Hyperuricosuric calcium oxalate nephrolithiasis

FREDRIC L. COE

Renal Division, Department of Medicine, Michael Reese Hospital, and Pritzker School of Medicine, University of Chicago, Chicago, Illinois

Many investigators have observed that renal calcium stones may be associated with uric acid disorders. Prien and Prien [1] noted that patients with gout who had stone disease frequently passed stones which contained or were composed of calcium oxalate. Gutman [2] also observed a high frequency of calcium oxalate stones in patients who had gout; and he called attention to crystallographic studies of Lonsdale [3, 4] which showed that a significant enough structural correspondence existed between crystals of uric acid, sodium hydrogen urate, and calcium oxalate to allow one to grow upon the surface of another or to act for one another as heterogeneous seed nuclei. Dent and Sutor [5], on the other hand, found that patients with calcium oxalate stone disease were hyperuricemic more often than normal subjects were, even though none of the patients had clinical gout. Smith et al [6] made a similar observation and suggested that calcium stone-formers with uric acid disorders represented a significant metabolic subgroup of calcium stone disease.

Our own observation that hyperuricosuria was very frequent among patients with calcium oxalate nephrolithiasis [7, 8] was consonant with what had come before and provided evidence for an abnormality of urine chemistry that could link uric acid disorders to the formation of calcium stones in the kidney or upper urinary tract. Subsequent research has centered mainly on hyperuricosuric calcium oxalate stone-formers, because they have a decisive urine chemistry abnormality and offer immediate research opportunities. Study of such patients has provided four kinds of evidence linking their hyperuricosuria to calcium stone formation and setting them apart from other calcium stone-formers. The evidence includes an atypical natural history of stone disease, *in vitro* evidence for heterogeneous nucleation of calcium oxalate crystallization by seed crystals of so-dium hydrogen urate or uric acid, a reduction by urate or uric acid of the inhibiting effect which urine normally has upon the aggregation of calcium oxalate crystals, and an apparently dramatic effect of allopurinol to reduce new stone formations. Taken altogether, the weight of evidence supports the existence of a distinct syndrome of hyperuricosuric calcium oxalate nephrolithiasis.

Frequency of hyperuricosuria in calcium stone-formers

Before describing later and more specific research, it seems worthwhile to review the basic statistical association which, in large measure, initiated subsequent investigation. A recent survey of 460 calcium oxalate stone-formers illustrates the very large fraction of patients who excreted above 800 mg (men) or 750 mg (women) of uric acid in at least one of two 24-hr urine samples collected for the purpose of making such measurements (Table 1). Of the 121 hyperuricosuric patients, 40 men (39%) and 4 women (22%) were hyperuricemic by usual definition. Normal men and women, who had no history of stone disease, excreted such large amounts of uric acid only infrequently (Table 2). If higher limits are used, stone-formers depart more drastically from normal subjects, who rarely contributed values above 900 mg/24 hr (men) or 800 mg/24 hr (women).

There is a natural difficulty in defining upper limits of normal for uric acid excretion, because there is no obvious bimodality to the distribution of excretion rates among patients with stone disease or normal people, but only a tendency, quite marked, for higher values to occur in patients (Table 2). Gutman [2], facing the same problem, suggested the limits of 800 and 750 mg for men and women, respectively, which we have used to define hyperuricosuria. A point, 2 SD's above the mean values of uric acid excretion by our normal subjects of each sex, could replace these arbitrary limits, because only five percent of the normal points depart so widely from the mean. But such limits might not offer a diagnostically useful

Table 1. Metabolic and clinical disorders in 460 consecutive calcium stone-formers

	No. of patients	%
Idiopathic hypercalciuria	95	20.7
Marginal hypercalciuria[a]	53	11.5
Hyperuricosuria	67	14.6
Hypercalciuria and hyperuricosuria[b]	54	11.7
Hyperuricemia alone	26	5.7
Primary hyperparathyroidism	24	5.2
Renal tubular acidosis[c]	17	3.7
Inflammatory bowel disease[d]	21	4.6
Medullary sponge kidney	7	1.5
Sarcoidosis	3	0.7
No disorder found	93	20.2
Total	460	

[a] Urine calcium > 140 mg/g creatinine
[b] Marginal hypercalciuria not included
[c] Distal, hereditary form
[d] Regional enteritis, ulcerative colitis, granulomatous ileocolitis

advance, because the extent of urine saturation with uric acid, sodium hydrogen urate, or both, determined mainly by the urine concentrations of the substances and not by the amount excreted daily, is the property which can influence crystallization in the urine. Given the indirect relationship that exists between uric acid excretion rate and uric acid concentration, it may be just as useful in predicting supersaturation to use the lower limits that Gutman proposed. These lower limits proved reasonably effective in selecting patients for treatment. Pak [9] has recently shown that urine was metastable with respect to sodium hydrogen urate, as judged by a concentration product ratio above 1, when total uric acid concentration exceeded 300 mg/liter. This could become the basis for clinical diagnosis of an abnormal urine uric acid level, especially as urine sodium concentration was deliberately kept low. An uncontrolled diet is likely to provide more sodium, increasing the extent of supersaturation.

Mechanisms of hyperuricosuria

Excessive dietary purine intake, a natural mechanism to explain so widespread a tendency to high uric acid excretion rates, is a major factor. Uric acid overproduction from endogenous purine metabolism also contributes in some patients. A tubule defect of urate reabsorption is an unattractive hypothesis in view of the absence of hypouricemia in our patients.

