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# Renal urate excretion in patients with Wilson's disease

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**Renal urate excretion in patients with Wilson's disease.** Because many patients with Wilson's disease have hypouricemia, a study was made of 10 patients and 10 control persons to determine the nature of the renal excretory defect. Uric acid excretion was studied before and after the administration of pyrazinamidem—an agent which is postulated to selectively block urate secretion. Urate excretion was also correlated with the quantity of various types of amino acids excreted. In the presence of pyrazinamide, total urate excretion is decreased markedly just as in normal individuals. It appears that proximal reabsorption of urate may not be impaired. There is a positive correlation between excessive urate excretion and that of serine, arginine, valine, and glutamine.

**Excrétion rénale des urates chez les malades atteints de maladie de Wilson.** Du fait que beaucoup de malades atteints de maladie de Wilson ont une hypouricémie une étude a été réalisée chez dix malades et dix sujets témoins afin de déterminer la nature du trouble de l'excrétion des urates. L'excrétion d'acide urique a été étudiée avant et après l'administration de pyrazinamide, agent dont on suppose qu'il bloque électivement la secrétion d'urate. L'excrétion d'urate a été aussi corrélée avec la quantité de divers acides aminés excrétés. En présence de pyrazinamide l'excrétion totale d'urate est notablement diminuée, comme chez les témoins. Il apparaît que la réabsorption proximale des urates n'est probablement pas diminuée. Il existe une corrélation positive entre l'excrétion excessive d'urate et l'excrétion de sérine, d'arginine, de valine et de glutamine.

Renal urate excretion is increased in Wilson's disease. Most patients with untreated Wilson's disease have hypouricemia, and the clearance of urate is from 20 to 30 ml/min, which is two to three times normal [1–3]. Urate turnover and metabolism have been examined in these patients, and $^{14}$C-uric acid injection studies have revealed that the urate pool size is markedly diminished [4, 5]. This has led to the conclusion that the hypouricemia in these patients is secondary to a renal lesion which causes renal urate wasting.

The nature of the renal lesion responsible for urate wasting has been difficult to establish because there is no adequate animal model for studying the problem. Renal urate excretion is thought to involve filtration, reabsorption, and secretion from the tubule [6]. Consequently, direct analysis of urine urate excretion sheds little light on whether the hypouricemia is due to decreased reabsorption or to an increased rate of urate secretion.

Recently, studies of urate excretion using the antituberculosis drug pyrazinamide have been used in an attempt to clarify the mechanisms for urate transport under various conditions. In man, the administration of pyrazinamide depresses urate excretion by 95% [7]. Stop-flow experiments have revealed that pyrazinamide inhibits the secretory peak in mongrel dogs while leaving the reabsorption dip unaffected [8]. In Dalmatian dogs, where there is little reabsorption of urate, pyrazinamide blocks urate excretion [9]. This has led to the concept that pyrazinamide selectively blocks secretion of uric acid at a site distal to the reabsorptive site. Urate excretion has been characterized in normal man [10] and in patients with renal impairment [11], with gout [12], and under the influence of chlorothiazide diuretics [13], using pyrazinamide as a tool. Recent studies, however, have shown that the action of pyrazinamide on tubular transport may affect both reabsorption and secretion rates in a dose-related way so that any analysis of pyrazinamide-induced changes of urate excretion will be influenced by a complete understanding of the segmental site of net secretory or reabsorptive processes along the nephron.

We have examined urate filtration, reabsorption, and secretion using pyrazinamide in ten patients with Wilson's disease in an attempt to determine whether these patients have defective reabsorption.

