^+-K^+-ATPase. The ICF is therefore available to "buffer" K^+ until renal epithelial cells allow for regulated secretion and necessary loss in urine to match intake and maintain external balance.

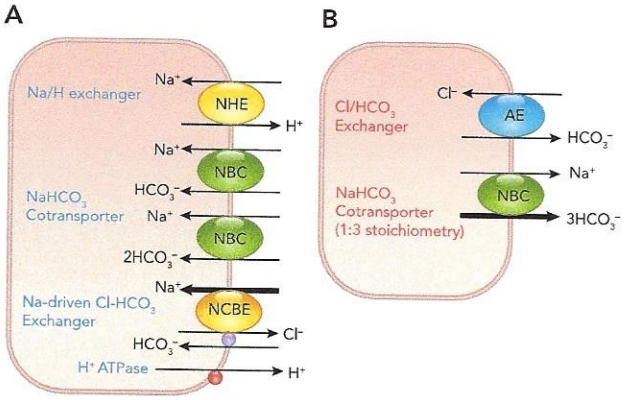

FIGURE 1. **Cellular transport mechanisms involved in regulation of ICF pH**

A: mechanisms that protect cells from excess acidity. *B*: mechanisms that prevent excess alkalinization. For NBC transporters, both electroneutral with 1:1 Na^+ to HCO_3^- and electrogenic transporters with 1:2 and 1:3 stoichiometry are shown. The direction of transport depends on a favorable electrochemical potential and a necessary coupling ratio. These will vary depending on cell type.

External Balance of Acid-Base

When we speak of metabolic acid-base balance, we generally think of non-volatile, or fixed, acids produced from dietary substances such as proteins, nucleic acids, and phospholipids that contain sulfur and phosphorus. Cl^- salts of organic cations including basic amino acids and inorganic cations (Na^+, K^+, or Ca^{2+}) also contribute to the net acid load (67). In certain vegetarian diets, net alkali may be produced. Na^+, K^+, or Ca^{2+} salts of an organic anion species that can undergo metabolism to CO_2 and OH^- essentially become HCO_3^- salts. Those anions include CO_3^{-2}, lactate$^-$, citrate^{-3}, and acetate$^-$. To maintain external balance (the steady state), net acid produced through metabolism must equal net acid excreted in the urine. The fixed acids or alkali produced within cells are transported to the ECF by one of many ubiquitous plasma membrane transport mechanisms (8), shown in FIGURE 1, that use the metabolic energy of ATP hydrolysis. The thermodynamic requirement for movement of H^+ into the ECF against its electrochemical gradient may directly derive from ATP as in plasma membrane vacuolar V-type H^+ ATPases (primary active), or be indirectly dependent on ATP hydrolysis when coupled to inwardly directed electrochemical Na^+ gradients produced by Na^+-K^+-ATPases (secondary active). Examples of the latter are the Na^+/H^+ exchangers (NHE in the SLC9 gene family) and Na HCO_3 cotransporters (NBC transporters in the SLC4 gene family). As shown in FIGURE 1A, the efflux of H^+ from a cell or the influx of HCO_3^- into the cell from the ECF simultaneously protects cells from acidification and acidifies the ECF. As the net acid accumulates in the ECF, it is transported in the circulation to the kidney for excretion. In the case where cells become alkalinized, other plasma membrane transporters utilize the favorable outwardly directed electrochemical HCO_3^- gradient to extrude HCO_3^- and restore cell pH. Transporters in this group, shown in FIGURE 1B, include electrogenic NBC (NBC3) with a 1:3 Na^+ to HCO_3^- stoichiometry, or electroneutral Cl^-/HCO_3^- anion exchangers (AE) (8). The acid or alkali transported from cells into the ECF is then eliminated in the urine through an integrated process of HCO_3^- filtration and reabsorption, H^+ secretion, and then excretion in the urine as NH_4^+ and acid phosphate salts (net acid excretion) or as HCO_3^- salts (net alkali excretion). Quantitatively, the amount of fixed acids usually produced is on the order of 1 meq H^+ · kg body wt^{-1} · day^{-1}, a value much less than volatile acid cleared as CO_2 by the lungs, ~20 moles/day (67). When the metabolic acid burden is increased,

ammoniagenesis is increased in renal proximal tubular cells to enhance net acid excretion.

Gastrointestinal and Renal Epithelia Contribute to External Acid-Base Balance

In addition to diet, there exists an ongoing movement of H^+ and HCO_3^- into the ECF by polarized gastrointestinal and renal epithelial cells, which function to secrete or absorb fluids of widely variable volume, electrolyte and acid-base content into or out of the gastrointestinal tract lumen or urinary space. Daily amounts of gastrointestinal secretions are not trivial. For example, 1.5 liters of gastric secretions at pH 1.5 would amount to 45 meq H^+, a value close to a normal metabolic acid load from diet. For the gastrointestinal tract as a whole, 10 liters of fluid secreted during a single day combined with additional fluid and electrolytes consumed in the diet (27, 46) would require a similar total volume and electrolyte content to be absorbed in the absence of diarrhea. Epithelial cell polarity is important in this transcellular secretion and absorption. In general, when acid is secreted across the apical membrane, the cells alkalinize, and base is returned across the basolateral membrane to the ECF. And when base is secreted across the apical membrane, acid is returned to the ECF across the basolateral membrane. This polarity of the epithelial cells not only determines whether the secretion is an acidic fluid as low as pH 1 (100 mM $[H^+]$) in the stomach or an alkaline secretion as high as pH 8 (140 mM $[HCO_3^-]$) in the pancreatic ducts, but also allows those cells to maintain an intracellular pH within a constant range. Some examples of the many ion transport processes of various cells of the gastrointestinal tract are shown in FIGURE 2.

