URIC ACID IN ADVANCED RENAL FAILURE

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SUMMARY

1. The results of studies of renal uric acid excretion in eleven patients with advanced chronic renal failure are presented.

2. The pyrazinamide suppression test was used to separate secretion from reabsorption of uric acid in the renal tubule.

3. There is a marked increase in the excretion and clearance of uric acid as renal function deteriorates. This was due to a striking increase in tubular secretion of urate and to incomplete reabsorption of filtered urate.

4. The remarkable functional capacity of the remaining nephrons of the chronically diseased kidney with respect to uric acid transport might be due to a uricosuric factor in uraemic serum.

Key words: uric acid, pyrazinamide, tubular secretion, renal failure, uricosuric.

In normal man uric acid is secreted by the kidneys by bi-directional transport whereby almost all of the filtered urate is reabsorbed and most of the urate appearing in the urine results from secretion further down the proximal tubule (Steele & Reisselbach, 1967a; Gutman & Yu, 1957). In the failing kidney a relatively small increase in plasma uric acid concentration has been shown to be due to a relative increase in urate clearance indicating the functional adaptation of the residual nephrons to the increasing requirements for uric acid secretion. Until the glomerular filtration rate (GFR) falls to the range of 10–15 ml/min bi-directional transport seems to remain intact with near-total reabsorption and substrate-regulated secretion accounting for the increased urate clearance. At a GFR of less than 10 ml/min, however, glomerular tubular imbalance may develop in which glomerular filtration accounts for the majority of uric acid excreted, uric acid secretion being significantly diminished (Steele & Reisselbach, 1967b). Since this differs strikingly from the behaviour of the residual nephrons of advanced renal failure with regard to sodium, potassium, chloride, ammonia and phosphate (Bricker, 19...
Klahr, Lubowitz & Reisselbach, 1965; Berlyne, Van Laethem & Ben Ari, 1971; Allison & Kennedy, 1971), we decided to study the pattern of uric acid excretion in far-advanced renal disease.

MATERIALS AND METHODS

Eleven patients (age range 19–64 years) with chronic advanced renal failure from the Department of Nephrology of the Negev Central Hospital, Beer Sheva, Israel, were chosen for study. The diagnoses are shown in Table 1. In all patients the inulin clearance was less than 10 ml/min. Patients with gouty nephropathy, a past history or a family history of gout were excluded in view of the known defect in uric acid secretion in the gouty ‘normoproducers’ of uric acid (Reisselbach, Sorenson, Shelp & Steele, 1970). None of the subjects had a history of Fanconi syndrome, Wilson’s disease, or heavy metal poisoning and none was receiving diuretics or any other medicament known to affect uric acid secretion in the week before the investigation. Patients with inulin clearance of less than 7 ml/min were receiving a modified Giordano–Giovannetti diet (Berlyne, Shaw & Nilwarangkur, 1965), but in those with inulin clearance of 7–10 ml/min protein intake was not restricted. No attempt was made at controlling dietary purine intake. No patient had been treated with haemodialysis or peritoneal dialysis within 3 months of the study.

Fifteen clearance studies were completed. In view of the particular danger in these patients of further impairment of renal function resulting from catheterization and infection, only four underwent bladder catheterization, under the usual strict aseptic conditions. These patients were suspected of having significant urinary tract infection, and the clearance procedure was undertaken whilst a bladder catheter was inserted for purposes of obtaining bladder urine for culture. Standard clearance techniques were used (Smith, 1956) with certain modifications. The study was started after an overnight fast, extracellular space expansion was produced by ingestion of 1–1.5 litres of water before and during the study. Saline and glucose infusions were not used in view of their uricosuric capacity which appears to be on the basis of a shared transport mechanism between sodium, glucose, and uric acid (Skeith, Healey & Cutler, 1967; Steele, 1969, 1971). In view of the degree of renal failure and the slow rate of inulin loss in the urine a constant rate infusion was unnecessary. Inulin (60 mg/kg) was given as a single intravenous bolus dose 45 min to 1 h before the start of the first clearance period. Bladder emptying was at 20–40 min intervals, depending on urine flow. After three clearance periods pyrazinamide (3.0 g) was given orally. After an interval of 1 h the first of three further clearance periods was commenced. On three occasions administration of pyrazinamide was followed by nausea and vomiting and the study was abandoned. Several patients complained of transient headaches and hot flushes. There were no other untoward effects.

