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Uric acid saturation in calcium nephrolithiasis

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Uric acid saturation in calcium nephrolithiasis. Hyperuricosuria appears to cause calcium oxalate nephrolithiasis by promoting the formation of monosodium urate or uric acid crystals, which either act as seed crystals for calcium oxalate or adsorb normally occurring macromolecular inhibitors of calcium oxalate crystallization. Both mechanisms require that hyperuricosuria cause excessive supersaturation of the urine, but this has not yet been studied under conditions of normal lifestyle. We have measured the saturation with respect to sodium hydrogen urate and the concentration of undissociated uric acid in the urine samples of 67 patients with calcium nephrolithiasis, who had idiopathic hypercalciuria, hyperuricosuria, both, or neither disorder. Patients with hyperuricosuria excreted urine that was supersaturated with respect to monosodium urate or undissociated uric acid more frequently than did other stone formers or normal subjects, and are therefore at a greater risk of forming a solid phase of monosodium urate or uric acid. Treatment measures that lowered uric acid excretion also lowered urine saturation, and this may be the reason that such treatment tends to prevent calcium stone recurrence.

Solution saturée d'acide urique dans la lithiase calcique. L'hyperuricosurie semble déterminer des lithiases d'oxalate de calcium en favorisant la formation de cristaux d'urate monosodique et d'acide urique qui agissent comme germe de cristallisation pour l'oxalate de calcium ou bien adsorbent les inhibiteurs macromoléculaires physiologiques de la cristallisation de l'oxalate de calcium. Les deux mécanismes exigent une sursaturation des urines en ce qui concerne l'acide urique, mais cela n'a pas encore été étudié dans de conditions de vie normale. Nous avons mesuré la saturation en ce qui concerne l'urate acide de sodium et les concentrations d'acide urique non dissocié dans les urines de 67 malades atteints de lithiase calcique qui avaient une hypercalciurie idiopathique, une hyperuricosurie, les deux désordres, ou encore aucun de ces désordres. Les patients atteints d'hyperuricosurie élaborent une urine qui est plus souvent sursaturée, en ce qui concerne l'urate monosodique ou l'acide urique non dissocié, que celle des autres individus lithiasiques ou normaux. Les malades sont donc exposés à un plus grand risque de formation d'une phase solide d'urate monosodique ou d'acide urique. Les mesures thérapeutiques qui abaissent l'excrétion d'acide urique diminuent aussi la sursaturation de l'urine, et ceci peut être la raison pour laquelle de tels traitements tendent à empêcher la récidive de la lithiase calcique.

Hyperuricosuria appears to contribute to the genesis of calcium oxalate renal stones [1–5], but the mechanisms by which it does this are not yet established. One possibility is that uric acid or sodium hydrogen urate crystals form in the urine or renal tubules, because of hyperuricosuria, and act as seed crystals on whose surfaces crystals of calcium oxalate may form [4, 5]. This theory is supported by the fact that crystals of sodium hydrogen urate and, to a lesser extent, of uric acid are heterogeneous seed nuclei for calcium oxalate [6, 7]. An alternative theory [8] is that excessive supersaturation leads to production of a colloidal phase of uric acid or monosodium urate that adsorbs, and thereby removes from solution, the highly charged macromolecular inhibitors of calcium oxalate crystal growth that normally [8–10] protect against calcium oxalate crystallization. Both theories require that urine become excessively supersaturated with uric acid or sodium hydrogen urate as a consequence of hyperuricosuria.

Pak et al [9, 11] have established that hyperuricosuria can raise the urine's saturation with respect to sodium hydrogen urate under conditions of controlled sodium and water intake, and at a constant urine pH. These positive findings make it worthwhile to determine the extent to which hyperuricosuria causes oversaturation under routine, outpatient conditions, in which urine pH, volume, sodium concentration, and uric acid concentration are all conditioned by the individual habits of the patient.

