Evidence for a direct effect of parathyroid hormone on urinary acidification

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Although the effects of parathyroid hormone on calcium and phosphorus metabolism have been widely investigated, less attention has been paid to its effect on urinary acidification. In 1935, Ellsworth and Nicholson (12) reported an immediate rise in urinary pH, bicarbonate, sodium, potassium, and phosphate in normal male subjects following the injection of parathyroid extract (PTE), and postulated that the hormone produced an increase in the excretion of sodium, with secondary increases in phosphate and bicarbonate excretion. In 1951, Kleeman and Cooke (23) observed similar changes in urinary composition following the administration of PTE to two normal subjects, but drew no conclusions from this observation. Recently Nordin (25) reported increases in urinary bicarbonate, sodium, potassium, chloride, and phosphorus following the administration of PTE, but could not determine whether the changes resulted from increases in glomerular filtration rate or from a direct action of the hormone on the renal tubules.

Since a separate action of parathyroid hormone on the renal tubular transport of sodium or hydrogen ions would have important physiological and clinical implications, experiments were performed to determine the pattern of solute excretion following the administration of PTE and of a purified preparation of parathyroid hormone, and to study the mechanism of action of the hormone in the kidney. The results suggest that parathyroid hormone inhibits the sodium-for-hydrogen ion exchange in the renal tubules, possibly by interfering transiently with the ability of the tubule to maintain a hydrogen ion gradient between the body fluids and the tubular urine.

METHODS AND MATERIALS

The subjects for this study consisted of three normal young women, a man with diabetes insipidus, and six thyroparathyroidectomized dogs trained to lie quietly during the performance of clearances. After thyroparathyroidectomy, the dogs were maintained on 60 g of calcium gluconate and 120 mg of desiccated thyroid extract daily. All studies were performed between 8 AM and 1 PM so that circadian fluctuations in solute excretion (3, 24) would have a uniform effect. All studies were performed after a 12-hr fast. Subjects received a liter of water by mouth 45 min before the start of each experiment, and dogs 500 ml of 4% fructose intravenously for 10 min before the start of each experiment to assure an adequate urine flow.

In all experiments “priming” and “sustaining” solutions of inulin and para-aminophenylene (PAH) were infused in 4% fructose. Following several control periods, during which urine pH was stable or declining slightly, 100 units of PTE (Eli Lilly & Co., assayed according to USP specifications) were injected intravenously over a 2-min interval, and sufficient PTE was added to the sustaining solution to infuse 5 U/min. Several clearances...
periods, varying in duration from 15 to 20 min, were obtained during infusion of PTE, and urinary pH was measured at 10-min intervals. Blood was drawn from an indwelling catheter in the brachial or femoral artery at the midpoint of each clearance period and separated immediately, and the serum was frozen until chemical determinations were performed. Separate specimens of blood were collected under oil for determinations of serum bicarbonate and analyzed on the day of study. Separate specimens of urine, withdrawn from the bladder anaerobically for determinations of bicarbonate and ammonia, were analyzed on the same day. Separate specimens of urine were also withdrawn from the bladder for determinations of pH and analyzed immediately on a Beckman pH meter. No correction of pH values for temperature was made. Clearance periods were closed by washing the bladder with 30 ml of air followed by manual compression. Samples of urine were checked frequently to ascertain the absence of reducing substances.

Studies in dogs. A total of 30 studies were performed in the dogs. With the exceptions noted below, the experimental protocol included a) high-sodium diet (220 mEq/day); b) the oral administration of 100 mmoles of ammonium chloride in divided doses on the day prior to each experiment to assure the excretion of an acid urine; and c) the administration of one of four different lots of a commercial preparation of PTE (Lilly). The exceptions were as follows:

1. Four experiments were performed after the dogs were fed a low-sodium diet (9 mEq/day) for 21 days.
2. Six experiments were performed following induction of a severe metabolic acidosis with ammonium chloride (100 mmoles/day) for 4 days prior to study.
3. Three experiments were performed using a purified parathyroid hormone\(^1\) rather than the commercial extract (Aurbach and Potts, assayed according to Munson).

