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KIDNEY STONES: COMPOSITION, FREQUENCY AND RELATION TO METABOLIC DIAGNOSIS

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Abstract Nephrolithiasis is one of the most frequent urologic diseases. The aim of this paper is to study the composition and frequency of 8854 patient kidney stones and in a subset of them their metabolic risk factors to be related to their type of calculi. Physicochemical and crystallographic methods were used to assess kidney stone composition. In a subset of 715 patients, we performed an ambulatory metabolic protocol with diagnostic purposes. From the total sample 79% of stones were made of calcium salts (oxalate and phosphate), followed by uric acid stones in 16.5%, calcium salts and uric acid in 2%, other salts in 1.9% and cystine in 0.6%. Male to female ratio was almost three times higher in calcium salts and other types of stones, reaching a marked male predominance in uric acid stones, M/F 18.8 /1.0. The major risk factors for calcium stones are idiopathic hypercalciuria, followed by unduly acidic urine pH and hyperuricosuria. In uric acid stones unduly acidic urine pH and less commonly hyperuricosuria are the most frequent biochemical diagnosis. Our results show that analysis of kidney stones composition and the corresponding metabolic diagnosis may provide a scientific basis for the best management and prevention of kidney stone formation, as well as it may help us to study the mechanisms of urine stone formation.

Key words: kidney stone composition, metabolic diagnosis

Resumen ***Litiasis renal: composición, frecuencia y su relación con diagnósticos metabólicos.*** La litiasis renal es una de las enfermedades urológicas más frecuentes. El objetivo de este trabajo fue estudiar la composición y frecuencia de 8854 cálculos renales y evaluar en un subgrupo de ellos la relación de los factores de riesgo metabólicos con el tipo de cálculo hallado. Se utilizaron métodos fisicoquímicos y cristalográficos para evaluar la composición de los cálculos renales. En un subgrupo de 715 pacientes, se pudo realizar un protocolo metabólico ambulatorio con fines diagnóstico. De la muestra total, 79.0% de los cálculos fueron de sales de calcio (oxalato y fosfato), seguido por cálculos de ácido úrico en 16.5%, sales de calcio y ácido úrico en 2.0%, otras sales en 1.9% y cistina en 0.6%. La relación hombre/mujer fue casi tres veces mayor en las sales de calcio y otros tipos de cálculos, alcanzando un marcado predominio en varones con cálculos de ácido úrico, M/F 18.8/1.0. Los principales factores de riesgo para los cálculos de calcio fueron la hipercalciuria idiopática, seguida del pH urinario excesivamente ácido y la hiperuricosuria. En los cálculos de ácido úrico el pH urinario excesivamente ácido y con menor frecuencia la hiperuricosuria fueron los diagnósticos más frecuentes. Nuestros resultados muestran que el análisis de la composición de los cálculos renales y el correspondiente diagnóstico metabólico pueden proporcionar una base científica para el mejor manejo y prevención en la formación de cálculos renales, así como que nos puede ayudar a estudiar los mecanismos de formación de los mismos.

Palabras clave: composición de cálculos renales, diagnósticos metabólicos

Nephrolithiasis is one of the most frequent urologic diseases. In industrialized countries, up to 12% of men and 7% of women will suffer from kidney stones in their lifetime, and the prevalence appears to be increasing[1]. This tendency is considered by some authors like a pandemic[2]. We found in Buenos Aires city, a nephrolithiasis prevalence of 4.3% in men and 3.6% in women[3].

Urinary calculi analysis is important to determine the possible etiology of stone formation and the pathophysiology of urolithiasis, as previously reported[4]. Stone analysis plays a valuable role in the diagnosis of kidney stone disease, specifically in uncommon kidney stones such as uric acid, cystine, infection-induced, drug-induced, and NH4-urate stones[5]. There are many different methods available for urinary stone analysis, but the fact is that no single method is sufficient to provide all the clinically useful information about stones structure and composition.

