RENAL STONES OF CALCIUM PHOSPHATE ORIGIN

Medical Grand Rounds

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One of the most intriguing and unresolved problems in clinical medicine has been that of the recurrent passage of calcium-containing renal stones. Although there has been a significant advancement in the surgical management of patients with renal stones, comparatively little progress has been apparent in the medical management and in prophylactic measures. A brief retrospective look into the history of medicine of renal stones clearly illustrates this point.

Around the end of the 17th century, Frere Jacques de Beaulieu, a self-styled lithotomist, gained considerable fame with his revolutionary approach to cystolithotomy. His biographer wrote:[1] "He acted with the ruthlessness of an ignoramus who lacked all thorough knowledge of anatomy. He drove his scalpel close by the rectum, straight into the bladder, measured the size of the stone with the top of the knife and then enlarged the incision until the stones could be easily removed. At the end of each operation he declared 'I have cut the stone out of him. God will heal him.' Thereafter, he did nothing more for his patient." Needless to say, such operations left many of his patients grossly mutilated and frequently resulted in death. Today, sophisticated surgical techniques allow relatively easy removal of stones, usually without significant morbidity or mortality. Despite these surgical advances, the general medical community continues to be in the dark as regards medical prevention of renal stones. Frequently the only measures resorted to are the institution of a low-calcium diet and forcing of fluids, the same measures utilized by the lithotomists in the era of Frere de Beaulieu. Not too infrequently, surgical removal of stones or of involved kidney has been resorted to without examination of the cause for stone formation and without a serious trial with medical preventive regimen. Finally, the basis for the various medical treatment regimens has been largely empirical. Too often these treatments have been resorted to without a clear appreciation of hazards and indications.

Recently, however, there has been considerable advancement in the understanding of the pathogenesis as well as treatment of calcium-containing renal stones. I would like to review with you the results of these recent investigations, focusing first on the pathogenesis of nephrolithiasis, secondly, on the rationale for various forms of treatment, and finally, on the practical aspects of work-up or evaluation of nephrolithiasis.

THEORIES OF STONE FORMATION

Several theories have been invoked for the pathogenesis of nephrolithiasis. The precipitation-crystallization[2-5] theory considers stone formation as a physicochemical process of precipitation from a supersaturated solution. In the matrix theory [6-9]the stone develops in an organic matrix, probably under the influence of the organic matrix. The organic matrix of stones has been identified as a mucoprotein.[6] It is believed that the matrix of renal stones contains an immunologically unique substance, called matrix substance A. The major component of this substance is believed to be a protein lacking in hydroxyproline.[10] Its exact composition however, is not known. Further, there is no convincing evidence that the matrix induces nucleation or the formation of stone. On the other hand, Vermeulen and associates[2,3] have clearly shown that stones may form in the total absence of organic matrix, and have suggested that the matrix may represent adventitious deposits. The inhibitor theory[8,9,11-14] assumes that certain peptides or pyrophosphates normally prevent stone formation by inhibiting nucleation. The lack or the absence of these inhibitors would permit the development of the nidus.

The inhibitor theory of stone formation received a big impetus when Howard and associates introduced the concept of "good" and "evil" urine in 1959.[15]

In brief , it was found that the urine of stone-formers tended to calcify the rat rachitic cartilage, whereas that of non-stone-formers did not. This observation was believed to explain in part the defeat of the Germans during World War I. Allegedly, the German soliders, unable to find ready access to rest rooms from constant shelling of the Allies, urinated on the freshly-built concrete bunkers. Since their urines were presumable "good" the concrete failed to solidify, and the bunkers became easy prey to the Allies.

Howard and associates subsequently identified the factor in urine which inhibits calcification as comprised of two peptides.[8,11] The peptide B had a molecular weight of approximately 500 and the peptide C a molecular weight of approximately 1000. As assayed by the cartilage calcification system, the peptide B was considered to be approximately five times more potent on a weight basis than was pyrophosphate in inhibiting calcification. Peptide C was found to be 1/5 as potent as peptide B. Other workers have confirmed these observations of Howard and associates.[16] However, Smith and McCall at the recent Renal Stone Research Symposium reported that these peptides probably represent contaminants, and that inhibitory activity is due to as yet unidentified smaller substances.[17] Further, even if they exist, it is doubtful that these inhibitors play a significant role in the formation of renal stones as initially suggested by Howard and associates. First, the studies of inhibition by these workers are of limited biological significance since they were performed with altered urine specimens which were adjusted to pH 7.4 and diluted to a specific gravity of 1.01. Secondly, these workers made no attempt to correlate the calcification process with the state of saturation of the urine specimens with respect to any solid phase. Thus their studies do not clearly exclude the possibility that the calcification of rachitic cartilage by stone-forming urine resulted from the urinary state of supersaturation rather than from a deficiency of the inhibitors of calcification. Thirdly, Robertson and associates[18] isolated the peptides from the stone-forming as well as control urine specimens. The quantity as well as the inhibitory activity of the peptides was not significantly different in the two groups.