If the acid and alkaline luminal secretions of different cell types were perfectly timed and matched in quantity, one could see the two processes as offsetting where neutralization occurs within the gastrointestinal tract by downstream mixing of secretions. Similarly, offsetting effects could occur within the ECF. However, if such timing and matching of quantity of secretions were not perfect, then some alkalinization or acidification of the ECF would occur, depending on gastrointestinal motility, and thus transit time, following a meal. For instance, the "alkaline tide" refers to the post-prandial alkalinization of the ECF and the urine, accompanying HCl secretion into the stomach for digestion (52). The alligator provides an extreme example of this in that 75% of all Cl^- in the ECF is secreted into the stomach as HCl after a meal (77). The blood pH rises to 8. In human disease, the net loss to the external environment by vomiting or diarrhea or sequestration of secretions within the intestinal luminal spaces would generate an imbalance of alkalinizing or acidifying processes on the ECF. And since the source of luminal

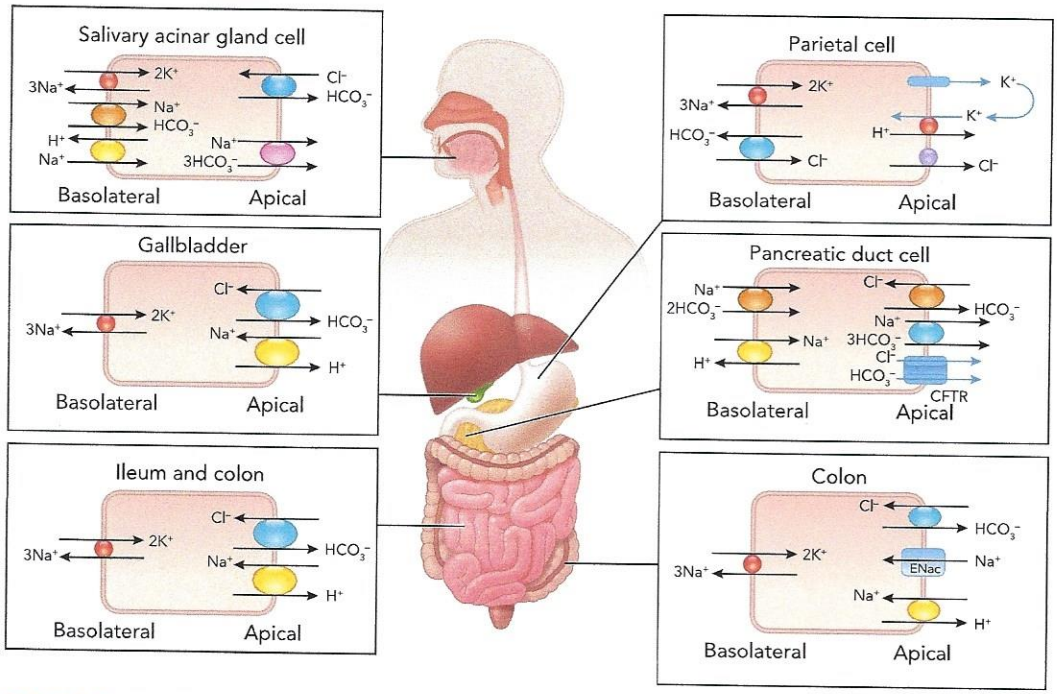

FIGURE 2. Simplified view of some important plasma membrane transporters in various segments of the gastrointestinal tract

Similar mechanisms used by cells to maintain intracellular pH are used by the epithelial cells to either acidify (stomach) or alkalinize (salivary glands and pancreas) the luminal content. Acidification of the lumen results in alkalinization of the adjacent ISF. Alkalinization of the lumen results in acidification of the adjacent ISF.

secretions by polarized intestinal epithelia is the ECF, the loss of H^+ will be accompanied by a net loss of Cl^-. In contrast, a net loss of HCO_3^- will require a net loss of Na^+ and K^+.

The renal epithelial cells shown in FIGURE 3 are at the interface of the renal ISF and the urinary space, which constitutes the regulated and final step for excretion of acid or alkaline loads appropriate to maintain external balance and preserve constancy of acid-base and electrolyte status in the ECF. Just as the apical and basolateral membranes of an epithelial cell regulate its intracellular pH by the transport of opposites in terms of acid and base, acid-base balance of the ECF as a whole is maintained nearly constant by renal epithelia that in the aggregate would need to function as a "mirror image" of cells in the gastrointestinal tract. That is, net acid lost to the gastric lumen must equal the net base lost to the urine during an "alkaline tide." Alternatively, any net base lost, even temporarily, to the intestinal secretions must be offset by net acid lost in the urine (a process that could be considered an "acid tide"). In the course of a day, there may be no net accumulation of acid or base, but different excretion patterns may occur depending on the timing of gastrointestinal secretions involved in digestive processes. The net acid excretion during any period of time might best be reflected by the sum of the acids produced by metabolic processes and those resulting from even normal gastrointestinal function. Even though the volume and acidity of gastric secretions and the alkalinity of pancreatic duct secretions are influenced by neural and humoral stimuli, digestion is a slow enough process so that there are multiple boluses of acid or alkali into the ECF during a day. The pancreatic duct cells have both acidifying and alkalinizing transporters on the apical membrane that create a switch from HCO_3^- to H^+ secretion, a process known as salvage of HCO_3^- secretions (47, 53, 76).