The methods employed for these analyses are based on diverse analytical principles. Chemical methods are used to detect individual ions; infrared spectroscopy is used to examine molecular structures, and X-ray diffraction to determine the crystalline structure of a substance. Classification of urinary stones was suggested by many investigators using the chemical method[6]. Indeed, more than 100 chemical components have been identified in urinary calculi, and more than 100 different etiologies may be involved in stone formation. Among analytical methods for

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identifying the stone components, chemical and physical methods can be used although they are unsuccessful to identify rare purine stones resulting from genetic disorders such as 2,8-dihydroxyadenine or drug-induced calculi[7].

This is an observational study to report the composition and frequency of 8854 patients with urinary stones, by physicochemical and crystallographic methods and to evaluate in a subset of them their biochemical risk factors according to the type of calculi they formed.

Materials and methods

From January 2000 to January 2013, we analyzed 8854 consecutive urinary stones coming from different patients referred to our institution by their urologists. The patients either spontaneously eliminated the stone or it was obtained by urologic intervention. In Argentina, most people are of European origin so we assume our sample of calculi belongs mostly to patients of this origin. As an institution specialized in renal calculi analysis and evaluation of metabolic risk factors for urolithiasis, we know that spectroscopy and X- ray crystallography are the present methods to calculi analysis. As we receive patients referred by their urologists to be studied we performed according to urologists demands the methods required such as qualitative chemical method (colorimetric, visual comparison) and optical crystallography with polarized light, methods still preferred due to their low cost and proven utility. From the 8854 patients with kidney stones analysis there were only 715 (8.1%) that were asked to fulfill a biochemical protocol to establish risk factors for urolithiasis.

Informed consent was obtained from all individual participants included in the study. Patients were evaluated at least one month after the symptomatic kidney stone or no longer than 12 months since the last episode, all of them urinary infection free.

This subset of 715 patients was studied with a standard ambulatory protocol for urolithiasis, while following their usual diet. This protocol included two 24-hour urine samples, followed by 2-hour fasting urine sample collected in the morning of the following day along with a venous blood sample. Blood samples were drawn after urine collections and analyzed for creatinine, phosphorus, uric acid, calcium, ionic calcium, potassium and urea. Urine was kept avoiding extreme heat or cold, between 8-12 centigrade degrees during collection and analyzed for calcium, sodium, potassium, creatinine, phosphorus, uric acid, urea, citrate, oxalate, cystine, and magnesium. Urine volume was measured in the two 24-hour urine collections, and urinary pH was determined immediately post-voiding urine sample, if pH was less than 5.5 another sample was taken. Patients with creatinine clearance < 60 ml/min, prolonged immobilization, or those who were taking drugs that could affect mineral metabolism (corticosteroids, diuretics, anticonvulsants, potassium citrate, sodium bicarbonate, allopurinol or febuxostat) were not included. Idiopathic hypercalciuria (IH) was defined as calcium excretion > 220 mg and 300 mg/24 h (5.5 and 7.5 mmol/24 h) in women and men respectively, or in both > 4 mg/kg/24h (0.1 mmol/kg/24 h); hyperuricosuria (HU) as uric acid excretion > 700 mg/24 h (4.13 mmol/24 h) for women, and > 800 mg/24 h (4.72 mmol/24 h) for men; hypocitraturia (CIT) as urinary citrate excretion < 350 mg/24 h (1.8 mmol/24 h), hypomagnesuria (MG) as magnesium excretion < 60 mg/24 h, and hyperoxaluria (OX) as oxalate excretion > 45 mg/24 h. We called the persistent acid urinary pH as "unduly acidic urine pH" (UAU) when pH was below 5.5, in at least two measurements in the same day. A urine output less than 1000 ml /24 h was considered low urine volume (LUV).

All analyses (except ionic calcium) in serum and urine were measured using Synchron CX9 automated analyzers (Beckman, Beckman Instruments, Brea, CA). Serum and urine creatinine were measured using automated Jaffe kinetic method. Serum and urine phosphorus were measured using phosphomolibdate UV method. Serum and urinary uric acid were measured using uricase peroxidase no ascorbate oxidase method. Urine magnesium excretion was measured using calmagite method. Serum and urine urea were measured using UV urease kinetic method. Urinary citrate was determined by an enzymatic reaction by citrate lyase method procedure using reagents from SIGMA- Aldrich Corp. (St. Louis, Missouri, USA). Urinary oxalate (done in an acidified aliquot) was determined by an enzymatic procedure (Trinity Biotech, Bray Co., Wicklow, Ireland). Urinary pH was measured with a pH electrode. Calcium, sodium and potassium were measured using specifics electrodes (ISE method). Cystine was determined by qualitative Brand's reaction and quantitative by Shinohara and Padis modified reaction. Urinary calculi physicochemical analysis was performed using BIOPUR diagnostics kit, (Rosario, Santa Fe, Argentina). The other method employed was optical crystallography with polarizing microscopy by comparison of crystal samples used as standards.

