Human Stones

Limited studies give some details of composition, rates of growth, distribution, and possible causes.

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Stones, which are found in all parts of the urinary tract, may vary in size from that of a pin's head to that of a coconut. The largest human stone recorded (*1*) weighed over 1.36 kilogram (Sir Walter Ogilvie, 1808). The shape, hardness, and general appearance of stones vary considerably. Some stones can be easily sectioned, some crumble, others cannot be cut or ground at all. Bladder stones are often ellipsoidal, having a well-defined nucleus and successive layers, with crystalline material radiating from the nucleus (*2*). Others are conglomerates with no nucleus and only a roughly spherical or asymmetric shape. Others again are rounded tetrahedrons, especially when there are a number of stones packed tightly together. Sometimes they have the typical shapes known as hempseed, mulberry, staghorn, or jackstone. Their surfaces may be smooth, flaked, uneven, or covered with sharp crystals. Kidney stones are usually much rougher in shape, but they may also be layered.

The period of growth varies widely. Sir Walter Ogilvie was paralyzed by a blow at 23 years of age; he developed symptoms of bladder stone 20 years later, but postponed an operation (which was then fatal) for another 10 years. A Mr. William Hay, who also had symptoms of stones (which he treated himself) for 10 years from 1765, was found on postmortem to have a stone, but it weighed only about 0.5 gram. He had directed that it should be placed in a gold box, with its history on vellum in a gold frame; it was given to the Royal College of Surgeons (*1*) by Sir Joseph Banks. Cases have been known where symptoms had been experienced for up to 50 years or more; but, on the other hand, stones have been formed and voided regularly two or three times a week. Thomson (*3*) found that 50 to 100 years ago for 3500 cases from south China the average period of symptoms before hospitalization was 3½ years.

Definite evidence, based on tagging with colored or fluorescent material, has been given in two recent publications. Gasser and Preisinger (*4*) record the case of a 37-year-old female who had a phosphatic (struvite-apatite) stone removed from her right kidney by operation in a Vienna hospital. Six weeks later she went to a German spa to take the waters for 31 days. While there she also daily took an alizarin-based drug called Rubia, which has an intense red color; this treatment she continued, though not regularly, for another 11 days. She was operated on 24 weeks later (21 January 1958), and another stone was removed from the same kidney. This had colorless central and outer zones, together with a red middle zone which had 40 fine, unequal layers—one for each day of medication with Rubia. The colored organic compound was attached to the apatite.

More recently, Mulvaney, Beck, and Qureshi (*5*) treated 25 patients with stones with the drug oxytetracycline for up to 1 week prior to surgery. As a control, they also soaked struvite and apatite stones in tetracycline solution (250 mg in 30 ml of H_2O) for 2 to 7 days. Fluorescence due to a complex of apatite and tetracycline was found in all stones (including controls) except one which was pure uric acid and one which was pure calcium oxalate dihydrate (weddellite). Most of the yellow fluorescent complex was on the surface, except in the case of a patient who had had the same drug 8 years previously; here there was internal fluorescence with a tendency to ring formation. The authors remark that this seems to be a useful tagging method for studying the biophysics of calculogenesis.

Age, Period, and World Distribution

These are erratic. Endemic primary bladder stones occur in some places but not now in others, although at one time their incidence was much more widespread. In Ubol Hospital, in northeast Thailand, between 1960 and 1962, one boy patient in three had a bladder stone. Most occurred in boys under 5 years of age. The number of kidney stones, almost all in adults, was much less, although the number increased with time (Fig. 1). Some indication of the age and geographical distribution in three areas of Thailand is shown in Tables 1 and 2 (*6*) where bladder and kidney stone cases are compared. It is clear that the incidence of kidney stones is much the highest in the urban area of Bangkok and that of bladder stones is highest in the "stone belt," which includes Ubol province, although Bangkok has child cases also. In central and south Thailand there are few stones of any kind. Of the total population of about 23 million in 1959, some 5300 patients with stones were admitted to hospitals; of these patients more than 90 percent had bladder stones. Thus, an average of one person in 4500 is a stone case in hospitals in Thailand each year; most of these are little boys. In some villages, however, the frequency is as much as 1 in 125 per year.

The situation in the United States is quite different (*7*). Children have less than 1 percent of all stones found, most of which are kidney and ureter stones. The nationwide average 15 years ago was 1 per 1000 inhabitants per year; most stones occurred in whites. In South Carolina and Georgia the incidence was highest, about 2 per 1000 per year, an incidence four times as high as that in Wyoming and Missouri; but there were differences also within states. For instance, the number of patients with stones in northern Alabama was less than half that in southern Alabama. The sex ratio found in hospitals was 54 percent male, 46 percent female, but postmortems revealed a high proportion of undiagnosed stones, their numbers being equal in males and females. Perhaps women complain less of pain or discomfort. Statistics are not easy to come by (the above data were obtained from 537 questionnaires from 4924 hospitals), but kidney stones are

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said to be on the increase, absolutely and not merely by diagnosis.

More precise information is available for Czechoslovakia (*8*), where a detailed study over a period of years has been made by Mates and Křížek. In a total population of 12.74 million, the annual number of patients with stones increased steadily from 11.8 thousand in 1950 to 14.2 thousand in 1954. Thus, the average occurrence was again approximately 1 in 1000 per year, but rising. (In postmortems the incidence was more nearly 1 in 100.) As in Thailand and the United States, there is a big geographical variation, with a maximum annual incidence of above 3 per 1000 in Ostrava to one of less than 1 in 2000 in some districts. Prague has about the average incidence, 1 in 1000. As in the United States, almost all are adults with kidney and ureter stones, and nearly all of the few cases with bladder stones are elderly men. (Of 4073 patients in the Mariánské Lázně—formerly Marienbad—clinic in the 5 years from 1945 to 1950, only 73 had bladder stones, and, of all patients, only 39 were children under 15 years; 64.8 percent were men and 35.2 percent were women. But again the ratio at postmortem was 50:50.)

The inequalities in geographical distribution in Czechoslovakia (Fig. 2) could not be correlated with density of population, presence of a hospital with a urological department, height above sea level, type of climate, or character of soil or vegetation or drinking water, except insofar as these are themselves correlated with occupation; the incidence of cases with kidney stones was primarily correlated with occupation and changed in any district which changed its character in that respect. Comparison of the numbers of patients with stones with the numbers in the total population engaged in the main occupations showed that the incidence among agricultural workers was less than one-twelfth of the expected average, that among manual workers in industry was just under the average, that among administrative workers (of which there were 1.75 million) was nearly 1.6 times the average; however, among health workers (presumably more conscious of stones) hospitalization for stone was four times the average rate. An administrative worker was, therefore, more than 20 times more likely to develop a kidney stone than an agricultural laborer was.

