M.Sc. Biochemistry

THE CHEMICAL COMPOSITION OF URINARY CALCULI AND ITS SIGNIFICANCE

by

SARAH MENDELSON KORENBERG

Submitted to the Faculty of Graduate Studies and Research in partial fulfilment of the requirements for the degree of Master of Science.

McGill University
Montreal

April, 1944

ACKNOWLEDGMENT

I gratefully acknowledge indebtedness to

Dr. John F. McIntosh

for invaluable suggestions and criticisms

in the preparation of this report.

Assistance in the work was obtained through

a grant from the Cooper Fund awarded by the

Faculty of Medicine of McGill University.

C O N T E N T S

REVIEW OF LITERATURE

The history of urinary calculi dates back many thousands of years when their occurrence was quite marked; as living conditions have become better, and people have become healthier, their frequency has decreased.

The earliest listed publication describing urinary calculi dates back to 1614 when Untzerus published, in Latin, a treatise on stones. In 1739, all of England was in an uproar because an Englishwoman claimed to have concocted a cure for kidney stones. Her formula included the use of dried birds' eggs and soap. Parliament convened in a special session to give her a grant to continue her work. It was not until 1776 that a scientific approach was applied to the problem of kidney stones. At that time Scheele first described the uric acid calculus, calling it "lithic acid" and he noted that "lithic acid" was a natural constituent of urine. In 1792 Wilson discussed the cause of urinary calculi, and suggested that it lay in the faulty action of the kidneys and the skin.

As far back as 1810 Wollaston (1) observed the effect of diet on the formation of uric acid calculi and suggested a vegetable diet rather than a fish and meat diet for their prevention. He observed, too, for the first time, the cystine calculus which he termed "cystic

oxide" calculus.

For more than a hundred years little was attempted in solution of the problem of the cause of urinary calculi. But in 1917 Osborne and Mendel (2) observed that rats "without an adequate source of the fat-soluble vitamin for some time" developed calculi, which consisted mainly of phosphate.

In 1925 the association of infection with stone formation was noted by Hager and Magath (3). During a study of cases of encrusted cystitis with alkaline urine, they observed the presence of bacteria in catheter specimens of urine. Amongst the bacteria, they found Salmonella ammoniae which is capable of splitting urea into ammonia and carbon dioxide in a very short time with resultant formation of an alkaline urine and precipitation of calcium and magnesium salts. Salmonella ammoniae is a natural inhabitant of the gastro-intestinal tract. The authors suggested that the urinary calculi commence to grow on a primary lesion, salts precipitating out on this lesion due to the action of bacteria.

McCarrison (4) produced kidney stones in rats fed a diet low in protein and vitamin A, and rich in phosphates, lime and magnesia. The faulty diet may have had a toxic action on the urinary tract. The following

year (5), he confirmed these experiments and showed that a diet rich in cereal foods and phosphates and deficient in vitamin A (the diet common in Northern India) produced stone formation in rats. The same year (5) he noted that addition of whole milk, two-thirds ounce per rat daily, completely prevented the development of phosphatic calculi. He concluded that renal calculus formation was due to insufficiency of vitamin A and that cystitis was not a necessary forerunner.

In 1929 Joly (6) suggested that calculi should be divided into pure and mixed types, and noted that low standards of living were associated with renal stone formation, whereas high standards were not.

Spitzer and Hillkowitz (7) believed that the abnormal solubility of the stone-forming salts is a consequence of the presence of certain colloids in the urine. Newcomb (8) investigated this hypothesis and concluded that the influence of colloids in the precipitation of urinary salts was of doubtful significance.

Ranganathan (9) tried to correlate diet with the composition of stones artifically produced in rats. He found a close relationship between calcium-rich calculi and extra lime in the diet, and magnesium-ammonium-phosphate calculi and no lime in the diet. The calcium

stones occurred usually as calcium carbonate and were poor in phosphate. Neither the calcium nor the magnesium stones contained uric acid. There was no association between the location of the stone and its chemical composition.

In 1932 Medes (10) showed that urea increases the solubility of calcium oxalate, uric acid and sodium urate in the urine.

In 1933 Bliss (11) observed that phosphate stones predominate in vitamin A deficient individuals; that diets deficient in vitamins A and D may produce stones by improper phosphorus metabolism which may result in other metabolic upsets; that renal infection and stasis may cause calculus formation; and that calcium calculi are the result of a disturbed calcium metabolism.

Bugbee (12) reviewed a series of 23 cases, and showed that pyelonephritis was a forerunner of calculus formation. In the acid urine of 16 patients, he found the colon bacillus with a predominance of calcium oxalate and few uric acid stones. In alkaline urine and in the presence of cocci, he found a preponderance of phosphate stones. All the patients had chronic constipation. He concluded that the calculus requires a nucleus, and that this nucleus may consist of mucus, pus (bacteria) or

desquamated epithelium. To him the role of infection was important.

Higgins (13) investigated the relationship between faulty diet and calculus formation. He noted that the incidence of the occurrence of vesical calculi was greater in poorly fed children than in those on better diets. Feeding vitamin A deficient dates to a group of 200 rats (with 25 controls) he observed no stone formation in the controls; at the end of 200 days, 88% of the vitamin A deficient animals showed urinary stones. A deficiency of vitamins B, C or D did not produce the same results. Injections of streptococci produced abscesses in many organs but did not cause calculus formation. He observed that alkalinuria is constant in vitamin A deficiency. A diet of citrus fruits produced phosphates in the urine. Increase of vitamin A in the diet dissolved a few stones.

In 1935 Berglund and Medes (14) discussed the role of vitamin A deficiency as a cause of urinary calculus formation and concluded that other factors were involved as well, and that the nature of the diet had an influence on the composition of calculi. They pointed out that Europeans have a predominance of urate stones, while the Japanese have a predominance of oxalate stones. In

general, calculi are common where the diet is very monotonous, and are uncommon where the diet is varied. They suggested that conditions favoring acidity of urine or a rapid excretion of calcium would produce conditions favorable for coagulation of any irreversibly precipitating colloid present in urine.

Keyser (15) too, pointed out that vitamin deficiency was not the only factor involved in stone formation. He suggested changes in the pH of the urine as a controlling factor in stone formation.

Snapper (16) suggested that the renal calculus has a central nucleus consisting of mucin, fibrinogen, foreign body, etc., and that growth of the stone is due to incrustation of concentric colloid layers. Calcium carbonate and phosphate calculi were precipitated only in alkaline urine; acidification of the urine prevented their formation. He recommended the use of acid ash diets supplemented by large amounts of vitamin A.

Randall (17) suggested that there was a fundamental single cause of stone formation with secondary factors which cause chemical composition to vary in individual cases. He was of the opinion (18) that vitamin A deficiency causes injury to the epithelial lining of the urinary tract and that this acts as forerunner to calculus

precipitation. He suggested hyperparathyroidism, avitaminosis, urinary colloid imbalance and infection as possible causes of calculus formation. From his experiments on animals he concluded that renal calculus formation is dependent upon a pre-existing lesion in the renal papilla.

Domanski (19) reported the qualitative analysis of 35 "mixed" stones, i.e., stones composed of more than one single component. He pointed out the universal occurrence of phosphates, almost always accompanied by calcium oxalate, but less often associated with calcium carbonate. Triple phosphate he found to be a most insoluble substance, its solubility varying greatly with changes in pH.

Sisk (20) investigated the solubility of the relatively insoluble salts in the urine and found that phosphates are more soluble in an acid pH, that uric acid is less soluble in acid pH, that calcium oxalate is not greatly affected by pH change over physiologic ranges, and that neutral salts increase the solubility of all three. He discounted the influence of colloidal substances in the urine, pointing out that calcium oxalate solubility is the same in water as in the presence of urinary colloids.