The results are expressed as mean X ± SD. Statistical analyses was performed, (Student test, Chi square test and proportionality), using StatSoft, Inc, Tulsa, OK, USA.

Results

From 8854 kidney stones analyzed 4971 (56.1%) were pure, only one salt found. (Table1). Calcium oxalate (CaOx) clearly predominated, followed by uric acid composition.

Table 2 shows the distribution of mixed kidney stones, 3883 (43.9%) of the total sample. Oxalate and calcium phosphate were the most frequent associated salts.

Total sample of kidney stones, pure and mixed, are described in Table 3. As calcium salts and uric acid were the main components of the stones, we arbitrarily wanted to consider the stones with both salts present (184 stones, 2%) as a different group.

From the total sample of kidney stones analyzed, we could only obtain the sex distribution in a subset of 4834 kidney stone formers, 3779 were men and 1055 women, and we show their kidney stone analysis in Table 4.

Uric acid kidney stones predominated in men compared to women, as well as in those mixed kidney stones, (uric

TABLE 1.– *Composition of pure kidney stones of all 8854 kidney stones sample*

	N	%
Calcium oxalate	3206	36.2
Calcium phosphate	102	1.2
Uric acid	1458	16.5
Cystine	56	0.6
Nonspecific organic material	149	1.8
Total	4971	56.1

acid and calcium salts), where male to female ratio was 7.3/1.0 ($p < 0.001$).

We selected 715 patients studied with a kidney stone metabolic risk factor protocol together with the study of their type of calculi (Table 5). From 715 kidney stones, calcium-oxalate [CaOx] (M/F: 1.4/1.0), was the composition of 477 (66.7%), uric acid [UA] (M /F: 15.6/1.0) was present in 150 stones (21%), calcium-phosphate [CaP] (F/M: 3.5/1.0) in 18 (3%), calcium-phosphate [CaP] + struvite (F/M: 3/1) in 16 (2.5%), struvite in 16 (2.2%) and in 7 (1.0%) calcium oxalate-uric acid [CaOx + UA] (M/F: 1.3/1.0) was found. Calcium oxalate kidney stones were mainly present in patients with idiopathic hypercalciuria, followed by unduly acidic urine pH and hyperuricosuria, reaching as a group 68%. In uric acid stones, unduly acidic urine pH reached 70.6% of the total risk factor diagnosis. Idiopathic hypercalciuria was the main abnormality observed in calcium phosphate, struvite and calcium phosphate-uric acid kidney stones. Multiple risk factors were observed in 14.7% of calcium-oxalate, 25.0% of struvite, 25.0% of oxalate-calcium phosphate, 11.6% in uric acid stone and 28.6% in calcium oxalate-uric acid kidney stones. LUV was present in some calcium oxalate stones, uric stones and calcium phosphate stones.

TABLE 2.– *Composition of mixed kidney stones of all 8854 kidney stones sample*

	N	%
Oxalate and calcium phosphate	2551	28.8
Calcium oxalate + calcium phosphate + magnesium ammonium phosphate (struvite)	410	4.6
Calcium oxalate + uric acid	184	2.1
Calcium phosphate + magnesium ammonium phosphate (struvite)	718	8.1
Oxalate + uric acid	20	0.2
Total	3883	43.9

TABLE 3.– *Analysis of the total sample of kidney stones (n = 8854)*

	N	%
Calcium salts	6987	79.0
Uric acid	1458	16.5
Calcium salts + uric acid	184	2.0
Other salts*	169	1.9
Cystine	56	0.6
Total	8854	100.0

**It includes struvite*

No metabolic abnormality (NMA) was only present in 17 (2.4%) of the 715 patients with metabolic evaluation and renal stones. There were 11.6% of patients with uric acid stones, with mixed alterations. Low urinary volume was observed in 26 (5.4%) of de 477 patients with calcium oxalate stones, in 30 (15.2%) of the 197 patients with uric acid stones, and in 4 (22.2%) of the 18 patients with calcium phosphate stones.