Role of diet. We have estimated purine and calorie intake by using the diaries of 10 men who were normouricemic, hyperuricosuric calcium oxalate stone-formers and five age- and weight-matched normal subjects who were drawn from a comparable social and economic class. For 18 days, each person

Table 2. Frequency of various uric acid excretion rates among calcium oxalate stone-formers (P) and normal subjects (N)[a]

Urinary urate mg/24 hr	Men[a]		Women	
	N (N = 128)	P (N = 1046)	N (N = 77)	P (N = 302)
<200	0	0	0	0
200–400	2	1	36	25
400–600	38	17	54	53
600–800	48	50	9	8
800–900	6	14	0	6
900–1000	4	11	—	5
>1000	2	7	—	3

[a] Numbers are the percentages of 24-hr urine samples containing the amounts of urate indicated. Total number of urine samples in each group is shown in parentheses.

Table 3. Purine and caloric intake by patients and normal subjects[a]

	Purine intake (as nitrogen) mg/24 hr	Caloric intake calories/24 hr
Patients (N = 10)	259 ± 29[b]	2109 ± 161
Normal men (N = 5)	155 ± 21	2104 ± 147

[a] Values are means ± 1 SEM.
[b] F test for equality of variances = 9.16, $P < 0.01$, for patients vs. normal men.

kept a detailed diary of all foods consumed. Using standard listings of purine and calorie contents of foods and beverages, a nutritionist computed daily intakes of both [10]. The final conclusion (Table 3) was that patients invested a higher proportion of their dietary intake in purine-rich foods [11]. By chance, the average caloric intakes of patients and controls were virtually identical. The specific diet abnormality in patients was preferential consumption of meat, fish, and poultry at the expense of breads, grains, and starches.

Role of overproduction. In addition to consuming excessive purine, some of the 10 patients we studied appeared to overproduce uric acid. The 95 percent confidence band relating urinary uric acid excretion to dietary purine intake in normal people is shown as the crosshatched area in Figure 1. Three of the 10 patients we studied excreted more uric acid than would normal subjects eating the same amount of purine. During days 8, 9, and 10 of a purine-free diet, these three patients continued to excrete more uric acid than normal subjects usually do, and certainly more than the five normal subjects we studied, shown by open circles. Presumably, the surplus uric acid they excreted on their own high purine diet or a purine-free diet reflected overproduction of uric acid during the course of endogenous purine metabolism.
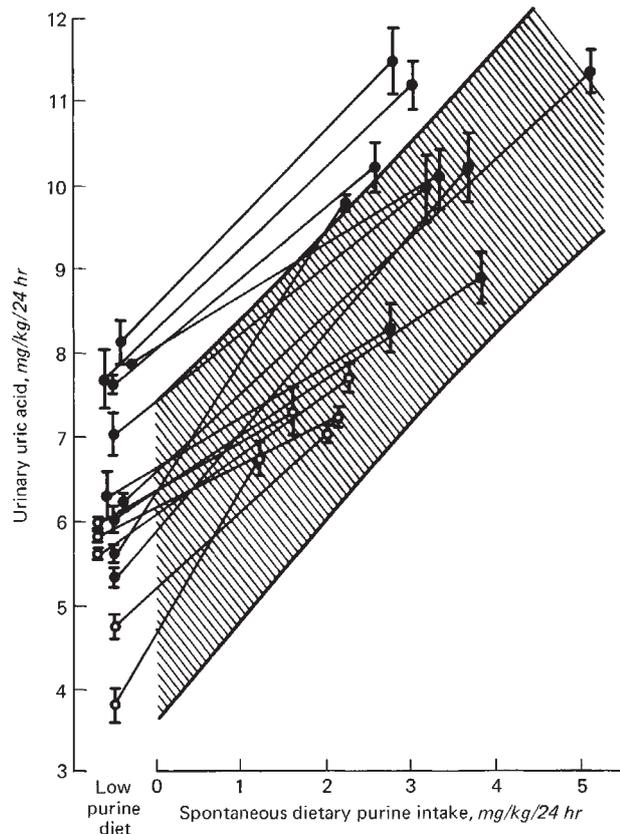
Fig. 1. *Relationship between purine intake and uric acid excretion in hyperuricosuric patients compared to normal subjects.* The *crosshatched area* denotes the 95% confidence band limits for the normal regression. Data from three of the 10 patients *(closed circles)* exceeded the upper limit of the band, indicating an abnormal rate of uric acid excretion for the corresponding purine intake. After seven days of a purine-free diet, these three patients continued to excrete an abnormal amount of uric acid, compared to the five normal subjects *(open circles)*. All values are means ± 1 SEM of three separate determinations. Purine intake is expressed as purine nitrogen. (Reprinted with permission from *N Engl J Med* [8]).

Natural history of stone disease

Idiopathic hypercalciuria, of marginal or severe degree, occurred alone in 32.2% of calcium stone-formers and in association with hyperuricosuria in 11.7%. Another 20.2% of patients had no discernible metabolic defect, and 14.6% had only hyperuricosuria (Table 1). Because of their numbers, it is possible to draw reasonably clear conclusions about the natural history of stones in patients within these metabolic subgroups. All of the remaining diseases which cause calcium stones, including primary hyperparathyroidism, renal tubular acidosis, hyperoxaluric states, and other, rarer, entities, are represented by too few patients for reliable measurement of stone formation rates.