In addition, the effect of changing the buffer excretion in the urine was examined by paired experiments performed in two dogs as follows: studies performed while buffer excretion was low were compared with studies performed after buffer excretion had been raised by the intravenous administration of sufficient creatinine to raise the serum concentration to 60 mg/100 ml and sufficient sodium acid phosphate (0.7 M, pH 4.8) to raise the serum phosphorus concentration to 15 mg/100 ml.

Four control studies without PTE and one each with infusion of 40 units of ACTH, 1.0 mg of purified human growth hormone, 10 units of thyrotropic hormone (TSH), 10 units of insulin, and 0.5 \(\mu\)g of angiotensin (each given within 3 min) were performed at the same time of day to check the specificity of the results described below.

Studies in man. A total of seven experiments were performed in the four human subjects. All subjects were on a high-sodium diet (220 mEq/day) and all received 100 mmoles of ammonium chloride orally in divided doses on the day prior to each experiment.

1. In one subject, paired experiments were performed with the commercial extract of PTE and with the purified hormone.\(^2\) In the other three subjects, only the commercial preparation was used.

\(^1\) Kindly donated by Drs. Gerald Aurbach and John Potts of the National Institutes of Health.

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and Marshall (7), respectively. Urinary titratable-acidity-minus-bicarbonate was determined by the method of Dawson et al.

$$NaH_2PO_4 =$$ Bonsnes and Taussky (4), Walser et al. (26), and Bratton (9, p. 1).

mined by the methods of Fiske and SubbaRow (15), nitrogen was determined by the method of Conway (9, p. 1).

phosphorus, creatinine, inulin, and PAH were deter-

Aminco-Bowman osmometer (6). Serum and urinary

serum chloride by the method of Cotlove et al. (1).

uring the osmolar clearance (estimated by multiplying the

Calculations. Glomerular filtration rate (GFR) was estimated from the clearance of inulin or exogenous creatinine, renal plasma flow (RPF) from the clearance of PAH. The reabsorption of phosphate (TRP) was calculated by subtracting the amount of phosphorus excreted in milligrams per minute from the amount filtered in milligrams per minute (estimated by multiplying the GFR by the serum phosphorus concentration). Free water clearance (Cf in) was calculated by subtracting the osmolar clearance (estimated by multiplying the urinary osmolality by the urine flow in milliliters per

2. In two subjects, the effect of changing the excretion of buffer in the urine was examined as follows: buffer excretion was decreased by feeding a low-phosphorus diet for 10 days and aluminum hydroxide gel, 120 ml/day, for 4 days prior to the experiment. These studies were compared with studies following 10 days of a high-phosphorus diet, to which sodium phosphate (Na$_2$HPO$_4$: NaH$_2$PO$_4$ = 4:1), 14 g/day, had been added. In the latter group, sufficient neutral isotonic sodium phosphate (pH 7.4) was given intravenously to raise the serum phosphorus concentration to 16 mg/100 ml during the clearance.

3. Comparable observations were made in a subject with documented diabetes insipidus in order to observe the effect of PTE on the excretion of free water.3

Laboratory methods. Serum and urinary sodium and potassium were determined on the Process and Instrument flame photometer. Serum and urinary osmolality were determined by freezing-point depression on an Aminco-Bowman osmometer (6). Serum and urinary phosphorus, creatinine, inulin, and PAH were determined by the methods of Fiske and SubbaRow (15), Bonsnes and Taussky (4), Walser et al. (26), and Bratton and Marshall (7), respectively. Urinary titratable-acidity-minus-bicarbonate was determined by the method of Dawson et al. (11), in which undiluted urine is freed of HCO$_3^-$ and back titrated to pH 7.4. Ammonium was determined by the method of Conway (9, p. 111-112). Serum and urinary bicarbonate were determined by the method of Conway (9, p. 210-213), and serum chloride by the method of Cotlove et al. (10).