The uneven distribution of bladder stones in Thailand is typical of what it was in Britain a century and more ago, as well as in various other parts of the world. The Norfolk and Norwich Hospital, England, which has excellent records going back into the 18th century, had some 19,000 patients during the period of 1772 to 1816, of whom 1 in 38 was there for bladder stone (Table 3). In Norwich, 1 in each 21,000 inhabitants per year was a stone case, whereas for the rest of Norfolk the proportion was 1 in 38,000, compared with 1 in 188,000 for England and Wales generally. In East Norfolk there

Table 1. Comparison of stone incidence in 1959 in Thailand. (1) Ubol Province (northeast Thailand), 1959 population 1.125 million; (2) Bangkok and district, population 1.549 million; (3) seven central and southern provinces, population 1.242 million (*26, 29*).

Province	Stone cases	Incidence (% of population)	Number of stones for 1953 to 1959 in				
			Bladder	Urethra	Kidney	Ureter	Other
1	581	0.052	2524	122	127	31	1
2	561	0.036	1335	188	928	601	44
3	12	0.001	85	10	5	1	0

Table 2. Distribution (for period 1953 to 1959) in age groups in Thailand. (1) Ubol Province, (2) Bangkok and district, (3) seven central and southern provinces (*26, 29*).

Province	Age (years)							
	Under 1	1–10	11–20	21–30	31–40	41–50	51–60	61–90
	Upper urinary tract (kidneys and ureters)							
1	0	0	2	13	28	36	10	0
2	2	19	89	391	324	323	235	132
3	0	0	0	1	0	0	1	0
	Lower urinary tract (bladder and urethra)							
1	18	1619	230	207	186	183	135	72
2	14	342	136	192	88	102	112	230
3	0	52	2	5	12	9	10	7

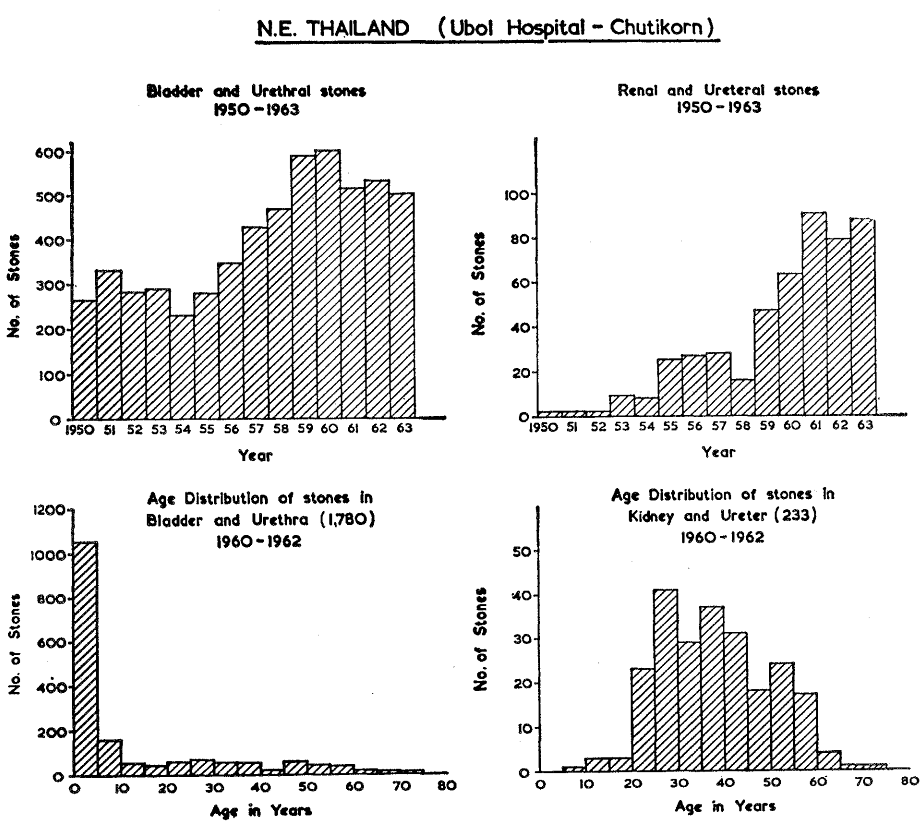

Fig. 1. (Top) Rate of hospital entries for bladder stone (left) and for kidney stone (right) over the years 1950 to 1963 in Thailand. Kidney stones, although less in number, are clearly increasing (*26*). (Bottom) Age distribution for the 1780 stones from lower urinary tracts (left) and for the 233 stones from upper urinary tracts (right) (in Ubol Hospital, 1960 to 1962). Note the very high incidence in (mainly) boys under 5 years old. Peak hospital entries were at 2½ years old, for both boys and girls.

were five times as many patients with stones as in West Norfolk, and even neighboring villages varied widely (*9*). During the years 1772 to 1830, out of 663 patients with stones in the Norfolk and Norwich Hospital only 31 were female; 292 were under 14 years old, and 161 were over 50 years old (Table 3). In Ireland, in 19 counties with a total population of 3.2 million, there were no stone patients in the 40 years before 1830. In seven counties with a total population of 1.2 million, there were nine such patients in the same 40-year period. In Cork County (800,000 people) there were 13 cases in 18 years (1 per 1.1 million per year), and in Dublin (350,000 people) there were six cases per year (1 in 58,000). It is recorded that in one boys' school in London there were so many boys with stones that a special hospital ward was kept for this school only. The bladder stones from boys and from elderly men were, in general, not of the same kind. This was shown by chemical analysis then and has been confirmed by us using museum specimens (Table 6 and Fig. 4) (*10*). Both types of stones have almost disappeared in Britain during this century, but, whereas the ammonium acid urate stones in children diminished in number rapidly during and after World War I and are now never seen, the numbers of uric acid stones in adults decreased more gradually; they still occasionally occur (Table 4) (*9*).

Among other places where bladder stones either have been, or still are, endemic are Syria, Bulgaria, China, Iceland, India, Indonesia, Madagascar, and Turkey. Yet they are very scarce in Africa today. Bladder stones, once common in Sicily, have disappeared since World War II.

