Proceedings of the Royal Society of Medicine

Vol. 51
183

Section of Urology

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[*October* 24, 1957]

The Calcium-containing Renal Stone [*Abridged*]

PRESIDENT'S ADDRESS

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THE calcium-containing renal calculus, like chronic duodenal ulcer and many cases of hormone-controlled carcinoma of the prostate and of the breast, is not a local disease of a part of the organ concerned; such a stone is usually the result of pathological changes affecting the renal parenchyma as a whole, and sometimes it results from abnormalities in organs remote from the kidney, for instance the parathyroid gland.

For a long time the attention of the surgeon was mainly concerned with the local lesion, because of the pain that it caused and because it was so often associated with infection and ultimately with serious damage to the renal parenchyma. The practical difficulties which face the surgeon, as well as the need for wider knowledge, are shown by the following case:—

Fig. 1 shows the control film and also the intravenous pyelograms of a male patient aged 56 years, who had a stone in the upper left major calyx, upon whom it was intended, after considering the pre-operative radiograph, to do an upper polar partial nephrectomy, for the relief of pain, removing the stone together with the upper major calyx in which it lay. When the kidney was exposed at operation, in addition to a stone a small, yellow, cortical tumour of 3 cm. diameter, shown later to be either a small hypernephroma or a latent carcinoma of the kind described by Franks (1954), was discovered, so the kidney was removed. A radiograph of the kidney (Fig. 2) after removal demonstrates the complicated problem which faces the surgeon:

(1) The pre-operative radiograph suggested one stone, but in fact in at least three of the calyces (upper, middle and lower) there were multiple tiny stones or calcific foci.

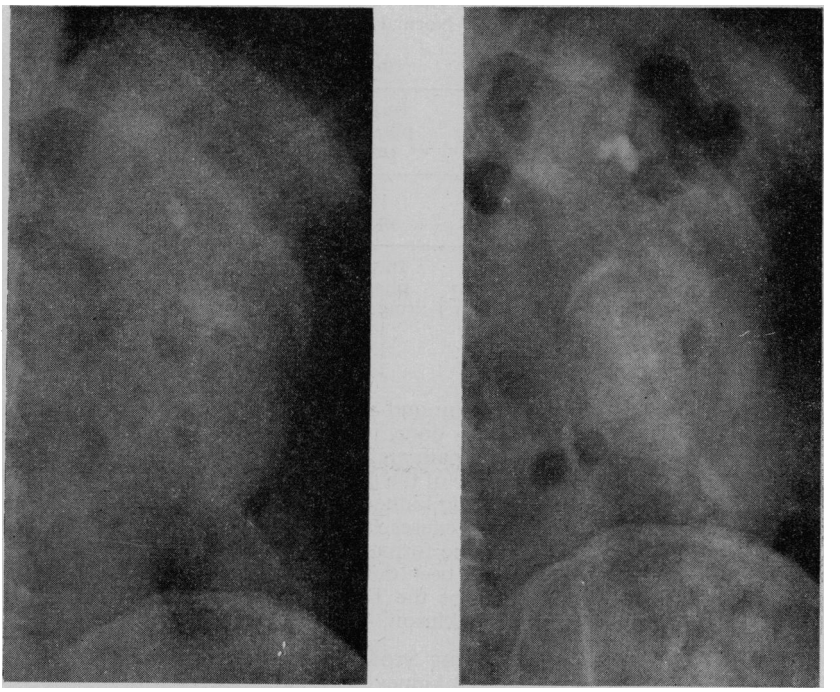


FIG. 1.—Straight X-ray and intravenous pyelogram of male patient, W. S. I., aged 56, showing a stone in the upper major calyx of the left kidney.

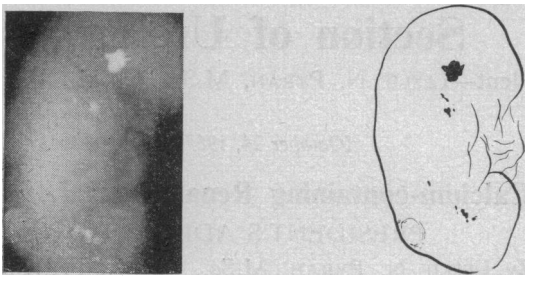


FIG. 2.—Radiograph of the excised kidney of the patient referred to in Fig. 1, showing in addition to the large stone in the upper calyx, multiple smaller calculi and calcific foci which had not been detected in the pre-operative radiograph.

(2) The partial nephrectomy operation which it was intended to do would not have dealt with these other gritty particles, nor have prevented their further maturation into large stones, nor indeed would any conservative operation.

(3) Although the largest stone was probably the cause of his pain, this was not certain. Nothing short of a nephrectomy would have removed all the calcific foci and thus have prevented further clinical symptoms later; yet the extent of the calcific process at the time of operation was not severe enough to indicate such a radical procedure in a well-preserved kidney had it not been for the presence of the tumour.

(4) The extensive, though mostly tiny, calcific deposits raise the question as to whether the patient may not develop stones in the remaining kidney at a later date. The second kidney is believed to be free from stones because of the control radiograph, but it may already harbour tiny calcific calyceal foci. Indeed, a guide to the prognosis in the remaining kidney is shown by his urinary calcium output after unilateral nephrectomy (Table I), which reveals a moderate hypercalciuria, unassociated with any elevation of his serum calcium; so it seems likely that the stone-forming potentiality still exists in his remaining kidney.

TABLE I.—BLOOD AND URINE CHEMISTRY IN A CASE WHOSE RADIOGRAPHS ARE SHOWN IN FIGS. 1 AND 2. There is a Moderate Hypercalciuria when the Patient is on a Normal Ward Diet. The Blood Calcium is Normal

W.S.I. ♂
Aged 59

	BLOOD		
Date	Calcium (mg%)	Inorganic phosphate (mg%)	Protein (g.%)
20.9.56	9·9	2·2	6·6

	URINE		
Date	Calcium (mg/24 hr.)	Inorganic phosphate (mg/24 hr.)	Volume (ml.)
15.9.56	321	1,111	2,020
16.9.56	431	1,450	2,230
17.9.56	374	1,550	2,215

The present surgical treatment of many and perhaps of most calcium-containing renal stones, however carefully the operation is done, is very often a relatively crude attack upon the disease designed primarily to relieve pain and to conserve renal function.

So it is proposed now, to examine some of the general factors (some of which may seem to be academic) concerning the stone-bearing kidney and also the calculus itself; then to refer to our limited knowledge of the general causes of stone; and finally to the attempts which are being made to prevent recurrent stone formation.

Most of the work here referred to has been done in the Department of Urology in Leeds by the clinical and research members of the Department, with important contributions from Dr. C. K. Anderson, Dr. A. Hodgkinson, Mr. B. T. Murphy and Mr. M. J. Purton.

PATHOLOGY OF THE STONE-BEARING KIDNEY

The histological findings in the normal kidney are first compared with those found in the stone-bearing kidney at a time before it has been seriously damaged by disease. Nephrocalcinosis (by which is meant calcification in the renal parenchyma which is demonstrable

radiologically) and also renal calcification resulting from known extra-renal diseases, are excluded from consideration.

The normal kidney.—Does calcification occur in the *normal* kidney? The answer is that it does and very commonly. 380 apparently normal kidneys have been submitted to microscopic examination and tiny foci of calcification were present in a percentage which varied from 14% to 25% in different groups of autopsy cases according to the disease causing death; the overall incidence was about 15%. The calcific foci were sparsely scattered in the cells and sometimes around the upper collecting tubules, while a few lay within the lumina of the tubules; they are shown as black, globular deposits in almost normal cells. (Fig. 3). The cause of these calcific deposits is unknown.