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2 Study performed in collaboration with Dr. John R. Gill, Jr.

3 Mary, normal female volunteer) received 5.4 g of ammonium chloride orally on the day prior to the experiment.

* Lilly extract 3077-789295. † Sustainer II identical to sustainer I except for PTE.

TABLE I. EFFECT OF PTE ON H+ EXCRETION

<table>
<thead>
<tr>
<th>Time, min</th>
<th>GFR, ml/min</th>
<th>Serum P, mg/100 ml</th>
<th>Urinary P, mg/min</th>
<th>Urinary pH</th>
<th>Urinary TA-HCO$_3^-$, pEq/min</th>
<th>Urinary HCO$_3^-$, pEq/min</th>
<th>Urinary NH$_4^+$, pEq/min</th>
<th>Urinary PAH, pEq/min</th>
<th>Urinary Na, pEq/min</th>
<th>Urinary K, pEq/min</th>
<th>Serum HCO$_3^-$, mEq/liter</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-90</td>
<td>Oral hydration with 850 ml H$_2$O</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90-135</td>
<td>10% inulin (15 ml) and 20% PAH (1 ml) primer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>145-180</td>
<td>Start sustainer I 4% fructose with 10% inulin (30 ml/liter) and 20% PAH (8 ml/liter) at 5.0 ml/min</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

RESULTS

Changes in urinary pH, bicarbonate, titratable acidity-minus-bicarbonate, and ammonia. During the control periods, urinary pH was constant or declined slightly, and urinary bicarbonate, titratable acidity-minus-bicarbonate (TA - HCO$_3^-$), and ammonia showed no significant change. Following the administration of PTE, there was an immediate increase in urinary pH, with comitant increases in urinary bicarbonate and decreases in TA - HCO$_3^-$ and ammonia (Fig. 1). The change in urinary pH usually was evident within 5 to 10 min, and the other changes in urinary composition uniformly occurred within the first 15 hr. Changes similar to those produced with PTE occurred in the studies in which the purified hormone preparation was used (Fig. 1), a result which suggests that the changes in urinary acidification were not produced by contaminants in the Lilly extract. The results in normal human subjects were the same as those in the dogs (Fig. 1). The data from a typical study are shown in Table 1. In four separate experiments, PTE was administered twice, with similar changes in urinary composition.

Serum bicarbonate remained constant or declined slightly during the course of the study (Fig. 2). Indeed, since many of these experiments were performed following the oral administration of ammonium chloride, serum bicarbonate was often low during the control periods. In spite of this mild metabolic acidosis, PTE uniformly increased bicarbonate excretion.

Changes in phosphorus excretion. Phosphorus (P) excretion usually began to increase by 40 to 80 min following the beginning of the PTE infusions. The change in urinary pH usually preceded or appeared in the absence of any change in urinary P. Indeed, in some studies urinary P showed an initial decline at a time when urinary pH had already risen substantially. Furthermore, urinary pH had frequently begun to decline towards control values at the time excretion of P became maximal. In Fig. 3, the changes in P excretion in the first 90 min after the start of PTE infusion are plotted against the sum
TA – HCO₃⁻ + NH₃ it is apparent that the effect of PTE on hydrogen ion excretion and that on P excretion are separate phenomena.

Changes in glomerular filtration rate and renal plasma flow. In accord with previous studies (2, 19, 20), GFR and RPF rose, usually in parallel fashion, in most of these studies. Again, however, these changes usually did not appear until 40-80 min after infusion of PTE was begun. Furthermore, there was often an initial decline in GFR at a time when urinary pH and bicarbonate were rising (Fig. 4). Thus, the hemodynamic changes that follow the administration of PTE cannot explain the decrease it produces in urinary hydrogen ion excretion.

Changes in sodium, chloride, and potassium excretion. In most studies a rise in urinary sodium and potassium excretion accompanied the rise in urinary pH and bicarbonate. Chloride excretion, which was measured in nine experiments, rose in four and remained unchanged in five. Four studies were performed in three dogs after 3 weeks of sodium restriction (Fig. 5). The changes in urinary pH were comparable to those seen in these animals on liberal-sodium intake. Sodium excretion rose in two studies and remained unchanged in two, chloride excretion rose in one study and remained unchanged in three, while potassium excretion rose in all four studies.