In 1937 Albright (21) suggested the forcing of fluids as an aid in the treatment of kidney stones. He pointed out that the more dilute the urine, the less chance for the precipitation of salts, the dilution also having a mechanical flushing-out effect. He considered that cystine stones, which were hereditary, and uric acid stones (found in gout), could be prevented from forming, by maintaining the urine alkaline. He found that urinary infections with urea-splitting organisms were a common cause of alkaline urine, with precipitation of phosphate salts, and he suggested the use of an acid ash diet and the administration of ammonium chloride in such conditions. Neither acid nor alkali therapy could prevent precipitation of calcium oxalate stones.

Siddall (22) reported that in Southern China renal stones were rare, but that vesical calculi were quite common in occurrence. He found stones in rats fed a diet rich in vitamins A and D, and calcium. In 37 human cases with vesical calculi, which included uric acid, urate and oxalate stones, there was no endocrine factor involved. The diet was rich in carbohydrate and vegetables, and poor in meat and fruit, but adequate in its vitamin A and D content.

In a discussion of the influence of the dietary

calcium/magnesium ratio, Hammarsten (23) suggested that a diet low in magnesium or calcium or both caused the formation of calculi, and that a low vitamin A and D intake was contributory. If the diet yielded a low urinary pH, calcium oxalate stones were formed; in the presence of a higher pH, phosphate, carbonate and citrate stones occurred. Out of a total of 64 renal stones which had been experimentally produced in rats by diet, this author was able to show roentgenographic evidences of decalcification in 40%. The decalcification was produced by means of a regulated diet. However, only 2 out of 15 bladder stones showed evidences of decalcification after the feeding of a similar diet.

Albright (24) considered that some disturbance causes precipitation of crystalloids from the urine and that treatment should aim to alter the composition of the urine to favor solution of the crystalloid. He proposed that urine should be made acid for dissolving calcium phosphate stones, and alkaline for uric acid and cystine stones. However, changing the pH of the urine had no effect on calcium oxalate stones. He administered a citrate solution by ureteral catheter and was successful in dissolving some phosphatic precipitates. The latter treatment was employed because attempts to dissolve

phosphate stones by making the urine acid were ineffective, due to the increased excretion of calcium and phosphate in acid urine. Later it was discovered that the citrate solution caused inflammatory reactions in the mucous membrane of the urinary tract. The addition of magnesium to the citrate solution ("solution G") caused an inhibition of this irritative effect.

Flocks (25) studied the quantitative excretion of calcium and phosphorus in the urine of 23 patients with urinary tract infections. Included in the group were two patients with hyperparathyroidism but without bone changes. All cases that presented rapidly growing urinary calculi manifested a high urine calcium excretion. The feeding of an acid ash diet to these individuals resulted in no significant change in the rate of progress of the renal lesion. It is of significance that such a diet actually produced harmful effects when fed to persons whose urine cultures revealed the presence of urea-splitting organisms. Total calcium and phosphorus excretion was found to be independent of water excretion. Since precipitation of these substances is dependent in part, upon their concentration in the urine, this tendency may be inhibited by maintaining a large volume of urine excretion.

Schneider (26) fed rats a diet low in phosphorus but adequate in vitamin D content and obtained a high urine citric acid excretion in these animals. The urinary calculi which were formed consisted mainly of calcium citrate. Similar stones have been but rarely reported to occur in human beings. This rarity may be more apparent than real, since analysis for the citrate radicle is only uncommonly performed.

Chute (27) found that 75% of a series of 90 patients afflicted with renal calculi showed evidences of infection in the urinary tract. Urea-splitting organisms were isolated from 54% of all urines studied. Such urines are rendered alkaline by the free ammonia produced by the action of these bacteria, and calcium phosphate and carbonate salts are precipitated. On the other hand, urines which are sterile on culture are apt to be of acid pH. Only 29% of cases with sterile urine cultures showed recurrence of kidney stone after surgical removal, whereas 73% of patients whose urines were infected with urea-splitting bacteria had recurrences.

Bodansky (28) has noted that in many instances of renal calculus formation the urine is alkaline in reaction. Thus he found that the incidence of occurrence of these stones in Florida, California and Kentucky is

seven to fifteen times that in New York, Ann Arbor, etc., suggesting that the higher incidence is related to the alkaline ash diet prevalent in southern states. Kidney stones are found four times more frequently in whites than in negroes, and this is attributed to the high acid ash, high vitamin A diet of the negro. This author believes that hyperparathyroidism is the cause responsible for 4% to 5% of all cases of renal stone formation.

Hammarsten (29) has commented upon the change in composition of present-day stones as compared with those of former times. Whereas formerly the phosphatic and uric acid calculi predominated, the present day is characterized largely by oxalate stones.

White (30) states that calcium oxalate and calcium phosphate predominate in renal stones, whereas uric acid and urates predominate in vesical calculi. He regards all stones as "mixtures" consisting of calcium oxalate, calcium-magnesium-phosphate and ammonium-magnesium-phosphate. He points out that serious infection may or may not develop in patients with urinary stones and that infection of the urinary tract bears no relationship to the size of the stone. Since the surface of uric acid and urate stones is smooth they tend to escape more readily down the ureter. On the other hand,

oxalate stones which are usually rough, tend to become impacted, contaminated and large.

Barrett (31) has observed that the presence of calcium oxalate crystals in the urine may lead to the formation of calcium oxalate stones, and that such crystals are usually found in the urine after eating rhubarb and spinach which are rich in oxalates. In humans, he found that urinary excretion of oxalate may be constant over a period of several days if the diet is kept constant. Since the absorption of oxalate from the intestines is closely associated with that of calcium, he suggests that a meal containing much soluble oxalate be accompanied by the ingestion of milk. In this way the tendency to alimentary oxaluria is minimized and the formation of oxalate stones inhibited.

Mention must be made of two instruments which were introduced in 1942 to further aid in the study of urinary calculi. The teleprobe (32) is "a hypersensitive electrical instrument so constructed as to detect by means of sound amplitude, calculi within the ureter and kidney". The polarizing microscope (33) is important in the identification of urinary calculi. However, it cannot be used by itself but must be accompanied by chemical analyses to verify the results obtained.

In 1943 Dowling and Lepper (34) pointed out that of 82 patients receiving sulfadiazine for the treatment of meningitis or endocarditis, 5 developed renal calculi; of 9 patients with meningitis or endocarditis treated with sulfapyridine, one developed renal stone; and of 4 patients receiving sulfathiazole, none developed calculi. Therapy consisted of forcing fluids and cystoscopy. They showed that the formation of renal calculi is a serious and sometimes lethal complication of sulfonamide therapy and that the proper relationship between fluids and sulfonamide intake is the key to their prevention.

In a study of 98 individuals suffering from urinary calculi, Jewett et al (35) noted no evidences of vitamin A deficiency. These workers were unable to confirm the theory that subclinical vitamin A deficiency may serve as an etiologic factor in kidney stone formation.

LaTowsky (36) has recently reported his results of the qualitative analyses of 150 renal stones. He listed the stones in the following order of decreasing frequency: calcium oxalate; calcium phosphate; ammonium magnesium phosphate; calcium ammonium phosphate;

calcium carbonate; ammonium urate; uric acid; cystine; magnesium carbonate; sulfadiazine stones. His methods of qualitative analysis differed from those employed in our laboratory.

PURPOSE OF PRESENT STUDY

The present study was undertaken to extend the series of observations noted by McIntosh. (37,38) A larger number of stones was analysed and then grouped according to the classification outlined by that author. The data obtained from analysis of this series of calculi were compared with those published previously by other workers, in order to observe differences in the composition of stones occurring in various countries.

