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Conference Secretary: R. M. Schaefer, M.D., Urologische Universitätsklinik, D-5300 Bonn (FRG)

Editorial

Since 1972 W. Vahlensieck (Bonn) and G. Gasser (Vienna), supported by an advisory board of internal experts have been organizing Urolithiasis Symposia alternating in Bonn and Vienna. Characteristics are lectures and discussions on epidemiology, pathogenesis, diagnostics and therapy. In the meantime these are internationally appreciated meetings with the great advantage of interdisciplinary discussions. Of each symposium a report by Steinkopff-Publisher exists. To inform more interested searchers about the topics and to give the possibility to get in contact with the experts in this issue the abstracts of the 1986 Symposium will be published.

W. Vahlensieck

I. Epidemiology and Pathogenesis

1 Incidence and Prevalence of Urolithiasis in the Federal Republic of Germany in 1979 and 1984

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1985 we conducted again a nationwide survey with the Institute for Applied Social Sciences (INFAS, Bonn-Bad Godesberg) to find out the incidence and prevalence of urolithiasis in the German population in 1984 and to compare the results with the findings for 1979 on occasion of our survey of 1980. In 1985 a total of 10,228 individuals aged over 18 were interviewed. The incidence was with 0.85% in 1984 higher than in 1979 with 0.54%. The first manifestation rate in 1984 was 0.22% (1979: 0.12%) and the recurrency rate 0.62%. The prevalence in 1984 was with 4% the same as we had registered for 1979. Again in 1984 we found out that there was no significant difference between the sexes and that the prevalence increases linearly with age.

2 Natural History of Cystinuria and Cystine Lithiasis

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The described experiences are founded on 287 cases of homozygous cystinuria studied in Mariánské Lázně (Czechoslovakia) during the past 25 years. Cystine urolithiasis was present in 236, i.e. 82% (116 males and 120 females).

Cystine urolithiasis always develops on a basis of inborn cystinuria. In old age (from about 60 years upwards), over 80% of subjects homozygous for cystinuria are afflicted. The mean age of the onset of lithiasis (24 ± 17 years) is significantly lower than for other types of lithiasis. In 37% of the males and 24% of the females, lithiasis appeared before the age of fifteen; later sex ratio incidence of lithiasis evented out. The curve for the onset of lithiasis has two peaks – one at about five and the other at about 25 years.

In a retrospective evaluation of the 287 cystinuria homozygotes, graphic expression showed the course of the disease to be correlated to age, with relative frequencies ranging from a signfree stage to stage of cystitis and pyelitis, colic, the spontaneous expulsion of calculi, conservative lithotomy, nephrectomy and renal insufficiency.

Thirty-eight deaths of cystinuria patients (20 males, 18 females) during the 25 years were also analysed. Only 31 had urolithiasis. Their mean age at death was 55 ± 18 years. Only four (10.5%) died as a result of uraemia; ten died from ictus, eight from heart failure (myocardial ischaemia) and ten from cancer.

3 Lithogenous Metabolic Disturbances Associated with Cystine Lithiasis

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The Problem. Cystine-stone patients can also produce mixed stones and changes in stone type. Apart from cystine, other lithogenous substances are not infrequently excreted in excessive quantities, too. Hence we undertook to determine the parameters applicable to urinary stones in patients with recurrent cystine lithiasis.

Material and Methods. The metabolic processes of 26 cystine-stone patients were investigated under clinical conditions. The patients were placed on a standard diet and their 24-h urine analysed. After it had attained its steady state, tolerance tests were performed for calcium, purine and ammonium chloride. 6 cystine-stone patients (23.1%) had stones with calcium oxalate admixtures, or calcium oxalate stones in addition to their cystine calculi. Admixtures of calcium phosphate were found in three patients. 57.7% of patients suffered from a manifest or latent disturbance of their uric acid metabolism, and additionally or independently, 57.7% displayed hypercalciuria. 53.8% had hyperoxaluria. It is thus evident that combinations of metabolic anomalies are a common occurrence. 30.8% of

the patients suffered from disturbed uric acid metabolism in conjunction with hypercalciuria. One patient was diagnosed as suffering from primary hyperparathyroidism.

Due to the fact that alternative forms of stone may be possible, when diagnosing cystine stones diagnosis should always be extended to include any accompanying metabolic anomalies. The role played by these anomalies in cystine lithogenesis is still unclear.

4 The Diagnosis of Excretory Anomalies Based on 354 Patients Suffering from Recurrent Calcium Oxalate Stones

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The Problem. The causes of recurrent urinary stone formation can often only be discovered by investigation of the metabolism under clinical conditions. Our investigations were conducted according to a standard pattern.

Material and Methods. The metabolism of 354 patients with recurrent calcium oxalate stones (119 females, 235 males) was the subject of a 12-day clinical investigation. The composition of the urine was analysed under conditions of uncontrolled diet, standardised diet and high excesses.

Results. Hypercalciuria was found in 62.2% of the women and 68.1% of the men. 48.7% of the women and 61.3% of the men displayed hyperuricosuria. A clear majority of the men (61.3%), in contrast to the women (29.4%), was found to have hyperoxaluria. Primary hyperparathyroidism was discovered in 6.4% of all patients. Deviations from the standard composition of urine were detected in a total of 93.3% of the male and 83.2% of the female patients.

Conclusion. The results of these investigations into the metabolism of patients with recurrent Ca-oxalate stones provide a firm foundation upon which to base a specifically directed therapy.

5 Sex-Dependency of Lithogenic and Inhibitory Substances in the Urine of Recurrent Calcium Stone Formers

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It is well known that men suffer more often from recurring calcium stone formation than women. The reason for it is still not clear. In our stone clinic the ratio men:women of recurrent stone formers is 1.5:1.

For question of sex-dependency excretion values of calcium, oxalate, phosphate, uric acid, sodium, citrate, magnesium and cAMP of patients with recurrent sterile calcium stone formation were analyzed. For male (m) $n = 100$, average age 45.5 years, for female (f) $n = 65$, average age 44.8 years.

Volume of urine per 24 h under free diet did not differ between the groups (m: 2,043 ml/24 h, f: 2,026 ml/24 h). Concentration of calcium, phosphate, uric acid and magnesium was significantly higher in 24 h urine of men (p-value < 0.01). Hyperuricosuria was diagnosed in 47% of male and 38.5% of female patients. Oxalate excretion was not different between the groups. In females 24 h excretion of citrate and sodium (expressed per kg body weight) was found significantly above males ($p < 0.01$), as was urinary cAMP (expressed in nmol/100 ml GF, $p < 0.01$); concentration of citrate and sodium in 24 h urine though did not differ between the groups.

Results show distinct differences of urinary lithogenic substances between sexes, that may explain higher risk of calcium stone formation in men. Further analysis of age dependency and comparison of results to healthy controls will be presented.

6 Pathophysiological Factors in Calcium Stone Formation

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The presentation will focus on three elements in our pathophysiological understanding of the formation of calcium containing renal calculi. First, there will be an update of our present understanding of renal calcium transport under normal and pathophysiological conditions. This will include a discussion of newer data involving the role of metabolic acidosis and alkalosis in which we have now shown that metabolic acidosis retards calcium transport in the straight portion of the proximal tubule and alkalosis enhances calcium reabsorption at the site. We will also present data in an animal model of hypercalciuria due to cisplatinum toxicity in which chlorothiazide actually increases rather than decreases calcium excretion.

Second, we will review the present animal models of idiopathic hypercalciuria and try to draw conclusions as to possible sites of defects within the renal tubule responsible for the calcium lossing tendency.

Third, we will review our present understanding of the key factors in renal stone formation in the collecting duct. We will use data which have been observed in the distal convoluted tubule and the papillary collecting ducts. An assessment will be made of calcium, phosphate, magnesium, and oxalate transport vis-a-vis the rates of water reabsorption and osmolality in the collecting duct system.

It is hoped that this presentation will give further understanding of the formation of renal calculi and generate new ideas for research.

7 Acute Acid Loading in Healthy Subjects and Idiopathic Oxalate Stone Formers

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Acid loading test for diagnosis of renal tubular acidosis is an established procedure. We extended the test to recurrent idiopathic oxalate stone formers with the following question in mind. Is there a different response to acute acid ingestion between normals and idiopathic oxalate stone formers?

10 healthy subjects and 12 recurrent oxalate stone formers without RTA and renal hypercalciuria ingested 0.1 g ammonium chloride per kg body weight. The following parameters were analyzed in urinary spot samples before and until 4 h after acid intake: pH, sodium, potassium, calcium, phosphate, sulfate, uric acid, oxalate and citrate. Calcium excretion increased significantly in both groups. In patients, increase was significantly higher than in normals ($2p < 0.05$). Citrate decreased significantly, there was no difference between the groups.

There seems to be a disturbance of renal calcium transport in idiopathic oxalate stone formers which can be unmasked by acute acid loading. Dietary acid restriction in oxalate stone formers may be derived from this test. These findings support further evidence for the stone promoting role of high acid food.

8 Lack of Evidence for the Primary Role of 25(OH) and 1,25 $(OH)_2$ Vitamin D_3 in Idiopathic Urolithiasis

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Because of its important role in calcium homeostasis Vitamin D has recently implicated in the pathogenesis of idiopathic hypercalciuria. The evidence for this, however, is conflicting.

Each of 11 normal subjects and 9 recurrent idiopathic stone formers was studied in detail on 4 days. The studies were performed on each after overnight fasting. On day 1, the subjects remained in the fasting state throughout the test period. On days 2, 3 and 4 a test

meal of isocaloric quantities of glucose, animal protein and fat was given respectively at 9.00 a.m. Plasma calcium, inorganic phosphate, 25(OH) and $1,25(OH)_2D_3$ were monitored every 2 h for 8 h. Urinary calcium and creatinine was measured between 8.30 a.m. and 11.00 a.m.

There was no significant difference in the blood parameters between the two groups on any of the days either during fasting or after the test meal. There was no correlation between plasma $1,25(OH)_2D_3$ and serum phosphate, calcium or plasma $1,25(OH)_2D_3$ and urinary calcium.

These findings are in conflict with some of the published reports and do not support the view that 25(OH) and $25(OH)_2D_3$ play an important role in idiopathic urolithiasis.

9 Oxalate and Calcium Absorption Tests in Patients After Jejunoileal Anastomosis and in Idiopathic Renal Stone Formers in Comparison With Healthy Subjects

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The concentration of calcium and oxalate in urine are major risk factors for the formation of renal stones. Patients who have undergone jejunoileal anastomosis in order to control morbid obesity are prone to develop hyperoxaluria and renal calcium oxalate calculi. Hpyeroxaluria is common also in patients with idiopathic stone formation.

Methods and Material. Intestinal absorption of ^{47}Ca and ^{14}C-oxalate was measured in 21 healthy subjects, 19 patients who had undergone jejunoileal anastomosis (12 stone formers and 7 non-stone formers) and to date 5 idiopathic stone formers.

Results. After jejunoileal bypass both stone formers and non-stone formers had a significant hyperoxaluria. In comparison with healthy subjects these patients showed an increased intestinal absorption of oxalate. The rate of excretion was, however, also decreased. The intestinal absorption of calcium was lower in this patient group than in the control group.