Diet, Drink, and Drugs

The causes of urate stones in children and the reasons for their disappearance are not known. It is difficult to find any common denominator between small boys in Thailand today (where the ordinary country diet is glutinous rice, fruit, and—except in hot weather—fermented freshwater fish, with seeds and leaves of forest plants and salt from soil or water suspensions); boys in Norwich or in Westminster School, London, one and a half centuries ago; and Dalmatian dogs, which (as we have ourselves confirmed) have urate stones which are seldom found in other breeds (*11*). Such stones are hardly ever pure urate; they usually contain calcium oxalates also. Oxalic acid occurs in many dietary substances (Table 5) and of course in common herbs. The difficulty in trying to relate the incidence of pri-

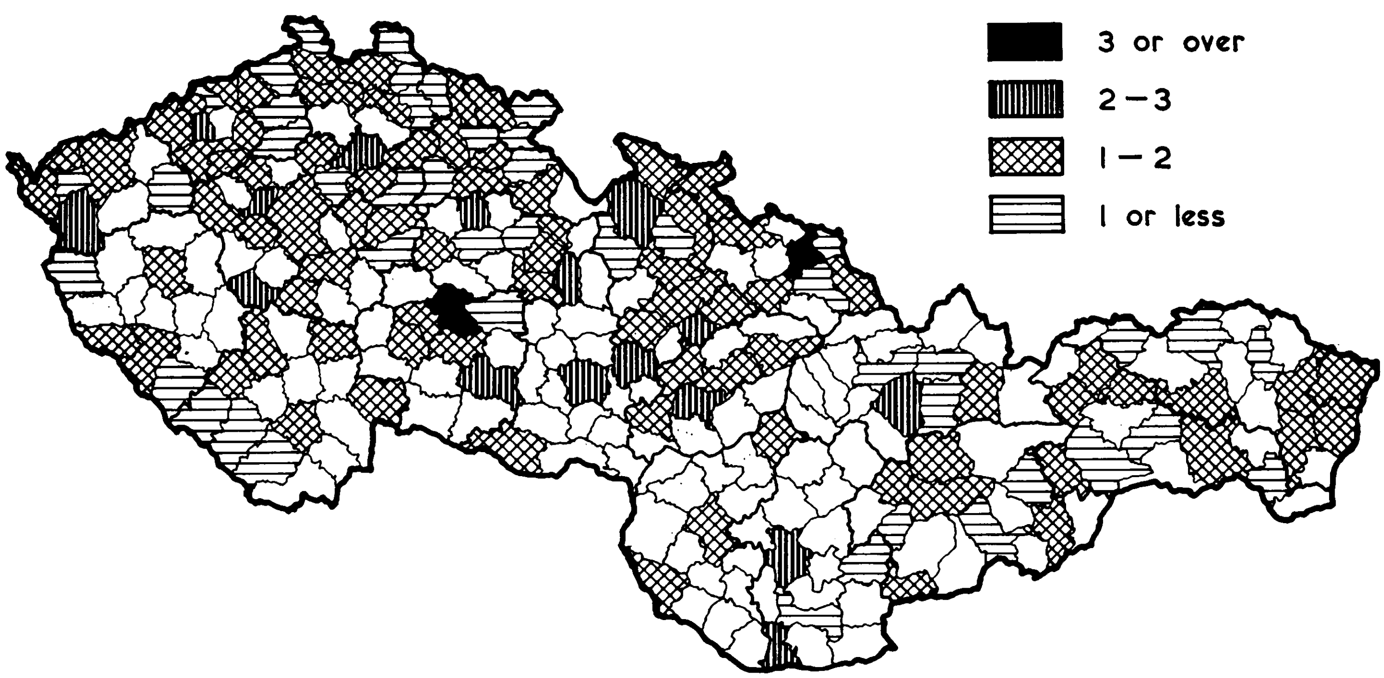

Fig. 2. Density of urolithiasis in Czechoslovakia, showing distribution of urinary calculi (1950 to 1954) measured in incidence per thousand of population (*8*).

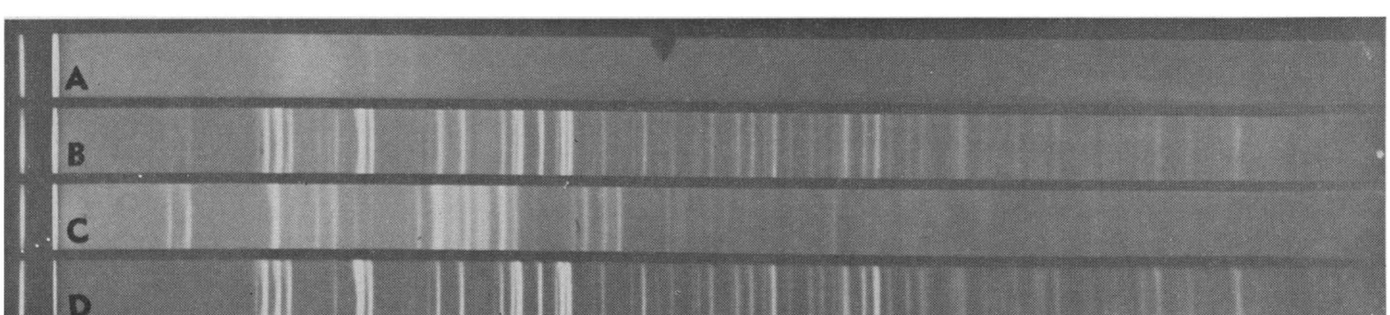

Fig. 3. X-ray diffraction patterns, Nonius camera. (A) Control: no specimen, backing and cover only. (B) Crushed fragment of bladder stone from Napoleon III, 1873 [from Sir Henry Thompson's collection (*13*)]. (C) Ammonium acid urate standard. (D) $MgNH_4PO_4 \cdot 6H_2O$ standard.

Table 3. Variable incidence of urinary calculi (mostly bladder stones) in Britain and parts of Europe in the 18th and 19th centuries, relative to all hospital admissions (*14*).

Location	Proportion of stone cases
Norfolk and Norwich Hospital (1772–1816), good records, 18,859 patients	1:38
Guy's Hospital, London (about 1800), records incomplete*	1:300
Gloucester, Worcester, Hereford, Exeter	1:394
Newcastle, York, Leeds, Manchester	1:420
Cambridge (up to 1779)	1:1140
Edinburgh	1:3000
Liverpool, Chester, Shrewsbury, North Wales	1:3223
Paris, France (adults)	1:250
Paris, France (children)	1:500
Amsterdam, Holland (1700–1733); total cases, 277 †	1:300
Amsterdam, Holland (1733–1766); total cases, 147 †	1:500
Amsterdam, Holland (1766–1799); total cases, 78 †	1:1000

* Occurrence decreasing over period. † Total admissions to hospital about 1800 to 2000 per year.

mary stones with diet, when only one person in 5000 suffers from them, is that those who have stones may be the exceptions to the general dietary pattern either because their particular diet differs in some way that seems too unimportant to mention or because they cannot assimilate the diet that others can or because some particular social occasion (harvest festival, marriage feast) or custom cuts across the normal pattern. Halstead and Valyasevi (*12*) have found that in Thailand persons in the same household (not necessarily of the same family) as a person with a bladder stone have twice the chance of developing a stone themselves; this fact does point to some dietary or social causal factor. It is important to note that these urate stones are not accompanied by the stigmata of any nutritional deficiency diseases, nor is the urine found to be infected. Another

Table 4. Age and period distribution of patients with bladder stones in Norwich and district (1871 to 1947) (*9*).