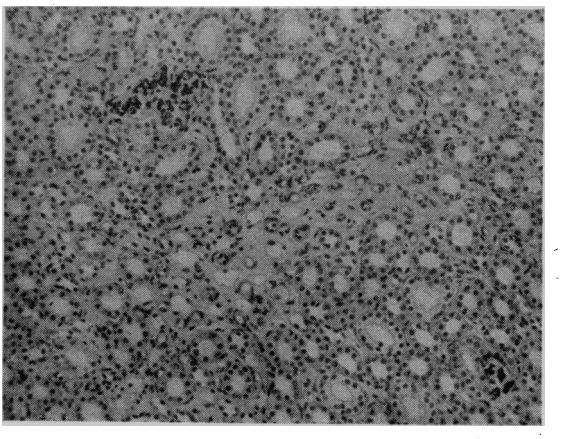
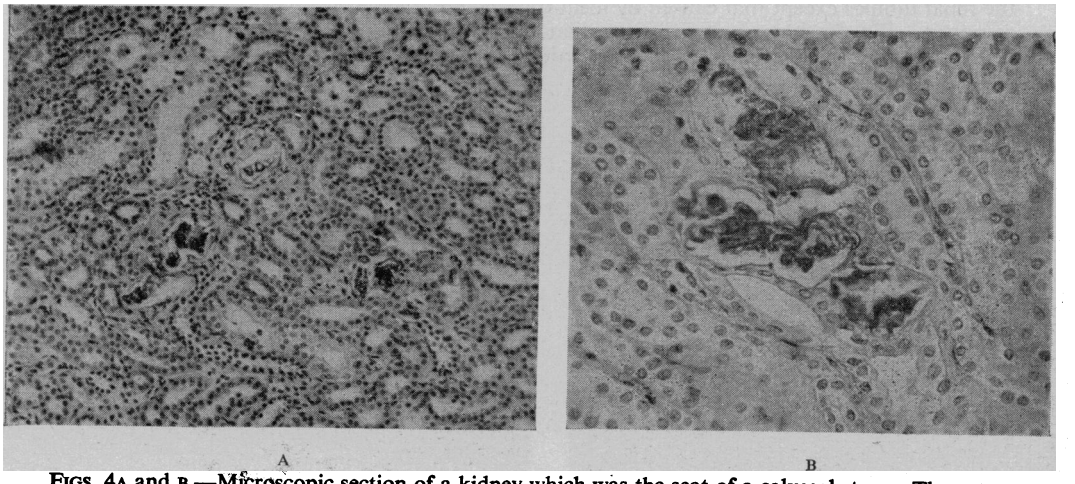


FIG. 3.—Microscopic section of a normal kidney showing two foci of calcification (stained black). ×80.

The stone-bearing kidney.—Examination of the renal parenchyma of partial nephrectomy specimens removed at operation for aseptic calcium-containing stones and also of stone-bearing kidneys removed at autopsy, has shown approximately a 75% incidence of calcification in the renal pyramids. The calcification here is usually found in the upper collecting tubules which may be dilated and contain calcium casts, occasionally in the convoluted tubules and also outside the tubular lumina, when they have ulcerated through (Fig. 4A and B). In the vast proportion of cases the calcific deposits in the stone cases are far more



FIGS. 4A and B.—Microscopic section of a kidney which was the seat of a calyceal stone. There are multiple calcific foci in the renal papillæ (for description *see* text). A ×120. B ×200.

numerous and much closer together than the occasional sparse and scattered calcific deposits in normal non-stone-bearing kidneys. This intra-renal lesion is regarded as *the one* which is commonly associated with a calcium-containing stone.

In attempting to find the early lesion of the calyceal stone, Randall (1937) described plaques of calcium phosphate which started in the sub-epithelial region of the renal pyramids. Fig. 5 shows an example of such a plaque lying immediately beneath the

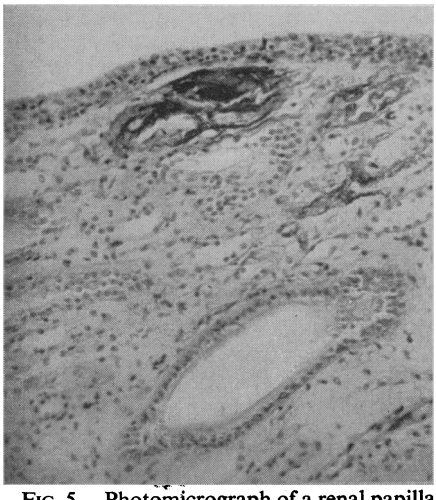


FIG. 5.—Photomicrograph of a renal papilla showing a Randall's plaque (stained black). ×93.

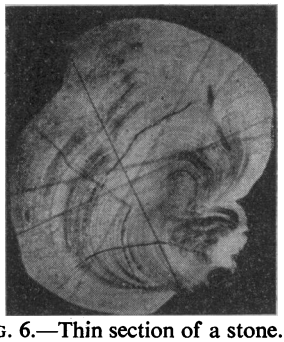


FIG. 6.—Thin section of a stone. The pale part at the hilus (right) of the stone is calcium phosphate derived from a Randall's plaque. The rest of the stone is laminated calcium oxalate.

calyceal epithelium and lifting it slightly as if preparatory to ulceration. Randall believed that the epithelium covering the plaque was subsequently lost and that upon the calcium phosphate nucleus thus exposed to the action of the urine, calcium oxalate or other urinary salts could be deposited, leading to the maturation of a calculus (Fig. 6). Of the many kidneys that have been examined, however, Randall's plaques have not been found with the frequency described by him.

A much rarer type of aseptic calcification of which only three or four examples have been found, is that seen in the kidney of a male patient aged 24, who had bilateral renal calculi. The urine was free from infection. Partial nephrectomy for the removal of the lower calyceal stone in the left kidney revealed, in addition to the large stone, three other calculi within a renal papilla, far removed from its calyceal epithelium (Fig. 7A). Microscopically there were a few intra-tubular calcific deposits but there was no cellular damage of the renal tubules except that caused by local trauma, and there was no inflammatory cellular response. Fig. 7B shows a deposit in a dilated duct of Bellini of some inspissated colloidal debris partly impregnated with calcium salts.

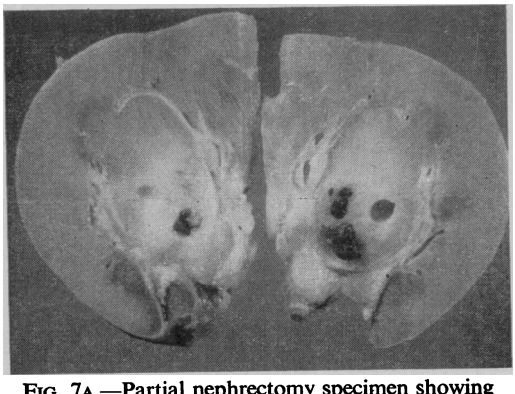


FIG. 7A.—Partial nephrectomy specimen showing two biggish and two smaller calculi located in the renal papilla itself and not in a calyx.

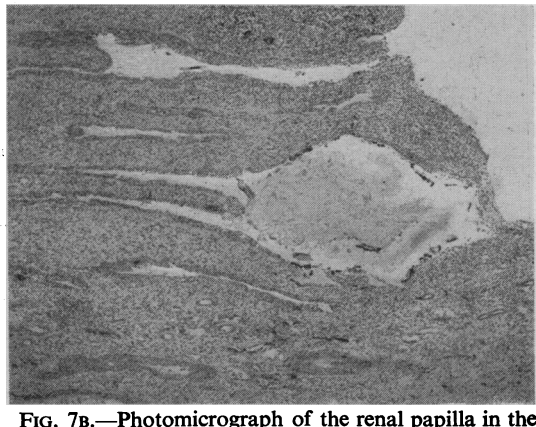


FIG. 7B.—Photomicrograph of the renal papilla in the same case showing a dilated duct of Bellini containing colloidal debris partly impregnated with calcium salts (stained black). ×25.

These, then, are the three types of calcification which have been found in the aseptic stone-bearing kidney, and the first is considered to be the most important.

