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Composition of Renal Stones and Their Frequency in a Stone Clinic: Relationship to Parameters of Mineral Metabolism in Serum and Urine

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Summary. Stone analyses (kidney, upper urinary tract) of the department of Urology, University of Erlangen, from a four-year-period (1974-1977) have been recorded with emphasis to stone composition, sex and age of the pertinent stone forming patients.

During this time period there were no substantial changes as regards the per cent frequency of the various stone types. The most frequent type was calcium oxalate (CaOx), followed by uric acid, calcium phosphate (CaP), struvite and cystine. Stone analyses were mostly requested for patients between 46 and 55 years of age. Stone incidence in our clinic is calculated to be 1.22 times higher in males than females, especially beyond 36 years of age. The frequency peaks are: pure (= 100 per cent) CaOx 36-45 years; CaOx with additional mineral phases (mostly CaP) 46-55 years; uric acid 56-65 years; CaP 26-35 years.

From those patients who underwent further investigations in searching for metabolic abnormalities serum concentrations, urine mineral clearances in fasting urine samples, and activity products of stone forming mineral phases in sequentially collected specimens from 24 h and 2 h fasting urine had been measured and compared with values from healthy control subjects. In urolithiasis (idiopathic) there is a normal parathyroid hormone blood level, a generally lower serum inorganic phosphate and magnesium concentration.

In pure (= 100 per cent) CaOx and uric acid lithiasis serum uric acid and creatinine are higher than in controls, urine pH and calcium clearance in some groups are different too. Clearances of magnesium, uric acid, phosphate, sodium are within normal limits in urolithiasis. When expressing the propensity to form stones in terms of activity products, then only uric acid lithiasis deviates substantially from normal. All other stone types differ only slightly or not at all from each other and controls respectively.

It is concluded that 1) in our geographic region the various stone types prevail in different age periods; 2) there are distinct alterations of parameters of mineral metabolism in urolithiasis; 3) measuring urine clearances may lead to assume falsely normal mean urine excretion of stone forming constituents.

Key words: Kidney stone analyses, Sex and age, Mineral metabolism data, Serum and urine, Activity products.

In the past years European (1, 6) and worldwide (4, 10, 11, 21) investigators have reported data on the frequency of urolithiasis, but very dissimilar conditions have been encountered. As regards the relative contribution of the various stone types there are different opinions, especially in respect to uric acid lithiasis where figures vary from 5 to 30 per cent. Markedly less information is available on the activity products of stone forming mineral phases in a given stone type included.

The aim of this work is threefold: 1) to report the frequency of upper urinary tract stones in our stone clinic within a short period as based on stone analysis records; 2) to describe, when knowing stone composition in a representative number of stone types, changes of mineral metabolism utilising those criteria presently practised in many hos-

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Table 1. Renal stone types as analysed by polarisation microscopy (January 1974-July 1977); Σ: sum of stones (male and female)

Stone Types		1974			1975			1976			1977			1974-1977			Relative Contribution %
		♂	♀	Σ	♂	♀	Σ	♂	♀	Σ	♂	♀	Σ	♂	♀	Σ	
1a)	CaOx (= 100%)	56	35	91	51	29	80	26	16	42	57	43	100	190 61%	123 39%	313	44%
1b)	CaOx (<100<75%)	11	10	21	16	14	30	7	2	9	14	9	23	48 58%	35 42%	83	12%
2)	Uric acid (>75)	26	10	36	24	8	32	9	3	12	27	13	40	86 72%	34 28%	120	17%
3)	CaP (>75%)	5	11	16	2	13	15	-	4	4	9	15	24	16 27%	43 73%	59	8%
4)	Struvite (>75%)	2	2	4	-	2	2	-	-	-	4	3	7	6 46%	7 54%	13	2%
5)	Cystine (>75%)	4	-	4	1	3	4	-	-	-	-	-	-	5 63%	3 37%	8	1%
6)	Mixed stones	12	21	33	14	12	26	4	7	11	12	31	43	42 37%	71 63%	113	16%
Total		116	89	205	108	81	189	46	32	78	123	114	237	393 55%	316 45%	709	100%