The analytic technique was designed principally for qualitative determinations. However, a rough quantitative estimate of the different substances present could be made employing the methods described below and this was recorded according to the usual + to ++++ grading.

CLINICAL MATERIAL

The stones analysed were all obtained from humans; they included concrements which were either passed spontaneously or were removed surgically. Of the three hundred and fifty-five stones analysed, 214 stones were obtained from patients treated at the Royal Victoria Hospital and 141 stones were received from the Montreal General Hospital (the latter through the kindness of Dr. I. M. Rabinowitch). The Royal Victoria Hospital stones included calculi obtained from patients hospitalized in the urology wards; on the other hand, the Montreal General Hospital stones included specially selected calculi.

Actually, many more than the 355 stones reported were analysed. The reason for this is that each patient was counted once only, irrespective of the number of recurring stones he developed. Only when these recurring calculi differed from their predecessors were they counted as separate stones.

METHODS

The chemical analyses were carried out according to the methods previously described by McIntosh and Salter (37) in 1942.

Reagents.

Hydrochloric Acid, Concentrated.

Nitric Acid, Concentrated.

Ammonium Hydroxide, Concentrated.

3 per cent Ammonium Molybdate.

Nessler's Reagent.

Sodium Acetate, Saturated Solution.

2 M Ammonium Chloride -- 10.7 grams NH_4Cl dissolved in 100 ml. of water.

0.4 M Oxalic Acid -- 5.0 grams $C_2H_2O_4$, 2 H_2O in 100 ml. of water.

1 M Disodium Hydrogen Phosphate -- Dissolve 35.8 grams Na_2HPO_4, 12 H_2O in 100 ml. of water.

1 N Sodium Hydroxide.

5 per cent Sodium Cyanide.

Sodium Nitro-prusside Reagent. Dissolve 10 grams of the solid in 100 ml. of distilled water, adding 2 ml. of concentrated sulphuric acid.

Diazo Reagent. This must be freshly prepared by adding 0.3 ml. of 0.1 per cent Sodium Nitrite to 10 ml. of 0.1 per cent Sulphanilic Acid, which has been made up in a solution containing 15 ml. of concentrated Hydrochloric Acid per litre.

Procedure

The stone is weighed, measured, and examined with the hand lens. Adherent blood is removed as far as possible. If necessary, the stone is sectioned to determine its homogeneity. One or more samples are taken, depending on the uniformity of the stone, and reduced to powder in a small mortar.

1. Ignite some of the powder. Cystine, fat or wax, and blood clots will burn with a flame, if present in sufficient amounts. The purines glow without flame production. If no ash remains, it is unnecessary to carry out the tests for inorganic constituents, except for ammonia.

3. Uric Acid. Every sample should be tested for the presence of uric acid. The well-known murexide test is satisfactory. One milligram or more of the powder is treated with 2 or 3 drops of concentrated HNO_3 in a porcelain dish. The mixture is carefully evaporated to dryness, and heating continued until the colour change is complete. If the test is carried out on the water bath, uric acid gives first a yellow colour, which may be mistaken for the reaction for xanthine. If heating is continued for a few minutes longer, xanthine shows no further alteration, but in the case of uric acid the colour

changes to orange and finally to scarlet. On addition of a drop of ammonia, the uric acid oxidation product assumes a brilliant purple colour, while xanthine changes to orange, which becomes a red on further heating.

Since uric acid may occur as ammonium urate as well as the free acid, the test for ammonia should be made. The powder is extracted with hot dilute HCl and the extract tested for ammonia as in Step 9.

3. Xanthine. This substance may be identified as described in the previous paragraph. On account of its extreme rarity, a positive nitric acid test calls for confirmation. Ehrlich's diazo test may be used since uric acid is the commonest substance which might be mistaken for xanthine. A little of the powder is boiled with 1 to 2 ml. of freshly-prepared diazo reagent, and a few drops of Normal NaOH are added. Xanthine couples with the reagent to produce a brilliant red wine colour. Uric acid gives no colour or a pale yellow, depending on the purity of the specimen. The test is not specific; it is given by many substances including the purines which are not substituted at positions 7 and 8. Its use, however, assures that uric acid will not be mistaken for xanthine. The test might serve to detect xanthine in the presence of uric acid.

4. Cystine. A pinch of the powder is boiled with 2 to 3 ml. of water, then treated with an equal amount of 5 per cent NaCN solution. After 5 minutes, a few drops of sodium nitro-prusside solution are added. Cystine is indicated by a beautiful magenta colour. This test, described by Brand, is much quicker than the older method of recrystallizing from ammonia, and identifying the hexagonal crystals under the microscope. The solubility of the specimen in NH_4OH and in dilute HCl should be tested as a rapid means of confirmation, and as a test of its purity, since no other common constituent of calculi is soluble in both. Cystine stones, as a rule, contain only small traces of other substances, and for ordinary purposes these do not need to be further identified.

5. Microscopic examination. This step is conveniently carried out at this time, in conjunction with Step 6. A little of the powder is mounted in water under a cover slip, and examined under the microscope. This gives added information as to the homogeneity of the specimen, and may afford a clue as to its composition. The "triple phosphate" crystals of ammonium magnesium phosphate are sometimes easily recognized. Calcium oxalate may often be recognized under the hand lens as sharp, knife-edged

crystals; when powdered, the crystals fracture irregularly, so that under the microscope the fragments resemble broken glass. Though calcium carbonate crystals may sometimes be recognized, other calcium salts are often amorphous or difficult to identify.

6. Test for carbonate. A little of the powder is placed on a glass slide and intimately mixed with a drop of water, to expel air bubbles. A cover slip, carrying a small drop of concentrated HCl is then inverted upon the powder. The evolution of CO_2 can be readily recognized under the microscope.

Aside from this test for the identification of carbonate, which has been described by Newcomb, the behaviour of the powder after the addition of acid is often characteristic and sufficient to indicate its composition. Phosphates and carbonates go rapidly into solution, oxalates dissolve slowly, while uric acid is insoluble. Cystine, on contact with concentrated HCl, undergoes an instantaneous recrystallization which has been described by Wollaston.

7. Test for phosphate. A small amount -- roughly 2 to 3 mgm. -- of the powder is dissolved in 3 or 4 drops of concentrated HNO_3, by boiling in a test tube. The solution is transferred to a centrifuge tube and 3 or 4 drops of 3 per cent ammonium molybdate solution are added. A

yellow precipitate indicates the presence of phosphate. This reaction may be slow, so that it is sometimes necessary to allow the tube to stand an hour or more before precipitation is complete. If proteins are present, they are thrown down by the reagent with formation of a white flocculent precipitate.

Experience has shown that tests carried out in HNO_3 solution as described above are more sensitive than similar tests carried out in HCl solution. When dealing with stones which contain large amounts of phosphate it is more convenient to use a portion of the HCl solution prepared in Step 8. When small amounts of phosphate are to be detected, however, such as are often present in calcium oxalate stones, HNO_3 solution is to be preferred, since HCl tends to increase the solubility of the phosphomolybdate.

8. Separation of acid-insoluble material. About 5 to 10 mgm. of the powder are boiled in a test tube with 1 to 2 drops of concentrated HCl and a little water, until the inorganic constituents have gone into solution. The solution is transferred to a centrifuge tube, diluted to about 0.7 ml., and insoluble residue is spun down. The supernatant fluid is removed with a dropping pipette and divided into two parts, or into three, if this solution is to be

tested for phosphate. The insoluble residue, if any, is then examined under the microscope. It will usually consist of cellular and other protein debris. Uric acid may be present, as well as yellow-coloured hemoglobin derivatives. In stones from herbivorous animals, silica may be found.

