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Received May 10, 1954. P.S.E.B.M., 1954, v86.

Uric Acid in Two Patients with Wilson's Disease (Hepatolenticular Degeneration).* (21124)

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In the course of a complete laboratory examination of a brother and sister both suffering from Wilson's disease, it was discovered that the serum urate levels in both individuals were unusually low (1-2 mg %), according to the colorimetric method(1). To elucidate the mechanism of this behavior it was decided to determine uric acid pool size and turnover rate by injecting N^{15} uric acid in the manner previously described(2).

The male subject was injected intravenously with 21.7 mg of N^{15} uric acid (14.81 atom % excess), and all urine was collected *ad libitum* for 5 days. From these results the pool size was calculated to be 442 mg and the turnover rate, 1.95 pools per day. The mean excretion for 4 days, determined by the isotope dilution method in the period just after the other measurements was 848 mg per day. The turnover was 442 x 1.95 = 862 mg and the per cent of the turnover excreted was 848/862 x 100 = 98%(4).

A similar study was performed on the female subject, using 19.5 mg of N^{15} uric acid. The pool size was calculated to be 304 mg and the turnover rate was 1.78 pools per day. The turnover was therefore 541 mg. The mean excretion for 8 days immediately following the test period was 391 mg and the per cent of the turnover that was excreted was 72%.

To test the possibility that the kidney tubules were completely inhibited in so far as their resorption of uric acid was concerned, the drug, Benemid, [p(di-n-propylsulfamyl) benzoic acid] was administered to the female subject and the uric acid injection was repeated. Sirota *et al.*(3) have demonstrated that this drug selectively inhibits tubular resorption of uric acid. The subject was given 3 × 0.5 g Benemid per day by mouth for 6 days and was then injected intravenously with 20.8 mg of isotopic uric acid. The pool size was determined to be 167 mg and the turnover rate 2.34 pools per day. The turnover was therefore 391 mg and the per cent turnover excreted was 86%, based on a mean excretion of 452 mg during 12 days on Benemid. The mean urinary excretion after Benemid was not statistically different from the control value, the P value for the t test being well above the 10% level.

After Benemid therapy was started on the female subject, her clinical condition became considerably worse. After cessation of the therapy she had not improved. Her present serum uric acid level is approximately 1 mg

* This study was supported in part by a grant-in-aid from the National Institutes of Health, Bethesda, Md.

TABLE I. Effects of Feeding 2 × 2 g of Commercial Ribonucleic Acid (RNA) on Uric Acid (UA) Levels in a Patient with Wilson's Disease.

	Serum UA, mg %	Urinary UA, mols N/day	Extra UA, % of ingested purine	Non-UA purines, mols N/day
Before RNA	1.3 to 1.6	20.6		8.9‡
After 9 days RNA feeding	3.0			
" 16 " " "	1.8			
During RNA feeding (Wilson's disease)		34.1*	55	9.9
Idem (normal controls) †			61, 73	
" (gouty patient) †			47	

* Statistically significant at 0.1% level.
† See reference(5). N^{15}-nucleic acid fed in one dose.
‡ " " (6).

%. Because of the coincidence of relapse and therapy, the same regimen was not instituted in the male subject.

To test the hypothesis that the neurological symptoms of the disease might be related to the low serum uric acid level, nucleic acid was fed with the results shown in Table I.

Discussion. The pool size of both the individuals with Wilson's disease was markedly below normal and the turnover rate was approximately twice the normal value. This would be consistent with an inhibition of tubular rate resorption, especially in the male where 98% of the uric acid turned over was excreted via the kidney. The female, on the other hand, had a normal per cent of turnover excreted and was susceptible to Benemid action insofar as the pool size and turnover rate were concerned. That Benemid did not cause a significant increase in urate excretion is in agreement with other studies from this laboratory(7) which indicate that unless there are increased serum urate levels, Benemid seems to have no uricosuric effect.

It has been reported(8) that the blood amino acid level in Wilson's disease is normal even though an aminoaciduria is present. In contrast to this behavior, the serum uric acid levels and the uric acid pool size are decreased, according to the data presented here.

Several mechanisms could be suggested to account for the difference in behavior of these 2 types of substances but more data are needed before any explanation could be validated. It is apparent that any relationship between uric acid and the etiology or pathogenesis of Wilson's disease is purely speculative on the basis of these studies, but the findings are interesting nevertheless.

Summary. A brother and sister with Wilson's disease (hepatolenticular degeneration) were found to have low serum urate levels and were injected with isotopic uric acid for pool size and turnover rate determination. The pool size of both was well below normal and the turnover rate was approximately twice the normal value. Benemid accentuated these findings in the female but was not tried in the male because of its adverse clinical effect. The rapid rate of removal of uric acid is compared to the phenomenon of aminoaciduria that is common in this disease. When ribose nucleic acid was fed to the male subject there was a statistically significant increase in urinary uric acid and this "extra" uric acid was equivalent to about 55% of the calculated purine ingested. There was no significant rise in the excretion of non-uric acid purines after nucleic acid feeding and this suggests that exogenous purine is mainly converted to uric acid before excretion.

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Received May 13, 1954. P.S.E.B.M., 1954, v86.