

**Bruce M. Koeppen**

*Advan Physiol Educ* 275:132-141, 1998.

**You might find this additional information useful...**

---

Medline items on this article's topics can be found at <http://highwire.stanford.edu/lists/artbytopic.dtl> on the following topics:

- Biophysics .. Metabolism
- Physiology .. Kidneys
- Physiology .. Nephrons
- Physiology .. Plasma Balance
- Physiology .. Lungs
- Medicine .. Diet

Additional material and information about *Advances in Physiology Education* can be found at:

<http://www.the-aps.org/publications/advan>

---

This information is current as of July 4, 2009 .

## RENAL REGULATION OF ACID-BASE BALANCE

Bruce M. Koeppen

*Departments of Medicine and Physiology, University of Connecticut School of Medicine,  
Farmington, Connecticut 06030*

**T**his article reviews the role of the kidneys in the regulation of acid-base balance. It is intended as a guide for those who teach this aspect of renal physiology to health professions students. An approach is described, which begins with an overview of acid-base balance and then proceeds to describe the details of renal  $H^+$  transport and the important role the production and excretion of  $NH_4^+$  plays in the ability of the kidneys to generate new  $HCO_3^-$ . In the overview, the role of the kidneys in acid-base balance is placed in context for the student by examining the impact of diet and cellular metabolism on acid-base balance. Also, the interactions between the kidneys and lungs to maintain extracellular  $HCO_3^-$  concentration within a narrow range are described. This is followed by a detailed look at the cellular mechanisms of  $H^+$  secretion along the nephron, how these mechanisms are regulated, and how they result in the reabsorption of the filtered load of  $HCO_3^-$ . Finally, the important role of  $NH_4^+$  production and excretion in the generation of new  $HCO_3^-$  is reviewed and highlighted.

*AM. J. PHYSIOL. 275 (ADV. PHYSIOL. EDUC. 20):S132-S141, 1998.*

**Key words:** urine acidification; renal ammoniogenesis

Our knowledge of renal acid-base physiology has progressed over the years as we have been able to study and understand the mechanisms of  $H^+$  and  $HCO_3^-$  transport in increasing detail (i.e., from the level of specific nephron segments to single renal tubule cells, individual cell membranes, and, most recently, the membrane transporters themselves). In general, the teaching of renal acid-base physiology has paralleled this progression of knowledge and has focused on the mechanisms and regulation of  $H^+$  secretion in the various portions of the nephron.

Typically, students are taught that the kidneys reabsorb the filtered load of  $HCO_3^-$  and in addition excrete acid by titrating urinary buffers, with both processes being the result of specific  $H^+$  secretory mechanisms. Traditionally, and for simplicity of presentation to students, the processes of  $HCO_3^-$  reabsorption and acid excretion are ascribed to different portions of the nephron. Accordingly, the proximal tubule is the

primary site in which the filtered load of  $HCO_3^-$  is reabsorbed, and the distal portions of the nephron are involved in acid excretion. Acid excretion assumes central importance in this scheme because it results in the generation of "new  $HCO_3^-$ ," which is returned to the body to replenish that lost during the titration of metabolically produced acids. The principal urinary buffers used for acid excretion are usually said to be phosphate and  $NH_3$ .

Although much of this simplified scheme of renal acid-base physiology is essentially correct, our understanding of the mechanisms involved in the production and excretion of  $NH_4^+$  have changed dramatically in recent years, and it is now clear that  $NH_3$  cannot simply be viewed as a urinary buffer. Consequently, the teaching of renal acid-base physiology must emphasize our new understanding of the role of  $NH_3/NH_4^+$  in renal acid excretion. In addition, students must understand the role of the kidneys as they relate to the

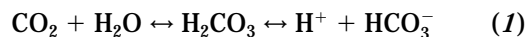
function of other organs that also influence acid-base balance (e.g., lungs and liver).

In this article the role of the kidneys in the maintenance of acid-base balance is reviewed from the perspective of teaching this material to health professions students. First, an overview of the role of the kidneys in acid-base balance is presented. The cellular mechanisms of  $H^+$  secretion along the nephron are then briefly reviewed, with recent discoveries from molecular biological studies highlighted. This is followed by a description of our current understanding of renal  $NH_4^+$  production and excretion. Finally, the integrated function of the kidneys and lungs in the setting of acid-base disturbances (i.e., compensation) is considered.

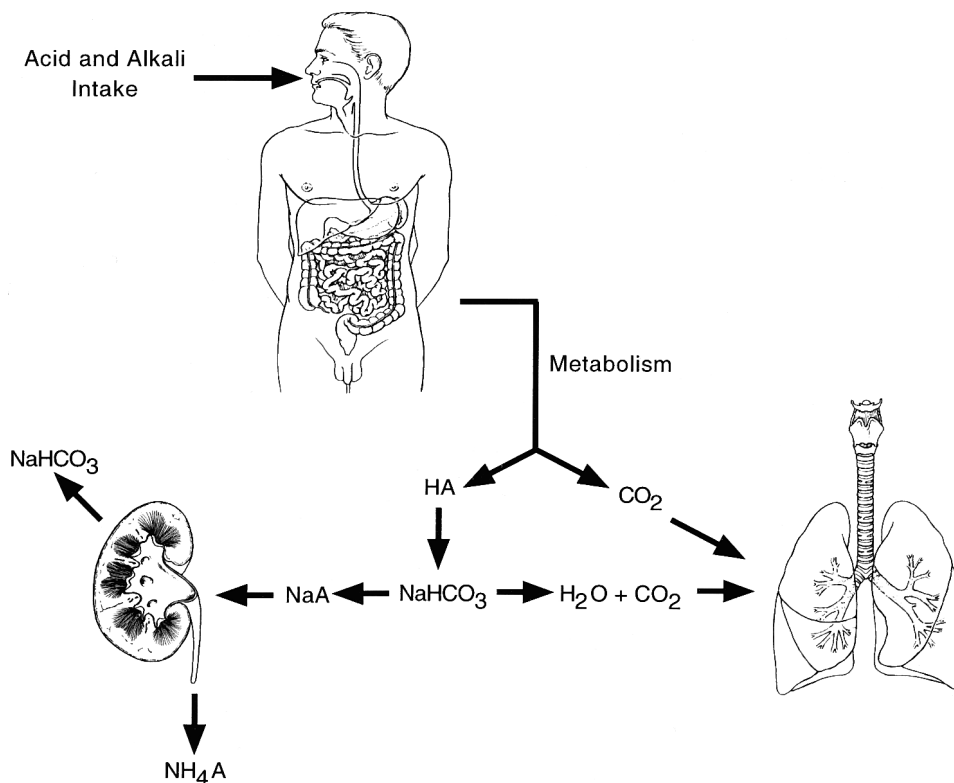
**OVERVIEW**

Figure 1 provides a general overview of acid-base balance and the role of the kidneys. Also depicted is the role of the lungs in the excretion of metabolically

produced  $CO_2$ . The interrelationships between  $H^+$ ,  $CO_2$ , and  $HCO_3^-$  are central to understanding acid-base balance and reflect the physiological importance of the  $CO_2/HCO_3^-$  buffer system.