Period	Average number per annum by age groups			Total for period
	Under 20	20–50	Over 50	
1871–1880	3.6	2.5	12.6	187
1901–1910	3.5	2.1	6.2	118
1929–1938	0.4	1.3	5.9	76
1943–1947	0.2	0.6	4.6	27

factor that must be taken into account is the large amount of heavily adulterated white bread that used to be eaten one or two centuries ago in Europe in general and England in particular, the adulterants being alum, chalk, $(NH_4)_2CO_3$, and so forth. Some other possible predisposing causes are discussed later.

Uric acid stones in adults formerly occurred in Britain among wealthy elderly men [for example, in the private practice of Sir Henry Thompson (*13*)] who may have suffered from malnutrition, but certainly not from hunger. These stones were related to a high-protein, unbalanced diet with the wrong kinds of drink (water was, in any case, not safe) and to insufficient exercise. They have largely disappeared with the disappearance of gargantuan meals ("The goose is a silly bird: too much for one and not enough for two"), and with the appearance of wartime rationing and the knowledge of dietetics. Since uric acid stones can only form from an acid urine, alkalization by means of diet or drugs has been a standard treatment. But this can be overdone. Marcet (*14*) warned against the "daily and most wanton use of magnesia," and the Royal College of Surgeons catalogue (*1*) tells a horrid tale of a 77-year-old man who, having passed seven small uric acid stones, treated himself with large quantities of alkalis; after this treatment he had to be operated on, and from his bladder were removed 307 irregular pieces of stone weighing altogether 300 grams—uric acid and urates encrusted with calcium and magnesium phosphates.

As has been said already, the presence of kidney stones in adults appears to be, in part, correlated with occupation, at least in Czechoslovakia, there being many more cases among those who do a lot of sitting about than among those who are forced to lead a very active life; and it may well be that the increase in people with kidney stones parallels the increased use of cars, office desks, and armchairs. Air pilots are believed to be particularly liable to kidney stones and are advised when in tropical slip stations to "take in enough extra water or soft drinks to prevent the outward and visible sign of dehydration, which is the passing of comparatively small quantities of strong concentrated urine," and to avoid attempting to quench thirst in hot climates with beer, spirits, or strong coffee which, taken alone, "aggravate rather than improve the situation" (*15*). Diet, or adulterants in diet, such as the Rubia

Table 5. Relative occurrence of possible stone-forming substances in some common articles of food or drink. These data are very selective and must not be taken as indicating that the foods in question are harmful, since such dietary substances are also necessary to health. Units are milligrams per 100 g of fresh material (*30*).

Material	Oxalic acid	Ca	Mg	P
Stewed rhubarb	260–620	12–266	13	9–28
Spinach	460–780	112	77	60
Boiled ham	0.4	8	26	245
Boiled beetroot	121	19	38	47
White bread	5	108	24	100
Cocoa	623			
Coffee	1			
Tea (dry leaves)	1450			

previously referred to, and silica, such as that in silicate antacids at one time much used in the United States, certainly must also play some part in the formation of kidney stones.

On the other hand, kidney stones which are mainly phosphate can also be secondary to some disease (for example, bilharzia in Egypt, where the earliest such stone was found by Elliott Smith in the 7000-year-old mummy of a 15-year-old boy) or infection, especially in women. Or phosphate can deposit on any foreign body accidentally or deliberately introduced into the bladder.

Constituents of Urinary Calculi

Few stones are pure, that is, composed of only one substance. As received for crystallographic analysis they are usually dry, with most if not all high-molecular-weight organic matter gone. But Vermeulen (*16*) found that, in stones grown in the laboratory from saturated urine, the organic content was considerable. However, it is also possible to grow artificial stones from pure aqueous solution (Dr. June Sutor has done this in my laboratory with oxalate stones), and it cannot, therefore be claimed that complex organic substances are essential to crystallization in stone form.

The compounds that normally occur in urinary calculi are shown in Table 6. The key given there is based on that used in the original catalogue of the Royal College of Surgeons, England (*1*). Not all these are primary constituents; newberyite, for example, is almost certainly a product of struvite decomposition. It is found only in old stones on surfaces that have been exposed: either the surface of the stone itself or of a section (for a museum or laboratory specimen). Whewellite sometimes occurs as a pseudomorph on weddellite, and it can be obtained from weddellite by prolonged grinding, but it also certainly and frequently occurs as a primary constituent. The calcium oxalates are indeed the most common constituent of all stones. Calcium oxalate trihydrate occurs in artificial stones and may perhaps occur rarely in natural ones (*17*). The conditions for conversion of uric acid dihydrate to anhydrous uric acid I and II are not yet fully understood, but we have x-ray diffraction photographs of specimens (Fig. 6) which have been dissected out of stones without grinding and which show the actual transformation in progress. X-ray diffraction patterns often show the existence of somewhat modified forms of ordinary constituents, especially of ammonium acid urate and of octacalcium phosphate. These are not separately listed, but the possibility of mixed crystals and of modifications by impurities should be borne in mind.

Two of the constituents listed refer to very special types of stone. Cystine stones are often, though not invariably, pure. They may occur in all parts of the urinary tract in the same patient, and they often recur; they are hereditary, both in humans and in dogs. There is little, if any, evidence of a genetic factor for other types of calculi.

Xanthine stones are extremely rare, although we have found one or two. They are pinkish or yellow in color, and their cause is unknown except, perhaps, in one instance. There was, about 40 years ago (*18*), an epidemic of xanthine stones among sheep in the Nelson district, South Island, New Zealand. (We recently obtained one of these stones for analysis.) The pasture land was poor, and the epidemic died out when the land was improved by fertilization. It was later believed that the trace element originally missing was molybdenum, which normally helps to promote the oxidation of xanthine to uric acid. Xanthine stones, therefore, may probably be classed as being caused by a rare deficiency condition.

Calcium carbonate has not been found to be a constituent of human urinary calculi although it does occur in gallstones (and in some animal stones), in all three of its crystallographic forms (calcite, aragonite, vaterite), together with cholesterol as a major constituent, and occasionally with apatite, as well as with more complex organic coloring matter (*19*, *20*).

