Renal phosphate adaptation in uraemic dogs
with a remnant kidney

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Summary

1. Clearance and micropuncture studies were performed in 27 dogs made uraemic by segmental infarction to examine the factors responsible for phosphate adaptation in chronic renal failure.

2. The animals were studied before and after extracellular volume expansion to 10% of body weight in the presence and absence of parathyroid glands. The results were compared with 19 normal dogs studied under similar experimental conditions.

3. In the dogs with a remnant kidney and intact parathyroids adaptation of phosphate transport was evident, with a high fractional excretion of phosphate. Thyroparathyroidectomy 3 days before study in the dogs with a remnant kidney and moderate renal failure reduced fractional excretion of phosphate to near normal values, indicating a major role of parathyroid hormone in phosphate adaptation. Extracellular volume expansion in these thyroparathyroidectomized uraemic dogs led to an exaggerated phosphaturic response with fractional excretion of phosphate returning towards the value in the uraemic dogs with intact parathyroid glands. Thus acute extracellular volume expansion could also contribute to the increase in fractional phosphate excretion, but extracellular volume probably plays a relatively minor role in the adaptation of phosphate excretion.

4. With more advanced renal failure fractional excretion of phosphate remained high, even after thyroparathyroidectomy, indicating that parathyroid hormone-independent factors become important for phosphate adaptation in the advanced stage of renal failure. The nature of parathyroid hormone-independent changes in fractional phosphate reabsorption in chronic renal failure remains unknown.

5. Proximal tubular fluid/plasma ultrafiltrate phosphate ratios were high in all groups of dogs with a remnant kidney regardless of thyroparathyroidectomy or the degree of renal failure. The non-specific nature of the proximal tubule pattern of phosphate transport indicates that phosphate adaptation is primarily determined by alterations in phosphate transport at a site distal to the proximal convoluted tubule. Alternatively, deep nephrons may play a greater role in determination of the overall phosphate adaptation in the chronically diseased kidney.

Key words: experimental renal disease, micropuncture, parathyroid hormone, phosphate adaptation, phosphate transport, proximal tubule, uraemia, volume expansion.

Abbreviations: GFR, glomerular filtration rate; RK-TPT-I, remnant-kidney intact parathyroid glands group I; RK-TPT-II, remnant-kidney intact parathyroid glands group II; RK-TPTX-I, remnant-kidney thyroparathyroidectomized group I; RK-TPTX-II, remnant-kidney thyroparathyroidectomized group II; N-TPT, normal intact parathyroid glands group; N-TPTX, normal thyroparathyroidectomized group.

Introduction

As chronic renal disease progresses, functional adaptation takes place to increase the absolute
excretion of phosphate per nephron to maintain phosphate homeostasis in the face of a reduced nephron population (Slatopolsky, Gradowska, Kashemsant, Keltner, Manley & Bricker, 1966; Slatopolsky, Robson, Elkan & Bricker, 1968a; Bricker, 1972). Generally, it has been thought that phosphate adaptation in chronic renal failure is mainly the result of secondary hyperparathyroidism, since the removal of parathyroid glands restored fractional tubular reabsorption of phosphate towards the normal value (Slatopolsky et al., 1966, 1968a). Conversely, it has also been shown that uraemic animals can maintain phosphate homeostasis in the absence of parathyroid hormone (Swenson, Weisinger, Ruggeri & Reaven, 1975). In addition, renal phosphate transport is known to be related to sodium transport and extracellular volume expansion leads to significant phosphaturia even without parathyroid hormone (Massry, Coburn & Kleeman, 1969; Suki, Martinez-Maldonado, Rouse & Terry, 1969; Hebert, Rouse, Eknoyan, Martinez-Maldonado & Suki, 1972; Gradowska, Caglar, Rutherford, Harter & Slatopolsky, 1973; Wen, 1974). Therefore, sodium adaptation of chronic renal failure (Slatopolsky, Elkan, Weerts & Bricker, 1968b) may also contribute to phosphate adaptation. Our present clearance and micropuncture studies were designed to re-examine the role of parathyroid hormone in phosphate adaptation in uraemic dogs with segmental infarction. Further, the response to extracellular volume expansion was evaluated in these animals to examine whether factors other than parathyroid hormone, such as extracellular volume, could affect phosphate adaptation.

