Two processes permit the urine pH and the medullary interstitial pH to remain in an “ideal range” to minimize the risk of forming kidney stones. First, a medullary shunt for NH₃ maintains the urine pH near 6.0 to minimize uric acid precipitation when distal H⁺ secretion is high. Second, excreting dietary alkali as a family of organic anions—including citrate—rather than as bicarbonate maintains the urine pH near 6.0 while urinary citrate chelates ionized calcium, which minimizes CaHPO₄ precipitation. In patients with idiopathic hypercalciuria and recurrent calcium oxalate stones, the initial nidus is a calcium phosphate precipitate on the basolateral membrane of the thin limb of the loop of Henle (Randall’s plaque). Formation of this precipitate requires medullary alkalinization; K⁺-depletion and augmented medullary H⁺/K⁺-ATPase may be predisposing factors.

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KEYWORDS acid-base, citrate, kidney stones, renal medulla pH, urine pH

Acid Balance and Precipitation of Uric Acid Stones

Acid balance has 3 components: the production of H⁺ in the liver from the oxidation of dietary proteins, titration of these H⁺ by HCO₃⁻ and the addition of new HCO₃⁻ to the body when ammonium ions (NH₄⁺) are excreted in the urine. The major acids of dietary origin requiring renal disposal are phosphoric acid and H₂SO₄. Only the H⁺ from H₂SO₄ is derived from the oxidation of sulfur-containing amino acids in the liver, require NH₄⁺ excretion to eliminate these protons because of the low affinity of SO₄²⁻ for H⁺. Support for this version of acid balance is that the daily urinary excretion of NH₄⁺ and SO₄²⁻ are very similar in milliequivalent terms.

Traditional Analysis of the Excretion of NH₄⁺

The major renal response to a large chronic acid load is to increase the rate of excretion of NH₄⁺. There are 2 sites where NH₄⁺ is added to the lumen of the nephron: the proximal convoluted tubule (PCT) and the medullary collecting duct (MCD). Our focus will be on the transfer of NH₄⁺ from the lumen of the thick ascending limb of the loop of Henle (TAL) to the MCD, the medullary shunt of ammonia (NH₃). In the traditional view, an increased secretion of H⁺ in the distal nephron drives the medullary shunt of NH₄⁺ because it de-
creases the urine pH and thereby the concentration of NH₃ in the lumen of the MCD, which allows for a more rapid rate of diffusion of NH₃ down its concentration difference from the medullary interstitium into the lumen of the MCD. This poses a conundrum because if a low urine pH were required to have high rates of excretion of NH₄⁺, there would be an increased risk of precipitation of uric acid in the urine because the negative log of the dissociation constant (pK) of uric acid in the urine is approximately 5.3.⁹ This led us to re-examine this traditional view of the physiology of NH₄⁺ excretion.

Data in Conflict With the Traditional Interpretation of the Physiology of NH₄⁺ Excretion

If a low luminal pH were needed to drive the diffusion of NH₃ into the MCD, one would expect to find a low urine pH when NH₄⁺ excretion is increased markedly. Nevertheless, this is not the case because when human subjects were given a large chronic acid load the urine pH was close to 6.0 when the rate of excretion of NH₄⁺ was greatly augmented.¹⁰,¹¹ In addition, when human beings were deprived of food for prolonged periods and developed chronic ketoacidosis, the urine pH was again close to 6.0 when the rate of NH₄⁺ excretion was at its peak.¹²

Another problem with the assumption that a low pH is important for augmenting the diffusion of NH₃ into the lumen of the MCD becomes evident when this process of diffusion is examined in quantitative terms (Table 1). Although diffusion depends on a concentration difference, the magnitude of the concentration difference for NH₄⁺/NH₃ is almost exclusively a result of the high concentration of NH₄⁺/NH₃ in the medullary interstitial compartment because changes in the concentration of NH₄⁺/NH₃ in the luminal fluid of the MCD are very small at luminal pH values lower than 6.3.

