ON THE PRESENCE OF INSOLUBLE SALTS OF CALCIUM
(OXALATE AND PHOSPHATE) IN RENAL CALCULI
IN LARGE AMOUNT IN A PREPONDERATING
NUMBER OF CASES, AND THE BEARING OF THIS
FINDING UPON CALCIUM METABOLISM IN GOUT
AND ALLIED CONDITIONS

By W. W. MACKARELL, M.B., Ch.B., *Thelwall-Thomas Research Fellow*; BENJAMIN MOORE, M.A., D.Sc., *Johnston Professor of Bio-Chemistry*; AND W. THELWALL THOMAS, *Associate-Professor of Surgery, University of Liverpool*.

From the Bio-Chemical Laboratory, University of Liverpool

(Received May 9th, 1910)

In a previous paper from this laboratory by J. S. Rowlands¹ it was pointed out from qualitative experiments on a considerable number of renal calculi, that the usual view that a considerable percentage of such stones are very rich in urates of an insoluble character is erroneous, for in a majority of the cases uric acid could not be demonstrated at all by the usual qualitative tests, and in only two or three stones of the series was any appreciable amount of uric acid present. The preponderating number of the stones were, on the other hand, found to contain calcium oxalate and phosphate in very considerable amount.

The current view that a large percentage of kidney stones contain urates in high amount is important from two aspects. In the first place the supposed urate content is placed in correlation with the clinical observation that renal calculi occur most frequently in gouty subjects, and the gouty diathesis is set down as the cause for the formation of these concretions supposed to be very rich in insoluble urates.

Secondly, such supposed urate concretions are used as a support for the very popular view that the faulty nucleic acid metabolism and associated production and accumulation of urates and allied bodies is the chief factor in the causation and symptomatology of gout.

1. This Journal, Vol. III, p. 346, 1908.

Now, if it is a fact which can be experimentally demonstrated that renal calculi nearly always consist not of insoluble urates, but mainly of calcium oxalate and calcium phosphate in varying ratios, a new and important standpoint in relationship to gout is established, which may be of considerable importance, both in understanding, and in treating that condition.

Such a result would indicate that the calcium metabolism in gout may be more at fault than that of the purins and nucleo-proteins, and would give a new aspect to both dieting and treatment.

The calcium oxalate, it is true, would indicate a diminished oxidizing power of the organism, just as does uric acid and the allied purin bases; and the disturbed nuclear metabolism would yield the accumulation of calcium phosphate from the rich phosphorus content of the nucleic acids of the nuclei. So that, in one way, the oxalate and phosphate might be produced in the same pathological derangement which would lead to uric acid accumulation. Also, the calcium salt of uric acid is one of the least soluble of the urates, as shown by Little, so that calcium urate, phosphate and oxalate might readily occur in association.

Still, the presence of calcium, as practically the only base present in such calculi, is an experimental point of considerable importance which seems to us to be little known, and still less appreciated.

It may well be that calcium is as much or more to be avoided in treating gout as are the much dreaded purins and uric acid producers, and it is interesting from this point of view to note, in passing, that nearly all wines contain inorganic calcium salts in considerable quantity, due to treatment of the wines to free them from tartaric acid and other organic acids. Milk in various forms and cheese with a high calcium content are rarely prohibited to the gouty, and yet may, from the evidence we shall give, be more dangerous than other protein food; and our experience is that gouty subjects cut off from other proteins have usually acquired the habit of consuming cheese in increased quantities.

As regards treatment for prevention of gouty concretions, if these, like the renal calculi, are rich in calcium oxalate and phosphate, then the alkaline treatment is the exact opposite of what is required, for these bodies, unlike the urates (including calcium urate), are insoluble in alkali and soluble in acid.

But, whatever may be the pathological and clinical bearings of the problem, it is obviously of considerable experimental importance

to determine in a considerable number of cases as closely as possible the quantitative chemical composition of renal calculi.

For this purpose we have quantitatively analysed, and describe in this paper, a series of twenty-four renal calculi, taken indiscriminately as they came, twenty-one of the series being from the practice of one surgeon (W. T. T.).

The water supply of the district inhabited by most of the patients, viz., Liverpool district and North Wales, may be taken as a rule as being very soft surface water containing very little calcium salts, so that there is no reason to suppose that the high percentage of calcium oxalate and phosphate found in the great majority had any origin in the water supply.

There is no other cause, which we can trace, why this series of stones should differ in chemical composition from a similar series taken from any other district, and we are at a loss to find a basis for the usual text-book description of the so-called urate stone.

Only two of the stones, both found in the bladder, consisted almost wholly of urates, and it is interesting to the radiographer to note that these stones, both inside and outside the body, were transparent to the X-rays, while all the others, with one exception on one occasion, were opaque and diagnosable by X-ray methods.

Gall stones are poor in or lacking entirely in calcium salts, and, as we shall show, renal calculi consist nearly always almost wholly of calcium salts (oxalate and phosphate), and herein lies the reason that renal calculi show up with X-ray illumination, while biliary calculi are invisible or almost so.

Taking our series as a whole in regard to urate content, uric acid is so low as to give no positive or a very uncertain result in many cases; and to quantitative methods *even if all the nitrogen present be taken to be urate nitrogen*, the calculated uric acid lies away down at 2 or 3 per cent., and rarely over 10 per cent. Estimation of the uric acid by permanganate titration in the portion insoluble in moderately strong hydrochloric acid, leads to still lower results, and in several cases it is obvious that the small amount of organic nitrogen present is there as protein and other non-urate forms.