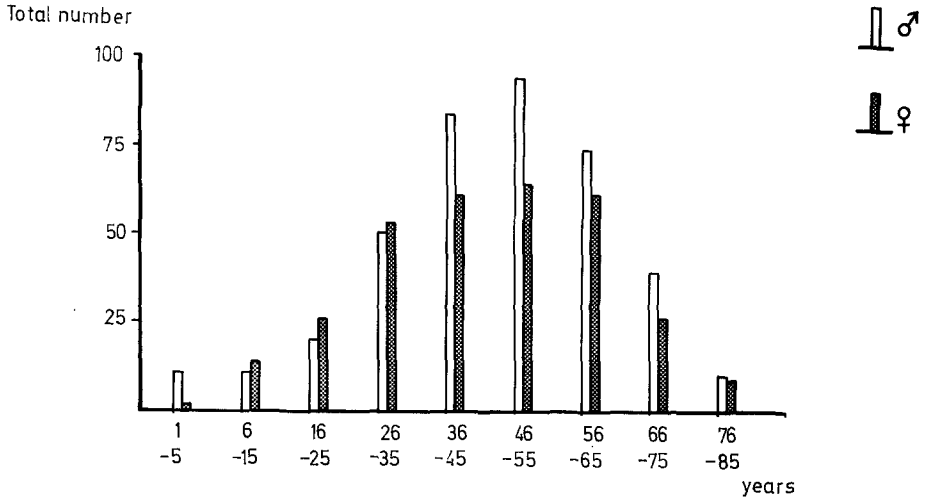

Fig. 1. Frequency of renal stones (no bladder stones; see Methods section) in relation to age and sex

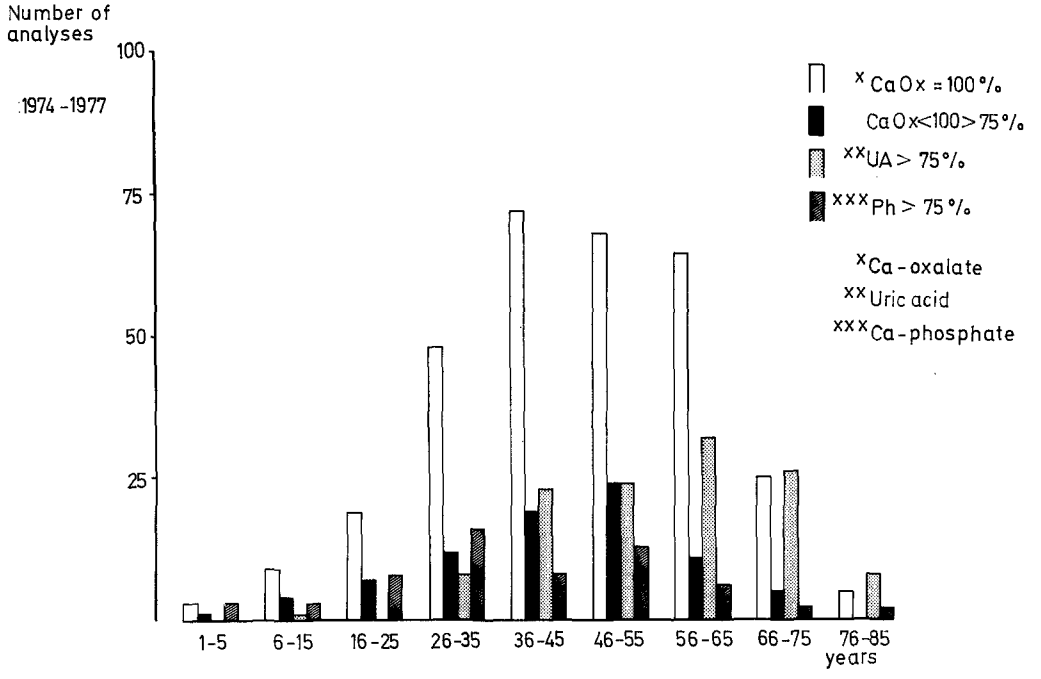

Fig. 2. Distribution of stones composed of pure CaOx (CaOx = 100%), CaOx (CaOx < 100 > 75%), CaP (pH > 75%) and uric acid (UA > 75%) according to age. For details see Methods

pitals; 3) to evaluate activity products using a published nomogram (9).

MATERIALS AND METHODS

The study comprises two parts: A - Determination of absolute and relative stone frequency; and stone composition; B - Clinical investigations.