There are similarites in process for secretions of the salivary glands and pancreatic duct cells of the gastrointestinal tract, the secretion of sweat by sweat glands, and the production of urine by renal tubules. All of these transcellular spaces start with a primary fluid derived from ECF, which is then

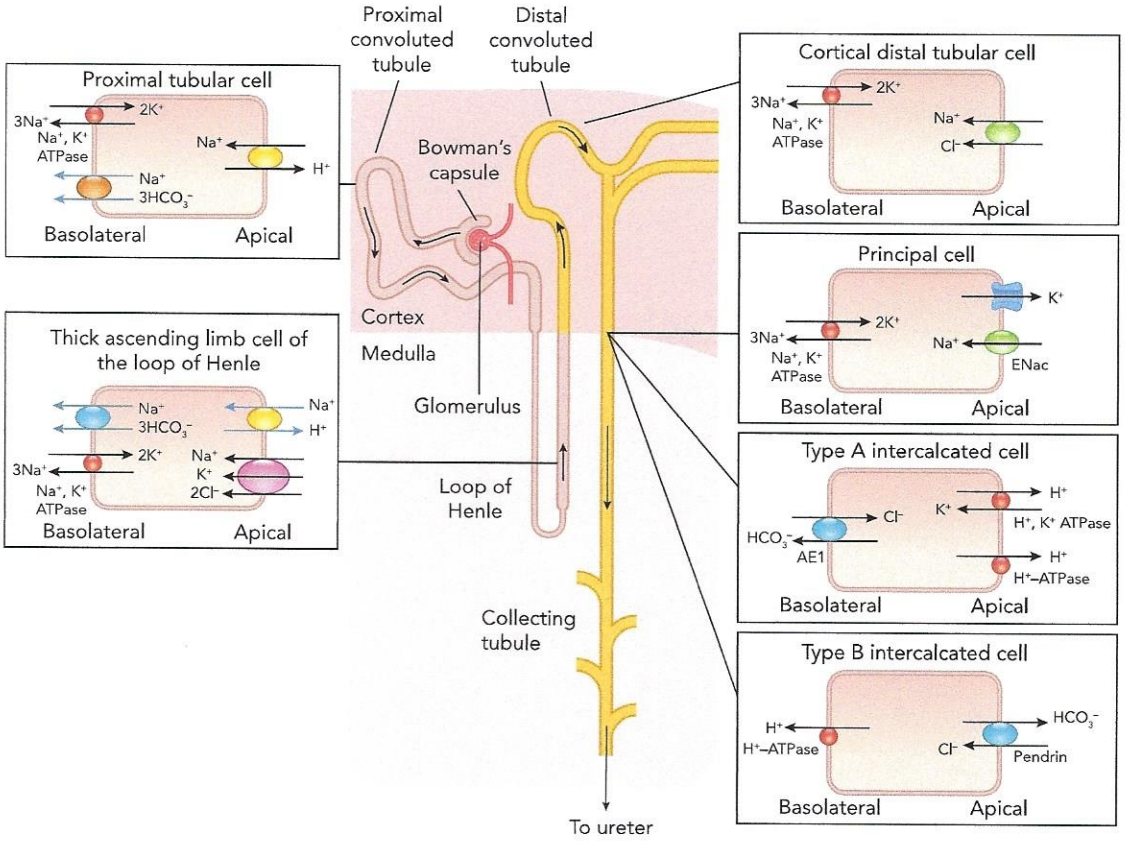

FIGURE 3. **Simplified view of some important plasma membrane transporters in various segments of the nephron**

Similar mechanisms used by cells to maintain intracellular pH are used by the epithelial cells to reabsorb large amounts of filtered HCO_3^- (proximal tubule and collecting duct) or to excrete net acid by titrating filtered weak acids, like HPO_4^-, to form $H_2PO_4^-$ and by increasing NH_4^+ excretion as the lumen acidifies in the collecting duct. Here too, acidification of the lumen results in alkalinization of the adjacent ISF. Alkalinization of the lumen results in acidification of the adjacent ISF when net alkali needs to be excreted.

altered in content and pH as the primary filtrate flows through the tubular or ductal system. In the salivary glands, the acinar cells serve the purpose, whereas the pancreatic and sweat duct cells change the nature of the fluid as it flows distally. In the kidney, glomerular filtrate, essentially an ultrafiltrate of the ECF, perfuses the apical side of the proximal tubules; the ISF on the basolateral side initially is similar in content to the glomerular filtrate. Compared with the pancreas, and salivary and sweat glands, the glomerular filtration rate is normally at least 100-fold larger in volume. To maintain overall acid-base balance where net acid produced must equal net acid excreted, almost all of the large amount of filtered HCO_3^- must first be reabsorbed. The proximal tubule apical membranes possess the NHE3 and H^+-ATPase transporters that acidify the lumen and alkalinize the cell contributing to nearly 85% of total HCO_3^- reabsorption, even when net acid must be excreted. In the alkaline cell environment, carbonic anhydrase catalyzes the reaction of CO_2 and OH^- to form HCO_3^-. As [HCO_3^-] increases within the proximal tubule cell, the NBC (9, 60), with stoichiometry of 1 Na^+ to 3 HCO_3^-, provides enough driving force to transport HCO_3^- across the basolateral membrane, a process that maintains proximal cell pH and returns filtered HCO_3^- to the ECF (FIGURE 3). HCO_3^- reabsorption continues in the loop of Henle and cortical collecting duct until the urine is at maximally acid pH in the medullary collecting duct. Type A intercalated cells of the collecting duct will complete net acid excretion as NH_4^+ and $H_2PO_4^-$ salts. Small increases in ISF [HCO_3^-] could decrease HCO_3^- reabsorption and/or favor HCO_3^- secretion via the Cl^-/HCO_3^-, known as Pendrin of type B intercalated cells of the collecting duct (75). A third type of intercalated cell (non-A, non-B) in the collecting duct has an apical electroneutral Na^+-dependent $2Cl^-/HCO_3^-$ exchanger (NDCBE) capable of NaCl reabsorption coupled to HCO_3^- secretion.

The principal cells in the renal collecting duct have apical epithelial Na^+ channels (ENaC) that are aldosterone sensitive and create a lumen-negative potential difference that enables secretion of K^+ through K^+ channels, and electrogenic active H^+ secretion by neighboring type A intercalated cells. Sweat gland ducts are also aldosterone sensitive and have ENaC on the apical membrane, which renders the lumen electronegative. With intact cystic fibrosis transmembrane Cl^- conductance regulator (CFTR), Cl^- absorption follows the lumen-negative potential difference generated by ENaC. In cystic fibrosis and loss of function of CFTR, the lumen becomes much more electronegative, decreasing further Na^+ and Cl^- absorption, leading to increased sweat flow and higher NaCl content. The colon is a site of Na^+ absorption, with water is aldosterone-sensitive, and has apical ENaC and K^+ channels.