In describing the analyses of each stone in our protocols, we give a very brief summary of the history of the case, and a concise description of the macroscopic appearance and physical properties of the stone.

After a cast of the stone had been prepared in each case, the whole

stone was powdered up and used for the analyses; so that a good average sample of each calculus was obtained for the quantitative work.

METHODS OF ANALYSES

Moisture. After the physical characteristics of the stone had been noted, it was weighed carefully and then crushed and ground to a fine powder in a mortar, noting as far as possible the degree of hardness. The powder was weighed on a watch-glass, and then dried for about two hours at 100° C. and again weighed, the loss in weight being taken as moisture. The analyses proper were then carried out upon the dried material, the first process being a thorough qualitative analysis.

Qualitative testing. In each case ammonia, xanthine, cystine, magnesium and sulphates were tested for carefully, and invariably found to be absent.

Uric acid and total nitrogen. Uric acid was tried for by the murexide test, with negative results in some cases and feeble positive results in some others. Uric acid was determined by titration in sulphuric acid solution with N/20 potassium permanganate, in the residue obtained after treatment of a weighed amount of calculus with dilute hydrochloric acid (1 in 4 of strong hydrochloric acid solution). Also, in certain cases the uric acid was estimated by Hopkin's method, but as the results almost coincided with those obtained by direct titration after acid treatment, this simpler method was more often employed. As a control, the total nitrogen in another weighed sample of the stone was determined by Kjeldahl's method; this result in some cases lay near to the uric acid nitrogen value and in others was considerably higher, showing that nitrogen was present in other forms than urates. In stating the results below, in each case total nitrogen is calculated out as if it were present as uric acid. This is done not on the idea that all the total nitrogen is uric acid, which would be a very erroneous basis for some of the calculi, but rather to show that even on this simple basis of all the nitrogen being urate nitrogen, the percentage is still much too low to countenance the conception of a urate stone.

Calcium oxalate and calcium phosphate. The determination of oxalates was carried out by precipitation as calcium oxalate, filtering by the Bunsen pump through a Gooch filter and dissolving in sulphuric acid and titrating with N/20 potassium permanganate. The amount of phosphate was estimated as P_2O_5 by destroying organic matter by

Neumann's method of oxidation with strong sulphuric and nitric acids, then precipitating by ammonium molybdate, filtering, breaking up the phospho-molybdate by alkali, and titrating back with N/10 alkali, as described below.

The order of events in carrying out the various analyses was as follows:—

A quantity, varying according to the amount of stone available, was taken and accurately weighed. This was then placed in a porcelain dish, treated with hydrochloric acid (1 in 4 of strong solution) and heated on a steam bath until as much as possible had been dissolved. It was next filtered through a weighed Gooch filter, the residue well washed, and then dried at 100° C. for from one to two hours until the weight was constant, and this was noted. The residue in the Gooch, asbestos and all, was next treated with strong sulphuric acid. The acid was then diluted and titrated with N/20 potassium permanganate solution, 1 c.c. of which equals 0.0075 gramme of uric acid, and the amount thus estimated. A control had always to be performed with the sulphuric acid and water alone in order to get an accurate result, the amount of permanganate taken by the control being deducted from the result of the former titration.

This method of estimating uric acid was found to be fairly accurate when tested with a pure uric acid stone. Hopkin's method was adopted, as above stated, in three or four of the stones, but it is a somewhat lengthy process, and for the small amounts of uric acid, already in insoluble form, which were dealt with, it was not found to be any more accurate than this direct method.

The filtrate obtained after digesting the stone with hydrochloric acid and the washings of the residue were next mixed, and ammonium chloride and ammonia added in excess, the whole boiled, and whilst boiling ammonium oxalate was added. This was the procedure in the majority of the stones; in a few, however, the precipitate obtained after adding ammonium chloride and ammonia was filtered, thoroughly washed until free from chlorides, the washings being tested with silver nitrate, and then dried and weighed. The filtrate obtained after the addition of ammonia was then boiled and ammonium oxalate added as before. The precipitate thus obtained was allowed to settle, the liquid filtered off, and the precipitate washed by decantation until free from chlorides, which would otherwise interfere with the permanganate titration. The precipitate then, in a few of the stones, was dried and

weighed, but in the majority it was washed from the filter paper into a beaker by means of hot water first, then fairly strong sulphuric acid, and finally all the acid was washed into the beaker by means of hot water. The whole was then thoroughly mixed, cooled, and made up to 500 c.c. or 1,000 c.c., and 50 c.c. pipetted and titrated with N/20 potassium permanganate solution, 1 c.c. of which was equivalent to 0.0019 gramme of calcium or 0.00608 gramme of calcium oxalate.

Another portion of the stone was now weighed out, and the total nitrogen estimated by the Kjeldahl process.