Hyperuricosuric patients formed the majority of

Table 4. Characteristics of stone disease in patients with hyperuricosuria, hypercalciuria, or no discernible disorder[a]

	HU	HU+IH	IH	MIH	Neither
Number of patients	51	43	81	45	64
Percent men	81	90.5	71.5	67.6	69.5
Mean age at stone onset, yr	35.6	33	33.3	35.2	36.3
Stones/patient	4.17	4.6	4.8	4.24	3.59
Stones/100 patients/ yr	64.9	53.1	41	37.7	42.8
Hospitalizations/100 stones	33.8	16.1	17.1	27.7	21.7
Cystoscopies/100 stones	20.5	19.8	9.8	11.7	16.5
Surgical procedures/ 100 stones	16.8	14.1	13.4	17.3	13.4

[a] Abbreviations used are: HU, hyperuricosuria; IH, idiopathic hypercalciuria; MIH, marginal hypercalciuria.

their stones at a slightly later average age than other types of patients (Fig. 2). This was not due simply to a later age of stone onset (Table 4) but mainly to a more prolonged course of disease [12]. The severity of stone disease also was greater for hyperuricosuric patients (Table 4); stone formation rates were higher, and rates of cystoscopy and surgical procedures were also higher, partly because of the greater number of stones formed and partly because of a higher rate of complications for each 100 stones formed [12]. The later onset and greater severity of their stone disease support the notion that hyperuricosuric calcium oxalate stone-formers constitute a separate metabolic subclass of renal stone disease [12]. They also suggest that treatment may be a more urgent matter in hyperuricosuric than in other calcium oxalate stone-formers because their disease is likely to be more severe and more protracted.

Urate-oxalate epitaxy

Lonsdale [3, 4] has summarized the most critical data concerning structural similarities between uric acid and calcium oxalate crystals. Anhydrous uric acid crystals, commonly found as a constituent of human stones [4], have network dimensions for their 100 face which are very close to those of the 001 face of calcium oxalate monohydrate or the single face, 101, of calcium oxalate dihydrate crystals (Table 5). For epitaxy to occur, the dimensions must match within a few percent either directly or as an integral multiple of one another. The percentage misfits for the corresponding dimensions of the 001 face of whewellite and the 100 face of uric acid dihydrate, for example, are 1.1 and 1.6%, if one divides the 14.57 Å dimension of whewellite by 2 to obtain the closest integral result, 7.285. Both forms of uric acid and calcium oxalate are well enough matched to
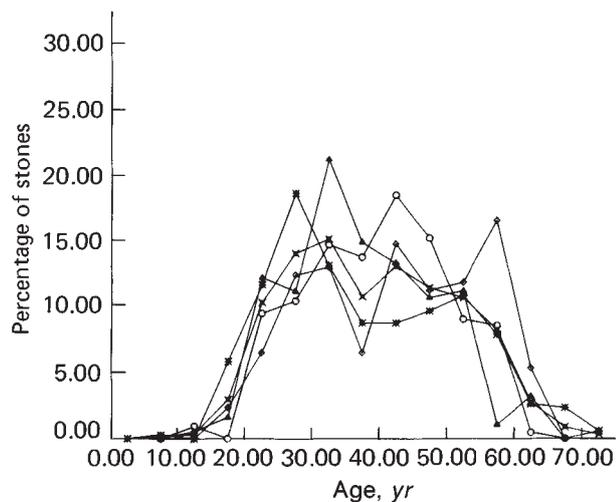
Fig. 2. *Occurrence of calcium stones at various ages.* Each *point* shows the fraction of all stones formed by the population of patients in each metabolic subgroup in each five-year age interval. *Open circles* denote hyperuricosuria; *X,* hyperuricosuria and hypercalciuria; *open triangles,* hypercalciuria; *open diamonds,* marginal hypercalciuria; *asterisks,* no metabolic defect. Average age at stone onset is shown in Table 4 for each subgroup. Peak stone occurrence in hyperuricosuric patients occurred in the interval of 40 to 45 yr. The other groups had peak ages of 25–30 yr (no defect) and 30–35 yr (hypercalciuria and admixed hypercalciuria and hyperuricosuria). Marginally hypercalciuric patients had three peaks of stone formation, at 30–35, 40–45, and 55–60 yr of age. (Reprinted with permission from *JAMA* [12].

Table 5. Geometrical correspondences between naturally occurring faces of uric acid and calcium oxalate crystals

	Face	Dimensions Å
Uric acid	100	6.21 × 7.40
Uric acid · 2 H₂O	100	6.35 × 7.40
Calcium oxalate · H₂Oᵃ	001	6.28 × 14.57
Calcium oxalate · 2 H₂Oᵇ	101	12.30 × 14.32

ᵃ Whewellite, calcium oxalate monohydrate
ᵇ Weddellite, calcium oxalate dihydrate

allow epitaxy in any order among them. Sodium hydrogen urate is not listed in the table. However, the sodium-oxygen distances in the sodium ion coordination of the 100 face of the mono-hydrate are 2.384 and 2.535 Å [13]. The dimensions of the calcium oxalate crystals (Table 5) are very close integral multiples.