The  $CO_2/HCO_3^-$  buffer system is not only of quantitative importance in acid-base balance [extracellular fluid (ECF) contains 350–400 meq of  $HCO_3^-$ ], but the  $H^+$  concentration ( $[H^+]$ )/pH of the body fluids is influenced by both  $P_{CO_2}$  and  $HCO_3^-$  concentration ( $[HCO_3^-]$ ). Thus acid-base balance can be effected by both the lungs and the kidneys, the lungs through control of  $P_{CO_2}$  and the kidneys through control of  $[HCO_3^-]$ . This dual impact of  $CO_2$  and  $[HCO_3^-]$  on pH has led to the distinction between  $CO_2$ -derived or “volatile acid” and “nonvolatile acid” such as lactic acid. Although this distinction is in widespread use, it is important to recognize that  $CO_2$  itself is not an acid, and under normal conditions the production and



**FIG. 1.** Overview of role of kidneys in acid-base balance. See text for details. HA, nonvolatile acid.

excretion of  $\text{CO}_2$  does not impact acid-base balance (3). However, as indicated by *reaction 1*, retention of  $\text{CO}_2$  (production > excretion) will produce an increase in  $[\text{H}^+]$  and thus the development of acidosis. Conversely, if  $\text{CO}_2$  production is less than excretion, there will be a decrease in  $[\text{H}^+]$ , and alkalosis results. Acid-base disorders resulting from primary alterations in the  $\text{PCO}_2$  are termed “respiratory” disorders.

As depicted in Fig. 1, nonvolatile acids are buffered by  $\text{HCO}_3^-$  (other non- $\text{HCO}_3^-$  buffers are also involved in this process). Thus, if nonvolatile acid production exceeds the excretion of acid from the body,  $[\text{HCO}_3^-]$  decreases and  $[\text{H}^+]$  increases (see *reaction 1*), and acidosis results. Conversely, if nonvolatile acid production is less than the excretion of acid from the body, then  $[\text{HCO}_3^-]$  increases and  $[\text{H}^+]$  decreases, and alkalosis results. Acid-base disorders resulting from nonvolatile acid or alkali are termed “metabolic” disorders. They are readily detected by the associated change in  $[\text{HCO}_3^-]$ .

Each day, acid and alkali are ingested in the diet. In addition, cellular metabolism produces acid-base equivalents. The majority of energy (i.e., the largest source of calories) is derived from the metabolism of dietary carbohydrates and fats. When tissue perfusion is adequate, and insulin is present at normal levels, cellular metabolism of carbohydrates and fats results in the production of  $\text{CO}_2$  and  $\text{H}_2\text{O}$ . On a typical diet, ~15–20 mol of  $\text{CO}_2$  are produced. Normally, this large quantity of  $\text{CO}_2$  is effectively eliminated by the lungs, and there is no impact of this metabolically derived  $\text{CO}_2$  on whole body acid-base status.

With inadequate tissue perfusion, hypoxia, or in the absence of insulin, the cellular metabolism of carbohydrates and fats does not yield  $\text{CO}_2$  and  $\text{H}_2\text{O}$  but instead results in the production of significant quantities of nonvolatile acids such as lactic acid and ketoacids. With restoration of tissue perfusion (i.e., delivery of adequate amounts of  $\text{O}_2$ ) or treatment with insulin, many of these nonvolatile acids are then further metabolized to  $\text{CO}_2$  and  $\text{H}_2\text{O}$ . In this later process, much of the  $\text{HCO}_3^-$  lost during titration of the nonvolatile acids is regenerated.

Cellular metabolism of other dietary constituents also impacts acid-base balance. Amino acid metabolism

results in the addition of either acid or alkali to the body. For example, the sulfur-containing (e.g., methionine) and cationic (e.g., arginine) amino acids result in acid production on metabolism, whereas alkali results from the metabolism of anionic (e.g., aspartate) amino acids. Given the mix of amino acids in the typical diet, acid production exceeds alkali production. Organic anions (e.g., citrate), when metabolized, result in the generation of alkali.

Several points must be considered when one is trying to determine the impact of nonvolatile acid and alkali on acid-base balance.

1) The source of the nonvolatile acid and alkali is multifactorial and not limited to cellular metabolism. Direct ingestion of acid or alkali can and does occur and, depending on diet, can have a significant impact on acid-base balance.

2) Acid and alkali can be and are lost from the body. For example, vomiting results in the loss of gastric acid, which from an acid-base perspective is equivalent to adding alkali to the body. As a result, vomiting can result in the development of a metabolic alkalosis. Conversely, diarrhea results in the loss of alkali (equivalent to addition of acid), and can result in metabolic acidosis.

3) The impact on acid-base balance of nonvolatile acid or alkali derived from cellular metabolism is highly variable and critically dependent on diet. The ingestion of a vegetarian diet, for example, results in a much reduced acid load to the body, and in some instances may even impart a net alkali load.

Most textbooks state that the direct intake of acid and alkali in a typical diet, the normal loss of some  $\text{HCO}_3^-$  in the feces, and the production of nonvolatile acid and alkali from metabolism result in the net addition of acid to the body. Collectively, these processes are referred to as nonvolatile acid production and ascribed a value of ~1 meq·kg body wt<sup>-1</sup>·day<sup>-1</sup> (70 meq/day for an average adult). It should be apparent from the previous discussion that using 70 meq/day as a value for nonvolatile acid production may not always be accurate. Nevertheless, for the purposes of this review, and to illustrate to students the role of the kidneys in acid-base balance, we will assume that

there is net addition of this amount of nonvolatile acid to the body on a daily basis.