Methods

Patients and normal subjects. Using our usual clinical and laboratory protocol [3], we studied 67 consecutive patients, 45 men and 22 women ranging in age from 17 to 72 years. All of them had formed at least one calcium stone and had either idiopathic hypercalciuria, hyperuricosuria, both, or neither disorder. Idiopathic hypercalciuria was defined by a daily urinary calcium excretion above 300 mg (men), 250 mg (women), or above 4 mg/kg (either sex), normocalcemia, and the absence of a specific

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cause for hypercalciuria [12, 13]. Diagnostic criteria for hyperuricosuria were a daily urinary uric acid excretion above 800 mg (men) or 750 mg (women) [1-3]. In addition, we studied the 24-hour collections from 10 normal men and 10 normal women (ages, 24 to 50 years). Each patient collected three 24-hour urine samples, with thymol as a preservative [3], under outpatient conditions. Each patient was on the diet of his choice. A blood sample was obtained at the completion of each collection, in the postabsorptive state. Urine samples that appeared grossly infected or had a pH value of above 8 were rejected.

Saturation measurements for sodium hydrogen urate. Two samples from each 24-hour urine collection were seeded with 5 mg/ml of sodium hydrogen urate monohydrate crystals, prepared by us [6, 7]. Six drops of chloroform were also added, to control bacterial growth. The pH was adjusted back to its original value, during incubation, using 1.0 M sodium hydroxide. After the samples were incubated at 37° C for 48 hours, at a constant pH, the solid and liquid phases were separated by filtration through a 0.22-μ pore diameter filter. Pak et al [9] have shown that this filter gives results identical to those using a filter of 0.05-μ pore diameter. Sodium and uric acid concentrations were measured in the filtrate, as well as in the original urine sample, and the ratio of the initial to the final product of the sodium and uric acid concentrations was calculated [11]. If duplicate values of the concentration ratio differed by more than 10%, the sample was discarded. In addition to measuring the concentration product ratio at the ambient pH of the urine, we also measured it at a controlled pH, of 6.3 to 6.5, in 76 urine samples, from 28 of the 67 patients. Unless specified, all saturation results refer to those obtained at the ambient urine pH. The concentration product ratio was measured in urine samples from 16 of the 20 normal subjects. Because the concentration product after 2 days of incubation represents the final equilibrium value for that urine sample [9, 11], the ratio of the preincubation to the postincubation product is essentially the ratio of the ion product in the original urine sample to the equilibrium product in that urine sample [11]. Values above 1 indicate growth of the seed crystals, and therefore supersaturation; values below 1 reflect undersaturation.

Undissociated uric acid. The concentration of undissociated uric acid (A) was calculated for each 24-hour urine sample by the equation

$$[A] = [T] \div (1 + 10^{pH-pK})$$

where T is the total uric acid concentration of the urine. The value of pK (5.345) was obtained by correcting the thermodynamic dissociation constant (pK, 5.47) [14] by the monovalent ion activity coefficient for urine, which, at the ionic strength characteristic of urine, is close to 0.75 [15]. Twenty-six urine samples that had a pH of below 5.6 were seeded with 5 mg/ml of uric acid crystals prepared by us [7], to determine uric acid solubility; each sample was studied in duplicate. After 48 hours of incubation, with stirring, at 37° C and constant pH, the urine was filtered through a 0.22-μ filter and calculated the undissociated uric acid concentration of the filtrate. The mean equilibrium concentration was 90 ± (SEM) 5 mg/liter. The mean ratio of the initial to the final concentration, an estimate of the degree of supersaturation in each urine, was 2.41 ± 0.2 and was correlated closely (r = 0.81) with the initial urine undissociated uric acid concentration.

Calcium oxalate saturation. The concentration product ratio for calcium oxalate monohydrate was measured in each urine sample by the method of Pak and Holt [16], as described from our laboratory [17]. Previously, we have determined a range of normal to be from 0.6 to 2.85 for this test, close to that reported by Pak [16]. Patients whose mean value exceed 2.85 were classified as having abnormally elevated calcium oxalate supersaturation.