Patients with an idiopathic stone formation and hyperoxaluria also had an increased intestinal absorption of oxalate.

Conclusions. Hyperabsorption of oxalate to hyperoxaluria in patients after jejunoileal anastomosis and also to hyperoxaluria in patients with idiopathic renal stone formation. The delayed excretion of oxalate suggests a changed renal handling.

Reduced absorption of calcium is the probable explanation of the hypocalcuria seen in patients who have gone through jejunoileal anastomosis.

10 Glucose-Induced Hypercalciuria in Renal Stone Formers – Further Evidence of the Role of Insulin

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The mechanism for the calciuretric effect of refined carbohydrates is not clear but it may be mediated through insulin.

Eight recurrent idiopathic renal stone formers and 9 normal subjects were given a test meal of glucose in a fasting state. Blood glucose and plasma insulin were measured before the test meal and at regular intervals thereafter for 8 h. Urinary calcium and creatinine were monitored in the fasting state and after the test meal.

The fasting urinary calcium was significantly higher in stone formers ($P < 0.01$). Following ingestion of glucose, the calcium excretion increased in both patients and normal subjects but it was exaggerated in the former. The blood glucose curve was normal in both the groups but the plasma insulin response was significantly higher in stone formers. There was a strong positive correlation between plasma insulin levels and urinary calcium (Patients $r = 0.9$; $P < 0.01$: Controls $r = 0.8$; $P < 0.02$).

The results suggest that insulin is calciuretic and the hypercalciuria induced by glucose in stone formers is mediated through insulin.

11 Pattern of Serum Parathyroid Hormone (PTH), Calcitonin (CT) and Calcium in Renal Calcium Stone Disease Following an Oral Calcium-rich Test Meal*

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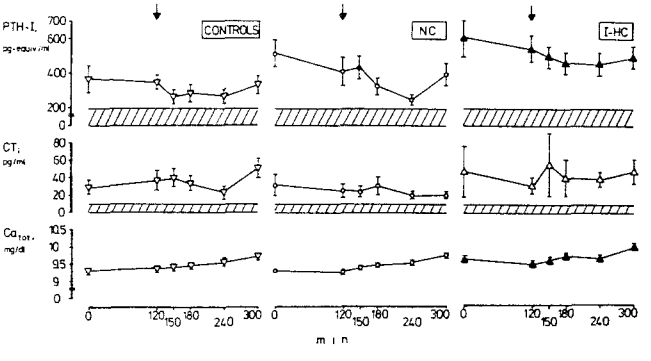
Although PTH has been widely studied in the calciuria subgroups of recurrent calcium urolithiasis, CT has found little attention. Because the response to oral calcium may be considered an indicator of suppressibility of PTH secretion and of CT secretory reserves, we studied 12 healthy male control subjects, 12 normocalciuric (NC), 12 hypercalciuric (idiopathic; I-HC) male stone patients, after prior careful exclusion of overt hypercalcemia and/or other signs of parathyroid hyperfunction. The load (for details see D. Scholz et al.; Urologe A19: 202, 1980) was administered near 10:00 a.m., after a 12–15 h nocturnal fasting period and after having taken a pre-load fasting blood sample. The time course of blood sampling is visible in the figure ($\bar{x} \pm$ SEM; ////// assay detection limit). The CT assay utilized homologous materials, the mid-regional PTH assay (PTH-I; antibody S-478, European PTH Study Group) employed purified bovine PTH as standard and tracer. Under these ambulatory conditions of laboratory examination PTH is suppressible and CT slightly stimulable by the oral calcium load (1,000 mg ions); the degree of suppression and stimulation, respectively, appears almost equal in the three groups. However, both the NC and I-HC moiety of idiopathic stone patients clearly exhibit higher PTH, and the I-HC patients higher calcium as well, whereas the CT differences were statistically insignificant (Fig. 1. Filled symbols: $p < 0.05$ or smaller vs controls). Urinary cAMP and phosphate, as measured in urine collected before and after the load, did not show any differences among groups. Integrated (log area) PTH was highest in I-HC ($p < 0.01$), intermediate in NC ($p < 0.10$), compared with controls.



We conclude that in a segment of (male?) stone patients 1) there is a tendency toward enhanced parathyroid gland function which is not reflected by indirect parameters (cAMP; phosphate); 2) the nature of this anomaly is yet unknown but possibly related to differences in circulating bioactive PTH fragments; 3) normal CT argues against involvement of this hormone in stone disease.

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12 Ammonium Urate Stone Formation After Portocaval Shunt (PCS) in the Rat – Preliminary Report

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Previously we have shown that PCS inteferes substantially with regulation of serum minerals in the intact and parathyroidectomized rat (P. O. Schwille et al.). This study elucidates further aspects of mineral metabolism in the parathyroid intact sham-operated (n = 3) and PCS (n = 6) rat, especially intestinal absorption of calcium, magnesium, phosphate, urinary excretion and balance of minerals. In addition the relative supersaturation products (RSPs) of several stone forming phases were calculated, and the urinary tract examined for concretions. After PCS the mean fractional intestinal absorption (= per cent of ingestion) decreased by 13 (calcium), 6 (magnesium), 12 (phosphate) per cent, respectively, whereas there was a median increase in urinary excretion by 133 (calcium), 70 (magnesium), phosphate (7) per cent, respectively, all as compared with control rats (significance of differences not tested). Also, the urinary pH, uric acid, citrate, ammonium (100 per cent increase!) rose, and pyrophosphate decreased (63 per cent of controls) after PCS. All PCS, but none of the controls, formed pure ammonium acid urate stones found over the entire length of the urinary tract, as documented by polarisation microscopy and X-ray dispersion microprobe analysis. No urinary tract infection was detectable. The RSPs (table) revealed that there was no extreme supersaturation (> 1.0: spontaneous precipitation) of urine with this phase, and, hence, simple homogenous nucleation probably did not occur. The RSPs of struvite and sodium acid urate (not shown) increased as well due to PCS and suggest some role of these compounds in inducing heterogenous nucleation of ammonium urate.

	Relative supersaturation products; medians (range)	
	PCS; n = 6	Sham; n = 3
Calcium oxalate	0.73 (0.59–0.99)	1.20 (1.25–1.5)
Brushite	0.11 (–0.23–0.19)	0.53 (0.50–0.62)
Octacalcium phosphate	0.22 (–0.61–0.57)	0.76 (0.55–0.93)
Ammonium acid urate	0.53 (0.46–0.55)	–0.28 (–0.11 – –0.32)
Struvite	1.2 (–1.2–2.4)	–0.05 (–0.25–0.2)

These results allow to conclude that in the rat 1) ammonium urate stone formation is initiated by PCS and is associated with renal and intestinal functional abnormalities otherwise exhibited by subgroups of stone forming humans; 2) PCS induced stone formation may give insights into stone forming processes in general.

Reference: Schwille PO, Linnemann U, Issa S, Klein P (1985) In: Norman AW, Schaefer K, Grigoleit HG, Herrath D, v (eds) Vitamin D, chemical, biochemical and clinical updata. De Gruyter, Berlin New York, pp 1085–1086

13 Hormone-Induced Acceleration of de Novo Purine Synthesis

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Overproduction of uric acid is often associated with uric acid lithiasis. The reasons for purine overproduction, when not associated with one of the rare inborn errors of purine metabolism, are not yet known. As part of a research of the mechanisms underlying purine overproduction, the present study was aimed to clarify the role of the glycogenolytic hormones in the regulation of purine synthesis. Administration (i.p.) of the following hormones was found to accelerate purine synthesis in mouse liver within 10 min by 2 to 3 folds: Glucagon (2 mg/kg), L-epinephrine (1 mg kg), angiotensin II (65 μg/kg) and vasopressin (25 μg/kg). cAMP (40 mg/kg) had the same effect. These hormones caused at the same time a 2 to 6 fold increase in liver content of phosphoribosyl-pyrophosphate (PRPP), the rate limiting substrate for purine synthesis. All the above hormones are known to exert glycogenolytic effect in the liver, through either cAMP-dependent or calcium-dependent mechanisms. The hormone-induced increase in the synthesis of PRPP in the liver could reflect a metabolic effect of the hormones, such as glycogenolysis-associated increased formation of substrate ribose-5-phosphate. On the other hand it could reflect activation of PRPP synthetase by an as yet unidentified mechanism, such as activation through phosphorylation. Preliminary results did not furnish evidence in support of these mechanisms. In contrast it was found that at least some of these hormones cause a prompt and marked reduction in liver ATP content. This could lead to a compensatory acceleration of purine synthesis, such as following fructose administration and as in glycogen storage disease type I.

The results suggest that increased concentration of glycogenolytic hormones should be considered as a possible cause of uric acid overproduction and therefore also of uric acid lithiasis.

14 The Influence of Hyperuricosuria on Growth Centres of Calcium Oxalate Calculi

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The effect of increased uric acid excretion on the formation of calcium oxalate calculi has not yet been fully established. A number of theories are under discussion.

On the basis of polarization microscopic examinations of grain and thin section preparations we have classified calcium oxalate stones into four types. 1/3 of 50 patients with calcium oxalate calculi proved to have hyperuricosuria. In almost all of these patients with hyperuricosuria we found stones of texture type I. In contrast to this, textures types III and IV were mostly diagnosed in patients with normal uric acid excretion. Also the growth centres of such calcium oxalate calculi found in conjunction with hyperuricosuria was clearly distinct from those of patients with normal uric acid excretion.

In order to investigate the effect of uric acid on the genesis of calcium oxalate stones we applied scanning electron microscopy and electron probe microanalysis. Out of 30 calcium oxalate calculi with hyperuricosuria, 4 showed a greater share of sodium within the calcium oxalate. By contrast, out of 30 stones with normal uric acid excretion no one proved to contain any sodium. These findings support the theory that the influence of uric acid on the formation of calcium oxalate calculi may occur by way of heterogeneous nucleation of sodium urate.

15 Analyses of Zinc from Nutrient Media During the Growth of Urea-Splitting and Non-Urea-Splitting Bacterial Cultures

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Several research teams found high concentrations of zinc in phosphate stones. Other authors described in-vitro-experiments and animal experiments, in which urea-splitting bacterial cultures could be determined to be causing the formation of struvite stone. Moreover,

proteus mirabilis in particular could be isolated from phosphate stones.

In a clinical study of 141 patients affected by urolithic disorders the concentration and the daily secretion of zinc in the urine was measured and it was observed that in the 14 patients with struvite stones the results were significantly lower than in the other patients.

On an experimental basis, we tested whether the increase of bacteria and the concentration of zinc were connected. In the experiment, we cultivated *proteus mirabilis, pseudomonas aeruginosa* and *e. coli* on different nutrient media, then watched the increase of the germs and determined the concentrations of zinc in the cultures at defined points in time. Measuring was carried out by means of atomic absorption spectrometry. We will give a report of essential partial results.

16 Studies of Sulfate Excretion in the Urine of Healthy Individuals Compared to Recurrent Calcium Oxalate Stone Formers

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The hyperacidity of urine is often a coexisting factor in calcium oxalate stone formers. So far it has not been clear, whether nutritional or metabolic factors play a more important role.

