Papers and Originals

Control of Idiopathic Hypercalciuria*

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The definition of the term "hypercalciuria" is not absolute, for among normal people the daily output of calcium in the urine varies considerably, although for each individual this output remains reasonably constant. This was shown by Knapp (1947). She found that neither age nor sex affected urine calcium, except as they related to skeletal weight, and suggested that urine calcium excretion was governed by some endogenous factor, probably endocrine.

Hodgkinson and Pyrah (1958) estimated the 24-hour urine calcium excretion in a large group of normal men and women on a normal calcium intake of between 600 and 1,000 mg./day. They found that the excretion of calcium could be plotted on a bell-shaped distribution curve. There was no clear upper limit of normality, and they chose arbitrarily the figure of 300 mg./day for males and 250 mg./day for females, above which they thought calcium excretion was abnormally high. By this definition approximately 8% of normal adults came into the hypercalciuric range.

Hypercalciuria occurs in association with a number of diseases in which the cause is known, and these are listed in Table I.

TABLE I.—*Causes of Hypercalciuria*

Hyperparathyroidism
Cushing's syndrome and administration of corticosteroid drugs in large doses
Thyrotoxicosis
Osteoporosis in the acute phase
Immobilization
Metastatic cancer and multiple myeloma
Excessive doses of vitamin D
Renal tubular acidosis
Sarcoidosis
Fanconi syndrome
Paget's disease

Flocks (1940) was the first to draw attention to the fact that patients who form calcium-containing renal stones often excrete abnormally large amounts of calcium in the urine. This association has been confirmed by other workers but is not absolute. The incidence of hypercalciuria in patients with calcium-containing renal stones who appear to have no local or other known predisposing factor varies in different series from 20% to 60%.

Albright, Henneman, Benedict, and Forbes (1953) studied a series of cases of renal stone with hypercalciuria and found they had several features in common. There was a large preponderance of males, a low plasma inoraginc phosphate level was common, and there appeared to be a frequent associated urinary infection with *Staphylococcus albus*. They suggested that the condition might represent a clinical entity which they called "idiopathic hypercalciuria." It is difficult, however, to accept that a condition defined largely by exclusion could represent a clinical entity. Stone-formers are in any event predominantly male, and they may intermittently have low inorganic phosphate levels, as shown by McGeown (1957). The high incidence of *Staph. albus* infection in these patients has not been confirmed by Harrison (1959).

Although hypercalciuria is not a necessary condition for renal stone formation, the association is frequent enough to warrant further investigation of this relation and to attempt its control.

Preliminary Screening Tests

During the past four years we have taken the opportunity of studying a group of 15 patients with recurrent renal stones and hypercalciuria. The investigation consisted of routine screening tests to exclude the known causes of hypercalciuria listed in Table I. Renal function tests and metabolic balance studies for calcium and phosphorus were carried out.

The results of the preliminary screening tests are shown in Tables II and III. Three of these patients were found to have primary hyperparathyroidism, one had sarcoidosis, and one Paget's disease. In the remainder no known cause for the hypercalciuria was apparent and they were labelled as idiopathic. It must be stressed that all these patients presented in a similar manner—that is, with renal stones—and clinically there was no obvious difference between them. Normal plasma calcium values were initially found in the patients with parathyroid adenoma, and only on repeated estimations did increased values appear. Most patients had low inorganic phosphate levels at one time or another.

Table III shows the results of renal function tests. Repeated urine examination showed small numbers of pus cells in only half the patients with idiopathic hypercalciuria. Organisms were cultured from most of these urines, but no particular

TABLE II.—*Results of Preliminary Investigations*

Case No.	Sex	Diagnosis	Urine Calcium mg./day	Plasma Calcium mg./100 ml.	Plasma Phosphorus mg./100 ml.	Serum HCO_3 mEq./l.	Blood Urea mg./100 ml.
1	F	Primary hyperparathyroidism	383	11·1	3·1	24·0	23
2	M	" "	301	10·8	3·6	31·3	27
3	M	" "	396	10·4	2·8	28·9	24
4	M	Sarcoidosis	356	9·4	3·8	25·5	28
5	M	Paget's disease	370	9·6	3·1	25·3	38
6	M	Idiopathic hypercalciuria	318	9·8	3·8	29·3	34
7	M	" "	460	9·3	3·5	28·4	21
8	M	" "	525	11·0	3·8	25·8	24
9	M	" "	517	9·2	3·2	27·2	24
10	M	" "	364	9·1	3·6	25·3	31
11	M	" "	360	9·6	2·9	25	30
12	M	" "	551	9·6	3·4	27	35
13	M	" "	424	9·0	3·0	30	27
14	F	" "	407	9·6	3·4	25	22
15	F	" "	313	9·2	2·9	29	27

* This paper is based on the Langdon-Brown Lecture given by Dr. J. R. Nassim to the Royal College of Physicians of London in November 1963.

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organism predominated. *Streptococcus faecalis* was found twice and *Escherichia coli* and *Staph. albus* on three occasions. In over half the patients the maximum concentrating power was impaired: that is, that after 16 hours' fluid deprivation they did not concentrate better than a specific gravity of 1020. The ammonium chloride test, which comprised giving 8 g. of ammonium chloride in the morning and measuring the changes in urinary *p*H over the following six hours, was performed on four patients with idiopathic hypercalciuria and in three with hypercalciuria due to a definite cause. In no case was there an inability to acidify the urine below a *p*H of 6, as has been shown to occur in cases of renal tubular acidosis by Albright and Reifenstein (1948). Blood urea and urea or creatinine clearance were normal in all patients on whom the test was performed.

