References

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Uric Acid, Uric Acid Dihydrate, and Urates in Urinary Calculi, Ancient and Modern

Abstract. *Uric acid, uric acid dihydrate, and ammonium acid urate occur in bladder stones both ancient and modern. They are seldom abundant in stones from technically developed areas. Urates are usually confined to children's endemic bladder stones; uric acid dihydrate is rare, but uric acid used to be common in bladder stones from elderly men.*

Uric acid was a major constituent of vesical calculi 100 years and more ago. For instance, a "Catalogue of the Collection of Calculi of the Bladder removed by Operation by Sir Henry Thompson FRCS (1893)" (*1*) tabulates details of 1007 stones (1854–1892), all weighing over 20 grains, 977 from adult males, 13 from adult females, 16 from boys, and one from a girl (names, ages, and after-history given). Of these, 571 consisted of pure uric acid, 97 of mixed uric acid and phosphates. Urates (mixed with oxalates) were found in only 36 stones, oxalates (pure or mixed with urates or phosphates) in 89, phosphates in 362 (247 pure), cystine in three. No mention is made of hydrates; for example, whewellite (calcium oxalate monohydrate) and weddellite (2 to 2½ water per formula weight of calcium oxalate) are not listed separately. Thompson's patients were not typical. Most of them were over 60 years of age. They were probably wealthy.

Details of the uric acid and urate content of some other collections, given in Table 1, show that even among ordinary hospital patients, uric acid stones used to be common, though more so in men than in boys (stones were and are rare in females). Urates were common in children. In modern stones, ammonium acid urate is now common from children in the endemic bladder stone areas only. Uric acid is generally a minor constituent, although amounts of up to 17 percent have been reported from Stockholm (*2*) and Chicago (*3*).

Formerly, bladder stones were predominant and kidney stones were rare. This is still true in the endemic stone belts, but the reverse is now the case in North America and most western European countries (*4*). The only collection of renal stones from children that we have examined (*5*) contained a relatively high proportion of ammonium acid urate, but only one stone contained a little uric acid.

Parsons (*6*) distinguished between uric acid and hydrated uric acid (which he called the monohydrate but has since confirmed by correspondence to be the dihydrate). Out of 880 stones from the Detroit area he found 61 pure uric acid, 14 pure hydrate, 13 mixed anhydrous and hydrated uric acids, and 17 anhydrous mixed with other constituents.

Table 1. Uric acid, uric acid dihydrate, and ammonium acid urate percentage occurrence in various collections of human urinary calculi. A strict comparison is not possible because of divergence of techniques and methods of presentation of data. In some cases, figures given in original papers have been weighted if the stone is reported as "pure." V, bladder or urethra; V+, mostly V; R, kidney or ureter; *a*, uric acid; *b*, uric acid dihydrate; *c*, ammonium acid urate.

Ref.	Place	Period	No. of stones	Ages (yr)	Site	Percentages in stones *a*	*b*	*c*
(*12*)	Britain (Norwich)	1772–1828	663	292<14 161>50	V	..........78..............		
(*13*)	Britain	Before 1842	39	<21	V+	....12......		32
			41	>20	V+	....62......		0.2
			649	All	V+	....43......		18
(*14*)	India	1843–1871	83	<21	V+	....15......		22
			65	>20	V+	....29......		3
			148	All	V+	....22......		14
(*15*)	Britain	1843–1871	208	All	V+	....37......		12
(*16*)	Britain (Norwich)	1773–1909	51	<21	V	18	1	27
			33	>20	V	59	3	11
			84	0–75	V	35	1	21
(*17*)	China (Canton)	1861–1919	3371 121	43%<20	V R	..........78..............		
(*18*)	Lebanon (Beirut)	1880–1907	288	<21	V	..........54..............		
			144	>20	V	..........59..............		
(*19*)	Thailand	1960–1962	58	<21	V	4	0.4	49
			18	>20	V	2	1	7
			65	17–68	R	6	0	2
(*20*)	Thailand	1963	200	Children	V	....11......		42
(*5*)	Turkey	1965	23	2–15	V	5	0	42
			53	2–14	R	1	0	34
(*21*)	Indonesia	?	40	?	V?	2	0	15
(*8*)	Denmark	1941	111	?	?	.....7......		0
(*22*)	U.S.	1949	1000	?	R?	.....5......		0
(*23*)	U.S.	1948–1961	24000	?	R?	....6–10....		0
(*2*)	Sweden	1955	140	?	V	....17......		5
			460	?	R	.....2.5		0.2
(*24*)	S. Korea	1954–1958	88	All	V,R	.....3......		17
(*25*)	Britain (Norwich)	1932–1940 1941–1961	56	3–67	V V,R	7.5	3	2.5
(*26*)	Britain	1962	250	?	?	.....1.4		1.2
(*6*)	U.S.	1964	880	?	V,R	9	2	0
(*27*)	Australia	1965	73	20–50	R	.....1.4		0

Table 2. Particulars of bladder stones found, by x-ray diffraction techniques, to contain uric acid dihydrate (see also *6*). Symbols used: *A*, uric acid; *A2*, uric acid dihydrate; *B*, ammonium acid urate; *C1*, calcium oxalate monohydrate; *C2*, calcium oxalate dihydrate; *G*, magnesium hydrogen phosphate trihydrate. The more abundant constituent is given first; parentheses indicate a minor constituent or trace; ? means doubtful or not known.