No significant changes were seen in either serum sodium or serum potassium concentration.

Effect of urinary buffer content. Changes in urinary pH following administration of PTE in two dogs and in two human subjects excreting urine of lower buffer content were compared to those in the same subjects excreting urine of high buffer content. A representative study is shown in Table 2, and Fig. 6 shows the results in all four studies. Although the initial pH of the urine was lower in all subjects when urinary buffer content was low, the final urinary pH with PTE during the period of high buffer excretion was nearly identical in each subject to the final pH during the period of low buffer excretion (Fig. 6). Significant increases in urinary pH occurred in each subject after the excretion of TA – HCO₃⁻ had been increased nearly 10-fold. It thus appeared that the change in urinary hydrogen ion concentration that resulted from PTE was independent of buffer excretion in the urine.

Response to PTE in dogs with moderately severe metabolic acidosis. Seven studies were performed in dogs made acidic by administration of 100 mmol of ammonium chloride daily for 4 days before study. Arterial pH varied from 7.18 to 7.24, serum bicarbonate from 10 to 16 mEq/liter, and serum chloride from 110 to 124 mEq/liter. In three of these studies there was a minimal rise of urinary pH (0.6, 0.8, and 0.8) with a transient fall in TA – HCO₃⁻ and ammonium excretion following administration of PTE. In the other studies, no significant change in acid excretion occurred. In five of these studies, urinary sodium and potassium rose with PTE and in a sixth urinary potassium rose. It thus appeared that an increased stimulus to hydrogen ion secretion could prevent the alkalinization of the urine induced by PTE.

Changes in serum calcium. Serum calcium concentration was measured in seven studies. In a single experiment an increase of 1.0 mg/100 ml in serum calcium occurred in the 4th hr following administration of purified parathyroid hormone. In the other six experiments, no change in serum calcium concentration occurred during the 3 hr of PTE administration.

Changes in urine flow. Changes in urine flow were variable and showed no relationship to the changes in urine pH. In some studies there was an abrupt reduction in urine flow with PTE, associated with a decline in C₃H₂O,
a finding which suggests an increased release of endogenous antidiuretic hormone. However, since the opposite change or, indeed, no significant change was observed in other studies, no conclusions can be drawn regarding the effect of PTE on urine flow or on \( \text{HTO} \). In the patient with diabetes insipidus, PTE caused no significant change in inulin clearance, a rise in urinary pH from 4.75 to 6.59, a doubling of urinary sodium and potassium, and an increase of \( \text{HTO} \) from 6.7 to 8.6 ml/min.

**Control studies.** In studies performed in four of the dogs at the same time of day as the experiments with PTE, there was no significant change in urinary pH in two, and a progressive fall in pH with a rise in excretion of \( \text{TA} - \text{HCO}_3^- \) and ammonia in the other two. There was no change in urinary pH following intravenous administration of a total of 40 units of ACTH gel, 10 units of TSH, 10 units of insulin, or 1.0 mg of purified human growth hormone. Administration of 0.5 µg of angiotensin was followed by a transient elevation of systolic blood pressure and a fall in urinary pH.