If the supernatant is cloudy, it may be necessary to filter with suction through a small filter paper, about 1 cm. in diameter, supported by a filter plate. The filter should be washed with a few drops of water to avoid loss of the solutes. The clear fluid obtained by centrifuging or filtration is known as Solution 1.

9. Test for ammonia. To part of Solution 1, a few drops of Nessler's solution are added, sufficient to make the mixture definitely alkaline. The formation of a white precipitate is disregarded. An orange colour or precipitate indicates the presence of ammonia. Formalin interferes with this test.

10. Test for calcium oxalate. To another part of Solution 1, add a few drops of saturated sodium acetate, until the acidity of the solution is brought to pH 5 approximately, as indicated by Hydrion paper. If calcium oxalate is present it will be precipitated almost quantitatively. The solution is mixed, permitted to stand for 15 minutes

to allow complete precipitation, and the calcium oxalate thrown down in the centrifuge. The supernatant fluid (Solution 2) is transferred to another centrifuge tube.

This test for calcium oxalate is essentially that of Domanski. In our experience, the microscopic examination of the precipitate, and the permanganate test for confirmation are unnecessary refinements.

11. Test for non-oxalate calcium. To Solution 2, a drop of ammonium chloride is added, to prevent the precipitation of magnesium salts. Then 2 to 4 drops of oxalic acid solution are added, or sufficient to precipitate calcium which has not been precipitated in Step 10. Calcium, originally present as carbonate, phosphate, or citrate, is thrown down at this stage. The mixture is stirred, allowed to stand for 15 minutes, and centrifuged as before. The supernatant (Solution 3) is transferred to another centrifuge tube.

12. Test for magnesium. To Solution 3, sufficient ammonium hydroxide is added to bring the pH to about 8 by Hydrion paper. In order to make the reaction more sensitive, 1 or 2 drops of disodium hydrogen phosphate are also added. A crystalline precipitate indicates the presence of magnesium. The star-shaped crystals which form should be checked by microscopic examination. Carried out in this way, the test is sufficiently sensitive to detect the magnesium present in a small sample of bone.

RESULTS.

Three hundred and fifty-five stones were analysed. They were grouped into classes as follows:-

1. Calcium oxalate stones
2. Magnesium stones
3. Uric acid stones
4. Calcium-phosphate-carbonate stones
5. Cystine stones.

As can be seen in the table below, the largest number of calculi were placed in the calcium oxalate group, the smallest number appearing as cystine stones.

	Calcium-oxalate	Magnesium	Uric acid	Calcium-Phosphate-carbonate	Cystine
Total	138	133	41	39	4
	39%	37.5%	11.5%	11%	1%
R.V.H.	93	69	26	24	2
	43.5%	32.5%	12%	11%	1%
M.G.H.	45	64	15	15	2
	32%	45%	11%	11%	1%

Group 1: Most of the stones designated as "calcium oxalate" were contaminated by other substances which were

present only in small quantities or appeared merely as traces. None of the stones contained magnesium, and two presented only a trace of uric acid. Forty-three and a half per cent of the R.V.H. stones were placed in this group, as compared with only thirty-two per cent of the M.G.H. calculi.

Group 2: In all these stones except four, the magnesium existed as magnesium ammonium phosphate. All the stones except two were found to contain calcium carbonate as well as magnesium ammonium phosphate, indicating a close relationship between the two compounds as regards their precipitation in the form of renal calculi. Uric acid, (present probably as ammonium urate) was detected in 26 stones, most commonly as a trace substance. Here again, a difference in composition was noted between the R.V.H. and the M.G.H. groups. Whereas 45% of the M.G.H. calculi contained magnesium, this element was present in only 32.5% of the R.V.H. series.

Group 3: Twenty-six stones consisted of uric acid. Eight stones appeared to be composed principally of ammonium urate. One stone was difficult to classify because it was found to contain calcium carbonate, calcium phosphate, and uric acid, all in large amounts. This stone formed the nucleus of a much larger stone

whose cortex contained, in addition, magnesium ammonium phosphate. It is of interest to note that a few of the remaining calculi were contaminated by calcium oxalate, one by calcium phosphate, and two by a non-oxolate-calcium compound whose anion component could not be determined.

Group 4: Three stones consisted wholly of calcium carbonate. In thirteen, ammonia was detected in traces only; the remainder gave a negative reaction for ammonia. One calculus contained a small amount of uric acid. In none of this group was there any magnesium present.

Group 5: All four stones were composed of cystine, without admixture of any other major constituent.

CALCIUM-OXALATE STONES

No.	Carbonate	Phosphate	Ammonia	Calcium oxalate	Non-oxalate calcium	Magnesium	Uric Acid
1	-	+	-	+++	+	-	-
2	V.F.T.	-	Tr	+++	?	-	-
3	-	-	-	+++	-	-	-
4	-	-	-	+++	-	-	-
5	-	-	-	+++	-	-	-
6	-	Tr	-	+++	-	-	-
7	V.F.T.	-	-	++++	+	-	-
8	-	+	-	++++	+	-	-
9	-	Tr	Tr	+++	-	-	-
10	Tr	V.F.T.	-	++++	+	-	-
11	Tr	-	-	++++	+	- ?	-
12	-	-	-	++++	-	-	-
13	Tr	Tr	Tr	++++	Tr	- ?	-
14	-	-	V.F.T.	+++	+	-	-
15	+	-	-	++++	+	-	-
16	-	-	-	++++	+	- ?	-
17	+	-	-	++++	+	-	-
18	Tr	Tr	-	++++	+	-	-
19	Tr	++	-	++++	+++	-	-
20	++	-	-	+++	+++	-	-
21	Tr	-	-	++++	+	-	-

CALCIUM-OXALATE STONES (contd.)

No.	Carbonate	Phosphate	Ammonia	Calcium oxalate	Non-oxalate calcium	Magnesium	Uric Acid
22	Tr	-	-	++++	+	-	-
23	Tr	+	-	+++	++	-	-
24	Tr	V.F.T.	-	++++	+	-	-
25	-	V.F.T.	-	++++	Tr	-	-
26	Tr	+	-	++++	+++	-	-
27	++	V.F.T.	-	+++	++	-	-
28	F.T.	-	-	++++	+	-	-
29	-	V.F.T.	-	++++	+	-	-
30	F.T.	+++	-	++++	++	-	-
31	Tr	+	?	+++	?	-	?
32	-	-	-	+	+	-	?
33	F.T.	-	-	+++	+	-	-
34	F.T.	++++	-	+++	+++	-	-
35	-	-	-	+++	+	-	-
36	-	-	-	++++	+	-	-
37	-	-	-	++++	+	-	-
38	-	++	-	++++	++	-	-
39	Tr	F.T.	Tr	++++	++++	-	-
40	-	- floc.ppt	-	++++	+	-	-
41	-	-	-	++++	+	-	-
42	-	-	-	++++	+	-	-
43	-	+	-	++++	++	-	-

CALCIUM-OXALATE STONES (contd.)

No.	Carbonate	Phosphate	Ammonia	Calcium oxalate	Non-oxalate calcium	Magnesium	Uric Acid
44	-	+	-	++++	+	-	-
45	-	+++	-	+++	++	-	-
46	V.F.T.	-	-	++++	+	-	-
47	V.F.T.	-	-	++++	+	-	-
48	-	-	-	++++	++	-	-
49	-	-	-	++++	+	-	-
50	-	-	-	++++	Tr	-	-
51	Tr	+	-	++++	+	-	-
52	Tr	++	-	++	++	-	-
53	-	Tr	-	++++	++	-	-
54	Tr	Tr	Tr	++	++	-	-
55	-		F.T.	++	+	-	-
56	-	-	-	++++	+	-	-
57	Tr	-	-	++++	+	-	-
58	-	-	-	++	+	-	-
59	-	fluf.ppt. -	F.T.	++++	+++	-	-
60	+	+++	F.T.	++++	+++	-	-
61	-	++	+	++++	++	-	-
62	V.F.T.	+	Tr	++++	++		-
63	-	+++	-	++++	+++	-	-
64	-	-	-	++++	+	-	-
65	++	Tr	-	++++	+	-	-
66	-	+	Tr	++++	++	-	-

CALCIUM-OXALATE STONES (contd.)