Irrespective of a particular theory proposed for stone formation, an essential requirement is a state of supersaturation of urine with respect to the constituents of stone. It is obvious that a crystal nidus cannot be established in urine which is undersaturated with respect to that nidus. Since the inhibitors of nucleation prevent nucleation from a supersaturated solution, their role in an undersaturated solution probably has no significance.

NIDUS OF RENAL STONES

Major impediments to the understanding of renal stone formation has been two-fold: first, an uncertainty regarding the exact solid phase which constitutes the crystal nidus and two, lack of techniques for precise determination of the state of saturation of urine with respect to that nidus. These problems have been largely resolved. A number of crystal constituents, including uric acid, cystine, calcium oxalate, and calcium phosphate, have been implicated as the initial nucleating material. For the majority of calcium-containing renal stones, there is extensive evidence suggesting that calcium

phosphate may constitute the nidus.

Numerous workers have demonstrated that the central core of large stones is frequently composed of calcium phosphate.[19-21] Among very small stones of two mm in diameter or less, Chambers and associates[22] demonstrated the nidus of calcium phosphate measuring approximately 40 microns in diameter by electron probe analysis. These workers found that the majority of calcareous renal stones were of such calcium phosphate origin (Figure 1). Pure calcium oxalate stones constituted approximately 16% of all stones.

GROUP	DESCRIPTION	NO. OF STONES
a	Calcium oxalate with no calcium phosphate	22
b	Calcium phosphate with no calcium oxalate	6
c	Mainly calcium oxalate but containing small areas of calcium phosphate	52
d	Mainly calcium phosphate with an outer rim of calcium oxalate	12
e	Mainly calcium oxalate with an outer rim of calcium phosphate	7
f	Incomplete alternating bands of calcium oxalate and calcium phosphate	7
g	Similar to f, but with a hollow center	4
h	Miscellaneous stones	5

Figure 1.

For the renal stones of calcium phosphate origin, which constitute the majority of stones, the most likely candidate for the crystal nidus is brushite or dicalcium phosphate dihydrate ($CaHPO_4 \cdot 2H_2O$). This conclusion was initially suggested to us from the studies of Strates and associates.[23] They showed that brushite is stable below a pH of 6.9. The solid phase precipitated from an artificial solution of calcium phosphate was brushite. At pH greater than 6.9, it was transformed into calcium phosphate of higher calcium-to-phosphorus ratio such as hydroxyapatite. We have subsequently shown that brushite is the solid phase formed from urine under the influence of an organic matrix[24] or by spontaneous precipitation.[25]

The solid phase obtained from urine of pH of 6.9 or less by the addition of calcium chloride was identified as brushite by X-ray diffraction (Figure 2).

Identification of the solid phase by x-ray diffraction

pH	No. of samples	Predominant phase
5.2–6.65	24	brushite
6.90	1	brushite
6.95	1	hydroxyapatite
7.56	1	hydroxyapatite
7.75	1	hydroxyapatite

The pH represents the final pH of the urine sample. In the four specimens with pH of 6.90 or greater, the initial pH was purposely increased.

Figure 2.

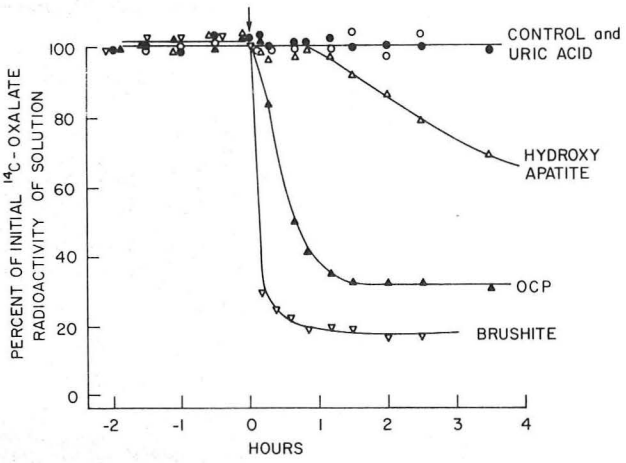


Figure 3.

At pH greater than 6.9, the predominant phase was apatite. Francis has recently shown that brushite may represent the logical precursor in the formation of hydroxyapatite.[26] Thus, even at alkaline pH where brushite is unstable, the formation of brushite may precede the formation of apatite.