All stones stem from patients admitted to the Department of Urology between January 1974 and July 1977, and who either underwent surgery or conservative intervention (loop extraction, antispas modic drugs etc.). Cases with primary hyperparathyroidism as a cause of stone formation were excluded. Stones, once analysis was available, were not further categorized into organ regions (calix, kidney, ureter) or whether they necessitated surgery. The number of stone analyses also does not correspond exactly with the number of stone patients seeking medical care during the same time in this hospital as analysis was occasionally not performed.

Each stone was analysed by polarisation micro-

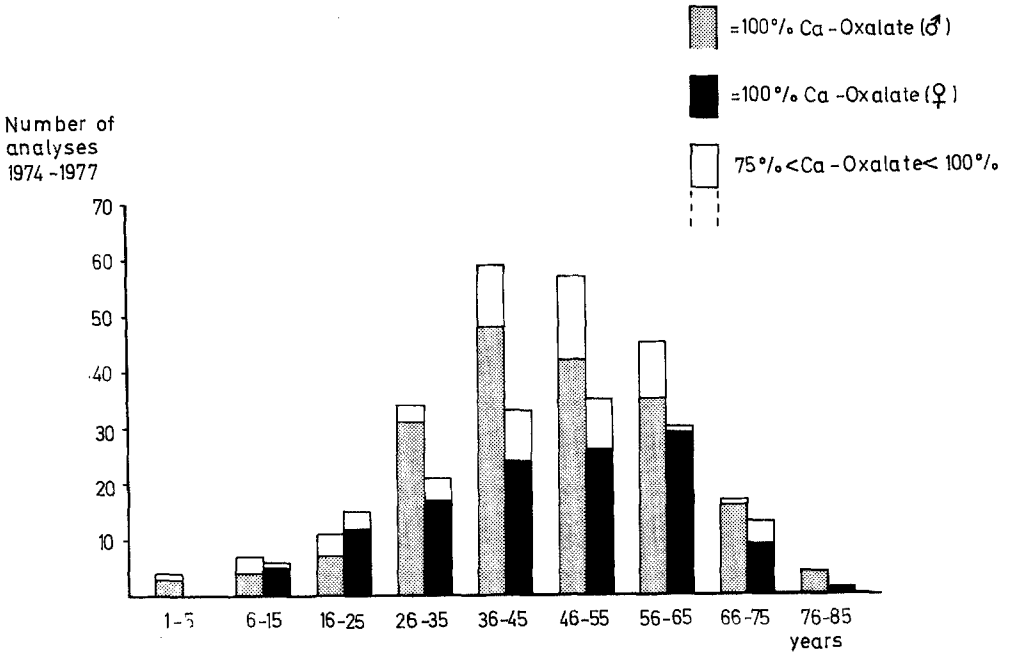

Fig. 3. Frequency of CaOx containing stones in relation to age and sex

scopy (20). When grouping on the basis of mineral components we, from practical reasons, started with the assumption that the dominant mineral phase either took part in initial processes of nucleation resulting in formation of a nidus or, in later growth periods, would better reflect the prevailing urine milieu and metabolic circumstances. Therefore, the lower limit for a detected mineral was set at 75 per cent. Stones containing < 75 per cent or more than two phases were assigned "mixed" stones. Calcium oxalate (CaOx) had been subclassified: 1) 100 per cent (= pure) CaOx; 2) at least > 75 per cent but < 100 per cent CaOx, the remaining constituent(s) being mostly calcium phosphate (CaP)[1]. In the uric acid type stone the minor part (1-25 per cent) either was CaOx or CaP, in the CaP[1] type stone CaOx and in some cases struvite.

The clinical investigations were carried out according to guidelines previously set out (17). In brief: record of serum values, kidney function test by a 2 h morning creatinine clearance, supply of a 24 h urine having been carefully collected according to our written information while on unlimited home diet. Only in struvite cases a previous proteus infection of urine was documented, in all others bacteria were missed several months preceding examination. Healthy controls were hospital personnel, students and physicians and family members without a stone history or disorders of metabolism.

Analyses in serum and urine: total and free (= ultrafiltrable) calcium (fluorimetric titration by EGTA, Calcein indicator), the latter after anaerobic filtration of serum through Millipore filters/chambers; phosphate and creatinine (colorimetry; autoanalyser); sodium (flame photometry); magnesium (AAS); uric acid and oxalic acid enzymatically (7, 15); urine pH (glass electrode); activity products by the Marshall and Robertson nomogram (9).