There are 2 sets of data that provide insights on the quantitative importance of this medullary NH₃ shunt. The micropuncture data from studies in rats by Jaeger et al¹³ and Sajo et al¹⁴ revealed that 100% of the NH₃ to be excreted was present in the lumen of the PCT, whereas 33% to 50% of this NH₄⁺ remained in fluid samples obtained from the earliest distal convoluted tubule. Hence, there was a large addition of NH₄⁺ between this distal site and the final urine. If these were the only data evaluated, one would mistakenly conclude that the medullary NH₃ shunt accounted for the majority of NH₄⁺ excreted. This, however, is not the case because in the study by Sajo et al¹⁴ in which fluid also was sampled form the terminal cortical collecting duct, this fluid contained 75% of the NH₄⁺ to be excreted in rats with chronic acidosis, and therefore only a small amount of NH₄⁺ actually was added via the medullary NH₃ shunt.

To explore this issue further, we examined the rate of excretion of NH₄⁺ and the concentration of NH₄⁺ in the medullary interstitial compartment before and after inhibition of LOH function with a dose of furosemide that did not lead to

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**Table 1** Concentration Difference of NH₃ in the Renal Medullary Interstitial Compartment

<table>
<thead>
<tr>
<th>Lumen pH</th>
<th>Interstitial [NH₃]</th>
<th>Lumen [NH₃]</th>
<th>Difference in [NH₃]</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.0</td>
<td>20</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>6.7</td>
<td>20</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>6.3</td>
<td>20</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>6.0</td>
<td>20</td>
<td>1.0</td>
<td>19.9</td>
</tr>
<tr>
<td>5.0</td>
<td>20</td>
<td>0.1</td>
<td>19.9</td>
</tr>
</tbody>
</table>

In this calculation, we assumed that the interstitial fluid pH was 7.3. The concentration of NH₃ in the interstitial compartment is set at 20 in arbitrary units. Decreasing the urine pH toward 6.3 is the only pH range in which there may be a quantitatively important effect on the concentration difference for NH₃ between the interstitial compartment and the lumen of the MCD. In other words, only a large defect in the distal H⁺ secretion (a very high urine pH) will have a large negative impact on the rate of diffusion of NH₃ into the MCD.
a decrease in the urine pH in a rat model with high rates of excretion of NH$_4^+$. Although there was a significant decrease in the medullary concentration of NH$_4^+$, there was actually a small increase, rather than a significant decrease, in the rate of excretion of NH$_4^+$. These findings provide further evidence to suggest that there are other primary functions of this medullary shunt pathway for NH$_3$/NH$_4^+$ than to achieve high rates of excretion of NH$_4^+$; this raised questions about the traditional view of the physiology of excretion of NH$_4^+$.

**Revised View of the Physiology of the Medullary Shunt of NH$_3$**

The insights gained from our study and the recent findings of Khademii et al., Verlander et al., and Weiner et al. provide the basis for suggesting a new function for the medullary shunt pathway for NH$_3$ and NH$_4^+$—we surmised that this function is to prevent too large a decrease in the urine pH when distal H$^+$ secretion is stimulated (Fig 2). Its components require that NH$_4^+$ (rather than NH$_3$) be the compound that diffuses through the renal medullary interstitial compartment because of its higher concentration. Because NH$_3$ (and NH$_4^+$) cannot cross cell membranes by simple diffusion, an additional component such as an NH$_3$ channel is needed to aid the diffusion of NH$_3$ across both the lipid-containing the basolateral and luminal cell membranes of the MCD. This channel has a very critical property, its mouth is extremely hydrophobic and this causes the pK of NH$_4^+$ to decrease by orders of magnitude. The resultant local increase in the concentration of NH$_4^+$ would be enormous in the mouth of the channel, which provides the driving force for rapid rates of diffusion of NH$_4^+$ through membranes that contain this channel in its open configuration. The combination of NH$_4^+$ entry into the mouth of these channels in conjunction with H$^+$ exit completes the H$^+$ balance in the renal medullary interstitial compartment when NH$_4^+$ enters from the basolateral surface of medullary thick ascending limb (mTAL) cells (Fig 2).