We have measured the sulfate excretion in 263 recurrent oxalate stone formers (152 male, 71 female) under individual and standard diet. As a reference group we examined 326 healthy individuals (163 male, 163 female) under an individual diet and 30 healthy individuals under an individual and standard diet. Sulfate was measured nephelometricly in the 24 h urine.

Under an individual diet in the healthy males the medium sulfate excretion was 21.6 mmol/d, in females it was 16.9 mmol/d (significance $p < 0.001$). In oxalate stone formers the excretion in males was 23.6 mmol/d, in female 18.0 mmol/d (significance $p < 0.001$).

Under a special standard diet we measured the daily excretion after having reached a steady state after 7 days. In healthy males it was 23.9 mmol/d, in stone formers it was 17.2 mmol/d, the difference was not significant though. In healthy females the excretion was 20.4 mmol/d in stone formers it was 15.7 mmol/d (significance $p < 0.05$). The question is discussed whether sulfate acts as a complex-former for calcium and in this way is an inhibitory substance in stone formation, and the role of nutrition is evaluated by means of studies under individual and standardized diet.

17 Further Histological and Histochemical Findings in Rat Kidneys Due to Experimental Stone Formation

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Previously we have already given an account that in the kidneys of rats treated with sodium oxalate strongly positive PAS and ABT / aldehyde-bisulfite-tolnidine blue / reaction can be seen in several epithelid cells of the distal kidney tubules already in three days. This positive reaction remains unchanged also after the diastase digestion, and from this we think that these cells do not contain glycogene but glycoprotein.

This time we attempted to analyze the material of the cells showing strongly positive ABT reaction with the help of an immunohistochemical reaction. The possibility for this was offered by V. Tomaházy working for the Pathological Institute, who at that time was engaged in production anti-Tamm-Horsfall protein, and was kind enough to supply us with the materials required for the purpose of our analysis.

From the renal tissue chriostat sections were prepared, and on the parallel sections ABT and immunohistochemical reactions, respectively, were carried out.

In the course of the examination of the parallel sections we found that corresponding to the area showing positive ABT reaction a colour reaction indicating the presence of the Tamm-Horsfall protein can be seen. From this the conclusion can be drawn that Tamm-Horsfall protein is secreted by the ABT positive cells.

Our results refer to the fact that organic matrix of the renal stone, or at least a part of it, the Tamm-Horsfall protein, may come from the damaged tubule cells.

18 New Urates IV. Urates with Organic Cations

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(1) In kidney stones, urates with K^+, Ca^{2+}, Zn^{2+} (Dosch W (1981) Fortschr Urol Nephrol 17:240; Dosch W, Matzke A (1984) ibid, 22:279) are less common than those with Na^+, NH_4^+. (2) Also in native "stabilized" uric acid-dihydrate (UADH, Dosch W (1981) Fortschr Urol Nephrol 17:255) inorganic cations as stabilizers are not common. (3) The X-ray pattern of UADH from kidney stones sometimes shows additional lines, not included in ASTM-card 19-1996* but consistent with the supposed structure of UADH. (4) Organic cations like 2-amino-ethanole, methylamine, dimethylamine, choline, piperidine and some-amino-acids like 1-histidine form well-crystallized urates. In some cases the solubilities for uric acid are exceptionally high. (5) On careful addition of acid, urates according to (4) are transformed to UADH, the X-ray pattern of which is identical with (3). From UADH in kidney stones, organic cationic stabilizers are detectable. (6) Above ca. 50 °C organic stabilized UADH is transformed to a new third modification of uric acid. In contrast, inorganic stabilized UADH is dehydrated to uric acid-I.

19 Light and Electron Microscopic Examinations into Morphological Changes of Rat Kidneys by Nephrocalcinosis

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Animal models represent an interesting starting point for studies on nephrocalcinosis. Within a few weeks a nephrocalcinosis could be induced by an atherogenous diet in the rat. Light-microscopically deposits could be seen in the cortico-medullary zone. Decisively new starting points were found by electron-microscopy examinations which made possible a localisation in the tissue and demonstrated an association to the nephron. Most of the deposits were found in the interstitium. Morphologically these conglomerates represent themselves with a concentric arrangement in layers indicating an appositional growth. Only few deposits were found intraluminarily. Morphologically these differed markedly from the interstitial ones, presenting themselves as longish cristal needles, structurally corresponding to apatite. The stone analysis by polarising microscopy and x-ray diffraction technique demonstrated as main components calcium and phosphate. The pathophysiological fundamental principles are still unknown. We have to discuss whether these deposits form primarily in the interstitium or consecutively result from alterations of the tubular cells.

20 Stone Formation in Human Kidneys

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Aim of this study was to define sites, causes and triggers of calcium stone formation in the human kidney. Specimens from cortex, medulla and papilla were taken from 20 non-stone forming kidneys

(e.g. in most cases hypernephromas) and 10 stone-bearing kidneys. One part was prepared for scanning electron microscopy and the other for chemical analysis (Ca, Na, K, Mg, Zn, Cd, Pb and Cu). A 12 h urine sample – collected before nephrectomy – was analysed for Na, K, Ca, Mg, Oxalate, Urate, Citrate. Urine saturation with respect for calcium oxalate was calculated by a FORTRAN IV program. Microscopic calcifications were identified only in the collecting ducts near the papillary tip in all but one of the stone bearing and in 9 of the non-stone forming kidneys. The primary phenomenon was a cobble-stone like cover of the epithelium followed by spheroids obstructing the tubules over long distances. Electron dispersive X-ray analysis detects in almost all calcifications calcium, in some spheroids in combination with phosphate. Chemical analysis of the tissue showed an inhomogenic distribution of the elements evaluated by stripe specimens from cortex to papilla. Kidneys with microcrystallisation showed also in the papilla high contents of calcium and cadmium in combination with a relative low content of magnesium. There are no differences in tissue or urine concentrations concerning the other salts, but in general stone formers exhibited a higher urine saturation with respect to calcium oxalate.

21 Composition and Structure of 500 Passed Renal Calculi

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Five hundred consecutively passed renal calculi, belonging to a same area with 40,000 residents in a district of Madrid, were studied under a stereoscopic microscope with the complement of scanning electronic microscopy and I.R. spectroscopy. Papillary calculi amounted to 142 (28.4%), almost two thirds of them with typical or atypical Randall's plaques.

Stones with different shapes but showing no papillary pattern were found in 237 cases (71.6%). Seventeen round whewellite stones showed after fragmentation small apatite nuclei and, as we stated in a previous paper, it was logical to assume that some detached plaques could become hidden after a further whewellite deposition during a freely transient staying of the stone in a calyx. Demonstration was given by the finding of calcified renal tubuli in the central nucleus of a round stone. A single chemical constituent was found in 237 non-papillary stones (calcium oxalate in 176, uric acid in 45, apatite in 14 and cystine in 2 specimens) and a mixed composition appeared in 121 stones. Several morphological patterns found in non-papillary stones are discussed. Microscopic morphology of small passed calculi was, until recently, an almost unexplored and unclassified field. However, in this early stage of the calculi one can more easily recognize the primary composition and even the original nucleus of the stone.

22 Examination of Microelement Level in Urinary Stones

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In our examination we have studied the microelement contents in different kinds of stones (oxalate, phosphate, uric acid) by means of atom absorption. Previously the stones were examined by analytical methods of infrared spectroscopy and UMKA for the exclusion of contamined calculi from the studied group. We have performed the quantitative analysis of the following bioelements: Ca, Mg, P, Na, K, Zn, Fe, Mn, Li, Cu, Pb, Cr.

We have found the highest microelement level in phosphate calculi, and the lowest level was in uric acid stones. We can explain the difference by the enrichment of the microelements, and the "sponge" effect, caused by the special composition and structure of phosphate stones. Our result correspond with the literary data.

A high level of Fe were demonstrable in all the three types of stones. This result refutes that the Fe originates from the haemoglobin. The level of Zn and Pb was higher in the oxalate and uric acid calculi agree with literary data, and it may be considered as a factor of urinary stone formation.

At present we cannot explain the cause of high percent rate of Li in stones.

23 Potassium in Sodium Urate Calculi

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In continuation of our studies on urate urinary calculi, a series of sodium urate stones have been examined by infrared spectroscopy, X-ray diffraction, scanning electron microscopy, EDAX and atomic absorption spectrophotometry.

Potassium was found in some areas of a few samples. Our new results have shown the existence of a complex urate containing sodium and potassium in varying proportions. This type of complex urate can be clearly differentiated from the monosodium urate monhydrate which is the main component of sodium urate stones.

A parallel study on synthetic complex urates confirms the above mentioned results.

24 "Fasermatrix" – A Mechanism to Fix Renal Stones

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25 Are There Analogies in the Formation of Urinary Calculi and Gall-Stones? The Active Role of Cholesterol in the Calculogenesis

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In 1977 we reported on the active role of free and esterified cholesterol in the calculogenesis. We found that cholesterol agglomerates crystals of different composition (oxalate, phosphate, urate) even at the lowest concentrations occurring in urine and that this effect was increased if γ-globulin was present. In powdered stones an average enrichment of cholesterol, compared with urinary content, of 70–700 and in organic stone-matrix a corresponding cholesterol enrichment of 2,300–23,000 could be found.

In 1975, Schwille et al. reported a high nephrocalcinosis and a massive renal stone formation following a cholesterol rich diet in animal model.

Based on a novel quantitative technique, developed in our laboratory, the strong and selective crystal agglomeration propensity of free and esterified cholesterol could be quantified in experiments with Ca-oxalate, brushite, hydroxylapatite, tricalciumphosphate, struvite and uric acid crystals. The crystal suspensions contained 1; 2; 5; 10; 20; 50; 100 and 200 mg/l crystals. The cholesterol was finely dispersed in watery medium by sonification or via methanol in various concentrations. The crystal suspensions were incubated for 10 min in the presence or absence of different concentrations of free and esterified cholesterol. After a 2 min centrifugation at 250 *g*, the cholesterol concentration in the supernatant was determined quantitatively. A high degree of cholesterol binding up to 90% could be found with oxalate, phosphate and urate crystals, the effect being strongly supported by γ-globulins, moderately supported by protamine sulfate, lysozyme and DNA and inhibited by albumin, α-globulin, mucine, RNA.

26 Porphyrins as Components of a Certain Kind of Black Renal Calculi

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The porphyrin content in eight black renal stones which showed infra-red absorption spectra previously known as "protein-containing organic material" was analyzed. A positive reaction to bencidine was observed in them. To establish the different polycarboxyl porphyrins, a highly sensitive thin layer chromatographic method was used.

Porphyrins were found in each of the eight blackish calculi analyzed: ranged from 2.7 to 439.1 ng/mg of calculi (average 80.6 ng/mg of calculi). Two patterns of porphyrin were found: A) In four calculi, tetracarboxyl porphyrin (coproporphyrin) was the predominant porphyrin, as it is usually observed in normal urine. B) In the remaining four stones octacarboxyl porphyrin (uroporphyrin) predominates with less content of heptacarboxyl and tetracarboxyl porphyrins. This latter pattern is similar to that found in the urine of patients with chronic renal failure. Porphyrin concentration in one of the black calculi (439.11 ng/mg calculi, mainly uroporphyrin) approached the values of porphyrin accumulation found in the liver of patients with hepatic porphyria cutanea tarda (about 200–400 ng/mg tissue) and in rats with hexachlorobenzene-induced experimental porphyria (about 500 ng/mg tissue). Porphyrins were not detected in four control calculi composed of oxalate, struvita or cystine. The source of porphyrin content in blackish renal calculi remains unclear. However, the possible origin of porphyrins from haematuria associated with urolithiasis seems unlikely since the dicarboxyl protoporphyrin (the almost only porphyrin present in red blood cells) could not be detected in these stones.