By producing close-to-maximal inhibition of uric acid secretion (Yu, Berger & Gutman, 1957, 1962; Davies, Field, Rodnan & Kedes, 1964), pyrazinamide permits separate consideration of the vectors involved in the bi-directional uric acid transport. Tubular secretion of urate is represented by the maximal decrement in uric acid excretion/ml of GFR after pyrazinamide administration, the uric acid remaining in these circumstances being that which has escaped reabsorption. The amount of uric acid reabsorbed per unit nephron may thus be easily calculated. (The terms ‘per ml of GFR’ and ‘per nephron’ are often used interchangeably. The term ‘per ml of GFR’ is a more accurate one and is a factor of the term ‘per nephron’ which is much smaller in absolute terms.)
### Table 1. Summary of data for all patients before administration of allopurinol

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Disease*</th>
<th>Blood urea nitrogen (mg%)</th>
<th><strong>C\text{inulin}</strong> (ml/min)</th>
<th><strong>P\text{urate}</strong> (µg/ml)</th>
<th><strong>C\text{urate} \times 100</strong></th>
<th>UV\text{urate} <strong>C\text{inulin}</strong> (mg/ml)</th>
<th>Tubular secretion of urate (µg/ml)</th>
<th>Fractional excretion of urate (%)</th>
<th>Fractional excretion of urate (µg/ml)</th>
<th>Filtered urate (µg/ml)</th>
<th>Reabsorbed urate (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.S.</td>
<td>24</td>
<td>C.G.N.</td>
<td>92</td>
<td>5.1</td>
<td>9.3</td>
<td>50.3</td>
<td>49.3</td>
<td>23.5</td>
<td>28.0</td>
<td>25.8</td>
<td>91.7</td>
<td>65.9</td>
</tr>
<tr>
<td>S.M.</td>
<td>42</td>
<td>C.P.N.</td>
<td>61</td>
<td>3.2</td>
<td>7.6</td>
<td>84.4</td>
<td>66.5</td>
<td>31.3</td>
<td>46.7</td>
<td>35.2</td>
<td>76.0</td>
<td>40.8</td>
</tr>
<tr>
<td>B.Y.</td>
<td>64</td>
<td>Malig. B.P.</td>
<td>71</td>
<td>3.6</td>
<td>9.2</td>
<td>58.3</td>
<td>54.6</td>
<td>44.3</td>
<td>11.2</td>
<td>10.3</td>
<td>91.5</td>
<td>81.2</td>
</tr>
<tr>
<td>B.F.</td>
<td>38</td>
<td>Malig. B.P.</td>
<td>116</td>
<td>8.1</td>
<td>7.7</td>
<td>22.0</td>
<td>19.5</td>
<td>12.5</td>
<td>9.2</td>
<td>7.0</td>
<td>75.6</td>
<td>68.6</td>
</tr>
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<td>J.M.</td>
<td>45</td>
<td>C.P.N.</td>
<td>73</td>
<td>7.8</td>
<td>8.2</td>
<td>30.8</td>
<td>32.8</td>
<td>14.2</td>
<td>23.2</td>
<td>18.6</td>
<td>80.1</td>
<td>61.5</td>
</tr>
<tr>
<td>Z.S.</td>
<td>19</td>
<td>F.M.F. amyloid</td>
<td>69</td>
<td>7.5</td>
<td>6.7</td>
<td>68.0</td>
<td>35.1</td>
<td>10.2</td>
<td>37.2</td>
<td>24.9</td>
<td>66.9</td>
<td>42.0</td>
</tr>
<tr>
<td>L.H.</td>
<td>22</td>
<td>C.G.N.</td>
<td>37</td>
<td>3.7</td>
<td>8.3</td>
<td>83.5</td>
<td>67.7</td>
<td>47.8</td>
<td>24.3</td>
<td>19.9</td>
<td>81.7</td>
<td>61.8</td>
</tr>
<tr>
<td>F.N.</td>
<td>41</td>
<td>C.R.F.?</td>
<td>71</td>
<td>1.6</td>
<td>8.5</td>
<td>62.5</td>
<td>70.2</td>
<td>17.5</td>
<td>62.6</td>
<td>52.7</td>
<td>84.6</td>
<td>31.9</td>
</tr>
<tr>
<td>B.D.M.</td>
<td>40</td>
<td>C.R.F.?</td>
<td>22</td>
<td>9.7</td>
<td>8.8</td>
<td>25.7</td>
<td>24.1</td>
<td>18.2</td>
<td>6.4</td>
<td>5.9</td>
<td>91.2</td>
<td>85.3</td>
</tr>
<tr>
<td>B.L.D.</td>
<td>37</td>
<td>C.R.F.?</td>
<td>120</td>
<td>0.7</td>
<td>7.7</td>
<td>73.7</td>
<td>180.5</td>
<td>133.7</td>
<td>59.8</td>
<td>44.8</td>
<td>79.0</td>
<td>34.2</td>
</tr>
<tr>
<td>G.M.</td>
<td>42</td>
<td>C.R.F.?</td>
<td>60</td>
<td>4.2</td>
<td>7.2</td>
<td>59.5</td>
<td>33.1</td>
<td>142</td>
<td>27.2</td>
<td>18.9</td>
<td>69.8</td>
<td>50.9</td>
</tr>
</tbody>
</table>