Analytical methods and materials. Serum and urinary uric acid concentration was measured by the uricase method; sodium, by flame photometry [1, 3]. Serum and urinary calcium concentrations were measured by atomic absorption spectrophotometry [12]; and urine oxalate, by zinc reduction [17, 18]. Crystals of sodium hydrogen urate, of uric acid, and of calcium oxalate·H_2O were confirmed by X-ray crystallography.

Statistics and nomenclature. Confidence limits, t values, and regression equations were calculated by the least squares method by a standard computer program (BMDP, U.C.L.A. Health Sciences Computing Facility, Los Angeles, California). In the case of urine pH, values of urinary proton concentration were used for calculating the means and Student's t values for comparison of patients to normal; the pH values of the mean proton concentrations are presented because they are a familiar index.

Results

Sodium hydrogen urate saturation. Mean values of the urinary concentration product ratio (CPR) were not different for patients and normal subjects

(Table 1), even though the urinary concentration of uric acid was higher in hyperuricosuric patients. The CPR of hypercalciuric and metabolically normal stone formers tended to be lower than that of hyperuricosuric patients or normal people. The urine volume was higher than the control value among hypercalciuric and hyperuricosuric patients.

The final, postincubation, concentration products were all within a narrow range of between 11.0 and 13.2 $M^2 \times 10^{-5}$ (Table 1), and therefore the CPR was very closely correlated (Fig. 1) with the initial uric acid concentration ($r = 0.70$), the initial urate concentration ($r = 0.79$), the initial sodium concentration ($r = 0.68$), and the initial product of urate and sodium concentrations ($r = 0.85$). All values of r are significant at $P < 0.01$. Judging from the 95% confidence limits, which were calculated for use with the means of three separate samples, we found that a patient whose mean initial uric acid concentration exceeds 860 mg/liter (Fig. 1) will have an average concentration product ratio below 3 less than 5% of the time, whereas patients whose corresponding mean values are below 350 mg/liter will have a mean that exceeds 3 less than 5% of the time. The mean postincubation concentration products exceeded the mean postincubation activity product for urine (3.45 ± 0.7 $M^2 \times 10^{-5}$) observed by Pak et al [11], as expected.

In the present study, urine pH was often below 6 (Table 1), rather than between 6.3 and 6.5 as in previous studies [9, 11]. To estimate the effect of this pH difference, we compared the concentration product ratio values of 76 urine samples, having a pH below 6.0, from 28 patients, incubated at their ambient pH and at a controlled pH of 6.3 to 6.5. The means (± 1 SEM) of the differences between the controlled pH and the ambient pH values for the concentration product ratio were 0.33 ± 0.15, 0.7 ± 0.13, 0.45 ± 0.22, and 0.21 ± 0.15 for urine samples from patients with idiopathic hypercalciuria (30 samples), hyperuricosuria (11 samples), both (9 samples), and neither disorder (26 samples), respectively. The corresponding mean increments in urine pH (controlled pH − ambient pH) were 0.45, 0.45, 0.48, and 0.44 pH units, respectively. In other words, a systematic overestimate of the concentration product ratio occurred when these urine samples were incubated at a higher pH; but the change was small, and attained statistical significance ($t = 2.146$, $P < 0.05$) only for the 30 samples from patients with idiopathic hypercalciuria.

Men and women differed significantly from one another with respect to six findings (Table 1): the undissociated uric acid for normals was 77 vs. 41 mg/liter for men and women, respectively; the sodium concentration was 148 vs. 116 mEq/liter (nor-

Table 1. Summary of urinary uric acid saturation measurements[a]