Methods

Animals

Clearance and micropuncture studies were carried out in 46 mongrel dogs of either sex weighing 12–20 kg. All animals were placed on pellet dog-food regimens (1% phosphorus) and the daily intake of phosphate was approximately 80–100 mmol. In 27 dogs ligation of the 2/3 to 5/6 branches of the left renal artery, followed by contralateral nephrectomy 3–8 weeks later, produced a unilateral remnant kidney. Another week was allowed before micropuncture experiments were performed. Ten of the 19 normal dogs and 13 of the 27 dogs with a remnant kidney were thyroparathyroidectomized 3 days before the experiments. Resection of the thyroid and parathyroid glands was carried out through a midline neck incision and after careful identification of the glands. The completeness of thyroparathyroidectomy was confirmed by the development of significant hypocalcaemia. These animals were given oral calcium carbonate or intramuscular calcium gluconate as necessary to prevent tetany. The following groups of animals were studied.

(1) Nine normal dogs with intact parathyroid glands (N-TPT). (2) Ten normal dogs studied 3 days after thyroparathyroidectomy (N-TPTX).

(3) Fourteen dogs with a remnant kidney, with intact parathyroid glands. This group was further divided into two subgroups according to the level of glomerular filtration rate (GFR). Seven dogs had baseline GFR values over 10.5 ml/min (RK-TPT-I) whereas the remaining seven dogs had GFR values below 10.5 ml/min (RK-TPT-I1).

(4) Thirteen dogs with a remnant kidney, studied 3 days after thyroparathyroidectomy. This group was also subdivided into six dogs with GFR greater than 10.5 ml/min (RK-TPTX-I) and seven dogs with GFR less than 10.5 ml/min (RK-TPTX-I1). The four remnant-kidney groups of dogs divided in this manner provided a comparable degree of renal failure for RK-TPT-I and RK-TPTX-I groups and for RK-TPT-II and RK-TPTX-II groups respectively. (5) Three dogs with a remnant kidney studied 2 h after thyroparathyroidectomy. Only clearance experiments were performed in these animals.

Experiments

Animals were prepared for micropuncture as previously described (Wen, 1974). Under pentobarbital anaesthesia, an endotracheal tube was inserted and adequate respiration was maintained by a Harvard respirator. The jugular, foreleg and femoral veins were cannulated for infusion of fluids or sampling of blood and the femoral artery was cannulated for monitoring blood pressure. The left kidney was exposed by a flank incision and immobilized in a lucite holder. The ureter was catheterized with PE 160 polyethylene tubing for collection of urine and the main renal artery was cannulated with a 27-gauge needle connected to PE 20 tubing for injection of lissamine green. A small area of renal capsule was removed for visualization of the surface tubules. Late or the last accessible segments of the proximal tubule were deliberately selected for micropuncture by injection of 5% lissamine green into the renal artery and timing of its appearance to the surface tubules. A long block of castor oil coloured with Sudan black was injected into the tubular lumen and maintained immediately distal to the puncture site during the collection of tubular fluid. The collection was
timed for calculation of single nephron filtration rate. Late proximal tubular fluid samples were collected (2–6) from each phase of the experiments. Simultaneous 15–30 min clearance collections of urine were made for 3–4 periods in each phase of the experiments and blood samples were drawn at the midpoint of each period. Inulin clearance was used to estimate GFR and p-aminohippurate clearance was obtained for renal plasma flow.

All animals were studied during the control phase of hydropenia and the second phase of extracellular volume expansion. The latter was carried out by infusion of modified Ringer’s solution (containing (mmol/l) sodium 145, potassium 4, calcium 1·5, magnesium 0·75, chloride 128·5 and bicarbonate 25) at 24–48 ml/min until the expanded volume reached 10% of body weight, and thereafter a sustaining infusion of Ringer’s solution was continued at an appropriate rate to replace the urinary loss. The second phase was started immediately after the volume expansion was completed, with each phase lasting 60–90 min.