Direct evidence for nucleation of calcium oxalate from aqueous solutions by uric acid and its salt has been presented by Pak [14] and ourselves [15]. In our experiment, a metastable calcium oxalate solution, buffered at a pH of 5.7 in 5 mM acetate barbitol, was labelled with ¹⁴C-oxalate. Incubated with shaking, the solution lost none of its labelled oxalate to the solid phase over a 30-min period (Fig. 3), as judged by determining the ¹⁴C-radioactivity level of aliquots passed through a 5-μ pore diameter Milli-
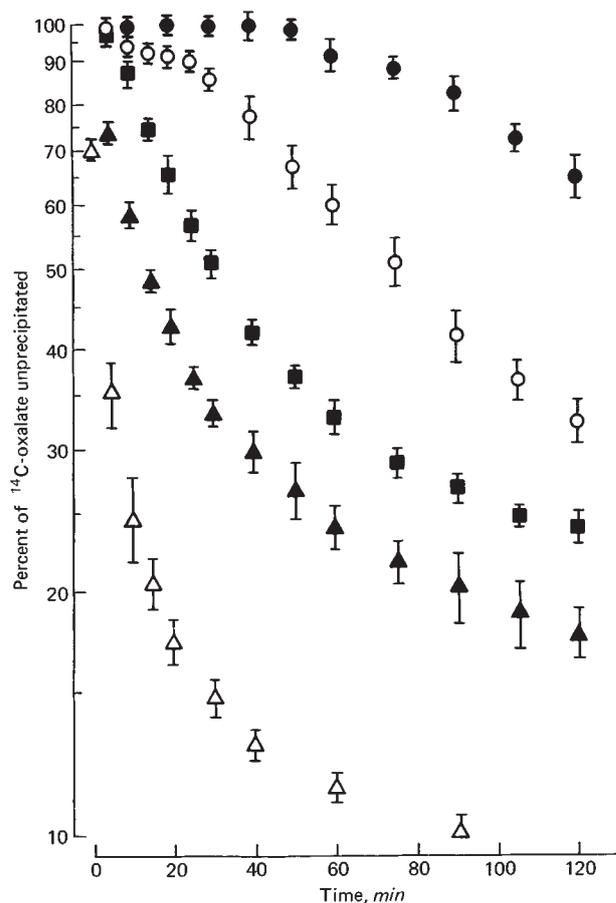

Fig. 3. *Heterogeneous nucleation of calcium oxalate by sodium hydrogen urate seed crystals.* A saturated solution containing 5mM calcium and 200 μM ¹⁴C-sodium oxalate (pH, 5.7), 5 mM barbitol-acetate buffer, and 150 mM potassium chloride was shaken at 24°C. At intervals, aliquots were filtered through 5-μ-diameter filters, and the radioactivity of the filtrate was determined. In the absence of seed crystal (●), precipitation began after 40 min. Sodium acid urate crystals (○), 0.1 mM/liter, greatly accelerated precipitation; 2.5 mM/liter (■) was more effective. Equivalent amounts of calcium oxalate monohydrate seed crystals (▲ and △) were far more effective, especially during the first few minutes. All points are means ± 1 SEM of three determinations (Reprinted with permission from *Proc Soc Exp Biol Med* [15]).

pore filter, which would retain crystal nuclei. Addition of even small amounts of preformed sodium hydrogen urate crystals caused a rapid loss of counts, reflecting the accretion of oxalate to the solid phase. Crystal growth, not adsorption of radio-labelled oxalate to a urate surface, was occurring, as shown by the absence of a fall in radioactivity when calcium was omitted and, in separate experiments, by simultaneous equimolar loss of oxalate and calcium from the filtrate.

Uric acid seed crystals were also able to initiate calcium oxalate crystal growth, although a lag phase was present (Fig. 4), and initial growth appeared to
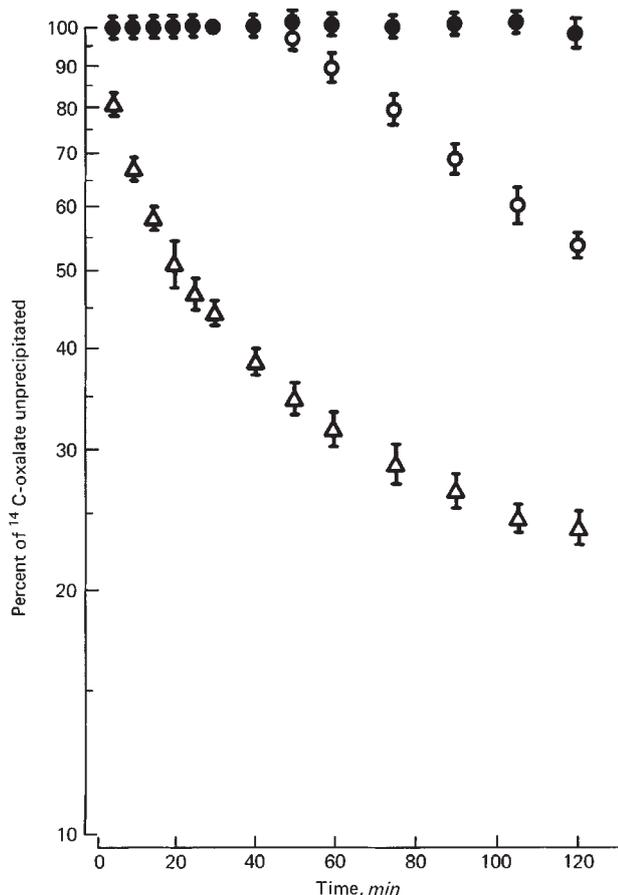
Fig. 4. *Nucleation of calcium oxalate by seed crystals of uric acid.* The pH of the system described in Figure 3 was altered to 4.4. When unseeded (●), no precipitation of oxalate occurred during two hours. Uric acid crystals (○), 2.5 mM/liter, promoted precipitation, but less than did the same amount of calcium oxalate monohydrate crystals (△). All values are means ± 1 SEM of three experiments (Reprinted with permission from *Proc Soc Exp Biol Med* [15]).

be slower. With time, crystal growth rose toward the level seen with sodium hydrogen urate. These experiments were performed at a pH of 4.4, rather than at a pH of 5.7, to prevent conversion of uric acid to urate. Unseeded, the system remained stable for a longer period than at the higher pH values used for the urate experiments, and growth of added, preformed, calcium oxalate crystals was also slower. The difference in growth rates with both seed crystals makes it difficult to compare the effects of urate and uric acid directly.