No.	Carbonate	Phosphate	Ammonia	Calcium oxalate	Non-oxalate calcium	Magnesium	Uric Acid
67	F.T.	+++	F.T.	++++	+++	-	-
68	+	Tr	Tr	++++	+++	-	-
69	-	-	+	++++	+	-	-
70	Tr	-	Tr	++++	+	-	-
71	-	-	V.F.T.	++++	+	-	-
72	-	-	Tr	++++	Tr	-	-
73	-	+	Tr	++++	++	-	-
74	-	-	Tr	++++	+	-	-
75	-	-	-	++++	Tr	-	-
76	+++	-	-	++++	+++	-	-
77	-	++	-	+++	+++	-	-
78	-	+	-	++++	+	-	-
79	-	Tr	-	++++	+	-	-
80	-	Tr	-	++++	++	-	-
81	-	Tr	-	++	F.T.	-	-
82	-	+++	Tr	++++	++++	-	-
83	+	-	-	+++	++	-	-
84	-	-	F.T.	+++	++	-	-
85	-	-	F.T.	+++	+	-	-
86	-	-	-	++++	-	-	-
87	-	-	-	++	Tr	-	-
88	-	+	-	+++	+	-	-
89	F.T.	+	-	++++	+++	-	-

CALCIUM-OXALATE STONES (contd.)

No.	Carbonate	Phosphate	Ammonia	Calcium oxalate	Non-oxalate calcium	Magnesium	Uric Acid
90	-	H.Tr	-	+++	+	-	-
91	-	Tr	-	++	H.Tr	-	-
92	-	+	-	++++	++	-	-
93	-	-	-	+++	+	-	-
94	-	-	-	++	-	-	-
95	-	Tr	-	++++	+	-	-
96	-	++	-	++++	+	-	-
97	-	-	-	+++	Tr	-	-
98	Tr	Tr	-	+++	++	-	-
99	-	+	-	+++	+++	-	Tr
100	-	-	-	+++	+	-	-
101	-	+	-	+++	++	-	-
102	Tr	+	-	+++	++	-	-
103	+	-	-	+++	++	-	-
104	-	++	-	+++	+++	-	-
105	-	+	-	++++	+	-	-
106	Tr	++	Tr	+++	++	-	-
107	Tr	Tr	Tr	+++	++	-	-
108	-	V.F.T.	-	++++	++	-	-
109	H.Tr	V.F.T.	-	++++	++	-	-
110	Tr	++	-	++++	++	-	-
111	-	Tr	-	++++	+	-	-
112	-	-	-	++++	+	-	-

CALCIUM-OXALATE STONES (contd.)

No.	Carbonate	Phosphate	Ammonia	Calcium oxalate	Non-oxalate calcium	Magnesium	Uric Acid
113	-	-	-	++++	V.F.T.	-	-
114	-	-	-	++++	Tr	-	-
115	+++	-	-	++++	++	-	-
116	-	Tr	Tr	++++	Tr	-	Tr
117	-	-	-	++++	Tr	-	-
118	-	-	-	++++	Tr	-	-
119	-	-	F.T.	+++	+	-	-
120	Tr		-	++++	+	-	-
121	Tr	-	-	++++	+	-	-
122	-	-	-	+	+	-	-
123	-	-	-	+	-	-	-
124	-	-	-	+++	-	-	-
125	+	+	-	+++	++	-	-
126	-	-	-	+++	+	-	-
127	+	+	-	+++	++	-	-
128	-	-	-	+++	+	-	-
129	-	V.F.T.	Tr	++++	V.F.T.	-	-
130	-	V.F.T.	V.F.T.	++++	+	-	-
131	-	-	-	+++	H.Tr	-	-
132	+	-	Tr	+++	++	-	-

CALCIUM-OXALATE STONES (contd.)

No.	Carbonate	Phosphate	Ammonia	Calcium oxalate	Non-oxalate calcium	Magnesium	Uric Acid
133	-	-	-	++++	+	-	-
134	-		-	++++	+	-	-
135	-	-	-	++++	++	-	-
136	-	Tr	-	+++	+	-	-
137	-	+++	V.F.T.	+++	++++	-	-
138	Tr	-	-	++++	+	-	-

MAGNESIUM STONES

No.	Carbonate	Phosphate	Ammonia	Calcium oxalate	Non-oxalate calcium	Magnesium	Uric Acid
1	++++	+	H.Tr	+	++++	++	-
2	++++	+++	++	-	+++	++++	-
3	++	++	-	++++	++++	+	-
4	++++	++	F.T.	++++	++++	++	-
5	++++	++	++	++++	++++	+++	-
6	++++	++	+++	-	++++	++	-
7	++++	+++	+++	+	++++	++++	-
8	++++	+++	++	-	++	+	-
9	++++	++	+++	+	+++	+++	-
10	++++	+++	+++	-	+++	+++	-
11	++++	+	+++	-	++	++	-
12	Tr	++	+	++	+++	Tr	-
13	++++	++	Tr	+++	++++	+	-
14	++++	H.Tr	++	H.Tr→+	++	++	-
15	++++	+	+++	Tr	++++	++++	-
16	++++	+	+++	-	++	+++	++
17	++++	+++	+++	-	++++	++++	-
18	++++	++++	+++	-	++	+++	-
19	++++	++	Tr	V.F.T.	+++	+++	++
20	++++	H.Tr	+	V.F.T.	+++	++	-
21	++++	+++	+++	-	++	+++	-
22	+	++	+++	-	-	++++	-
23	++++	++	++	-	++	+++	+

MAGNESIUM STONES (contd.)

No.	Carbonate	Phosphate	Ammonia	Calcium oxalate	Non-oxalate calcium	Magnesium	Uric Acid
24	+	+	+	Tr	++++	+	-
25	++++	++++	++++	++	+++	++	-
26	Tr	+	++	+++	+++	++	-
27	++++	++++	-	V.F.T.	+++	++	-
28	++++	++	+++	Tr → +	++++	+++	-
29	+++	+++	+++	-	+	+++	-
30	++++	+++	+++	-	++	+++	++
31	+++	++++	+++	-	++++	++++	-
32	++++	++++	+++	Tr	+++	+++	++
33	++++	++++	++++	-	+++	+++	++
34	++++	+++	+++	-	++++	++++	-
35	+++	+++	Tr	-	+++	+	-
36	++++	++	++++	-	+++	+++	-
37	++	++++	+	-	++++	+	-
38	++++	H.Tr	++++	-	++++	++++	-
39	+++	++	+	-	++++	+	-
40	++++	++++	+	-	++++	+++	-
41	+++	+++	+	++	+++	+	-
42	++++	++++	++++	-	+++	++++	-
43	++++	++++	++++	+	++	+++	-
44	++++	++++	+++	-	++++	+++	Tr
45	++++	++++	++	+	++++	++	Tr
46	++++	++	++++	-	++++	+++	-

MAGNESIUM STONES (contd.)