Internal Balance of Acid-Base

Internal balance for acid-base homeostasis, as proposed in this review, is necessary when the ECF pH is threatened. Most cells within the body have plasma membrane ion transporters available to them for regulating intracellular pH within an acceptable range (8). Transporters that alkalinize the cell prevent excessive acidification of those cells from metabolically produced acid loads and, by the same process, acidify the ECF. These same transporters should also serve to alkalinize cells when ECF alkalinization is generated by secretion of HCl into the gastric lumen (the alkaline tide). Other transporters on cell membranes are important to protect the cell from excessive alkalinization. Those transporters include outwardly directed NBC with 3 HCO_3^- per Na^+ or the electroneutral AE, Cl^-/HCO_3^- (FIGURE 1).

In ECF acidosis or alkalosis, any cell that can regulate its own pH is well-equipped to transport acid or base into the cell, which has a well-buffered internal milieu with a total ICF volume twice that of the ECF. The fact that plasma [HCO_3^-] is in mM concentrations and [H^+] in nM demonstrates the large buffer capacity of the body. It has been become increasingly apparent that carbonic anhydrase enzymes are present in a large number of cells, suggesting the involvement of a variety of cells in acid-base homeostasis (10). Furthermore, at least the red blood cell carbonic anhydrase has one of the highest turnover numbers of all mammalian enzymes (40). The buffering capacity of the ICF is greater than in ECF. Another large reservoir of buffering, besides hemoglobin, weak acids, proteins, and the HCO_3^- system, is bone, containing hydroxyapatite crystals [$Ca_{10}(PO_4)_6(OH)_2$] (42). In chronic acidosis, plasma [HCO_3^-] may be maintained constant at the expense of bone demineralization. Bone Ca^{2+} is released from the ECF matrix by action of H^+-ATPases of osteoclasts.

The cellular uptake of acid or base will at the same time help regulate both intracellular and extracellular pH. And as the net acid or base is eliminated from ECF into the urine, cells will export the additional buffered acid or base back to the ECF to be excreted. Ultimately, internal and external balance is achieved.

Analogy of cell and plasma interactions in acid-base homeostasis can be made to the respiratory CO_2 transport function of red blood cells. CO_2 produced in body cells through respiration diffuses from those cells into adjacent ISF, then into capillary plasma water, and then into circulating red

Table 1. *Acid-base disorders of gastrointestinal origin*

Epithelial Cell	Cause: Transporter/Gene	Associated Findings
Pancreatic duct	Chronic pancreatitis; CFTR (Cl^- and HCO_3^- channel) mutations increase risk; sequestration in bowel loop; Jejunal tube drainage; Cl^-/HCO_3^-	Hyperchloremic acidosis; hypokalemia; ECF volume depletion; losses of $NaHCO_3$; losses of K^+
Small intestine, colon	Inflammatory, secretory, diarrhea; ileostomy, small intestinal or colonic; vasoactive intestinal peptide (VIPoma); congenital Na^+ losing diarrhea–autosomal recessive loss-of-function mutations of NHE3 exchanger (SLC9A3), the major intestinal brush border Na^+/H^+ exchanger (35)	Hyperchloremic acidosis; hypokalemia; ECF volume depletion; losses of $NaHCO_3$ or Na^+ and K^+ with bacterial organic anions-acetate, butyrate, proprionate in colonic diarrhea
Stomach parietal cell	Vomiting, nasogastric suctioning; gastrinoma (Zollinger Ellison, ZE syndrome); gastric H^+-K^+-ATPase	Hypochloremic alkalosis; hypokalemia, with GI and renal K^+ wasting; ECF volume depletion; high Cl^- diarrhea in ZE
Small intestine and colon	Congenital Cl^- losing diarrhea (39); loss of function Cl^-/HCO_3^- exchanger (SLC26A3), normally functions with NHE3 on apical membrane for NaCl absorption	Hypochloremic alkalosis; hypokalemia; ECF volume depletion
Colon	Some villous adenomas cause Cl^- losses via apical Cl^-/HCO_3^- exchanger (25)	Hypochloremic alkalosis; hypokalemia; ECF volume depletion; high stool Cl^-

blood cells. The CO_2 can combine with hemoglobin (Haldane effect) or combine with H_2O in the presence of carbonic anhydrase to form H^+ and HCO_3^-. The H^+ binds to hemoglobin (Bohr effect) and the HCO_3^- exchanges for Cl^- through an anion exchanger that accounts for as much as 30% of the red cell plasma membrane (2). Consequently, venous plasma $[HCO_3^-]$ increases, and $[Cl^-]$ decreases. Venous blood plasma HCO_3^- is the major form by which tissue CO_2 is delivered to the lungs, where the process reverses, starting with CO_2 diffusion from pulmonary ISF into the alveolar airspace, followed by a fall in plasma CO_2, red cell CO_2, and reversal of the Cl/HCO_3 exchanger (AE1). It is likely that RBC anion exchanges would not be advantageous as a means of compensation for metabolic alkalosis since high plasma $[HCO_3^-]$ (and low $[Cl^-]$) of alkalosis would impede CO_2 transport and thus worsen respiratory acidosis (increase both P_{CO_2} and $[HCO_3^-]$ independently).

Two Models of Acid-Base Homeostasis

Two popular views of the physiological basis of metabolic acid-base disturbances have been debated. In the traditional HCO_3^-/CO_2 model, measurement of blood pH, P_{CO_2}, and $[HCO_3^-]$ and the chemical relationship between CO_2 and $[H^+]$ and $[HCO_3^-]$ is emphasized (1, 32). The relationship is shown in the Henderson-Hasselbalch equation below, where pK represents the equilibrium constant and 0.03 is the solubility of CO_2 in aqueous solution:

$$pH = pK + log[HCO_3^-]/[0.03(P_{CO_2})]$$

In this approach, the $[HCO_3^-]$ is an independent variable in metabolic disorders. Loss of HCO_3^- or gain of H^+ with consequent lowering of the $[HCO_3^-]$ leads to metabolic acidosis, whereas addition of HCO_3^- or loss of H^+ raises the $[HCO_3^-]$, generating metabolic alkalosis.