Finally, we analyzed the demographic characteristics and some biochemical parameters in the 715 patients with kidney stones according to their type of calculi (Table 6). We observed that patients with uric acid stones were predominantly male, with older age, higher weight and BMI, higher serum, and urine uric acid with lower urinary pH compared with the rest of the patients with analyzed kidney stones. Calcium oxalate and uric acid kidney stones predominated in men, while struvite, calcium-phosphate and oxalate-calcium phosphate kidney stones predominated in women.

Discussion

An accurate analysis of kidney stone composition may provide a scientific basis for the best management and prevention of kidney stone formation, as well as it may help us to study the mechanisms of urine stone formation[8]. There are many methods of stone analysis, such as chemical and various physical analyses, which provide valuable

TABLE 4.– *Kidney stones analysis according to gender in 4834 stones*

	Men	Women	Ratio	p
Calcium salts	2297	783	2.9	< 0.001
Uric acid	1257	67	18.8	< 0.0000
Calcium salts + uric acid	73	10	7.3	< 0.001
Struvite	117	176	1.5	< 0.05
Other salts	23	9	2.5	< 0.01
Cystine	12	10	1.2	NS
Total	3779	1055		

TABLE 5.– *Biochemical diagnosis and kidney stones in 715 patients. Physicochemical and/or crystallographic features of the stones*

Biochemical diagnosis	CaOx (%)	UA (%)	CaP (%)	Struvite (%)	CaOx + UA (%)
IH	150		14	11	4
	(31.4)		(77.8)	(68.8)	(57.1)
UAU	107	139			–
	(22.4)	(70.6)			
HU	68	3			1
	(14.2)	(1.5)	–		(14.3)
NMA	15	2			
	(3.1)	(1.0)	–		–
CIT	23			1	
	(4.8)			(6.3)	–
MG	16				
	(3.3)	–	–		–
OX	2				
	(0.4)	–	–		–
Mixed alterations	70	23		4	2
	(14.7)	(11.6)	–	(25.0)	(28.6)
LUV	26	30	4		
	(5.4)	(15.2)	(22.2)		
Total	477	197	18	16	7
	(100)	(100)	(100)	(100)	(100)

CaOx: calcium oxalate; UA: uric acid; CaP: calcium phosphate; IH: idiopathic hypercalciuria; UAU: unduly acidic urine pH; HU: hyperuricosuria; NMA: no metabolic abnormality; CIT: hypocitraturia,;MG: hypomagnesuria; OX: hyperoxaluria; LUV: low urine volumen.

TABLE 6.– *Demographic characteristics and biochemical parameters in 715 kidney stone formers*

	Sex	Age	Weight	BMI	Serum uric	Urine pH	Uricosuria
Calcium oxalate	M: 287	44.7 ± 1.9	73.2 ± 15	25.8 ± 4.3	5.1 ± 1.2	5.7 ± 0.1	627 ± 208
	F: 220	43.6 ± 1.6	62.5 ± 17	24.7 ± 5.1	5.2 ± 1.1	5.8 ± 0.3	548 ± 189
Uric acid	M: 107	47.2 ± 11.2	84.9 ± 16.7	27.3 ± 5.5	5.5 ± 1.5	5.4 ± 0.5	660 ± 186
	F: 13	45.8 ± 10	70.6 ± 14.4	26.9 ± 5.7	5.4 ± 1.2	5.5 ± 0.5	589 ± 221
Calcium phosphate	F: 24	42.2 ± 13.8	64.1 ± 14.4	23.5 ± 4.2	4.0 ± 0.9	5.8 ± 0.6	527 ± 71
	M: 14	41.2 ± 14	54.7 ± 13.2	23.6 ± 3.7	4.8 ± 0.8	6.0 ± 0.7	498 ± 66
Ox + Ca P	F: 20	47.7 ± 13	65.3 ± 11	24.7 ± 4.9	3.9 ± 1.1	5.8 ± 0.3	513 ± 209
	M: 7	45.5 ± 12	58.7 ± 12	23.6 ± 3.4	4.1 ± 0.9	5.7 ± 0.4	478 ± 176
Struvite	F: 15	40.1 ± 9.7	62.1 ± 9.9	23.1 ± 2.8	4.3 ± 0.8	6.07 ± 0.4	511 ± 81
	M: 8	23.6 ± 3.4	57.7 ± 10	23.2 ± 3.0	4.2 ± 0.9	5.9 ± 1.2	487 ± 90