**DISCUSSION**

In 1930, Albright et al. (1) administered a crude preparation of PTE to a patient with a large ossified hematoma of the right thigh and noted an increased excretion of water, chloride, and "total base." Of special interest was a decrease in urinary \( \text{TA} - \text{HCO}_3^- \) in spite of a marked simultaneous increase in phosphorus excretion. In 1935, Ellsworth and Nicholson (12) observed with crude PTE changes very similar to those described in the present report. In four healthy male subjects receiving PTE, they observed immediate increases in urinary pH and bicarbonate, associated with decreases in ammonium and \( \text{TA} - \text{HCO}_3^- \). Chloride excretion rose in two subjects and remained unchanged in two. Sodium excretion increased in the three subjects in whom it was measured, and potassium excretion increased in the two subjects in whom it was measured. Phosphorus excretion also showed a prompt rise accompanying the changes in urinary pH. They concluded from these observations that parathyroid hormone may have a direct effect on sodium reabsorption, with a secondary rise in urinary bicarbonate and phosphate. Similar results were noted without comment by Kleeman and Cooke (23), who measured changes in urinary pH, ammonium, and \( \text{TA} - \text{HCO}_3^- \) in only two subjects. The changes in urinary acidification in their subjects did not coincide with the periods of maximal phosphorus excretion. Nordin (25) made similar observations although he was unable to distinguish a direct tubular effect of parathyroid hormone from an effect on glomerular filtration rate.

It is well known that PTE may increase urinary P excretion, probably by decreasing tubular reabsorption of P. In the present experiments, the initial rise in pH was accompanied by some increase in urinary P in most instances. In some instances, however, urinary P did not change or declined as pH rose. A decrease in the reabsorption of P should have the effect of adding filtered P

![Figure 4](https://example.com/fig4.png) **FIG. 4.** Relationship of change in urinary pH to percent change in GFR during first 20 min following PTE infusion.

![Figure 5](https://example.com/fig5.png) **FIG. 5.** Effect of PTE on urinary pH, sodium, chloride, and potassium in Na-depleted dogs. PTE values are those observed in first \( \frac{1}{2} \) hr after administration of hormone.
carbonate, together with the unreabsorbed bicarbonate would decrease the amount of ammonia attracted to the ammonium. Without a change in H ion secretion, however, bicarbonate, and, as pH rose, decrease urinary ammonia would increase the pH as some HPO\(_4^{2-}\) was converted to carbonic acid are "accepted" instead by HPO\(_4^{2-}\), urinary excretion (pH \(\approx 4\)) to the urine. Such P, acting as hydrogen acceptor, could increase urinary pH, increase urinary bicarbonate, and, as pH rose, decrease urinary ammonium. Without a change in H ion secretion, however, the addition of such P could have no effect on the sum of TA - HCO\(_3^-\) plus ammonium, is constant (This conclusion derives immediately from the fact that phosphate at pH 7.4 was added, and the titration to determine titratable acidity has the same end point, 7.4.) increases in urinary titratable-acidity-minus-bicarbonate plus ammonium, is not changed unless the actual secretion of H ion changes. (This conclusion derives immediately from the fact that phosphate at pH 7.4 was added, and the titration to determine titratable acidity has the same end point, 7.4.) The effect of PTE on the excretion of hydrogen ions could also be clearly separated from its effects on glomerular filtration rate or renal plasma flow. A significant rise in urinary pH frequently preceded any rise in glomerular filtration rate (Fig. 4). In a number of studies, indeed, there was no significant change in GFR, whereas there were uniformly clear-cut changes in hypercalciuria. It is unlikely, however, that changes in calcium metabolism were deleterious effects on renal function. Defects in urinary potassium (14) and in urinary hydrogen ion excretion had been reported in subjects with clinical or experimental hypercalcemia and hypercalciuria. It is un-