The role of heterogeneous nucleation *in vivo* is uncertain. Sodium hydrogen urate crystals are not seen in fresh warm human urine, which raises a natural barrier to the direct extension of the present *in vitro* studies to human stone disease. Furthermore, Robertson et al [16] have shown that urine from stone-formers and normal subjects often appears to be undersaturated or metastable with respect to urate or uric acid, and that in the few cases where uric acid concentrations were above the formation product, calcium oxalate activity products were high enough that crystallization of calcium oxalate could have occurred without a need for heterogeneous nucleation. Furthermore, by his calculations, urine would remain below the urate formation product even if 2,000 mg of urate were excreted at a pH of 6.3 in one liter of urine.

Pak et al [9], on the other hand, have provided evidence that urine from patients with hyperuricosuria is usually metastably supersaturated with respect to sodium hydrogen urate. The formation product of sodium hydrogen urate, however, has not been determined in urine. The values in urine may be different from that determined in simple solution by Robertson et al [14]. Until the upper limit of metastability is known, the plausibility of urate crystals behaving *in vivo* as heterogeneous nuclei is unknown.

In any event, the urine is itself an uncertain locale for stone development. Nascent nuclei in urine will tend to wash away, as their dimensions, even when unusually large, are certainly below one millimeter, compared to urinary structures many millimeters in diameter. If mere growth and aggregation of newly formed nuclei cause stones to form in the urine, the bladder should be a frequent site of stones, whereas it is in the kidneys themselves, in the calyces and on the renal papillae, that most calcium stones are formed. In order to develop there, stones must grow on anchored nuclei. Nuclei could lodge in the niches of calyces or infundibula. Alternatively, the open ends of collecting ducts may plug with crystals that form a permanent surface of anchored seed nuclei. Terminal collecting ducts are about 200 to 300 μ in diameter, with a luminal diameter of 20 to 60 μ. Individual calcium oxalate crystals commonly exceed 12 μ in diameter and may approach 200 μ in urine from stone-forming patients [17] and could form a large enough mass to plug a duct. Even though crystals may not attain sufficient size to cause occlusion from heterogeneous nucleation alone (FINLAYSON, this issue), the critical size may be achieved by crystal aggregation or the impedance of urine flow. Uric acid crystals can occlude even the ureter under extreme conditions, and certainly do occlude renal collecting ducts in some hyperuricosuric patients [18]. It may be that detailed study of renal tissue from stone-formers will reveal intratubular or calyceal masses of urate that have been hitherto overlooked, or that future studies of filtered urine sediments will reveal that sodium urate crystalluria is

not rare. Alternatively, it may be that uric acid itself, which surely does plug tubules and may produce copious crystalluria, is an important source of heterogeneous nuclei which compensate for their inefficiency by being widely distributed.

The potential importance of heterogeneous nuclei from calcium oxalate is much greater in urine than it would be in simple salt solution because urine contains potent inhibitors of nucleation and crystal growth which raise the formation product and slow the growth of calcium oxalate nuclei, retarding the development of an appreciable crystal mass [19]. One of these inhibitors is inorganic pyrophosphate [20]; the other(s), one or more larger molecules [21], are of uncertain composition. These inhibitors do not affect uric acid or sodium hydrogen urate, which crystallize in urine at the same rate as in a similarly constructed salt solution.

Reduced urine inhibitors

Robertson [17] has recently presented evidence for the intriguing idea that sodium acid urate may promote calcium oxalate stone disease by forming a gel phase in urine which adsorbs or interferes with naturally occurring urine inhibitors of calcium oxalate crystal growth, inhibitors which he believes may be acid mucopolysaccarides (AMP's) [19]. His method for measuring inhibitors is to observe the effects of one percent urine on the rate at which seed crystals of calcium oxalate grow and aggregate in a metastable calcium oxalate solution. He has observed that urines which contain more urate have less inhibitory effect per milligram of AMP's than urines with lower urate concentrations, a rather indirect fact whose interpretation depends upon the unproven assumption that AMP is the major inhibitor present and not merely one of many inhibitors. A more direct demonstration which he has presented is that urate added to urine *in vitro* reduces, and removal of urate restores inhibitory activity [17, 19], but as yet this has not been documented in detail, only described in an overall review fashion. Moreover, this interpretation should be made with caution, since studies were performed in diluted urine and not whole urine. (see Dr. Finlayson's article and Dr. Fleisch's article, this issue).

These observations may be of extreme importance. If generally correct, they could explain the syndrome of hyperuricosuric calcium oxalate stones without a need to invoke massive urate or uric acid crystalluria, neither of which are especially common in the urine of calcium oxalate stone-formers. Instead, one could envision the urate (or uric acid) as a stable gel suspension which may be undetected during routine urine microscopy. The problem of anchored nuclei is also lessened as, uninhibited by the usual properties of urine, calcium oxalate crystal nuclei could more readily grow and aggregate to occlude collecting ducts in the renal papillae or lodge in calyces. Reduced inhibition could also explain the critical, and as yet unpublished, observations by Pak that induction of hyperuricosuria leads to producing a urine in which the formation product for calcium oxalate, usually very elevated in urine compared to simple salt solutions, presumably because of the inhibitors urine contains, is reduced towards levels seen in simple media. Heterogeneous nucleation could cause such a reduction of formation product, but so could a reduction of inhibitory activity. Unfortunately, AMP's probably do not cause inhibition of nucleation of calcium oxalate (FLEISCH, this issue), a fact that reduces the attractiveness of the hypothesis. An alternative hypothesis, which incorporates certain features from both theories, is that the colloidal urate itself may participate in heterogeneous nucleation of calcium oxalate [9].