Chemical analyses
Tubular fluid samples were analysed for inulin by a microfluorimetric method (Vurek & Pegram, 1966) and for phosphate by a microcolorimetric method (Chen, Toribara & Warner, 1956) with an Aminco fluoricolorimeter (American Instrument Co., Inc., Silver Spring, MD, U.S.A.). Tubular fluid volume was measured in 1 μl constant-bore glass capillary tubes (Microcap disposable micropipettes, Drummond Scientific Co., Broomall, PA, U.S.A.) with a Gaertner measuring microscope (Gaertner Scientific Corp., Chicago, IL, U.S.A.) for measurement of the length of fluid column in the capillary tubes. Autoanalyser methods were used for determination of inulin (Steele, 1969), p-aminohippurate (Harvey & Brothers, 1962) and phosphate (Kraml, 1966) in plasma, plasma ultrafiltrate and urine. Plasma ultrafiltrate was obtained by centrifugation of plasma samples in a collodion bag with optimal pH and temperature control (Osmun, 1967). Calcium in plasma ultrafiltrate was measured by atomic absorption spectrophotometry and sodium in plasma and urine by flame photometry. Blood urea nitrogen and plasma creatinine were determined by autoanalyser methods (Chasson, Grady & Stanley, 1961; Marsch, Fingerhut & Miller, 1965).

Statistical analyses
Both clearance and micropuncture data were analysed statistically by paired or unpaired Student’s t-test (Steel & Torrie, 1960) for comparison of the mean values in each phase. All micropuncture data were averaged for each phase of the experiments and the numbers of dogs were used in the calculation of statistical significance.

Results
Clearance data
For comparison with the clearance data from the two groups of dogs with a remnant kidney, the data from 19 normal dogs, of which 10 were studied 3 days after thyroparathyroidectomy, are summarized in Table 1. Packed cell volume fell after volume expansion from 44 ± 2 to 35 ± 2% in the intact group and from 42 ± 2 to 31 ± 1% in the thyroparathyroidectomized group, but the mean blood pressure did not change significantly at 122 ± 4 and 126 ± 5 mmHg and at 120 ± 3 and 128 ± 6 mmHg before and after volume expansion respectively. The mean GFR of the micropunctured kidney was about 33 ml/min in

<table>
<thead>
<tr>
<th>Test</th>
<th>Control</th>
<th>Experimental</th>
<th>Control</th>
<th>Experimental</th>
<th>Control</th>
<th>Experimental</th>
<th>Control</th>
<th>Experimental</th>
<th>Control</th>
<th>Experimental</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-TPT</td>
<td>32.6</td>
<td>±2.5</td>
<td>34.5</td>
<td>±2.7</td>
<td>108</td>
<td>±11</td>
<td>102</td>
<td>±9</td>
<td>1.88</td>
<td>±0.2</td>
</tr>
<tr>
<td>N-TPTX</td>
<td>33.4</td>
<td>±1.8</td>
<td>35.2</td>
<td>±2.1</td>
<td>98</td>
<td>±10</td>
<td>94</td>
<td>±9</td>
<td>2.23</td>
<td>±0.17</td>
</tr>
</tbody>
</table>

Table 1. Clearance data before and after 10% extracellular volume expansion in the normal and thyroparathyroidectomized dogs

Values are means ± SEM and indicate those of the micropunctured kidney only, when applicable. The numbers in parentheses denote the number of dogs. Significance of differences: *P < 0.05; **P < 0.01. N-TPT, normal group with intact parathyroids; N-TPTX, normal group with thyroparathyroidectomy.
in the intact group and 3.1 umol/min and 25.7 ± 2.9 umol/l, respectively. The
was comparable with that of dogs. Plasma ultrafiltrate phosphate was 1.9-
both intact and thyroparathyroidectomized groups of dogs. Plasma ultrafiltrate calcium in the latter group was 0.85 ± 0.08 mmol/l, which was lower than 1.45 ± 0.09 mmol/l for the intact group, indicating the effect of 3-day thyroparathyroidectomy. Plasma ultrafiltrate phosphate was 1.9–2.2 mmol/l in both groups and absolute excretion of phosphate by the single kidney was 4.6 µmol/min in the intact group and 3.1 µmol/min in the thyroparathyroidectomized group. Fractional excretion of phosphate for the two groups was 7.5 and 4.2% respectively. After volume expansion marked phosphaturia occurred in the intact group with fractional phosphate excretion reaching 27.4%, but the response was blunted in the thyroparathyroidectomized group with the value rising to only 12.6%. The natriuretic effect of volume expansion was similar for the two groups with fractional sodium excretion reaching 5–6%.

