Relative Hypercalciuria in Nephrolithiasis

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Hypercalciuria has long been suspected of being of importance in the pathogenesis of renal calculi. Several studies, however (Hodgkinson and Pyrah, 1958; Boyce and King, 1959; Gershoff and Prien, 1960; Litin *et al.*, 1961; Lathem and King, 1963; Modlin, 1965), have shown no consistent differences in either the 24-hour output or the concentration of urinary calcium in stone-forming and normal subjects.

A possibility that has not been considered is that of hypercalciuria, not of absolute amount, but relative to the other urinary solutes. Under conditions producing maximal urinary osmotic concentration, such initial relative hypercalciuria would lead to greater urinary calcium concentrations than normally possible, and these may be high enough to precipitate calcium salts in otherwise normal urine.

Methods

Twenty-four-hour urine samples were obtained from 54 normal adults and from 25 stone-forming adult patients. The latter harboured, or had recently passed, radio-opaque renal calculi, but were otherwise in apparently good health, were ambulant, and ate *ad lib.* diets.

Random urine samples were also obtained from 50 acutely ill hospital in-patients, all suffering from renal or electrolyte disorders. Their diagnoses were (number of patients in parentheses): nephrotic syndrome of unknown cause (4); idiopathic hypercalciuria (1); subacute glomerular nephritis (1); proteinuria of unknown cause (2); diabetes insipidus (1); diabetes mellitus, four of whom were in severe ketosis (6); malignant hypertension (1); parenchymatous hepatitis with jaundice (6); systemic lupus erythematosus, on prednisone therapy (1); cerebrovascular accident, dehydrated and in coma (1); tuberculous ascites (3); subacute bacterial endocarditis (2); dehydration and collapse of unknown aetiology (1); carcinomatous ascites (1); amoebic liver abscess (2); carcinoma of the breast, with bilateral adrenalectomy, in Addisonian crisis (1); bronchopneumonia (1); congestive cardiac failure, on digitalis and diuretic therapy, secondary to hypertension (5); rheumatic heart disease (2), severe anaemia, myocardial infarction, or respiratory failure (4), and of uncertain cause (4).

All urines were collected under toluene and stored at 4° C. while awaiting analysis. The volume of each 24-hour aliquot and the osmolality and calcium concentration of each of the normal and stone-formers' urines were then determined. Na, K, NH₄, Ca, Mg, inorganic sulphate, and phosphate concentrations were determined on each of the urines of the normals and of each of the non-stone-forming acutely ill patients.

Na and K were determined by flame photometry, and Ca and Mg by flame spectrophotometry (Jackson and Irwin, 1957; Isaacson, 1963). Inorganic phosphate was estimated as described by Chen *et al.* (1956), and ammonium as described by King and Wootton (1956). Inorganic sulphate was measured by the technique described by Dodgson (1961). Osmolality was determined by observation of depression of freezing-point, by means of a Fiske osmometer.

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Results

The mean 24-hour urinary calcium excretion was greater in the stone-formers than in the normals (Table I); their mean urinary calcium concentrations did not differ significantly, however. The stone-formers excreted fewer osmoles ($P < 0.001$) in a greater volume of urine than did the normals.

TABLE I.—Twenty-four-hour Urinary Excretion

	Normals (54)		Stone-formers (25)	
	Mean	S.D.	Mean	S.D.
Volume (ml./24 hr.)	1,178	434	1,587	581
Ca (mEq/l.)	5.8	2.8	6.9	2.5
Osm. (mOsm/kg. water)	980	223	563	215

The Chart depicts the urinary calcium/osmolar relationships observed in the stone-formers and normal subjects. The highest calcium/osmolar ratio found in normal urine was 0.012 (where calcium concentration is expressed in mEq/l., and osmolality in mOsm/kg. water). This figure was exceeded in 14 of the 25 stone-formers' urines, and in seven of these was above 0.016.

Urinary calcium/osmolar relationships in normal subjects and in patients with renal calculi.