Methods for Determining Constituents

The major techniques for analysis of stones are (i) chemical, (ii) crystallographic (optical), (iii) x-ray diffraction, and (iv) microprobe analysis. This last-named method is almost too sensitive to minor impurities, and it does not distinguish between, for example, the various calcium phosphates. The chemical method requires the destruction of part of the stone, and one is not usually able to distinguish between different crystallographic phases. Nor can one identify the various calcium phosphates, except by a quantitative analysis. Chemical methods are useful, however, in distinguishing between carbonate apatite and hydroxy apatite, which is not easily done by other methods. All the early analyses were chemical ones, and the occasional reports of $CaCO_3$ were almost certainly explained by the presence of carbonate apatite. Crystallographic techniques based on the skillful use of the polarizing microscope have been widely used in recent years (*17*, *21*).

All our analyses have been made by x-ray diffraction, the photographic powder technique being used for straight identification, and stationary or rotating single crystal methods being used for the determination of texture and orientation. These methods do not analyze the whole stone, but only samples from the nucleus and surface and from such interior layers as are required to give a representative picture. The procedure and the method of analyzing and tabulating the powder data are described in references *10*, *22*, and *23*. The technique is essentially one of matching x-ray powder patterns against standards and of identification (by the fingerprint method, or by checking hunches) of any unknowns. Most stones are mixtures, and the proportions can be very roughly measured by relative line intensities, although it is not possible to detect very minor constituents except by a slower and more precise technique than would be justified in a general survey (*23*). A typical pattern, with the corresponding identification standards, is shown in Fig. 3. The specimen came from Sir Henry Thompson's collection (*13*) and was part of a bladder stone (the size of a "large date") removed by lithotrity from Napoleon III (1808 to 1873), who died after the operation. The presence of ammonium acid urate makes it likely that the stone was begun in his childhood, although the major constituent, struvite, may not have been deposited until late

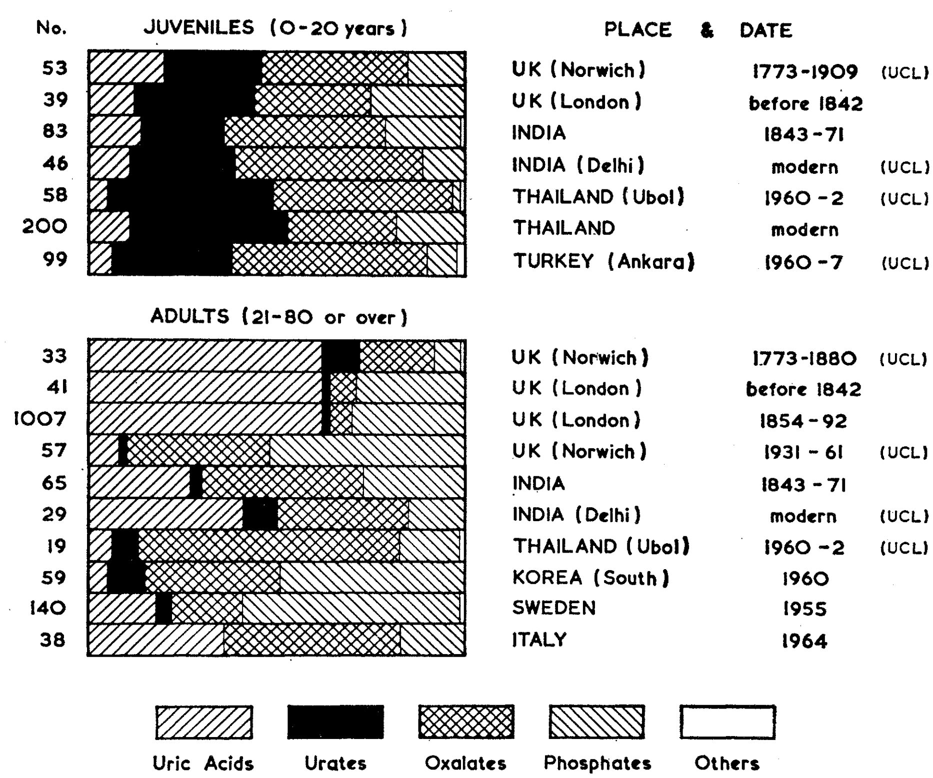

Fig. 4. Percentage composition of samples taken from various collections of stones from the lower urinary tract. Compare Table 6, where more details are given of studies made at University College, London. References and notes corresponding with successive rows are as follows: Juveniles: *31*, *1*, *55*, *32*, *33*, *6*, *34*; adults: *35*, *1*, *13*, *36*, *55*, *37*, *38*, *56*, *57*, *58*.

in life. He was known to have had symptoms of stone for a number of years, but he refused examination. It is interesting that this stone, although nearly 100 years old, contained little if any newberyite, presumably because it had been kept in a closed container.

The collected data are shown, with other results from the literature, in Figs. 4 and 5. More detailed results are given in Table 6 and in the original references, but in Figs. 4 and 5 there is a grouping which brings out certain major features. It is clearly seen that ammonium acid urate is characteristic of children's stones. It may well be that, where it occurs in adult stones, these were in fact begun in childhood. The highest proportion of urate in bladder stones (and the lowest of uric acid) is found in modern Thailand. Ammonium acid urate is also found in children's kidney stones, but these themselves are rare. They appear to occur in quantity only in modern Turkey, and the reason for this is unknown. Dietary surveys have been carried out, but they reveal no obvious cause. The uric acid content of such stones is lower than that in juvenile bladder stones. The oxalate content of all juvenile stones is very high; and, since both oxalates and urates occur together in the nucleus (whereas phosphates are more often found near to and on the surface), either of them may constitute the actual seed from which growth begins.

Early adult bladder stones in Britain contained a very high proportion of uric acid. Amounts in modern stones vary, but are consistently less. It is interesting that the incidence of uric acid in stones from American males seems to be higher than that in females (*24*), who perhaps eat less meat. The apparently high incidence in Spain is not reliable because the sample is small. Adult kidney stones generally are mainly oxalates and phosphates.

No survey of gallstones has been undertaken at University College, London, although we have studied a few interesting ones (*20*).

Crystal Nucleation and Growth

Crystal growth in vivo consists of deposition from a saturated or supersaturated solution or of precipitation from a chemical reaction (possibly by diffusion of the reactants through a gel), followed by deposition on the nucleus

Table 6. Weighted percentage composition of collections studied at University College, London, determined with x-ray diffraction techniques. Numbers in parentheses are references describing the collections.