Parathyroid hormone by radioimmunoassay utilising antibody 211/32, showing carboxy- and amino-terminal antigenic recognition sites in a modified earlier assay technique (16). Clearances were calculated conventionally. Results are given in means and 1 standard error (Gaussian distribution) or as median and range (non-Gaussian data). Total variance of all groups was tested by the non-parametric Kruskal-Wallis method (13), and significance of differences between two groups by U-test (Mann-Whitney, 13).

RESULTS

A. Stone Frequency and Composition

1. Distribution of Analyses in the Observation Period (Table 1). The number of analyses, separated for males and females and per year, are depicted. The second last column contains the figures for the total period 1974-1977 and per cent frequency of males and females. The last column gives the per cent contribution of each stone type in relation to the total number. The greatest frequency

[1] In this context synonymous with brushite/apatite

Table 2. Serum values (means ± 1 SE, except age: mean and range) relevant to stone formation in patients with various types of renal stones and in healthy control subjects. Creat, creatinine; TP, total protein; UA, uric acid; Na, sodium; Ca_t and Ca_d, total and ultrafiltrable calcium resp.; Mg_t, total magnesium; P_i, inorganic phosphate; PTH, immunoreactive parathyroid hormone (number of determinations in brackets); n, number of individuals

	n ♂ ♀	Age Mean Range	Creat mg/dl	TP g/dl	UA mg/dl	Na mval/l	Ca_t mg/dl	Ca_d mg/dl	Mg_t mg/dl	P_i mg/dl	PTH ng-equival/ml
Controls	36	42.3	0.94	7.30	5.17	143	9.76	6.00	2.02	3.59	0.33
	21 15	19-69	0.03	0.08	0.22	1	0.07	0.06	0.03	0.09	0.03 (13)
CaOx (= 100%)	40	45.6	1.06[a]	7.35	6.05[b]	144	9.82	5.98	1.93[b]	3.28[a]	0.40
	28 12	18-68	0.03	0.08	0.23	1	0.05	0.06	0.02	0.1	0.05 (19)
CaOx (<100>75%)	20	40.9	0.97	7.42	5.54	145	9.65	5.91	1.90[a]	3.16[b]	0.40
	13 7	20-63	0.05	0.12	0.33	1	0.08	0.06	0.04	0.11	0.09 (10)
Uric acid (> 75%)	19	49.2	1.07[a]	7.46	6.70[b]	143	9.80	5.98	1.88[b]	2.94[c]	0.39
	10 9	35-67	0.04	0.09	0.40	1	0.07	0.06	0.03	0.09	0.06 (11)
CaP (>75%)	11	37	1.02	7.57	5.21	143	9.69	5.90	1.95	3.37	0.41
	2 9	20-51	0.07	0.19	0.45	2	0.14	0.07	0.06	0.22	0.06 (6)
CaP/Struvite (50%/50%)	7	50.7	1.11	7.50	5.79	144	9.73	5.75	1.83[b]	3.24	0.42
	2 5	41-64	0.11	0.15	0.39	2	0.09	0.12	0.04	0.18	0.12 (6)

[a] $P < 0.05$; [b] $P < 0.01$; [c] $P < 0.001$ vs controls (Wilcoxon)

Table 3. Clearances (C) of creatinine, calcium, magnesium, uric acid, sodium in the same individuals as depicted in Table 2, and urinary pH. For abbreviations see Table 2. Median and range are given; number of individuals in brackets

	C_{Creat} ml/min	pH	C_{Ca} ml/min	C_{Mg} ml/min	C_{P_i} ml/min	C_{UA} ml/min	C_{Na} ml/min
Controls	95.60 51.30-173.60 (36)	6.10 5.20-7.90 (36)	1.45 0.16-2.70 (36)	3.03 0.20-8.80 (36)	9.72 1.34-22.7 (36)	9.13 3.00-17.10 (36)	0.79 0.17-1.90 (36)
CaOx (= 100%)	92.02 33.15-186.33 (39)	5.95 4.90-7.65 (38)	1.69 0.44-3.30 (36)	2.77 1.02-9.60 (34)	8.90 2.64-20.96 (37)	7.52 1.61-16.68 (37)	0.76 0.12-2.19 (35)
CaOx (< 100 > 75%)	93.55 46.20-312.20 (20)	6.38 5.20-7.55 (20)	2.12[a] 0.32-4.81 (20)	3.16 0.63-9.50 (20)	9-16 2.90-20.10 (20)	8.36 1.14-20.14 (20)	0.80 0.03-1.84 (20)
Uric acid (> 75%)	85.00 25.20-181.00 (18)	5.37[c] 5.10-6.70 (16)	0.87 0.12-2.26 (17)	2.49 0.54-3.71 (16)	11.63 4.44-22.00 (17)	7.08 2.05-14.80 (17)	0.65 0.03-2.03 (17)
CaP (> 75%)	94.00 65.20-125.40 (11)	6.71[a] 6.04-7.42 (10)	1.51 0.55-3.58 (10)	2.34 0.05-5.61 (9)	11.03 6.77-16.99 (11)	8.65 0.16-20.80 (11)	0.74 0.49-1.13 (10)
CaP/Struvite (50%/50%)	81.80 47.70-120.00 (6)	6.62 5.57-7.33 (6)	1.57 0.80-2.74 (6)	3.57 2.61-3.83 (6)	12.55 6.69-19.79 (6)	9.08 5.52-12.65 (6)	0.94 0.36-1.27 (6)