Nonvolatile acids are quickly buffered throughout the body. This buffering occurs in both the intracellular fluid (ICF) and the ECF. As already noted,  $\text{HCO}_3^-$  is a major ECF buffer, and in this titration process it is consumed producing the sodium salts of the nonvolatile acids. To maintain acid-base balance, the kidneys must excrete the anions of the nonvolatile acids and replenish the  $\text{HCO}_3^-$  lost during the titration process. This later process, frequently referred to as “new  $\text{HCO}_3^-$  generation,” results from the excretion of titratable acid (i.e., the excretion of  $\text{H}^+$  with urine buffers) and from the production and excretion of  $\text{NH}_4^+$ . In addition, the kidneys must reabsorb the filtered load of  $\text{HCO}_3^-$  to prevent its loss in the urine, because any lost in the urine would be equivalent to the addition of acid to the body. This overall process is termed “net acid excretion” (NAE) and is quantitated as

$$\text{NAE} = [(\text{U}_{\text{NH}_4^+} \times V) + (\text{U}_{\text{TA}} \times V) - (\text{U}_{\text{HCO}_3^-} \times V)] \quad (2)$$

where  $U$  is the urine concentration,  $V$  is the urine flow rate,  $\text{U}_{\text{NH}_4^+} \times V$  is the amount of  $\text{NH}_4^+$  excreted,  $\text{U}_{\text{TA}} \times V$  is the amount of titratable acid excreted, and  $\text{U}_{\text{HCO}_3^-} \times V$  is the amount of  $\text{HCO}_3^-$  excreted. To maintain acid-base balance, net acid excretion must equal nonvolatile acid production. If nonvolatile acid production exceeds net acid excretion, metabolic acidosis results (serum  $[\text{HCO}_3^-]$  and pH decrease). Conversely, if nonvolatile acid production is less than net acid excretion metabolic alkalosis results (serum  $[\text{HCO}_3^-]$  and pH increase).

Several important points regarding net acid excretion by the kidneys require comment and emphasis.

1)  $\text{NH}_4^+$  excretion, titratable acid excretion, and  $\text{HCO}_3^-$  reabsorption all result from  $\text{H}^+$  secretion along the nephron.

2) Very little acid is excreted by the kidneys as “free  $\text{H}^+$ .” Even with urine of pH 4.0, only 0.1 meq/l of  $\text{H}^+$  is excreted in this form.

3) Titratable acid represents  $\text{H}^+$  excreted with urinary buffers, with the principal urinary buffer being phosphate.

4) When urine pH is  $<6.5$ , very little  $\text{HCO}_3^-$  is excreted, and therefore NAE is simply equal to the sum of titratable acid and  $\text{NH}_4^+$  excretion.

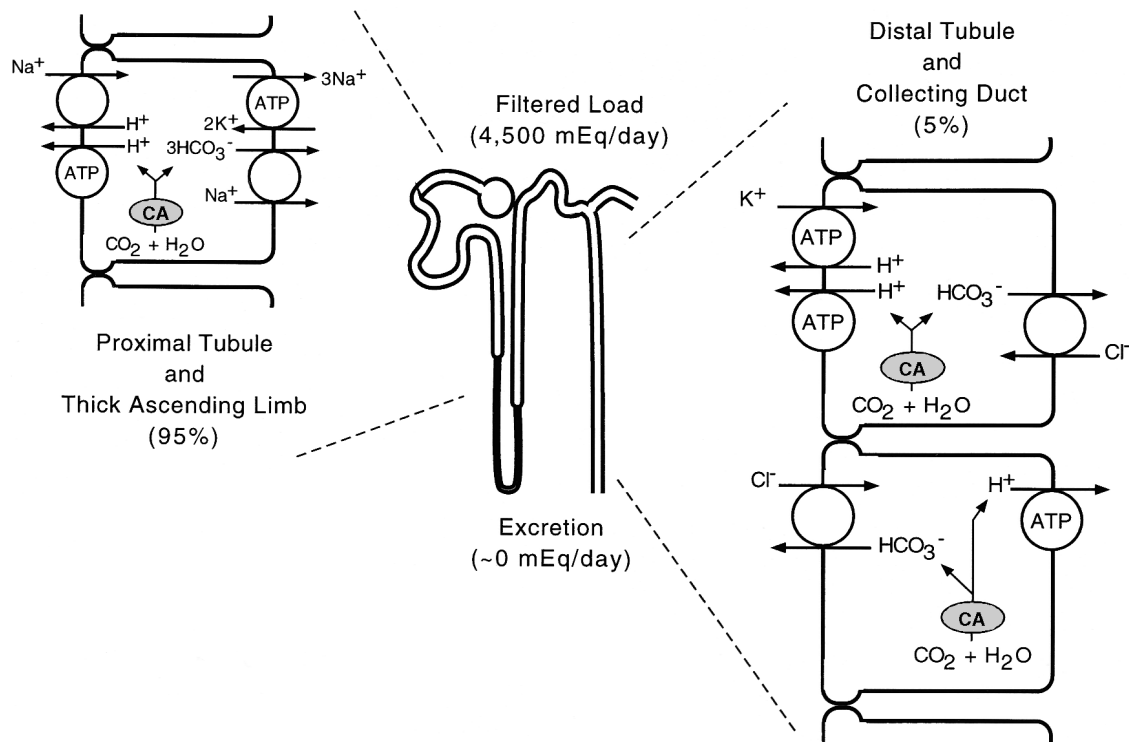
5) The production and excretion of  $\text{NH}_4^+$  is critically important in this process, because it is regulated by the kidneys in response to alterations in acid-base balance. The role of  $\text{NH}_4^+$  excretion in renal acid-base physiology is emphasized in Fig. 1, in which the anions of the nonvolatile acids are shown as being excreted with  $\text{NH}_4^+$ . Importantly, for every  $\text{NH}_4^+$  excreted in the urine an  $\text{HCO}_3^-$  is returned to the body.

### **$\text{H}^+$ TRANSPORT ALONG NEPHRON**

$\text{H}^+$  secretion by the cells of the nephron serves to reabsorb the filtered load of  $\text{HCO}_3^-$ , lower the pH of the urine, titrate urinary buffers, and cause the excretion of  $\text{NH}_4^+$ . Of these processes, the reabsorption of the filtered load of  $\text{HCO}_3^-$  is quantitatively the most important, because the filtered load of  $\text{HCO}_3^-$  is  $\sim 4,500$  meq/day, whereas the amount of  $\text{H}^+$  required for  $\text{NH}_4^+$  excretion plus the amount excreted with urine buffers is generally  $<100$  meq/day.