### TABLE 2. Comparison of changes in urinary pH following administration of PTE during low and high buffer excretion

<table>
<thead>
<tr>
<th>Time, min</th>
<th>GFR, ml/min</th>
<th>Serum HCO(_3^-), mEq/liter</th>
<th>Urinary pH</th>
<th>Urinary TA-HCO(_3^-), aEq/min</th>
<th>Urinary NH(_4), aEq/min</th>
<th>Urinary HCO(_3^-), aEq/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-90</td>
<td>840 ml H(_2)O by mouth</td>
<td>10% inulin (20 ml) and 20% PAH (1 ml) primer</td>
<td>21.4</td>
<td>101</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>99</td>
<td>10% inulin (60 ml/liter) and 20% PAH (8 ml/liter) in 4% fructose at 5.0 ml/min</td>
<td>5.25</td>
<td>20</td>
<td>49</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>130-145</td>
<td>130</td>
<td>21.4</td>
<td>5.25</td>
<td>20</td>
<td>49</td>
<td>0</td>
</tr>
<tr>
<td>145-160</td>
<td>126</td>
<td>21.4</td>
<td>5.40</td>
<td>28</td>
<td>102</td>
<td>0</td>
</tr>
<tr>
<td>160-175</td>
<td>109</td>
<td>21.4</td>
<td>5.50</td>
<td>12</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>175-188</td>
<td>100 units PTE; iv and 900 U/liter sustainer II; at 5.0 ml/min</td>
<td>6.35</td>
<td>10</td>
<td>24</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>175-195</td>
<td>139</td>
<td>21.4</td>
<td>6.35</td>
<td>0</td>
<td>24</td>
<td>80</td>
</tr>
<tr>
<td>185-215</td>
<td>20</td>
<td>20.4</td>
<td>6.40</td>
<td>4</td>
<td>34</td>
<td>54</td>
</tr>
<tr>
<td>215-235</td>
<td>97</td>
<td>20.4</td>
<td>6.00</td>
<td>4</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>235-255</td>
<td>125</td>
<td>21.4</td>
<td>6.10</td>
<td>18</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

A: low buffer excretion

B: high buffer excretion

Subject: S.R., normal female volunteer. * 350 mg P diet and 120 ml Basal gel orally each day for 5 days before experiment. Ammonium chloride, 5.4 g, orally on day before experiment. † Lilly extract 3077-789295* Sustainer II identical to sustainer I except for PTE. § 1.5 g P diet and 5.0 g P orally daily for 1 week prior to study. Ammonium chloride 5.4 g orally on day before experiment.
It is unlikely, however, that changes in serum or urinary calcium can account for the observed changes in hydrogen ion excretion.

The studies with a purified parathyroid hormone showed effects essentially identical to those obtained with PTE. Thus the changes could not have been produced by contaminants in the Lilly extract. Further studies are in progress to determine if digestion of the purified polypeptide with trypsin will abolish its effects on the mobilization of bone calcium.

The results of the present study do not allow a precise definition of the tubular site of this action of parathyroid hormone. The hormone may inhibit the reabsorption of filtered anions from the tubular urine in some nonspecific manner. This would explain the rise in the excretion of both bicarbonate and phosphate that follows infusion of the hormone. However, chloride excretion did not rise uniformly, and the rise in urinary phosphate with the extract seldom coincided with that of urinary bicarbonate. Thus, the results do not suggest that parathyroid hormone has a general effect on reabsorption of anions.

Many of the results could be explained as an effect of PTE on distal sodium reabsorption. This appears unlikely, however, as it would not explain the effects on potassium excretion, or the results in a patient with diabetes insipidus. The increase of urinary pH was associated in almost all instances with an increase in urinary potassium. If distal exchange of sodium-for-potassium-or-chloride had been decreased, potassium excretion should have decreased as hydrogen ion transport decreased. In the patient with diabetes insipidus, urinary potassium rose slightly with the extract. A decrease of sodium reabsorption at the site of formation of free water should have produced a decrease instead of an increase in urinary potassium.

Parathyroid hormone could directly inhibit proximal tubular reabsorption of sodium. If the reabsorption of sodium in the proximal tubule involves the exchange of sodium for hydrogen ions, this would cause a reduction in hydrogen ion secretion. Consequently, a corresponding amount of bicarbonate would escape reabsorption. Furthermore, more sodium would be delivered to the distal tubular site where potassium is secreted, and allow a rise in urinary potassium such as that seen with PTE. In all but three of the studies, urinary potassium, or sodium plus potassium, rose with the rise of urinary pH following administration of PTE. In the severely acidic dogs (see above), in which PTE failed to change the urinary pH, it did cause a rise in urinary potassium (five studies out of six). This suggests a distal exchange of potassium for the sodium released by the action of PTE on proximal tubular sodium reabsorption, even when, in animals secreting hydrogen ions at greatly increased rates, all bicarbonate so released was later reabsorbed.