Clearance data before and after 10% extracellular volume expansion in the dogs with a remnant kidney, with and without thyroparathyroidectomy

Table 2. Clearance data before and after 10% extracellular volume expansion in the dogs with a remnant kidney, with and without thyroparathyroidectomy

<table>
<thead>
<tr>
<th>Dog group</th>
<th>GFR (ml/min)</th>
<th>Renal plasma flow (ml/min)</th>
<th>Plasma ultrafiltrate PO4 PO4 excretion (µmol/min)</th>
<th>Absolute Na excretion (µmol/min)</th>
<th>Fractional Na excretion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Experimental</td>
<td>Control</td>
<td>Experimental</td>
<td>Control</td>
</tr>
<tr>
<td>RK-TPT-I</td>
<td>13.2</td>
<td>14.9*</td>
<td>33.4</td>
<td>33.5</td>
<td>2.06</td>
</tr>
<tr>
<td>(7)</td>
<td>±0.7</td>
<td>±1.2</td>
<td>±1.9</td>
<td>±2.6</td>
<td>±0.10</td>
</tr>
<tr>
<td>RK-TPT-II</td>
<td>7.8</td>
<td>8.7*</td>
<td>20.3</td>
<td>20.6</td>
<td>2.21</td>
</tr>
<tr>
<td>(7)</td>
<td>±0.6</td>
<td>±0.6</td>
<td>±1.2</td>
<td>±1.6</td>
<td>±0.14</td>
</tr>
<tr>
<td>RK-TPTX-I</td>
<td>14.7</td>
<td>16.2</td>
<td>37.5</td>
<td>35.8</td>
<td>1.87</td>
</tr>
<tr>
<td>(6)</td>
<td>±1.1</td>
<td>±1.9</td>
<td>±5.8</td>
<td>±4.4</td>
<td>±0.04</td>
</tr>
<tr>
<td>RK-TPTX-II</td>
<td>7.7</td>
<td>9.3**</td>
<td>17.8</td>
<td>16.2</td>
<td>1.91</td>
</tr>
<tr>
<td>(7)</td>
<td>±1.0</td>
<td>±1.1</td>
<td>±2.8</td>
<td>±2.2</td>
<td>±0.08</td>
</tr>
</tbody>
</table>

Values are means ± sem. The numbers in parentheses denote the number of dogs. Significance of differences: * P < 0.05; ** P < 0.01. RK-TPT, remnant-kidney group of dogs with intact parathyroids; RK-TPTX, remnant-kidney group of dogs with thyroparathyroidectomy.

In all four remnant-kidney groups of dogs, packed cell volume fell similarly after volume expansion owing to haemodilution. Mean arterial blood pressure of 144 ± 3 mmHg in the remnant-kidney groups of dogs was significantly higher than the normal value of 121 ± 3 mmHg (P < 0.001). Plasma ultrafiltrate calcium was normal at 1.68 ± 0.03 mmol/l in the remnant-kidney groups of dogs with intact parathyroids but was decreased to 0.93 ± 0.03 mmol/l in the thyroparathyroidectomized dogs with a remnant kidney, supporting the completeness of thyroparathyroidectomy in the latter groups. Mean plasma ultrafiltrate phosphate in both remnant-kidney groups of dogs was in the range 1.9–2.2 mmol/l, which was not significantly different from the values in the normal groups, and although plasma ultrafiltrate phosphate in the TPT-II group with more advanced renal failure was slightly higher than that in the TPT-I group, the difference was not statistically significant. Absolute phosphate excretion in the remnant-kidney groups of dogs with intact parathyroids at 8.6–12.3 µmol/min was comparable with that of the two kidneys in the intact normal group, indicating maintenance of phosphate homeostasis in the former groups of dogs. The homeostasis of phosphate was maintained as a result of functional phos-
TABLE 3. Proximal tubule micropuncture data before and after 10% extracellular volume expansion in the normal dogs and dogs with a remnant kidney

Values are means ± SEM. The numbers in parentheses denote the number of dogs. Significance of differences: * P < 0·05; ** P < 0·01. N-TPT, normal group with intact parathyroids; N-TPTX, normal group with thyroparathyroidectomy; RK-TPT, remnant-kidney group of dogs with intact parathyroids; RK-TPTX, remnant-kidney group of dogs with thyroparathyroidectomy.