Figure 2 summarizes  $\text{H}^+$  secretion ( $\text{HCO}_3^-$  reabsorption) along the nephron. The proximal tubule reabsorbs  $\sim 80\%$  of the filtered load of  $\text{HCO}_3^-$ , and an additional 15% is reabsorbed by the thick ascending limb of Henle’s loop. The cellular mechanisms involved are essentially the same in these segments.  $\text{H}^+$  secretion occurs by two apical membrane transporters,  $\text{Na}^+/\text{H}^+$  antiporter and  $\text{H}^+$ -ATPase. Of these transporters the  $\text{Na}^+/\text{H}^+$  antiporter is the predominant pathway for  $\text{H}^+$  secretion. Thus  $\text{H}^+$  secretion is dependent on the lumen-to-cell  $\text{Na}^+$  gradient. Because of this coupling, factors that regulate  $\text{Na}^+$  transport in these segments will secondarily effect  $\text{H}^+$  secretion (see below).

Recent studies on the molecular biology of  $\text{Na}^+/\text{H}^+$  antiporters found that the  $\text{Na}^+/\text{H}^+$  exchanger 3 (NHE-3) isoform is present in the apical membrane of both the proximal tubule and thick ascending limb cells and is the physiologically important antiporter for  $\text{H}^+$  secretion in these segments (14). The  $\text{H}^+$ -ATPase provides a parallel pathway for  $\text{H}^+$  secretion across the apical membrane. The isoform in the proximal tubule appears to be different from the isoform found in the



**FIG. 2.** Summary of cellular mechanisms of H<sup>+</sup> secretion (HCO<sub>3</sub><sup>-</sup> reabsorption) along nephron. Approximately 80% of filtered load of HCO<sub>3</sub><sup>-</sup> is reabsorbed by proximal tubule and 15% by thick ascending limb of Henle's loop. Collecting duct contains both H<sup>+</sup>-secreting and HCO<sub>3</sub><sup>-</sup>-secreting intercalated cells.

intercalated cells of the collecting duct (Refs. 4, 5; see below).

Carbonic anhydrase plays an important role in H<sup>+</sup> secretion by the cells of the proximal tubule and thick ascending limb. It is found in the cytoplasm of these cells, in which it catalyzes the production of H<sup>+</sup> and HCO<sub>3</sub><sup>-</sup> from CO<sub>2</sub> and H<sub>2</sub>O. In the proximal tubule, but not the thick ascending limb, carbonic anhydrase is also found in the apical membrane. The isoforms for the cytoplasmic (CA-II) and apical membrane enzymes (CA-IV) differ (12).

HCO<sub>3</sub><sup>-</sup> generated in the cell from the hydration of CO<sub>2</sub> exits the cell across the basolateral membrane by a symporter that couples the movement of 3 HCO<sub>3</sub><sup>-</sup> with 1 Na<sup>+</sup>. An additional portion of basolateral HCO<sub>3</sub><sup>-</sup> exit may also occur in exchange for Cl<sup>-</sup>.

The distal tubule and collecting duct reabsorb the portion of the filtered load of HCO<sub>3</sub><sup>-</sup> that escapes

reabsorption by the proximal tubule and thick ascending limb of Henle's loop (~5% of the filtered load). HCO<sub>3</sub><sup>-</sup> is reabsorbed as a result of H<sup>+</sup> secretion by the intercalated cells found in this region of the nephron. H<sup>+</sup> secretion occurs by two transporters, H<sup>+</sup>-ATPase and H<sup>+</sup>-K<sup>+</sup>-ATPase. The H<sup>+</sup>-ATPase, as already noted, is a distinct isoform from that found in the proximal tubule. The H<sup>+</sup>-K<sup>+</sup>-ATPase is similar to, but distinct from, the isoform found in the gastric parietal cells (15). As in the proximal tubule and thick ascending limb cells, CA-II catalyzes the intracellular production of H<sup>+</sup> and HCO<sub>3</sub><sup>-</sup>. The predominant mechanism for HCO<sub>3</sub><sup>-</sup> exit across the basolateral membrane is via a Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> antiporter similar to that found in red blood cells (i.e., Band-3).

In addition to the H<sup>+</sup>-secreting intercalated cell, there is a second intercalated cell subtype that secretes HCO<sub>3</sub><sup>-</sup> (see Fig. 2). Because of nonvolatile acid production, and thus the need to excrete acid, H<sup>+</sup> secretion predominates in the collecting duct. However, HCO<sub>3</sub><sup>-</sup>

**TABLE 1**  
**Factors influencing H<sup>+</sup> secretion by the nephron**

Factor	Principal Nephron Site of Action
<i>Increase H<sup>+</sup> secretion</i>	
<b>Primary</b>	
Decrease in plasma [HCO <sub>3</sub> <sup>-</sup> ] (↓ pH)	Entire nephron
Increase in blood PCO <sub>2</sub>	Entire nephron
<b>Secondary (not directed at maintaining acid-base balance)</b>	
Increase in filtered load of HCO <sub>3</sub> <sup>-</sup>	Proximal tubule
Decrease in ECF volume	Proximal tubule
Increase in angiotensin II	Proximal tubule
Increase in aldosterone	Collecting duct
Hypokalemia	Proximal tubule
<i>Decrease H<sup>+</sup> secretion</i>	
<b>Primary</b>	
Increase in plasma [HCO <sub>3</sub> <sup>-</sup> ] (↑ pH)	Entire nephron
Decrease in blood PCO <sub>2</sub>	Entire nephron
<b>Secondary (not directed at maintaining acid-base balance)</b>	
Decrease in filtered load of HCO <sub>3</sub> <sup>-</sup>	Proximal tubule
Increase in ECF volume	Proximal tubule
Decrease in aldosterone	Collecting duct
Hyperkalemia	Proximal tubule

secretion is important in states of metabolic alkalosis, when renal HCO<sub>3</sub><sup>-</sup> excretion must be enhanced.