Identification key for substances found in urinary calculi

A1	Anhydrous uric acid I	$C_5H_4N_4O_3$ (usual form)	C2	Weddellite	$CaC_2O_4 \cdot 2H_2O$ (to 2½ H_2O)	F4	Whitlockite	β-$Ca_3(PO_4)_2$
A2	Uric acid dihydrate	$C_5H_4N_4O_3 \cdot 2H_2O$	D	*l*-Cystine	$[-SCH_2CH(NH_2)COOH]_2$	F5	Octacalcium phosphate	$Ca_8H_2(PO_4)_6 \cdot 5H_2O$
A3	Anhydrous uric acid II	$C_5H_4N_4O_3$ (rare)	E	Xanthine	$C_5H_4N_4O_2$	G1	Newberyite	$MgHPO_4 \cdot 3H_2O$
B	Ammonium acid urate	$NH_4C_5H_3N_4O_3$	F1	Carbonate apatite	$Ca_{10}(PO_4,CO_3,OH)_6(OH)_2$	G2	Struvite	$MgNH_4PO_4 \cdot 6H_2O$
C1	Whewellite	$CaC_2O_4 \cdot H_2O$	F2	Hydroxy apatite	$Ca_{10}(PO_4)_6(OH)_2$	J	Sodium acid urate	$NaC_5H_3N_4O_3 \cdot H_2O$
			F3	Brushite	$CaHPO_4 \cdot 2H_2O$	X	Unidentified	

Country	Period (century)	Stones (No.)	Uric acids			Urates		Oxalates		Calcium phosphates					Magnesium phosphates		Others
			A1	A2	A3	B	J	C1	C2	F1	F2	F3	F4	F5	G1	G2	D, E, or X
								Bladder and urethra; juvenile									
U.K. (*31*)	18–19	53	19	>1	0	26	0	35	4	<2	<2	<1	0	>0	8	3	>0
India (*32*)	20	46	10	1	0	27	1	39	11	0	<1	0	<1	0	0	10	0
Thailand (*33*)	20	58	4	1	0	44	>0	26	22	1	>0	0	0	0	0	1	<1
Turkey (*34*)	20	99	5	1	>0	32	0	38	14	2	1	0	0	0	0	5	2
								Bladder and urethra; adult									
U.K. (*35*)	18–19	33	59	3	0	9	1	19	1	<1	<1	0	0	0	4	1	<1
U.K. (*36*)	20	57	6	2	0	2	0	28	10	11	6	<1	<1	>1	<1	31	0
India (*37*)	20	29	40	2	0	9	<1	30	5	>1	3	1	<1	0	0	9	0
Thailand (*38*)	20	19	5	1	0	7	0	32	37	5	<1	1	0	0	0	9	<1
Turkey (*39*)	20	5	0	0	0	12	2	40	14	2	10	0	6	2	0	11	0
								Bladder and urethra; ages uncertain									
U.K. (*40*)	19	8	26	0	0	19	0	24	0	0	10	0	0	0	3	3	15
Indonesia (*41*)	20	40	1	0	0	13	0	46	6	2	2	>0	0	0	12	18	0
								Kidney, ureters, and pelvis; juvenile									
Turkey (*42*)	20	110	2	0	0	24	2	45	12	4	1	0	1	0	>0	7	2
India (*43*)	20	12	<1	1	0	16	0	49	13	3	>1	0	0	0	0	11	5
								Kidney, ureters, and pelvis; adult									
U.K. (*44*)	20	10	0	0	0	0	0	10	17	20	4	0	3	0	0	38	9
U.K. (*45*)	20	70	2	1	0	1	>0	28	15	18	15	6	3	2	>0	9	0
India (*46*)	20	28	0	0	0	3	0	55	19	2	10	0	1	1	0	8	1
Thailand (*47*)	20	106	4	0	0	2	1	43	5	18	6	0	2	2	2	15	>0
Turkey (*48*)	20	30	4	1	0	3	0	60	20	4	2	0	>1	0	0	5	0
Spain (*49*)	20	18	21	>0	0	1	0	12	1	21	11	0	0	0	0	28	5
								Type uncertain or ages not known									
U.K. (*50*)	20	38	10	3	0	<1	0	17	9	14	8	0	<1	0	0	30	8
Turkey (*51*)	20	18	8	4	<1	22	4	35	14	3	1	0	0	0	0	8	0
Spain (*52*)	20	99	20	1	0	4	<1	26	10	12	7	0	<1	<1	0	16	2
Sicily (*53*)	20	9	4	0	0	6	0	51	10	11	4	0	3	0	2	9	0
Rhodesia (*54*)	20	3	4	0	0	26	0	22	0	9	0	0	0	0	0	39	0

so formed. If the material deposited is of the same kind as the seed, then it occurs from a just-saturated urine, but if the composition of the urine (or the bile) changes, deposition can still occur, but a degree of supersaturation is required. All stone-forming compounds are relatively insoluble. If it were not so, any stones formed would soon redissolve, but, more important still, it would be impossible to attain the degree of saturation necessary for stone formation. Vermeulen (*16*) has shown that the solubilities of the common stone-forming compounds in urine increase markedly with an increase of temperature, a change in *p*H, or a change in the chemical composition of the solvent. Uric acid is so soluble in alkaline urine that it cannot form stones; the same is true, in reverse, of phosphates in an acid urine. The calcium oxalates are so insoluble that they can, unfortunately, easily form supersaturated solutions in urine at any *p*H in the range normally found in humans, and it is likely, therefore, that whewellite or weddellite forms the nucleus of many stones. Deposition from a supersaturated solution can occur with a lowering of temperature, a change of *p*H, or violent agitation, although the original state of supersaturation may depend on a condition of quiet for its attainment.

It follows that the formation of a nucleus occurs most easily when the urine has become very concentrated either as the result of too little water having been taken in to replenish the body fluids [and it is well known (*3*, *25*, *26*) that symptoms of stone often appear first in very hot weather or, as in the case of air pilots (*15*), where the body has become temporarily dehydrated] or when a condition of high temperature plus acute acidity (or alkalinity) is followed by an abrupt change. In the case of malaria or other diseases, dehydration, fever, and acidity may all occur simultaneously, and it is possible, therefore, that the disappearance of stones in children in some areas may match the disappearance of malaria or the discovery of those drugs which reduce fever before it has had time to effect any serious dehydration, and which correct acidosis.