TABLE III.—*Results of Preliminary Investigations*

Case No.	Urine Protein	Urine Pus Cells	Organisms	Max. S.G.	Min. *p*H	Urea Clearance ml./min.	Creatinine Clearance ml./min.
1	Trace	Many	None	1016	—	71	
2	Trace	None	None	1020	—	—	
3	None	None	None	1014	5·3	—	
4	None	None	None	1016	5·9	62	
5	None	None	None	1024	5·3	—	
6	None	Few	*Str. faec.* *E. coli.*	1026	5·56	—	
7	None	None	None	1012	—	98	
8	60 mg. % (trace)	Few	*Str. faec.* *E. coli.*	1012	5·9	78	
9	None	Few	*S. albus*	1012	4·9	93	
10	None	Few	*E. coli.*	1016	4·9	—	
11	None	None	*S. albus*	1026	—	—	97
12	None	Few	*S. albus*	1016	—	—	108
13	None	None	None	1030	—	—	144
14	None	None	None	1022	—	—	187
15	None	None	None	1015	—	77	—

Sodium Bicarbonate

In some patients the effects on urine calcium excretion after giving sodium bicarbonate in a dosage of 10 g. daily were studied. Farquharson, Salter, Tibbetts, and Aub (1931) have shown that bicarbonate has no effect on urine calcium excretion in normal subjects, and Albright, Burnett, Parson, Reifenstein, and Roos (1946) that bicarbonate considerably reduces urine calcium in cases of renal tubular acidosis.

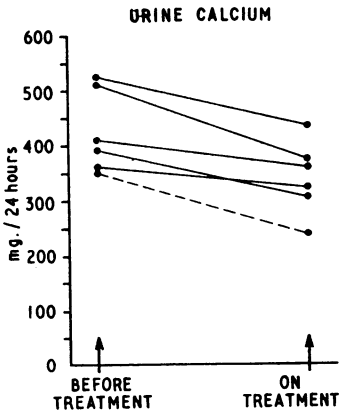

FIG. 1.—Effect on urine calcium excretion of sodium bicarbonate 10 g./day, in six cases of hypercalciuria. The dotted line represents the case of sarcoidosis. The figures are taken from full calcium balance data and represent the average of two or three six-day collection periods.

The results in six patients are shown in Fig. 1. They consisted of four cases of idiopathic hypercalciuria, one of primary hyperparathyroidism, and one case of sarcoidosis. In every case there was a fall in urine calcium. Since none of the patients had systemic acidosis or gross impairment of urine acidification the finding is difficult to explain. It could be that a mild, well-compensated acidification defect similar to that described by Wrong and Davies (1959) in the incomplete form of renal tubular acidosis may be present. Some impairment of water concentration found in our patients and by Gill and Bartter (1961) in patients with hypercalciuria suggests that these abnormalities of tubular function may be due to tubular damage caused by hypercalciuria itself. Demonstration of tubular lesions in cases of hypercalciuria due to known and unknown causes supports this hypothesis. Alternatively, since Flocks (1940) showed that hypercalciuria individuals when placed on an acid ash diet had an exaggerated increase in urine calcium when compared with normal individuals, our findings with sodium bicarbonate may represent a reversal of the effects of an acid ash diet. At present we have no other explanation for this finding.

Cortisone

As part of the routine investigation many of the patients were given cortisone 150 mg. daily and the changes in calcium balance observed. It is well known that patients with sarcoidosis and vitamin-D intoxication respond in a specific way. There is a lowering of serum and urine calcium and a rise in faecal calcium. It is for this reason that the hypercalciuria and hypercalcaemia sometimes found in sarcoidosis are thought to be caused by a hypersensitivity to vitamin D. The results of our findings are shown in Figs. 2 and 3. In Fig. 2 the changes in faecal and urine calcium in cases of idiopathic hypercalciuria are contrasted with the case of sarcoidosis. It can be seen that the response is different, with a slight fall in faecal calcium and either a rise or no change in urine calcium, in contrast to the clear-cut change in sarcoidosis. In Fig. 3 the changes in calcium balance in the case of sarcoidosis, a case of primary hyperparathyroidism, and two cases of idiopathic hypercalciuria are compared. It can be seen that the case of primary hyperparathyroidism responded in a similar way to the cases of idiopathic hypercalciuria and quite differently from the case of sarcoidosis. From these findings it seems unlikely that idiopathic hypercalciuria is due to a hypersensitivity to vitamin D.

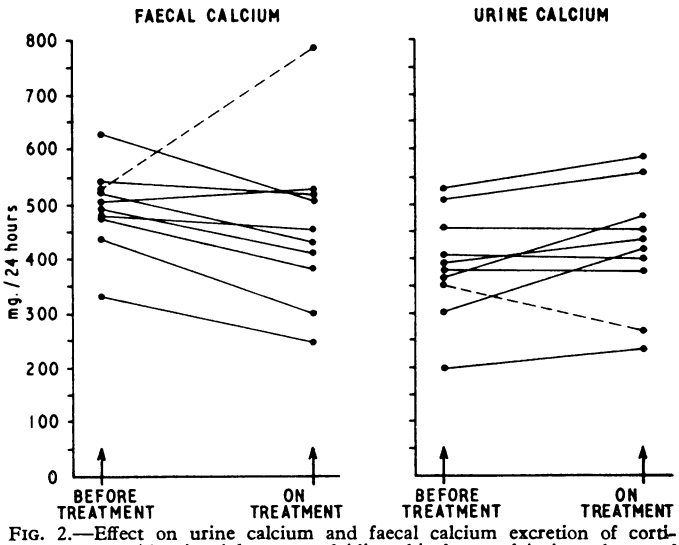

FIG. 2.—Effect on urine calcium and faecal calcium excretion of cortisone 150 mg./day in eight cases of idiopathic hypercalciuria and one of hyperparathyroidism (continuous lines) and one case of sarcoidosis (dotted line). The figures are taken from full calcium balance data and represent the average of two or three six-day collection periods.