There are no data at present as to how the open probability of these NH$_3$ channels may be controlled. If they were to open by a sufficient degree, the addition of NH$_3$ into the lumen of the MCD could force the urine pH upward (toward 6.0) by removing luminal H$^+$ despite continuing H$^+$ secretion by the H$^+$-adenosine triphosphatase (ATPase). The net result is a final urine pH that is approximately 6.0, with a somewhat higher rate of NH$_4^+$ excretion. Hence, we suggested previously that the major function of this medullary shunt pathway may be to adjust the urine pH when distal H$^+$ secretion is stimulated and therefore to minimize the risk of precipitation of uric acid rather than to augment the excretion of NH$_4^+$.

**Base Balance and Precipitation of Calcium Phosphate Stones**

The ingestion of fruit and vegetables provides an alkali load, which must be eliminated to maintain base balance. Examining the net acid excretion formula (equation 1), which describes the role of the kidney to maintain acid-base balance, would suggest that this alkali load is eliminated by markedly increasing the excretion of HCO$_3^-$.

\[
\text{Net acid excretion} = U_{NH_4} + U_{\text{Titrated acid}} - U_{HCO_3^-} \tag{1}
\]

There was a conundrum for base balance if bicarbonaturia were an important way to eliminate dietary alkali because this would increase the urine pH markedly. This high urine pH would create an important risk for CaHPO$_4$ precipitation because of the large increase in the concentration of urinary divalent phosphate (HPO$_4^{2-}$). In quantitative terms, a urine pH of 6.8 would be sufficient to cause the ion product of ionized calcium (Ca$^{2+}$) and HPO$_4^{2-}$ to exceed its solubility constant (Table 2). Hence, we doubted that base balance would be maintained by excreting dietary alkali in the form of HCO$_3^-$. In contrast, the ECF volume is expanded in the experiments performed by Pitts and Lotspeich because NaHCO$_3$ was infused to add HCO$_3^-$. As shown by Kurtzman, this led to a depressed tubular maximum for the reabsorption of HCO$_3^-$ during the

<table>
<thead>
<tr>
<th>Urine pH Level</th>
<th>H$_2$PO$_4^{-}$, mmol/L</th>
<th>HPO$_4^{2-}$, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>6.8</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>7.1</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>7.3</td>
<td>7.5</td>
<td>22.5</td>
</tr>
<tr>
<td>7.4</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>7.5</td>
<td>5</td>
<td>25</td>
</tr>
</tbody>
</table>

For this calculation, we used a total 24-hour excretion of inorganic phosphate of 30 mmol/d and a urine volume of 1 L/d. At a urine pH of 7.1, two thirds of the total phosphate is in the divalent form. There is a small increase in HPO$_4^{2-}$ concentration when the urine pH increases from 7.1 to 7.5.

**Data in Conflict With the Traditional View of Base Balance**

Because the urine pH is close to 6.0 for the majority of the 24-hour period (Fig 1), the urine contains very little HCO$_3^-$. A second conclusion is that there is no renal threshold or tubular maximum for the reabsorption of HCO$_3^-$. Because the plasma HCO$_3^-$ concentration increases each time HCl is secreted in the stomach. If there were a tubular maximum or a renal threshold for HCO$_3^-$ reabsorption as proposed by Pitts and Lotspeich, this bicarbonaturia should occur on a regular basis, but frequent measurements of the urine pH did not reveal this high pH (Fig 1). To explain this difference in interpretation, one must examine the associated findings with the gain of HCO$_3^-$. When HCl is secreted, there is no expansion of the extracellular fluid (ECF) volume (there is a loss of Cl$^-$ and a gain of HCO$_3^-$ in the ECF compartment). In contrast, the ECF volume is expanded in the experiments performed by Pitts and Lotspeich because NaHCO$_3$ was infused to add HCO$_3^-$. As shown by Kurtzman, this led to a depressed tubular maximum for the reabsorption of HCO$_3^-$ during the.
alkaline tide in the proximal convoluted tubule and an apparent renal threshold for HCO$_3^-$.