Allopurinol treatment

Perhaps the most dramatic evidence linking hyperuricosuria to calcium oxalate stones is the seeming ability of allopurinol to reduce new stone formation far below pretreatment rates. Thus far, we have observed 48 patients with recurrent calcium stones who had hyperuricosuria as the sole detected metabolic disorder and who were treated with allopurinol for at least one year [22]. Before treatment, these patients formed 67.1 stones/100 patient years (Table 6) and therefore would be expected to form 124.8

Table 6. Effects of allopurinol treatment in patients with hyperuricosuric calcium oxalate stones[a,b]

	HU	IH+HU	Untreated patients
Number of patients	48	42	34
Pretreatment interval, *patient years*	298	357	292
Pretreatment stones	200	188	123
Stones/patient	4.17	4.48	3.62
Years/patient	6.21	8.5	8.6
Stones/100 patients/yr	67.1	52.7	42.2
Treatment interval, *patient years*	186	119	109
Years/patient	3.88	2.83	3.21
New stones formed	8	6	29
Predicted new stones	124.8	62.7	46.2
New stones/predicted, %	6.4	9.6	62.8
χ^2, *predicted vs. observed*	109.3	51.3	6.4
P	<0.001	<0.001	<0.05

[a] These patients are the subset of those shown in Tables 1 and 4 for whom detailed follow-up data were available.

[b] Abbreviations used are: HU, hyperuricosuria; IH, idiopathic hypercalciuria.

stones during the 186 patient years of treatment if the pretreatment stone production rate continued to apply. In fact, they formed only eight stones (Fig. 5) (χ^2 = 109.3, P 0.001), indicating that stone production rate had altered greatly.

The interpretation of these results is limited by the absence of a parallel control population, with the same characteristics, left untreated; factors other than allopurinol may have produced the fall in stone production. Some estimate of the likely effects of nonspecific factors such as diet, better attention to fluid intake, avoidance of dehydration, and continued contact with the stone clinic can be derived from the response of a separate group of calcium stone-formers, who had no detectable metabolic disorders and, therefore, were given no specific form of treatment.

This group of 34 patients had a less active form of stone disease before entering the program (Table 6), a fact mentioned previously. During the follow-up interval, new stone formation declined, so that only 62.8% of the stones that would have been predicted actually occurred (Fig. 6). This suggests that nonspecific factors related to our follow-up program probably do foster a moderate decline in stone formation, but one that is far less impressive than that which occurs with allopurinol. Even though these 34 patients were relatively less active before entering the program, compared to hyperuricosuric patients, they formed nearly 10 times more stones per 100 patients per year during the follow-up interval, suggesting that allopurinol treatment did indeed appear to contribute to stone prevention in hyperuricosuric patients.
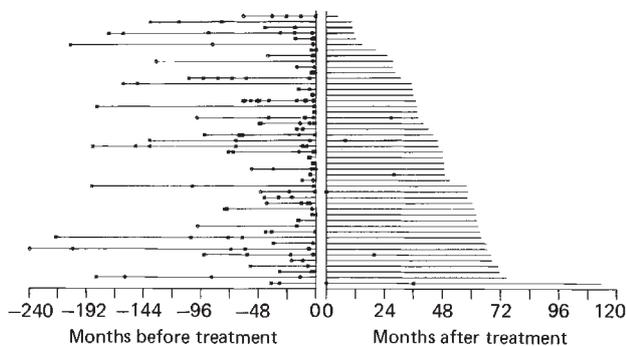
Because it is a common disorder, hyperuricosuria was often found to coexist with idiopathic hypercalciuria in a single patient [22]. Their coexistence was almost precisely what would be expected by chance alone, given their independent rates of occurrence. In this group of patients, the only treatment data available were based upon combined use of thiazide, an agent that has an established effect to lower urine calcium excretion [23], and allopurinol. These combined treatment data, which show a marked fall in stone production (Table 6, Fig. 7), are mainly confirmatory; either agent alone may well have been sufficient, and only a failure of treatment, which would be unexpected, could have any major impact upon the hypothesis that hyperuricosuria may contribute to calcium stone production.