Suppose, however, that a seed has formed. If it remains small, it may be soon washed out; even if it becomes attached to a wall, it may be relatively harmless provided that it grows no bigger. Vermeulen (*16*) has shown that of 50 healthy male students, two-thirds had urine that was either saturated or supersaturated with respect to uric acid. This would not matter, provided that the urine did not contain or develop any seed on which uric acid could deposit as an overgrowth. Such deposition would occur most readily (*27*) only if a close epitaxial relationship existed between the substrate and the deposit; that is, if the faces normally occurring on each happened to match each other geometrically. The match can be either between $a \times b$ and $a' \times b'$ or between $na \times mb$ and $n'a' \times m'b'$, where a (a') and b (b') are the network translations and n, n', m, and m' are small integers. If they do match, then an orientated overgrowth results. The degree of misfit that is tolerated is dependent upon the degree of supersaturation in the depositing solution (*28*). Some degree of structural matching may also be important, but that the geometrical fit is the essential factor may be seen from the wide range of substances between which such an epitaxial relationship has been found to occur; for example, ice on AgI, camphor on quartz, urea on NaCl, anthraquinone on NaCl, and so on (*29*). It is the basis of the seeding of rain clouds and the basis of many useful industrial processes, such as the manufacture of synthetic diamonds. Table 7 shows the amazingly close geometrical fit between naturally occurring faces in uric acid, whewellite, and weddellite. It is no wonder that uric acid deposits on a seed of either of the calcium oxalates. If this quite fortuitous dimensional match did not occur, a urine highly supersaturated with uric acid could continue to exist until it was voided, without much danger of deposition except in the form of sand or gravel, easily washed away. The passing of sandy urine, however, should be taken as a danger signal, because any calcium oxalate nucleus might well cause retention of the uric acid solute as an epitaxial deposit which would grow the more easily the longer the acid condition lasted, until the stone became too big to void. The "tree-ring" layers in many stones almost certainly correspond with diurnal or seasonal varia-

Table 7. Geometrical relationship between the orthogonal network dimensions (Å) for common faces of uric acid, whewellite, and weddellite (*27*).

Substance	Face	Dimensions	Misfit (%)	
Uric acid	(100)	6.21 × 7.40		
Whewellite	(001)	6.28 × 14.57	1.1	1.6
Weddellite	(101)	12.30 × 14.32	1.0	3.3

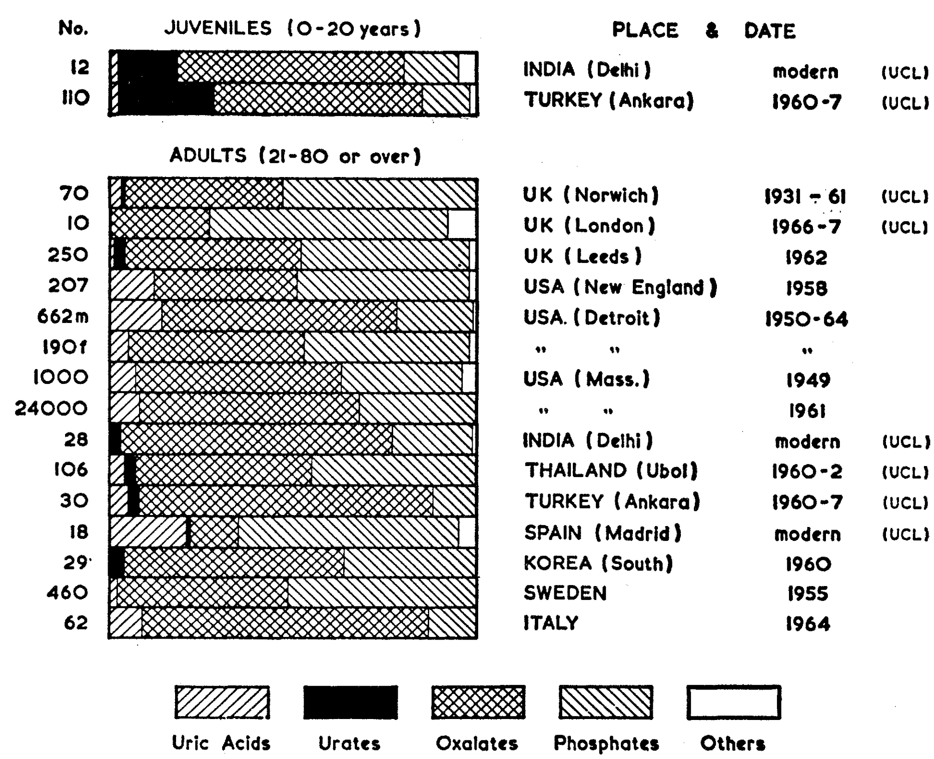

Fig. 5. Percentage composition of samples taken from various collections of stones from the upper urinary tract. Compare Table 6. For successive rows references and notes are as follows: Juveniles: *42, 43*; adults: *45, 44, 59, 60, 24, 24, 21, 17, 46, 47, 48, 49, 61, 57, 58*.

tions in *p*H (or less certainly, urine temperature). Other possible epitaxial relationships are listed in reference *27*, where it is also shown that the limited number of compounds that do crystallize with cystine in cystine stones, or with cholesterol, or each other, in gallstones are just those for which a possible geometrical fit exists. Uric acid does not have a network that could match any in cystine, even if an alteration of *p*H caused high supersaturation with respect to uric acid in the presence of a cystine nucleus.

Epitaxy involves orientated overgrowth, and therefore, if epitaxy occurs, crystalline orientation in stones should exist. There may, of course, be several simultaneous orientations if the substrate or seed has symmetrically equivalent faces on which growth occurs. If there is appreciable misfit, deposition will occur from an appropriately supersaturated solution, but the deposit will be of small crystallites and not of large single crystals. X-ray photographs (Fig. 6) taken from numerous specimens cut without powdering do show marked orientation (indicated by the breaking up of the powder rings into a symmetrical pattern of arcs or spots) when the specimen is either left stationary or allowed to rotate about a particular direction of preferred orientation, for example, a radial direction in the stone. So far, we have found such preferred orientation in various stones containing uric acid, uric acid dihydrate, whewellite, weddellite, brushite, xanthine, and struvite (also in cholesterol in gallstones); and although ammonium acid urate and apatite occur only in finely divided powdered form, yet even these sometimes also show preferred orientation (by symmetrical intensity variations in the powder rings). It is not possible, by x-ray techniques, to ascertain which crystal faces actually grow on one another, but the dependence of stone growth on epitaxial relationships seems certain. This raises the question of whether habitual stone-growing might be controlled by normal crystallographic techniques of habit modification. The procedure from which the most benefit might come would perhaps be to synthesize compound stones, based on epitaxy, in the laboratory and then to attempt to hinder growth by the deliberate introduction of habit-modifying or size-modifying impurities at the stage of nucleus formation.