## Methods

Ten patients with Wilson's disease were tested in the Renal Function Laboratory. All ten patients had Wilson's disease diagnosed on the basis of decreased serum ceruloplasmin concentration or the findings of copper turnover studies, which showed failure of intravenously injected copper tagged with radioactive carbon to incorporate with

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serum ceruloplasmin, or increased urinary copper excretion (greater than 100 μg/24 hr), or both. In addition, Kayser-Fleischer rings were seen either with the naked eye or on slit-lamp examination. Eight patients had been treated with penicillamine from 2.5 to 13 years. All of these eight patients had been off penicillamine therapy for at least 2 weeks (usually 4 weeks) before the renal studies. Two patients were studied before penicillamine therapy was given. These latter two patients did not have any clinical evidence of hepatic, neurologic or renal disease but were discovered during the screening of family members of affected patients. All 10 patients had a glomerular filtration rate (GFR) greater than 50 ml/min.

Patients came to the Renal Function Laboratory in a hydrated but fasting state. Standard inulin clearance determinations were performed. A bladder catheter was inserted, and the bladder was twice-rinsed with saline solution and air at the end of each clearance period. Plasma samples were obtained at the beginning and end of each period. If plasma concentrations of inulin or urate changed, the plasma concentration was extrapolated to a point 5 minutes before the midpoint of each period. After four adequate 20-minute periods, the patient was given 3.0 g of pyrazinamide as crushed tablets orally. Subsequently, two 30-minute periods and then 15- to 20-minute clearance periods were obtained for at least another 2 hours. Plasma and urine uric acid concentrations for the current studies were measured by the uricase method [14]. Measurements of uric acid concentration prior to 1963 were performed by a different method. Inulin clearance was determined by a modification of the Roe Autoanalyzer technique [15], and blood pressure was monitored at 30-minute intervals throughout the test.

The rate of secreted urate (Ts urate) was calculated as the amount of urate excreted per ml GFR before the drug was given minus the amount excreted per ml GFR after the drug was given at the point where the maximal suppression of urate secretion was evident (Table 1):

$$\text{Ts urate} = \frac{UV_{urate}}{C_{In}}\,(\text{control}) - \frac{UV_{urate}}{C_{In}}\,(\text{drug}),$$

where $C_{In}$ is the clearance of inulin and $UV_{urate}$ is the urinary excretion of urate.

The tubular reabsorption (Tr) of urate was expressed as a percentage of the filtered load. This was calculated in the period of the lowest $UV_{urate}$ per nephron after pyrazinamide was given:

$$\text{Tr urate} = \frac{C_{In} \times \text{plasma urate} - UV_{urate}}{C_{In} \times \text{plasma urate}} \times 100.$$

Fractional urate excretion (FE) was expressed as the percentage of the filtered urate that was excreted during the administration of pyrazinamide:

$$FE_{urate} = \frac{UV_{urate}}{C_{In} \times \text{plasma urate}} \times 100.$$

**Table 1.** Representative study of one patient with Wilson's disease[a]

| Time | $C_{In}$, *ml/min* | Urate, *mg/ml* | | $C_{Ur}$, *ml/min* | UV urate/$C_{In}$, *μg/min* |
|---|---|---|---|---|---|
| | | Urine | Plasma | | |
| 10:15–10:37 | 100 | 0.78 | 0.064 | | |
| 10:37–10:58 | 89 | 0.74 | 0.064 | 15.5 | 8.79 |
| 10:58–11:17 | 152 | 0.63 | 0.064 | (mean) | (mean) |
| Pyrazinamide given at 11:25 (3.0 g) | | | | | |
| 11:17–11:39 | 71 | 0.74 | 0.059 | 16.4 | 13.6 |
| 11:39–12:00 | 114 | 0.17 | 0.059 | 14.1 | 7.3 |
| 12:00–12:40 | 98 | 0.089 | 0.057 | 7.0 | 4.1 |
| 12:40–1:05 | 99 | 0.060 | 0.056 | 4.1 | 2.3 |
| 1:05–1:28 | 99 | 0.046 | 0.056 | 2.8 | 1.6 |
| 1:28–1:56 | 99 | 0.027 | 0.056 | 1.9 | 1.1 |
| 1:56–2:22 | 96 | 0.029 | 0.056 | 1.6 | 0.95 |
| 2:22–2:50 | 100 | 0.047 | 0.056 | 3.9 | 2.2 |