[a] $P < 0.05$; [c] $P < 0.001$ vs controls (Wilcoxon)

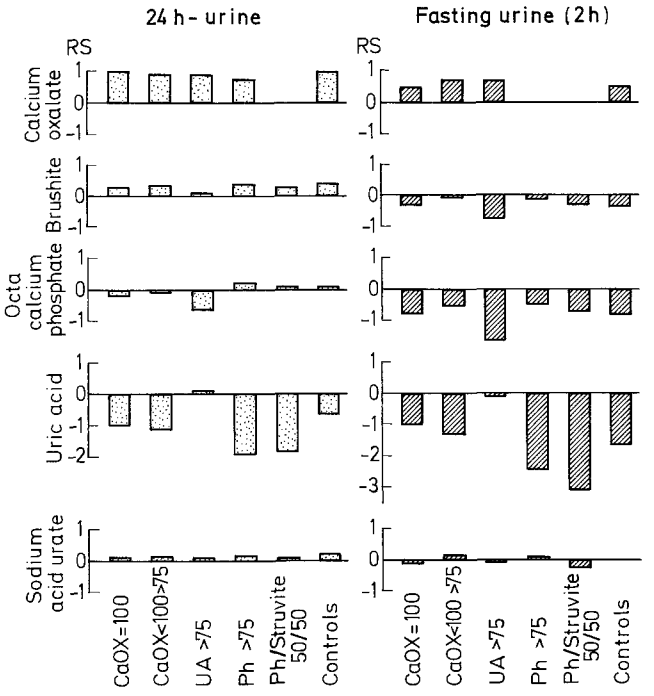

Fig. 4. Relative saturation products (medians) of different stone forming mineral phases in 24 h urine (left panel) and 2 h fasting urine (right panel). For total number of specimens see figures in Table 3. Calcium oxalate relative saturation products are not available from CaP/Struvite stones (Ph/Struvite 50/50; 24 h, 2 h urine) and from CaP (Ph > 75; 2 h urine) owing to lack of oxalate determinations

(per cent) have CaOx stones (=56), followed by uric acid (= 17), CaP (= 8), struvite (= 2), cystine (= 1) and "mixed" stones (s. Methods) (= 16). The table also shows that, in the material available to us, there is no shift toward a single concrement. Except 1976, when the stone investigator of these authors was not available throughout, the number of stones analysed per year was comparable. It is evident that males dominate in the uric acid stones and females in the CaP stones.

2. Relationship of Analyses to Sex and Age of Patients. Figure 1 shows all analyses obtained and sub-divided in the underlying males and females and into age periods of 10 years respectively. As already visible from Table 1 (second last column, bottom row), stones occur more frequently in males than females. Up to five years of age stones also are more frequent in boys than girls but evaluation is hampered by the small number. Females are preponderant until the 35th year, whereas males are preponderant in the remaining age ranges. In both sexes stone frequency peaks between 46 and 55 years.

3. Stone Types and Age of Patients. Figure 2 depicts the stone types 1a-3 from Table 1 (CaOx, uric acid, CaP) in age ranges of 10 years irrespective of sex. Pure CaOx (= 100 per cent) represents the most frequent stone type and it peaks between 36-45 years. This coincides with clinical experiences that stone disease requires medical treatment most often in this age. CaOx with additional phases does not peak until 46-55 years which, on the basis of numerous reports, is the period of life with most cases of documented primary hyperparathyroidism. In younger years uric acid stones are a rare or missing disorder. Its peak is between 56-65 years. Conversely, when related to the total number of analyses, CaP is a relatively frequent stone only in younger people.