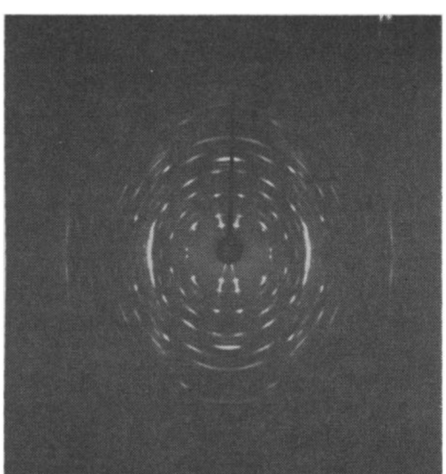

Fig. 6. X-ray pattern, Unicam camera, from a specimen cut without powdering and set in the camera with the "layer" direction horizontal (that is, parallel to the equator on the photograph). This specimen was from the stone shown on the cover of the 10 June 1966 issue of *Science*. The pattern shows clearly the actual transition from uric acid dihydrate to anhydrous uric acid, the whole having strong preferred orientation (*62*).

Summary

X-ray diffraction studies have shown that there are several different kinds of human urinary calculi, with different age, sex, period, and geographical distributions. Juvenile bladder stones are typically urate and oxalate in small boys in certain stone belts. They have disappeared in some areas, particularly in Britain, but are still common in Thailand, India, and Turkey. Their cause is unknown. Adult bladder stones, formerly common in elderly men, were largely of uric acid and were due to a faulty diet. Juvenile kidney stones are rare, except in Turkey where they are similar to juvenile bladder stones. Adult kidney stones are by far the most universally common, especially in technically developed communities. They are found in both sexes (equally at postmortem), and in the United States and in Czechoslovakia the average number of hospital entries for stones, relative to the whole population, is about 1 per 1000 per annum (increasing) although the incidence in different districts varies by 4 to 1 or more. Such stones are mainly calcium oxalates and calcium and $MgNH_4$ phosphates. The incidence among the administrative class is at least 20 times that among agricultural workers, relative to their numbers. Stones are reported also to be an occupational hazard for air pilots. It is probably that much more exercise and the drinking of more water to prevent kidney dehydration (spirits and coffee are not effective for this purpose) would lower the high rate of incidence. Moderate acidification would prevent phosphate supersaturation of the urine, but is not effective for oxalates.

It seems certain that, once a suitable seed is formed, epitaxy is largely responsible for deposition from urines that would otherwise remain supersaturated until voided. This would explain the curious radial and layered texture of many stones. Laboratory experiments might suggest ways of preventing orientated overgrowth.

References and Notes

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33. Collection from Ubol Hospital, northeast Thailand (1960 to 1962), by courtesy of Dr. Cholvit Chutikorn. All are bladder stones; 49 from males, 9 from females; ages 10 months to 12 years; weights 0.05 to 16 g. Studied at UCL.
34. Collection (1963 to 1967) from Ankara Hospital, Turkey, by courtesy of Dr. Remzi and Dr. Eckstein; 74 bladder stones from males, 5 from females; 19 urethral stones from males, 1 from female. Ages 2 to 17 years; weights 0.04 to 13 g. Studied at UCL.
35. From collection described in *31*, but 30 stones from males, 3 from females: ages 21 to 75 years; weights of half-stones 10 to 171 g. Studied at UCL.
36. Collection from Norfolk and Norwich Hospital (1931 to 1961) by courtesy of Dr. J. M. R. Thomas. There were 50 bladder stones and 3 urethral stones: 4 others were from the lower tract; 32 from males, 5 from females; and 20 for which the patient's sex was not recorded; 4 from juveniles 5 to 17 years old, 53 from adults 21 to 78 years old: weights 0.1 to 51 g. Studied at UCL.
37. From collection described in *32*, but from patients 22 to 77 years old; 28 from males, 1 from a female; weights 1.3 to 88 g. Three are urethral stones. Studied at UCL.
38. From collection described in *33*, but these are all bladder stones from male patients 25 to 89 years old. Weights 0.2 to 8.2 g. Studied at UCL.
39. From collection described in *34*, but these from patients 24 to 75 years old; all from males; weight 3.8 to 7.4 g. Studied at UCL.
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43. From collection described in *32*; 7 kidney and 5 ureter stones from males 3 to 16 years old; weights 0.14 to 1.3 g. Studied at UCL.
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45. From collection described in *36*; 60 kidney stones (23 from males, 22 from females, 15 not recorded); 10 ureter stones (5 from males, 4 from females, 1 not recorded). 2 from juveniles (9 to 10 years old), 68 from adult (24 to 71 years old). Weights 0.08 to 68 g. Studied at UCL.
46. From collection described in *32*; 16 kidney stones from males, 5 from females; 7 ureter stones from males; ages 20 to 52 years. Weights 0.6 to 28 g. There was some partially dehydrated octacalcium phosphate in one stone. Studied at UCL.
47. From collection described in *33*. All are kidney stones, 70 percent from males; one 17 years old, remainder 21 to 68 (+) years old. Weight 0.05 to 10 g. Studied at UCL.
48. From collection described in *34*; 14 kidney stones from males, 4 from females; 8 ureter and pelvis stones from males, 4 from females. Weights 0.1 to 3.4 g. Studied at UCL.
49. Madrid, Spain, by courtesy of Dr. Font-Altaba, Presumably modern; 8 from males, 5 from females, 5 not recorded; ages not recorded. Weights 2.5 to 182 g. Studied at UCL.
50. From collection described in *44*, but including also 6 from males, 11 from females, 21 sexes not recorded; ages recorded, 26 to 72 years. Weights 0.1 to 30.7 g. Studied at UCL.
51. From collection described in *34*; probably kidney stones, but no record of age; 13 from males, 5 from females. A high percentage of ammonium acid urate indicates that the stones were probably from juveniles. Weights 0.1 to 3.4 g. Studied at UCL.
52. From collection described in *49*, but type not recorded; 57 from males, 26 from females, 16 sexes not recorded; ages not recorded. Weights 0.01 to 105 g. Studied at UCL.
53. Palermo, Sicily, by courtesy of Dr. D. A. Andersen; 3 bladder stones, all from males aged 18, 22, and 33 years; 6 kidney stones, no further information given. Weights 2.4 to 13.7 g. Studied at UCL.
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63. This work was supported by a grant from the Medical Research Council, Great Britain. I thank Dr. D. A. Anderson for introducing me to this problem and for much help in obtaining collections, and my colleagues Dr. D. June Sutor and Mrs. S. E. Wooley for all experimental data.