Ts urate = 8.79 − 0.95 = 7.84 μg/ml GFR
Tr urate = 56 − 0.95/56 × 100 = 98.30%
FE urate = (0.95/56) × 100 = 1.70%

[a] $C_{In}$ = clearance of inulin; $C_{Ur}$ = clearance of urate; UV urate = urate excretion; Ts urate = secretion rate of urate; Tr urate = rate of tubular reabsorption of urate; FE urate = fractional excretion rate of urate; and GFR = glomerular filtration rate.

Data on amino acid excretion were collected within 3 months of the study of urate excretion, while patients were off penicillamine therapy. Amino acids were measured on an amino acid analyser (Phoenix).

## Results

All but two patients (6 and 9) had been on penicillamine therapy for several years; one patient was treated for 13 years (Table 2). In the eight treated patients, the serum uric acid concentration had been low, and in all but one

**Table 2.** Patients with Wilson's disease

| Patient | Plasma urate, *mg/100 ml* | | $C_{In}$,[a] *ml/min/1.73 m²* | Treatment, *years* |
|---|---|---|---|---|
| | Initial | Present | | |
| 1 | 1.3 | 3.0 | 65 | 12 |
| 2 | 1.3 | 4.2 | 100 | 12 |
| 3 | 1.7 | 4.0 | 51 | 13 |
| 4 | 2.4 | 5.3 | 91 | 2.5 |
| 5 | 3.4 | 5.2 | 107 | 2.5 |
| 6 | 5.0 | 3.8 | 63 | 0 |
| 7 | 1.0 | 5.4 | 95 | 4 |
| 8 | 1.9 | 5.1 | 99 | 7 |
| 9 | 4.8 | 4.8 | 133 | 0 |
| 10 | 2.5 | 5.6 | 113 | 3 |
| Mean | 2.33 | 4.65 | 91.7 | 5.6 |

[a] $C_{In}$ = clearance of inulin.

**Table 3.** Clearance data on 10 patients with Wilson's disease and on 10 control subjects[a]

| Patients | $C_{In}$, *ml/min/1.73 m²* | $P_{urate}$, *mg/100 ml* | UV urate (baseline), *μg/min/ml GFR* | $C_{urate}/C_{In}$ | Ts urate, *μg/ml GFR/mg* | FE urate, % | Secreted urate/ excreted urate, % |
|---|---|---|---|---|---|---|---|
| 1 | 65 | 3.0 | 5.7 | 0.20 | 1.40 | 1.7 | 73.7 |
| 2 | 100 | 4.2 | 8.6 | 0.17 | 1.85 | 1.6 | 90.6 |
| 3 | 51 | 4.0 | 7.5 | 0.39 | 1.24 | 2.5 | 66.5 |
| 4 | 91 | 5.3 | 16.7 | 0.20 | 2.92 | 8.1 | 92.8 |
| 5 | 107 | 5.2 | 9.4 | 0.16 | 1.72 | 3.6 | 94.3 |
| 6 | 63 | 3.8 | 6.1 | 0.26 | 1.42 | 1.5 | 88.5 |
| 7 | 95 | 5.4 | 12.3 | 0.09 | 2.22 | 2.4 | 97.5 |
| 8 | 99 | 5.1 | 5.4 | 0.13 | 0.83 | 1.4 | 78.4 |
| 9 | 133 | 4.8 | 6.9 | 0.11 | 1.08 | 2.3 | 75.3 |
| 10 | 113 | 5.6 | 8.4 | 0.13 | 1.24 | 2.0 | 82.2 |
| Mean ± SD | 91.7 ± 25.2 | 4.64 ± 0.85 | 8.7 ± 3.5 | 0.188 ± 0.086 | 1.59 ± 0.61 | 2.71 ± 2.0 | 84.0 ± 10.3 |
| Control | | | | | | | |
| 1 | 117 | 5.6 | 7.1 | 0.11 | 0.93 | 2.6 | 72.9 |
| 2 | 97 | 6.4 | 5.5 | 0.09 | 0.77 | 1.2 | 89.6 |
| 3 | 108 | 6.1 | 5.5 | 0.08 | 0.67 | 1.8 | 74.4 |
| 4 | 107 | 4.8 | 5.5 | 0.08 | 0.75 | 0.6 | 65.6 |
| 5 | 106 | 4.8 | 3.8 | 0.06 | 0.52 | 1.3 | 66.1 |
| 6 | 110 | 5.9 | 4.9 | 0.07 | 0.63 | 0.9 | 75.8 |
| 7 | 101 | 4.3 | 7.6 | 0.16 | 1.42 | 2.7 | 80.0 |
| 8 | 114 | 3.8 | 3.4 | 0.14 | 0.76 | 6.6 | 83.7 |
| 9 | 119 | 5.8 | 5.3 | 0.08 | 0.74 | 1.4 | 81.4 |
| 10 | 113 | 5.8 | 3.2 | 0.07 | 0.46 | 2.6 | 83.9 |
| Mean ± SD | 109.0 ± 6.9 | 5.33 ± 0.85 | 5.5 ± 1.4 | 0.098 ± 0.034 | 0.765 ± 0.27 | 2.17 ± 1.7 | 77.3 ± 7.8 |