24-Hour urine values	Metabolic group				
	Normal ($N = 20$)	IH ($N = 24$)	HU ($N = 12$)	Both ($N = 14$)	Neither ($N = 17$)
No. of samples	24	69	36	42	51
Total uric acid, *mg/liter*	503 ± 32	421 ± 23	575 ± 28	616 ± 27[g]	462 ± 32
Urine volume, *ml*	1268 ± 65	1717 ± 133[h,j]	1501 ± 79[f]	1397 ± 70	1387 ± 90
Urine pH	6.22	5.92	5.62[g]	5.74[g]	5.67[h]
Undissociated uric acid[b], *mg/liter*	57 ± 8[j]	84 ± 11	155 ± 21[h]	150 ± 16[i]	128 ± 18[g]
CPR, monosodium urate	2.8 ± 0.3[e]	2.2 ± 0.2	2.7 ± 0.2	3.1 ± 0.2	2.2 ± 0.2
Initial [Na] · [urate][c], $M^2 \times 10^{-5}$	37 ± 4	27 ± 3	35 ± 4	42 ± 3[j]	29 ± 3
Final [Na] · [urate][d], $M^2 \times 10^{-5}$	13.2 ± 0.7	11.0 ± 0.5	12.0 ± 0.6	12.9 ± 0.5	13.2 ± 1.0
Sodium concentration, *mEq/liter*	131 ± 8[j]	118 ± 7	130 ± 7	149 ± 7[k]	132 ± 7[j]

[a] All values, except for the numbers of samples and the numbers of people in each metabolic group (in parentheses), are the means ± SEM. Abbreviations used are: IH, idiopathic hypercalciuria; HU, hyperuricosuria; CPR, concentration product ratio; [Na], sodium concentration (mEq/liter); [urate], urate concentration (mmoles/liter).

[b] The mean equilibrium value, determined in 26 urine samples of pH below 5.6, after 48 hours of incubation with crystals of uric acid, was 90 ± 5 mg/liter.

[c] Before incubation with crystals of sodium hydrogen urate

[d] After 48 hours of incubation with crystals of sodium hydrogen urate

[e] Based upon the study of the 16 of the 20 normal subjects who had CPR measurements

[f] $P < 0.05$, compared with control.

[g] $P < 0.02$, compared with control.

[h] $P < 0.01$, compared with control.

[i] $P < 0.001$, compared with control.

[j] $P < 0.05$, men vs. women.

[k] $P < 0.02$, men vs. women.

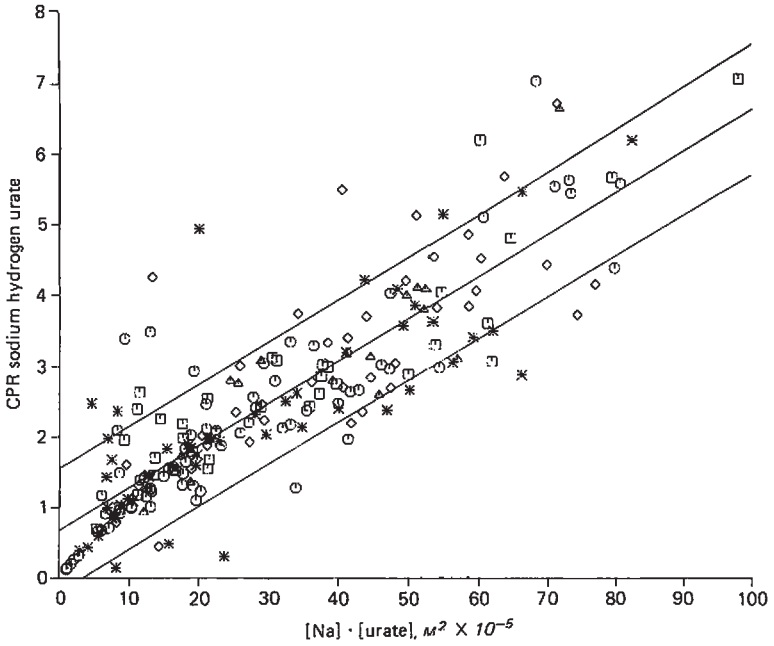

Fig. 1. *Correlation between the urine sodium hydrogen urate concentration product ratio (CPR) and total uric acid concentration.* Symbols are: ▲, normal subjects; ○, idiopathic hypercalciuria; □, hyperuricosuria; ◇, both; *, neither. The regression has a slope of 4.87 $\times 10^{-3}$ and an intercept of 0.056. The confidence interval is calculated so that the likelihood that the mean value from three samples from the data will be outside of the interval is less than 5%. Each *point* represents a single urine sample. Mean values are shown in Table 1.