In addition, brushite may be epastaxic for calcium oxalate, but not vice versa.[27] In other words, brushite may induce the crystallization of calcium oxalate (Figure 3). In a urine specimen which was metastably super-saturated with respect to calcium oxalate, a trace amount of of C^{14}-oxalic acid was added. The ability of various solid phases to induce crystallization of calcium oxalate was measured from the change of C^{14}-oxalate radioactivity of the urine supernatant after the addition of the solid phase to urine. Note the decline in C^{14}-oxalate radioactivity was most rapid and prominant when brushite was added. Octacalcium phosphate and hydroxyapatite also induced crystallization of calcium oxalate, but to a much lesser extent than that by brushite. Uric acid in this experiment was without effect, although in some urine specimens, it had a small effect. However, the converse situation did not hold: calcium oxalate did not induce the crystallization of brushite. These in vitro results suggest that brushite could theoretically serve as a nidus for certain stones of both apatite and calcium oxalate.

In pure calcium oxalate stones, which may comprise up to 16% of all stones, the nidus of brushite cannot be incriminated. The characteristic features of patients who pass pure calcium oxalate stones are 1) passage of urine of unusually low pH (usually less than 5.5), and marked hypercalciuria. Because of low urinary pH, urine specimens are usually undersaturated with respect to brushite. Thus, brushite nidus cannot form. However, because of the marked hypercalciuria, urine specimens are markedly supersaturated, probably allowing the formation of the nidus of calcium oxalate and subsequent stone formation.[22] For these stones of pure calcium oxalate, Robertson[28] has postulated the aggregation theory for their formation. Among control subjects without stones, he postulated the presence of certain substances which

inhibit the aggregation of calcium oxalate crystals, thereby allowing ready passage through the urinary tract even when the crystals form. Such inhibitors of calcification are deficient or lacking in the urine of stone-formers. Thus, the crystals of calcium oxalate aggregate into large clusters often exceeding 100 microns in diameter. Preliminary studies indicated that the inhibitor of aggregation is probably a sulfated polysaccharide.[29] Unfortunately these studies of aggregation were performed in urine specimens which were diluted 100 times with synthetic solution of calcium and oxalate.[29-31] The biological significance of these studies on the formation of calcium oxalate stones must await further experimentation.

ACTIVITY PRODUCTS

The next problem was the formulation of simple techniques for the assessment of the state of saturation of urine with respect to brushite or other constituents of stones. The concentration products, although very often resorted to, rarely reflected the true solubility, since they are dependent on pH and ionic strength.[32] Several laboratories, particularly at Leeds, England, have resorted to the calculation of activity products as a measure of solubility. Thus, Robertson and associates[33] were able to calculate the urinary activity products for hydroxyapatite, octacalcium phosphate, brushite, as well as calcium oxalate. These calculations were achieved, taking into account the pH-dependent dissociation of various anions, the effect of ionic strength on activity coefficients, and formation constants for various complexes of calcium.

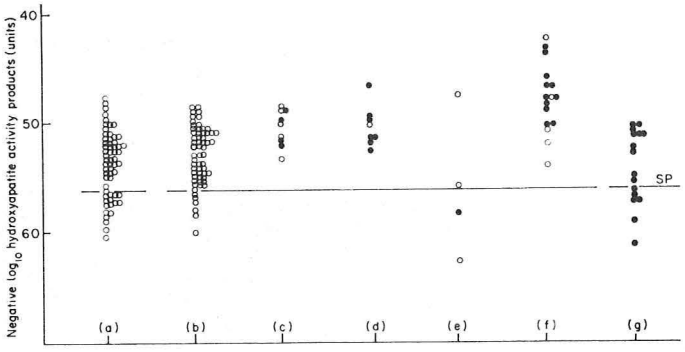


FIG. 3. The distribution of hydroxyapatite activity products (expressed in negative logarithms) in 24-hr urines from various groups of stone-formers and their controls in relation to the solubility product (SP) of hydroxyapatite (○, male; ●, female). (a) Male controls, (b) idiopathic, (c) hyperparathyroid, (d) 'RTA', (e) hyperoxaluric, (f) infected, (g) female controls.

Figure 4.

