

Significance of circadian variations of uric acid elimination

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To investigate the significance of inverse circadian variations of renal excretion of uric acid¹ and enteral uricolysis^{2,3} it is necessary to demonstrate that they are affected by sleep and that there is a tendency for serum urate to change, even though this may be masked by effective homeostasis. If during sleep the rate of urate production exceeds elimination by increased enteral uricolysis and reduced renal excretion there should be a detectable increase in serum urate under controlled metabolic conditions.

A three day study comprising two six-hour periods of sleep separated by 42 hours' 'normal' activity was undertaken. During the awake periods the subject was on a low-purine mixed liquid diet of 0.69 MJ (165 k cal) four hourly with a water intake of 200 ml hourly.

Blood samples for estimation of urate concentration were taken every four hours at the midpoint of four hourly pooled urine collections for uric acid (apart from the first sleep period). Urate was measured in one batch by autoanalyser and urine pH by radiometer.

Normal diurnal variation of urate excretion was lost during the 42 hours

without sleep and was associated with a fall in serum urate of 0.036 mmol/l (0.6 mg/100 ml). There were two peaks of increased excretion after 22 and 34 hours during this period.

After both periods of sleep there was an increase in serum urate of 0.024 mmol/l (0.4 mg/100 ml), and 0.03 mmol/l (0.5 mg/100 ml). Initially there was fluctuation of urine pH, which then stabilised and fell dramatically during the second period of sleep from pH 6.1 ((H⁺) 794 nmol/l) to pH 5.35 ((H⁺) 4467 nmol/l) and increased with feeding to pH 6.5 ((H⁺) 224 nmol/l). Weight loss during the study was 1.5 kg and modest negative fluid balance occurred during sleep and on two occasions during the 42 hours.

As reduced urate clearance should be regarded 'as normal response of the kidneys to the endogenous hyperuricaemia (of primary gout)'^{4,5} a combination of reduced urinary excretion and increased enteral uricolysis suggests that there is increased urate production at night as shown by a rise in serum urate.

Enteral uricolysis is increased at night whether fasting or not, yet the normal daily variation of urine urate excretion is lost during fasting.⁶ This indicates that circadian elimination via

the gut is independent of renal function and food intake. As uricolysis is increased at night it is suggested that complex metabolic changes occur as a result of sleep that causes nucleoproteolysis and increased urate production with secondary renal effects of increased tubular reabsorption and reduced secretion of urate.

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Familial gout, hyperuricaemia, and renal impairment

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We report the case of a woman who suffered recurrent attacks of acute gout from the age of 15. When first seen at this unit 10 years later she gave a family history of gout and was found

to be mildly hypertensive. Investigations showed hyperuricaemia uncontrolled by the dose of allopurinol she was receiving and a glomerular filtration rate (GFR) of 15 ml/min. On

intravenous pyelography a small right kidney suggestive of damage by ureteric reflux was seen, though this was not confirmed by micturating cystography. Gamma camera

renography measured 80% of isotopic uptake over the normal sized left kidney. Histological examination of a biopsy specimen from this kidney showed pronounced glomerulosclerosis, tubular atrophy and fibrosis, and round cell infiltration of the interstitium, but urate crystals were not identified. Despite good control of hypertension and hyperuricaemia the GFR gradually fell over the next two years when malignant hypertension and a rapid deterioration in renal function supervened and the patient has now been admitted to a programme of renal dialysis.

Metabolic studies were performed on the patient's siblings and her close maternal relatives; the paternal relatives were not available for study. Subjects were questioned for a history of gout and resting blood pressure was measured. Serum concentrations and 24-hour urinary excretion of urate were measured by a uricase method on samples taken from subjects receiving a low purine diet. GFR was determined by EDTA clearance. The family tree is shown.

Of the 20 subjects studied, GFR was reduced in half (mean 52% of expected, range 15–74%). Five of these also had gout or hyperuricaemia that was associated with decreased renal clearance of urate. A sixth subject had reduced GFR and urate clearance without hyperuricaemia. These findings were detected by the second decade, common by the third, and most pronounced in elder members of this kindred. Seven subjects with renal impairment were also hypertensive.

The familial occurrence of juvenile

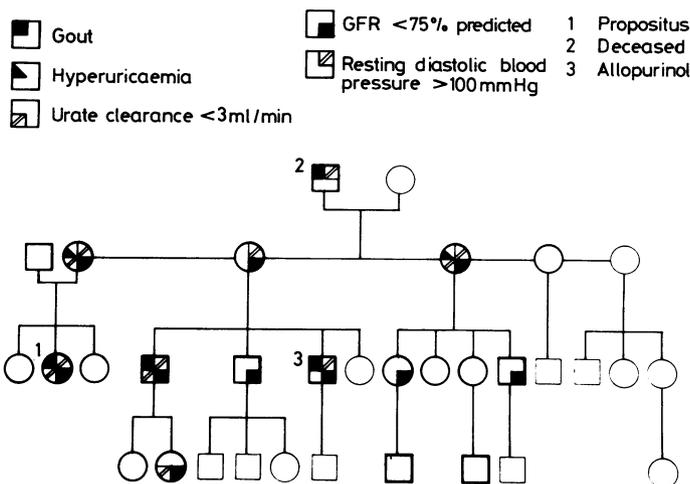


Fig. 1 *Family tree. Heavy lines denote subjects studied, circles females, and squares males.*

onset of gout associated with rapidly deteriorating renal function has been reviewed.¹ Inheritance appeared to be dominant and sometimes exclusive in females. The usual pattern was of hyperuricaemia predating or being disproportionate to the degree of renal impairment, though renal failure without hyperuricaemia was occasionally observed in these families. It remains undetermined whether the hyperuricaemia was responsible for, or consequent to, disordered renal function.^{2,3}

As the constant metabolic abnormality in this family was a reduction in the GFR, with impaired urate clearance and hyperuricaemia occurring only in elder members, it appears that a renal abnormality is the primary event rather than

hyperuricaemia. In contrast to previous reports, the family history of gout and renal failure was not striking in the case described here and might easily have been overlooked. This familial association may be more common than suggested by the few families described.

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Renal failure associated with crystal-induced nephropathy and gout in a baby boy

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There has been much controversy¹ over the relative roles of crystal deposition, vascular disease, and age

in the genesis of the renal lesion in gout, where nephropathy was formerly common but is now extremely rare.²

Considerable debate as to whether the origin of the lesion was interstitial³ or stemmed from intratubular deposition