Two Possibilities

In the absence of significant bone disease idiopathic hypercalciuria may arise in two possible ways. Firstly, there may be a primary increase in the urinary excretion of calcium due to reduced tubular resorption, this leading to a secondary stimulation of intestinal absorption as suggested by Jackson and Dancaster (1959). In these circumstances the serum calcium would tend to fall, causing stimulation of the parathyroid glands, and this would account for the low serum phosphate so often encountered in these cases. The original tubular lesion giving rise to the impaired tubular resorption of calcium may have been caused by infection, possibly *Staph. albus*, as suggested by Albright *et al.* (1953).

The second possibility is a primary increase in the intestinal absorption of calcium, the subjects absorbing more than they need to keep in zero balance and the excess being cleared by the kidney. On this theory the serum calcium would tend to rise, which would inhibit the parathyroid glands, and this is difficult to reconcile with the finding of a low serum phosphate.

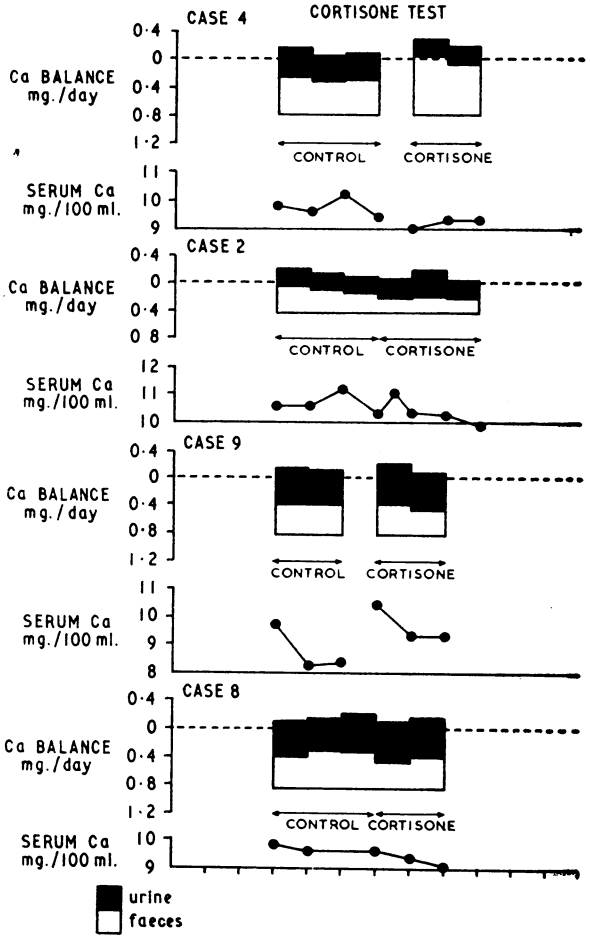

FIG. 3.—Effect on the calcium balance of cortisone in one case of sarcoidosis, one case of primary hyperthyroidism, and two cases of idiopathic hypercalciuria. The balance data are plotted in conventional fashion (Reifenstein *et al.*, 1945). The intake of calcium is measured downwards from the zero line. The output of faecal and urinary calcium is measured upwards. A clear space below the zero line represents a positive balance. Each block represents a six-day collection period.

At first sight it would seem a simple matter to distinguish between these two possibilities, for if the primary renal theory is correct then a drastically low calcium intake should produce very little or no effect on urinary calcium excretion, whereas if the second possibility was the cause then this restriction should produce an appreciable fall in urine calcium. The effects of a low calcium intake on the calcium balance of two individuals with idiopathic hypercalciuria are shown in Fig. 4. They both went into a markedly negative balance with little change in urine calcium. Bauer, Albright, and Aub (1929) showed that normal individuals on a very low intake of 100 mg. of calcium per day all went into a negative balance, and that there was a considerable variation in calcium excretion not only among different individuals but also in different periods in the same individual. Henneman, Carrol, and Albright (1956), in a balance study of one patient with idiopathic hypercalciuria on an intake of 130 mg./day, found a faecal calcium of 160 mg., which was about half of that to be expected on this intake, and a urinary calcium of 150 mg., which was double that expected, so that neither theory is proved. The effects on urine calcium of acute lowering of calcium intake in patients with idiopathic hypercalciuria have been observed by several workers (Pyrah, 1958 ; Harrison, 1959 ; Litin, Diessner, and Keating, 1961), and all have found a variable response, as occurs with normals. It would seem that as a test the results are difficult to interpret.

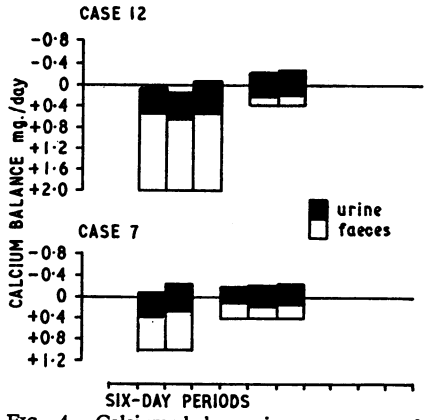

FIG. 4.—Calcium balance in two cases of idiopathic hypercalciuria showing the effect of low calcium diet.

Methods of Control

The theoretical methods of control of idiopathic hypercalciuria are simple. The most obvious is the lowering of the dietary intake ; secondly, by giving substances which interfere with the absorption of calcium, thereby achieving the same result ; and thirdly, by giving substances which have a direct action on the kidney to diminish the renal excretion of calcium. Each of these methods or a combination of them has been attempted.

Malm (1958), in his study of normal individuals with varying levels of calcium intake, found that all went into a negative balance when moderate reduction from their habitual intake was made. On following the balance for some time he showed that the majority were able to adapt and once again achieve zero balance, whereas a few were non-adapters and continued in a negative balance during the period of observation. It would therefore seem that restriction of calcium intake in some patients might eventually lead to bone disease. Most cases of idiopathic hypercalciuria do not have bone disease and therefore must be well adapted. In any event a very low calcium intake is difficult to achieve and the diet is unlikely to be adhered to except by the exceptional obsessive type of patient.