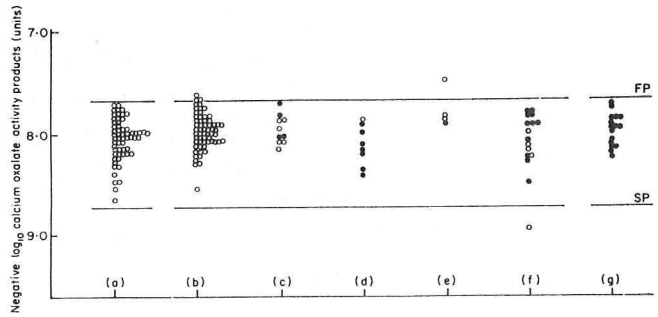


FIG. 4. The distribution of calcium oxalate activity products (expressed in negative logarithms) in 24-hr urines from various groups of stone-formers and their controls in relation to the solubility product (SP) and formation product (FP) of calcium oxalate dihydrate (○, male; ●, female). (a) Male controls, (b) idiopathic, (c) hyperparathyroid, (d) 'RTA', (e) hyperoxaluric, (f) infected, (g) female controls.

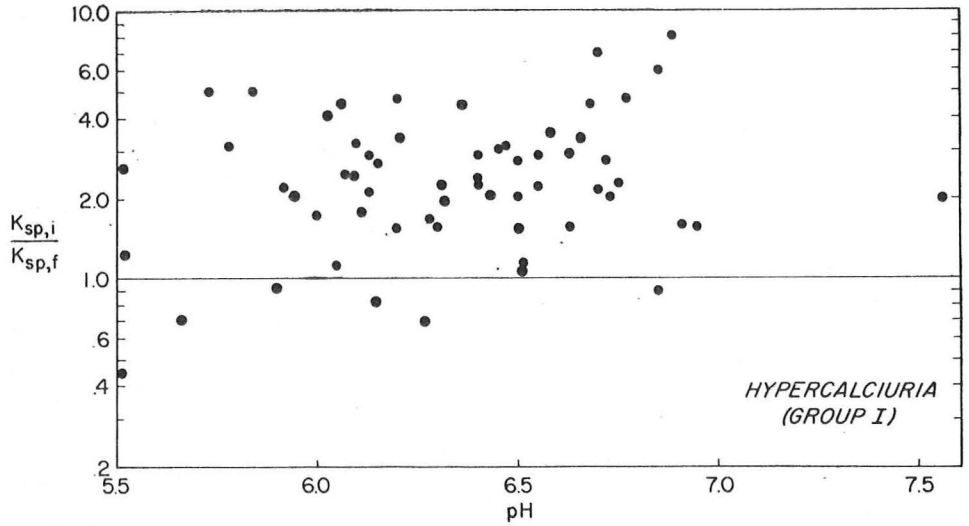
Figure 5.

These workers found that the urine specimens from both stone-formers and control subjects were generally supersaturated with respect to hydroxyapatite (Figure 4). Only a small or no significant difference in the activity products was found among stone-forming urines and among control urine specimens. Similar conclusion was reached for activity products of calcium oxalate, octacalcium phosphate, and brushite (Figure 5).

Thus, they reported that all urine specimens, including those from control subjects were markedly supersaturated with respect to calcium oxalate. However, these calculations may represent an incorrect estimation of the urinary state of saturation. The composition of urine may be much too complex to allow an accurate analysis of the ionic strength, dissociation of anions, and of ionic activities. Acknowledging this limitation, we introduced a modification to the method which we believe gives us a more accurate measure of the state of saturation.[32,34]

The activity products are calculated for the same specimen before and after incubation of urine with the synthetic solid phase, such as brushite or calcium oxalate. In other words, the activity product of the original urine is compared with the solubility of synthetic brushite or calcium oxalate in urine. The ratio of the activity products before and after incubation represented the state of saturation of urine where the ratio of 1 represented saturation, greater than 1 supersaturation and less than 1 undersaturation. Thus, the activity product ratio indicated the extent to which the synthetic solid phase undergoes growth or dissolution in urine.