mals), 157 vs. 115 mEq/liter (both), 142 vs. 113 mEq/liter (neither); the initial [Na] · [urate] was 45 vs. 30 $M^2 \times 10^{-5}$ (both); and the urine volume for idiopathic hypercalciuria was 1986 vs. 1415 ml. None of these differences affect any conclusions, in that comparison of normals to patients of the same sex are indistinguishable statistically from comparison based upon pooled data from men and women.

Undissociated uric acid concentration. Unlike the situation with sodium hydrogen urate, stone formers who were hyperuricosuric produced urine samples whose mean concentrations of undissociated uric acid were about 100 mg/liter higher than normal (Table 1). The majority of the increase was due to low urine pH; the mean concentrations of undissociated uric acid were more than twice normal in hyperuricosuric patients even though the mean concentration of total uric acid in the urine of stone formers who were hyperuricosuric (575 mg/liter) or hyperuricosuric and hypercalciuric (616 mg/liter) exceeded that of normals by only 14.3% and 22.5%, respectively. Note that the exact mean values of undissociated uric acid shown in Table 1 cannot be calculated from the corresponding mean values for pH and total uric acid concentration because the relationship between pH and the ratio of undissociated to total uric acid is nonlinear. Patients with no metabolic disorder also had an average urinary undissociated uric acid concentration above that of normal people (Table 1) even though their average total uric acid concentration in urine was below that of normal subjects.

Supersaturation in individual patients. To classify patients in a preliminary way, we adopted some arbitrary upper limits for the concentration product ratio and for the undissociated uric acid concentration. Only 4 normal subjects had mean values of CPR above 3.2 (4.0 to 6.7), and there was a noticeable break between 3.2 and 4.0 in the normal group and in all of the patients except those with combined hypercalciuria and hyperuricosuria. So, counting statistics would not be changed drastically, for the most part, if we chose any value in this range as a limit. We have therefore used a mean value of 3.2 as a provisional upper limit for CPR. In the case of undissociated uric acid, no normal values were above 138 mg/liter, and this value was 2 SD above the normal mean (57 ± [SD] 40) and is considerably above the equilibrium solubility of undissociated uric acid in water at 37° C [19]. Accordingly, we have classified patients whose mean urinary concentration of undissociated uric acid was above 138 mg/liter as having high, as opposed to unremarkable, values.

Using these limits, we found high values for the concentration product ratio and for the undissociated uric acid, alone or with other abnormalities,

in 32 of the 67 patients, 47.8% (Table 2); they would be expected to occur together by independent chance association in 8.71% of patients, or 5.8 patients in this series, not significantly different from the eight instances we observed. Of interest, five of the eight instances of their concurrence were in the 14 patients with combined hypercalciuria and hyperuricosuria (Table 2), compared to only three in the remaining 53 patients ($\chi^2 = 9.53$, $P < 0.01$). Overall, there were 18 patients with abnormally high supersaturation of undissociated uric acid and sodium hydrogen urate among the 26 patients who were hyperuricosuric, compared to only 14 among 41 patients who were not hyperuricosuric ($\chi^2 = 7.8$, $P < 0.01$), and 4 of 16 normal subjects ($\chi^2 = 7.77$, $P < 0.01$), so that hyperuricosuria was associated with excessive uric acid supersaturation.

Elevated mean urine calcium oxalate concentration product ratios (above 2.85, Methods) were found in 17 of the 67 patients (25%), 10 of whom (58.8%) were hypercalciuric; 7 of these 17 patients also had a high mean sodium hydrogen urate concentration product ratio (Table 2), a concurrence rate compatible with chance alone.