In the infected stone-bearing kidney, the picture is different; in such cases there is usually widespread calcification and microlith formation in the renal parenchyma, mainly in the pyramids. Fig. 8A shows the renal tract of a woman of 26 with calculous disease of both kidneys and one ureter; the clinical symptoms were not severe though she had a very resistant staphylococcal infection. The calcification here is distributed in the collecting tubules causing a complete blockage of the nephrons involved, and there are

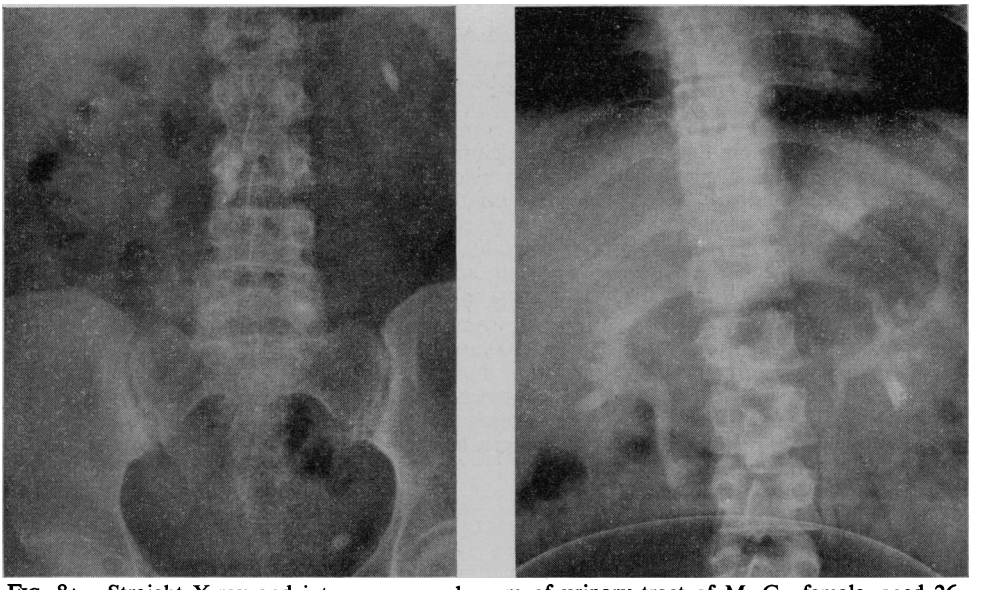


FIG. 8A.—Straight X-ray and intravenous pyelogram of urinary tract of M. G., female, aged 26. There was calculous disease of both kidneys and left pelvic ureter. The urine was infected.

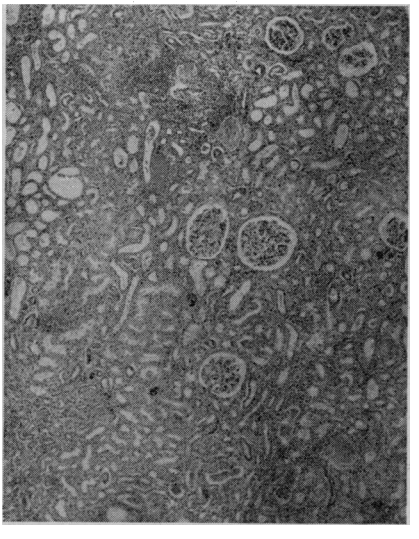


FIG. 8B.—Patchy foci of papillary calcification together with round cell infiltration in a kidney the seat of an infected stone (partial nephrectomy specimen obtained from the case in Fig. 8A). Low power.

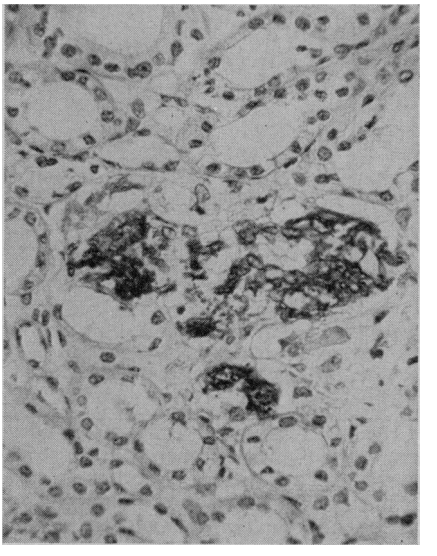


FIG. 8C.—As Fig. 8B. High power. ×233.

scattered foci in the convoluted tubules, usually the proximal ones (Fig. 8B and C). The infected cases show the grossest and most widely-spread calcification of any in the stone group; the deposits of calcific debris are larger and there is more general cellular reaction than in the non-infected stone group; there are foci of reactionary cells, often fibroblasts, without necessarily pus formation, and there is peritubular fibrosis.

Finally, calculi may be deposited in kidneys which are the seat of hydronephrosis or hydrocalycosis, possibly of congenital origin, and then stasis of particulate matter probably has an important role, intra-renal calcification not being any more common than in the normal kidney.

Excretion of Urinary Calcium and Phosphorus in Stone Cases

Since it appears that in the parenchyma of the stone-bearing kidney there is a much greater tendency for calcium phosphate to be precipitated than in the normal kidney, the excretion in the urine of calcium and of phosphorus in patients with calcium-containing stones, and in normal controls, has been compared.

In addition to examining the urinary calcium and phosphorus in a series of cases on a low calcium diet, a larger series of urinary calcium and phosphorus on an ordinary ward diet has been examined, since the accommodation in the metabolic ward would not allow every patient with a renal calculus to be given the controlled diet. Certain conclusions have been reached regarding the practical value of the two methods, and criteria have been selected for a diagnosis of hypercalciuria on an ordinary ward diet.

Normal urinary excretion of calcium.—Fig. 9 shows the urinary excretion of calcium in a group of 132 normal men and 126 normal women on an intake of 800 ±200 mg. of calcium per day. The majority excreted between 100 and 200 mg. of calcium per day. On looking at the figures in greater detail, it was found that at least 90% of the men excreted less than 300 mg. per day, and at least 90% of the women excreted less than 250 mg. per day. A few individuals in each sex group excrete exceptionally large amounts of calcium, the incidence of these very high calcium values being greater in normal men than in normal women (Hodgkinson and Pyrah, 1958).

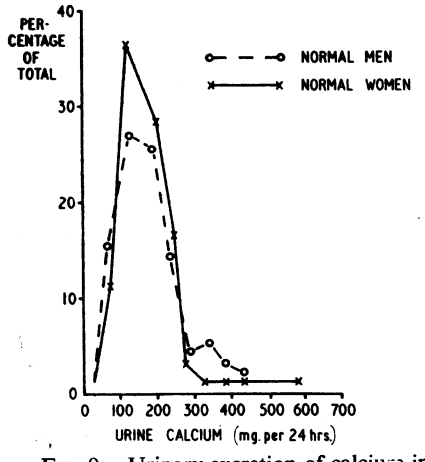


FIG. 9.—Urinary excretion of calcium in a group of 132 normal men and 126 normal women on an intake of 800±200 mg. of calcium per day (Hodgkinson and Pyrah, 1958).

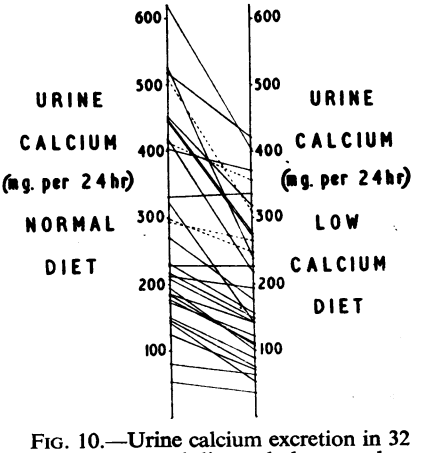


FIG. 10.—Urine calcium excretion in 32 patients on a ward diet and also on a low calcium diet (for explanation *see* text).

Urinary excretion of calcium on normal and low calcium diets.—The urinary calcium excretion was then compared in 32 stone patients firstly on a ward diet (containing 800± 200 mg. calcium per day) and then on a low calcium diet (containing 130 to 170 mg. of calcium per day), and the results are shown in Fig. 10. The corresponding measurements for each individual on the two diets are joined by solid or dotted lines, the latter representing cases of stone in association with proved hyperparathyroidism. In general there is a decrease in the urinary calcium, but it is not necessarily a marked decrease; in some cases (in fact, in quite a proportion) there is little change.

It has already been shown that the approximate upper limit of normal for men is 300 mg. per day, and for women 250 mg. per day. If these values are accepted, then 14 of these 32 stone patients had abnormally high urine calcium values. Similarly on the low calcium

diet, it is considered that the approximate upper limit of normal is 175 mg. of calcium per day; so in the 32 patients considered here, 16 had urinary calcium values greater than 175 mg. The figures, therefore, for the incidence of hypercalciuria, when the estimations are done on a low calcium diet and also on a normal calcium diet, are reasonably close. It seems, therefore, that for practical purposes an abnormality of calcium excretion may be detected as readily with the patient on a normal diet as on a carefully controlled low-calcium diet.

Calcium excretion by normal adults and by stone patients on a normal diet.—Fig. 11A shows the distribution of urine calcium values for normal men compared with that of a group of 220 male stone patients. In the case of the stone patients there is a shift to the right, showing a higher incidence of hypercalciuria; 35% of the stone cases had values higher than 300 mg. compared with 10% of the normal controls.