Another approach, the strong ion model (12, 21, 22), treats the $[HCO_3^-]$ as dependent on the requirement to maintain electroneutrality, and therefore the $[HCO_3^-]$ must change to fill a charge gap developed if the independent strong electrolytes, the charged species within the ECF, were gained or lost disproportionately compared with their concentrations in the ECF. Specifically, strong ions are those that are fully dissociated, and the difference between all cations and anions, termed the strong ion difference (SID), is:

$$[Na^+]+[K^+]+[Ca^{2+}]+[Mg^{2+}]-[Cl^-] = [SID]$$

In the situation where lactate builds up in the body fluids because production exceeds clearance, the $lactate^-$, acting as a fully dissociated strong anion (because its pK is 3.8), must contribute to the SID. The dissociated anion concentrations of albumin, phosphates, and other weak acids (HA), termed $[A^-]_{total}$, are dependent on the acid dissociation constant and the amount of $HA + A^-$ for each weak acid. Maintaining overall electroneutrality, $[SID - A_{tot}^-]$ must equal the $\{[OH^-] - [H^+]\} + \{[CO_3^{-2}]+[HCO_3^-]\}$, which will in this review be simplified as:

$$[SID]-[A_{tot}^-] \approx [HCO_3^-]$$

since concentrations of H^+, OH^-, and CO_3^{-2} are very small relative to $[HCO_3^-]$. Further simplification of [SID] to $[Na^+] + [K^+] - [Cl^-]$ is made for the purpose of this review to represent only the major extracellular strong ions.

The control of acid-base, osmolality, ECF volume, and Na^+, Cl^-, and K^+ balance are interconnected.

Table 2. *Causes of hyperchloremic metabolic acidosis of renal origin*

Renal Epithelial Cell Disorder	Cause: Protein (Gene) (56)	Associated Findings
Proximal tubule; type 2 RTA/loss of HCO_3^-; reabsorption function	Carbonic anhydrase CA2 mutations	Hypokalemia; ECF volume depletion Osteopetrosis
	Basolateral NBCe1 NBC1; SLC4A4 (60)	Keratopathy, glaucoma, cataracts
	Cause: disease or drug	**Associated findings**
	Multiple myeloma; Wilson's disease; cystinosis; amyloidosis	Fanconi's syndrome
	Carbonic anhydrase inhibition; acetazoleamide	Diuretics and other drug effects
	Drugs: ifosfamide, tenofovir	
Collecting duct; type 1 intercalated cell; type 1 RTA/loss of function of H^+ secretion	**Cause: transporter (gene) (56)**	**Associated findings**
	Autosomal dominant; basolateral Cl^-/HCO_3^- exchanger (2) AE1 (SLC4A1) mutations cause defect in trafficking	Hypokalemia; ECF volume depletion
	Autosomal recessive; vacuolar H^+-ATPase B1-subunit of H^+ATPase (15, 70)	Hearing loss
	Autosomal recessive a4 subunit of apical H^+-ATPase	No hearing loss

Metabolic acid-base disorders (or metabolic compensations for respiratory disorders) are always associated with at least one other abnormal electrolyte concentration. It is also evident that many plasma membrane electrolyte transporters of strong ions are directly coupled to transport of H^+ and HCO_3^-. These transporters, shown in FIGURE 1, have been discussed in the context of cell pH regulation (8), gastrointestinal epithelial cell secretions, and mechanisms for urinary acidification or alkalinization by renal epithelial cells (9). The connection of strong ion and H^+ and HCO_3^- exchanges between compartments provides a mechanism by which reciprocal changes in HCO_3^- and Cl^- could maintain electroneutrality within the ECF in either acid-base model described above. Another coordinated function of strong ions and acid-base is the exchange of K^+ and H^+ in the family of H^+, K^+ ATPases. The systems also overlap with the dual stimulus of ammoniagenesis in the renal proximal tubule cell by acidosis and K^+ depletion. Na^+ and NH_4^+ are interrelated in the ability of NH_4^+ to substitute for H^+ in NHE3 and for K^+ in the Na-K-2Cl cotransporter (NKCC2) of the thick ascending limb in the loop of Henle. In the situation in which both Na^+ and K^+ must be conserved, NH_4^+ excretion is Na^+ and K^+ sparing (63).

A clear example of the interconnection is found in renal maintenance of the metabolic alkalosis generated by vomiting (24). At first, the increased HCO_3^- is excreted in the urine with Na^+ and K^+ as a defense against metabolic alkalosis. However, as a result of development of ECF volume depletion and the need to conserve Na^+ and water, activation of the renin-angiotensin-aldosterone axis increases proximal tubule NHE3 and NBC, resulting in greater, not less, HCO_3^- reabsorption. Hypokalemia resulting from urinary K^+ losses due to bicarbonaturia and hyperaldosteronism also increases NHE3 and NBC, further decreasing HCO_3^- excretion to minimal values despite sustained elevation in plasma [HCO_3^-]. This phenomenom is known as the paradoxical aciduria of metabolic alkalosis (24, 67). The interconnections between ECF volume depletion, acid-base abnormality, and potassium depletion seems advantageous compared with a system that would correct the acid-base disorder at all costs. In such an instance, loss of Na^+ and K^+ with bicarbonaturia would likely lead to life-threatening hypokalemia and hypotension.