Abbreviations: C\text{inulin}, inulin clearance; P\text{urate}, plasma urate concentration; C\text{urate}, urate clearance; UV\text{urate}, urinary excretion of urate.

* C.G.N., chronic glomerulonephritis; C.P.N., chronic pyelonephritis; Malig. B.P., malignant hypertension; F.M.F. amyloid, familial mediterranean fever amyloidosis; C.R.F.?, end stage renal failure of uncertain aetiology.
To determine whether tubular secretion of uric acid remains a substrate-regulated mechanism as in normal man (Steele & Reisselbach, 1967a) and is not a substrate-independent leak, the studies were repeated in four patients after the plasma uric acid had been decreased to normal values (plasma uric acid 3.5–5.5 mg/100 ml) by administration of the xanthine oxidase inhibitor, allopurinol (200–300 mg/day) for 2–4 weeks. In all cases allopurinol administration was stopped at least 3 days before the repeat study, to minimize the concentration of drug metabolites and enzyme inhibition by-products.

All biochemical measurements were made by an AutoAnalyzer; inulin was measured by a modification of Heyrovsky’s method (Dawborn, 1965); uric acid by a specific uricase method; blood urea nitrogen by method N 4 (Technicon methods).

RESULTS

The results of eleven clearance studies in patients who had not received allopurinol are shown in Table 1. The details of a representative study are shown in Table 2 (patient S.M.). The following is a typical example of a calculation derived from the results in Table 2.

<table>
<thead>
<tr>
<th>TABLE 2. Representative clearance study: patient S.M.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C\text{inulin}</strong></td>
</tr>
<tr>
<td>(ml/min)</td>
</tr>
<tr>
<td>3.6</td>
</tr>
<tr>
<td>2.6</td>
</tr>
<tr>
<td>3.0</td>
</tr>
<tr>
<td>86.6</td>
</tr>
</tbody>
</table>

1 h after pyrazinamide (3.0 g) orally

| 3.8 | 7.6 | 1.9 | 50.0 | 36.7 |
| 2.8 | 7.6 | 1.7 | 60.7 | 45.3 |
| 3.0 | 7.6 | 1.4 | 46.7 | 35.2 |

Total mean 3.1 7.7

Excretion/ml of GFR = \( \frac{UV\text{urate}}{C\text{inulin}} \) before pyrazinamide = 66.5 μg/ml.

Tubular secretion/ml of GFR = maximal decrease in \( \frac{UV\text{urate}}{C\text{inulin}} \) induced by pyrazinamide = 66.5 – 35.2 = 31.3 μg/ml.

Fraction of filtered urate excreted (FE) = maximally depressed \( \frac{C\text{urate}}{C\text{inulin}} \) after pyrazinamide = 46.7% = FE%.
Fraction of filtered urate excreted per ml of GFR = maximally depressed \( \frac{\text{Uric acid in renal failure}}{\text{pyrazinamide}} \) after pyrazinamide = 35·2 µg/ml = FE.

Filtered urate (F)/ml of GFR = \( \frac{\text{FE}}{\text{FE} \times 100} = 76 \mu g/ml = F. \)

Reabsorbed urate/ml of GFR = F - FE = 76 - 35·2 = 40·8 µg/ml.

Blood urea nitrogen varied between 22 mg/100 ml and 120 mg/100 ml. GFR as measured by inulin clearance varied from 0·7 to 9·3 ml/min, and plasma uric acid concentration varied from 7·2 to 9·3 mg/100 ml. In five patients uric acid concentrations were below or very close to the upper limit of normal for plasma uric acid as quoted for normal males (Gjorup, Poulsen & Pretorius, 1955). There was only a modest increase in plasma uric acid at a time of marked diminution of renal function and uraemia as illustrated in Figs. 1(a) and 1(b).