4. CaOx-Lithiasis. This type (groups 1a) and 1b) of Table 1) has been considered as one group and sub-classified according to age and sex of pertinent patients. Pure CaOx (= 100 per cent) in males peaks between 36-45 years, in females between 56-65 years. CaOx with additional phases (mostly CaP) is most frequent from 46-55 years in either sex. Thus, although every stone type has its frequency maximum in a different age period, the sum of all stones is highest in the fifth and sixth decade (s. Fig. 3).

B. Metabolic Data

1. Serum Values. Table 2 shows values of stone types already characterised in Table 1 and two additional groups of controls (n = 36; s. Methods) and CaP/struvite lithiasis (50%/50%; n = 7). The mean age is comparable but the ranges are smaller in uric acid and CaP/struvite stones (35-67 and 41-64 years) than in other stones and controls. Except CaP all stones have lower magnesium than controls and CaOx and uric acid stones have in addition lower phosphate. Immunoreactive parathyroid hormone, total and ultrafiltrable calcium are only insignificantly higher in stones than controls and the same holds for total protein. Uric acid in serum is significantly elevated in pure CaOx and uric acid lithiasis, whereas sodium concentration is equal in all groups. Mean creatinine concentration in the stone population, although in the normal range, is slightly higher than in controls and the differences are significant with pure CaOx and uric acid stones, but not with CaOx containing additional mineral phases.

2. Urine Values. Table 3 shows clearances and pH of controls and the stone groups. Only pH and calcium clearance are different. pH is higher than in controls in CaP stones[2], and pH is lower than

[2] In this group four out of eleven CaP stones contained 5-10 per cent struvite.

in controls and other stones in those patients with uric acid lithiasis; between pure CaOx and CaP pH is different too.

Calcium clearance in uric acid stones is markedly lower than in CaOx and CaP stones, and it is higher than in controls in CaOx stones with additional mineral phases. Mean clearance values of all other parameters studied, endogenous creatinine clearance included, are not significantly different from values of the control group.

3. Activity Products (= relative saturation products; RSP) of Stone Forming Mineral Phases in Urine. Figure 4 depicts RSP as estimated by the nomogram (9), in aliquots of 24 h and 2 h fasting urine. From the data of both urine qualities (24 h; 2 H) it is evident that RSP of calcium oxalate is in the metastable range (0 until +1) in all groups. Median values are: controls 0.98; CaOx (Table 1; 1a) 0.95; CaOx (Table 1; 1b) 0.88; uric acid 0.80; CaP 0.70. The total variance under either condition (24 h; 2 h collection period) does not allow to consider RSP values as belonging to different populations, as already published in a previous study (14).

RSP of brushite (24 h) is lowest in uric acid stones (H-value: 11.97, $P < 0.05$), but in all groups brushite RSP is in the metastable range. In fasting urine, generally undersaturated with respect to brushite again this is most expressed in uric acid stones (H-value 18.76, $P < 0.01$). The quality difference in RSP of brushite, i.e. metastable range (24 h) versus undersaturation range (2 h) mainly is based upon the higher urine concentration of phosphate and calcium in 24 h urine and the lower pH in the latter.

RSP of octa-calcium-phosphate (H-values. 24 h 16.06, $P < 0.01$; 2 h 25.2, $P < 0.001$) shows a pattern similar to RSP of brushite, i.e. relative saturation is least in uric acid stones. Conversely, uric acid stones show the expected high RSP of uric acid (H-values: 24 h 25.3, $P < 0.001$; 2 h 16.7, $P < 0.01$). RSP of sodium acid urate is greatest in 24 h urine of controls and in 2 h urine of CaOx stones ($< 100 < 75$) (H-value: 11.3, $P < 0.05$).

DISCUSSION

A critical appraisal of data regarding occurrence of stones is difficult as other investigators have used different techniques and stone types have been differently classified (e.g. consideration of calcium oxalate hydrates). In addition we deal with a hospital population, whereas others deal exclusively or mostly with stones referred to the mineralogist/chemist.