It is difficult to distinguish with results such as these an effect of parathyroid hormone on sodium reabsorption from an effect on hydrogen ion secretion. Indeed, if these two processes represent an exchange, they probably cannot be separated. However, a single feature of the results suggests that parathyroid hormone may interfere with the kidney's ability to produce or maintain a hydrogen ion gradient across the tubular wall. When the increase with PTE in any of the studies in which it was measured and the GFR decreased as often as it increased with the increase in bicarbonate excretion. Accordingly, the increase in bicarbonate excretion must depend on a decrease in reabsorption of filtered bicarbonate by the renal tubules.

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It is difficult to distinguish with results such as these an effect of parathyroid hormone on sodium reabsorption from an effect on hydrogen ion secretion. Indeed, if these two processes represent an exchange, they probably cannot be separated. However, a single feature of the results suggests that parathyroid hormone may interfere with the kidney's ability to produce or maintain a hydrogen ion gradient across the tubular wall. When the increase with PTE in any of the studies in which it was measured and the GFR decreased as often as it increased with the increase in bicarbonate excretion. Accordingly, the increase in bicarbonate excretion must depend on a decrease in reabsorption of filtered bicarbonate by the renal tubules.

Parathyroid hormone could directly inhibit proximal tubular reabsorption of sodium. If the reabsorption of sodium in the proximal tubule involves the exchange of sodium for hydrogen ions, this would cause a reduction in hydrogen ion secretion. Consequently, a corresponding amount of bicarbonate would escape reabsorption. Furthermore, more sodium would be delivered to the distal tubular site where potassium is secreted, and allow a rise in urinary potassium such as that seen with PTE. In all but three of the studies, urinary potassium, or sodium plus potassium, rose with the rise of urinary pH following administration of PTE. In the severely acidic dogs (see above), in which PTE failed to change the urinary pH, it did cause a rise in urinary potassium (five studies out of six). This suggests a distal exchange of potassium for the sodium released by the action of PTE on proximal tubular sodium reabsorption, even when, in animals secreting hydrogen ions at greatly increased rates, all bicarbonate so released was later reabsorbed.
action of PTE in subjects excreting small amounts of buffer was compared with that in the same subjects excreting large amounts of buffer, the final urinary pH was the same in each subject, and the lowest pH under the influence of PTE was 6.6. Thus, a gradient of 0.8 pH units (7.4–6.6) (a sixfold hydrogen ion gradient) was the highest found with PTE. The change was the same whether net hydrogen ion secretion was relatively low or, as with the experiments on high-phosphate intake, relatively high (Fig. 6).

These observations may have certain clinical implications. There are recurring reports that impairment of urinary acidification may occur with hyperparathyroidism and disappear or improve after removal of parathyroid adenomas (8, 16, 28). This may represent an influence of parathyroid hormone on urinary acidification similar to that reported in the present studies. However, persistent hypercalcemia and hypercalciuria may have produced tubular damage in the subjects of these reports, and this may explain the effect on acidification without a direct action of parathyroid hormone.

REFERENCES


In 1953, Böttiger (5) published a case report on a patient with hyperparathyroidism whose chief symptoms were related to severe hypokalemia. Although no values for urinary pH were recorded, it is possible that interference with hydrogen ion secretion, produced by excessive amounts of circulating parathyroid hormone, had produced in turn an increased excretion of potassium and hypokalemia. Following removal of a parathyroid adenoma, the patient's serum potassium concentration returned to normal and the symptoms of hypokalemia were completely relieved.

The results suggest that parathyroid hormone has an effect on hydrogen ion secretion whose relationship, if any, to the established actions of parathyroid hormone cannot be defined at present. Further studies, perhaps at cellular or subcellular levels, will be needed to show whether the influence of PTH on hydrogen ion transport is related to its effects on calcium ion, or on phosphate ion transport. Elucidation of this property may indeed provide insight into the mechanism of both of the other known actions of parathyroid hormone.