Phosphates were estimated as phosphorus pentoxide by the following method:—A portion of the powdered stone having been weighed was put into a Kjeldahl's flask and 20 c.c. of a mixture of equal parts of strong sulphuric and strong nitric acids added, and the whole boiled until quite clear, as recommended by Neumann; if it was not clear at the end of about two hours a further 10 c.c. of the acid mixture was added and the boiling proceeded with. When quite clear it was made up to 150 c.c. with distilled water and again boiled. Whilst boiling 50 c.c. of 50 per cent. ammonium nitrate and 30 c.c. of 10 per cent. ammonium molybdate were added. A yellow precipitate appeared, in the presence of phosphates, and the whole was allowed to cool. The liquid was filtered off, and the precipitate washed by decantation with cold distilled water until quite free from acid. If much of the precipitate is allowed to get into the filter the filtering becomes a very tedious process. The whole precipitate, together with the filter paper, was next transferred back into the flask, and the whole dissolved in standard decinormal sodium hydrate solution. When the precipitate was entirely dissolved, the liquid was boiled for about fifteen minutes to get rid of the ammonia, cooled and titrated with decinormal sulphuric acid, phenolphthalein being used as indicator. We in this way found the amount of sodium hydrate required to dissolve the phosphomolybdate precipitate, and know that 1 c.c. of the N/10 sodium hydrate solution is equivalent to 0.2325 milligramme of phosphorus pentoxide. The amount of calcium phosphate was then obtained from this. As calcium was practically the only base found present by exclusive qualitative analysis, the estimations and calculations were greatly simplified.

The details were necessarily modified in analysing some of the stones, but these modifications will be indicated in the account which follows, of the individual stones. A brief history of the length of time

of the symptoms, together with the district from which the patient came, is also given.

DETAILS OF ANALYSES OF THE TWENTY-FOUR CALCULI

Calculus No. I. [R. W.] A male, age 17, residing in Liverpool. He had had symptoms of stone for nine years. Neither blood nor pus were ever found in the urine. The stone was removed from the right kidney. It weighed 6.202 grammes, was smooth, dark brown in colour, extremely hard, the hardest in fact of the whole series, and great difficulty was experienced in dissolving it. It contained 2 per cent. moisture, and qualitatively consisted of calcium oxalate and phosphate and uric acid. In order to dissolve it, it was left in hydrochloric acid (1 in 4) for four days, but only 20 per cent. dissolved; strong hydrochloric acid was next used and 30 per cent. more dissolved; a total of 54 per cent. of the dried stone was thus dissolved in the acid, and of this 50.14 per cent. was found to be calcium oxalate.

The total nitrogen determined by Kjeldahl yielded from 0.951 gramme of stone 0.038 gramme. If all this be taken as uric acid, it calculates out at 11.9 per cent. of the dried stone.

By the ordinary method described above 9.9 per cent. of uric acid was obtained.

Another portion of the stone, 0.339 gramme, yielded 0.00263 gramme of phosphorus pentoxide, or 1.7 per cent. of calcium phosphate.

From a percentage point of view these results are the most unsatisfactory of the whole series, and being the first they were rather discouraging; but even later, when several calculi had been examined, on coming back to this one no better results were obtained. By incinerating a portion and estimating the calcium, 0.579 gramme of the stone yielded 0.1216 gramme of calcium or 67.2 per cent. oxalate, and by boiling 0.878 gramme of the stone with strong hydrochloric acid it yielded a higher figure still, namely, 0.19 gramme of calcium or 69.12 per cent. of oxalate.

No difficulty was experienced in dissolving any of the subsequent calculi, and the oxalate in this had undoubtedly been deposited in a very insoluble form.

Calculus No. II. [M. M.] A female, age 44, residing in St. Helens. She had had symptoms of calculi for eleven years; blood was noticed in the urine twice, never any pus. The stone was removed from

the left kidney. It weighed 1.691 grammes, was rough, light brown in colour, soft, very friable, and contained 17.9 per cent. of moisture. Qualitatively it consisted of calcium oxalate and phosphate, and only a trace of uric acid.

For the estimation of calcium oxalate 0.23 gramme of the stone was taken, yielding 0.0285 gramme of calcium or 87.3 per cent. of oxalate, and 4.27 per cent. uric acid by the direct method. By a Kjeldahl 0.192 gramme yielded 0.005 gramme of nitrogen, or as uric acid 7.8 per cent. The phosphorus pentoxide obtained from 0.471 gramme of the stone was 0.0126 gramme or 5.8 per cent.

Calculus No. III. [E. T.] A male, age 43, residing in Cheshire. He had suffered from symptoms of stone for two years. Haematuria was noticed once; never any pus. The stone was removed from the left kidney. It weighed 3.562 grammes, was rough, brownish white in colour, and very hard. It consisted chiefly of calcium oxalate, with a small percentage of uric acid and phosphate, and contained 3.5 per cent. moisture. A Kjeldahl yielded 0.0056 gramme of nitrogen from 0.208 gramme of the dried stone, or if all was present as uric acid 8 per cent.

A calcium oxalate estimation yielded 0.0589 gramme of calcium from 0.217 gramme of stone or 87.6 per cent. of calcium oxalate.

The phosphorus pentoxide yield from 0.383 gramme was 0.01298 gramme or 7.4 per cent. calcium phosphate.

By the direct method 6.9 per cent. uric acid was found.