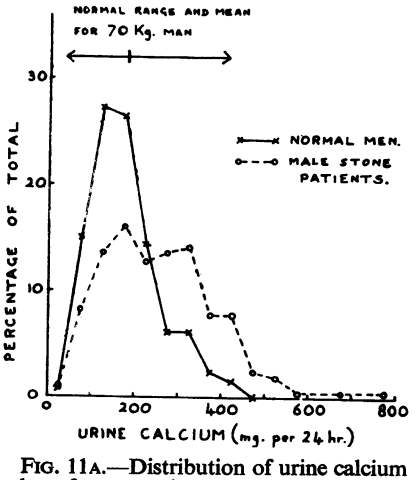


FIG. 11A.—Distribution of urine calcium values for normal men compared with a group of 220 male stone patients.

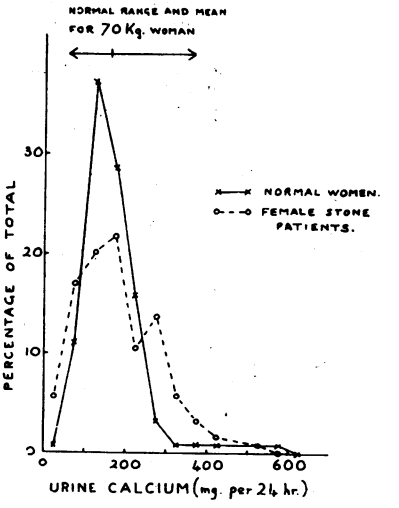


FIG. 11B.—Distribution of urine calcium values for normal women compared with a group of 124 female stone patients.

Fig. 11B shows the distribution of urine calcium values of normal women compared with those of 124 female stone patients. Once again there is a shift to the right in the stone patients showing an incidence of hypercalciuria, but this is not so marked as in the men. In fact 25% of the women with stone had values of urinary calcium higher than 250 mg. compared with 6% of normal women.

Calcium excretion and impaired renal function.—Stone patients with marked impairment of renal function had a low excretion of urinary calcium. When the urinary calcium is plotted against urea clearance, in no case was it found that the urine calcium was high when the urea clearance was low. Fig. 12 shows the relationship between urinary calcium

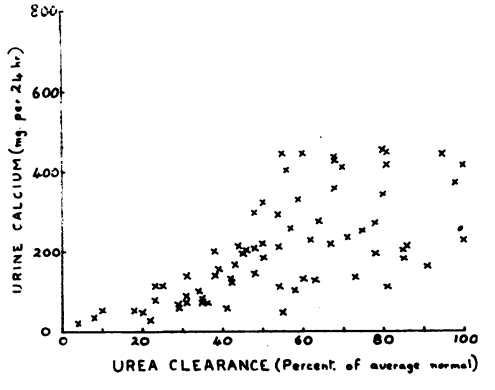


FIG. 12.—Relationship between urinary calcium excretion and urea clearance in 72 renal stone patients on a normal diet.

excretion and urea clearance for 72 patients on a normal diet. If the cases having poor renal function are omitted from the series, then it is found that the incidence of hypercalciuria is rather higher, namely 37% in the case of men stone-formers and 31% in the case of female stone-formers.

Calcium excretion and type of stone.—The incidence of urinary excretion of calcium and hypercalciuria was then compared with the type of renal stone (Table II). The incidence

TABLE II.—THE RELATIONSHIP BETWEEN THE URINARY EXCRETION OF CALCIUM AND THE TYPE OF STONE

Group	Total No. of individuals	Percentage with urine calcium values greater than 200 mg. per day
Normal adults	258 (56)	26% (31%)
Calcium phosphate stones..	14 (11)	30% (54%)
Calcium oxalate stones ..	46 (26)	53% (69%)
Mixed calcium oxalate and calcium phosphate stones	53 (15)	77% (93%)
Mixed struvite and calcium phosphate stones	17	17%

(Figures in brackets—Cottet and Vittu, 1955)

in the series is compared with that in a similar group of 52 calcium stone cases analysed by Cottet and Vittu (1955). It was found that the incidence of high urine calcium values was greatest in the mixed calcium oxalate—calcium phosphate calculi and almost as great in the pure calcium oxalate stones; hypercalciuria had the lowest incidence in cases composed of mixed magnesium ammonium phosphate and calcium phosphate; in the case of pure calcium phosphate calculi, the figures are intermediate, and in the last two groups most of the stones are the result of infection.

The findings agree with those of Cottet and Vittu (1955) but the incidence of high calcium values in each group in the series is lower than in the corresponding group reported in their series; and even when cases of impaired renal function in the series are omitted the figures of hypercalciuria are still lower than those of Cottet and Vittu.

Thus 66% of patients with calcium oxalate or mixed calcium oxalate—phosphate stones had average urine calcium values greater than 200 mg. per day compared with 26% of normal individuals. It is suggested, therefore, that in this group of cases of stone, hypercalciuria is an important contributory factor.

Phosphorus excretion in normal individuals and in stone patients on a normal diet.—The daily excretion of inorganic phosphate in healthy adults averages 800 mg. though there is a considerable variation above and below this value. The urinary excretion of inorganic phosphate is influenced by the dietary intake of phosphorus (though other factors also play a part) and it was estimated that an intake of phosphorus on the normal ward diet is within the range 1,100 ±300 mg. per twenty-four hours, which corresponds to a variation in the urinary excretion of inorganic phosphate of ±11%.

The distribution of the urinary phosphate per twenty-four hours, for 92 normal men and 118 normal women, on phosphorus intakes within the range of 1,100 ±400 mg. per day, is shown in Fig. 13 (Hodgkinson and Pyrah, 1958), the numbers of the cases being

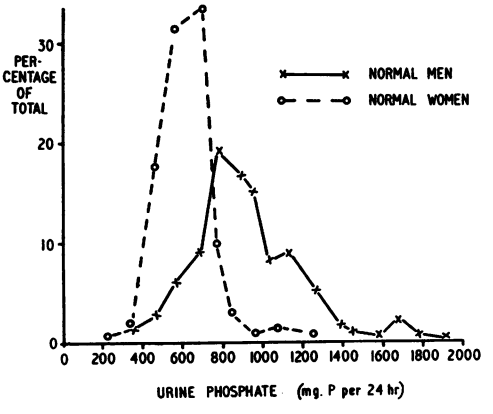


FIG. 13.—Urinary excretion of inorganic phosphate for 92 normal men and 118 normal women.

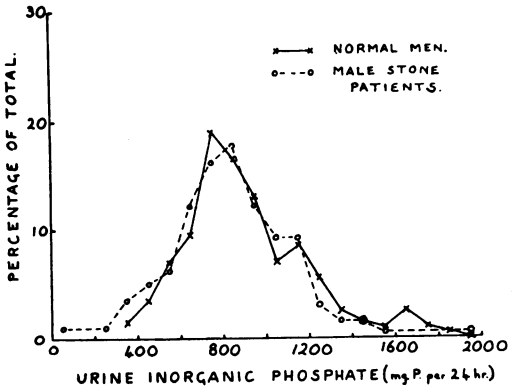


FIG. 14A.—Distribution of urinary phosphate for normal men compared with that for 198 renal stone male patients on normal ward diet.

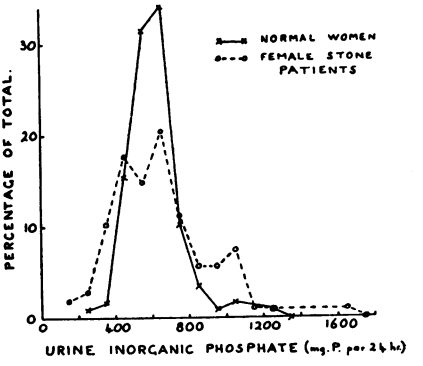


FIG. 14B.—Distribution of urinary phosphate for normal women compared with that for 108 female stone patients on a normal ward diet.

shown as a percentage of the total. The distribution of urine phosphate values for normal men varies between the figures of 450 and 1,600 mg. per twenty-four hours and thus differs significantly from that for normal women which varies between 350 and 950 mg. per twenty-four hours; so that in comparing the excretion in normal adults and in stone patients, allowances should be made for differences of sex.