No.	Carbonate	Phosphate	Ammonia	Calcium oxalate	Non-oxalate calcium	Magnesium	Uric Acid
47	+	+++	Tr	+	++++	+	-
48	+	Tr	+	+	++++	+	-
49	++++	+	+++	-	++	+++	-
50	-	-	++	++++	+	Tr	-
51	++++	+++	++++	-	++++	++++	-
52	+++	++++	++++	-	+++	+++	Tr
53	+++	+++	++++	-	++	++	-
54	++++	+++	++++	-	++++	+++	-
55	++++	+++	+++	-	+++	+++	-
56	+++	++++	+++	-	+	++	Tr
57	+++	++++	+++	-	+	+	Tr
58	++++	++	+++	-	++++	+	-
59	++++	+++	++++	-	++++	+++	-
60	++++	++++	++	-	++++	++	-
61	++++	+++	++++	-	+++	+++	Tr
62	++++	++	++++	-	++++	++++	-
63	++++	++++	+++	-	++++	++++	-
64	++++	++	+	-	++++	++	Tr
65	++++	+++	+++	-	++++	++++	-
66	++++	++++	++	-	+++	++	-
67	++++	++++	++++	-	++++	+++	-
68	++++	++	++++	-	++	+++	+
69	++	+++	++++	-	+	+	-

MAGNESIUM STONES (contd.)

No.	Carbonate	Phosphate	Ammonia	Calcium oxalate	Non-oxalate calcium	Magnesium	Uric Acid
70	++++	++	+++	-	+++	+++	-
71	+++	+++	+++	-	+++	+++	-
72	+++	+++	++	-	++	+	-
73	++++	++++	++++	-	++++	+	+
74	++++	+	++++	-	++++	+++	-
75	+++	+++	++++	-	+++	+++	++
76	++++	++	++++	-	++++	Tr	-
77	++++	++++	++++	-	++++	++++	-
78	++++	Tr	+	-	++	++	-
79	Tr	-	Tr	++++	+++	+	-
80	+++	+++	++++	-	+++	+++	+
81	+++	+	+++	-	++++	+	-
82	++++	++	++++	-	+++	+	-
83	+++	Tr	++++	-	++++	+++	-
84	++++	Tr	++++	-	++++	+	-
85	++	++	++	-	+++	+++	-
86	++++	+	+	-	++++	++++	-
87	Tr	++++	++++	-	++++	++++	-
88	-	+++	+++	+	+++	+	-
89	+++	++++	+++	V.F.T.	++	++	+
90	+++	++++	+	-	+++	+++	-
91	+	++++	++++	-	+	++++	-
92	+	++++	++++	-	+	++++	Tr

MAGNESIUM STONES (contd.)

No.	Carbonate	Phosphate	Ammonia	Calcium oxalate	Non-oxalate calcium	Magnesium	Uric Acid
93	++	+	++	+	++++	+	-
94	++++	++++	++++	-	+++	+	Tr
95	++	++++	++	-	++++	+	-
96	Tr	++++	++++	-	+	++++	-
97	++++	++	+	-	++++	+	-
98	++++	Tr	++++	Tr	+++	++	+
99	+++	++++	Tr	-	+++	Tr	-
100	+++	+++	+++	-	+++	++	-
101	+	++++	++++	-	+	+++	-
102	++++	++++	+++	-	++++	+++	-
103	++++	++	+++	-	+	++	-
104	+++	++	+++	-	+++	+	-
105	++++	++	++++	-	++	++	-
106	++++	++++	+++	-	++++	+	-
107	+++	+++	++++	-	+++	+	-
108	+++	++	++++	-	+++	++	-
109	++++	++++	++++	-	+++	++++	-
110	+	++++	+++	-	++	++	+
111	++	++++	+	-	++++	Tr	-
112	+++	++++	++++	+	+++	+++	-
113	+	++++	+	-	++++	+	-
114	Tr	++++	++++	-	Tr	+++	-
115	++++	+++	+++	-	++++	Tr	-

MAGNESIUM STONES (contd.)

No.	Carbonate	Phosphate	Ammonia	Calcium oxalate	Non-oxalate calcium	Magnesium	Uric Acid
116	++	+++	Tr		+++	+	-
117	++++	+++	+++	-	++++	++	-
118	++++	++++	++++	-	++++	++	-
119	++++	+	++++	-	++	++++	Tr
120	+++	+	+	-	+++	+	+
121	+++	++++	++++	-	+++	+++	-
122	++++	++++	++	-	++++	++++	-
123	+++	++++	++++	-	+++	+++	-
124	++++		+++	Tr	++++	++++	-
125	++++	++++	++++	Light floc.ppt.	++++	++	+
126	++++	++++	++++	-	++++	+++	-
127	++++	++++	++++	-	++++	++++	Tr
128	++++	++++	++++	-	++++	++	-
129	Tr		++++	-	+	+++	
130	++++	++++	++	-	++++	+	-
131	++++	++	++	+++	+++	Tr	-
132	+++	++	Tr	-	++++	+	-
133	++++	+++	Tr	-	+++	+	-

URIC ACID STONES

No.	Carbonate	Phosphate	Ammonia	Calcium oxalate	Non-oxalate calcium	Magnesium	Uric Acid
1	-	-	-	-	-	-	++++
2	-	-	-	-	-	-	++++
3	-	-	++++	-	-	-	++++
4	-	-	-	-	-	-	++++
5	-	-	-	-	-	-	++++
6	-	-	-	-	+	-	++++
7	-	-	-	-	-	-	++++
8	-	-	-	-	-	-	++++
9	-	-	-	-	-	-	+++
10	-	-	-	-	-	-	++++
11	+++	++++	++++	-	++++	-	++++
12	-	-	-	-	-	-	++++
13	-	-	-	-	-	-	++++
14	-	-	-	-	-	-	++++
15	-	-	-	-	-	-	++++
16	-	-	Tr	-	-	-	++++
17	-	-	-	-	-	-	++++
18	-	-	-	-	-	-	++++
19	-	-	-	-	-	-	++++
20	-	-	++++	-	-	-	++++
21	-	-	-	-	-	-	++++

URIC ACID STONES (contd.)

No.	Carbonate	Phosphate	Ammonia	Calcium oxalate	Non-oxalate calcium	Magnesium	Uric Acid
22	-	-	+++	-	-	-	+++
23	-	-	-	-	-	-	++++
24	-	-	-	-	-	-	++++
25	-	-	-	-	-	-	++++
26	-	-	-	-	-	-	++++
27	-	-	-	-	-	-	++++
28	-	-	Tr	-	-	-	++++
29	-	-	+	-	-	-	++++
30	-	-	-	-	-	-	++++
31	-	-	++++	-	-	-	++++
32	-	-	-	Tr	Tr	-	+++
33	-	-	-	-	-	-	++++
34	-	-	-	-	-	-	++++
35	-	-	-	Tr	-	-	++++
36	-	-	-	++	-	-	++++
37	-	+	-	-	++	-	+++
38	-	-	-	-	-	-	+++
39	-	-	-	+	-	-	++++
40	-	-	++++	-	-	-	+++
41	-	-	-	-	-	-	++++

CALCIUM-PHOSPHATE-CARBONATE STONES

No.	Carbonate	Phosphate	Ammonia	Calcium oxalate	Non-oxalate calcium	Magnesium	Uric Acid
1	+	+	V.F.T.	-	+++	-	-
2	+	++++	-	-	++	-	-
3	+++	++++	-	-	++++	-	-
4	+++	++++	F.T.	-	+++	-	-
5	++	++++	+	-	++++	-	-
6	+	++++	V.F.T.	-	++++	-	-
7	+	++++	Tr	Tr	+++	-	-
8	+	++++	Tr	+	++++	-	-
9	+++	++++	-	V.F.T.	+++	-	-
10	++	+++	-	-	+++	-	-
11	+	++++	-	-	++	-	-
12	Tr	+++	Tr	+	+++	-	-
13	+	+	Tr	+++	++++	-	-
14	++++	+	-	-	++++	-	-
15	+	++	-	+++	+++	-	-
16	++++	+	-	-	++++	-	-
17	+++	+	-	++	+++	-	-
18	++++	+	-	+++	++++	-	-
19	+	++	-	+++	+++	-	-
20	++++	+++	F.T.	-	++++	-	-

CALCIUM-PHOSPHATE-CARBONATE STONES (contd.)