<table>
<thead>
<tr>
<th>Dog group</th>
<th>Single nephron GFR (nl/min)</th>
<th>Tubular fluid inulin/plasma inulin</th>
<th>Tubular fluid PO₄/plasma ultrafiltrate PO₄</th>
<th>Fractional PO₄ delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Experimental</td>
<td>Control</td>
<td>Experimental</td>
</tr>
<tr>
<td>N-TPT (9)</td>
<td>66·4</td>
<td>71·3</td>
<td>1·71</td>
<td>1·36**</td>
</tr>
<tr>
<td>±4·1</td>
<td>±4·7</td>
<td>±0·05</td>
<td>±0·04</td>
<td>±0·04</td>
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<tr>
<td>N-TPTX (10)</td>
<td>67·8</td>
<td>74·5</td>
<td>1·67</td>
<td>1·37**</td>
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<td>±3·9</td>
<td>±5·6</td>
<td>±0·06</td>
<td>±0·05</td>
<td>±0·03</td>
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<tr>
<td>RK-TPT-I (7)</td>
<td>116·8</td>
<td>137·4</td>
<td>1·44</td>
<td>1·23**</td>
</tr>
<tr>
<td>±7·4</td>
<td>±12·3</td>
<td>±0·03</td>
<td>±0·04</td>
<td>±0·06</td>
</tr>
<tr>
<td>RK-TPT-I (7)</td>
<td>106·1</td>
<td>104·8</td>
<td>1·43</td>
<td>1·24**</td>
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<tr>
<td>±11·3</td>
<td>±12·8</td>
<td>±0·04</td>
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<tr>
<td>RK-TPT-II (6)</td>
<td>110·0</td>
<td>119·6</td>
<td>1·49</td>
<td>1·25**</td>
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<td>±8·5</td>
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<td>RK-TPT-II (7)</td>
<td>93·4</td>
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<td>±5·6</td>
<td>±4·3</td>
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<td>±0·02</td>
<td>±0·05</td>
</tr>
</tbody>
</table>

Phosphate adaptation, which raised fractional phosphate excretion to 44·9–49·4% and it increased further to 57·6–64·2% after volume expansion. In the thyroparathyroidectomized remnant-kidney groups of dogs, conversely, absolute phosphate excretion was low: 2·0 μmol/min in the TPTX-I and 4·4 μmol/min in the TPTX-II groups. Fractional phosphate excretion of 7·8% in the TPTX-I group was close to the normal value, whereas that in the TPTX-II group was 31·7%, which was far greater than normal indicating emergence of a parathyroid hormone-independent component of phosphate adaptation. However, the latter value was still slightly lower than the TPT-II value of 49·4% (P < 0·05), suggesting a partial contribution to phosphate adaptation by parathyroid hormone in the TPT-II group. Volume expansion led to an exaggerated phosphaturic response in the TPTX-I group with fractional phosphate excretion reaching 40·5%, which was close to 44·9% of the TPT-I group before volume expansion. In the TPTX-II group, the phosphaturic response to volume expansion was in proportion to the baseline fractional phosphate excretion, which increased to 49·7%, a value similar to that of the TPT-II group before volume expansion. Thus volume expansion appeared to correct the low value of fractional phosphate excretion in both groups of the thyroparathyroidectomized remnant-kidney groups of dogs. In three dogs with a remnant kidney and acute thyroparathyroidectomy of 2 h duration fractional phosphate excretion during hydropenia was 32·8 ± 8·5%, which was similar to that of the TPTX-II group. This suggests that the duration of thyroparathyroidectomy was not the major determinant for the parathyroid hormone-independent phosphate adaptation. In all four remnant-kidney groups of dogs, fractional sodium excretion was higher than that for the normal groups, indicating functional sodium adaptation in uraemic dogs. After volume expansion, there were exaggerated natriuretic responses in the remnant-kidney groups of dogs with fractional sodium excretion reaching 12–17% as compared with normal values of 5–6%.