A difficulty presented itself at this stage for the first time. In the previous two stones allowance had been made in the first figures for the calcium which was there as phosphate. This having been found, it was deducted from the amount obtained for the oxalates. It was thought that the calcium phosphate on the addition of ammonium oxalate would be changed into calcium oxalate and precipitated as such, but in this case it was noticed that although only about 7 per cent. of the stone remained undissolved, only 86.7 per cent. of calcium oxalate was obtained as a precipitate. This meant that although it was dissolved by the hydrochloric acid, about 7 per cent. of the stone was unaccounted for. A portion of the stone was incinerated, but this gave a similar result. This difficulty remained unsolved until the eighth stone of the series was being estimated, when, although no other base could be discovered, the calcium was only 9.84 per cent. by this method, which would only give a 30 per cent. yield of calcium oxalate if all the calcium was in the stone as oxalate, and there was still a large amount of phosphates to be

provided with a base. It then occurred to us that the phosphates were precipitated by the ammonium hydrate as phosphates, and consequently, when the ammonium oxalate was added later, it had no effect on them, and this was found to be the case, and the difficulty was solved. The permanganate only estimated that amount of calcium in the stone which was there as oxalate, and consequently the figures obtained by this method had to be taken as oxalate alone, the amount which combined with the phosphates being calculated from the figures obtained from the estimation of phosphorus pentoxide.

Calculus No. IV. [M. L.] A female, age 26, residing in Wigan. There was a history of symptoms of calculus for twelve months. The stone was removed from the right kidney. It weighed 1·063 grammes, was rough on the surface, friable, light yellow in colour, and contained 6·8 per cent. moisture.

Qualitatively it consisted almost entirely of calcium oxalate, with a trace of calcium carbonate and a very small amount of uric acid.

A Kjeldahl yielded 0·0042 gramme of nitrogen from 0·156 gramme of stone, or 7·38 per cent. uric acid if all the nitrogen was there as such.

By the direct method there was a yield of 1·7 per cent. uric acid.

The calcium obtained from 0·118 gramme was 0·038, which gives a percentage of 99 if all was as oxalate, but there was a small portion carbonate, which accounts for the high figure.

Calculus No. V. [W. L.] This was a male, age 27, residing at Litherland. The symptoms of calculus had commenced twelve months before. Neither blood nor pus were at any time found in the urine. The stone was removed from the right kidney. It weighed 0·673 gramme, was rough on the surface, friable, brown in colour, and contained 2·72 per cent. moisture.

It was practically a pure calcium oxalate stone, no uric acid being demonstrable either by qualitative or quantitative tests.

By a Kjeldahl 0·084 gramme of stone yielded 0·0014 gramme of nitrogen, which, being calculated as uric acid, gives 3·9 per cent.

No uric acid was found by the direct method.

The yield of calcium from 0·076 gramme of stone was 0·02375 gramme, or, if calculated as oxalate, 99·77 per cent., but here again a little carbonate was present.

Calculus No. VI. [W. A.] A male, age 23, residing in Wrexham. He gave a history of symptoms lasting two years. Blood was found in the urine once; never any pus. The calculus was removed from the lower

end of the ureter. It weighed 14·222 grammes, was smooth on the surface, dark brown in colour, extremely hard, and contained 2·43 per cent. moisture. Qualitatively it consisted chiefly of calcium oxalate, with a small quantity of phosphate and only a very faint trace of uric acid.

In the estimation of calcium 0·4 gramme of stone yielded 0·1064 gramme, or 85·12 per cent. of oxalate, and by the direct method 1·5 per cent. uric acid.

By a Kjeldahl 0·653 gramme yielded 0·00616 gramme of nitrogen, which gives 2·82 per cent. uric acid if all the nitrogen is present as such.

There was 0·0256 gramme of phosphorus pentoxide from 0·383 gramme of stone, or 14·5 per cent. calcium phosphate.

Calculus No. VII. [J. H. E.] A male, age 55, residing at Hoylake. This patient was X-rayed in London on account of indefinite pain in the left loin, and although no calculus was shown on the plates, he was advised to have the kidney explored. Again in Liverpool he was X-rayed, and, in spite of good negatives being obtained, no calculi were shown by them. On sounding the bladder, however, stones were discovered, and this one was one of eight removed. It weighed 0·443 gramme, was fairly smooth on the surface, soft and friable, pale pink in colour, and contained 6·5 per cent. moisture.

Qualitatively uric acid alone was found, and, being estimated quantitatively by Hopkin's method, 0·121 gramme yielded 97·5 per cent. pure uric acid.

This, therefore, is purely a uric acid stone; it was found in the bladder and was transparent to X-rays.

Calculus No. VIII. [M. C.] A female, age 22, residing in Liverpool. This patient was X-rayed on account of symptoms pointing to stone in the right kidney, but although good negatives were obtained, no shadow was shown on them. Sixteen months later, she came back with similar symptoms, and an X-ray plate now taken showed a calculus at the lower end of the right ureter. It weighed 4·405 grammes, was friable, a light yellow in colour, and contained 13·2 per cent. of moisture.

Qualitatively it consisted of calcium phosphate and oxalate, and a small amount of uric acid.

The phosphorus pentoxide yielded by 0·39 gramme of stone was 0·1081 gramme or 60·9 per cent. of calcium phosphate. From 0·386 gramme of the stone 0·038 gramme of calcium was obtained or 31·48 per cent. calcium oxalate, and by the direct method 6·73 per cent. of uric acid.

A Kjeldahl yielded 0.02914 gramme of nitrogen from 0.416 gramme of the stone, or, calculating it all as uric acid, 21.01 per cent. This was a very high reading, and can only be accounted for by the supposition that the stone when ground up was not thoroughly mixed, and that the nucleus or other portion which contained a large percentage of uric acid was taken for this Kjeldahl estimation. This reading should in all probability be rejected, and the lower figure given by the portion taken for the oxalate estimation be accepted.