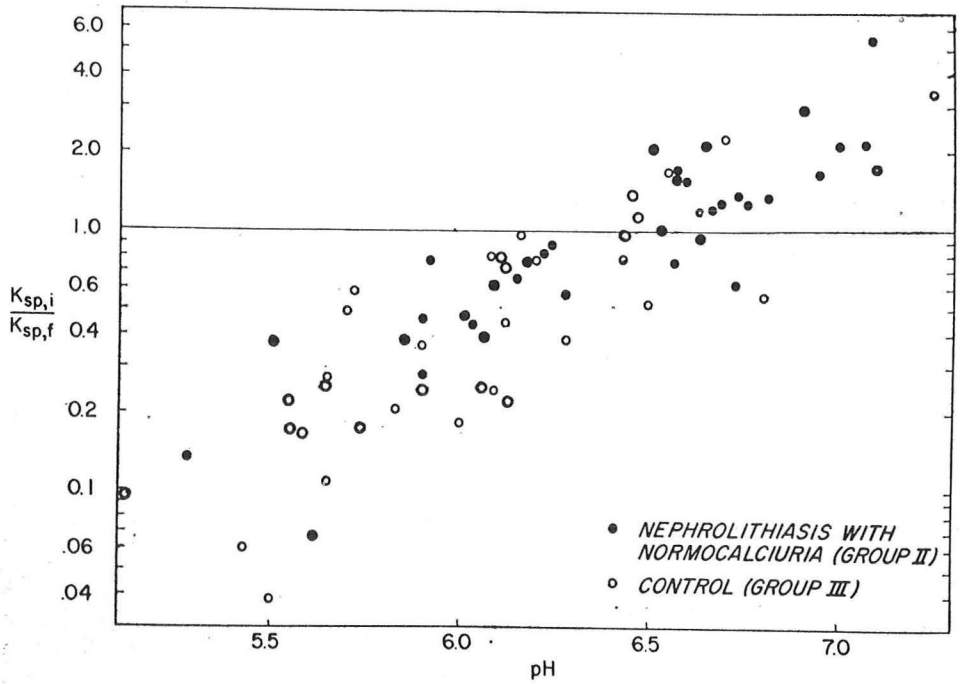
In contrast to the results of studies from the Leeds group, we find that control urines are usually undersaturated or only slightly supersaturated with respect to calcium oxalate, whereas majority of stone-forming urines were supersaturated. Further, we find that the stone-forming urines are invariably supersaturated with respect to brushite. In certain conditions which are associated with the recurrent passage of calcareous renal stones, such as idiopathic hypercalciuria, primary hyperparathyroidism, sarcoidosis and renal tubular acidosis, urine specimens were in general supersaturated or oversaturated with respect to brushite (Figure 6).



Activity product ratio ($K_{sp,i}/K_{sp,f}$) of urine of patients with hypercalciuria. The horizontal line at the activity product ratio of 1 represents the saturation line with respect to brushite. The values above this line estimate the number of times the urine is supersaturated. Most of the urine specimens (from 36 patients) were supersaturated.

Figure 6.

In contrast, among control subjects without stones, urine specimens were usually undersaturated except at high urinary pH [34] (Figure 7).



Activity product ratio ($K_{sp,i}/K_{sp,f}$) of urine of subjects with normocalciuria. The activity product ratio was pH-dependent. The supersaturation (activity product ratio of greater than 1) was encountered only at high pH. Urine specimens from 35 subjetcs without stones and 19 patients with stones were evaluated.

Figure 7.

Among patients with primary hyperparathyroidism and renal stones, removal of hyperplastic or adenomatous parathyroid glands led to a marked reduction in the state of saturation of urine with respect to brushite, commensurate with clinical improvement.[35]

SCHEME FOR FORMATION AND PREVENTION

These considerations led us to formulate the following scheme for the formation and prevention of renal stones of calcium phosphate origin [36] (Figure 8). In this schematic diagram, the state of saturation with respect

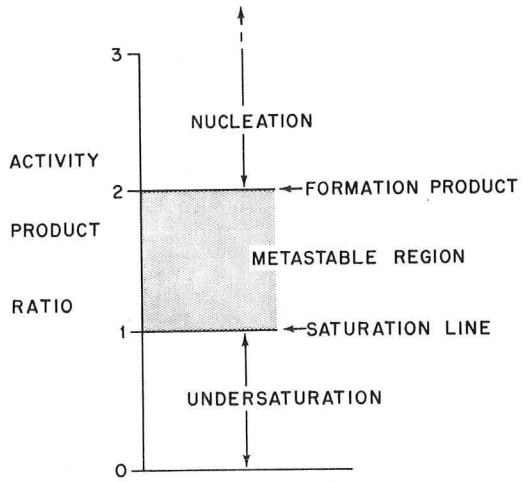


Figure 8.

to brushite is indicated by the activity product ratio. The activity product ratio of 1 indicates saturation. Points below this line represent undersaturation, whereas points above this line represent supersaturation. The shaded area between saturation and twice saturation indicates metastably supersaturated state. In this region, even though urine specimens may be as much as twice saturated with respect to brushite, nucleation of brushite does not take place. The point at which nucleation commences is the formation product. In this schematic diagram, the formation product ratio is 2: that is, nucleation is initiated when the specimen is twice saturated with respect to brushite. Above the formation product, nucleation takes place. This is the area of oversaturation. It is obvious that an effective treatment for the control of renal stones formation should be one that increases the formation product ratio or decreases the activity product ratio. Such treatment should increase the region of metastability or render the urine specimen less saturated with respect to brushite.