Low-calcium/High-phytate Diet

Boyce, Garvey, and Goven (1958) claim to have followed patients for over a year on a diet containing 150 mg. of calcium, low in vitamin D, and with high phytate. They state: "We have not demonstrated any patient with idiopathic hypercalciuria to be refractory to the low-calcium/high-phytate diet, *if it is followed*, and no evidence that any patient who responded well has become refractory to sodium phytate or has adapted to the low calcium diet by increased absorption." Whether they were in a negative balance is not stated.

In view of the fact that severe dietary restriction of calcium is not a practical method of treatment, and because of the absence of any other means of lowering urinary calcium, attempts have been made to restrict the intestinal absorption of calcium by giving a suitable non-toxic substance which would combine with it and achieve this result. Since Mellanby (1950) pointed out the anticalcific effect of oatmeal on growing puppies, much work has been done on this subject. It was found that the active principle responsible for this effect was inositol hexaphosphoric acid (phytic acid). It was further shown that the amounts likely to be consumed were not of significance in human nutrition. Nevertheless, sodium phytate when given in much larger amounts undoubtedly interferes with calcium absorption and has been used for this purpose in the treatment of sarcoidosis (Henneman, Dempsey, Carrol, and Albright, 1956) and in idiopathic hypercalciuria (Henneman, Carrol, and Albright, 1956 ; Boyce *et al.*, 1958).

Sodium phytate given by mouth is hydrolysed by an enzyme, phytase, in the gut to the extent of 30–40% into inorganic phosphate and inositol; this leads to an increased phosphate absorption from the gut and a rise in urinary phosphorus. To determine the effect of this extra phosphorus on the lowering of urine calcium we studied the effect of giving sodium phosphate in a dosage containing a similar amount of phosphate to that contained in phytate.

Although extra dietary phosphorus may interfere with calcium absorption in experimental animals, there is no evidence that this occurs in man. A fall in urine calcium without change in faecal calcium was found in normal subjects by Farquharson, Salter, and Aub (1931) and Malm (1963), and was observed in the treatment of resistant rickets by Saville, Nassim, Stevenson, Mulligan, and Carey (1955). In all cases given sodium phosphate there was no significant change in faecal calcium, but in each case there was a definite fall in urine calcium, as can be seen in Figs. 5 and 6. Nearly all the extra phosphate was absorbed and 80% of this appeared in the urine. However, enough was retained to produce a positive phosphorus balance (Fig. 6). This extra phosphorus was partly retained in extracellular fluid as there was a rise in serum phosphorus, and partly in bone, as indicated by increased calcium retention. It is unlikely that the fall in urine calcium is due directly to the rise in urine phosphorus, as a large acute increase in urinary phosphorus by intravenous infusion leads to a rise in calcium excretion (Jahan and Pitts, 1948). This effect was also noted on sodium phytate by Henneman *et al.* (1956) in a case of sarcoidosis. Whether this effect would be sustained we do not know.

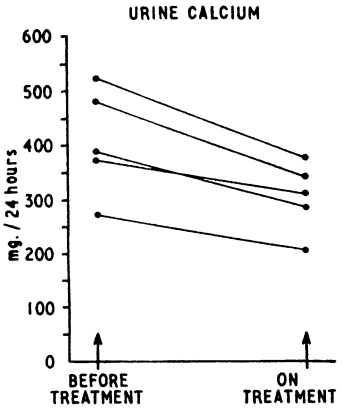

FIG. 5.—Effect on urine calcium excretion of neutral sodium phosphate in five cases of idiopathic hypercalciuria. The figures are taken from full calcium balance data and represent the average of two or three six-day collection periods.

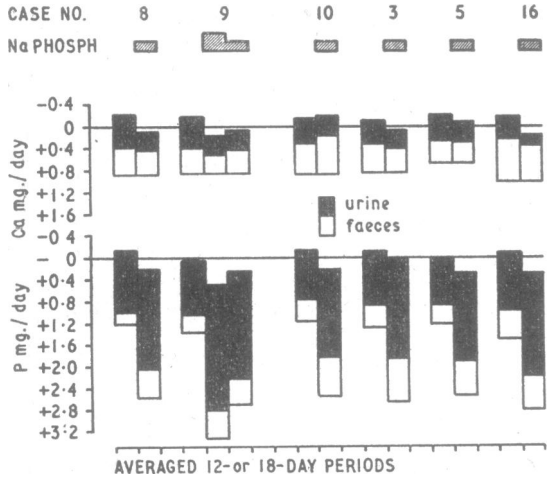

FIG. 6.—Effect on calcium and phosphorus balance of sodium phosphate. Each block represents the average of two or three six-day collection periods.

Sodium Phytate

The effect of sodium phytate was next investigated. This was given in divided doses of 6 to 8 g./day. Mild diarrhoea occurred initially in each patient and was not prevented by starting with a smaller dose and gradually increasing. In each case (Fig. 7) there was a substantial fall in urine calcium and a rise in faecal calcium.

The fall in urine calcium was greater than that produced by giving sodium phosphate alone. It can be seen that, depending on the amount of phosphorus retained, the calcium balance tended to become more positive. It is reasonable to assume that the inorganic phosphate derived from the hydrolysis of phytate would have similar effects to those of inorganic phosphate given as such by mouth, and the increased retention of phosphorus and calcium and a fall in urine calcium would be expected to occur independently of any increase in faecal calcium, which would produce its own effect in reducing urine calcium in addition to the phosphate effect. When sodium phytate was stopped urine calcium promptly rose to control levels, and this was usually accompanied by excretion of some of the retained phosphorus. Thus the effect of sodium phytate is due not only to calcium binding in the gut but also to the effect of liberated inorganic phosphate.