Tables II and III list and compare the concentrations and variability of the urinary electrolytes in the normal subjects and in the acutely ill non-stone-forming patients. The latter had, on the average, lower sodium but higher potassium and inorganic sulphate concentrations than the former. Individual ionic constituents showed greater variability in both relative

TABLE II

	Normals (54)		Ill Patients (50)	
	Mean	S.D.	Mean	S.D.
Na (mEq/l.)	199	35.8	91.1	65.2
K	66.5	18.9	78.7	55.5
NH ₄	92.6	27.5	58.5	36.6
Ca	5.8	2.8	3.3	3.9
Mg	9.8	4.2	6.9	4.1
SO ₄ .. (inorganic) ..	33.8	18.8	55.5	37.3
PO ₄ (mM/l.)	26.6	9.2	14.8	11.2
Osm. (mOsm/kg. water) ..	980	223	695	207

and absolute concentrations in these patients than in the normal controls. Only two of these 50 patients passed urine of calcium/osmolar ratio above 0.012. One (calcium/osmolar ratio of 0.016) had idiopathic hypercalciuria; the other (0.025) alcoholic cirrhosis with jaundice.

TABLE III

	Normals (54)		Ill Patients (50)		P
	Mean	Coeff. of Variation	Mean	Coeff. of Variation	
Na (mEq/l.) . . .	203	17.9	131	71.5	< 0.001
K " " " " "	67.9	28.4	116	70.6	< 0.001
NH ₄ " " " " "	94.5	29.7	84.2	62.6	
Ca " " " " "	5.9	48.3	4.8	118	
Mg " " " " "	10	42.9	9.9	59.4	
SO ₄ " " " " "	34.5	55.6	79.8	67.2	< 0.001
PO ₄ (mM/l.) . . .	27.1	34.6	21.3	75.7	

Direct comparison of the data for the two groups presented in Table II is effected here by correcting all concentrations to unit osmolality. Each standard deviation is expressed as a percentage of the mean—that is, as the coefficient of variation.

Discussion

Inasmuch as all the stone-formers had sought medical opinion prior to our seeing them, and had presumably been advised to drink extra fluids, no significance can be attached to the greater urine volume observed in these patients. Their 24-hour urinary calcium excretion was greater than that of the controls, but remained within the generally accepted limits of normal. The urinary calcium concentrations in the two groups were not significantly different. In these respects our results do not differ from those of previous investigators.

The stone-formers excreted fewer osmoles per 24 hours than did the normals. They thus had disproportionately higher concentrations of calcium, relative to their other urinary solutes, than did the latter. The non-stone-forming patients were examined to test the specificity of this finding. The sole criterion of their selection was that they manifest either renal or electrolyte disorder. Despite greater variability in both relative and absolute urinary electrolyte concentrations, only two of these patients passed urine of abnormally high calcium/osmolar ratio, and one of these had idiopathic hypercalciuria.

Removal of "free" water by the distal nephron is among the last of the processes undergone by the glomerular filtrate in its conversion to urine. Both obligatory and facultative reabsorption of calcium occur proximal to this site. The final urinary calcium concentration is thus a function of both the calcium/osmolar ratio of the tubular fluid entering the site of "free" water reabsorption, and of the intensity of the latter process. It follows that, could they have been stimulated to produce maximal osmotically concentrated urine, our stone-forming patients would have attained greater urinary calcium concentrations than would have been possible in our other subjects.

This suggests the following hypothesis. Otherwise normal subjects who for any reason develop relative hypercalciuria may, under conditions producing maximal urinary osmotic concentration, elaborate urine of such high calcium concentration as to precipitate calcium salts; these then initiate the formation of renal calculi.