Fig. 14A shows the distribution of urinary phosphate values for normal men compared with the distribution for 198 male patients with renal stones; the number of cases is again expressed as a percentage of the total. There is no significant difference in the phosphate excretion in the normal patients and in the stone patients.

Fig. 14B shows the distributions of urinary phosphate for normal women and for 108 female stone patients on a normal ward diet. A few of the female stone patients appear to have abnormally high values; thus 17 female stone patients (15·7%) had urine phosphate values greater than 900 mg. per day compared with 3·4% of the normal women. In 11 of these 17 patients the high phosphate excretion was associated with high calcium excretion and 4 of these had high or moderately high serum calcium values. One of them had, in fact, a parathyroid adenoma and the others are under continuous observation as possible cases of primary hyperparathyroidism.

The following points, therefore, have emerged from this investigation. The incidence of high urinary calcium excretion is appreciably greater in stone patients than in normal individuals and in men than in women. The incidence of hypercalciuria is greatest (60%) in cases of the aseptic calcium oxalate and the mixed calcium oxalate and phosphate stones. A high urinary excretion of calcium is not, however, found in *all* stone patients notably in those whose stones result from infection. A high urinary excretion of calcium is not *restricted* to patients with calcium stone since approximately 8% of normal adults were found to have urinary calcium values greater than 300 mg. for men and 250 mg. per day for women, whereas the incidence of calcium stones of renal origin in the general population is probably less than 0·2%. The evidence, however, suggests that the hypercalciuria is of ætiological importance for many renal calculi. Hyperphosphaturia does not appear to be a factor in the formation of calcium stones.

Possible Causes of Hypercalciuria

If, then, hypercalciuria has an ætiological significance, we must search for the causes, but so far none has been found to explain the majority of cases. A few are the result of hyperparathyroidism, but such cases are usually diagnosed because of the raised serum calcium.

Some possible explanations of the hypercalciuria may be:

(1) That there is a high intake of calcium in the diet accompanied by a high absorption and a high urinary excretion of calcium. If, however, these hypercalciuric patients are placed on a low calcium diet, they still excrete a large amount of calcium. If increased absorption is due to sensitivity to vitamin D, it should be possible to reduce calcium absorption and therefore excretion by giving cortisone (Anderson *et al.*, 1954); in the cases, however, that have so far been submitted to this test, cortisone does not result in any reduction of calcium excretion, in fact, there may even be an increase.

(2) There may be a renal tubular defect in that calcium which is passed down the tubules in the glomerular filtrate is not reabsorbed in normal quantities by the tubular epithelium. Although Albright and Reifenstein (1948) postulated that in one group of cases of idiopathic hypercalciuria a mild infective pyelonephritis caused by the *Staphylococcus albus* had resulted in tubular damage, with resulting impairment of the calcium-reabsorption mechanism, we have not ourselves so far found much clear evidence of an infective origin of the hypercalciuria. If there is damage to the enzyme system responsible for the reabsorption of calcium by the tubules, it is possible that other tubular functions are also damaged, and we have some evidence to support this view, and it is under active investigation.

(3) The third working hypothesis is that there is some abnormal form of calcium in the blood which is excreted from the blood stream by way of the glomerular filtrate and with which the renal tubules cannot deal; the calcium, therefore, passes into the urine in abnormally high amounts. Thus, if calcium is bound to citrate or to another organic acid in excessive amounts, the tubules may not be able to reabsorb it. In such cases the urine might be expected to contain an excess of the organic radical to which the calcium is bound. This possibility is under investigation.

It is impossible here to go into greater detail either in regard to the fundamental cause of the hypercalciuria, or even in assessment of the clinical diagnosis of such cases; the following case illustrates the difficulties with our present available resources:

Case report.—A. W., a man aged 48, had a nephrolithotomy for the removal of an oxalate calculus in 1953; recurrent stones were found in 1954 and these are still present. He was then found to have marked hypercalciuria.

The blood chemistry has been investigated thirty-two times since 1953, the only abnormalities found being a moderately elevated alkaline phosphatase (10 to 18 King-Armstrong units), and a slightly raised serum calcium (10·5 to 11·0 mg.%). We considered the possibility that the moderately elevated serum calcium level and the excessive urinary excretion of calcium (600 to 800 mg. per day) might be due to *multiple myeloma* but there were no bone changes, no Bence-Jones protein in the urine and no abnormality in the serum proteins.

A moderate glycosuria was found, but Cushing's disease was excluded on clinical grounds and also because the glucose tolerance curve was found to be normal and it seemed probable that the glycosuria was renal in origin.

Calcium, phosphorus, and nitrogen balance studies were carried out in 1955 (Fig. 15A). On a low calcium diet the patient was in marked negative calcium balance, the urine calcium averaging

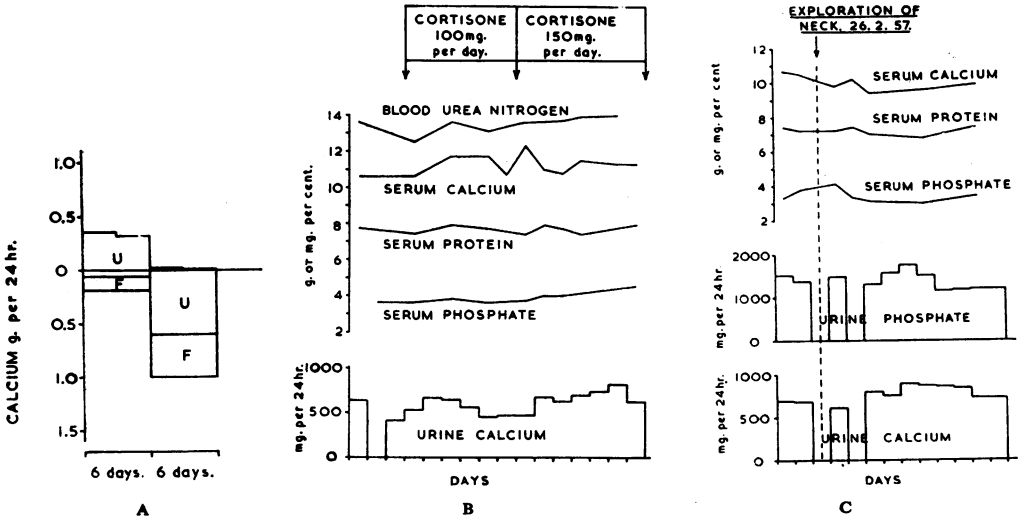


FIG. 15 (Case A. W.).—A, Calcium balance study on low and normal calcium intake. F=fæces. U=urine. B, effect of cortisone on serum calcium and urine calcium showing biochemical changes in the urine (for full explanation *see* text). C, Blood chemistry.

400 mg. per day compared with normal values of 100 to 150 mg. per day. On a normal calcium intake (1,000 mg. per day) however, the patient was in balance. The ratio of urinary to fæcal calcium was greater than normal which suggests that the patient is able to maintain himself in balance on a normal calcium intake by absorbing a greater proportion of the dietary calcium than is usual, hence the absence of bone decalcification.

Is it possible that an excessive absorption of calcium from the gut is the primary defect? Anderson *et al.* (1954) and Henneman *et al.* (1956) have shown that in sarcoidosis, which

occasionally leads to renal stone formation, hypercalcæmia and hypercalciuria are due to excessive intestinal absorption of calcium, the condition resembling hypervitaminosis D. In such cases treatment with cortisone, 100 to 150 mg. per day for one to two weeks reverses this excessive absorption and results in a decrease in the intestinal absorption of calcium and a reduction in the serum and urine calcium levels. In the present case, treatment with cortisone, 100 mg. per day for six days followed by 150 mg. for a further seven days, resulted in a slight rise in both the serum and urine calcium levels (Fig. 15B). It was concluded from this investigation that excessive intestinal absorption of calcium from any cause is not the primary defect in this case; sarcoidosis as a diagnosis also appeared to be excluded.

An increase in the serum calcium level may occur when cortisone is given to patients with primary hyperparathyroidism and the possibility of parathyroid adenoma was considered. The serum calcium level of this patient varied within the range of 10·5 to 11·0 mg.% (Fig. 15C). Until recently we had considered this to be a high normal value but Keating (1955) in reporting the Mayo Clinic findings, has described many cases of primary hyperparathyroidism with average serum calcium values within this range; it was therefore decided to explore the neck for a possible parathyroid adenoma, which was done in February of this year. No evidence of parathyroid adenoma or hypertrophy was found. Following the operation the serum calcium level fell to 9·5 mg.%, but the urine calcium remained high at about 800 mg. daily. It was concluded that this is probably *not* a case of primary hyperparathyroidism although one must bear in mind the considerable difficulty which the surgeon has in locating the very smallest parathyroid adenoma.