The emphasis on the principle of electroneutrality is arguably the most important aspect of the strong ion approach. As a charged species, the [HCO_3^-] must be involved in that relationship, and it exists in equilibrium with neutral H_2O and CO_2. The [HCO_3] could be viewed as either a dependent or independent variable since HCO_3^- can be exchanged across cell membranes with a strong ion. If one favors the HCO_3^- model of acid-base physiology, then it is the H^+ in NHE or HCO_3^- in NBC or AE family of transporters that is important; in the strong ion approach, it is the Na^+, K^+, or Cl^- that changes the SID, and thus the [HCO_3^-] must change.

Generation of Reciprocal Changes of HCO_3^- And Cl^- in the ECF

Changes in the relationship of plasma [Na^+] to [Cl^-] result from either hydration or acid-base disorders. For example, in hypotonic conditions, the plasma [Na^+], [Cl^-], and [Na^+]-[Cl^-] would all fall proportionately. To predict a change in the plasma [Cl^-] caused by urinary losses attrib-

Table 3. *Causes of hyperkalemic hyperchloremic metabolic acidosis of renal origin*

Epithelial Cell	Causes: Disease, Drug, or Transporter (Gene)	Associated Findings
Collecting duct principal cell; RTA type 4	Sjogren's syndrome; autoimmune diseases; amyloidosis; sickle cell anemia; urinary tract obstruction; interstitial nephritis	Nephrogenic diabetes insipidus; hyperglobulinemia
	K^+-sparing diuretics; spironolactone; triamterene; amiloride; trimethoprim; calcineurin inhibitors	
	Adrenal insufficiency	High renin, low aldosterone; hypocortisolism; ECF volume depletion
	Hypoaldosteronism (autonomic neuropathy)	Low renin, low aldosterone; ECF volume depletion
	Pseudohypoaldosteronism type 1; autosomal dominant mineralocorticoid receptor (NR3C2); autosomal recessive loss of function, ENaC (SCNN1)	High renin; high aldosterone
	Pseudohypoaldosteronism type 2 (73); gain of function distal NCC; WNK 1 and WNK 4 mutations	Hypertension; ECF volume expansion

utable to a disorder of acid-base and not tonicity, it is necessary to normalize the electrolyte concentrations in the urine to the plasma electrolytes.

The development of hyperchloremia with reciprocal hypobicarbonatemia is an acidifying condition that could indicate a hyperchloremic acidosis (20), but hyperchloremia is also the renal compensation of chronic respiratory alkalosis in which the renal response to hypocapnea is to excrete $NaHCO_3$. Hypochloremia with reciprocal hyper-bicarbonatemia is an alkalinizing process that could be a metabolic alkalosis or the renal compensation of chronic respiratory acidosis in which the kidneys excrete NH_4Cl.

Body fluid losses that would leave the ECF with a high $[Cl^-]$ and reciprocally low $[HCO_3^-]$ could occur if Na^+ and K^+ were lost with HCO_3^-, but if the lost anion was not HCO_3^- or Cl^-, hyperchloremic acidosis could still develop. One example of this scenario is the loss of Na^+ and K^+ with butyrate or acetate anions of bacterial origin in colonic diarrhea (27); another example is the loss of urine containing ketoacid anions with Na^+ and K^+, as long as the ratio of fluid $\{[Na^+] + [K^+]\}$/plasma $[Na^+]$ exceeds the fluid [Cl]/plasma $[Cl^-]$.

These examples are explained by the exchanges of electrolytes between the ISF and the lumen of the gastrointestinal tract or the ISF and the urinary space. In cystic fibrosis, the losses of sweat with high $[Cl^-]$ could cause hypochloremic alkalosis (5). More examples of acid-base disorders originating at different sites of the gastrointestinal and renal systems are shown in Tables 1–4, along with the transport mechanisms on plasma membranes that could generate the disorder.

Some acid-base disorders are generated without direct involvement of H^+ or HCO_3^-. For example, diuretics that inhibit NaCl reabsorption in the distal tubule (thiazides) or NKCC2 in the thick ascending limb of Henle (loop diuretics) cause hypochloremic alkalosis due to the relative loss of Cl^- exceeding that of Na^+. As shown in Table 4, the hereditary syndromes Bartter's and Gitelman's also lead to chloride-wasting alkalosis (14). Administration of NaCl in intravenous solutions adds proportionately more Cl^- than Na^+ to the ECF and can cause hyperchloremic acidosis.

Generation of Reciprocal Changes of HCO_3^- and Non-Cl^- Anions Within the ECF

As shown in FIGURE 4, the circulating plasma component of the ECF is capable of transporting or shuttling metabolic fuels or precursor substrates between tissues like brain, heart, liver, and skeletal muscle. In starvation, the catabolic state breaks down fat in adipose tissue, allowing free fatty acids to be carried to the liver where mitochondrial ketoacid production occurs. The β-hydroxy butyrate and acetoacetate exit the hepatocytes by carriers known as H^+-linked monocarboxylate transporters (MCT) and are cleared from the circulation by similar transporters in brain and cardiac muscle cells as an alternative source of energy when glucose is scarce (29, 33, 49, 58). The H^+-MCT cotransport cannot be distinguished from anion exchange of the organic anion with OH^-, which in the ECF would lower $[HCO_3^-]$. Some ketoacids will be filtered and lost in urine (ketonuria), but if hepatic production remains low, an increase in plasma and ECF concentrations may be minimal. Several MCTs, as well as di- and tri-carboxylate and other organic anion transporters, have been described. Some MCTs are Na^+-linked (SLC5A8) and are present in the apical membranes of renal proximal tubules and colon, where they can transport ketoacids and lactate in the kidney or short-chain fatty acids from the gastrointestinal tract (6). In diabetic ketoacidosis where insulin is lacking, the ketoacid