Calculus No. IX. [H. F.] A male, age 21, resident in Liverpool. He stated that he had had the symptoms which he then complained of ever since he could remember. The calculus was the larger of two removed from the kidney. It weighed 1.712 grammes, was rough, very dark brown, and very hard, and contained 1.5 per cent. moisture. It was composed of calcium oxalate, uric acid, and a trace of phosphate.

The amount of calcium obtained from 0.374 gramme of the stone was 0.0931 gramme or 79.6 per cent. By the direct method 10.6 per cent. of uric acid was obtained. A Kjeldahl gave 0.01792 gramme of nitrogen from 0.384 gramme, or, reckoned as uric acid, 14 per cent.

The amount of phosphate was very small, 0.403 gramme of the stone yielding only 0.0035 gramme of phosphorus pentoxide or 1.9 per cent. of calcium phosphate.

Calculus No. X. [T. L.] A male, age 55, residing in Cardigan-shire. His symptoms had lasted two years. He had noticed blood in his urine once; pus was not found on any occasion. The calculus was removed from the right kidney. It weighed 1.143 grammes, was rough, crystalline, hard, and contained 1.9 per cent. moisture.

Qualitatively its chief constituent was calcium oxalate together with a small quantity of phosphate and uric acid.

There was 0.077 gramme of calcium in 0.271 gramme of the stone, or 90 per cent. calcium oxalate, and 4 per cent. uric acid by the direct method. In 0.239 gramme, 0.01 gramme of phosphorus pentoxide was found, or 8.7 per cent. calcium phosphate, and by a Kjeldahl 0.247 gramme yielded 0.00308 gramme of nitrogen, or, calculated as uric acid, 3.6 per cent.

Calculus No. XI. [E. T.] A female patient, age 39, residing in Liverpool. She had suffered from pain, haematuria and pyuria for ten years. The calculus was found in the right ureter. It weighed 0.483 gramme, was rough, dark brown in colour, hard, and contained 1.9 per cent. moisture.

There was insufficient of the stone to do a qualitative analysis, and the following modifications were adopted in the quantitative:—

For a Kjeldahl 0.205 gramme was taken, which yielded 0.0049 gramme of nitrogen, or, calculated as uric acid, 6.8 per cent. Then 0.197 gramme was heated with hydrochloric acid on a water bath and filtered, the residue being dried and weighed, and by the direct method yielded 2.5 per cent. uric acid. The filtrate was treated as before for calcium oxalate, but instead of dissolving the precipitate, which was obtained on the addition of ammonium oxalate, with strong sulphuric acid, it was dried and weighed, and then this precipitate was tested for phosphates. If any phosphates had been found, which they were not in this case, they would have been estimated in this precipitate, as was done in some of the later calculi, and the amount of oxalate obtained by difference.

From this 0.197 gramme, 0.186 gramme of calcium oxalate was obtained, or 94.4 per cent.

Calculus No. XII. [C. H.] A male, age 50, residing at Oldham. Calculi had been twice removed from the bladder, but a shadow had never been obtained on an X-ray plate. This one was no exception; it also did not give a shadow on the negative.

It was removed from the bladder, weighed 6.224 grammes, was smooth on the surface, reddish brown in colour, and contained 9 per cent. moisture.

It was found on analysis to be a pure uric acid stone. A Kjeldahl yielded 0.0522 gramme of nitrogen from 0.158 gramme of stone, or 98.5 per cent. uric acid.

Calculus No. XIII. [F. R.] A male, age 40, a resident of Liverpool. Blood and pus had been found in the urine, and oxalates in great quantities. The calculus was removed from the right kidney. It weighed 11.365 grammes, was rough, having white crystals in places, the main portion of the stone being dark brown. It was hard, and contained 2.5 per cent. of moisture.

Qualitatively it consisted entirely of calcium oxalate and phosphate, no murexide reaction being obtained.

An estimation of calcium in 0.925 gramme of the stone gave 0.2489 gramme, or 86.1 per cent. calcium oxalate. By the direct method 1.8 per cent. uric acid was obtained, and by a Kjeldahl 0.0072 gramme of nitrogen was found in 0.716 gramme of stone, which, being calculated as uric acid, gives 3 per cent. The phosphorus pentoxide was estimated in

0.768 gramme, which yielded 0.02346 gramme, or 6.6 per cent. calcium phosphate.

Calculus No. XIV. [A. S.] A male, age 34, residing in Liverpool. His symptoms had lasted for four years. Both haematuria and pyuria were present. It was the larger of two stones removed from the left kidney.

It weighed 1.028 grammes, was very rough, crystalline on the surface, light coloured, except in one place where it was dark brown, and contained 2.1 per cent. moisture.

Qualitatively it consisted of calcium oxalate and phosphate, and again no murexide reaction was obtained.

The calcium oxalate yield was 84.7 per cent., 0.323 gramme of stone yielding 0.0855 gramme of calcium. By the direct method 3.7 per cent. uric acid was obtained, and from a Kjeldahl 4 per cent. uric acid, 0.0045 gramme of nitrogen being found in 0.334 gramme of stone. Calcium phosphate was estimated at 13 per cent., 0.314 gramme yielding 0.01879 gramme phosphorus pentoxide.