On the evidence so far obtained this case would appear to be a true case of idiopathic hypercalciuria.

Crystallography

Turning now to the stone itself, crystallographic methods of study have enabled its mineralogical nature and its structure and mode of growth to be studied in about 400 cases of renal calculi. The techniques used have been those of X-ray diffraction, the polarizing microscope, studies of thin sections, and microradiography. The composition of calculi using similar methods has been previously investigated by Jensen (1938, 1940, 1941), Prien and Frondel (1947) and Prien (1949), Carlstrom (1955) and Lagergren (1956).

(1) *X-ray analysis.*—By irradiating finely powdered, crystalline material prepared from different parts of the stone, with a beam of monochromatic X-rays, the rays diffracted from the intra-atomic planes of the crystal lattice can be recorded upon a photographic film as a series of lines of variable spacing and intensity, producing a powder pattern which is distinctive for each crystalline substance. This method has enabled it to be shown that there are two different types of oxalate. Chemically the two oxalates are calcium oxalate monohydrate (whewellite) and calcium oxalate dihydrate (weddellite).

Calcium phosphate occurs in three forms which can be distinguished by this technique, namely calcium hydrogen phosphate dihydrate, tricalcium phosphate and apatite (a complex phosphate probably with adsorbed carbonate). The common triple phosphate is magnesium ammonium phosphate hexahydrate or struvite.

(2) *Polarizing microscope.*—A few particles of finely powdered samples of different parts of the calculi (the nucleus or the various layers) are immersed in a liquid of known refractive index under a cover slip, and a comparison is made between the two refractive indices for the purpose of identification. This is the most sensitive method for the study of small amounts of crystalline material.

(3) *Thin-section techniques.*—A thin-section technique has been used for the study of 96 cases of stone. The stone is first embedded in Perspex (methyl methacrylate); various other resins have also been tried; part of the stone is cut away and the flat cut surface is secured to a glass slide. The opposite pole of the stone is then cut or filed away until a section the thickness of 10μ is obtained which is then examined through the polarizing microscope.

(4) *Micro-radiography.*—Using the techniques of micro-radiography of thin sections of stones, 25 cases have so far been examined and this study is continuing. Different components of the stones will absorb the rays in different proportions and these differences are recorded on the film.

Calcium oxalate calculi.—Their crystallographic structure has been found to be of two types, in which the habits of the crystals differ, suggesting that the calculi are formed by two different mechanisms. In Type I, the stone, which is composed of calcium oxalate monohydrate (whewellite) only, has a nodular surface; the fractured surface often shows that the stone has a laminated structure, the laminæ being upwards of 1 μ thick; radial striation is characteristic. This type of stone is believed to have been formed by crystals deposited in a colloid matrix, the slow diffusion of ions taking place to form the needle-like crystals which grow out from the centre (Fig. 16).

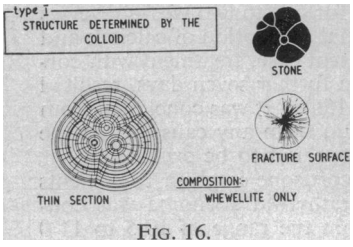


FIG. 16.

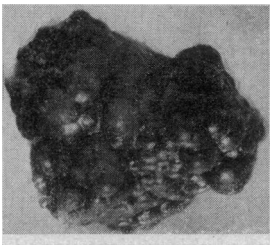


FIG. 17A.


FIG. 17B.

FIG. 16.—Calcium oxalate stone (Type I). The structure is determined by colloid. The stone has a nodular surface and cross section shows lamination and radial striation.

FIG. 17A.—Calcium oxalate stone (Type I), magnified, showing nodular surface.

FIG. 17B.—Fractured surface showing radial striation and lamination.

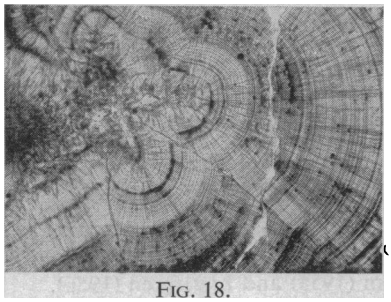


FIG. 18.

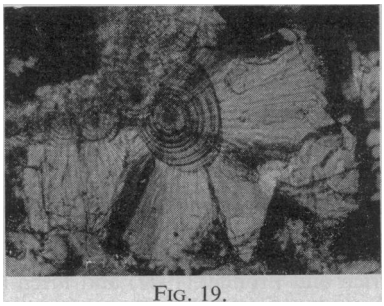


FIG. 19.

FIG. 18.—Thin section of nodular calcium oxalate stone (Type I). There is well-marked lamination and radial striation. ×15.

FIG. 19.—Calcium oxalate monohydrate stone (Type I). There is radial striation from the centre to the periphery. The lamination is limited to the central part of the stone. ×15.

Fig. 17A shows a stone having the characteristic nodular surface of a Type I oxalate stone. Fig. 17B shows the fractured surface revealing both the lamination and the radial striation. Fig. 18 is a thin section of a Type I stone; the centre is a mass of crystals of calcium monohydrate which were originally dihydrate; the characteristic radial striation and the lamination is shown. The dark lines between the laminæ represent the colloid matrix.

Fig. 19 (Type I stone) shows a laminated nucleus of calcium oxalate monohydrate (whewellite), of which the entire stone is composed. There is radial striation which is characteristic of the type of stone from the centre to the extreme periphery, so there is no interruption in the fundamental structure of the calculus; the striation is due to long acicular crystals growing close together, disposed radially. The colloid in the centre is concentrated in the dark rings. The lamination here is unusual, since it usually extends throughout the entire stone.

In Type II oxalate calculi the crystallographic appearances are different from those in Type I. Here, there is either a disorganized mass of calcium oxalate dihydrate (weddellite) crystals alone; or the interstices between the dihydrate crystals are filled with colloid, or with calcium phosphate (apatite) and colloid; or such a stone serves as a nucleus for a further deposition of a laminated zone, the layers alternating between apatite (calcium phosphate) and calcium oxalate dihydrate. The appearances of these stones with their perfectly normal crystals and no embedding colloidal mass, suggest that the dihydrate has been formed by a primary crystallization process and not by secondary crystallization in a gel or by passing through an intermediate colloidal phase. The stone itself has a coarse or a fine crystalline surface, with the crystals also visible on the fractured surface; radial striation is absent and the fine lamination of the monohydrate stone is also absent; sometimes there is rough layering (Fig. 20).

Fig. 21A shows the typical crystalline surface of a Type II stone. Fig. 21B shows the fractured surface; the white patches are layers of apatite which appear powdery; the rest of the stone is composed of colourless or yellowish crystals of dihydrate (weddellite); the rather crude layering indicates stages of growth in the stone.

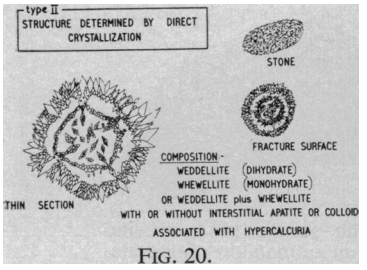


FIG. 20.

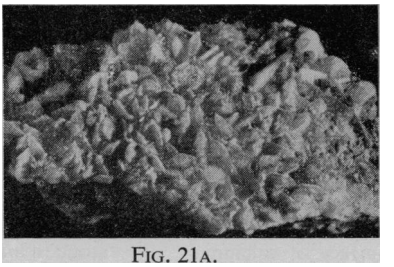


FIG. 21A.

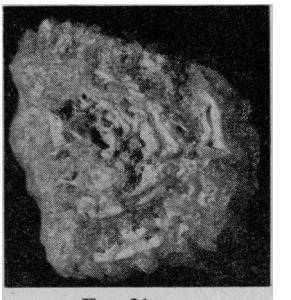


FIG. 21B.

FIG. 20.—Calcium oxalate stone (Type II). The structure is determined by crystallization. The surface is highly crystalline. The fractured surface is also crystalline. There is rough layering rather than well-marked laminations and there is no radial striation.

FIG. 21A.—Calcium oxalate stone (Type II). The surface is highly crystalline.