In summary, renal stones will form from the persistent passage of urine supersaturated with respect to brushite, particularly when the state of saturation exceeds the formation product. Such a condition allows the formation of the nidus of brushite. In specimens which are supersaturated with respect to calcium oxalate or other solid phases, renal stones may form by the deposition of these phases over the nidus of brushite. In contrast, the formation of renal stones of calcium phosphate origin may be prevented by treatments which reduces the activity product ratio and/or increases the formation product ratio of brushite. Since the urinary state of saturation is decreased and/or the degree of metastably supersaturated state is increased, the propensity for the nucleation of brushite is reduced. Inhibition of the development of the brushite nidus may, therefore, prevent the formation of renal stones of calcium phosphate origin. Thus, the determinations of the activity product ratio and of the formation product ratio for brushite allow a quantitative evaluation of various forms of treatment. We shall discuss now evaluation according to this scheme of treatment with oral sodium phosphate, hydrochlorothiazide, and cellulose phosphate.

QUANTITATIVE ASSESSMENT OF THERAPY

We shall examine the effect of a short-term treatment with oral sodium phosphate (equivalent to 1.5 gm phosphorus per day) among ten patients with renal stones.[35,37] The mean of the results of the 4-day control, 4-day treatment,

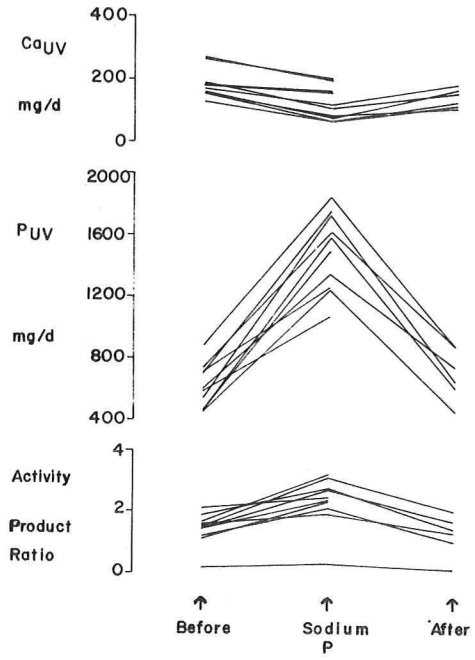


Figure 9.

and 4-day post-treatment periods is shown for each patient (Figure 9). In all patients, there was a significant decrease in urinary calcium excretion during treatment. However, there was a more marked increase in urinary phosphorus. Thus, the activity product ratio increased during treatment, that is, urine specimens became significantly more supersaturated with respect to brushite.

However, phosphate treatment increased the renal excretion of pyrophosphate[35,36] as has been shown by others.[13] Largely as a result of this increase, the formation product ratio of brushite increased.[36,37] In the majority of patients tested, the increase in the formation product ratio was sufficiently great so as to maintain the urine specimens in a metastably supersaturated state despite the increase in the activity product ratio. This probably accounts for the reported clinical improvement during therapy with phosphates.[38-40] Occasional patients, particularly with urinary tract infection have high urinary pyrophosphatase activity, and hence excrete only a small amount of pyrophosphate during orthophosphate load.[37] Therefore, the formation product ratio of brushite shows only a small increase, despite the marked increase in the urinary state of saturation. In our experience, such patients do poorly on long-term therapy with sodium phosphate and confirms the observation that the renal stone disease may be aggravated during phosphate therapy in the presence of urinary tract infection.

Even when it is efficacious in the prevention of renal stones, use of phosphates should be carefully monitored for potential side-effects. Riess and associates[41] have clearly demonstrated that phosphate therapy stimulates parathyroid function (Figure 10). The administration of 1 gm of phosphorus orally resulted in an increase in the plasma radioimmunoassayable parathyroid hormone concentration, commensurate with an increase in serum phosphorus and a decrease in serum calcium. The results may be explained by the following sequence of events: absorption of phosphate from the intestinal tract → increase in serum phosphorus → a decrease in serum calcium → stimulation of parathyroid hormone secretion. There is considerable evidence that the reduction in serum calcium concentration during phosphate therapy results from the extravasation of calcium phosphates

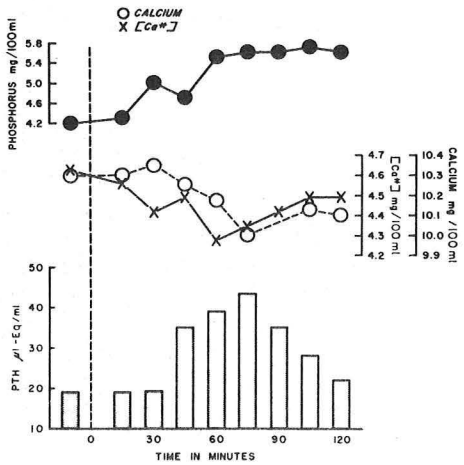


Figure 10.