Effects of treatment. Sixteen patients with hyperuricosuria, seven of whom also were hypercalciuric, were treated with allopurinol, 100 mg twice daily, or a low purine diet to lower their 24-hour urine uric acid excretion below 800 mg; some of the patients with hypercalciuria also received trichlormethiazide, 2 mg twice daily, to lower their urine calcium excretion [3] (Fig. 2). Urinary uric acid

Table 2. Occurrence of elevated uric acid or calcium supersaturation in each metabolic class[a]

Urine saturation increased with respect to	Metabolic class				
	IH	HU	Both	Neither	Totals
Undissociated uric acid[b]	2	4	3	5	14
Monosodium urate[c]	1	2	1	0	4
Both	2	0	3	1	6
Calcium oxalate · H_2O[d]	4	1	0	4	9
Calcium oxalate · H_2O and monosodium urate	2	1	1	1	5
Calcium oxalate · H_2O and undissociated uric acid	0	0	1	0	1
Calcium oxalate · H_2O and monosodium urate and undissociated uric acid	0	0	2	0	2
None	13	4	3	6	26
Total patients	*24*	*12*	*14*	*17*	*67*

[a] Table shows the number of patients whose mean urine values exceeded the upper limits used in this study: Abbreviations: IH, idiopathic hypercalciuria; HU, hyperuricosuria.
[b] Mean value exceeds 138 mg/liter.
[c] Mean value exceeds 3.2.
[d] Mean value exceeds 2.85.

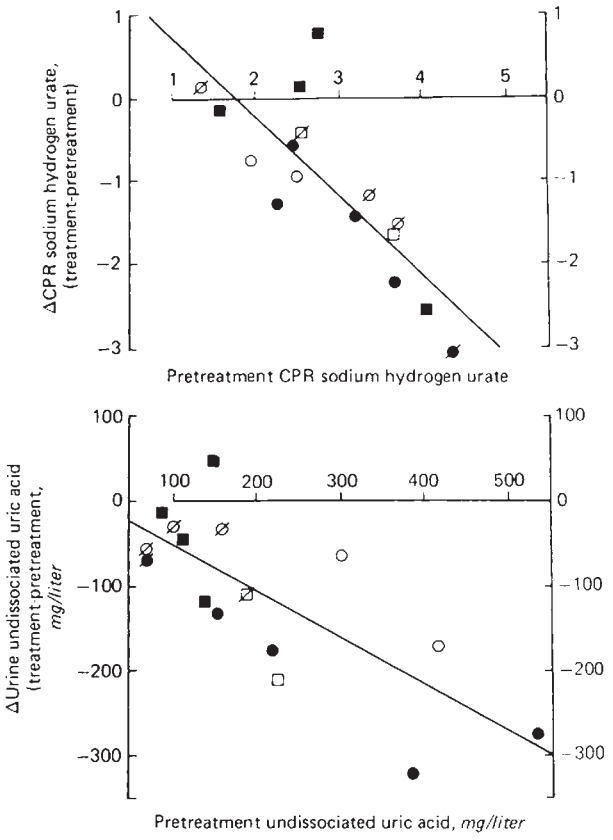

Fig. 2. *Response of urine saturation to treatment.* The difference between the mean initial value and the last treatment value of monosodium urate concentration product ratio (*a*) and undissociated uric acid (*b*) are plotted against corresponding mean pretreatment values for 9 patients with hyperuricosuria *(closed symbols)* and 7 patients with combined hypercalciuria and hyperuricosuria *(open symbols)*, treated with allopurinol *(circles)* or low purine diet alone *(squares)*. Some patients with both hypercalciuria and hyperuricosuria, and one patient with only hyperuricosuria, also received trichlormethiazide (2 mg, twice a day) (indicated by a *line through the symbol*).

saturation fell; the extent of the fall was strongly correlated with the magnitude of the mean pretreatment value for both the sodium hydrogen urate concentration product ratio (Fig. 2a) ($r = -0.80$) and the urinary undissociated uric acid concentration ($r = -0.76$). Undissociated uric acid concentration (Fig. 2b) remained above 138 mg/liter in only four instances, and the concentration product ratio fell below 3 in all but one case. Mean values of undissociated uric acid fell to 65 ± 20 and 95 ± 30 mg/liter for patients with hyperuricosuria and combined hyperuricosuria and hypercalciuria, close to the mean value observed in normal people (Table 1).