FIG. 21B.—The fractured surface shows crude layering. The white patches are apatite (calcium phosphate).

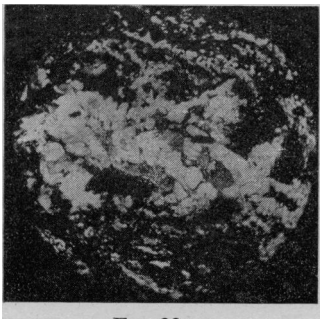


FIG. 22A.

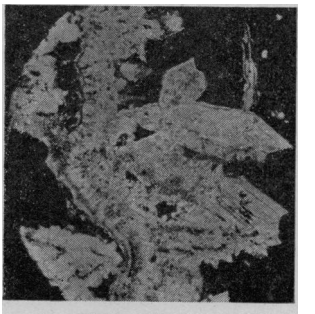


FIG. 22B.

FIG. 22A.—Thin section of calcium oxalate stone (Type II). (For description *see* text.)

FIG. 22B.—Thin section of calcium oxalate stone (Type II) showing much crystallization by calcium oxalate dihydrate. On the surface of the stone (right of the picture) lines parallel to the edge represent growth lines in the crystallization.

Fig. 22A shows an example of a Type II stone, namely a mixed calcium oxalate dihydrate and apatite stone (weddellite type). The crystals in the right centre of the field were large calcium oxalate dihydrate (weddellite) crystals, which have undergone recrystallization into the much smaller crystals of calcium oxalate monohydrate (whewellite). It is possible that the whole of the centre area in the field has been one large crystal of the dihydrate (weddellite) which has subsequently undergone recrystallization into monohydrate. The black parts in the field are again either colloid or apatite or a mixture of both. The small crystals in the upper and lower part of the field are of the monohydrate (whewellite).

The single crystals of the dihydrate (weddellite) are often especially obvious at the surface of these Type II calcium-oxalate-containing stones. The large crystals show lines which indicate their growth. The black part is either colloid or apatite (calcium phosphate) or a mixture of both (Fig. 22B).

If it is true that the Type II stones have been formed by primary crystallization, one would expect them to be associated with a high concentration in the urine of the stone-forming material. It has been found, in fact, that stones of this group are associated with hypercalciuria.

It is thought, therefore, that there are two types of calcium oxalate stone which are recognizable because of their structure by crystallographic techniques and which are probably ætiologically distinct. In the Type I stones it is suggested that the structure of the stone has been determined by the colloid; and that the incidence of hypercalciuria is no greater than in normal people. In this group, investigations into the urinary colloids may repay further study. In the Type II cases in which the structure of the stone appears to have been determined by direct crystallization, it has been found that the incidence of hypercalciuria is high, suggesting, in fact, that it is of ætiological importance.

FIG. 23.—Calcium phosphate stone showing fractured surface of calcium phosphate and magnesium ammonium phosphate hexahydrate. ×2.

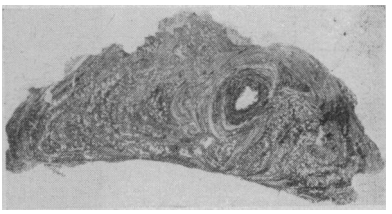


FIG. 24.—Thin section of a struvite stone (magnesium ammonium phosphate hexahydrate). (For description *see* text.) ×3·5.

Calcium phosphate calculi.—Fig. 23 is a stone (cut across) composed of calcium phosphate (apatite) and magnesium ammonium phosphate hexahydrate (struvite).

The structure of a phosphate stone is shown by the thin section of a struvite stone (Fig. 24). When the thin section is examined under polarized light, the stone has a laminated structure, with comparatively large single crystals of magnesium ammonium phosphate hexahydrate (struvite) arranged in rows along each band, the crystals being embedded in colloid or in apatite. The appearances suggest that each layer was deposited in the manner described by Schade, namely the primary formation of a nucleus followed by the deposition of successive layers of colloid, with crystal deposits in each layer.

PREVENTION OF STONE FORMATION

The principles that have been used for the prevention of stone have been firstly to try to provide physical conditions in the urine either by methods of dilution or by alterations of the pH, which will make it unlikely that the stone-forming substances will be precipitated. An alternative method is to deny access to the urine of stone-forming substances such as phosphorus and calcium.

It is, however, interesting to refer to what actually happens in badly functioning kidneys if a stone-forming substance such as calcium is denied normal access to the urine because of poor renal function, and alternatively what happens if a good deal of calcium is presented to such a kidney simply because it happens to be in the blood stream.

Fig. 25 shows two small calcium-containing calculi inadvertently left behind at operation

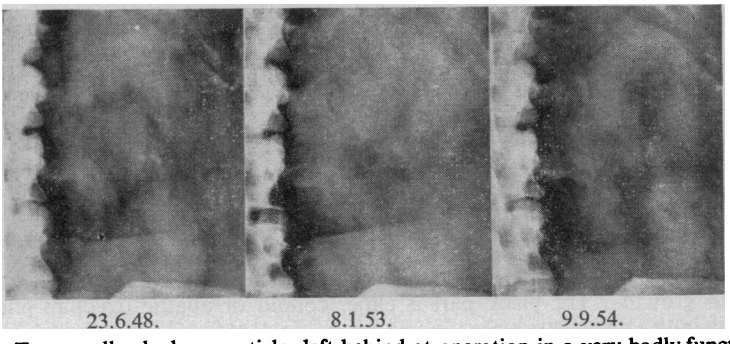


FIG. 25.—Two small calculous particles left behind at operation in a very badly functioning kidney. The stone disappeared without further interference (*see* text).

in a patient who had only one badly functioning kidney which was also infected with *Bacillus proteus*; in spite of the infection the stones were no longer visible radiologically when the patient was X-rayed three years later; they had probably undergone dissolution. The urinary excretion of calcium here was very small.

Similarly renal calculi never occur in kidneys which are the seat of chronic nephritis (unless, of course, the calculus has ante-dated the nephritis), because of the inability of the diseased kidneys to allow calcium to pass into the urine in any quantity. On the other hand, if in a patient who has advanced glomerulonephritis, large amounts of calcium are absorbed from the gut into the blood stream following, say, a very high intake of milk,

calcium salts may be deposited in the glomeruli producing a stippled type of calcification throughout the entire parenchyma of the kidneys (Fig. 26); and also in such cases the excess

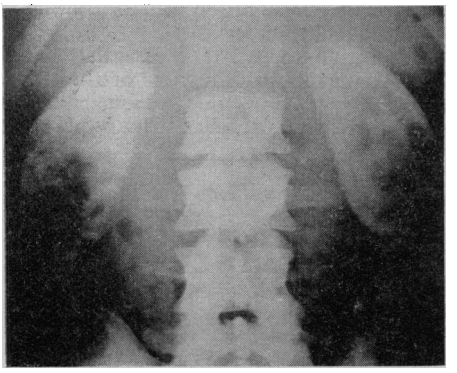


FIG. 26.—Bilateral calcification in both kidneys in a case of glomerulonephritis. The patient had had a high intake of calcium by mouth for a prolonged period. (By kind permission of Dr. Sosman, Peter Bent Brigham Hospital, Boston, U.S.A.)

of calcium salts may be deposited in subcutaneous and peri-articular tissues in an attempt to prevent the elevation of the serum calcium.

This summary will refer, briefly, to the ancillary methods which are being tried out to prevent the recurrence of calcium-containing renal calculi.

(1) *High intake of fluids.*—It is always advised that the stone-former should have an appreciably higher daily intake of fluids than a normal individual; apart from cystine stones (Dent, 1955), however, it is doubtful if sufficient urine volume can be achieved to obtain dissolution of existing calculi, though fluid may prevent the growth of crystalline matter into stones. An extreme example of the effect of a very high intake of fluids in the rat was shown by a simple experiment by Grove *et al.* (1950); these workers were able to induce bladder stones in rats by implanting tiny pieces of zinc through a suprapubic cystotomy; by substituting a solution of glucose for tap water for drinking which, by inducing thirst, caused a very high total daily intake of fluid, stones were prevented from forming around the zinc implants, and one-third of pre-formed calculi underwent dissolution.

(2) *Diet control: acidogenic diet.*—Higgins (1943) advocated an acid-ash diet to try to reduce the recurrence rate of renal calculi following operation. If the urinary pH is reduced, however, the increase in the urinary calcium which results may neutralize or outweigh any favourable effect from the change in pH. Moreover the urinary calcium salts do not differ in their solubility with the available range of pH to the same extent as do cystine and uric acid, so that the change in pH cannot be expected to give remarkable results.