Micropuncture data

Micropuncture data of the proximal tubule from two normal and four remnant-kidney groups of dogs are summarized in Table 3. The effect of volume expansion in the two normal groups was similar. In the remnant-kidney groups of dogs, functional adaptation led to a pronounced increase in mean single-nephron GFR, reaching a value of 93–117 nl/min as compared with 66–68 nl/min in normal groups (P < 0·01). Proximal tubular fluid/plasma inulin ratios in the control phase were generally lower in the remnant-kidney groups of dogs, supporting our previous observations of reduced fractional sodium reabsorption in the proximal tubule in a uraemic state (Wen, Wong, Lockhart, Evanson & Dirks, 1973; Wen, Wong, Evanson, Lockhart & Dirks, 1976b). After volume expansion there were further reductions in proximal tubular fluid/plasma inulin ratios. Proximal tubular fluid/plasma ultrafiltrate phosphate ratios in the control phase were greatly increased in all remnant-kidney groups of dogs,
Fig. 1. Comparison of the fractional delivery of phosphate to the late proximal tubule (●—○) and fractional excretion of phosphate in the final urine (▲—△) in the normal (N-TPT) and thyroparathyroidectomized (N-TPTX) dogs, and in the four remnant-kidney groups of dogs with and without thyroparathyroidectomy (RK-TPTX and RK-TPT). Mean ± SEM values before (●, ▲) and after (○, △) 10% extracellular expansion are shown. See the Methods section for group subdivisions.

Comparison of the fractional delivery of phosphate

In Fig. 1, the fractional delivery of phosphate to the late proximal tubule and fractional excretion of phosphate in the final urine for the normal and remnant-kidney groups of dogs are depicted for comparison. In the proximal tubule, the fractional delivery of phosphate was high in all four remnant-kidney groups of dogs regardless of thyroparathyroidectomy or the severity of renal failure, suggesting that phosphate adaptation in this segment was independent of these factors. In the final urine fractional phosphate excretion was low in the RK-TPTX-I group, indicating that the presence of parathyroid glands in the RK-TPT-I group was the major factor responsible for the phosphate adaptation observed. However, volume expansion raised fractional phosphate excretion in the RK-TPT-I group to a value similar to the adapted value in the RK-TPT-I group and, therefore, extracellular volume expansion could also have contributed to the high fractional phosphate excretion in the remnant-kidney groups of dogs in the absence of parathyroid hormone. In the RK-TPTX-II group, conversely, fractional phosphate excretion remained high without parathyroid hormone, indicating that the phosphate adaptation observed in the RK-TPT-II group was largely related to parathyroid hormone-independent factors. However, phosphate adaptation in the RK-TPTX-II group was incomplete, suggesting a remaining role of parathyroid hormone in phosphate adaptation in the advanced stage of renal failure.

Discussion

In our uraemic remnant-kidney model in the dog, adaptation of phosphate excretion by the kidney was evident in the markedly increased fractional excretion of phosphate observed in the remnant-kidney groups of dogs with intact parathyroids. Similar adaptation for a number of electrolytes and non-electrolytes has also been observed in chronic renal failure (Bricker, Klahr, Lubowitz & Rieselbach, 1965; Schultze, Taggart, Shapiro, Pennel, Caglar & Bricker, 1971; Bricker, 1972). The mechanism by which the diseased kidney undergoes functional adaptation to maintain homeostasis of various electrolytes is not well understood. Available information in the literature suggests that each electrolyte could have its own adaptive mechanism to maintain individual homeostasis. Thus sodium and potassium adaptation can be dissociated (Schultze et al., 1971; Wen et al., 1976b) and phosphate adaptation is thought to be mainly the result of stimulated parathyroid function observed in chronic renal failure (Slatopolsky et al., 1966, 1968a; Bricker, 1972). The close relationship between sodium transport and that of potassium (Wesson, 1969), calcium (Walse, 1961; Wesson, 1962), magnesium (Wesson, 1962) and phosphate (Massry et al., 1969; Hebert et al., 1972; Gradowska et al., 1973; Wen, 1974) has been well documented for the normal kidney, a similar relationship could also exist in chronic renal failure. According to the 'trade-off' hypothesis of
Bricker (1972), a secondary hyperparathyroidism in chronic renal failure is the consequence of an adaptation by the body to maintain phosphate homeostasis in the face of a reduced nephron population. Since parathyroidectomy under such conditions abolished phosphate adaptation and corrected fractional tubular reabsorption of phosphate towards the normal range in chronically uraemic animals, Slatopolsky et al. (1966) suggested that secondary hyperparathyroidism was primarily responsible for phosphate adaptation. However, the question remained whether phosphate adaptation could still occur in the absence of parathyroid hormone. Swenson et al. (1975) demonstrated that renal insufficiency induced in thyroparathyroidectomized dogs maintained on vitamin D was associated with normal serum phosphorus and increased fractional phosphate excretion. They concluded that parathyroid hormone was not required for phosphate homeostasis in renal failure. The degree of phosphate adaptation in these animals was modest, however, with fractional phosphate excretion at only 9.3% owing to the mild degree of renal insufficiency induced.