H<sup>+</sup> secretion by the cells of the nephron is regulated by a number of factors (see Table 1). From a cellular perspective, an important factor regulating the secretion of H<sup>+</sup> across the apical membrane is the cell-to-tubular fluid gradient for H<sup>+</sup>. This gradient depends on the pH of the tubular fluid relative to the pH within the tubular cells. Acidosis, whether of metabolic (decreased [HCO<sub>3</sub><sup>-</sup>] and pH) or respiratory (increased PCO<sub>2</sub>) origin, decreases intracellular pH, creating a more favorable cell-to-tubular fluid H<sup>+</sup> gradient, and thus stimulates H<sup>+</sup> secretion along the entire nephron. Alternatively, metabolic (increased [HCO<sub>3</sub><sup>-</sup>] and pH) and respiratory (increased PCO<sub>2</sub>) alkalosis inhibit H<sup>+</sup> secretion by their effect to increase intracellular pH. Although changes in intracellular pH can directly influence the cell-to-tubular fluid H<sup>+</sup> gradient and thereby H<sup>+</sup> secretion across the apical membrane of the cell, there is also evidence that changes in intracellular pH, perhaps mediated by other intracellular messengers, also alter the activity and expression of key H<sup>+</sup> and HCO<sub>3</sub><sup>-</sup> transporters in the cell (1, 4, 5, 9–11, 13, 14). For example, H<sup>+</sup>-secreting intercalated

cells in the collecting duct respond to acidosis by exocytotically inserting more H<sup>+</sup>-ATPase into the apical membrane (4, 5, 11, 13). Also, the abundance of Na<sup>+</sup>/H<sup>+</sup> antiporter in proximal tubule cells is increased in chronic metabolic acidosis (1, 9, 10, 14).

Other factors may alter renal H<sup>+</sup> excretion, but their influence is not directed at the maintenance of acid-base balance (see Table 1). Because, as noted, H<sup>+</sup> secretion is linked to Na<sup>+</sup> reabsorption in both the proximal tubule and thick ascending limb of Henle's loop, factors that are primarily related to Na<sup>+</sup> reabsorption also influence renal H<sup>+</sup> secretion. These include alterations in the filtered load (i.e., glomerulotubular balance) and changes in ECF volume. The effect of alterations in ECF volume are mediated by the renin-angiotensin-aldosterone system, with angiotensin II acting on the cells of the proximal tubule to stimulate the Na<sup>+</sup>/H<sup>+</sup> antiporter and aldosterone acting on the intercalated cells of the collecting duct to stimulate the H<sup>+</sup>-ATPase (7, 8, 10). Alterations in peritubular Starling forces that occur with changes in ECF volume also are involved in enhancing proximal tubule fluid (and HCO<sub>3</sub><sup>-</sup>) reabsorption in volume depletion and decreasing reabsorption during volume expansion.

#### PRODUCTION AND EXCRETION OF NH<sub>4</sub><sup>+</sup>

Although the reabsorption of the filtered load of HCO<sub>3</sub><sup>-</sup> is quantitatively an important process, simply preventing the loss of HCO<sub>3</sub><sup>-</sup> in the urine does not replenish the HCO<sub>3</sub><sup>-</sup> lost during the titration of non-volatile acid. This later process is accomplished through the excretion of H<sup>+</sup> with urine buffers (titratable acid) and by the production and excretion of NH<sub>4</sub><sup>+</sup>. It should be emphasized that the availability and thus excretion of urinary buffers is not regulated to meet the requirements for acid-base balance. For example, the most abundant urinary buffer is phosphate, the excretion of which is regulated not to effect acid-base balance but in response to phosphate balance needs. In contrast, NH<sub>4</sub><sup>+</sup> production and excretion by the kidneys is regulated to effect acid-base balance. Thus understanding how the kidneys produce and excrete NH<sub>4</sub><sup>+</sup> is critical to understanding the role of the kidneys in acid-base balance.

Traditionally, the excretion of NH<sub>4</sub><sup>+</sup> has been taught from the perspective of urinary buffering. Specifically, NH<sub>3</sub> was viewed as a urinary buffer that could accept

$H^+$ .  $HCO_3^-$  was generated in this process from the hydration of  $CO_2$  within the intercalated cell (i.e., the  $H^+$  was secreted into the tubular fluid and the  $HCO_3^-$  returned to the blood). However, new knowledge regarding the production and excretion of  $NH_4^+$  makes it clear that  $NH_3$  cannot be viewed simply as a urinary buffer (2).

The essential features of  $NH_4^+$  production and excretion are summarized in Fig. 3. Glutamine is metabolized by the kidneys to produce  $2NH_4^+$  and  $2HCO_3^-$ . The  $NH_4^+$  is excreted in the urine, and the  $HCO_3^-$  is returned to the body to replenish that which was lost earlier during the titration of nonvolatile acids. For every equivalent of  $NH_4^+$  excreted in the urine, an equivalent of  $HCO_3^-$  is returned to the body. Figure 3 also illustrates what happens if the kidneys are unable to excrete  $NH_4^+$ . When this occurs,  $NH_4^+$  returns to the liver, where it is metabolized to urea. The net result of this process is that  $2NH_4^+$  are converted to urea with the production of  $2H^+$ . These  $2H^+$  are then titrated by  $2HCO_3^-$ , thus negating the efforts of the kidneys to generate  $HCO_3^-$  from the metabolism of glutamine.

The details of  $NH_4^+$  production and excretion are summarized in Fig. 4. The cells of the proximal tubule are the site of ammoniogenesis. Here glutamine is metabolized to  $2NH_4^+$  and the tricarboxylic acid cycle intermediate 2-oxoglutarate<sup>-</sup>, which is then further metabolized to  $2HCO_3^-$  (2). The  $HCO_3^-$  is returned to

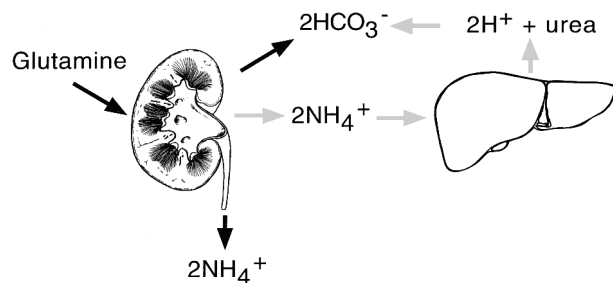


FIG. 3.