[a] $P_{urate}$ = plasma urate concentration. See Table 1 for remaining abbreviations.

(patient 1), after treatment the concentration had increased to normal. Neither of the two untreated patients had an abnormal concentration of serum uric acid, although when the clearance studies were done, one had a low-normal level. This patient (6) had an abnormally high clearance of urate, whereas the other (patient 9) had a clearance within normal limits (Table 3) when expressed as a percentage of $C_{In}$. None of the patients had an inulin clearance below 50 ml/min, and most were well within the normal range (Table 3). However, $C_{In}$ was significantly lower in patients with Wilson's disease than in control subjects. $C_{Ur}/C_{In}$ for our patients was 0.188, which was significantly higher than the 0.098 for the control population ($P<0.01$). The filtered urate load in the patients with Wilson's disease was somewhat higher per nephron, reflecting the slightly higher levels of plasma urate in this group of patients. The fractional excretion of urate reflects the filtered urate that escapes reabsorption and is 2.71% in the patients with Wilson's disease. This value is not significantly different from that of 2.17% in the control patients. This lack of difference is not related to a difference in filtered urate because there is no apparent change in the FE of either group as the rate of filtered urate changes. The Tr urate was 97.2% of the filtered load, which was not significantly different from the 97.8% reabsorbed by the controls. There was no difference noted in the reabsorption of urate at any filtered load.

In Fig. 1, the Ts urate was correlated to plasma urate concentration. It has been shown that Ts urate increases with an increase in the concentration of plasma urate or filtered urate, which is reflected in the solid line as plotted from Steele and Rieselbach's data [10] and can be seen in our normal control subjects. Most patients with Wilson's disease had plasma urate concentrations in the range of the controls, but the patients with Wilson's disease had higher Ts urate values than did the controls. Because only a minor error results if a linear correlation of Ts urate with plasma urate is assumed in controls, we corrected Ts urate for plasma urate (Table 3) in order to compare them with the patients who had Wilson's disease. Ts urate was significantly higher ($P<0.005$) in the patients with Wilson's disease. It was also significantly higher if this correction was not made and Ts was compared directly ($P<0.001$). Note that one of the patients off penicillamine therapy (patient 6, Table 3) had a high Ts urate in the same range as those who were receiving penicillamine. Because the GFR is higher in control subjects, Ts was plotted against GFR, but there was no change in Ts urate in either group as GFR changed. Steele and Rieselbach [11] have shown that Ts urate per nephron does not change until the GFR approaches 15 ml/min.