The excretion of uric acid per ml of GFR expressed as \( \frac{\text{Uric acid in renal failure}}{\text{inulin}} \) varied from 19·5 to 180 µg/ml and increased markedly as inulin clearance fell (Fig. 2a). The uric acid clearance, corrected to an inulin clearance of 100 ml/min, varied from 22·0 to 84·4 ml/min as compared with a range of 7·3–2·1 ml/min in normals (Gutman & Yu, 1957) corrected to an inulin clearance of 100 ml/min (Fig. 2b).

Uric acid reabsorption

The fractional excretion of uric acid (FE%), i.e. the percentage of uric acid that reaches the urine as a result of incomplete reabsorption varied from 6·4% to 62·2%. In Fig. 3 the amount of reabsorbed uric acid/ml of GFR is plotted against the filtered uric acid/ml of GFR and further illustrates the incompleteness of the reabsorption process.

Uric acid secretion

The tubular secretion of uric acid/ml of GFR varied from 10·2 to 133·7 µg/ml and increased strikingly as renal function diminished (Fig. 4a). The highest secretion rate was found in a patient with a GFR of 0·7 ml/min. When four patients were restudied the tubular secretion of three of them fell as anticipated when the plasma uric acid concentration was decreased (Table
FIG. 2. Relation between urate excretion (μg/ml of GFR) expressed as $UV_{urate}/C_{inulin}$ (a) and $C_{urate}$ corrected to 100 ml/min (b) to renal function as expressed by $C_{inulin}$ (ml/min) in eleven patients with advanced renal failure. The range of normal urate clearance corrected to 100 ml/min is indicated by the hatched area.

FIG. 3. Reabsorption of filtered urate (μg/ml of GFR) in fifteen clearance studies on eleven patients with advanced renal failure (inulin clearance < 10 ml/min). - - - - , Total reabsorption.
3). In the fourth there was a modest increase (patient G.M.). Tubular secretion is expressed on a ‘per ml of GFR’ basis and thus changes in renal function between investigations are obviated (Fig. 4b).

**DISCUSSION**

Our results indicate that the increased uric acid excretion and uric acid clearance per unit nephron in patients with a glomerular filtration rate of less than 10 ml/min (Fig. 2) are the net result of two processes: the failure of reabsorption of filtered urate and the substrate sensitive secretion of urate. The pattern of excretion thus differs from that in normals and that described in less-advanced renal failure (Steele & Reisselbach, 1967a, b) mainly in respect of the incompleteness of reabsorption and the increased tubular secretion. In normal patients 98% of the filtered urate is reabsorbed and 86% of the urate appearing the urine reaches there as a result of secretion (Steele & Reisselbach, 1967a). In our patients unreabsorbed uric acid contributed a greater proportion of the uric acid appearing in the urine (Fig. 5).

There is a striking increase in the capacity of the remaining nephrons to secrete uric acid in advanced renal failure. Fig. 4(a) illustrates the increasing rate of tubular secretion of uric acid as the number of nephron units decreases. In normal subjects tubular secretion of uric acid is substrate-sensitive and is increased by increasing plasma uric acid concentration by RNA feeding and is decreased by decreasing the plasma uric acid concentration with allopurinol.
(Steele & Reisselbach, 1967a). The remaining nephrons of the diseased kidney are also responsive to the raised plasma uric acid concentration and increase requirements for uric acid secretion in chronic renal failure. As in the normal kidney they appear to remain sensitive to a decrease of substrate availability when plasma uric acid concentrations are decreased by allopurinol (Fig. 4b).

These functional adaptations, particularly the enhanced secretory capacity for uric acid, are remarkable in the presence of the gross diminution in renal function in the patients studied.

### Table 3. Data of the clearance study on patients who received allopurinol

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Disease</th>
<th>Blood urea nitrogen (mg%)</th>
<th>$C_{\text{inulin}}$ (ml/min)</th>
<th>$P_{\text{urate}}$ (mg%)</th>
<th>$C_{\text{urate}} \times 100$ $C_{\text{inulin}}$ (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G.M.</td>
<td>42</td>
<td>C.R.F.?</td>
<td>56</td>
<td>4.6</td>
<td>5.0</td>
<td>47.9</td>
</tr>
<tr>
<td>B.F.</td>
<td>38</td>
<td>Malig. B.P.</td>
<td>70</td>
<td>1.1</td>
<td>3.5</td>
<td>50.0</td>
</tr>
<tr>
<td>J.M.</td>
<td>45</td>
<td>C.P.N.</td>
<td>80</td>
<td>2.7</td>
<td>4.5</td>
<td>16.9</td>
</tr>
<tr>
<td>S.S.</td>
<td>24</td>
<td>C.G.N.</td>
<td>95</td>
<td>2.3</td>
<td>5.5</td>
<td>34.2</td>
</tr>
</tbody>
</table>