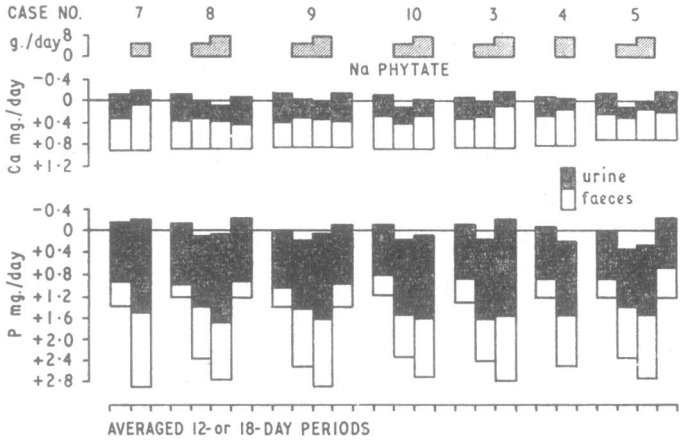

FIG. 7.—Effect on calcium and phosphorus balance of sodium phytate. Each block represents the average of two or three six-day collection periods.

Cellulose Phosphate

Because of the difficulty in getting regular supplies of sodium phytate we tried, at the suggestion of Dr. P. Walker, the effects of cellulose phosphate. This is an ion-exchange substance with a particular affinity for divalent cations due to the steric configuration of the phosphate groups. It is marketed for use in the ammonium form and was converted to the sodium form. Its properties suggested that it might be capable of interfering with calcium absorption in man. This substance is easier to handle and take by the patient than sodium phytate, which is very hygroscopic. The substance can be compressed into tablet form. It was given in water at a dosage of 12 to 15 g./day with meals. Unlike sodium phytate it produced no ill effects on the patients. The results are shown in Figs. 8 and 9. In each case it produced a rise in faecal calcium and a fall in urinary calcium. In contrast to sodium phytate there was a small increase in urinary phosphorus and a large increase in faecal phosphorus, as only slight hydrolysis occurs in the gut.

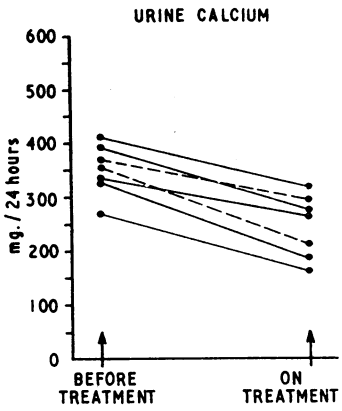

FIG. 8.—Effect on urine calcium excretion of cellulose phosphate 15 g./day in six cases. The figures are taken from full calcium balance data and represent the average of two or three six-day collection periods.

It would therefore seem that the main effect of this substance is to lower urine calcium by increasing faecal calcium and without producing a negative balance. Many patients have now been followed for well over a year as out-patients on a combination of moderate dietary restriction of calcium and cellulose phosphate, and there would seem to be no long-term ill effects from this type of regimen.

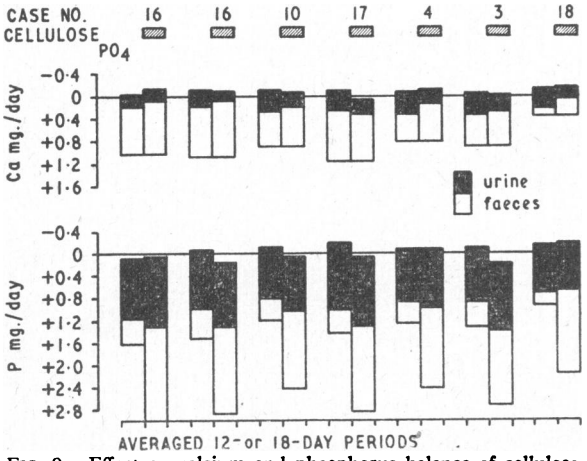

FIG. 9.—Effect on calcium and phosphorus balance of cellulose phosphate in seven cases of hypercalciuria. Each block represents the average of two or three six-day collection periods.

Benzthiazide Group

We next investigated the effects of a substance which might have a direct action on the kidney. Lamberg and Kuhlbäck (1959) reported that the benzthiazide group of drugs produced a fall in urine calcium excretion. They studied a group of 11 patients, six of whom had congestive cardiac failure, the remainder being normal controls. They found that chlorothiazide 1 g. twice daily and hydrochlorothiazide 100 mg. twice daily brought about a fall in urine calcium in every case without change in phosphorus excretion. They suggested that the effect was caused by an increased tubular resorption of calcium due to the reciprocal action on sodium and chloride excretion.

Lichtwitz, Parlier, de Seze, Hioco, and Miravet (1961) studied 130 individuals, some of whom had bone disease, either generalized or localized, and also cases of renal stone with and without hypercalciuria. They found that in all cases treated there was some lowering of urinary calcium excretion and that this was most pronounced in those cases where the urinary calcium was highest, such as in idiopathic hypercalciuria. A consistent effect occurred with different members of the chlorothiazide group of drugs but could not be produced by acetazolamide or by the sulphonamides. With a view to the possible therapeutic applications of these findings these experiments were repeated on patients with idiopathic hypercalciuria and some others. All the patients were studied under the usual metabolic-balance conditions on a diet constant in calcium and phosphorus and, where applicable, a constant sodium and potassium intake. After an equilibration period of three to four days, continuous 24-hour urine collections were made and analysed for calcium, phosphorus, nitrogen, potassium, sodium, magnesium, and creatinine. The magnesium estimations were carried out at the Postgraduate Medical School by Dr. I. McIntyre, to whom we are very grateful. The drug bendrofluazide was used throughout the studies, as the investigation was first suggested to us by Dr. T. J. Binns, of Glaxo Ltd.

Bendrofluazide

Bendrofluazide produced a reduction in urine calcium excretion of between 33 and 50% of the control values in every experiment except one, where the fall was only 12%. We confirmed that both the absolute reduction and the percentage fall were greatest in those patients who had a high control urine calcium, as noted by Lichtwitz *et al.* (1961).