In the case of some soft, non-infected, recumbency calculi consisting of almost pure calcium phosphate and a minimum of colloid (which are uncommon), the administration of ammonium chloride in biggish doses to render the urine acid, with or without an acidogenic diet, may effect a complete disintegration or dissolution of the calculi. A similar dissolution of soft phosphatic renal stones in certain cases of hyperparathyroidism with advanced skeletal changes, has been obtained; and such a treatment is the most reliable method of dealing with severe cases of phosphatic incrustation of the bladder.

(3) *Calcium excretion.*—Henneman *et al.* (1956) proposed the use of phytic acid (inositol phosphoric acid) for reducing urinary calcium excretion in sarcoidosis, in which the hypercalciuria is probably due to the excessive absorption of calcium from the intestine (Anderson *et al.*, 1954), and they suggested that this compound might be of value in the treatment of idiopathic hypercalciuria. In idiopathic hypercalciuria, however, it would appear that the defect differs from that in renal sarcoidosis in that it is renal rather than intestinal, so that the use of phytic acid in that condition would be of limited value.

(4) *Phosphate excretion.*—It has already been shown that in normal individuals and in stone patients the urinary excretion of phosphate is usually within normal limits. It is possible, however, that a reduction of the urinary phosphate may be of value in the treatment of recurrent calcium phosphate stone and the use of aluminium hydroxide gels is being recommended in suitable cases. This treatment can be used so as to cause an appreciable reduction in urinary phosphate by precipitating phosphate in the gut, but we find that it is sometimes accompanied by an increase in urinary calcium which is undesirable.

Various preparations of aluminium hydroxide are available (Pyrah and Smith, 1956) and the use of Hyalgel, which has the highest content of aluminium hydroxide with adsorbed carbonate has been preferred. This preparation is best used for the treatment of calcium-phosphate stones and probably it is not indicated with oxalate calculi. There has been

difficulty in inducing patients to stay on this treatment for long periods of time. Moreover it has not been certain that the treatment is of permanent value when there is a persisting urinary infection which cannot be cured. There has been a tendency, therefore, to limit the use of this treatment to co-operative patients in whom the urinary tract is free from infection and who also can attend hospital for adequate supervision.

Fair success has been achieved in reducing the phosphaturia. It is essential that the Hyalgel be given with meals in order to produce the maximum reduction of the urinary phosphate. It is also necessary for frequent tests on twenty-four-hour specimens of urine for phosphorus to be made. Fig. 27 shows the measure of reduction in urinary phosphate

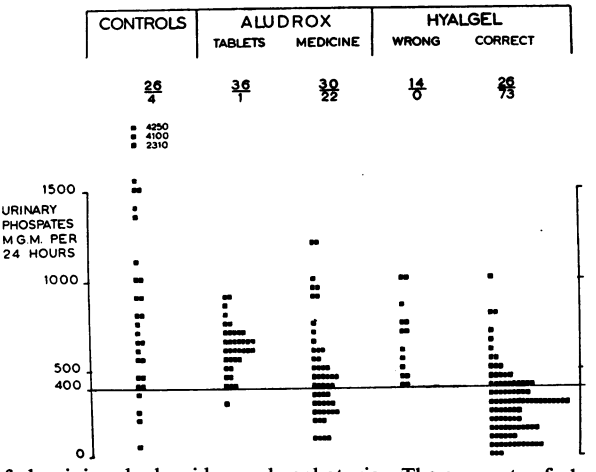


FIG. 27.—Effect of aluminium hydroxide on phosphaturia. The amounts of phosphate in the urine (mg./twenty-four hours) of 25 patients with renal stone while taking a normal diet with various preparations of aluminium hydroxide. 232 tests are each represented by one small square. Column 1, no aluminium therapy; column 2, Aludrox tablets; column 3, Aludrox medicine; column 4, Hyalgel taken inadequately or not with meals; column 5, Hyalgel 30 ml. q.i.d. with meals. 400 mg./twenty-four hours considered satisfactory, fractions represent the proportions of unsatisfactory to satisfactory results.

which can be achieved, and it has been found that Hyalgel is much better in this regard than Aludrox in doses which patients will tolerate.

Of 9 patients treated for periods of one and a half to three and a half years under what are regarded as optimum conditions, the clinical histories are as follows: These 9 patients between them have had 24 operations for stone; they had voided between them at least nineteen other stones. 3 patients had had nephrectomy and 4 had had partial nephrectomy. During the period of treatment one stone diminished markedly in size. Only one new stone has appeared in the 9 patients and this occurred during a period when treatment was not controlled; no existing stone has increased in size. The treatment, therefore, in a small group of patients, with the provisos that have been mentioned, is worth while, provided the criteria mentioned are also observed.

(5) *Oxalic acid excretion.*—Because of the lack of a suitable method for estimating oxalic acid in urine, few studies have been made of oxalic acid excretion in stone patients. A method has been recently developed which is considered to be sufficiently sensitive and specific. It has been found that urinary oxalic acid excretion is generally within normal limits in stone patients but that it may be slightly raised in patients with pure calcium oxalate stone. It is possible, therefore, that a reduction in the urinary excretion of oxalic acid may be of benefit in such cases; we have not yet tried this approach. Archer *et al.* (1957) described a case of hyperoxaluria in which there were 200 mg./day oxalic acid excreted in the urine (the normal figures being about 20 mg./day) and they reported that oxalic acid excretion could be reduced by feeding benzoic acid; the condition appears to be rare.

(6) *Excretion of organic acids:* (*a*) *Glucuronic acid.*—It is well recognized that, for reasons which are only partly understood, biological fluids including urine have a greater ability than water to hold calcium salts in solution. Mandl *et al.* (1953) emphasized the importance of organic acids in this process and Prien and Walker (1955) suggested that the ability of urine to hold calcium salts in solution might be enhanced by increasing the urinary excretion of glucuronic acid by the ingestion of salicylic acid. Trials in cases of recurrent stone have, however, shown that there is no significant reduction in recurrence rate when the excretion of glucuronic acid is thus increased (Vermeulen *et al.*, 1957).

(*b*) *Citric acid.*—Citric acid, which is excreted in the urine in amounts varying from 400 to 1,000 mg. per day, is one of the organic acids which probably plays an important part in helping to maintain calcium salts in solution. The excretion of citric acid is reduced in many cases of renal stone, and Shorr (1945) proposed the use of œstrogens to increase the urinary excretion of this acid. Conway *et al.* (1949) thought that the reduced excretion of citric acid could be explained by the presence of a urinary infection in these cases, but probably the infection does not account for all the low values which are found and further studies are being carried out on this aspect of the problem.

(7) *Calgon.*—The possibility of using the water-softener Calgon (sodium hexametaphosphate) as a therapeutic agent in the treatment of stone has been studied in our department (Care and Wilson, 1956). Calgon has the property of forming a soluble complex with calcium by an ion exchange process, and it was found that the experimental formation of stones in rats could be prevented by the addition of small quantities of Calgon to the drinking water. The suppression of stone formation was, however, accompanied by slight calcification in the renal parenchyma which was clearly undesirable. It may be possible to prevent this by using lower concentrations of Calgon and further long-term trials are proposed.

(8) *Chelating agents.*—Chelating agents are able to form complexes with various metals including calcium, and it is thought that this process may play a part in the formation or prevention of stones. Whereas in the case of phytic acid, citric acid, and Calgon, the combination with calcium involves an exchange of ions or the formation of a salt, chelation involves the formation of a ring structure with co-ordination linkages. The compound ethylene diamine tetra-acetic acid (E.D.T.A.) is a typical chelating agent commonly used for the decalcification of tissues *in vitro*. McGeown and Bull (1957) suggested that some of the urinary amino-acids may hold calcium in solution by forming soluble chelates, and reported that the urinary excretion of amino-acids is reduced in some stone patients. It is possible, therefore, that beneficial results might be obtained in some cases by increasing the urinary excretion of amino-acids if that is found to be possible.

ACKNOWLEDGMENTS.—The author desires to acknowledge the help and co-operation received from Dr. C. K. Anderson, Dr. A. Hodgkinson, Mr. B. T. Murphy and Mr. M. J. Purton.

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THE following Specimens were shown:

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