Overview of  $NH_4^+$  production and excretion by kidneys. Glutamine is metabolized by kidneys to produce  $2NH_4^+$  and  $2HCO_3^-$ .  $NH_4^+$  is excreted in urine, and  $HCO_3^-$  is returned to body ("new  $HCO_3^-$ "). Shaded arrows illustrate what happens to  $NH_4^+$  if it is not excreted in urine. When this occurs  $2NH_4^+$  are converted to urea by liver, in a process yielding  $2H^+$ . This production of urea from  $NH_4^+$  negates production of  $HCO_3^-$ , which occurred in kidneys from metabolism of glutamine.

the body, and the  $NH_4^+$  is secreted by the cell into the tubular fluid.

$NH_4^+$  secretion by the proximal tubule cells occurs by two mechanisms. The majority is exchanged for  $Na^+$  via the  $Na^+/H^+$  antiporter ( $NH_4^+$  substituting for  $H^+$ ). An additional small portion leaves the cell as  $NH_3$  and is re protonated in the lumen. At this point the process of generating  $HCO_3^-$  is complete (i.e.,  $NH_4^+$  has been secreted into the tubular fluid and  $HCO_3^-$  returned to the blood). However,  $NH_4^+$  must still be eliminated from the body, because as already noted, if any  $NH_4^+$  is reabsorbed by the nephron it will be metabolized to urea by the liver and in that process consume the  $HCO_3^-$  produced from ammoniogenesis (see Fig. 3). Unfortunately, significant amounts of  $NH_4^+$  are reabsorbed by the thick ascending limb of Henle's loop. Unlike the other portions of the nephron, which are highly permeable to  $NH_3$  but not  $NH_4^+$ , the thick ascending limb has the opposite characteristics (low permeability to  $NH_3$  and high permeability to  $NH_4^+$ ). The reabsorption of  $NH_4^+$  by the thick ascending limb occurs via transcellular and paracellular routes. Transcellular reabsorption involves uptake into the cell across the apical membrane via the  $Na^+K^+2Cl^-$  symporter ( $NH_4^+$  substituting for  $K^+$ ) and movement across the basolateral membrane via  $K^+$  channels. Paracellular reabsorption of  $NH_4^+$  is driven by the lumen positive potential difference. The reabsorbed  $NH_4^+$  accumulates in the interstitial fluid of the medulla by the processes of countercurrent multiplication and countercurrent exchange. As a result, this accumulated  $NH_4^+$ , which is in chemical equilibrium with  $NH_3$  ( $pK_a = 9$ ), is available for secretion into the tubular fluid by the cells of the collecting duct.

The secretion of  $NH_4^+$  by the collecting duct is indirect and involves nonionic diffusion of  $NH_3$  and diffusion trapping of the  $NH_4^+$  in the acidic tubular fluid. As indicated in Fig. 4, the secretion of  $NH_4^+$  by the collecting duct is critically dependent on  $H^+$  secretion. If  $H^+$  secretion is impaired in any way, reduced amounts of  $NH_4^+$  will also be secreted and more  $NH_4^+$  will be returned to the body. It should be emphasized that even though the secretion of  $NH_4^+$  by the collecting duct requires  $H^+$  secretion, no additional  $HCO_3^-$  is generated in this process (i.e., the  $HCO_3^-$  generated in the intercalated cell titrates the  $H^+$  generated in the

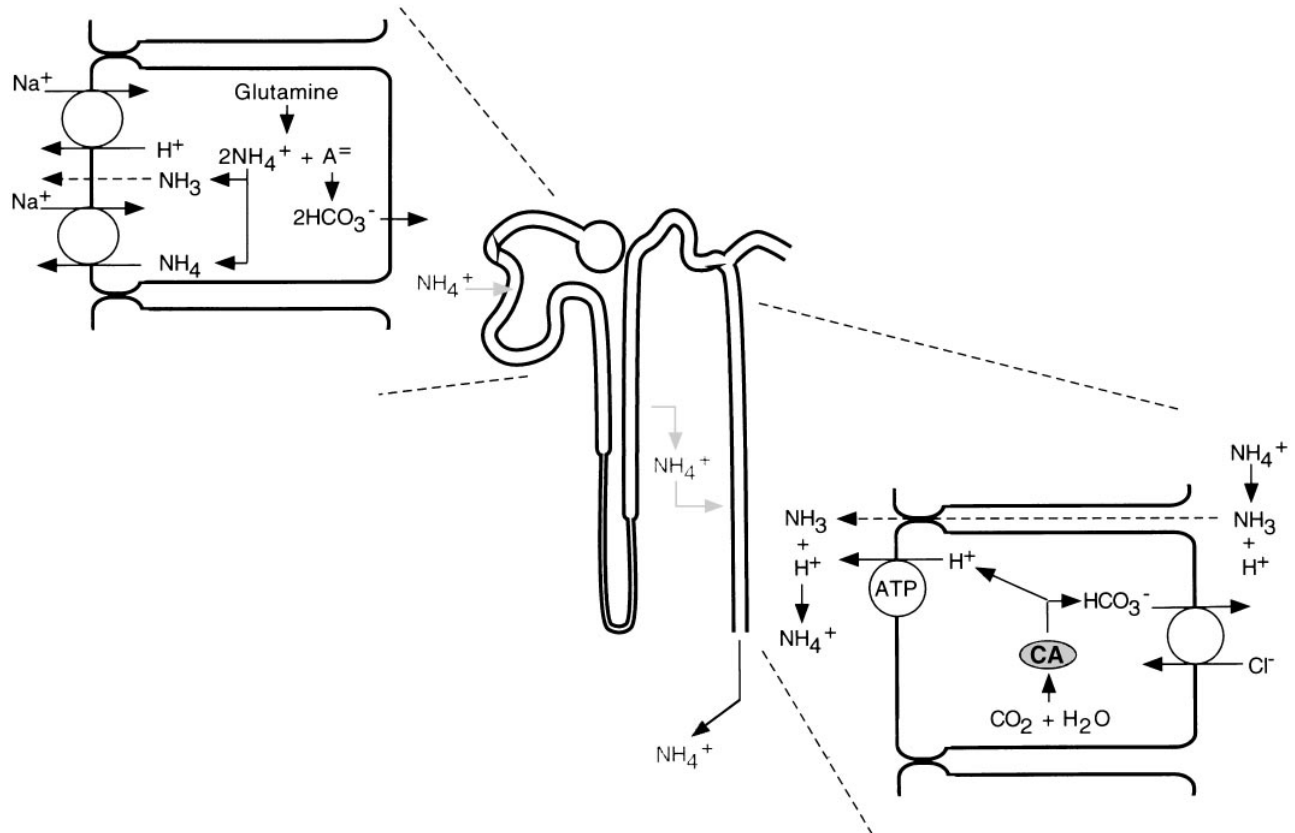


FIG. 4.