With this in mind our percentage of calcium containing stones (= 64) accords well with a US report (22; = 66), less well with the reports of Herring (4; = 76), Takasaki (21; = 73) and Pantanowitz (11; = 53). The figures for uric acid lithiasis vary strongly among investigators, while our percentage (= 17) holds a mean position. There is also no uniform view regarding the age maximum of stones: 20-29 years (21), 30-40 years (19), 41-45 years (1), 35-55 years (6) and 46-55 years (this study). The ratio male:female is reported to be 3:1 (6), 5:1 (19) and 1.22:1 (this study). The age peak of CaP (brushite/apatite) between 26-35 years appears noteworthy in regard to stones expected in later years from those patients: one might speculate that formation of phosphate in younger years generally could predispose to the later formation of oxalate or mixed stones (phosphate(s) + oxalate). An answer may be obtained by a careful analysis of all stones containing, according to our definitions, pure oxalate (= 100 per cent).

There is no shift detectable toward a single concrement type over the observation period. But this does not completely rule out small quantitative deviations in composition of e.g. stones containing calcium oxalate and phosphate, as reported by Hodgkinson and Marshall (5) using chemical analysis over a long interval (= relative increase of oxalate and decrease of phosphate content). The same authors find calcium phosphate as the predominent phase in stones of patients with primary hyperparathyroidism (5). For similarly composed stones (CaP, CaOx + additional mineral phases, mostly phosphate) we, in this work, are unable to confirm signs of hyperparathyroidism (vide infra).

A more critical representation of mineral metabolism parameters than is widely practiced in stones of varying composition seemed useful to us. When viewing the age of participants, their kidney function and general health state, all rather comparable, then especially serum calcium (total and free fraction) is unaltered in patients too. As compared with another report (12) showing a marked hypomagnesaemia in calcium lithiasis independent of glomerular filtration rate, serum magnesium in the present study, albeit distinctly lowered in stones, does not permit the diagnosis of hypomagnesaemia in this disorder. As magnesium clearance is normal it cannot account for our lower serum values. It is unsettled whether small extrarenal magnesium losses do occur and what role they possibly play in stone forming processes.

Serum parathyroid hormone which can be stimulated by hypomagnesaemia/hypocalcaemia is normal in all stone groups. Therefore, this data concerning the various mineral components of stones, does not help to substantiate the often suggested role of parathyroid glands in classes of patients with metabolically mediated lithiasis, at least not under resting conditions after an overnight fast.

Conversely, hypophosphataemia in calcium stones was repeatedly found by others and was clearly documented by us. In addition, its occur-

rence in uric acid lithiasis must be emphasised. Phosphate clearance as a measure of renal phosphate excretion is widely used. However, one should mistrust a normal phosphate clearance in the presence of low serum levels, e. g. in pure CaOx stones and CaOx stones with another mineral phase, where it may indeed mask a low phosphate excretion (18). Both, low serum phosphate and a low excretion rate in calcium stone formers, strongly suggest an increased tubular reabsorption of phosphate, what could be documented by us in a selected group of patients (16). Whether phosphate deficiency of extra-renal origin is operative in them is unsettled. According to latest reports a phosphate deficiency state could arise from diminished tubular phosphate reabsorption even in selected stone formers and may be associated with decreased tubular calcium reabsorption (3), thus substantiating what has been coined renal hypercalciuria.

Hyperuricosuria, repeatedly found by us (18) and others (2) in stones, is not reflected by the normal uric acid clearance. Three factors may be responsible: 1) hyperuricosuria is missed when studying stone types rather than younger calcium stone formers where the symptom is often found (18); 2) mild but significant hyperuricaemia results in calculated lower clearance values; 3) the slightly lower creatinine clearance also contributes to mean lower uric acid excretion rates. Most interestingly, hyperuricosuria in terms of clearance is not found in uric acid stone formers too. The expected higher clearance of these patients may have been prevented by the higher serum uric acid concentration. Nonetheless, the primum movens in idiopathic uric acid stone formation should not be recognised in alterations of purine metabolism but rather in the permanently low urine pH, a disorder of unknown origin.

An elevation of relative saturation product of calcium oxalate has been described for calcium lithiasis (8). We, under the present conditions of investigation (stone policlinic, home diet) are unable to confirm those findings, as we had been unable to confirm them in a large number of calcium stone formers and healthy controls (14). When using this nomogram (9) then it appears to us that pH differences do exert an unduly strong influence upon relative saturation products, especially on brushite, octa-calcium-phosphate, uric acid and, to a lesser extent, on sodium acid urate.

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