in the soft tissues. Spalding and Walser[42] have reported an increase in the content of calcium in the soft tissues particularly of the kidneys, after long-term treatment with orthophosphate in laboratory animals. In man, the deterioration of renal function[43] and calcifications of aorta, conjunctiva, heart, and kidneys have been reported even in normocalcemic subjects.[44] Recent studies of Jowsey and associates indicate that these extraskeletal calcifications occur at the expense of bone (personal communication). They reported an increase in the resorption of bone and a decrease in bone mineral density following phosphate therapy. These potential side-effects should be carefully considered before committing the patient to long-term treatment with orthophosphate. It is reassuring, however, that Smith and associates have found no significant rise in plasma concentration of PTH during long-term therapy with orthophosphate.[39]

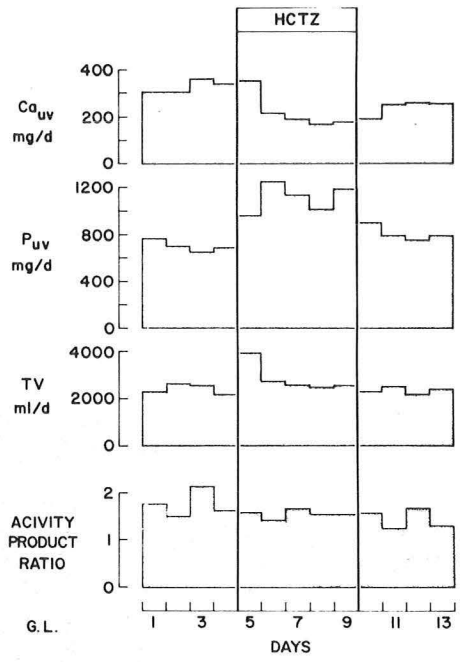


Figure 11.

Another widely used drug for the prevention of renal stones is the thiazide diuretic. Yendt and associates,[45] the leading proponents of this form of treatment, have reported a significant reduction in the frequency of new stone formation during therapy.

Their rationale for the use of thiazides in nephrolithiasis was based on the well-known observation that thiazides reduce the renal excretion of calcium. The typical effect of thiazides is shown by the response of a patient with idiopathic hypercalciuria to hydrochlorothiazide (50 mg twice a day orally for five days) (Figure 11).[37] During treatment, urinary calcium declined as the urinary phosphorus increased. The increase in urinary phosphorus raised the activity of divalent phosphate. Thus, despite the marked decrease in urinary calcium and the activity of calcium, the activity product of brushite was not significantly reduced.

In four of eleven patients studies, thiazides caused a small decrease or no significant change in urinary saturation with respect to brushite (Figure 12).[37] In others, thiazides significantly reduced the activity product ratio albeit to a lesser extent than was expected from the fall in urinary calcium.

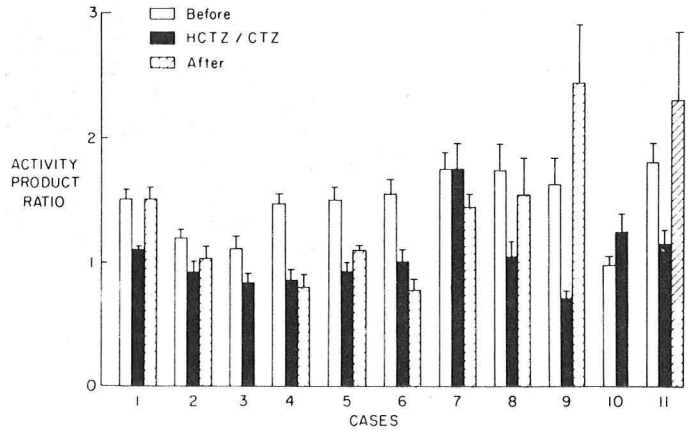


Figure 12.

In addition, thiazides stimulated the renal excretion of pyrophosphate, an excellent inhibitor of nucleation[37] (Figure 13). In this slide, each line represents studies in a separate patient. Note the increase in urinary pyrophosphate during hydrochlorothiazide therapy. The formation product ratio increased during treatment with hydrochlorothiazide in most patients commensurate with an increase in

urinary pyrophosphate (Figure 13). Thus, thiazides usually increased the formation product ratio and reduced the activity product ratio. That is, they usually increased the region of metastably supersaturated state and decreased the state of saturation of urine with respect to brushite. The propensity for the nucleation of brushite was thus reduced. These effects may underlie the reported beneficial clinical effect of thiazide in the prevention of calcareous renal stones. However, thiazides are not invariably effective in the prevention of renal stones, since some of the patients as in Case 5 here did not show any change in the urinary state of saturation or in the formation product ratio of brushite during therapy with thiazides.