Ox + CaP: oxalate-calcium phosphate; BMI: body mass index.

information of the etiology, pathology, and physiology of urolithiasis[9]. Among physical methods, X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FTIR) are currently used for stone analysis.

We mainly used for the analysis of kidney stones the physicochemical analysis and in part of the sample, we used the crystallographic study. Although wet chemistry is generally deemed to be obsolete because it has been reported a very high proportion of errors (6.5-94.0%), in our experience it is a very easy and low cost method, mainly required by urologists and moreover its results highly correlate to modern methods. As specialized physicians in mineral metabolism belonging to an institution that performs calculi analysis, we are aware that spectroscopy and X-ray crystallography have better accuracy and both methods are of our choice.

We found in our series of 8854 consecutive patients that had their kidney stones analyzed, 79.0% made of calcium salts (oxalate and phosphate), followed by uric acid stones in 16.5%, calcium salts and uric acid in 2.0%, other salts in 1.9% and cystine in 0.6%. When calcium stones are considered our findings are lower than the 93.8% found by Jing et al. in 625 stones analyzed using Fourier transform infrared spectroscopy (FTIR)[10], and also lower than the 90% composition of calcium salts, also analyzed with physicochemical method, reported by Massari et al. in Córdoba city, Argentina[11]. Our percentage is similar to those found in two series with more than 10 000 studied stones[12, 13]. Thus, our results confirm the high frequency of calcium salts as main stone composition.

Regarding uric acid kidney stones they were 16.5%, rather similar to 15.0% found in pure or mixed forms in the series of Jing in China[10] or the 16.0% observed in Okinawa, Japan[14]. Our results are greater than the 7% reported by Reed and Gitomer[15] and the 10% described by Riese et al. in United States[16]. These countries have a very different diet compared to Argentina where animal protein high intake predominates. On the other hand, our results are undoubtedly lower than the 25% observed in Germany[17] or the 40% in Israel[18].

Cystine stones are the diagnosis of congenital cystinuria; struvite or carbonate stones are indicative of urinary tract infection with urease-positive organisms; triamterene and indinavir stones are pathognomonic for the precipitation of these drugs[19-21].

As described in other series[15-21] we found struvite in mixed salts of oxalate and calcium phosphate in 12.7% of stones. Finally, similar as most series, the percentage of cystine stones was 0.6%[15-21]. We could only report sex distribution in 4834 patients of the total sample and we found a slight increase prevalence in men over women in cystine stones (M/F 1.2/1.0), on the contrary this difference was almost three times higher in calcium salts and other types of stones, reaching a marked male prevalence in uric acid stones, M/F 18.8/1.0.