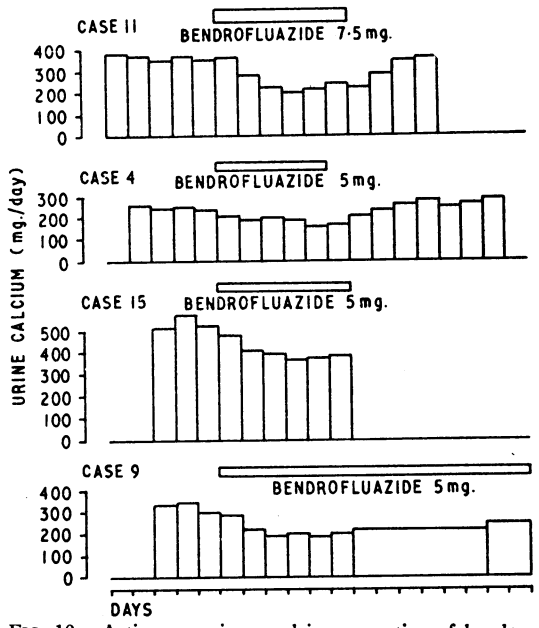

FIG. 10.—Action on urinary calcium excretion of bendrofluazide 5 or 7.5 mg./day in three patients with idiopathic hypercalciuria and one patient with sarcoidosis. Figure reproduced by permission of the editors of *Clinical Science*.

On the first day of administration of the drug there was little change, but there followed a stepwise fall, reaching a maximum in three to four days, and this persisted as long as the drug was given. On stopping treatment a delayed rise in urine calcium occurred, reaching previous control levels in three to four days. These findings can be seen in Fig. 10. There appeared to be no significant change in serum calcium levels. Fig. 11 shows the simultaneous excretion of calcium, phosphorus, sodium, and potassium, and the urine volume. It can be seen that the change in excretion of sodium and in urine volume was prompt. In the next day or two urine sodium and volume fall to control values or less and an equilibrium is established. It is to be noted that the maximum calcium-retaining effect is separate from the sodium and water diuresis. Limitation of the sodium diuresis is presumably due to the

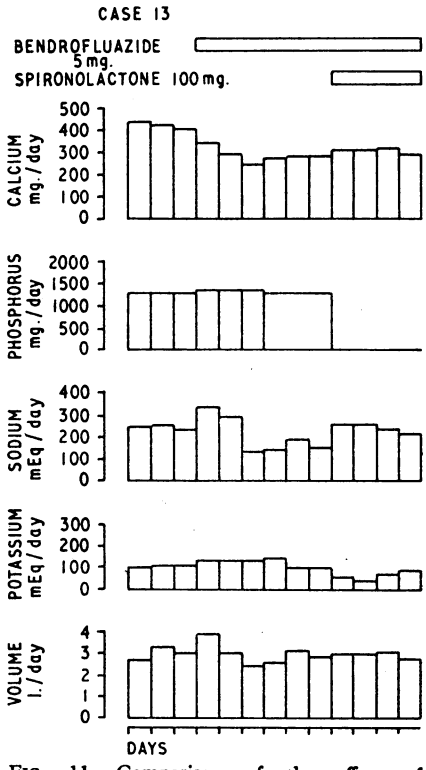

FIG. 11.—Comparison of the effect of bendrofluazide 5 mg. daily and spironolactone 100 mg./day on the 24-hour excretion of calcium, phosphorus, sodium, and potassium and the urine volume in a patient suffering from idiopathic hypercalciuria.

secretion of aldosterone. Reversal of the effect, as shown in Fig. 11, was produced by spironolactone 100 mg. daily with a further rise in urinary sodium but only a slight rise in urine calcium. It can be seen that bendrofluazide produced a small rise in urine potassium which was reversed by spironolactone. It is to be noted that bendrofluazide produced no change in phosphorus excretion.

The urinary excretion of magnesium was studied in four patients. In three of them bendrofluazide alone was given, and in the fourth the effect of mersalyl was contrasted with that of bendrofluazide. The results are shown in Fig. 12, where it will be seen that there was a small but immediate rise in magnesium excretion. This was similar in time and direction to the sodium and chloride excretion but different from that of calcium. Fig. 13 shows the action of mersalyl given as an injection of 2 ml. for three days. There is an immediate rise in both calcium and sodium excretion and a slight rise in magnesium output. In contrast, when bendrofluazide is given there is a drop in urine calcium and the usual prompt rise in sodium with a slight rise in urinary magnesium.

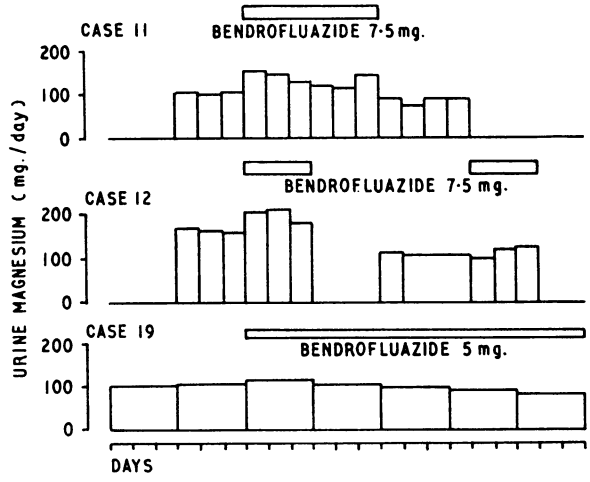

FIG. 12.—Action of bendrofluazide 5 or 7.5 mg./day on the 24-hour magnesium excretion in three patients.