II. Examination Methods

27 The Measurement of Plasma Oxalate and When This is Useful

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A method for measuring plasma oxalate has been developed from a published Auto Analyser method for urinary oxalate. It is shown that ascorbate in the plasma spontaneously converts to oxalate and precautions must be taken to prevent this. The normal range is 1–3 μmol/l. In chronic renal failure plasma oxalate rises and falls with the plasma creatinine. Plasma oxalate levels are always raised out of proportion to the creatinine in primary hyperoxaluria. Measurement of plasma oxalate is particularly useful: 1. For recognition of primara hyperoxaluria in infants and children and in any other patients where urine is not available. 2. For identifying patients at risk of developing oxalosis. 3. In helping to prevent oxalosis in renal transplants.

28 Experience with an Enzymatic Method for Determination of Oxalate in Urine

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For several years we have been determining the oxalate concentration in urine by an enzymatic method which was originally employed by Beutler et al. for oxalate determination in fruit juices. In doing so oxalate is first of all transformed at a pH of 5.0 into formate using oxalate decarboxylase. In a subsequent reaction the formate is dehydrated to hydrogen carbonate by formate dehydrogenase with NAD^+. The NADH which has formed is measured by the increase in extinction at 365 nm. In order to recover reasonable quantities, excessive amounts of oxalate decarboxylase and formate dehydrogenase must be used. In our test series the rate of recovery was around 80%. The reliability of the method was regarded as being very good with a variation coefficient of VC = 3.8%. In many cases urine is treated with thymol for preservation purposes. Thymol must not, however, be added to those urine samples in which the oxalate concentration is to be determined by the method described above since this substance inhibits oxalate decarboxylase. Unlike citrate, oxalate does not appear to be broken down by the bacteria contained in urine, Since, however, both oxalate and citrate were normally determined in the sample penicillin/streptomycin sulphate is used for preservation of urine samples collected over 24 h. Oxalate determination is not affected by either of these substances. We discovered, however, that in many cases urine contains inhibitors of both of the enzymes concerned, which can lead to false, low oxalate concentrations. Extraction of urine with ether carried out before determination of the oxalate concentration removes these inhibitory substances and the oxalate concentration after ether extraction was raised on average by a factor of around 1.8. The inhibitory substances seem to be unstable in the presence of acids. They can evidently be removed either by briefly boiling the urine which has previously been acidified to a pH of 2 or by leaving the acidified urine sample to stand at room temperature for at least 12 h. By using our methods we achieved the following standard values.

In 31 adults the eliminated oxalate/24 h was 18.2 ± 11.5 mg. In 30 children it was 13.4 ± 3.3 mg. There are further short reports on experiments carried out to determine the oxalate concentration in urine using oxalate oxidase. This method was too complicated and the results were not satisfactory.

29 In Vitro Formation of Oxalate in Urine

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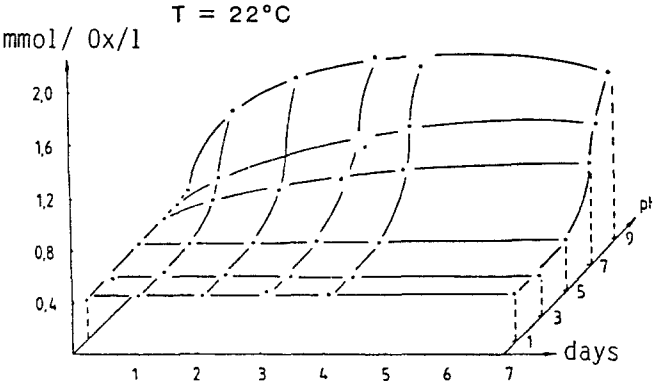
Urine has often to be stored for at least 24 h. During storage at room temperature the oxalate concentration in urine of normal pH increases remarkably. After two days the oxalate concentration is twice the initial value. The oxalate increase is even enforced by elevated excretion of ascorbic acid. This in vitro formation of oxalate in urine can be avoided by freezing the samples or by acidification to pH 1.

To measure the oxalate concentration a new method has been applied, which was developed in our laboratory: decomposition of oxalate by a decarboxylase, CO_2-measurement by isotope dilution in a mass-spectrometer, coefficient of variation within the series 3%, between the series 6%, linearity better than ± 3% (0–4 mmol/l), recovery 97–104% (0.5–3 mmol/l), specificity tested for 52 urinary compounds.



30 Stability of Urinary Oxalate*

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Measurement of urinary oxalate poses unsolved problems concerning the stability of oxalate during various conditions of storage, such as temperature, duration, pH, and the amount of non-oxalate substances present in urine. Using the anion chromatography technique (DIONEX 2000i), a method found reliable for oxalate in urine (Manoharan M et al, Fortschr Urol Nephrol, in press) we re-evaluated oxalate in samples, as obtained from 10 healthy volunteers by spontaneous bladder voiding. One aliquot from all samples was analyzed immediately. Three further aliquots were analyzed with delay, i.e. after prior storage, for 24, 48, 72 h at either room temperature, 4 °C, −30 °C, −80 °C. No acidification was carried out. It resulted (Table) that storage in general considerably impairs oxalate: increases at room temperature, a fall at both 4 °C and in the frozen state (−30 and −80 °C). The least alteration of oxalate is found with storage at −80 °C, suggesting that acurate results may be obtained from stop-frozen urine. Acidification (pH < 2.0) of urine either after bladder voiding (before storage) or after thawing (before analysis) helps to prevent some but not all drawbacks observed even with this chromatographic method.

	Storage induced per cent change ($\bar{x}$ ± SD) of oxalate[a]		
	24 h	48 h	72 h
Room temperature; $n = 10$	+3.31 ± 4.59	+4.59 ± 9.80	+11.70 ± 10.69
4 °C; $n = 10$	−0.72 ± 6.66	−7.77 ± 18.44	−18.86 ± 13.05
−30 °C; $n = 10$	+0.71 ± 4.94	−3.76 ± 13.21	−15.98 ± 10.63
−80 °C; $n = 10$	+1.35 ± 4.69	−5.94 ± 5.78	−2.81 ± 3.92

[a] versus oxalate in samples analyzed immediately

It is concluded that 1) substances accompanying oxalate in urine, most likely ascorbate, are converted in vitro to oxalate, thereby yielding falsely high oxalate in samples stored at room temperature; 2) oxalate losses occurring at lower temperatures due to precipitation in vitro of calcium oxalate may be prevented by deep-freezing urine soon after its collection, thereby circumventing the necessity of acidification; 3) urinary oxalate, especially in 24 h urine, in health and various disease states requires careful re-examination using adequate sample pretreatment and a reference method by which unspecifically introduced errors can be kept at a minimum.

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31 Circadian Biology of the Urinary Excretion of Calcium Oxalate, Phosphorus and Uric Acid in Renal Calculous Patients

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The formation of calcium oxalate stones is believed to occur in urine that is supersaturated with respect to calcium oxalate and/or has a low content of crystallization inhibitors. However, the prerequisities for crystal formation might be present only temporarily and thus, analysis of 24-h urine collection cannot account fully for the crystallization properties of urine. Thus, it is possible that a more detailed study of diurnal variation in excretion of urine constituents will provide a better estimate of the risk of stone formation. Such information will also be of value in designing prophylactic regimens.

Urine samples were collected in three-hourly fractions for 24 h from 15 patients with calcium-oxalate lithiasis. No dietary and fluid restrictions were imposed on them. The samples were analysed for calcium oxalate, phosphorus and uric acid. The data were analysed by the single cosinor procedure, and if the p-value of the t-statistics was ≤ 0.05, the fluctuation of the variable studied was considered to be cyclic. In the present set of renal stone formers there was no significant circadian rhythm in calcium oxalic acid and uric acid (calcium, $F_{2,5} = 2.260$; oxalate, $F_{2,5} = 0.20$; uric acid $F_{2,5} = 0.025$), while there was a statistically significant rhythm ($P < 0.05$) in the urinary excretion of phosphorus ($F_{2,5} = 7.29$). A similar study of circadian biology of urinary inhibitors will help to define the clear risk period for calcium oxalate stone formation and thus design appropriate therapeutic protocol. (This work was supported by a grant from I.C.M.R., New Delhi.)

32 Efficient Microdetermination of Urinary Citrate by Vertical Light Path Photometry in Microtitre Plates

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Introduction. Vertical light path photometry predominantly is used in enzyme linked immunological assays. Application to the determination of other substances like low molecular metabolites in clinical chemistry is rare. In the present work, the enzymatic assay for urinary citrate (Boehringer, Mannheim, FRG) has been adapted to a microtest in microtitre plates.

Experimental Conditions. Computer controlled pipetting station (TECAN sampler, Fa. Zinsser, Analytic) and microreader MR 600 (Fa. Dynatech). Measuring wavelength: 340 nm. Final sample volume: 300 µl per well in microtitre plates with 96 wells.

Results. Urinary citrate may be measured very efficiently using the device mentioned above. Compared with the macrotest used in "normal" horizontal light path photometry, 90% of the corresponding reagents could be saved. Manual work could be reduced to a minimum. RSD within series was smaller than 1.5%. There was an excellent agreement between the results from macro- and microtest measured by the different devices.

33 Valency of the UREA® Rapid Test for Identification of Urea-Splitting Bacteria

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In the formation of so-called infection stones (Struvite/Apatite) urea-splitting bacteria play an important part. A cristallisation of struvite and apatite is brought about by the alcalisation of the urine and hyperammoniuria. For the metaphylaxis the curing of urinary tract infections is necessary. In the investigation on hand the valency of the urease-rapid-analysis test, developed with the Temmler manufacturers was investigated on 423 strains of bacteria. We found that with this test about 30% of the strains were urease-positive, the conventional urease determination showed a positive reaction for 25%. With this rapid-analysis-test weaker urease formers showed positive reactions already when the number of bacteria was below a significant bacteriuria.

We found that the test is appropriate for daily use and still more sensitive than the conventional test.

34 Analyses of Zinc from Nutrient Media During the Growth of Urea-Splitting and Non-Urea-Splitting Bacterial Cultures – An Experimental Study

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Several research teams found high concentrations of zinc in phosphate stones. Different authors described in-vitro-experiments and animal experiments, in which urea-splitting bacterial cultures could be determined to be causing the formation of struvite stones. Moreover, it was especially *proteus mirabilis* that could be isolated from phosphate stones.

In a clinical study of 141 patients affected with urolithiasis, when we measured the concentration and the daily secretion of zinc in the urine, we observed 14 patients with struvite stones to have measuring results significantly lower than those of the other patients.

Experimentally we tested whether the increase of bacteria and the concentration of zinc were connected. In the experiment, we cultivated *proteus mirabilis, pseudomonas aeruginosa* and *e. coli* on different nutrient media, then watched the increase of the germs and determined the concentrations of zinc in the cultures at defined points in time. Measuring was carried out by means of atomic absorption spectrometry. We will give a report of essential partial results.