**How base balance is achieved**

The dietary alkali load is converted initially to HCO$_3^-$ in the liver. This is followed by the production of organic acids in the H$^+$ titrate HCO$_3^-$ hence the alkali load is eliminated, base balance is maintained by the excretion of organic anions$^{22}$ with dietary K$^+$ in the urine.$^{27}$ This description of base balance removes the less specific, *endogenous acid production*, while revealing that it is a component of the larger integrative physiology of elimination of dietary alkali. Therefore, to describe the role of the kidney in acid-base balance, it is essential to incorporate the excretion of the daily dietary alkali load in the form of organic anions that can metabolized to produce HCO$_3^-$ in the body into the net acid excretion formula as potential HCO$_3^-$ (equation 2).

Revised net acid excretion

\[ U_{\text{NH}_4} + U_{\text{titrated acid}} - U_{\text{HCO}_3} - U_{\text{Potential HCO}_3^-} \]  

To eliminate dietary alkali without increasing the likelihood of forming CaHPO$_4$, a family of organic anions, including citrate are excreted. Not only does this achieve base balance while maintaining the urine pH close to 6.0, it has a second advantage in stone-prevention terms because this minimizes the excretion of ionized calcium by increasing the excretion of its chelator, citrate.

**Pathophysiology of the Alkaline Urine pH in Patients With CaHPO$_4$ Stones**

In our recent publication,$^{28}$ we used these concepts of base balance to study the pathophysiology of persistently alkaline urine pH in patients with recurrent CaHPO$_4$ stones. Understanding the pathophysiology in these patients is especially important to design therapy to prevent the recurrence of stones because patients with this type of kidney stone develop progressive parenchymal damage and nephron loss as a result of plugging of the terminal collecting duct with CaHPO$_4$ crystals.$^{29}$ Our study illustrated that these patients represent a heterogeneous group with regard to the pathophysiology of their alkaline urine pH. Although dietary factors seemed to be important in many patients, we described 2 possible novel lesions that may cause persistently alkaline urine pH values in a subset of these patients. In 1 patient, the lesion seemed to be an acidified PCT cell pH because this patient had a high NH$_3$/SO$_4^{2-}$ and marked hypocitraturia. The other patient also had a high NH$_3$/SO$_4^{2-}$, however, the rate of excretion of citrate was not low. We suggested that the lesion may be a NH$_3$ channel in the MCD with a higher open probability (Fig 2).

**Medullary Interstitial pH and the Initiation of Kidney Stone Formation**

It is now clear from the exciting studies of Evan et al$^2$ that in patients with idiopathic hypercalciuria, calcium oxalate stones begin when a nidus of Ca$_3$(PO$_4$)$_2$ precipitates on the basolateral aspect of the thin limbs of the LOH (Randall’s plaque). Eventually, a calcified mass grows sufficiently to erode into the collecting system, where it provides a site for deposition of calcium oxalate and stone formation. The question we shall now address is, “What factors may lead to high enough concentrations of ionized calcium and trivalent phosphate (PO$_4^{3-}$) in the inner medullary interstitial compartment so that their ion product exceeds their solubility product constant?”

Although absorption of calcium from the LOH and changes in the ionic strength in the medullary interstitial compartment may modify the concentration of ionized calcium in this location, our emphasis will be on PO$_4^{3-}$. A high pH in this location is critical to increase the concentration of PO$_4^{3-}$. Although it is possible that the activity coefficient for HPO$_4^{2-}$ will be altered, there is a paucity of experimental evidence on which to base this.$^{30}$ Hence, we focus on ways to alter the pH of the renal medullary interstitial compartment.

The most important sites where alkali may be added to the interstitial compartment are the LOH and the MCD. In the LOH, this occurs when NaHCO$_3$ is reabsorbed in this nephron segment, but this is not known to be a major variable. In contrast, there can be a large addition of HCO$_3^-$ to this interstitial compartment when K$^+$ is absorbed in the MCD by the H$^+$/K$^+$-ATPase—hence, we focus on this cation exchanger.

To understand the role of H$^+$/K$^+$-ATPase in K$^+$ homeostasis, it is important to examine the regulation of the renal excretion of K$^+$ from a Paleolithic perspective because control mechanisms developed in response to major stimuli that were present at that time. It is very likely that these regulatory systems should persist because pressures of modern times do not have enough control strength to replace them.