No.	Carbonate	Phosphate	Ammonia	Calcium oxalate	Non-oxalate calcium	Magnesium	Uric Acid
21	++	++	+	-	+++	-	-
22	++	+	-	-	++	-	-
23	+++	++++	+	-	++++	-	-
24	++++	+++	-	-	++++	-	-
25	++++	++	-	-	+++	-	-
26	++	++	-	++++	++	-	-
27	++	++	-	+++	++	-	-
28	+++	++	Tr	-	+++	-	+
29	+	+++	-	-	++++	-	-
30	+	++	-	+++	+	-	-
31	+++	++	-	+++	++	-	-
32	++++	+++	-	-	+++	-	-
33	++	++++	-	+	++++	-	-
34	++++	H.Tr	-	-	++++	-	-
35	+	+++	-	++	++++	-	-
36	++++	-	-	-	++++	-	-
37	++++	-	-	-	++	-	-
38	++++	-	+++	-	++++	-	-
39	+++	++++	-	-	++++	-	-

CYSTINE STONES

No.	Carbonate	Phosphate	Ammonia	Calcium oxalate	Non-oxalate calcium	Magnesium	Uric Acid	Cystine
1	-	-	-	-	-	-	-	+++
2	-	-	-	-	-	-	-	+++
3	-	-	-	-	-	-	-	+++
4	-	-	-	-	-	-	-	++++

DISCUSSION

Analysis and Classification: The method of analysis described above has been employed in an attempt to classify urinary calculi in terms of their basic cation, rather than anion, constituents. Such a classification has the immediate advantage of diminishing the number of different categories into which such stones have heretofore been grouped.

The classification used by McIntosh (38) is based upon the possible pathogenesis of the formation of urinary calculi. Such a classification is of physiological significance since it may serve as an aid in elucidating the underlying metabolic disorders responsible for the precipitation of specific urinary calculi.

Determination of Magnesium: An important feature is the determination of the presence or absence of magnesium. In almost all of the stones in which magnesium was detected, it was associated with ammonia, and existed as magnesium ammonium phosphate. This compound has been found almost invariably to be an accompaniment of infection in the urinary tract when this is caused by

urea-splitting organisms. Thus, the presence of magnesium in a urinary calculus should immediately invite suspicion of the presence of an associated infection.

According to Chute and Suby, 54% of all patients attending the Stone Clinic of the Massachusetts General Hospital are afflicted with urinary tract infection caused by urea-splitting organisms. Urea is hydrolyzed by these bacteria, and the ammonia set free renders the urine alkaline, thus causing the precipitation of otherwise soluble salts. The important characteristic of stones formed under such conditions is the presence of magnesium.

McIntosh (38) cultured the urine of 15 individuals in whom magnesium stones had been found to occur, and showed that infection in the urinary tract was present in each instance. The infection was caused by P. ammoniae, micrococcus, urea-splitting staphylococcus or other organisms. Urea-splitting organisms were identified in 12 of the 15 cases.

As stated above, of the 133 magnesium stones, all except two contained in addition, calcium carbonate, showing the close association of the two compounds in urinary calculi. This may possibly be due to the insolubility of calcium carbonate in alkaline urine.

Thus, conditions which disturb the solubilities of urinary salts (such as the presence of urea-splitting organisms and/or some underlying metabolic disorder) may cause precipitation of these salts and the formation of urinary calculi.

Calcium Stones: The division of calcium-containing stones into oxalate and non-oxalate fractions is worthy of mention. That some calculi may consist mainly of calcium oxalate, whereas others may exist as calcium carbonate, or be merely contaminated by traces of non-oxalate calcium is evident from a study of the results obtained. This distinction is of more than academic interest; for although calcium oxalate stones appear to be quite resistant to changes in urinary pH (in the intact human being), the possibility exists (supported by a few reports in the literature) that calcium phosphate and calcium carbonate may prove to be more susceptible to dissolution by maintenance of appropriate hydrogen ion concentration in the urine. The division of the calcium into these two fractions is accomplished by employing individual tests, and a quantitative comparison

between the two fractions is thus made possible.

Geographic Variations: In an attempt to determine the influence of geographic variation on the composition of urinary calculi in general, a comparison has been made between the presently reported series and those of Jensen of Denmark, (39) of Hammarsten of Sweden, (29) and of Newcomb of India (40). The rather complex classifications employed by these authors have been somewhat simplified in order to obtain results which are more readily comparable.

	Jensen	Hammarsten	Newcomb	This Series
Calcium oxalate	61.2%	51.6%	4%	39%
Magnesium	26.1	17	29	37.5
Uric Acid	6.3	13.1	11	11.5
Phosphate-carbonate	3.6	3.7		11
Phosphate-oxalate	0.9			
Mixtures	1.8	10.9	56	
Cystine		0.5	0	1
Fibrin		0.2		
Uric Acid and Phosphate		2.9		
	99.9%	99.9%	100%	100%
Number of Patients	111	594	100	355

From the above table it may be seen that in general, the present series of calculi contains a larger percentage of phosphate-carbonate and of magnesium stones, and a smaller number of the calcium-oxalate variety than do the European series. Whether the observed differences are of real significance is difficult to determine because of variation in the choice of clinical material studied and in the technique of chemical analysis employed. It may be noted, too, that the Indian series of calculi (comprised entirely of bladder stones) contains a large number of "mixed" stones. A possible explanation for this may be found in the greater tendency for urinary salts to precipitate out in concentrated solution. Certainly the hot climate to which the Indian populace is exposed, must favour the tendency toward dehydration and the production of a concentrated urine.

Vitamin A: In a consideration of the probable causes of urinary calculus formation, the role of vitamin A deficiency has been stressed by some authors. (2,4,5,13) The latter point to the not uncommon association of severe vitamin A deficiency and the presence of urinary calculi.

The metaplastic changes that occur in the epithelial layers of the mucosa of the urinary tract are presumed to favour the abnormal precipitation of urinary salts upon their keratinizing and desquamating surfaces, with the consequent formation of urinary stones. It must be noted that the epithelial changes produced by a lack of this vitamin are not localized to the region of the urinary tract alone. Keratinizing metaplasia has been found in the conjunctiva, cornea, mucosa of the nares, accessory sinuses, including the maxillary antrums, trachea, bronchi, pancreas, renal pelves, ureters, salivary glands, uterus, and peri-urethral glands. The skin becomes dry and rough, and then a papular eruption appears. The papules are formed by hyperkeratosis of the hair follicles. Atrophy of sweat glands occurs. Sebaceous glands atrophy and undergo keratinizing metaplasia. Although there is no doubt that urinary stones may be produced experimentally in animals by diets deficient in vitamins A and D and imbalances in mineral content, it must be pointed out that lithiasis, when it does occur in the rat with avitaminosis, is a very late manifestation. Children with deficiency of vitamin A rarely develop urinary calculi. In human beings with calculi, epithelial keratinization, the specific lesion of avitaminosis A, is lacking. It

must be concluded that although urinary calculi may be produced in experimental animals by the feeding of special diets, the factors involved are not as yet clearly defined. The view that diets deficient in vitamin A cause urinary lithiasis in man is not supported by clinical evidence.