35 The Results of a Comparative Study of Infrared Spectroscopy and Chemical Analysis as Procedures for Analysing Urinary Stones

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The Problem. Knowledge of the composition of urine is a vital prerequisite for prophylaxis and therapy. In order to assess the true value of the information provided by analysis sets when analysing urinary stones a quality check was made using infrared spectroscopy as a reference method and the results evaluated according to a points system.

Material and Methods. 120 analyses were conducted in each case using three different chemical analysis sets and IR spectroscopy:

1. Merckognost
2. Temmler Diagnostika Reagent Set "Harnsteinanalyse" (urinary stone analysis)
3. Reagent Pack "Harnsteine" (Biotech GmbH)
4. Infrared spectroscopical analysis

The results achieved by the chemical methods were compared to those gained by the reference method and were evaluated according to a system of points.

The percentage of correct results obtained using the chemical sets displayed little variation, lying between 57 and 60%. These figures were slightly better for one- and two-component stones, but lay under 50% for three-component ones. The sets displayed different degrees of sensitivity in detection, and in the case of one- and two-component stones, they produced results in different ranges, too.

Conclusion. Chemical analysis of urinary stones can only be used in the sense of a useful screening test for routine laboratory testing, and the limitations of these methods must be taken into account when assessing the results obtained. A physico-chemical method such as infrared spectroscopy or X-ray diffraction should always be employed if a precise quantitative urinary stone analysis is required.

36 Methods to Explain the Structures of New Renal Stone Components

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37 An Experimental Model to Simulate Urodynamics in the Renal Collecting System

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The paper presents the problems in developing an experimental model to study physiologic or pathologic conditions of urinary flow in the renal collecting system. After a series of pilot tests we succeeded in developing a model which seems adequate both regarding the material as well as the mechanical conditions. The aim of the study is to simulate pathologic flow conditions and to study their role in pathogenesis of nephrolithiasis.

38 Evaluation of Crystallization Risk in Calcium Stone Formers

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The risk of calcium oxalate-crystallization (CaOx-CR) was measured in urine by determination of the increment in oxalate concentration required for formation of 100 crystals in the size range 3.5–5 μm. Similarly the risk of calcium phosphate crystallization (CaP-CR) was measured by alkalization. In 24 h urine both CaOx-CR and CaP-CR were slightly higher in stone formers than in normal subjects but not significantly different. Analysis of CaOx-CR in fractions of a 24 h urine suggested that a collection between 6.00 and 10.00 h might be more informative than a 24 h urine sample. Analysis of calcium, oxalate, citrate and magnesium showed a good correlation between 4 h and 24 h urines. Determination of CaOx-CR in 4 h urine samples from normal subjects, and patients with different types of stones showed clinically important differences.

39 The Relation Between Chemical Composition and Crystallization Conditions in Whole Urine of Calcium Stone Formers

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Most information on crystallization conditions in urine is derived indirectly from computer calculations and from experiments carried out in saline solutions or in highly diluted urine.

This study, in which preliminary results will be presented, is based on the direct measurement of the state of urinary saturation with respect to brushite and calcium oxalate monohydrate by equilibration experiments done in whole urine. As a measure of urinary inhibitor capacity the minimal supersaturation necessary to induce crystal growth of a small amount of calcium oxalate monohydrate was determined. Urine was analyzed for pH, calcium, magnesium, oxalate, phosphate, uric acid, citrate and pyrophosphate. Chemical analyses and physico-chemical tests were performed in 76 whole urines from 19 idiopathic calcium stone formers. Urinary composition was varied by the application of 4 diets with different calcium, oxalate, magnesium and fluid intake.

The data of chemical analyses and of physico-chemical studies are now evaluated by regression analyses. In addition, the effect of some components is tested by repeating the measurements of the state of saturation and of inhibitory capacity in saline solutions.

40 Measurements of Inhibitory Activity in the Urine of Calcium Oxalate Stone Formers

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A major disadvantage of nearly all methods for the study of crystal growth kinetics is the fact that diluted urine (1–5%) has to be used. The purpose of this study was to improve the constant composition

approach and measure the inhibitory activity in whole urine. 9 men with no history of stone disease and 12 men with recurrent CaOx stone disease were studied. After an overnight fast (5 ml distill. H_2O/kg at 10 pm) the freshly voided morning urine was centrifuged and filtered through a 0.22 µm Millipore filter. 50–70 ml of the filtrate were run through a cation exchange column (Lewatit SP1080, 50–150 mesh, Na-form) approximately 10 ml of the elute were discarded, the rest used for further experiments. To 25 ml of the filtered urine thermostated at 37 °C 3.33 ml of 0.005 molar $CaCl_2$ and $Na_2C_2O_4$ solutions (made up to 0.150 ionic strength with NaCl) were added. The Ca^{++} activity was brought to a predetermined level by addition of 0.1 molar $CaCl_2$ solution. 0.3 ml of a suspension of standardized CaOx monohydrate-crystals were added and the crystal growth rate measured by the constant composition approach. The supersaturation of the crystallization system is maintained constant by the addition of solutions containing the crystal lattice ions. This addition is controlled potentiometrically by means of a calcium-ion selective electrode. After 10–20 min 0.1 ml polyacrylic acid solution (PAA) 0.008 mg/ml were added and the crystal growth rate recorded for another 10–20 min. The inhibitory activity of a urine sample was measured on a relative scale by the quotient of the slopes after and before the addition of PAA. 11 of 12 recurrent CaOx stone formers showed a relative inhibitory activity of less than 50% whereas all urines of normal persons exhibited an inhibitory potential of more than 50%. Measurements in concentrated urine (90–95%) are much more sensitive to differences in the inhibitory potential compared to those in diluted urine. By this method one gets an excellent discrimination between recurrent CaOx stone fomers and normal persons.

41 Experience with the Gel Crystallization Method (GCM): Clinical Routine Measurement of Calcium Oxalate Crystal Growth Rate in Undiluted Urines

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Introduction. The GCM (Achilles et al. 1979, 1983, 1985) is a highly efficient photometric micromethod which allows the determination of relative crystal formation rates (Vcr) of calcium oxalate in gels by diffusion of calcium containing solutions into a gel matrix containing oxalate and seed crystals. In order to evaluate appropriate conditions of measurement for native undiluted urines, Vcr-values were measured using different gels and after different treatment of urine samples. Extended clinical routine measurements were carried out.

Experimental device. Computer controlled microscopic photometer equipped with 50 µm step scanning stage adapted for microtitre plates (Zeiss, Oberkochen, FRG).

Mode of measurement. Dark field. Efficiency: 150 kinetics/h.

Results. 3 gels (agar-agar, 2 sorts of agarose; SERVA) out of 7 were found to provide results of very good reproducibility (R.S.D. within series: 1–2%). Measuring values from different gels agreed very well.

In most cases, pretreatment of urine samples, except centrifugation, was not necessary before measurement. In some urines, falsely negative values were found caused by precipitation of calcium containing salts. This could be overcome by acidifying and subsequent neutralization to the original pH value.

Establishing "normal" pH, total calcium and magnesium concentration in native urines after a special ion exchange procedure and subsequent substitution of the corresponding cations resulted in subnormal Vcr-values thus demonstrating the presence of additional inhibitors in comparison to a corresponding "normal" artificial urine (= standard solution).

The gel crystallization method has been proved to be very useful in controlling the efficacy of prophylactic measures in calcium oxalate urolithiasis.

III. Therapy

42 The Use of EQUIL-2 in the Clinical Management of Patients with Stones

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Supersaturation for the precipitating crystalline phase must be present in urine where crystalluria and stone formation are occurring. To estimate the state of saturation for the important stone forming crystals in a complex biological solution such as urine requires multiple complex calculations. The major ion species and pH of the urine need to be measured, ionic strength must be calculated, and the effect of complexation taken into account. From this, free ion activity can be estimated allowing the calculation of activity products and supersaturation. EQUIL-2 makes these calculations possible (J Urol (1985) 134:1242–1244).

It calculates supersaturation for calcium oxalate monohydrate, brushite, hydroxylite, struvite, uric acid, sodium urate, ammonium urate, and potassium urate. It also provides a calculation for ΔG which is the Gibbs free energy of transfer from a supersaturated to a saturated solution. The ability of the program to predict calcium oxalate supersaturation in vitro was tested by equilibrating various solutions with calcium oxalate monohydrate crystals for 24 h at 38 °C. The performance of the program in predicting hydroxyapatite crystal formation was tested in patients with primary hyperparathyrodism who had hydroxyapatite crystalluria. The average supersaturation of solution equilibrated with calcium oxalate crystals was 1.01 ± 0.07 SE (theoretical value is 1). In testing hydroxyapatite there was an excellent correlation ($R = 0.84$) between estimated supersaturation and crystalluria in the patients with hyperparathyroidism.

In the clinical application of EQUIL-2, three potential uses have been identified all relating to its ability to account for multiple abnormalities or changes in a complex solution. These include: 1) identification of the net effect of multiple abnormalities in urine, e.g. enteric hyperoxaluria; 2) determination of multiple effects of treatment, e.g. potassium citrate; and 3) individual patient monitoring for workup and treatment. Since the major effect of most forms of treatment is on supersaturation, examples of these uses will be presented.

43 Effects of Water-Diuresis on the in Vitro Calcium Oxalate Tolerance

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8 healthy people were kept on a limited fluid intake of 1,000 ml/day for three days followed by a three day period of water diuresis with a daily fluid intake of 3,000 ml.

Urinary volume, calcium, oxalate, uric acid, citrate and osmolality were measured. The in vitro calcium oxalate tolerance was determined by a simple photometric procedure.

The results of the latter did in no way correlate to the above mentioned parameters. Neither was there a correlation to the calcium-citrate-index. The results will be discussed. The feasability of in vitro calcium oxalate tolerance tests to determine the individual urinary lithogenity is critically analysed.

44 Effects of Drinking Cures on the Water and Electrolyte Excretion in Renal Stone Formers

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The balneologic treatment of urolithiasis traditionally includes drinking cures with natural mineral waters, e.g. Ca-Mg-HCO_3-waters. Be-

cause of the increased nightly risk of stone formation (cf. Vahlensieck et al. 1982) we examined in a first study the influence of two Ca-Mg-waters on the circadian variations of the urinary volume and composition in two groups of 8 healthy male subjects under equally distributed food intake. Comparing the nightly Ca- and Mg-concentration after drinking 4 portions of 350 ml of mineral water with the concentration values after the same amounts of tap water the Mg-concentration was significantly increased ($\bar{x}$ = 3.95 mmol/l; s_M = 0.24 versus $\bar{x}$ = 2.91 mmol/l; s_M = 0.25; n = 16; $p < 0.01$). The increase of the Mg-concentration exceeded the increase of the Ca-concentration ($\bar{x}$ = 6.05 mval/l; s_M = 0.50 (mineral water), $\bar{x}$ = 5.31 mval/l; s_M = 0.61 (tap water), n = 16; n.s.^{M}).