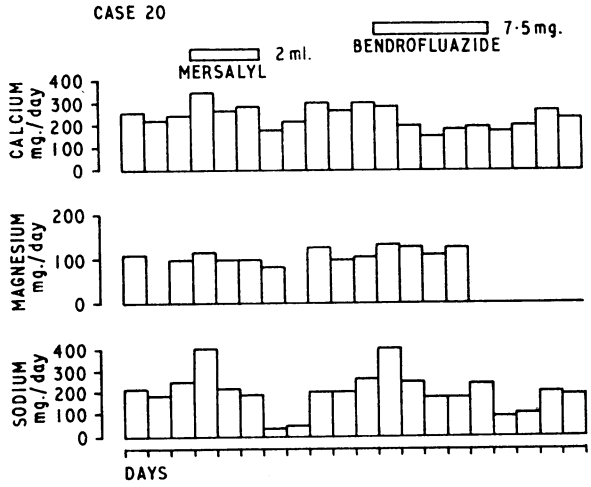

FIG. 13.—Comparison of the effect of bendrofluazide 7.5 mg./day and mersalyl 2 ml./day on the 24-hour urinary calcium, magnesium, and sodium excretion in a patient suffering from idiopathic hypercalciuria.

A reduction in urinary calcium should produce an improvement in the overall balance, unless it is accompanied by an increase in the faecal calcium. To clarify this point full calcium balance was performed on seven patients, and on one of them on two separate occasions. The results of their faecal and urinary output of calcium are shown in Table IV and Fig. 14. In all these balances there seemed to be a partition effect, a small rise in faecal calcium accompanying the drop in urine calcium. The tendency appears to be there, though the answer is not clear-cut, as it is very difficult by balance techniques to demonstrate relatively small changes in faecal calcium. However, our studies confirm the fact that bendrofluazide will cause a reduction in urinary calcium. The mechanism is not known. It would be tempting to explain it by the known hypotensive effect of the thiazide series of drugs in causing a reduction in glomerular filtration rate. We were unable to show any significant change in glomerular filtration rate by the rather imprecise method used—that is, measurement of fasting blood creatinine and 24-hour creatinine excretion, as shown in Fig. 15. Small changes in glomerular filtration may well be reflected by greater changes in calcium excretion. However, this is difficult to reconcile with the dissimilar changes produced in the excretion of phosphate and magnesium.

TABLE IV.—*Action of Bendrofluazide 5 to 7.5 mg./day on the Calcium Balance in Seven Patients. The Figures Represent the Average of Two or Three Six-day Collection Periods*

Case No.	Treatment	No. of Six-day Periods	Urine Calcium mg./day	Faecal Calcium mg./day
4	Control	3	250	728
	Bendrofluazide 5 mg./day	2	151	756
21	Control	3	139	580
	Bendrofluazide 5 mg./day	4	99	585
9a	Control	2	335	572
	Bendrofluazide 5 mg./day	2	220	681
9b	Control	1	388	556
	Bendrofluazide 12·5–15 mg./day	1	141	650
22	Control	3	280	777
	Bendrofluazide 5 mg./day	3	206	818
14	Control	2	411	665
	Bendrofluazide 7·5 mg./day	1	335	639
12	Control	3	551	1,405
	Bendrofluazide 7·5 mg./day	2	415	1,448
23	Control	3	545	559
	Bendrofluazide 7·5 mg./day	2	400	658

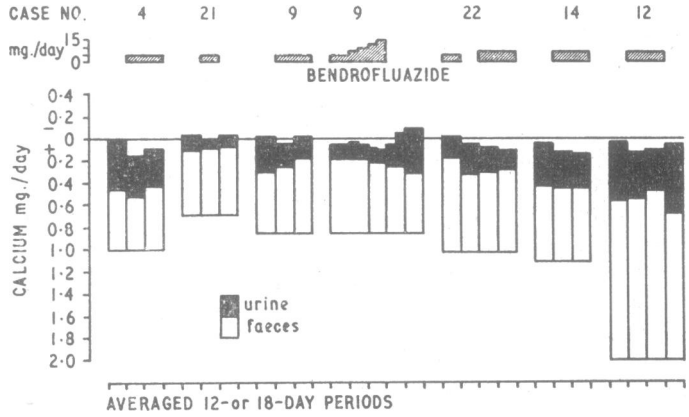

FIG. 14.—Action of bendrofluazide on the calcium balance in seven patients. Each block represents the average of two or three six-day collection periods.

As there are no significant changes in serum bicarbonate or in urinary *p*H, it is unlikely that an acid/base mechanism plays a significant part in the urinary-calcium-lowering effect of bendrofluazide. Indeed, this drug is still capable of lowering the rise in urine calcium produced by an ammonium chloride acidosis, as can be seen in Fig. 16.

If the tendency to a partition effect between urinary excretion and faecal absorption can be conclusively shown, then it may well be that bendrofluazide has a direct effect on the handling of calcium in both renal and intestinal epithelium. Another possible explanation of the partition effect is that bendrofluazide, by lowering urine calcium, may produce slight rises in serum calcium, too small to be reflected in serum calcium estimation but yet sufficient to diminish calcium absorption from the gut, according to the theory of Jackson and Dancaster (1959).

Conclusion

It may be said that idiopathic hypercalciuria can be controlled by the administration of sodium phytate, cellulose phosphate, and bendrofluazide. In view of the fact that in the balance studies with sodium phytate and cellulose phosphate the patients did not go into a negative balance it is possible that they are, in fact, hyperabsorbers of calcium. The lowering of urinary calcium by phytate is due to a combination of binding in the gut and the separate effect of the hydrolysed phosphate. The action of cellulose phosphate, on the other hand, seems mainly due to its gut-binding effect with little phosphorus absorption, and should be a better test substance for the evaluation of calcium deprivation.