Smith [24] has performed a controlled, randomized prospective study based upon allopurinol treatment of calcium oxalate stone-formers who had serum urate concentrations above 6 mg/100 ml, with
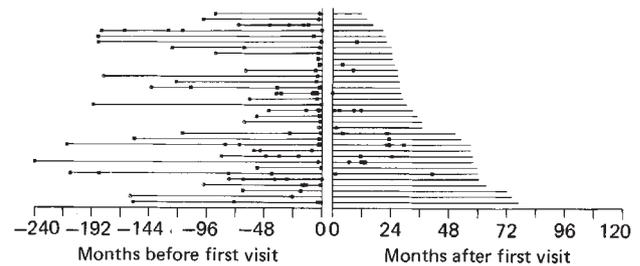
Fig. 6. *The course of calcium oxalate stone disease in untreated patients.* Symbols are the same as in Figure 5; statistics are shown in Table 6. Despite contact with the stone clinic and advice concerning diet and dehydration, new stone production was reduced by only 37.2% compared to the nearly ten-fold reduction observed in the allopurinol-treated patients. (Reprinted with permission from *Ann Intern Med* [22].)
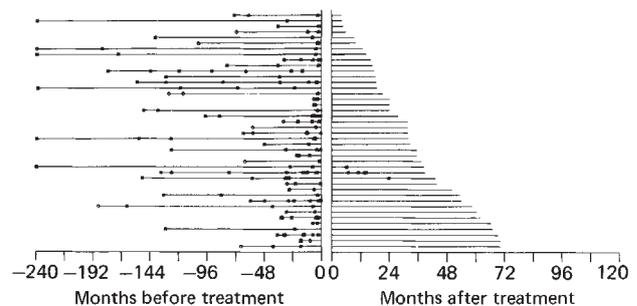
Fig. 5. *The effect of allopurinol upon new stone production in hyperuricosuric patients.* Each of 48 patients is shown as a horizontal line. Single (X) and multiple (○) events are shown. New stone production was greatly reduced during treatment. The statistical details are shown in Table 6. Allopurinol was given 100 mg twice daily except in three subjects who required 300 mg/day to reduce hyperuricosuria. (Reprinted with permission from *Ann Intern Med* [22].)

Fig. 7. *Effects of combined allopurinol and thiazide treatment of patients with hyperuricosuria and hypercalciuria.* Symbols are the same as in Figures 5 and 6; statistics are in Table 6. Combined treatment lowered stone recurrence dramatically. The thiazide used was trichlormethiazide, 2 mg twice daily; allopurinol was given 100 mg twice daily. (Reprinted with permission from *Ann Intern Med* [22].)

Table 7. Effects of allopurinol on new stone production by recurrent calcium oxalate stone-formers with serum urate concentrations above 6 mg/100 ml[a]

Year of follow-up	Allopurinol-treated patients		Placebo-treated patients		χ^{2c}	P^c
	stone-free	all[b]	stone-free	all		
Start of study	49	49	43	43	—	—
0.5	28	49	13	43	6.57	<0.01
1	27	38	3	27	20.70	<0.001
2	20	30	1	20	16.84	<0.001
3	17	23	1	13	14.54	<0.001
4	15	19	1	12	14.73	<0.001
5	10	12	1	5	5.97	<0.02

[a] This data is adapted from a study by Pak (personal communication). Numbers reflect patients who have or have not formed new stones at each follow-up interval.

[b] This includes all patients remaining in this study; some were lost due to failure of treatment compliance, personal decisions to leave the study, or drug intolerance. Patients entered the study at different times and therefore had varying lengths of total follow-up.

[c] Calculated χ^2 was for placebo- vs. allopurinol-treated patients; P values are for one degree of freedom.

or without hyperuricosuria. Apparently, hypercalciuric patients were excluded. The principle data from the study are summarized in Table 7. The number of stone-free, placebo-treated patients fell rapidly, from 13 patients at six months to one patient at one year; among the allopurinol-treated patients, the fraction of stone-free patients remained significantly more elevated throughout the study. The difference in occurrence of stone-free patients for each of the five years, tested by the χ^2 method, was significant at each interval. Smith divided the patients who continued to form new stones into those who improved, by which was meant a reduced rate of new stone production, and those who were unchanged. These two categories, which were distinguished on subjective grounds, and on the basis of the number of stone events in single subjects, a small and highly variable index which is notoriously capricious for stone disease, are not analyzed separately in the table.

Though quantitatively different from our own, these results lead to the same basic conclusion. In each year, 20 to 35% of treated patients formed new stones, whereas overall recurrence was below 10% in our 48 treated patients with hyperuricosuric calcium oxalate stones; still, Smith's data demonstrate an impressive allopurinol treatment effect. Quantitative differences in the magnitude of the effect could easily have arisen from the different patient populations studied. Our patients all were hyperuricosuric; some were hyperuricemic and some were not. In Smith's study [24], the selection criterion (serum urate level above 6 mg/100 ml) could have included

many patients whom we would have classified as idiopathic stone-formers.

The problem of selection is far from trivial, because both proposed mechanisms of stone production, heterogeneous nucleation and reduction of inhibitor activity, depend upon abnormally elevated urinary urate or uric acid concentrations, and though patients with normal urine urate levels could benefit from allopurinol by virtue of a reduction in the background effects which even normal amounts of urate may produce, the magnitude of the therapeutic response would predictably be reduced to the extent that factors other than the effects of urate were responsible for stones. Given this mechanism for potential degradation of allopurinol effect, the significant decrease in new stone production from allopurinol which Smith observed supports the notion that this drug, probably because of its effects upon urinary urate level, is an efficient treatment for certain forms of calcium oxalate stone disease.

Conclusion

It seems evident that a variety of observations support the existence of a new, gradually evolving, syndrome which may be called hyperuricosuric calcium oxalate nephrolithiasis. It consists of calcium oxalate stones, hyperuricosuria, and the absence of any of the well defined causes of calcium oxalate stones, such as hypercalciuric states, primary hyperparathyroidism, hyperoxaluria from any cause, and medullary sponge kidney disease. It seems to affect mainly men and is caused by a combination of dietary purine excess and, in some cases, endogenous uric acid overproduction. Stone disease is maximal during the fourth and fifth decades of life and is often of unusual severity. Allopurinol therapy appears to be an effective form of treatment, although this has not yet been established by a controlled, prospective study but only by prospective observation of treated patients. The mechanism linking hyperuricosuria to calcium oxalate stone production is not known; but heterogeneous nucleation of calcium oxalate by crystals of sodium hydrogen urate or uric acid, in the urine, in the calyceal niches, or at the open ends of plugged renal collecting ducts, is one attractive hypothesis that is supported by some *in vitro* evidence. Attenuation of urinary crystal growth inhibitors by an excess of urinary urate, perhaps existing in the form of a gel, is another.