Treatment: Although treatment for urinary lithiasis has been primarily surgical, at least up until comparatively recent times, it seems not at all improbable that a less radical form of therapy may be presently evolved, based upon a consideration of the factors (metabolic, infectious, etc.) involved in the formation of urinary calculi. Thus, obviously the treatment for the renal lithiasis that accompanies hyperparathyroidism -- whether due to tumor or hyperplasia -- does not demand primarily surgical removal of the kidney stone, but rather ablation of the excess of parathyroid tissue. Similarly, the formation and recurrence of other types of urinary calculus may be prevented (although, perhaps, the cause and effect relationship is somewhat less apparent) by a variation in the diet ingested. For example,

an acid ash diet will favour the precipitation and formation of cystine stones in the individual afflicted with permanent cystinuria; on the other hand, an alkaline ash diet may not only prevent this, but may even be instrumental in causing the dissolution of an already-formed concretion. Again, the individual with a tendency to develop uric acid calculi (which are more readily formed in highly acid urines) may benefit remarkably by an alteration in his diet so that an alkaline ash results.

The role of infection, in its association with urinary calculus formation, appears to be two-fold. In those instances in which culture of the urine reveals the presence of urea-splitting organisms, the infection may play a primary role. In other cases, the infection may supervene upon an already well-formed stone, and promote increased precipitation of urinary salts upon the surface of the calculus. Whether the urinary tract infection is primary or secondary, treatment must aim at its eradication.

SUMMARY

A review of the literature is presented.

The results of qualitative chemical analysis of 355 urinary calculi are reported.

The scheme used for classification of this series of urinary calculi has stressed the basic cation constituent rather than the anion.

The majority of the stones fell into one of two groups; either calcium-containing or magnesium-containing. The calcium-containing group could be further sub-divided into one containing oxalate and the other containing phosphate-carbonate or carbonate alone.

The importance of detecting the presence or absence of magnesium is emphasized.

The role of vitamin A deficiency as a causative agent in human urinary calculus formation is considered unimportant.

Possible modes of less radical treatment for urinary lithiasis are suggested.

BIBLIOGRAPHY

1. Wollaston, W. H., - On cystic oxide, a new species of urinary calculus. Proc. Roy. Soc., London, 1810, 100: 223

2. Osborne, T. B., Mendel, L. B., and Ferry, E. L., The incidence of phosphatic urinary calculi in rats fed on experimental rations. J. A. M. A., 1917, 69: 32

3. Hager, B. H., and Magath, T. B., - The etiology of encrusted cystitis with alkaline urine. J. A. M. A., 1925, 85: 1352

4. McCarrison, R., - The experimental production of stone in the bladder. Indian J.M. Research 1926, 14: 895

5. McCarrison, R., - The experimental production of stone in the bladder. Indian J.M. Research 1927, 15: 197, 485, 801

6. Joly, J. S., - Stone and Calculous Disease of the Urinary Organs, 1929

7. Spitzer and Hillkowitz, (Quoted by Newcomb (8))

8. Newcomb, C., - The role of urinary colloids in the prevention of stone formation. Indian J.M. Research, 1930, 18: 275

9. Ranganathan, S., - Chemical composition of urinary calculi in rats. Indian J.M. Research, 1930, 18: 599

10. Medes, G., - Solubility of calcium oxalate and uric acid in solutions of urea. Proc. Soc. Exp. Biol. and Med., 1932, 30: 281

11. Bliss, A. R. Jr., Livermore, G. R., Prather, E. O. Jr., - Relation of Vitamin A and Vitamin D. to Urinary Calculus Formation. J. Urol., 1933, 30: 639

12. Bugbee, H. J.,- Recurring pyelonephritis as an Etiological Factor in Nephrolithiasis. N.A. Assn. G.U. Surg., 1932, 25: 121

13. Higgins, C. C., - Experimental production of urinary calculi. J. Urol. 1933, 29: 157

14. Berglund, H., Medes, G., The Kidney in Health and disease, 1935.

15. Keyser, L. D., - Recurrent urolithiasis: etiologic factors and clinical management. J.A.M.A. 1935, 104: 1299

16. Snapper, I., Bendien, W. M., Polak, A. - Observations on Formation and Prevention of Calculi. Brit. J. Urol., 1936, 8: 337

17. Randall, A., Campbell, E. W., and Beeson, H. C., A simple method of chemical analysis of urinary calculi with a report of the chemical composition of a recent series. Urol. and Cutan. Rev., 1934, 38: 29

18. Randall, A., - The origin and growth of renal calculi. Ann. Surg., 1937, 105: 1009

19. Domanski, T. J., - Renal calculi: a new method for qualitative analysis. J. Urol. 1937, 37: 399

20. Sisk, I. R., and Toenhart, O., - Factors influencing solubility of relatively insoluble salts in urine. J. Urol., 1937, 37: 595

21. Albright, F., - Some medical aspects of the renal stone problem. New England J. Med. 1937, 217: 1063

22. Siddall, A. C.,- Primary Vesical Calculus. J. Urol., 1937, 37: 268

23. Hammarsten, G., - Dietetic therapy in the formation of calcium oxalate calculi in the urinary passages. Skand. Arch. F. Physiol., 1938, 80; 165

24. Albright, F., Sulkowitch, H. W., and Chute, R. Nonsurgical aspects of the kidney stone problem. J. A. M. A., 1939, 113: 2049

25. Flocks, R. H., - Calcium and phosphorus excretion in the urine of patients with renal or ureteral calculi. J.A.M.A. 1939, 113: 1466. Prophylaxis and medical management of urinary lithiasis: the role of the quantity and precipitability of the urinary calcium. J. Urol., 1940, 44: 183

26. Schneider, H., and Steenbock, H.,- Calcium citrate uroliths on a low phosphorus diet. J. Urol., 1940, 43: 339.

27. Chute, R., and Suby, H.I.,- Prevalence and importance of urea splitting bacterial infections of the urinary tract in the formation of calculi. J. Urol. 1940, 44, 590

28. Bodansky, M., and Bodansky, O., - The Biochemistry of Disease, The MacMillan Co., New York, 1940

29. Hammarsten, G., - Urinary calculi and their analysis. Nor. Med. (Hygeia), 1940, 7: 1329

30. White, E.C., Hill, J.H.,- Bacterial Urease; Critique of Methods Heretofore Used for Demonstrating Bacterial Urease and Presentation of Valid and More Sensitive Test, J.Urol.,1941,45: 744

31. Barrett, J. F., Absorption and Excretion of Oxalate. Lancet, 1942, 2: 574

32. Councill, W. A. H., The Teleprobe. J. Urol., 1942, 47: 395

33. Randall, A., Analysis of Urinary Calculi through the Use of the Polarizing Microscope. J. Urol., 1942, 48: 642

34. Dowling, H.F., Lepper, M.H., Toxic Reactions Following Therapy with Sulfapyridine, Sulfathiazole and Sulfadiazine. J. A. M. A., 1943, 21: 1190

35. Jewett, H.J., Sloan, L.L., Strong, G.H., Does Vitamin A Deficiency Exist in Clinical Urolithiasis? J. A. M. A. 1943, 121: 566

36. LaTowsky, L. W., Qualitative Chemical Analysis of Urinary Calculi. J. Urol., 1943, 49: 720

37. McIntosh, John F., Salter, Ruth W., The Qualitative Examination of Urinary Calculi. Journal of Clinical Investigation, 1942 21: 751

38. McIntosh, John F., The Classification and Chemical Pathogenesis of Urinary Calculi, 1942, J.Clin. Invest. 21: 755

39. Jensen, A. T., On Concrements from Urinary Tract. Acta Chir. Scandinav., 1941, 85: 473

40. Newcomb, C., and McCarrison, R., The composition of vesical calculi. Indian J. M. Research, 1928-29, 16: 1036