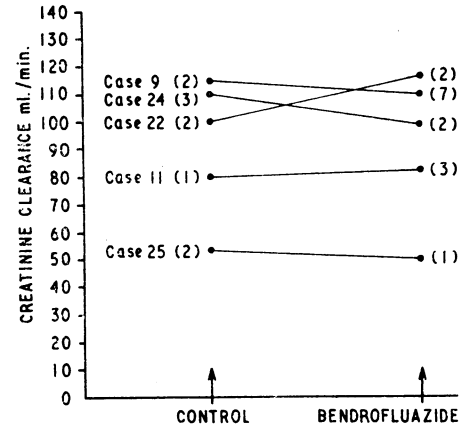

FIG. 15.—Endogenous creatinine clearance before and after bendrofluazide 5 to 7.5 mg./day in five patients. The figures in parentheses represent the number of estimations.

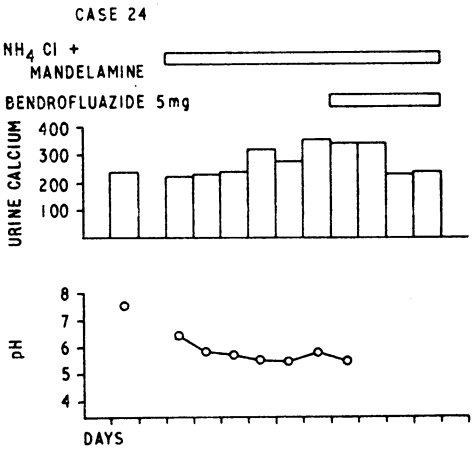

FIG. 16.—Action of bendrofluazide on a patient with chronic pyelonephritis who was given a combination of ammonium chloride and mandelamine to produce a metabolic acidosis.

Bendrofluazide lowers urinary calcium in all individuals, whether normal or with hypercalciuria of any cause. Each individual must be assessed on his response to treatment. In some persons satisfactory reduction of urine calcium will occur with sodium phytate or cellulose phosphate alone, in others the addition of bendrofluazide or related substances may achieve the best results.

Summary

The paper discusses the causes of hypercalciuria and describes 15 cases of different origins all of which presented similarly with renal stones. The diagnosis of idiopathic hypercalciuria was made by exclusion. The effects of dietary restriction of calcium, sodium bicarbonate, cortisone, sodium phosphate, sodium phytate, and cellulose phosphate were demonstrated by calcium and phosphorus balance techniques. All were shown to have some urinary-calcium-lowering effect. Finally, a chlorothiazide derivative—namely, bendrofluazide—was also demonstrated to have a hypocalciuric effect, and the mode of action is discussed.

The bendrofluazide used during the course of the investigations was supplied by Glaxo Ltd., Greenford, Middlesex. Cellulose phosphate was obtained from Reeve, Angel and Co., Ltd., London E.C.4. Sodium phytate was obtained from Brown and Polson Ltd., London W.C.2, and Ciba Ltd., Horsham, Sussex.

REFERENCES

Albright, F., Burnett, C. H., Parson, W., Reifenstein, E. C., and Roos, A. (1946). *Medicine (Baltimore)*, **25**, 399.
—— Henneman, P., Benedict, Patricia H., and Forbes, Anne P. (1953). *Proc. roy. Soc. Med.*, **46**, 1077.
—— and Reifenstein, E. C. (1948). *The Parathyroid Glands and Metabolic Bone Disease*. Williams and Wilkins, Baltimore.
Bauer, W., Albright, F., and Aub, J. C. (1929). *J. clin. Invest.*, **7**, 75.
Boyce, W. H., Garvey, F. K., and Goven, Carol E. (1958). *J. Amer. med. Ass.*, **166**, 1577.
Farquharson, R. F., Salter, W. T., and Aub, J. C. (1931). *J. clin. Invest.*, **10**, 251.
—— —— Tibbetts, Dorothy M., and Aub, J. C. (1931). Ibid., **10**, 221.
Flocks, R. H. (1940). *J. Urol. (Baltimore)*, **43**, 214.
Gill, J. R., and Bartter, F. C. (1961). *J. clin. Invest.*, **40**, 716.
Harrison, A. R. (1959). *Brit. J. Urol.*, **31**, 398.
Henneman, P. H., Carrol, Evelyn L., and Albright, F. (1956). The suppression of urinary calcium and magnesium by oral sodium phytate: A Preliminary Report.
—— Dempsey, Eleanor F., Carrol, Evelyn L., and Albright, F. (1956). *J. clin. Invest.*, **35**, 1229.
Hodgkinson, A., and Pyrah, L. N. (1958). *Brit. J. Surg.*, **46**, 10.
Jackson, W. P. U., and Dancaster, C. (1959). *J. clin. Endocr.*, **19**, 658.
Jahan, I., and Pitts, R. F. (1948). *Amer. J. Physiol.*, **155**, 42.
Knapp, Elizabeth L. (1947). *J. clin. Invest.*, **26**, 182.
Lamberg, B. A., and Kuhlbäck, B. (1959). *Scand. J. clin. Lab. Invest.*, **11**, 351.
Lichtwitz, A., Parlier, R., de Seze, S., Hioco, D., and Miravet, L. (1961). *Sem. Hôp. (Paris)*, **37**, 2350.
Litin, R. B., Diessner, G. R., and Keating, F. R. (1961). *J. Urol. (Baltimore)*, **86**, 17.
McGeown, Mary G. (1957). *Clin. Sci.*, **16**, 297.
Malm, O. J. (1953). *Scand. J. clin. Lab. Invest.*, **5**, 75.
—— (1958). *Calcium Requirement and Adaptation in Adult Men*. Oslo University Press, Oslo.
Mellanby, E. (1950). *A Story of Nutritional Research*. Williams and Wilkins, Baltimore.
Pyrah, L. N. (1958). *Proc. roy. Soc. Med.*, **51**, 183.
Reifenstein, E. C., Albright, F., and Wells, Shirley L. (1945). *J. clin. Endocr.*, **5**, 367.
Saville, P. D., Nassim, J. R., Stevenson, F. H., Mulligan, Lily, and Carey, Margaret (1955). *Clin. Sci.*, **14**, 489.
Wrong, O., and Davies, H. E. F. (1959). *Quart. J. Med.*, **28**, 259.