Calculus No. XV. [L. R.] A male, age 22, residing in Pwllheli. There was a history of symptoms of calculus for two years. Haematuria and pyuria were both present. X-rays showed the presence of calculi in both kidneys. This calculus was removed from the right kidney. It weighed 6.533 grammes, was rugged and soft externally, but very hard in the centre; it was light brown in colour, and contained 12.8 per cent. moisture.

In 0.453 gramme, 0.0732 gramme of calcium was found, or 51.7 per cent. calcium oxalate, and in 0.395 gramme, 0.073 gramme of phosphorus pentoxide, or 40.4 per cent. calcium phosphate. A Kjeldahl yielded 0.0063 gramme of nitrogen from 0.449 gramme of stone, or, calculated as uric acid, 4.2 per cent., and the direct method yielded a percentage of 2.4.

Calculus No. XVI. [J. G.] A male, age 22, residing at Ruthin. He had had pain for two years. Haematuria was present, but not pyuria. The calculus was removed from the left kidney. It weighed 0.744 gramme, was rough, dark brown in colour, very hard, and contained 1.7 per cent. moisture.

Exactly the same method was employed with this as with No. XI.

A Kjeldahl yielded 0.0021 gramme of nitrogen from 0.287 gramme of stone, being equivalent to 2.19 per cent. uric acid. By the direct method 5.8 per cent. uric acid was obtained. The calcium oxalate yield was 0.335 gramme from 0.357 gramme of stone, or 93.8 per cent. No phosphate was found.

Calculus No. XVII. [M. W.] A male, age 33, residing in North Wales. He had suffered from pain in the left side for ten years. Four years ago he had pain in the right side for a short time, but this left him after the passage of a small calculus. Haematuria and pyuria were present. The calculus was removed from the left ureter. A similar method to the one used in the case of the previous stone was employed, except that the portion which remained undissolved by the hydrochloric acid had the nitrogen in it estimated by the Kjeldahl process, and no other Kjeldahl was done. The calculus weighed 0.366 gramme, was irregular, dark brown in colour, very hard, and contained 3.9 per cent. moisture.

In 0.341 gramme there were found 0.0044 gramme of nitrogen, or, calculated as uric acid, 3.8 per cent., 0.0746 gramme of phosphorus pentoxide or 47.8 per cent. calcium phosphate, and 0.141 gramme of calcium oxalate or 41.3 per cent. This latter result was obtained by difference, the whole precipitate, after adding ammonium oxalate, being 0.304 gramme.

Calculus No. XVIII. [G. W.] This was one of three ureteral calculi. It weighed 0.968 gramme, was soft and crumbling, light coloured, and contained 15.7 per cent. moisture. No qualitative analysis was done in this or in any of the succeeding calculi, on account of the small quantity available.

A Kjeldahl yielded 0.0054 gramme of nitrogen from 0.231 gramme of stone, or 6.9 per cent. uric acid. By the direct method 9.6 per cent. uric acid was obtained.

In 0.325 gramme of the stone 0.0171 gramme of calcium was found, or 16.8 per cent. of calcium oxalate; and in 0.261 gramme of the stone 0.0829 gramme of phosphorus pentoxide or 69.3 per cent. calcium phosphate was obtained.

Calculus No. XIX. [E. E.] A female, age 21, residing in Liverpool. She had had symptoms of calculi for eight years. The calculus was removed from the right kidney. It weighed 0.797 gramme, was dark brown in colour, rugged on the surface and hard, and contained 2.6 per cent. moisture.

A Kjeldahl yielded 0.0126 gramme of nitrogen from 0.239 gramme of stone, or calculated as uric acid 15.8 per cent. The percentage of uric acid by the direct method was 11.9.

In 0.21 gramme, 0.0532 gramme of calcium was found, giving 81.04 per cent. calcium oxalate, and in 0.315 gramme of stone 0.006 gramme of phosphorus pentoxide or 4.1 per cent. calcium phosphate was found.

Calculus No. XX. [J. D.] A male, age 31, residing in Liverpool. Twelve months duration of symptoms. There was haematuria, but no pyuria. The calculus was removed from the right ureter. It weighed 0·138 gramme, was soft, light in colour, and contained 3·9 per cent. moisture.

The method employed in this and in the succeeding stones was similar to the one used in No. XVII.

From 0·123 gramme of stone there was yielded 0·00126 gramme of nitrogen, or 3·09 per cent. uric acid, and 0·117 gramme of a mixture of calcium phosphate and calcium oxalate. This latter mixture yielded 0·03583 gramme of phosphorus pentoxide or 63·5 per cent. calcium phosphate, and therefore by difference 0·0388 gramme of calcium oxalate, or 31·6 per cent.

Calculus No. XXI. [H. T.] A male, age 24, residing in St. Helens. There was haematuria, but no pyuria. The calculus was removed from the right kidney. It weighed 0·134 gramme, was rough, dark brown in colour, hard, and contained 9·375 per cent. moisture.

From 0·12 gramme of stone there was obtained 0·00154 gramme of nitrogen, or 3·83 per cent. uric acid, and 0·114 gramme of calcium oxalate, or 95 per cent. There was no phosphate present.

Calculus No. XXII. [M. H.] A female, age 27, residing in Liverpool. The symptoms had lasted twelve months. There was no haematuria or pyuria. The calculus was removed from the right ureter. It weighed 0·134 gramme, was soft, and contained 11·6 per cent. moisture.