Year	Sex	Age (yr)	Composition of stone: Nucleus	Intermediate layers	Surface
			Norwich Museum, England		
1778	M	57	*A*, *C1*	*A*, *A2*	*A1*, *A2* + (?)
1790	M	55	*A2*, *A*	*A*	*A*
1797	M	49	*A*, *A2*	*A*, *A2*	*G*
1877	M	12	*A*	*A2*	*C1*, *B*
			Norwich, England		
1932	M	64	*A*, *A2*	*A*, *A2*	?
1952	M	?	.........*A*, *A2*.......................		
1957	M	?	.........*A*, *A2*.......................		
?	?	?	*A*, *A2*	*A*, *A2*	*A*
			Ubol Hospital, Thailand		
1960	M	5	*B*, *C1*	*A*, *A2*, (*C1*,*C2*, *B*)	*A*, *A2*, *C2*
	M	46	*C1*	*C2*, *C1*, *A2*	*A1*, *A2*, (*C2*, *C1*)
			Turkey		
1964	M	?	*B*, *C1*, *C2*	*B*	*A2*, (*A* + ?)
	M	?	*B*	*C1*	*C1*, *C2*, (*A2*)

Ringertz (*7*) mentioned uric acid dihydrate as a rare constituent of urinary calculi. Jensen (*8*) had commented on different forms of uric acid and of uric acid calculi.

In spite of the occasional tendency for the dihydrate crystals to lose water (*9*) we have found uric acid dihydrate (generally with uric acid) in both ancient and modern stones (Table 2).

We have never found stones of the pure dihydrate, but a specimen of gravel deposited on cooling the urine of an adult patient at University College Hospital (*10*) was entirely uric acid dihydrate, apart from some coloring matter. It would be interesting to have results of statistical investigations of gravels from urines of various *p*H and from patients of various ages.

In their careful studies of uric acid concretions grown from human urine in the laboratory, Vermeulen *et al.* (*11*) make no mention of hydration. They give the solubilities of uric acid and the degrees of supersaturation attained under various conditions. Similar studies of uric acid dihydrate would be most valuable, especially if the nature of the crystals deposited from the supersaturated solutions were determined.