Amino acid excretion was studied in these patients within 3 months of the time the urate excretion studies were performed (Table 4). Again the Ts urate values in

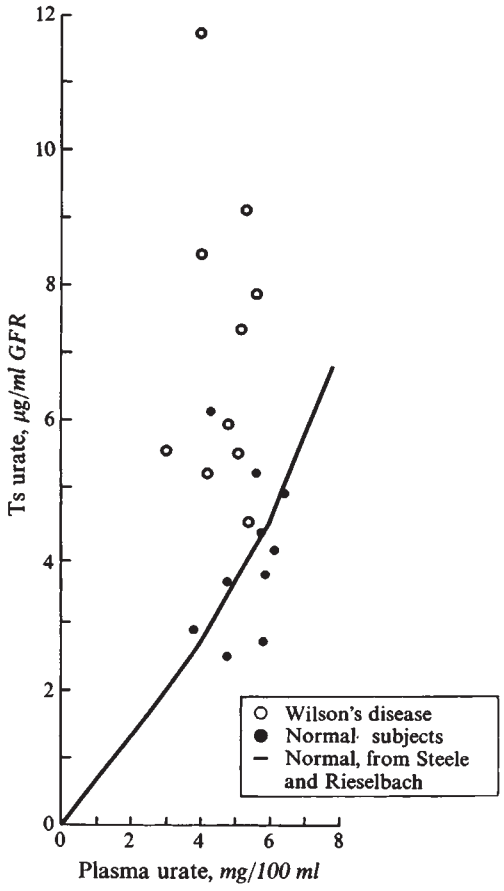


**Fig. 1.** *Urate secretion in normal persons and in patients with Wilson's disease in the presence of pyrazinamide. Solid line* taken from data by Steele and Rieselbach [10]. Ts urate = secretion rate of urate; plasma urate = plasma urate concentration; and *GFR* = glomerular filtration rate.

Table 4 have been corrected for the level of plasma urate. There was a generalized aminoaciduria in several of the patients. An attempt was made to relate the increased amino acid excretion to the increase in Ts urate. Serine excretion was positively correlated with Ts urate ($r = 0.63$, $P < 0.05$). There was also a positive correlation of Ts urate with arginine, valine, and glutamine (Table 4). Increased glycine excretion was not significantly correlated with increased Ts urate ($r = 0.31$).

## Discussion

In one study of Wilson's disease, untreated patients had a mean $C_{Ur}$ of 23.9 (16 to 30) ml/min, a mean $C_{In}$ of 97.3 (56 to 140) ml/min and a $C_{Ur}/C_{In}$ of 0.245 [2]. The serum uric acid concentrations in our patients improved virtually to normal on long-term penicillamine treatment, and their urate clearance values were lower, averaging 15.6 ml/min. However, they were clearing more urate than the normal subjects in our study or those reported by Steele and Rieselbach [10].

Uric acid clearance has been consistently high in patients with Wilson's disease even though some patients have total excretion values in the normal range. Sorensen and Kappas [5] have shown that the urate pool in these patients is small and that the metabolic turnover rate is normal. Their data, as well as those of Leu and associates [2], suggest that urate clearance returns toward normal after treatment with penicillamine. Several of our patients had been treated for more than 10 years. Urate clearance was still high in these patients, suggesting a continuing abnormality of urate excretion by the kidney in some patients.