From 0·114 gramme of stone there was obtained 0·0042 gramme of nitrogen, or 11·05 per cent. uric acid, and 0·096 gramme of a mixture of calcium oxalate and calcium phosphate, which gave 0·02703 gramme phosphorus pentoxide, or 51·7 per cent. calcium phosphate, and thus leaving 32·5 per cent. calcium oxalate.

Calculus No. XXIII. [A. C.] A male, age 39, living at Crosby. He had previously been X-rayed on account of symptoms of calculi, but none were found. Thirteen months later he was again radiographed, and a definite shadow was shewn on the right ureter. It weighed 0·158 gramme, was rough on the surface, dark brown in colour, hard, and contained 2·7 per cent. moisture.

A Kjeldahl from the residue was spoiled, but taking the whole residue as uric acid it was 0·007 gramme in 0·139 gramme of stone, or 5·03 per cent.

The oxalate and phosphate precipitate weighed 0.131 gramme, and from this 0.00245 gramme of phosphorus pentoxide was obtained, or 3.81 per cent. calcium phosphorus and 90.39 per cent. calcium oxalate.

Calculus No. XXIV. This was one of a number of calculi removed from the substance of the prostate. It was of a light brown colour and fairly hard. It weighed after drying 0.156 gramme. It consisted of 0.088 gramme of calcium oxalate, or 56.4 per cent., and 0.062 gramme of calcium carbonate. There was no uric acid present.

TABLE OF PERCENTAGE COMPOSITION OF THE CALCULI

No.	Origin	Moisture	Calcium oxalate	Calcium phosphate	Uric acid. Direct method	Total nitrogen. Kjeldahl	Total nitrogen calculated to uric acid
		Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.
1	R. Kidney	2	69.1	1.7	9.9	3.9	11.9
2	L. „	17.9	87.3	5.8	4.2	2.6	7.8
3	L. „	3.5	86.7	7.4	6.9	2.6	8.0
4	R. „	6.8	99	none	1.7	2.3	7.0
5	R. „	2.7	99.7	none	none	1.3	3.9
6	R. Ureter	2.4	85.1	14.5	1.5	0.9	2.8
7	Bladder	6.5	none	none	97.5	—	—
8	R. Kidney	13.2	31.5	60.9	6.7	7.0	21.0
9	R. Kidney	1.5	79.6	1.9	10.6	4.6	14
10	R. „	1.9	90.0	8.7	4.0	1.2	3.6
11	R. Ureter	1.9	94.4	none	2.5	2.2	6.8
12	Bladder	9.0	none	none	—	32.8	98.5
13	R. Kidney	2.5	86.1	6.6	1.8	1.0	3.0
14	L. „	2.1	84.7	13.0	3.7	1.3	4.0
15	L. „	12.8	51.7	40.4	2.4	1.4	4.2
16	L. „	1.7	93.8	none	5.8	0.7	2.2
17	L. Ureter	3.9	41.3	47.8	—	1.2	3.8
18	L. „	15.7	16.8	69.3	9.6	2.3	6.9
19	R. Kidney	2.6	81.0	4.1	11.9	5.2	15.8
20	Ureter	3.9	31.6	63.5	—	1.0	3.1
21	R. Kidney	9.3	95.0	none	—	1.2	3.8
22	R. Ureter	11.6	32.5	51.7	—	3.6	11.0
23	R. Ureter	2.7	90.4	3.8	5.0	—	—
24	Prostate	—	96.1	none	none	—	—

All the percentages, except that of moisture, are calculated in terms of the dried stone.

As pointed out in the text, all the total nitrogen is not present as uric acid; it is shewn in the final column *calculated* as uric acid to furnish an *a fortiori* proof that in nearly all these calculi the percentage of uric acid is a low one.

ANALYSIS OF THE TABULAR PERCENTAGES AND DISCUSSION OF THE
BEARING OF THE RESULTS

There are two calculi of the series absolutely different to all the others in chemical composition, viz., Nos. VII and XII, and it is remarkable that these two alone were from the bladder, all the others coming from the kidney, ureter or prostatic pouch. The two bladder calculi were almost pure uric acid, containing no trace of calcium, either as oxalate or as phosphate. All the other calculi contained calcium oxalate in large amount, only one less than 30 per cent., and more than two-thirds of them over 70 per cent. of this insoluble calcium salt. The next most abundant constituent was tri-calcic phosphate, also a very insoluble calcium salt; this constituent reached over 50 per cent. in four out of the twenty-two calculi, and was present in quite appreciable amount in six others.

The most remarkable fact, and perhaps most important, is the strikingly low uric acid percentage in all save the two bladder stones; the figures only reach the neighbourhood of 10 per cent. as a maximum in four out of the twenty-two calculi, when the direct titration method is taken for survey, and even the total nitrogen (Kjeldahl) figures show only slightly higher percentages, with one exception (No. 8), where a good deal of the nitrogen was obviously present in other than urate forms.

The contrast in the two bladder stones is so obvious as to raise doubts in our minds as to whether these two calculi ever were formed in the kidney, and it would be most interesting if these turned out to be concretions of vesicular origin.

It is also interesting to note that these two purely uric acid calculi were transparent to X-rays, and we find that the ordinary kidney and urethral calculi are opaque, because, like bone, they contain these large percentages of insoluble calcium salts (oxalate and phosphate).