Table 4. *Causes of metabolic alkalosis of renal origin*

Renal Epithelial Cell	Cause/Gene/Transporter	Associated Findings
Thick ascending limb; loop of Henle	Bartter's syndrome (14); apical NKCC (SLC12A1)' apical Cl^- channel (CLCNK); apical ROMK channel (KCNJ1)	Hypochloremic alkalosis; ECF volume depletion; hypokalemia; hypercalcuria; decreased concentrating ability
Loop of Henle	Furosemide (19)/loop diuretics	As above
Distal tubule	Gitelman's syndrome (56); loss of function; apical NCC (SLC12A3)	Decreased Na, Cl, and K reabsorption; hypocalciuria; hypomagnesemia
Distal tubule	Thiazides (55)	As above
Collecting duct principal cell	Liddle's syndrome; apical ENaC (56); gain of function	ECF expansion; hypertension; hypokalemia; low renin; low aldosterone
	Hyperaldosteronism; adrenal (primary)	ECF expansion; hypertension; hypokalemia; low renin; high aldosterone
	Hypercortisolism; adrenal; ACTH secreting tumor	Cushing's syndrome
	11-β OH-steroid dehydrogenase, Type 2; loss of enzyme function; licorice; apparent mineralocorticoid excess (AME); (11BHSD2) mutation	Cortisol activates MR; high cortisol/cortisone; low renin; low aldosterone

production may be severe, greatly exceeding plasma clearance so that the plasma ketoacid anion concentrations are increased. The negative charge associated with these anions is associated with a concomitant fall in ECF [HCO_3^-]. The traditional approach would maintain that it is the H^+, exiting with the ketoacid anion via the H^+-coupled MCT, which causes the [HCO_3^-] to fall. The strong ion approach would suggest that a rise in the organic anion concentration mandates a fall in

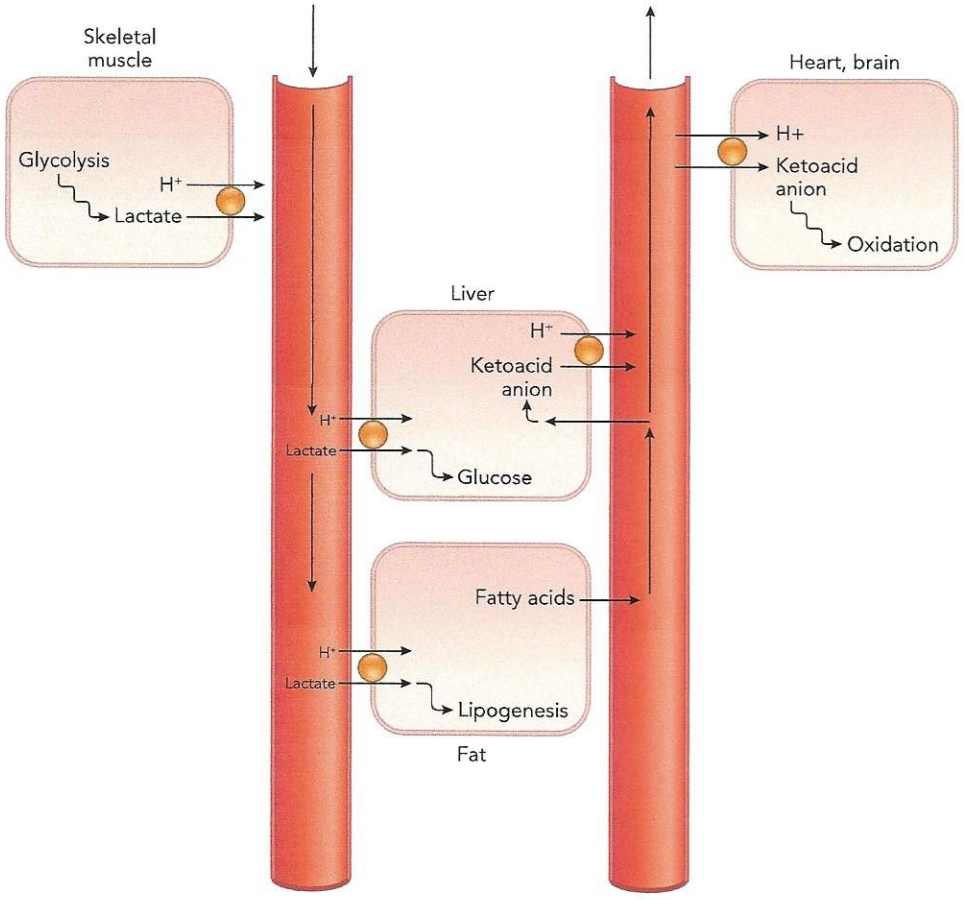

FIGURE 4. **Cell-to-cell transfers of important metabolites utilize many solute membrane transporters**
Substrates exiting one cell type or organ and entering another cell type or organ may utilize the same or similar transporters. Examples shown are the release of lactate from exercising muscle and uptake by liver cells of lactate, a precursor of glucose in gluconeogenesis. Glucose released by liver can be utilized by muscle. Ketoacids produced in hepatocytes when glucose is low are taken up by brain cells and heart as an alternative energy source.

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Table 5. *Organic anion acidosis*

Disorder (Organic Anion)	Cause Carrier/Transporter	Solute	Associated Findings
Ketoacidosis	Diabetes mellitus; acetoacetate; β-OH butyrate; MCTs		Hyperglycemia starvation ketosis; hypoglycemia; ethanol
L-lactic acidosis	L-lactate; MCTs		Sepsis; hypoxemia; hypotension; metabolite of propylene glycol
D-lactic acidosis	D-lactate; MCT-1		Bacterial overgrowth; short bowel; ataxia; confusion
Salicylate toxicity	Salicylate; OAT-1/Na^+-coupled MCT		Respiratory alkalosis
Ethylene glycol ingestion	Glycolate; glyoxalate; oxalate; MCT-1 and SO_4^{-2} exchanger		Renal failure; neurological symptoms
Methanol ingestion	Formaldehyde; formate (4, 37)		Blindness
Acetominophen	5-oxoprolinuria MCT-1		Gamma-glutamyl transpeptidase cycle; low glutathione

[HCO_3]. In contrast to hyperchloremic acidosis, organic acidoses are less likely to be associated with hyperkalemia (23), a finding that may relate to the movement of the organic anion from cells with H^+ rather than entry of H^+ into cells in exchange for K^+.