In 715 patients with kidney stones analyzed, we could correlate their metabolic abnormality to their stone composition. In 477 patients with calcium-oxalate stones, we found that idiopathic hypercalciuria, unduly acidic urine pH, hyperuricosuria, hypocitraturia and mixed disorders were the main alterations. In less than 5% of the calcium-oxalate stone formers, we did not find biochemistry alteration. Curhan describes about 20% to 40% of patients with calcium stone disease that have hypercalciuria[22], similar to our 31.4% of calcium stone formers. Unduly acidic urine pH can also promote calcium-oxalate stone formation; we found this alteration in 22.4% of calcium oxalate stones formers, similar to what the literature describes[23]. We know this biochemical alteration is an important risk factor for uric acid stone formation. Uric acid stone formation is favored at low pH, but it is not itself a cause of CaOx stone formation as monosodium-urate is. Monosodium-urate can lead to CaOx crystallization by heterogeneous nucleation[24]. In our study, hyperuricosuria was the cause of the 14.2% of calcium oxalate stones less than 20.0% found in other series[25]. In a major study of 2237 patients with nephrolithiasis[26], it could not be demonstrated that high urinary excretion of uric acid increases the risk for crystallization of calcium oxalate. However, other authors like us, agree that hyperuricosuria can lead to CaOx stone formation[27]. Although one study has attributed the physicochemical process to urinary supersaturation with colloidal monosodium-urate induced CaOx crystallization, another study has shown a lack of effect of monosodium urate and attributes CaOx stone formation to decreased solubility of CaOx in solution, a process described as “salting out”[8]. Hypocitraturia was found in 4.8% of calcium nephrolithiasis, less than 20-40% described by Pak[29]. In uric acid stones we found that, unduly acidic urine pH was more prevalent (70.6%) followed by mixed alterations (11.6%), low urinary volume (15.2%), hyperuricosuria (1.5%) and no metabolic abnormality (1.0%). These findings are similar to those found by Cameron and Sakhaee[30]. In struvite stones, we found a predominance of idiopathic hypercalciuria, followed by mixed alterations and hipocitraturia.

Finally, in the subset of 715 patients kidney stone analysis, demographic parameters and laboratory tests showed patients with uric acid stones were mainly men, older, with higher weight and BMI, and higher serum and urine uric acid with lower urinary pH than the rest of the stones analyzed. We reported similar findings in a previous study[31].

Kidney stone events should be studied from the first one because the metabolic alteration and the stone composition will be mostly the same independently of the previous number of stone episodes [32, 33].

We consider that in the majority of the patients even when stone analysis is not available, assessment of metabolic risk factors for nephrolithiasis is still the gold standard to reach the diagnosis and consequent specific therapeutics to avoid new stone formation.

Limitations of our study are the methodology used in kidney stone analysis and the lack of metabolic diagnosis in the total sample of patients.

In conclusion, our observational study confirms that calcium salts represent almost 80% of the total analyzed stone sample, followed by uric acid, the combination of uric acid and calcium oxalate, other salts and cystine. The prevalence of uric acid stones is higher in men compared to women. The major risk factors for calcium oxalate stones are idiopathic hypercalciuria, followed by unduly acidic urine pH and hyperuricosuria. In uric acid stones, unduly acidic urine pH is the biochemical alteration most frequently present. Although we know, there are more accurate methods to perform urinary calculi analysis our study could demonstrate similar results to the data already published.