The presence of calcium oxalate as an abundant and frequent constituent of renal calculi, in fact, as the chief constituent of such calculi, opens up a field of most interesting thought as to the metabolism of renal calculus formation. In the first place, the incompletely oxidised oxalate, just like uric acid, points unmistakably to embarrassed oxidation or increased reducing conditions attending their formation.

It might be supposed also that if under pathological conditions there is a tendency to production in the system of oxalic acid, then calcium oxalate being the least soluble oxalate, there would be a tendency to

formation of this insoluble salt, followed by its precipitation as a calculus around any available nidus of already precipitated material. Once started in such a system, slightly supersaturated with calcium oxalate in solution, the calculus goes on growing and increasing in size.

However, the fact that calcium oxalate is not the only calcium salt of these renal concretions, but that tri-calcic phosphate, also an insoluble calcium salt, is present and in considerable amount in a fair percentage of the calculi, leads to the view that the same faulty metabolism which leads to excess of oxalic acid also leads to excess of phosphoric acid. This view would be consonant with the importance assigned in such a condition to the uric acid and purin bases, for any exaggerated nuclear metabolism would probably simultaneously yield from the nucleic acids purin derivatives and phosphoric acid, since these bodies are chemically associated in the nucleins.

An alternative view would lay greater stress on the common kation, calcium, of both the oxalic acid and phosphoric acid, and see in the sequence of events a disordered calcium metabolism in which calcium ion in excess was set free and passed into union with those anions in the plasma which would form the most insoluble salts, namely, oxalic, phosphoric, and uric acid anions. This supposition would also explain the association of these three particular acids with calcium in our series of renal calculi.

There is no doubt possible, from abundant collateral evidence, that certain pathological processes associated with insufficient oxidation lead to deposition of excess of calcium salts in insoluble form. In witness of this, we may cite the calcareous deposits within tubercular areas; and, short of hard deposits, the visibility of smaller tubercular areas to X-rays is almost certainly associated with increased calcium percentage in such areas, as we have seen that it is in these renal calculi. Now in such areas the blood supply is very defective, and oxidation is undoubtedly embarrassed for want of oxygen. Also, in other areas, where structural change is occurring, due to diminished oxidation, we see a tendency towards calcification, as, for example, in arterio-sclerosis.

If the tendency to formation of renal calculi is associated with a gouty condition, as there appears to be good clinical evidence that it is, the large percentage of calcium as oxalate and phosphate in these stones, no less than the small amount of urate, leads to doubt as to whether uric acid is such an important factor in gout as has been generally believed, and further suggests some experimentation as to the composition of the

deposits of gout. One wonders whether these do consist so largely of insoluble urates, or if a careful examination would yield quantitative evidence of considerable amounts of calcium oxalate and phosphate. We have been on the outlook for 'tophi' and 'chalky knuckles,' but hitherto have not been able to find material; perhaps large gouty deposits are not so common as in the days of our forefathers.

In regard to treatment of the conditions leading to these renal calculi, the first thought which suggests itself is the elimination as far as possible of food rich in calcium from the diet. It must be pointed out, however, that although such an experiment would be well worth trying, yet calcium is in all our common foods, and if there is a strong tendency to diminished oxidation and oxalic acid production, there will always be enough calcium present to combine with such oxalic acid when produced. The only possible effect might be a slower rate of production on physico-chemical grounds if the calcium content of the plasma was lowered.

The richest food in calcium of all we consume is milk—although wines and, to a less extent, beers contain it in considerable amount. Now, milk in various forms enters so largely into the food of civilized man, that it would be almost as difficult wholly to exclude milk from a dietary as it is to shut the diabetic off from carbohydrates. We take milk not only directly as a drink, or mixed with other beverages, but in puddings, in biscuits, in various forms of baker's products, and lastly in cheese in all forms, either as cheese alone, or as a part of different dishes.

More success might attend an effort to get rid of the excess of calcium oxalate and phosphate by altering the reaction of the plasma and tissue-fluids.

It is extremely important to notice, however, that the therapeutic measures to this end must be the very diametrically opposite of those employed for uric acid, and if in any gouty case the trouble is a tendency towards calcium oxalate or phosphate deposition, as it sometimes may be, the usual anti-acid treatment is the very opposite of what is indicated.

Uric acid and its acid salts are soluble in alkaline media and insoluble in acid; the exact opposite holds for calcium oxalate and calcium phosphate, which are deposited in alkali and dissolved by acids.

The experimental evidence set forth in our analyses of the calculi is quite sufficient to show that there is no very great hope of dissolving calculi again by any diminished alkalinity which might be induced even

by vigorous therapeutic measures; for even the powdered calculi, as a rule, dissolve only slowly even in 1 in 4 hydrochloric acid.

This is not, however, the real clinical problem involved in such cases, but rather that of preventing growth and accretion of the calculi, and we would suggest that where such calculi have been obtained by operation, or otherwise, and have been shown by analysis to be calcium oxalate or phosphate, that certainly no ant-acid treatment should be recommended afterwards, as this will lead to more rapid growth, or to increased chance of growth, of such calculi, and it would be advisable to try a course of acid treatment.

For these reasons, a renal or vesical calculus should always be subjected to a rigorous chemical examination which may be the source of some clue, first, as to its origin, and, secondly, as to the nature of the disordered metabolism which has led to its formation.

Our thanks are due to Mr. Thurstan Holland for the radiographic observations and notes we have recorded and for the materials of calculi; and to Mr. Keith Monsarrat for the prostatic calculus described as Calculus XXIV.