$\text{NH}_4^+$  production and excretion. Two  $\text{NH}_4^+$  and two  $\text{HCO}_3^-$  are produced in proximal tubule from glutamine.  $\text{HCO}_3^-$  is returned to body as new  $\text{HCO}_3^-$ , and  $\text{NH}_4^+$  is secreted into tubular fluid. A significant amount of  $\text{NH}_4^+$  is reabsorbed by thick ascending limb, in which it accumulates in interstitial fluid of renal medulla. Some of this  $\text{NH}_4^+$  is secreted into tubular fluid by collecting duct. This secretion process is indirect and involves nonionic diffusion and diffusion trapping. Shaded arrows emphasize pathway for  $\text{NH}_4^+$  through nephron.  $\text{A}^-$ , 2-oxoglutarate $^-$ .

interstitial fluid from the dissociation of  $\text{NH}_4^+$  to  $\text{NH}_3$ ). All the  $\text{HCO}_3^-$  derived from ammoniogenesis was generated during the process of glutamine metabolism in the proximal tubule. The  $\text{H}^+$  secreted by the collecting duct in the process of  $\text{NH}_4^+$  secretion simply prevents the  $\text{NH}_4^+$  from being returned to the liver and converted to urea (see Fig. 3).

Importantly,  $\text{NH}_4^+$  production and excretion is regulated by the kidneys. With acidosis ammoniogenesis is enhanced, and as already noted,  $\text{H}^+$  secretion by the nephron is increased. Thus more  $\text{NH}_4^+$  is excreted, and more  $\text{HCO}_3^-$  is generated and returned to the body. This response to acidosis, frequently termed renal compensation (see COMPENSATION DURING ACID-BASE DIS-

TURBANCES), involves upregulation of the enzymes involved in proximal tubule glutamine metabolism. Therefore, hours to days are required for the full response.

Assessing  $\text{NH}_4^+$  excretion by the kidneys is done indirectly, because assays of urine  $\text{NH}_4^+$  are not routinely available. Consider, for example, the situation of metabolic acidosis. In the setting of metabolic acidosis, the appropriate renal response is to increase net acid excretion. Accordingly, little or no  $\text{HCO}_3^-$  will appear in the urine, the urine will be acidic, and  $\text{NH}_4^+$  excretion will be increased. To assess this, and especially the amount of  $\text{NH}_4^+$  excreted, the "urinary net charge" or "urine anion gap" can be calculated by

measuring the urinary concentrations of  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cl}^-$  (6)

$$\text{urine anion gap} = [\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-] \quad (3)$$

The concept of urine anion gap assumes that the major cations in the urine are  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{NH}_4^+$ , and that the major anion is  $\text{Cl}^-$  (with urine pH < 6.5, virtually no  $\text{HCO}_3^-$  is present). As a result, the urine anion gap will yield a negative value when adequate amounts of  $\text{NH}_4^+$  are being excreted. Indeed, the absence of a urine anion gap or the existence of a positive value indicates a renal defect in  $\text{NH}_4^+$  production and excretion.

### COMPENSATION DURING ACID-BASE DISTURBANCES

When there is a disturbance of acid-base balance the body uses several mechanisms to minimize the impact on the pH of the body fluids. These mechanisms are compensatory in that they do not correct the underlying disorder and include buffering (intracellular and extracellular), respiratory compensation, and renal compensation.

Buffering is the first line of defense because of the rapidity at which it occurs. Extracellular buffering is virtually instantaneous and involves titration of  $\text{H}^+$  by  $\text{HCO}_3^-$ , phosphate, and serum proteins (histidine groups). Intracellular buffering can take several minutes and utilizes the same buffering species. Although it is difficult to estimate, ~50% of nonvolatile acid and 70% of nonvolatile alkali is buffered in the extracellular fluid and the remainder is buffered inside cells.

With metabolic acidosis or alkalosis there is respiratory compensation. This compensatory response is mediated by changes in ventilatory rate, which in turn occur in response to  $\text{H}^+$ . With metabolic acidosis there is an increase in the ventilatory rate, which drives down  $\text{PCO}_2$ . Given the mechanics of breathing,  $\text{PCO}_2$  can be reduced to 10–15 mmHg in a young adult. However, lesser degrees of hypocapnia can be achieved in elderly or weakened patients. Conversely, there is a decrease in ventilatory rate with metabolic alkalosis. The concomitant hypoxia that develops as a result of hypoventilation limits the range of this response, and in general  $\text{PCO}_2$  cannot be maintained

above 60 mmHg. The respiratory compensation to metabolic acidosis and alkalosis is not as fast as the intracellular and extracellular buffers. However, an appropriate response can be developed in several minutes to hours.

As already noted, the kidneys respond to acidosis (metabolic and respiratory) by increasing  $\text{H}^+$  secretion by the nephron segments and by increasing the production and excretion of  $\text{NH}_4^+$ . Both responses are necessary to eliminate all  $\text{HCO}_3^-$  from the urine and to generate  $\text{HCO}_3^-$ . If the kidneys are responding to a metabolic acidosis, the serum  $[\text{HCO}_3^-]$  will still be less than the normal value but not as low as would be the case if the renal compensatory response had not occurred. In contrast, the serum  $[\text{HCO}_3^-]$  is increased above normal in response to respiratory acidosis, because additional  $\text{HCO}_3^-$  is added to the normal levels present before the development of the respiratory acidosis. Because of the need for upregulation of acid-base transporters and the enzymes involved in ammoniogenesis, the renal compensatory response can take a day or more to become fully developed.