References

1. Asplin JR. Nephrolithiasis: introduction. *Semin Nephrol* 2008; 28: 97-8.
2. Romero V, Akpina H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. *Rev Urol* 2010; 12: e86.
3. Pinduli I, Spivacow FR, del Valle EE, et al. Prevalence of urolithiasis in the autonomous city of Buenos Aires, Argentina. *Urol Res* 2006; 34: 8-11.
4. Anderson RA. A complementary approach to urolithiasis prevention. *World J Urol* 2002; 20: 294-301.
5. Sakhaee K, Maalouf NM, Sinnott B. Kidney stones: pathogenesis, diagnosis, and management. *J Clin Endocrinol Metab* 2012; 97: 1847-60.
6. Otnes B. Urinary stones analysis, methods, materials and value. *Scan J Urol Nephrol* Suppl 1983; 71: 1-109.
7. Cloutier J, Villa L, Traxer O, Daudon M. Kidney stone composition analysis: "Give me your stone, I will tell you who you are". *World J Urol* 2015; 33: 157-69.
8. Daudon M, Bouzidi H, Bazin D. Composition and morphology of phosphate stones and their relation with etiology. *Urol Res* 2010; 38: 459-67.
9. Wagner CA, Mohebbi N. Urinary pH and stone formation. *J Nephrol* 2010; 23 Suppl 16: S165-9.
10. Jing Z, GuoZeng W, Ning J. Analysis of urinary calculi composition by infrared spectroscopy: a prospective study of 625 patients in eastern China. *Urol Res* 2010; 38: 111-5.
11. Massari PU, Garay G, Holtz RM. La litiasis renal en Córdoba, Argentina: aspectos epidemiológicos, clínicos y metabólicos. In: Calculosis Renal: fisiopatología clínica y tratamiento, Schor N and Heilberg I.E., eds. San Pablo: Servier, 1995; Capítulo 34: 1.
12. Daudon M, Donsimoni R, Hennequin C, Fellahi S, et al. Sex- and age-related composition of 10 617 calculi analysed by infrared spectroscopy. *Urol Res* 1995; 3: 319-26.
13. Brien G, Schubert G, Bick C. 10 000 analysis of urinary calculi using x-ray diffraction and polarizing microscopy. *Eur Urol* 1982; 8: 251-6.
14. Hossain RZ, OgawaY, Hokama S, Morozumi M, Sugaya K, Hatano. Urolithiasis in Okinawa, Japan: a relatively high prevalence of uric acid stones. *Int J Urol* 2003; 10: 411-5.
15. Reed BY, Gitomer WL. The Genetics of Stone Disease. In: Urinary stone disease: the practical guide to medical and surgical management. Stoller, MV, Meng, MV, eds. Totowa, New Jersey: Humana Press Inc. 2007; pp 35-54.
16. Riese RJ, Sakhaee K. Uric acid nephrolithiasis: pathogenesis and treatment. *J Urol 1992*; 148: 765-71.
17. Hesse A, Schneide HJ, Berg W, et al. Uric acid dehydrate as urinary calculus component. *Invest Urol* 1975; 12: 405-09.
18. Atsmon A, De Vries A, Frank M. Uric acid lithiasis. Amsterdam, London, New York: Elsevier 1963.
19. Wu DS, Stolle ML. Indinavir urolithiasis. *Curr Opin Urol* 2000; 10: 557-61.
20. White D, Nancollas GH. Triamterene and renal stone formation: the influence of triamterene and triamterene stones on calcium oxalate crystallization. *Calcif Tissue Int* 1987; 40: 79-84.
21. Prien EL. Studies in urolithiasis: II. Relationships between pathogenesis, structure, and composition and calculi. *J Urol* 1949; 61: 821-36.
22. Curhan GC. Epidemiology of Stone Disease. *Urol Clin N Am* 2007; 34: 287-93.
23. Park S, Pearle MS. Pathophysiology and management of calcium stones. *Urol Clin N Am* 2007; 34: 323-4.
24. Chandhoke PS. Evaluation of the recurrent stone former. *Urol Clin N Am* 2007; 34: 315-22.
25. Curhan GS, Taylor EN. 24-h uric acid excretion and the risk of kidney stones. *Kidney Int* 2008; 73: 489-96.
26. Grover PK, Marshall VR, Ryall RL. Dissolved urate salts out calcium oxalate in undiluted human urine in vitro: implications for calcium oxalate stone genesis. *Chem Biol* 2003; 10: 271-8.
27. Pak CYC, Arnold LH. Heterogeneous nucleation of calcium-oxalate by seeds of monosodium urate. *Proc Soc Exp Biol Med* 1975; 149: 930-6.
28. Grover PK, Ryall RL. Urate and calcium oxalate stones: from repute to rhetoric to reality. *Miner Electrolyte Metab* 1994; 20: 361-70.
29. Pak CYC: Citrate and renal calculi: an update. *Miner Electrolyte Metab* 1994; 20: 371-7.
30. Cameron MS, Sakhaee K. Uric Acid Nephrolithiasis. *Urol Clin N Am* 2007; 34: 335-46.
31. Negri AL, Spivacow FR, del Valle E, Pinduli I, Marino A, Fradinger E. Clinical and biochemical profile of patients with "pure" uric acid nephrolithiasis compared with "pure" calcium oxalate stone formers. *Urol Res* 2007; 35: 247-51.
32. del Valle EE, Spivacow FR, Zanchetta JR. Evaluación metabólica ante el primer episodio de litiasis renal. *Medicina (B Aires)* 1995; 55: 69-74.
33. Coe FL, Parks JH, Asplin JR. The pathogenesis and treatment of kidney stones. *New Engl J Med* 1992; 827: 1141-52.

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ESCRIBIR LO NECESARIO. No es que me repugne lo extenso: me repugna lo extendido, que no es lo mismo.

Ernesto Sábato (1911-2011)

Heterodoxia. Buenos Aires: Emecé, 1970; p 46