The use of pyrazinamide to delineate the mechanism of urate excretion in Wilson's disease is limited because of the

**Table 4.** Amino acid excretion[a] in patients with Wilson's disease[a]

| Patient | Glycine | Aspartic acid | Leucine | Serine | Ornithine | Glutamine | Lysine | Cystine | Arginine | Alanine | Valine | Phenylalanine | Tyrosine | Ts urate per *mg* of plasma urate, *μg/ml GFR/mg* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 5,768 | 9.2 | 85 | 870 | 145 | — | 642 | 2,291 | 101 | 713 | 71 | 127 | 297 | 1.42 |
| 2 | 4,460 | 34 | 52 | 1,072 | 242 | 52 | 172 | 80 | 48 | 324 | TR | 96 | 184 | 1.85 |
| 3 | 2,543 | 71 | TR | 444 | — | 77 | 364 | 170 | 72 | 348 | 40 | 334 | 136 | 1.24 |
| 4 | 6,225 | 123 | 150 | 2,284 | 229 | 264 | 1,364 | 314 | 197 | 1,254 | 127 | 109 | 220 | 1.72 |
| 5 | 6,478 | 67 | 100 | 1,324 | 80 | 91 | 352 | 224 | 52 | 751 | 39 | 123 | 232 | 1.40 |
| 6 | 8,888 | 76 | 89 | 1,515 | 161 | 72 | 1,017 | 116 | 49 | 1,640 | 70 | 182 | 283 | 1.08 |
| 7 | 704 | TR | 61 | 202 | 27 | 18 | 80 | 31 | 37 | 175 | 29 | 23 | 48 | 2.92 |
| 8 | 1,060 | 82 | 48 | 358 | 16 | 48 | 517 | 60 | 49 | 237 | 36 | 156 | 94 | 0.83 |
| 9 | 2,009 | 77 | 61 | 680 | — | 104 | 245 | 175 | 37 | 391 | 60 | 224 | 257 | 1.24 |
| 10 | 1,749 | 4.0 | 107 | 246 | 186 | 26 | 56 | 80 | 62 | 260 | 37 | 105 | 125 | 2.22 |
| Normal | <4,565 | 12–113 | 33–73 | 264–573 | 7–38 | 25–84 | 700 | 40–228 | 44–82 | 852 | 163 | 76–399 | 45–280 | |
| *r* | 0.31 | 0.41 | 0.58 | 0.63[c] | 0.37 | 0.61[c] | 0.42 | 0.02 | 0.65[c] | 0.34 | 0.61[c] | 0.52 | 0.00 | |

[a] μmoles/24 hr.
[c] Significant ($P < 0.05$) (Ts urate compared with amino acid excretion).

controversy surrounding the effect of pyrazinamide itself on tubular function. Precise interpretation depends on a selective and complete blockage of secretion at a site distal to any reabsorptive site. There are serious questions about whether pyrazinamide may block reabsorption as well as secretion. Weiner and Tinker [16] have reviewed this problem and have shown that net secretion is blocked, but they also have shown that pyrazinamide is transported bidirectionally in different species. Although they showed that net reabsorption may be blocked only by extremely high doses, the possibility exists that the doses used in this study could have affected both reabsorption and secretion. A recent editorial has outlined the growing body of literature concerning the action and site of action of pyrazinamide [17], concluding that it is not possible at the present time to state with absolute certainty that the effect of pyrazinamide is a total and selective inhibition of uric acid secretion.

The validity of assuming that Ts urate as described herein measures the rate of secretion of urate quantitatively depends upon any secretory site being distal to the reabsorptive site(s). Any large area of overlap or the presence of a distal reabsorptive site makes it difficult to interpret urate excretion as being just a function of secretion, inasmuch as secreted urate may be normally reabsorbed distally. There is clear evidence of distal tubular secretion in several animals [7]. There is reasonably valid evidence that secretion, as well as the reabsorption of urate, may occur in the proximal tubule [16]. At this time, there is some evidence of distal tubular reabsorption in the rat [18] and possibly in man [19, 20]. Consequently, the analysis of pyrazinamide-induced changes of urate excretion will be influenced by a final and complete understanding of the sequential site of secretory or reabsorptive activity along the nephron. Nevertheless, a few comments and speculations may be in order.