In a second study we examined the influence of 4 week-drinking cures in 37 patients with the admission diagnosis of recurrent urolithiasis (26 calcium-oxalate-stones, 2 urate concrements, 1 mixed stone and 8 patients without stone analysis). The balneologic treatment of these patients included drinking cures with 3 x 200 ml/day of a Ca-Mg-HCO_3-CO_2-water from the 3rd to the 26th day. Urine probes were collected every night from 23.00 to 7.00 h. The urinary volume only showed a passing increase in the first week of the drinking cure whereas the urate concentration, the phosphate concentration and the calcium-magnesium-quotient were significantly reduced in the course of the treatment. The urate concentration values before the drinking cure showed a wide variability (VC = 21.4%) which was significantly decreased after the drinking cure (VC = 11.3%; $p < 0.001$) then coinciding with a group of 67 healthy test persons. This result is interpreted as a normalisation of the nightly urate concentration. In addition phases of increased urate concentrations occurred in the course of the treatment. The frequency of these maxima showed a characteristic circaseptan (about 7 days) periodic time structure. The normalisation of a parameter and its circaseptan periodicity represent characteristic features of functional adaptive cure processes (Hildebrandt 1985).

45 Is Beer Suitable for the Prophylaxis of Urinary Stone Disease?

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A change in dietary habits, especially an increased fluid intake, is the primary treatment for the prophylaxis of renal stone disease.

The purpose of this study is to assess the effect of different kinds of beer on the excretion of lithogenous and inhibitory in normal persons and stone forming patients.

The examinations were carried out with 43 healthy volunteers drinking different types of beer (16 Pils beer, 14 "Weizen" beer, 13 alcohol-free beer) and 7 patients with a history of stone formation, who consumed only "Weizen" beer.

After evaluation of the normal values in serum and 24 h urine the volunteers ingested 1,500 ml beer/day for 4 days. Blood and urine were analyzed before the beer intake, immediately after having drunken beer for 4 days and 3 days thereafter.

Results. 1) Differences in the total concentration of nucleosides and nucleic bases in the different kinds of beer did not influence uric acid excretion. 2) Uric acid excretion was 4 times higher in the stone forming group as compared to the controls. 3) Typical stone risk factors as an increase of uric acid, oxalic acid or an decrease of citric acid concentration could only be observed following the ingestion of alcoholic beer. Alcohol-free beer has no negative influence on urine composition.

46 The Results of an Empirical Experiment to Determine the Influence of Various Types of Beer on the Composition of Urine

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The Problem. The diuretic effects of beer and its influence on urinary pH-value are still providing grounds for its recommendation in urinary stone metaphylaxis. Although the consumption of alcohol is viewed with reserve, the number of studies conducted as yet into the effects of beer on urinary composition is small. Hence our investigation of the effects of three types of beer on diuresis, pH-value and electrolytes in urine.

Material and Methods. Three types of beer (Kölsch, Pils and soft (non-alcoholic) beer) were tested on 9 healthy male test subjects under standardised conditions of diet and a fluid intake of 2.4 litres per diem. On the day of the test, as opposed to the control day, 1 litre of this fluid intake was replaced by beer. Urine was collected at 2- to 3 hourly intervals throughout the 24 h, and the urolithic parameters were determined for each interval.

Results. After the consumption of alcoholic beer (Kölsch, Pils) an initial intensification of diuresis was recorded, which was then followed by a compensating "rebound" phase displaying peaks of concentration. Directly after drinking 1 l of Kölsch, the *oxalic acid* concentration in the urine, at 0.087 mmol/l, lay significantly below the comparative value of 0.161 mmol/l and was accompanied by intensified diuresis. Four hours later, the oxalate concentration in the urine increased significantly.

The peak *uric acid* concentration of 2.794 mmol/l was also recorded 4 h after consuming alcoholic beer (control value: 1.009 mmol/l). The peaks of concentration arising under the influence of alcoholic beer levelled off in the 24-h urine. On both days of the experiment the uric acid excretion level lay at 2.675 (without beer) and 2.705 mmol/l (with beer). No significant difference from the control day (1.862 and 1.947 mmol/die) was detected in the *citrate* concentration either over the 24 h or in the urine collected under the influence of Kölsch. After consuming soft beer, a so-called water-diuresis occurred in which the peaks of concentration, analogous to those found when drinking water, were levelled off by a more persistent reduction in diuresis. The circadian course of the urolithic parameters on the day of the test did not differ significantly from that displayed without soft beer. Pils and Kölsch tended to acidify the urine, whereas soft beer induced no changes in pH-value.

Conclusions. Their alcoholic content should perclude the employment of Pils and Kölsch as stone prophylactis. Our measurements revealed that alcoholic beer has no significant effect on pH-value, and also that no beneficial, evenly distributed dilution of the urine is achieved with them. Alcoholic beer should only be drunk for pleasure. In contrast to this, soft beer does provide a suitable alternative as our investigations showed that it achieved good dilution of the urine over the whole course of the day.

47 Experimental Investigations of the Effects Produced by a Bulk-food Preparation on the Composition of Urine

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The Problem. Individual constituents of bulk foods are able to bind specific ions. It has also been shown that, by curtailing the passage times, a diet rich in bulk can reduce absorption. These two findings formed the basis for our concept of administering a variety of brans to patients suffering from Ca-oxalate stones.

Material and Methods. The bulk food contained wheat-, malt- and soya-brans (1 : 1 : 1) with the addition of dipotassium tartrate, magnesium oxide, iron fumarate and zinc oxode. The 24-h urine of 10 healthy test-subjects (5 females, 5 males) was investigated daily under conditions of both uncontrolled and a standard diet rich in oxalate with and without the addition of the bulk preparation. All relevant urolithic parameters were determined.

Results. Under both conditions – uncontrolled and standard diet – a significant rise in pH-value was recorded, with a parallel increase in citric acid excretion. The preparation also resulted in a significant

drop in Ca excretion, and a reduction in uric acid excretion. Calculation of the relative supersaturation from all the parameters measured revealed that the risk of uric stone formation was reduced under both conditions of diet.

Conclusion. According to the results of this investigation conducted on healthy test subjects, the administration of the bulk-food preparation induced such a change in the composition of the urine that the risk of urinary stones forming was reduced.

48 Calcium Metabolism Under Therapy with Farnolith in Patients with Hypercalciuria and Normal Persons

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Farnolith is a new kind of preparation based on plants which by linking calcium and oxalic acid in the intestines reduces the resorption of these substances. Its administration seems to be apt for patients with absortive hypercalciuria of type I (according to Pak). These patients have so far been given sodium-cellulose-phosphate; this, however, often resulted in a secondary unwanted increase in the oxalic acid excretion in the urine. There are no investigations on hand at the moment, however, to fully explain the results of the application of this substance on calcium metabolism. We have been investigating patients with hypercalciuria and normals on calcium metabolism (ionized calcium, total calcium, parathormone, 1.25 vitamin D and calcium excretion).

After 4 weeks of administration no significant alterations were found in the calcium metabolism but a reduction of the calcium excretion only. We shall present the results of long-term therapy on the occasion of the Symposium.

49 Influence of L-Methionin on Urinary pH and Excretion of Stone-Relevant Parameters in Urine

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Struvite and carbonate-apatite-stone formation is due to the alcaline urinary pH. Alcalinization of urine mostly will be promoted by urinary infection with urea splitting gram-negative bacterias. The most important therapeutic measurement is – in addition to antibiotics – the acidification of urine (e.g. L-Methionin). With the present investigation we would intend to measure the influence of L-Methionin on lithogenic and inhibitoric substances in urine which was never done before.

Material and Method. In 12 healthy test persons (6 ♀, 6 ♂) the 24 h urine was collected and investigated under standardized nutrition. The first three days no medication was given. From the fourth to the tenth day of investigation 3 x 500 mg L-Methionin was administered. At the third and fifth day of investigation the circadian rhythm of stone-relevant parameters was determined. Following parameters were measured: pH, urinary volume, Na, K, Ca, Mg, Cl, SO_4, PO_4, NH_4, oxalic acid, uric acid, citric acid and creatinine. The relative oversaturation was calculated for calcium-oxalate and struvite.

Results. The urinary pH was significantly lowered by L-Methionin (from 6.3 to 6.07) without reaching unphysiological ranges. The excretion of Ca, Mg, uric acid, oxalic acid, PO_4 and citric acid decreased slightly whereas the SO_4 – and NH_4-excretion increased significantly. Serum concentrations of all parameters remained not influenced. The calculation of the relative oversaturation was normal as well as the circadian rhythm of all measured parameters.

Conclusion. L-Methionin is able to acidify the urine in physiological ranges. No pathological excretion of the stone-relevant parameters in the urine was observed.

50 Citrate and Intestinal Calcium Absorption (CaA) – in Situ Perfusion Studies in the Rat

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Citrate (C) forms stable and soluble calcium (Ca) complexes. It lowers the urinary activity products of Ca-containing stone phases and serves as an anti-stone drug in human urolithiasis. Since data on intestinal citrate absorption and the influence of oral alkali citrate on intestinal CaA are lacking, we studied the bidirectional fluxes (LP, lumen-to-plasma; PL, plasma-to-lumen) and the net absorption of Ca under progressive doses of C als well as the disappearance rate of C in the duodenum of the rat, using in situ perfusion [1].

Male Sprague-Dawley rats, mean B.W. 275 g, were fasted overnight. The duodenum was perfused at a rate of 12 ml/h with a solution containing 50 ml/l phenol red (a non-absorbable volume marker), 40 μCi/l ^{45}Ca and 4 mM $CaCl_2$, 160 mM NaCl, 25.4 mM KCl (vehicle; V1, V2) or two progressive doses of C which were obtained by replacing KCl by tri-potassium citrate (+ 8.22 mM C; dosis 1) and additional replacement of NaCl by tri-sodium citrate (= 33 mM C; dosis 2). Solutions were adjusted to pH 6.25 (V1; dosis 1, 2) or pH 5 (V2, dosis 2).

At pH 6.25, net CaA (μM Ca/g mucosal dry weight/h) in the V1 group was 65 ± (1 SEM) 6.2 and fell to 43 ± 4 (dosis 1; $p < 0.001$ vs V1, t test) and 13 ± 3 (dosis 2; $p < 0.0001$ vs V1). At pH 5, net CaA was 75 ± 4 (V2) and 20 ± 3.4 (dosis 2; $p < 0.0001$ vs V2). LP-flux changes paralled net CaA changes, while the PL-flux was unchanged under any of the citrate groups when compared to the respective vehicle group.

Citrate disappearance was 11.4% (pH 6.25) and 16.5% (pH 5; $p < 0.05$ vs pH 6.25) of the delivered citrate load under dosis 2 and 24.9% under dosis 1 (pH 6.25). Preliminary data from portal vein blood indicate that these disappearance rates are mainly due to intestinal absorption.

Conclusions. 1) Duodenal CaA is inhibited by citrate in a pH- and dose-dependent manner, indicating that absorption of the Ca-citrate complex is unlikely; 2) one might speculate that a larger portion of the citrate delivered to the intestinal mucosa is absorbed, $[citrate]^{2-}$ being the preferentially absorbed citrate anion.