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References and Notes

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5. Two very recent collections of stones from children were sent by Dr. Dogan Remzi, Hacettebe Medical Centre, Ankara, Turkey, and analyzed at University College, London. We have seen no other published records of frequent renal stones in children.
6. J. Parsons, *Henry Ford Hosp. Med. Bull.* **12**, 187 (1964); 880 stones from the Detroit area (bladder and kidney) contrasted with six bladder stones from Nepal, of which five contained uric acid and three contained NH_4H urate. In Nepal only 10 kidney stones had been found, as opposed to hundreds of bladder stones.
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8. A. T. Jensen, *Acta Chir. Scand.* **84**, 207 (1941). X-ray diffraction, crystallographic, and chemical techniques were used, but in many cases were confined to surface material from the stones. Details of ages and so forth were not in general recorded. There is some internal evidence (p. 217) that Jensen may have observed hydrated as well as anhydrous uric acid.
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11. C. W. Vermeulen, E. S. Lyon, W. B. Gill, *Invest. Urol.* **1**, 370 (1964); F. A. Fried and C. W. Vermeulen, *ibid.* **2**, 131 (1964).
12. J. Yelloly, *Phil. Trans. Roy. Soc.* **1829**, 63 (1829) and **1830**, 415 (1830). Chemical analysis of bladder stones (with a very few renal) from the Norfolk and Norwich Hospital, England. 632 male, 31 female. Separate data were not given for children and adults.
13. Analysis of data given in the *Descriptive and Illustrated Catalogue of the Royal College of Surgeons in London* (1842), where ages are given in only a few cases. Renal stones were rare enough to be mentioned specially.
14. *Supplement*, dated 1871, to *13*. Stones mostly from soldiers or laborers or their families, were sent by British surgeons at hospitals in India. Ages usually given.
15. *Supplement*, dated 1871, to *13*. Stones sent by surgeons in Britain. Ages not given.
16. Dated stones from the Norfolk and Norwich Hospital Museum, England, by courtesy of Ridley Thomas. Analyses by x-ray diffraction techniques at University College, London, 1965.
17. J. O. Thomas, *Surg. Gynecol. Obstet.* **32**, 44 (1921). Collection of 3492 stones from Canton Hospital, China: 2962 bladder, 409 urethra, 116 ureter, 5 renal; only 2 percent from females. Separate data were not given for children and adults.
18. J. M. R. Thomas, *Brit. J. Urol.* **21**, 20 (1949). Collection from the American University Hospital, Beirut; only 2 percent renal stones. Thomas refers also to the New York Hospital, where in 1820–1845, 83.3 percent of patients with stones were under 30 years old, whereas in 1912–1935 this percentage was only 10.9.
19. Stones sent from the Ubol Hospital (Dr. Cholvit Chutikorn), Thailand; samples were analyzed by x-ray diffraction at University College, London. Peak incidence at age 2½ years; of 1780 bladder (and urethra) stones removed in 1960–1962, 1056 were from children less than 4 years old. In the same 3 years, only 233 kidney (and ureter) stones were found, 220 from patients 20 to 60 years of age.
20. S. N. Gershoff, E. L. Prien, A. Chandrapanod, *J. Urol.* **90**, 285 (1963). Bladder stones from children in northeastern Thailand. Data recalculated to correspond with other figures given in Table 1. Original data given are: calculi pure or nearly pure uric acid, 6 percent; nucleus of uric acid, 6 percent; pure or nearly pure ammonium acid urate, 8 percent; nucleus of ammonium acid urate, 34 percent; nucleus of NH_4H urate and calcium oxalates mixed, 22 percent; 76 percent contain NH_4H urate.
21. A small collection of large stones from Indonesia; these are modern but there is no information about dates or patients. X-ray diffraction analyses were carried out at University College, London.
22. E. L. Prien, *J. Urol.* **61**, 821 (1949). Results of optical and x-ray crystallographic techniques, but without details of ages of patients, weights and sizes of stones; no information is given about proportion of bladder stones. The stones are assumed to be mostly renal because of mention of "occurrence in normal kidneys" (p. 823).
23. E. L. Prien, *ibid.* **89**, 917 (1963) continuation of *22*. Probably [see Gershoff (*4*)] less than 5 percent bladder stones, and less than 1 percent from children.
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25. Modern stones supplied by Ridley Thomas, Norfolk, and Norwich Hospital, England; analyzed by x-ray diffraction techniques at University College, London.
26. B. T. Murphy and L. N. Pyrah, *Brit. J. Urol.* **34**, 129 (1962). Stones from Leeds, England.
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28. We thank D. A. Andersen of the Institute of Urology, London, for initiating these studies and for obtaining collections for us; and the Medical Research Council for financial support.

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Uric Acid Dihydrate: Crystallography and Identification

Abstract. *Unit-cell dimensions and optical data for uric acid and uric acid dihydrate show that there are structural resemblances, but that either can be readily distinguished by x-ray methods or by optical techniques. Density separation may be unsatisfactory because the dihydrate can lose water rather easily. Powder diffraction data are given.*

Anhydrous uric acid $C_5N_4H_4O_3$ (see *1*) was discovered by Scheele in 1776 as a major constituent of some mammalian concretions. A crystalline hydrate has been mentioned by Ord (*2*), Brun (*3*), and Gaubert (*4*) and reviewed by Winchell (*5*). This compound has been characterized as the dihydrate by Ringertz (*6*), and also in this laboratory.

Ringertz compared optical and x-ray crystallographic data for the anhydrous and hydrated crystals, but the axes he chose obscure the similarity between the two substances, which becomes obvious if the following orientations are used:

Uric acid (monoclinic; pseudo-orthorhombic): $a = 13.12_0$ Å; $b = 7.40_3$ Å; $c = 6.20_8$ Å; $\beta = 90.5°$. Density (obs.) = 1.844 g/cm³ at 20°C (*7*).

Uric acid dihydrate (orthorhombic): $a = 17.55$ Å; $b = 7.40$ Å; $c = 6.35$ Å. Density (obs.) = 1.650 g/cm³ at 20°C.

Both crystals show a pronounced platy habit based on {100}, particularly

Table 1. List of spacings (*d*) and intensities (*I*) of powder lines given by uric acid and by uric acid dihydrate.

Uric acid		Uric acid dihydrate	
d (Å)	*I**	*d* (Å)	*I**
6.56	M	8.75	S
5.63	M	5.97	MW
4.91	MS	5.65	M
4.76	W	4.22	M
3.85	S	3.77	W
3.70	W	3.71	W
3.59	VW	3.41	W
3.28	W	3.24	MW
3.18	VS	3.20	VVS
3.09	VVS	3.15	VVS
2.86	MS	3.00	MW
2.80	M	2.79	W
2.62	VW	2.71	W
2.57	MW	2.61	VW
2.31	W	2.57	M
2.28	VW	2.50	W
2.26	MW	2.43	VW
2.19	VW	2.37	MW
		2.19	VW
		2.15	W

* S, strong; M, moderate; W, weak; V, very.