In our clearance studies the values for fractional phosphate excretion were markedly elevated in the remnant-kidney groups of dogs with intact parathyroids, indicating pronounced phosphate adaptation. Absolute phosphate excretions in these groups were comparable with that of the intact normal group, suggesting maintenance of phosphate homeostasis. Since the baseline fractional phosphate excretion was close to the normal value in the RK-TPTX-I group, phosphate adaptation appeared to be nearly completely abolished by thyroparathyroidectomy in this group. In the RK-TPTX-II group, however, considerable phosphate adaptation with high fractional excretion of phosphate was observed despite the absence of parathyroid hormone. As the GFR in the RK-TPTX-II group was lower than that in the RK-TPTX-I group, the emergence of parathyroid hormone-independent phosphate adaptation could, in part, be related to the severe degree of renal failure. The plasma ultrafiltrate phosphate level was not the major factor responsible for the higher fractional phosphate excretion observed in the RK-TPTX-II group since plasma ultrafiltrate phosphate in this group was comparable with that in the RK-TPTX-I group. It should be noted, however, that phosphate adaptation in the RK-TPTX-II group was incomplete in that the fractional phosphate excretion of 31.7% was less than the 49.4% in the RK-TPTX-II group (P < 0.05). The difference in the values of fractional phosphate excretion between the RK-TPTX-II and the RK-TPTX-II groups could probably be accounted for by the remaining effect of parathyroid hormone on phosphate adaptation in the RK-TPTX-II group. Whether phosphate adaptation would become completely independent of parathyroid hormone with a longer duration of thyroparathyroidectomy is not known. It is unlikely, however, that the duration of thyroparathyroidectomy was the sole factor for parathyroid hormone-independent phosphate adaptation since acutely thyroparathyroidectomized dogs with a remnant kidney studied within 2 h of thyroparathyroidectomy also showed high fractional phosphate excretion. In thyroparathyroidectomized remnant-kidney groups of dogs absolute phosphate excretions were less than those in the remnant-kidney groups of dogs with intact parathyroids. This indicates that either phosphate balance was not achieved in 3 days after thyroparathyroidectomy or that dietary phosphate intake was reduced in the thyroparathyroidectomized remnant-kidney groups of dogs. In the former situation, the failure to achieve phosphate balance was most likely the result of enhanced renal tubular reabsorption of phosphate in the absence of parathyroid hormone. If dietary phosphate intake was reduced it would only underscore the significance of a parathyroid hormone-independent component of phosphate adaptation since even higher fractional phosphate excretion would have been reached with continued high phosphate intake.

An increase in fractional phosphate excretion in the absence of secondary hyperparathyroidism has also been demonstrated in uraemic dogs with a remnant kidney by Kaplan, Canterbury, Gavellas, Jaffe, Bourgoignie, Reiss & Bricker (1978). In these animals the serum parathyroid hormone level remained normal owing to restriction of dietary phosphate intake in proportion to the reduction in the functioning renal mass. Nevertheless, fractional phosphate excretion was considerably elevated, which could not be explained on the basis of an elevated serum phosphate level at least in one group of their uraemic animals. Lack of correlation between fractional phosphate excretion and parathyroid hormone level has also been reported in patients with chronic renal failure who were placed on phosphate-restricted diets and/or phosphate-binding antacids (Popovtzer, Pinggera, Hutt, Robinette, Halmgrimson & Starzl, 1972; Fotino, 1977). These observations, as well as the results of our present studies, strongly suggest that functional adaptation in phosphate transport in chronic renal failure may not be solely dependent on
parathyroid hormone and certain factors other than parathyroid hormone may play an important role in the homeostasis of phosphate.