1. Engelhardt W, Rümenapf G, Schwille PO (1984) Mineral Electrolyte Metab 10:239–243

51 A Physicochemical Explanation for the Role of Citrate in Recurrent Stone Disease

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There is growing evidence that there is a causal relation between a tendency to form calcium oxalate monohydrate (C.O.M.) stones and low levels of urinary citrate excretion. In addition, recent data suggest that an elevation of citrate excretion with administration of citrate salts, is beneficial in C.O.M. stone disease. There is, however, no physicochemical explanation for the role of citrate apart from its known effect on C.O.M. solubility, which is not sufficiently large to explain its beneficial influence. Last year we demonstrated that urine from healthy persons has a strong inhibitory action not only on the growth but also on the agglomeration of C.O.M. crystals. We identified a group of urolithiasis patients in whom the recurrence rate was excessive and we found an isolated defect in the ability to inhibit agglomeration. This defect appeared to be associated with hypocitraturia.

We have now studied the effect of treatments aiming at increasing citrate excretion in six normocalciuric and two hypercalciuric patients with hypocitraturia (1.4 ± 0.38 mmol/24 h, mean ± SEM) and defective inhibition of agglomeration (t_m 76.1 ± 8.5 min^{-1}).

Administration of citrate or bicarbonate salts for periods between 6 and 24 months resulted in a significant increase in urinary citrate excretion (3.68 ± 0.32 mmol/24 h) accompanied by an improvement in the ability to inhibit C.O.M. agglomeration (186.8 ± 38.4 min^{-1}) which reached the normal range in 5 patients.

We have therefore, confirmed in vivo that a relationship between citrate excretion and crystal agglomeration exists. These results allow us to better define the various factors involved in this relationship and to optimize the effect of citrate on agglomeration inhibition.

52 The Effect of Alkalinizing Agents on the Growth Kinetics of Calcium Containing Precipitates in Human Urine

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Introduction. The gel crystallization method (GCM; Achilles et al. 1979, 1983, 1985) has been used to evaluate the effect of different agents (alkali citrates, sodium bicarbonate) on the relative crystal growth rate and calculated supersaturation of calcium oxalate hydrates and other calcium induced precipitations in human urine.

Experiments. Determination of parameters of crystal growth and concentrations of urinary constituents in 2-h urine fractions of normal persons without and with oral application of alkalizing agents under controlled diet. Parameters of oxalate and calcium induced crystallization or precipitation have been quantitatively measured using computer controlled microphotometry.

Results. While calcium oxalate crystal growth rate as assayed by the GCM could be significantly reduced by raising urinary pH and citrate, risk of calcium carbonate and calcium phosphate formation increased markedly at higher pH values.

Conclusion. Alkalinization of urine as a potential prophylactic measure in calcium oxalate urolithiasis should therefore be limited to an upper pH values of 6.5–6.7.

53 Oxalyt C Prophylactic Therapy in Patients with Recurrent Calcium Oxalate Stones

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The objective of our study was to prove the effect of a sufficient citrate concentration in urine to reduce the frequency of calcium oxalate stone formation as referred by Butz. "Oxalyt C" was used as a substrate. Calcium will be bound and kept in solution if a sufficient amount of citrate can be found in urine.

8 patients with stone recurrences in a range of 1 to 14 were treated over 18 months. During and after the treatment the patients remained stone-free. The insignificant side effects were tolerated by all patients.

Biochemical Changes. In the urine of all patients a significant increase of citrate reaching its highest level in month 9 to 15 was found. The pH of urine was adjusted to 6.8 and 7.4. In 50% of the patients a significant decrease of urinary calcium excretion was noted. In 25% of the patients this effect was only present during the treatment period; at the end of the therapy, however, hypercalciuria was found again.

Plasma. No significant alterations of sodium, potassium and calcium were noted. In seven patients the uric acid was remarkably lowered, in one it increased. "Oxalyt"-therapy can be recommended for motivated patients having a relatively high stone-forming rate and an inability of sufficient fluid uptake.

54 First Long-Term Results of Oxalate Stone Prevention by Alkali Citrate

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30 recurrent oxalate stone formers are treated with potassium-sodium-citrate (Oxalyt C^R) for a mean period of 38 months (range of 8–69 months).

The average daily dose is 10 g Oxalyt-C. Quarterly chemical analyses of 24 h urinary samples reveal a constantly increased citrate excretion (+93%) and a decreased calcium excretion (–27%). According to the biochemical base of these findings tachyphyllaxy does not occur. Every 6 months kidneys are examined either by X-ray or ultrasound.

With onset of therapy 6 patients had multiple stones, which did not grow during therapy. Long-term compliance is good, only 3 patients (10%) stopped therapy because they developed reluctance to the taste of the drug. Relapse occurred in 8 cases with a significant decrease of stone incidence in 3 cases. Serious side effects were not observed, so far 74% remained stone-free.

55 Primary Hyperoxaluria, the Effect of Long-Term Treatment

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In 1964 Hockaday et al. (Medicine 43:315, 1964) summarized the world's literature on primary hyperoxaluria identifying 64 patients at that time. Thirty-four (53%) of the patients were dead with a mean age at death of 13.6 years making this condition the most malignant of the disorders complicated by urolithiasis. In 1966 we began a treatment trial in patients with type I primary hyperoxaluria including pyridoxine and orthophosphate. Fourteen patients have been seen for long-term follow-up with 13 patients on the treatment program. The mean age at onset of symptoms was 11.4 ± 2.3 years. The mean time of total follow-up is 13.1 ± 1.5 years. The mean time of treatment in the 13 patients has been 12.4 ± 1.3 years. Before treatment 14 surgical procedures had been done in 10 of the patients including 4 nephrectomies and 1 cadaveric transplantation. On treatment five surgical procedures have been done in 4 patients, four of these were for old stones that had not grown on the treatment. One patient, age 53, has never formed stones and has normal renal function – she is receiving no treatment. Of the 13 patients on treatment 12 have had complete control of their stone formation with stable or improved renal function. One patient has had slow progression of stone formation with loss of renal function. Treatment reduced the urinary excretion of calcium, oxalate, magnesium, and crystalluria; it increased urinary excretion of phosphate and pyrophosphate along with the urine pH. These changes resulted in an increase in hydroxyapatite and calcium oxalate inhibition and a decrease in calcium oxalate supersaturation. The net effect of this treatment program has altered the natural history of primary hyperoxaluria in these 13 patients.

56 The Significance of Xanthine Excretion in Allopurinol Therapy

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The Problem. The aim was to discover whether Allopurinol therapy caused such high concentrations of xanthine in the urine that they might lead to the formation of urinary calculi. To this end, an investigation was conducted into the xanthine concentrations in the urine of healthy test-subjects after the oral administration of Allopurinol in various forms of galenic preparation.

Material and Methods. Under conditions of standardised diet, 14 test subjects were each given a single dose of 300 mg of Allopurinol, and 12 subjects were each given 300 mg of Allopurinol, on 5 conse-

cutive days. After the single dose, urine was collected at 3-h intervals over a period of 24 h, and after the multiple dose it was collected in two 12-h batches. Measurement of the xanthine concentrations in the urine was effected using high pressure liquid chromatography.

Results. After the single dose of Allopurinol none of the test-subjects displayed any critical concentration of xanthine in the urine. The peak values recorded lay around 0.686 mmol/l. Where repeated doses of Allopurinol were administered, 3 subjects displayed brief xanthine concentrations of up to 2.24 mmol/l, which greatly exceeds the solubility of xanthine in urine (at pH 7 = 0.855 mmol/l).

Conclusion. The study revealed that during Allopurinol therapy xanthine concentrations appeared in the urine which exceeded the solubility curve. However, no cases of xanthine stone formation during the course of Allopurinol therapy have been reported to date.

57 Testosterone Under Allopurinol Treatment

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It was reported that allopurinol may cause a decrease of serum testosterone (Graef et al. 1984).

We measured testosterone in 69 stone patients without and 75 under allopurinol treatment (300 mg/die, > 1–15 ys.) and found no statistical differences. P.e. the values in the group of 45–65 years old patients: 5.3 resp. 5.6 ng/ml.

In a follow-up 13 patients were examined over a period of 3–6 months. 11 out of them over 1.5–2 years. Testosterone levels before and after 1.5–2 ys. treatment: 5.9 resp. 5.6 ng/ml, $p > 0.4$. Thus, our study gives evidence that serum testosterone is not expected to be influenced by long-term allopurinol treatment.

58 Excretion of Pyrophosphate and Other Urolithiasis-Relevant Substances in Patients with Calcium Oxalate Hydrolithiasis Under Orthophosphate Therapy

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The application of orthophosphate for the metaphylaxis of patients with calcium oxalate stones is discussed very often. Two different mechanisms of action are attributed to this therapy: 1) increased excretion of pyrophosphate in the urine and thus improved solubility of calcium oxalate; 2) reduction of calcium excretion in the urine by lowering the 1.25 dihydroxycholecalciferol level.

We have thus been examining the effect of orthophosphate therapy (Reducto^R equal to 1.2 g orthophosphate/day) on patients with calcium oxalate stones. Besides lithogenic substances the excretion of pyrophosphate in 24-h-urine was determined. Our method of determination (pyrophosphatase, Boehringer, Mannheim GmbH) and our results are presented. Indication and valency of orthophosphate therapy are discussed.

59 Pentosan Polysulphate (Elmiron®): Pharmacokinetics and Effects on the Urinary Inhibition of Crystal Growth

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Pentosan polysulphate (PPS) is a semisynthetic low-molecular weight polysaccharide with characteristics similar to sulphated glycosaminoglycans. Using an autoradiographic technique it has been shown that PPS becomes accumulated in the urinary tract of the rat. Experimental data have also indicated a potential of PPS in the treatment of interstitial cystitis and renal stone disease, provided that the drug is excreted in the urine.

Methods. Eight healthy male volunteers, ranging in age from 30–46 years, and in weight from 64–99 kg, gave their informed consent to participation in the study. On one study day, after an overnight fast, 40 mg PPS was administered as an i.v. bolus (one minute) injection. Two weeks later a multiple-dose regimen was initiated over a 21 day period. Thereby 400 mg dose was administered once daily. PPS in plasma and urine was determined by a sensitive competitive binding assay for exogenous and endogenous heparins. Non-linear parameter disposition estimation was performed by the method of extended least-squares using the computer program ELSFIT. The inhibition of calcium oxalate crystal growth in urine was measured with a method, where the rate of crystal growth was calculated from the uptake of isotopic oxalate into the crystals.

Results. The PPS data could be fitted to the two-exponential equation. $T^1/_2$-α averaged 24 min (range 19–32) and $t^1/_2$-β 40 h (29–69). Peak plasma levels after PPS i.v. ranges 9–13 μg/ml and declined rapidly (2-h value ≅ 5% of peak value). However, one week later PPS was still detectable in plasma (22–50 ng/ml). The volume of distribution averaged 1.5 l/kg. Total body clearance averaged 32 ml/min. 24-h urinary recovery of unchanged drug was 8%. The bioavailability was low, with average values after three weeks of around 50–60 ng/ml and an urinary excretion of 60–100 μg/24 h. The inhibition of crystal growth of the urine increased in 6/8 subjects, both by i.v. and by oral administration of PPS. The mean increase was 18% at steady state on oral administration.