The true prevalence, clinical importance, and cohesiveness of the syndrome are all uncertain. Our data suggest a prevalence of about 20 to 30%, either alone or associated with idiopathic hypercalciuria. Prevalence will generally reflect diet, so the affluent may well suffer more frequently from hyperurico-

suria and its presumed consequences than will the poor. The syndrome may also vary in importance with time, depending upon cultural patterns of diet in this country and elsewhere. The clinical importance of the syndrome is supported mainly by the apparent success of allopurinol treatment. If this can be reproduced during a fully controlled study, confidence in the value of long term treatment will be much increased. Dietary measures have never been evaluated as a treatment measure. They may be as effective as allopurinol, and they offer the obvious advantage of simplicity and avoidance of a drug.

Acknowledgment

Reprint requests to Dr. F. Coe, Renal Division, Michael Reese Hospital, 2900 S. Ellis Avenue, Chicago, Illinois 60616, U.S.A.

References

1. PRIEN EL, PRIEN EL JR: Composition and structure of urinary stone. *Am J Med* 45.654–672, 1968
2. GUTMAN AB: Uric acid nephrolithiasis. *Am J Med* 45:756–779, 1968
3. LONSDALE K: Human stones. *Science* 159:1159–1207, 1968
4. LONSDALE K: Epitaxy as a growth factor in urinary calculi and gallstones. *Nature* 217:56–58, 1968
5. DENT ED, SUTOR DJ: Presence or absence of inhibitor of calcium oxalate crystal growth in urine of normals and of stone formers. *Lancet* 1:776–778, 1971
6. SMITH MJV, HUNT LD, KING JS JR, BOYCE WH: Uricemia and urolithiasis. *J Urol* 101:637–642, 1969
7. COE FL, RAISEN L: Allopurinol treatment of uric-acid disorders in calcium-stone formers. *Lancet* 1:129–131, 1973
8. COE FL, KAVALICH AG: Hypercalciuria and hyperuricosuria in patients with calcium nephrolithiasis. *N Engl J Med* 291:1344–1350, 1974
9. PAK CYC, WATERS O, ARNOLD L, HOLT K, COX C, BARILLA D: Mechanism for calcium nephrolithiasis among patients with hyperuricosuria: Supersaturation of urine with respect to monosodium urate. *J Clin Invest* 59:426–431, 1977
10. BRIDGES MA, MATTICE MR: *Food and Beverage Analyses,* Philadelphia, Lea and Febiger, 1942
11. KAVALICH AG, MORAN E, COE FL: Dietary purine consumption by hyperuricosuric calcium oxalate kidney stone formers and normal subjects. *J Chronic Dis* 29:745–760, 1976
12. COE FL, KECK J, NORTON E: The natural history of untreated calcium nephrolithiasis. *JAMA* 238:1519–1523, 1977
13. MANDEL NJ, MANDEL GS: Monosodium urate monohydrate, the gout culprit. *J Am Chem Soc* 98:2319–2323, 1976
14. PAK CYC, ARNOLD LH: Heterogeneous nucleation of calcium oxalate by seeds of monodosium urate. *Proc Soc Exp Biol Med* 149:930–932, 1975
15. COE FL, LAWTON RL, GOLDSTEIN RB, TEMBE V: Sodium urate accelerates precipitation of calcium oxalate in vitro. *Proc Soc Exp Biol Med* 149:926–929, 1975
16. ROBERTSON WG, MARSHALL RW, PEACOCK M, KNOWLES F: The saturation of urine in recurrent, idiopathic calcium stone formers, in *Urolithiasis Research,* edited by FLEISCH H, ROBERTSON WG, SMITH LH, VAHLENSIECK W, London, Plenum Press, 1976, pp. 335–338
17. ROBERTSON WG: Physical chemical aspects of calcium stone formation in the urinary tract, in *Urolithiasis Research,* edited by FLEISCH H, ROBERTSON WG, SMITH LH, VAHLENSIECK W, London, Plenum Press, 1976, pp. 25–39
18. EMERSON BT, GRAHAM-ROW P: Pathogenesis of the gouty kidney. *Kidney Int* 8:65–71, 1975
19. ROBERTSON WG, KNOWLES F, PEACOCK M: Urinary acid mucopolysaccharide inhibitors of calcium oxalate crystallization, in *Urolithiasis Research,* edited by FLEISCH H, ROBERTSON WG, SMITH LH, VAHLENSIECK W, London, Plenum Press, 1976, pp. 331–334
20. FLEISCH H, BISAZ S: Isolation from urine of pyrophosphate, a calcification inhibitor. *Am J Physiol* 203:671–675, 1962
21. MEYER JL, SMITH LH: Growth of calcium oxalate crystals: Inhibition by natural crystal growth inhibitors. *Invest Urol* 13:36–39, 1975
22. COE FL: Treated and untreated recurrent calcium nephrolithiasis in patients with idiopathic hypercalciuria, hyperuricosuria or no metabolic disorder. *Ann Intern Med* 87:404–410, 1977
23. EDWARDS BR, BAER PG, SUTTON RAL, DIRKS JH: Micropuncture study of diuretic effects on sodium and calcium reabsorption in the dog nephron. *J Clin Invest* 52:2418–2427, 1973
24. SMITH MJV: Placebo vs. allopurinol for renal calculi. *J Urol,* 1977, in press