In the RK-TPTX-I group with low fractional phosphate excretion extracellular volume expansion resulted in an exaggerated phosphaturic response with fractional phosphate excretion reaching 40.5%, which was similar to the adapted value of 44.9% in the RK-TPT-I group. A less marked but substantial increase in fractional phosphate excretion after volume expansion also occurred in the RK-TPTX-II group. These observations suggest that alteration in extracellular volume can modify the degree of phosphate adaptation in the absence of parathyroid hormone. However, extracellular volume expansion was carried out acutely and a rather sizeable expansion with fractional sodium excretion reaching 11.8% was required in the RK-TPTX-I group to achieve fractional phosphate excretion comparable with the adapted value. The contribution of extracellular volume to phosphate adaptation, therefore, is relatively small since such a degree of volume expansion is not always present in chronic renal failure.

Our micropuncture studies revealed that proximal tubular fluid/plasma ultrafiltrate phosphate ratios in all remnant-kidney groups of dogs were similarly increased to about unity regardless of thyroparathyroidectomy or the severity of renal failure. Thus phosphate adaptation in the proximal tubule must be independent of these factors. The high proximal tubular fluid/plasma ultrafiltrate phosphate values were probably caused by the markedly increased single-nephron GFR and reduced fractional sodium reabsorption in the proximal tubule. The non-specific nature of the altered proximal tubular phosphate transport in our dogs with a remnant kidney is in marked contrast to the observation by Bank, Su & Aynedjian (1978), in which acute parathyroidectomy markedly enhanced proximal tubular phosphate transport in uraemic rats with a remnant kidney. The reason for the different observations is not apparent but could be due to the difference in the susceptibility of phosphate transport to parathyroidectomy between the two species. Also, it is not clear whether the difference in the duration of parathyroidectomy played a role in the different patterns of proximal tubular phosphate transport. In our dogs wide variation in fractional excretion of phosphate was observed despite similar patterns of proximal tubular phosphate transport, suggesting that overall phosphate adaptation was not necessarily determined by the events in the proximal convoluted tubule. Fractional phosphate excretion in the dogs with a remnant kidney, therefore, appeared to be determined primarily by alteration in phosphate transport at a more distal nephron site. The exact location of the distal nephron site for phosphate adaptation is not clear but should include the pars recta of the proximal tubule, which is affected by parathyroid hormone (Dennis, Bello-Reuss & Robinson, 1977), and the cortical collecting tubule, which is not (Shareghi & Agus, 1979). Alternatively, if nephron heterogeneity significantly contributes to the regulation of urinary phosphate excretion, a reduction in phosphate reabsorption in tubular segments of the deep nephrons could be mainly responsible for the high fractional phosphate excretion observed in chronic renal failure.

The nature of phosphate adaptation in chronic renal failure in the absence of parathyroid hormone is not well understood. Hypocalcaemia could lead to increased urinary phosphate excretion, since hypercalcaemia has been shown to reduce phosphate excretion (Lavender & Pullman, 1963; Amiel, Kuntziger, Couette, Coureau & Bergounioux, 1976). However, hypocalcaemia in a hypoparathyroid state is usually associated with reduced phosphate excretion rather than phosphaturia, and calcium administration in such a state has been reported to increase phosphate excretion (Eisenberg, 1965; Wen, 1974). Thus it is unlikely that hypocalcaemia played a major role in increasing fractional phosphate excretion in the RK-TPTX-II group. Also, vitamin D metabolites are known to be deficient in chronic renal failure and this could lead to phosphaturia if these metabolites enhance tubular reabsorption of phosphate (Puschett, Moranz & Kurnick, 1972; Popovtzer, Robinette, DeLuca & Holick, 1974). In view of the conflicting reports in the literature concerning the effect of vitamin D metabolites on renal phosphate transport (Gutmann, Najad, Engle & Wen, 1973; Bonjour, Preston, Rizzoli & Fleisch, 1978), especially with regard to the need for the presence of parathyroid hormone on their action (Popovtzer et al., 1974) and the reported phosphaturic effect of these metabolites (Bonjour et al., 1978), their role in the regulation of renal phosphate excretion in our thyroparathyroidectomized remnant-kidney groups of dogs remains uncertain. Since inorganic phosphate is a major intracellular anion its content in the intracellular compartment of the renal tubular epithelium could be an important determinant for parathyroid hormone-independent phosphate adaptation. However, it remains to be demonstrated whether intracellular inorganic phosphate content is increased in chronic renal failure. Also, whether uraemic
plasma contains an increased amount of any phosphaturic factors other than parathyroid hormone is entirely unknown. Further studies are clearly needed to elucidate the possible mechanisms of phosphate adaptation in chronic renal failure.

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