Another transfer from tissue to tissue via the plasma component of the ECF involves lactate and is known as the Cori cycle (26, 38). L-lactate accumulates from pyruvate during anaerobic glycolysis during exertion of skeletal muscle and is transported from muscle, exiting to the ECF through MCTs and an outwardly directed solute gradient. Lactate is picked up by hepatocyte MCT, driven by its inwardly directed gradient. In the liver and in the presence of glucagon, lactate can form glucose through gluconeogenesis, returning glucose to the exerting muscle. One reason that plasma does not accumulate pyruvate to the same degree is that the MCT has greater specificity for lactate. Pyruvate remains in the cell as a potential energy source through acetyl coenzyme A. Many tumors utilize glycolysis for energy, growth, and angiogenesis, and produce large quantities of lactate from glucose (the Warburg effect), utilizing MCTs in transporting lactate across cell membranes (74, 79). Lactate and pyruvate appear to enable the accumulation of hypoxia-inducible factor-1α under aerobic conditions, thereby supporting the growth of cancer cells (45, 69, 71). Decreased expression of an isoform of H^+-linked MCT in skeletal muscle leads to failure of muscle to export lactate, causing a chronic fatigue syndrome (29). Toxic substances and drugs utilize solute transporters to eliminate anions in the bile or urine (50). D-lactate, which is metabolized more slowly than the more physiological L stereoisomer, is released by bacterial lactobacilli in bacterial overgrowth syndromes, absorbed by intestinal cells, and taken up by brain MCTs (36, 44). Since the effects of D-lactic acidosis on the central nervous system are prominent, and because inhibitors of tissue-specific MCTs have been developed (43), there is potential for treatment of this disorder.

Several clinically important toxicities develop from exogenous alcohols such as ethylene glycol. After metabolism by alcohol and aldehyde dehydrogenases, toxic acid anions are produced. Glycolate is exported via MCTs in hepatocytes into the ECF, from which tissues such as brain may accumulate these toxins (30, 64). Glyoxylate and oxalate are transported from cells in exchange for SO_4^{-2} and by anion exchangers in the SLC26 gene family (3, 17). In the case of oxalates, urinary excretion may lead to tubular obstruction by calcium oxalate precipitates, causing renal failure.

5-Oxoprolinuria in the acquired form is detected in debilitated patients with depleted intracellular glutathione (GSH) who are taking acetaminophen. The accumulation of 5-oxoproline (pyroglutamic acid) is caused by further GSH depletion by acetaminophen, through interference with the gamma-glutamyl transpeptidase pathway responsible for creating GSH, which shuttles amino acids into the cytosol. Normal glutathione levels are necessary for feedback inhibition of gamma-glutamylcysteine synthase, which regulates the activity of the cycle; when the enzyme is not inhibited, 5-oxoproline accumulates (4). As shown in Table 5, 5-oxoproline leaves cell via plasma membrane H^+-coupled SLC16A1/MCT1 transporter (57, 62). In the ECF, the presence of the H^+ and anion causes HCO_3^- to fall, and an organic acidosis develops.

Salicylate toxicity from aspirin ingestion leads to salicylate movement into cells by Na^+-dependent (SMCT) and independent organic anion transporters (OAT-1, MCT-1) (51, 59, 61). Thus many toxic substances may be ingested or produced endogenously and move into or out of cells, causing both intracellular and extracellular acidosis, using the mechanisms in place for normally transferring metabolic substrates between tissues and eliminating toxins from the body.

In these examples of organic anion metabolic acidoses, it should be appreciated that the organic

acids may be formed in one organ, acidifying those cells more severely than cells not involved in acid production. The ion transporters allow exit of these acids into the ECF and uptake across cell membranes of other tissues, depending on solute gradients.

Several large gene families encode these solute carrier proteins (2, 3, 31). Various cation and anion transporters that participate in normal function and clinical acid-base disorders are shown in FIGURE 1 and Tables 1–5. These transporters may be involved in disease states by several mechanisms. They can generate fluid content in a transcellular space that is lost from the body; they may increase or decrease their normal secretory function due to changes in solute gradients; the transporters may associate with loss- or gain-of-function mutations of the transport protein itself or regulatory proteins. In the case of organic anions, excessive production of organic acids or toxic substances ingested may occur within cells. Because of new genomic classification of transporters involved in disease, and because of drug design capable of targeting these transporters, new therapies may become available (16, 18). Targeting specific tissues to increase or decrease solute uptake (7, 66) may have therapeutic potential for organic anion acidoses since not all cells are equally affected by these disorders.

Summary

Acid-base disturbances are diagnosed and treated based on measurements made in blood, with the assumption that ECF pH reflects important intracellular events. Ion transport mechanisms utilized by virtually all cells to regulate their internal pH are also involved in the generation of acid and alkaline secretions in polarized epithelial cells of the gastrointestinal tract. As a result, these mechanisms contribute to normal alkalinization and acidification of the ECF in relation to meals and when the balance is disturbed by diseases of the gastrointestinal tract. Acid and alkaline loads can be buffered by transport between the ECF and ICF by internal balance and by external balance achieved by renal epithelial cells using similar ion transport processes to achieve a steady state of acid production and excretion. Disorders of the renal epithelial cells result in renal acid-base disorders. Acid-base homeostasis is interconnected with systems in place to regulate body fluid volume and K^+, and these connections are consistent with two approaches to acid-base physiology: the HCO_3^-/CO_2 approach and the strong ion model. Reciprocal changes in $[Cl^-]$ and $[HCO_3^-]$ are affected by electroneutrality requirements in the context of fluids lost or gained from the body. Non-Cl^- anions, including organic anions important in health and disease and toxic ingestions, depend on ion transporters that transfer these acidic toxins between cells and the ECF. The contributions of the ion transporters in various tissues and excretory organs are fundamental to a nuanced understanding of acid-base disorders. ■

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