The argument may be illustrated by a numerical example. As with calcium, the facultative adjustment of tubular fluid concentrations of sodium, potassium, and ammonium ions (and their accompanying anions) occurs proximally to, or at the same site as, the removal of "free" water. Assume a subject with far distal tubular fluid containing 3 mEq Ca, 50 mEq Na, 25 mEq K, 25 mEq NH₄, and 100 mM urea per litre; the osmolality will therefore be about 300 mOsm/kg. water. Should our subject suffer a pure water deficit, and possess kidneys capable of elaborating urine of 1,400 mOsm/kg. water, the tubular fluid solute concentrations will rise 1,400/300, or 4.7-fold, during the reabsorption of "free" water. The urinary calcium concentration attained will thus be 14 mEq/l. If the subject is now starved we may imagine the composition of the far-distal tubular fluid, after facultative adjustment of electrolyte con-

centration, to contain still 3 mEq Ca, but 1 mEq Na, 10 mEq K, 35 mEq NH₄, and 50 mM urea per litre. The total osmolar concentration is thus about 140 mOsm/kg. water. As "free" water is removed, urinary solute concentrations will rise 1,400/40, or tenfold. The final urinary calcium concentration will therefore be about 30 mEq/l., twice as much as before, and well above the normal range (Isaacson and Jackson, 1963).

It may be worth noting that the figures given are not inconsistent with known patterns of urinary electrolyte content in thirst and starvation; that urinary calcium excretion responds tardily to changes in dietary intake (Nicolaysen *et al.*, 1953); and that stone-formers excrete no less oxalate or phosphate than do normals (Flocks, 1939; McIntosh and Read, 1958; Gershoff and Prien, 1960).

The hypothesis presented above may be partially explored as follows. Calcium oxalate is among the commonest components of renal calculi (Prien and Frondel, 1947). Miller *et al.* (1958) have investigated the solubility of this salt in urine; their data permit the calculation of the solubility product of calcium oxalate in "average" urine as approximately 6.89×10^{-6} mEq/ml. The 24-hour urinary output of oxalic acid (dihydrate) in normal subjects has been variously given as 15 to 50 mg. (McIntosh and Read, 1958; Dempsey *et al.*, 1960; Gershoff and Prien, 1960), with a mean of about 33 mg., or 0.52 mEq. Our normal subjects had a mean 24-hour urinary volume of 1,178 ml.; their mean urinary oxalic acid concentration was therefore presumably about 0.44 mEq/l. Calcium oxalate would thus precipitate at an average urinary calcium concentration of $6.89 \times 10^{-6} / 0.44 \times 10^{-3}$, or 15.7 mEq/l. The average urinary osmolality was 980 mOsm./kg. water. The critical calcium/osmolar ratio (above which precipitation would occur, given an average urinary oxalic acid content and adequate urinary osmotic concentration) would therefore be about 0.016.

None of our normal subjects, and only 2 of the 50 patients with a variety of renal or electrolyte disorders, attained this figure. On the other hand, more than half the stone-forming patients had urinary calcium/osmolar ratios above that found empirically to delineate the upper limit of normal, and in more than a quarter this ratio exceeded that apparently necessary for the precipitation of calcium oxalate.

We have not analysed the individual osmotic constituents of our stone-formers' urines. However, in terms of the hypothesis elaborated above, the definitive factor predisposing to renal-stone formation should be a low *total* (24-hour) output of urinary solute rather than an abnormal contribution by any individual component. The occurrence of renal stones in prolonged heat exposure or dehydration (Davalos, 1945; Prince *et al.*, 1956) would be explicable on this basis. Conversely, renal calculi rarely occur in the Bantu (Vermooten, 1941); we have shown elsewhere (Modlin *et al.*, 1963) that these subjects pass urine of considerably greater osmolar, and somewhat lower calcium, content than do normal white South Africans. Their urinary calcium/osmolar ratios are so low as to preclude the possibility of their attaining the solubility product of calcium oxalate in even very (osmotically) concentrated urine.