Discussion

The primary question to which we have addressed ourselves in this study was whether or not

hyperuricosuria leads to abnormally high urinary supersaturation with uric acid under uncontrolled, ambient conditions of diet, fluid intake, and life style. The answer seems clearly positive. Of our 26 hyperuricosuric patients, 18 (69%) displayed excessive supersaturation with uric acid or sodium hydrogen urate compared to 14 of 41 (34%) patients who were not hyperuricosuric ($\chi^2 = 7.84, P < 0.01$), and 4 of the 16 normal people in whom both the concentration product ratio and undissociated uric acid concentration were measured ($\chi^2 = 7.77, P < 0.01$). Excessive uric acid and calcium oxalate supersaturation occurred as if they were independent of one another, as are hyperuricosuria and hypercalciuria [3].

As Pak et al [9, 11] have found, sodium hydrogen urate saturation varies strongly with urinary uric acid concentration, which was high in hyperuricosuric patients. The slope and the intercept of the regression equation (Fig. 1) between them are both higher in this study than they are in the study of Pak et al, probably because the urinary sodium concentration in the Pak study was held at about 50 mEq/liter, compared to our mean values of 118 to 149 mEq/liter (Table 1). Unlike Pak et al [13], we found undersaturation, values of the concentration product ratio below 1.0, only rarely, whereas they found it to be common when urine uric acid concentration was below 300 mg/liter. This difference, too, is probably due mainly to the higher sodium concentrations we encountered. In addition, we found very few values of total urinary uric acid concentration below 300 mg/liter, whereas many values were above 500 mg/liter, the upper limit achieved by Pak et al under controlled circumstances. Apparently, spontaneous conditions of diet and fluid intake lead to even higher values of total uric acid concentration and sodium excretion than those encountered under controlled conditions, even though urine volumes were higher among several groups of patients than they were among controls, so that urine is usually supersaturated with respect to monosodium urate.

Elevated urinary undissociated uric acid concentration was a striking feature of our stone formers and was due more to low urine pH than to a high urinary total uric acid concentration.

The low urine pH may have arisen, in part, from diet. In calcium stone formers, hyperuricosuria is produced mainly by a high intake of meat, fish, and poultry [2, 20], and all three foods impose a large load of acid, in the form of phosphoric and sulfuric acids, for eventual excretion [21]. This does not, however, explain why patients without hyperuricosuria or hypercalciuria (Table 1) also had a low average urine pH.

Increased undissociated uric acid concentrations can foster the formation of uric acid crystals, which can act as heterogeneous seeds for calcium oxalate [7]. Even if they were very inefficient heterogeneous nuclei, uric acid crystals that plug the end of a collecting duct [22] could, in theory, serve as an anchored site on which a plaque of calcium oxalate crystals might form. Alternatively, a gel phase of uric acid may be able to adsorb macromolecular inhibitors of crystal growth. In support of a link between uric acid crystals and calcium nephrolithiasis are the facts that patients with gout, who produce very acid urine, form an excess of calcium [23, 24] as well as uric acid stones, and that mixed stones, of calcium oxalate and uric acid, are not a rare occurrence among nongouty patients with combined hypercalciuria and hyperuricosuria or no metabolic defect [25].

From our study, treatment measures that lower uric acid excretion also reduce uric acid saturation, with respect to the undissociated uric acid and the monosodium urate solid phases, and therefore could reduce heterogeneous nucleation or the adsorption of crystal growth inhibitors by solid phases of uric acid or its monosodium salt. The response was excellent for undissociated uric acid, even though we did not attempt to increase urine pH by our treatment. The excellent response of supersaturation to treatment with allopurinol or reduced purine intake is consistent with the dramatic reduction in calcium stone recurrence that has been found in treated patients [1-3, 26].

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