The renal response to alkalosis is more complicated and can differ for metabolic and respiratory disorders. In general, it is expected that renal  $\text{H}^+$  secretion and ammoniogenesis are reduced, resulting in loss of  $\text{HCO}_3^-$  in the urine and reduced generation of  $\text{HCO}_3^-$ . Enhanced  $\text{HCO}_3^-$  secretion by the collecting duct also contributes to enhancing  $\text{HCO}_3^-$  excretion. These mechanisms typify the response seen in respiratory alkalosis and many cases of metabolic alkalosis. However, metabolic alkalosis can be seen in a setting of volume depletion. When this occurs, it is difficult for the kidneys to increase  $\text{HCO}_3^-$  excretion, because of the overriding need to reduce  $\text{NaCl}$  excretion. For example, loss of gastric contents produces a metabolic alkalosis and reduces extracellular fluid volume (volume depletion). The volume depletion in turn results in a decrease in the glomerular filtration rate, which limits the filtered load of  $\text{HCO}_3^-$ . In addition, proximal tubule  $\text{Na}^+$  reabsorption is stimulated, resulting in enhanced  $\text{HCO}_3^-$  reabsorption because  $\text{H}^+$  secretion and  $\text{Na}^+$  reabsorption are linked via the  $\text{Na}^+/\text{H}^+$  antiporter (see  $\text{H}^+$  TRANSPORT ALONG NEPHRON). Finally, collecting duct  $\text{H}^+$  secretion is also stimulated by the elevated aldosterone levels seen in the setting

of volume depletion. As a result, the kidneys cannot increase the excretion of  $\text{HCO}_3^-$  until the ECF volume is restored and the stimuli for enhancing renal NaCl reabsorption are turned off.

### SUMMARY

The role of the kidneys in acid-base balance is to excrete acid in an amount equal to nonvolatile acid production. In this way  $\text{HCO}_3^-$  is generated and returned to the body to replenish that lost during the titration of nonvolatile acids. The process of acid excretion involves the secretion of  $\text{H}^+$  by cells of the nephron. The secreted  $\text{H}^+$  serve to reabsorb the filtered load of  $\text{HCO}_3^-$ , acidify the urine, titrate urine buffers, and excrete  $\text{NH}_4^+$ . Because the production and excretion of  $\text{NH}_4^+$  can be regulated by the kidney, it assumes central importance in understanding the physiology of renal acid-base balance.

### Suggested Reading for Students

- Halperin, M. L., and M. B. Goldstein.** *Fluid, Electrolyte, and Acid-Base Physiology* (2nd ed.). Philadelphia, PA: Saunders, 1994, chapt. 1.
- Koeppen, B. M., and B. A. Stanton.** *Renal Physiology* (2nd ed.). St. Louis, MO: Mosby Year Book, 1997, chapt. 8.
- Rose, B. D., and H. G. Rennke.** *Renal Pathophysiology—The Essentials*. Baltimore, MD: Williams and Wilkins, 1994, chapt. 6.

Address reprint requests to the author at Univ. of Connecticut Health Ctr., MC-1915, Farmington, CT 06030.

### References

- Ambühl, P. M., M. Amemiya, M. Danczkay, M. Lotscher, B. Kaissling, O. W. Moe, P. A. Preisig, and R. J. Alpern.** Chronic metabolic acidosis increases NHE3 protein abundance in rat kidney. *Am. J. Physiol.* 271 (*Renal Fluid Electrolyte Physiol.* 40): F917–F925, 1996.
- Brosnan, J. T., M. Lowry, P. Vinay, A. Gougoux, and M. L. Halperin.** Renal ammonium production—une vue canadienne. *Can. J. Physiol. Pharmacol.* 65: 489–498, 1987.
- Gamble, J. L., Jr.** Moving more closely to acid-base relationships in the body as a whole. *Perspect. Biol. Med.* 39: 593–600, 1996.
- Gluck, S. L., M. Iyori, L. S. Holliday, T. Kostrominova, and B. S. Lee.** Distal urinary acidification from Homer Smith to the present. *Kidney Int.* 49: 1660–1664, 1996.
- Gluck, S. L., D. M. Underhill, M. Iyori, L. S. Holliday, T. Y. Kostrominova, and B. S. Lee.** Physiology and biochemistry of the kidney vacuolar  $\text{H}^+$ -ATPase. *Annu. Rev. Physiol.* 58: 427–445, 1996.
- Goldstein, M. B., R. Bear, R. M. A. Richardson, P. Marsden, and M. Halperin.** The urine anion gap: a clinically useful index of ammonium excretion. *Am. J. Med. Sci.* 292: 198–202, 1986.
- Hays, S. R.** Mineralocorticoid deficiency inhibits apical membrane H pump and basolateral membrane  $\text{Cl}/\text{HCO}_3$  exchange in parallel in the inner stripe of the outer medullary collecting duct (OMCD<sub>i</sub>) (Abstract). *J. Am. Soc. Nephrol.* 2: 702, 1991.
- Hays, S. R.** Mineralocorticoid modulation of apical and basolateral membrane  $\text{H}^+/\text{OH}^-/\text{HCO}_3^-$  transport processes in the rabbit inner stripe of outer medullary collecting duct. *J. Clin. Invest.* 90: 180–187, 1992.
- Laghmani, K., P. Borensztein, P. Ambühl, M. Froissart, M. Bichara, O. W. Moe, R. J. Alpern, and M. Paillard.** Chronic metabolic acidosis enhances NHE-3 protein abundance and transport activity in the rat thick ascending limb by increasing NHE-3 mRNA. *J. Clin. Invest.* 99: 24–30, 1997.
- Moe, O. W.** Sodium-hydrogen exchange in renal epithelia: mechanisms of acute regulation. *Curr. Opin. Nephrol. Hypertens.* 6: 440–446, 1997.
- Sabolic, I., D. Brown, S. L. Gluck, and S. L. Alper.** Regulation of AE1 anion exchanger and  $\text{H}^+$ -ATPase in rat cortex by acute metabolic acidosis and alkalosis. *Kidney Int.* 51: 125–137, 1997.
- Sly, W. S., and P. Y. Hu.** Human carbonic anhydrases and carbonic anhydrase deficiencies. *Annu. Rev. Biochem.* 64: 375–401, 1995.
- Tsuruoka, S. and G. J. Schwartz.** Metabolic acidosis stimulates  $\text{H}^+$  secretion in the rabbit outer medullary collecting duct (inner stripe) of the kidney. *J. Clin. Invest.* 99: 1420–1431, 1997.
- Wakabayashi, S., M. Shigekawa, and J. Pouyssegur.** Molecular physiology of vertebrate  $\text{Na}^+/\text{H}^+$  exchangers. *Physiol. Rev.* 77: 51–74, 1997.
- Wingo, C. S., and A. J. Smolka.** Function and structure of H-K-ATPase in the kidney. *Am. J. Physiol.* 269 (*Renal Fluid Electrolyte Physiol.* 38): F1–F16, 1995.