The Paleolithic diet provided a large episodic K$^+$ load with HCO$_3^-$ precursors (organic anions), and little NaCl. This large intake of K$^+$ should be excreted promptly to avoid the development of a cardiac arrhythmia, but K$^+$ excretion must diminish quickly when food (K$^+$) intake stops. To achieve this aim, a mechanism is needed to increase the distal delivery of Na$^+$ to augment the excretion of K$^+$ only while the K$^+$ load is present, and natriuresis must be avoided. In rats fed a diet that simulated the Paleolithic intake, the reabsorption of NaCl in the LOH was inhibited in response to a K$^+$ load.$^3$ This seemed to be mediated by an increase in concentration of K$^+$ in the renal medullary interstitial compartment in response to the K$^+$ load. We speculated that H$^+$/K$^+$-ATPase was involved in the reabsorption of K$^+$. Thus, the initial stimulus to upregulate the excretion of K$^+$ was, paradoxically, to reabsorb more K$^+$ in the inner MCD. Having this reabsorption of K$^+$ coupled with the secretion of H$^+$ seemed appropriate because the diet provided a large alkali load. There is an obvious problem, however, with our proposal—the H$^+$/K$^+$-ATPase in the MCD has an increased activity during K$^+$ depletion,$^{31,32}$ whereas our hypothesis requires an increased flux via H$^+$/K$^+$-ATPase in response to a K$^+$ load. To resolve this problem, we added another component to the hypothesis.$^{33}$ When the K$^+$ load is absorbed, the plasma K$^+$ (P$_k$)
concentration increases, but the H⁺/K⁺-ATPase is still active because of the prior period of diminished K⁺ intake. Therefore, there can be an increased delivery of K⁺ to the inner MCD, which can increase the medullary interstitial [K⁺] sufficiently to have a temporary but appreciably higher [K⁺]. This in turn will lead to a modest degree of inhibition of mTAL function. With time, as the increase in the P₂ is sustained, there will be fewer luminal H⁺/K⁺-ATPase units in the inner MCD, so the rate of K⁺ reabsorption decreases somewhat and the interstitial [K⁺] is less increased and hence the inhibition of reabsorption in the mTAL is not as marked. As a result, there could be enough distal delivery of Na⁺ and Cl⁻ to maintain high rates of K⁺ secretion in the cortical collecting duct, but not induce a large natriuresis.

Because modern diets provide much less K⁺, this transporter now has a different major function because it is needed to maintain high rates of K⁺ secretion in the renal medulla. The activity of which might be modulated by the interstitial fluid pH. Lesions affecting this transporter or the H⁺/K⁺-ATPase might be potential candidates for the development of medullary alkalinization and subsequent precipitation of calcium oxalate kidney stones.

# Conclusions

Although the excretion of NH₄⁺ generates new HCO₃⁻ to eliminate a H⁺ load, this function should be achieved while maintaining a urine pH of approximately 6.0 to minimize the risk of precipitating uric acid. We suggest that the medullary shunt process for NH₄ might not be quantitatively important for NH₄⁺ excretion—rather, its primary function could be to prevent a large decrease in the urine pH consequent to distal H⁺ secretion and thereby minimize the risk of forming uric acid precipitates. Base balance must be maintained while avoiding bicarbonaturia to prevent precipitation of CaHPO₄. Excreting dietary alkali as a family of organic anions—including citrate—achieves base balance while ensuring that the urine pH remains close to 6.0 and also minimizes the excretion of ionized calcium by increasing the excretion of its chelator, citrate. In patients with idiopathic hypercalciuria and recurrent calcium oxalate stones, the initial precipitate is Ca₃(PO₄)₂, which deposits on the basolateral aspect of the thin limbs of the LOH (Randall’s plaque). Precipitation of Ca₃(PO₄)₂ requires medullary alkalinization. A role of K⁺ depletion and activation of medullary H⁺/K⁺-ATPase is suggested.

# References