Pyrazinamide, apparently, has as much effect on decreasing net urate transport in Wilson's disease as in normal subjects. Copper toxicity could prevent the effect of pyrazinamide on either reabsorption or excretion, but an impairment of the effect of pyrazinamide by copper should result in a higher excretion of urinary urate than expected after pyrazinamide administration and it should cause an apparent decrease in the amount of reabsorbed urate, which we did not see. A major overlap of reabsorptive and secretory sites or a significant distal reabsorptive site would make quantitative analysis of our data difficult, but on the assumption that pyrazinamide blocks secretion and does not alter reabsorption, the lack of an alteration in the fractional excretion of urate, while secretion is blocked, would be inconsistent with the suggestion that excess excretion in our patients is due to a defect in proximal reabsorption.

The presence of a distal reabsorptive site with a decreased capacity in Wilson's disease is an alternative interpretation to that of an apparent increase in urate secretion. Our results are also consistent with the presence of such a defect in a distalmost reabsorptive site in association with an increased Ts urate at a more proximal or even somewhat overlapping site. However, assuming that the drug blocks secretion only, it would be likely that the FE of urate would be increased in the presence of pyrazinamide if there was a significant depression in the distal reabsorption of urate, unless the distal reabsorptive component is large and pyrazinamide reduces the load presented to such a site within the reduced limits of its reabsorptive capacity. This model for urate transport has been proposed [20].

Sorensen and Kappas [5] and Bearn and associates [21] have also suggested, on the basis of increased urate clearances, that net renal urate reabsorption was impaired in patients with Wilson's disease. They gave probenecid to a patient who had Wilson's disease, and they presumed that the reduced uricosuric effect was evidence for a defect in reabsorption. They cited, as evidence, a patient with the Fanconi syndrome in whom the same result was obtained.

There are other possible explanations for urate wasting in Wilson's disease and the action of pyrazinamide. Bluestone et al [22] have shown that plasma proteins are capable of binding urate. It may be that urate binding is decreased in Wilson's disease and increased by pyrazinamide administration, but this is purely speculation and our data do not bear on this point.

One problem in our study concerns the effect of penicillamine administration on either renal function or the action of pyrazinamide. Penicillamine may alter the rate of reabsorption or secretion selectively, leaving alterations in only one part of the transport mechanism. However, two patients had not taken penicillamine, and one of these had a definite elevation in urate secretion and no apparent abnormality in reabsorption just like the patients who received the drug. The other patient had no significant alteration in the rate of excretion, reabsorption, or secretion. Sorensen and Kappas [5] treated normal persons with penicillamine and found no alteration in urate clearance, suggesting that neither the secretion nor reabsorption of urate was altered.

There is a positive correlation between Ts urate and the quantitative excretion of some of the amino acids. It seems probable that the copper toxicity is affecting amino acid transport and urate transport independently. However, several studies have suggested that alterations in amino acid excretion may influence uric acid excretion [7, 23–25]. Yü, Berger and Gutman [7] have shown that glycine loading produces uricosuria. In our study, there was no significant correlation between the rates of glycine excretion and amino acid excretion; however, glycine loading caused excess serine excretion, and serine excretion correlated positively with amino acid excretion in both our study and that of Yü et al [7]. Furthermore, gouty patients with a relative decrease in Ts urate have a decrease in the renal excretion of several amino acids [12, 26]. Aminoaciduria and hypouricemia are closely linked in Wilson's disease [27–29], and

there are abundant references to other conditions in which aminoaciduria and hypouricemia are linked, such as patients with primary hyperglycinuria [30–32], Fanconi's syndrome [33] or lung carcinoma [34]. It may be that amino acids have a causal role, and affect urate excretion, or vice versa. If there is a distal reabsorptive defect for urate masked by pyrazinamide administration, it could be coupled with amino acid reabsorption in some way.

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