The attainment of a solubility product is presumably involved in cases of nephrolithiasis associated with the urinary excretion of abnormally large amounts of specific solutes—for example, primary hyperoxaluria, cystinuria. The role played by relative hypercalciuria, even in the presence of normal 24-hour excretion of calcium and oxalic acid, would seem to render the occurrence of calcium oxalate stones similarly intelligible. Further studies are needed to determine whether relative hypercalciuria is due simply to dietary idiosyncrasy or is a reflection of some anomaly of renal tubular function.

Summary

Urines obtained from patients with renal calculi were found to have significantly higher calcium/osmolar ratios than those of normal subjects.

It is suggested that at maximal osmolality, urinary calcium concentrations attained by the former would therefore be greater than those attained by the latter, and become high enough to precipitate calcium salts in otherwise normal urine.

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Lomotil in Treatment of Post-Vagotomy Diarrhoea

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Diarrhoea may be defined as a deviation from established bowel rhythm characterized by an increase in frequency and fluidity of the stools. It is thought that a patient's request for relief from diarrhoea is as important as the physician's opinion in deciding whether to treat it or not. In this trial it was the patient who decided when and how often to take a course of treatment.

Diarrhoea occurring after complete vagotomy with a drainage procedure has been variously described, but may be roughly divided into three types (Cox and Bond, 1964). Transient diarrhoea occurs for a short period after the operation. This is often manifested by sudden very loose bowel actions coming on with little or no warning and lasting from a few hours to a day or two. This type disappears within three to six months of the operation. If it recurs later and the attack of diarrhoea lasts longer it can be referred to as recurrent episodic diarrhoea. The third type is an increased daily bowel frequency, sometimes of disabling severity, but most often merely of pleasing contrast to pre-operative constipation.

It was thought that tablets of Lomotil (diphenoxylate hydrochloride 5 mg. and atropine sulphate 0.05 mg.) might be of particular value in the episodic type of diarrhoea because a single dose is said to lessen the desire to defaecate after approximately one hour (Hock, 1961) and to be effective for about six hours.

A double-blind control trial was carried out in order to find out if Lomotil was of greater value than codeine phosphate in treating both the episodic and the continual types of post-vagotomy diarrhoea.

Selection

Questionnaires were sent to 184 patients who had undergone a drainage procedure with complete vagotomy, as judged by the insulin test with Hollander's (1946, 1948) criteria in the treatment of duodenal ulcer: 154 replies were received. The follow-up period ranged from six months to six years. The patients were asked to state whether they had motions that

were (a) normally formed or (b) occasionally or always loose, (c) spasmodic attacks of diarrhoea, and (d) an increased number of bowel actions per day after operation. Those who replied that they had any looseness or diarrhoea or more than two bowel actions per day were interviewed. There were 63 such patients, and 32 of them were considered to have diarrhoea of such severity as to require treatment. These were the subjects of the controlled trial. The other 31 had little more than occasional loose motions in an otherwise normal bowel habit.

Method

Each patient was given a record card with instructions to enter the number of bowel actions and the consistency of the motion each day for one month. On studying these it became clear that only 23 of the patients had diarrhoea attacks of sufficient frequency for any conclusion to be drawn regarding the benefit from the treatments they were to be given. This is in accord with the findings of Feggetter and Pringle (1963) that routine observation failed on many occasions to confirm the severity of diarrhoea complained of by patients.

These 23 patients were asked to record the number and consistency of their motions and also the number of tablets taken and their efficacy in controlling the diarrhoea over a further period of three months. The patients were each given three treatments, to be taken for one month in an order dictated by random selection. These consisted of tablets, identical in appearance and taste, of Lomotil 5 mg., of codeine phosphate 15 mg., and of placebo that was identical in appearance to both drugs but contained sucrose.

The patients were instructed to take one tablet as soon as an attack of diarrhoea began and to continue to take a tablet morning, noon, and night for three days, then stop. If the diarrhoea continued they were told to start again after a lapse of three days. All the patients except two complied with these instructions. They were seen once a month and were asked whether the tablets had been of value or had caused any side-effects; a new supply was given and the tablets remaining from the previous month's treatment were collected so as to avoid confusion.

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