They are, however, to be fully anticipated in view of the known functional capacity and adaptability of the remaining nephrons in chronic renal failure. This functional capacity has been illustrated with regard to a number of substances, notably sodium, potassium, chloride, phosphate, ammonia (Bricker et al., 1965; Berlyne et al., 1971; Allison & Kennedy, 1971) and is the basis of the 'intact nephron hypothesis' (Bricker, 1969). The example of uric acid is particularly interesting in view of the bi-directional nature of its transport system and the maintenance of glomerulo-tubular balance with respect to uric acid at a time of gross diminution of renal function.

Our results in respect of tubular secretion of uric acid differ in some respects from the results of a similar study by Steele & Reisselbach (1967b) (Fig. 4a), which are, however, somewhat contradictory. They found that uric acid secretion at a glomerular filtration rate of less than 10 ml/min was considerably less than anticipated, i.e. uric acid secretion did not respond to the increased functional requirements resulting from increased substrate availability. However, tubular secretion of uric acid decreased when the plasma uric acid concentration was decreased.
Uric acid in renal failure

by allopurinol. It seems unlikely that the rate of tubular secretion which failed to respond appropriately to the increased plasma uric acid concentration and the requirements of advanced chronic renal failure would respond to decreased plasma uric acid induced artificially by administration of allopurinol.

The pyrazinamide suppression test which has been used widely to differentiate between secretion and reabsorption of uric acid (Steele & Reisselbach, 1967a, b; Reisselbach et al., 1970; Gutman, Yu & Berger, 1969; Postlethwaite & Kelley, 1971) is based on the premise that pyrazinamide produces maximal suppression of uric acid secretion. Although there is evidence that this premise is reasonable in normal man (Yu et al., 1957, 1962), there is as yet no proof that secretory suppression is maximal in the cases of advanced renal failure that we have studied, and the absolute values for tubular secretion should therefore be accepted with some reservation. The main conclusion of the present study, however, has been the demonstration of increased tubular secretory capacity for urate in advanced renal failure. If the pyrazinamide-induced suppression of tubular secretion that we obtained was incomplete, then the actual values for tubular secretion would have been even higher. The highest tubular secretion rate measured in this study was in the patient with the lowest glomerular filtration rate. A more serious objection to the pyrazinamide suppression test comes from a study of the excretion of uric acid in the Cebus monkey (Fanelli, Bohn & Stafford, 1970), where it was suggested that

![Graph of urate excretion](image-url)
pyrazinamide might also enhance tubular reabsorption of uric acid. Should this be true in man, then the basic premise on which the pyrazinamide suppression is based would be invalidated.

The mechanism by which the functional adaptation that we have demonstrated takes place remains uncertain. Studies in dogs have shown that uric acid excretion per nephron of diseased kidneys when in a non-uraemic environment is the same as that of a normal kidney (Reisselbach, Slatopolsky, Gradowska, Kashemsant & Bricker, 1964). This would indicate that the increased excretion of uric acid in uraemia is due to the functional adaptation of the nephron as such, or to the influence of an extrarenal factor present, or active, in uraemic patients only. The re-absorption of phosphate is largely under the control of parathyroid hormone (Slatopolsky, Caglar, Pennell, Taggart, Cantabury, Reiss & Bricker, 1971) and there is now considerable evidence that sodium reabsorption in chronic renal failure is under the control of an as yet undefined natriuretic factor (Bourgoignie, Klahr & Bricker, 1971). It is therefore conceivable that there also exists a uricosuric factor which depresses reabsorption and/or stimulates secretion in chronic renal failure. In this respect a study illustrating inhibition of uric acid transport by uraemic serum in isolated rat tubules is highly significant (Podevin, Paillard & Richet, 1969). It will be of interest to clarify the exact nature of the mechanism involved.

ACKNOWLEDGMENTS
We thank Mr M. Soroka, Chairman, and Dr H. Doron, Medical Director of the Mercaz Kupat Holim Health Insurance Institution, for the financial aid that made this work possible, and Mrs L. Goldfarb for secretarial assistance. We are most grateful to our patients with advanced renal failure who agreed to these studies after adequate explanation of the nature and purpose of the investigations.

REFERENCES
Uric acid in renal failure