Conclusion. At intravenous administration of PPS there is a rapid initial drop in the plasma concentration of PPS, followed by a slow elimination phase. The fractional gastrointestinal absorption is low, but yields detectable levels of PPS in the urine and a parallel increase of the urinary inhibition of calcium oxalate crystal growth.

60 Glycosaminoglycans and Renal Stone Disease: Clinical Effects of Pentosan Polysulphate (Elmiron®)

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Renal stone formation is basically a consequence of an imbalance between supersaturation of the urine and its inhibition of crystal formation and growth. Glycosaminoglycans (GAGs) including heparan sulphate (HS), chondroitin sulphate (CS) and dermatan sulphate (DS) are naturally occurring in human urine. It has previously been shown in an experimental model that the inhibitory potential of GAGs is dependent on the degree of sulphation, and that the inhibitory effect takes place because of the binding of the GAG to the crystal surface reversibly, whereby further crystal growth and aggregation becomes blocked. This prompted us to do the following study.

Material and Methods. So far 100 patients with recurrent renal calcium stone disease have been included and started medication with pentosan polysulphate (Elmiron®), 400 mg daily. In the initial 50 patients, who have been followed for more than 1 year, a follow-up has been made whereby stone recurrences and the stone operation frequency have been compared with the conditions prior to treatment. These 50 patients have been on treatment for 1–2.5 years.

Results. Four patients have undergone surgery of stones that had been formed prior to the PPS treatment. Twelve patients had continued to form stones or gravel, but judged by the intensity, the size of the stones and the degree of pain at stone passage, there was an improvement. Four of these patients also had an inflammatory bowel disease, whereby the gastrointestinal absorption of the drug could be questioned. Two of these four patients have experienced an improvement.

Conclusion. Experimental results favour the concept that PPS is a potent inhibitor of calcium oxalate crystal growth. Definite con-

clusions cannot be made as yet, because of fairly short time of follow-up, but the preliminary results seem promising.

61 New Stone Classification System to Validate Modern Stone Therapies (ESWL, PNL, URS), Transferable for Computer

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Problem. Due to the great variability of stone disease the validation of modern forms of stone therapy requires a stone classification scheme up to now not adopted to problems, taking into account above all the stone mass and the functional state of the urinary tract besides the stone localisation.

Methods. 1) The producing of a computer transferable documentation system (modified Roccosystem) to register stone localisation, size and number of stones as well as to judge the function of the kidney and the urinary tract with the help of a conventional IVP. 2) In-vitro examinations (n = 20) to evaluate the stone mass: a) determination of the stone volumes via displacement of liquid volumes serving as reference data; b) calculation of the stone volume by registering the stone planimetrically by a.p. and lateral x-rays of the stones; c) computer-supported verification of the correlation between real and calculated stone volumes to set up correction factors. 3) Investigation of the interindividual reproducibility of the stone classification system by 20 different stone constellations.

Results. a) Only by significantly modifying the Rocco-scheme the required stone classification can be achieved. The interindividual reproducibility ranges at > 95%. b) Planimetrically calculated stone volumes correlate with the real stone volume with a correlation factor of 0.99, if the calculation is based on an ellipsoid formula. Other calculations provide worse correlation factors.

Conclusion. The inaugurated stone classification system, for which a computer program can be written meets with the necessary conditions for the exact documentation of studies applying modern forms of stone therapies.

62 Laser Fragmentation of Ureteric Calculi

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A pulsed dye laser (Candela Corporation) has been used in bursts of pulses via a 200 micron core fibre (OD 0.25 mm) to fragment ureteric calculi in patients.

Physical Principles. The laser pulses are only 1 μs in duration. The light from the end of the fibre is divergent through 23 degrees. The fibre is used touching the stone; the wavelength is in the green where absorption is good but there is some penetration into the stone. The power density is sufficient to cause local fragmentation. Tissue more than 1 cm for the fibre tip is not damaged even by the direct laser beam because the energy density has become too diffuse; similarly light reflected from the stone surface is too diffuse to damage tissue. The method differs from ultrasound (US) which requires firm contact with the probe and from the electrohydraulic probe (EH) which creates its action primarily in the irrigant surrounding the stone. Here the disruption arises from within the stone itself which makes it more suitable for use in a confined space. The energy expenditure is never more than 400 mJ in one second and heat production is negligible.

Animal Experimentation. Laser fragmentation has been tested in the pig ureter. Stones were fragmented in the proximal ureter under vision using rigid ureteroscopes. There was no evidence of local damage secondary to fragmentation in all 9 cases treated by laser. The contralateral ureter was treated by EH probe in 6 cases and one of these ureters was perforated by the probe discharge.

Clinical Experience. We have treated 10 patients with ureteric calculi using the laser via the short 11.5F ureteroscope. The action is like the EH probe, but more controlled and the ureteric wall at the end of the procedure tends to look quite unaffected by the procedure. Stones can be fragmented to particles less than 1 mm diameter. However, there is some tendeny to propel the stone forwards (less than with EH and US). Some stones are fragmented in less than 5 s but dense, hard stones require prolonged "chipping".

Implications. The laser fragmentation uses a fibre which is 0.25 mm outer diameter and extremely flexible. This should act as a spur to the development of purpose-built flexible and continuously-irrigating rigid ureteroscopes.

63 Retrograde Percutaneous Nephrostomy

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64 Is There a Different Indication for PCN in Children Compared to Adults?

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Because ESWL cannot be used in the treatment of renal calculi in childhood, apart from open operation PCN is the only possible alternative. Special pediatric instruments are needed and the operating surgeon should have sufficient experience in percutaneous techniques.

From personal experience with PCN in 11 children it is found that indication in children has to be more rigorous than in adults. While staghorn calculi can usually be removed better by pyelonephro(litho)tomy, the typical, multiple obstructive calculi resulting from immobilisation, the struvite-calculi caused by infections, detritus and remaining calculi after previous surgery which are not spontaneously passable due to shape, localisation and size are indications for this new technique. A few examples are demonstrated. We also demonstrate the complications and the dangers of PCN.

65 Primary Simultaneous Extracorporeal and Percutaneous Litholapaxy – A Reasonable Method for Treatment of Staghorn Calculi?

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The treatment of incomplete and complete staghorn calculi by combined extracorporeal shockwave lithotripsy (ESWL) and percutaneous litholapaxy (PNL) on the next day, while the ureter is blocked by an ureteral catheter, is conversely discussed. Fourty cases, which would have been indications for this combined treatment were examined retrospectively. 23 patients were primarily treated percutaneously, only 13 of these 23 patients needed ESWL due to residual fragments. 17 patients underwent primarily ESWL treatment, only 12 out of these 17 patients required additional percutaneous nephrolitholapaxy. In summary, in 15 out of 40 patients one of the two therapeutic modalities was sufficient. Therefore there is no indication for the routine combination of ESWL and PNL. Nevertheless the combined treatment can reduce the frequency of endoureteral manipulations.

66 Experiences in the Combined Treatment of Branched Renal Calculi by Percutaneous Nephrolithotomy and ESWL

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Until August 1985 87 patients with branched renal calculi were treated with a combination of percutaneous nephrolithotomy and extracorporeal shock wave lithotripsy. Stone debulking was achieved

by percutaneous nephrolithotomy and residual fragments were then destroyed by extracorporeal shock wave lithotripsy. Two to three treatments were necessary in more than 80% of the patients. During the percutaneous procedures 6 complications were encountered, none of them requiring surgery. In one patient, a delayed nephrectomy had to be performed. In 25 patients postoperative chemolysis was performed. Compared to published data on percutaneous nephrolithotomy alone, our procedural time could be reduced by 56% and the fluoroscopy time by 52%. In our opinion, more than 90% of branched calculi can be treated with this combined technique. An attempt is made to outline the indications for percutaneous, open operative and extracorporeal shock wave treatment of branched and staghorn calculi.

67 The Relation of Stone Composition to Extracorporeal Shock Wave Lithotripsy (ESWL)

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During the period from December 1983 to November 1985, 1,290 patients were treated with extracorporeal shock wave lithotripsy. The excreted stone remains from 1,014 patients were analysed by means of X-ray diffraction in accordance with the Debye-Scherrer-method. Up to the present date the results obtained from 425 patients have already been evaluated. (The evaluation of all results will be completed by the date of the Symposium.) The patient average age was 43 years (12–86 years). 42% of the patients were female and 58% were male.

In 31% (131/425) of the cases, the stones consisted of one component only, 55% (236/425) had a mixture of 2 components and 14% (58/425) a mixture of 3 and more components. The most commonly occurring components were calcium oxalate and calcium phosphate 189/425 (44%) followed by pure calcium oxalate stones 41/425 (ca. 10%) and the two-component mixture of calcium-phosphate and magnesium-ammonium-phosphate 31/425 (7.3%). Other variations of stone components occurred between 3%–0.2%.

Diameter	*n*	up to 1 cm	1 to 2 cm	2 to 3 cm	3 to 4 cm
Number of stones	425	256	114	40	15
Shock waves	1,523	1,165	1,798	2,449	3,651
One-component stones	131	85	28	9	9
Shock waves	1,871	1,304	2,615	3,028	3,764
Mixed stones	294	171	86	31	6
Shock waves	1,397	1,097	1,532	2,280	3,482

The average number of shock wave discharges for all types of stones, irrespective of size, totalled 1,523. Independent of stone tpye, the increase in stone diameter resulted in the necessity for a higher number of shock waves, administered in two or more sessions. More shock waves were needed for the disintegration of one-component stones than for stones with a mixture of two or more components.

In the first ESWL-phase, 4/425 (0.9%) patients with cystin stones, larger than 2 cm, or partial stag horn calculus were treated. These types of stones required shock waves in the region of 1,800–7,869 (5 ESWL-sessions), combined with multiple auxiliary methods. Endourologic techniques and conservative therapies are recommended for the treatment of cystin stones.

68 Distribution of Particle Size and Determination of Mineral Composition by Extracorporeal Shock Wave Lithotripsy (ESWL)

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18,338 stone particles from 25 patients, the size of which had been determined, were used for calculation of maximum, minimum and average diameter.

The results were then related to the mineral composition and the radiologically determined size of the stones as well as the number of shock waves employed and their intensity. The question as to whether the results are of clinical importance, is to be discussed.

69 ESWL with Ultrasound Localisation

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An extracorporeal shock wave lithotritor using an ultrasound scan head pantograph location system was designed. Shock wave ellipsoïdal reflector position is adjusted to the stone with a computer assisted positioning device. Seven dogs in which stones were surgically implanted in the renal pelvis were treated in this manner. Stone fragmentation occurred in all cases; subsequently 45 patients with stones were treated. Stone size was 5 to 29 mm (mean 16 mm). Radio-opaque as well as poorly opaque or radioluscent stones were treated. Stone fragmentation was obtained in 85% of the cases. An auxillary manoeuver (endoscopic) was performed in 4 patients. Absence of fragmentation was observed in 4 cases. A second shock wave treatment was necessary in 2 patients who presented initially with stones larger than 2 cm. Radio-opaque, as well as poorly opaque stones can be treated with this procedure. Ultrasound localization together with elipsoid positioning device obviates the need for an expensive two fluoroscope equipment and hydraulic patient positioning device. Therefore, a significantly lower price could be achieved with this new system.