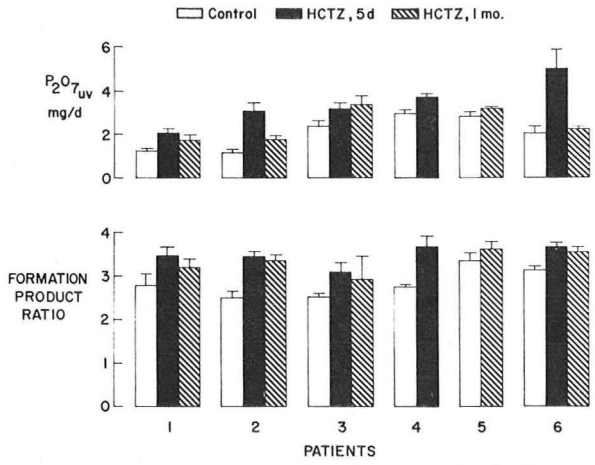


Figure 13.

The exact mechanism by which thiazides reduce the urinary calcium is not clearly known. Brickman and associates[46] and Middler and associates[47] have shown that this action of thiazides requires both an extracellular volume depletion and the presence of intact parathyroid glands. In patients with hypoparathyroidism, thiazides did not reduce renal excretion of calcium.

In addition, thiazides stimulated the renal excretion of zinc in patients with intact parathyroid glands [48] (Figure 14). Such increase was not seen in a patient with hypoparathyroidism. Other diuretics, such as triamterene, aldactone, furosemide, and mercaptomerin were without effect, whereas parathyroid hormone markedly stimulated renal excretion of zinc. Finally, the enhancement of renal excretion of phosphorus and pyrophosphate by thiazides was parathyroid hormone-dependent. It was not seen in patients with hypoparathyroidism.

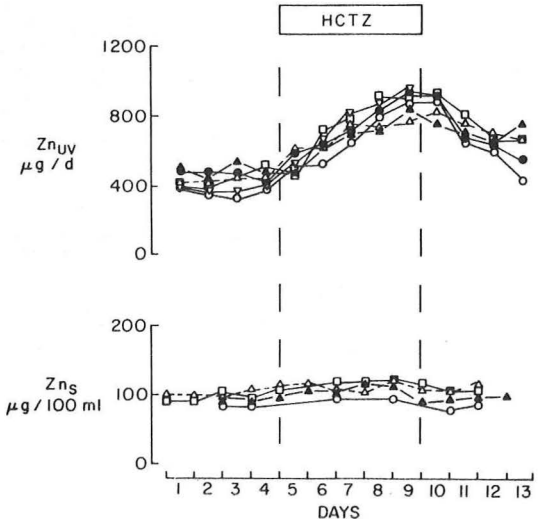


Figure 14.

These actions of thiazides however, could not be attributed to the stimulation of parathyroid hormone secretion, as has been suggested. Thus Coe and associates[49] have shown that in patients with normocalcemia, hypercalciuria, and hyperparathyroidism, thiazides reduced the plasma concentration of radioimmunoassayable parathyroid hormone. In our experience, thiazides reduce the renal excretion of cyclic AMP and hydroxyproline. Thus, in the majority of normocalcemic patients with renal stones, stimulation of parathyroid hormone secretion probably is not a significant hazard of thiazide therapy. However, in patients with accelerated bone turnover, thiazides should be used with caution because of the possible development of hypercalcemia.[50,51]

We shall now consider the effect of oral sodium cellulose phosphate,[52-55] currently an investigational drug in the United States. The short-term treatment of cellulose phosphate in 24 patients is represented here (Figure 15).[55] Each line represents studies in a separate patient. The mean of the results from each period is presented. In every case, there was a marked decrease in the renal excretion of calcium. Urinary phosphorus increased, but the extent of this increase was much less than the decrease in urinary calcium. As a result, urinary activity product ratio or the state of saturation decreased in every case. In the majority of cases, urine specimens became undersaturated with respect to brushite.[35] However, neither the urinary pyrophosphate nor the formation product ratio significantly changed during therapy with cellulose phosphate.[36] Thus, the major effect of cellulose phosphate was a reduction in the urinary state of saturation with respect to brushite.

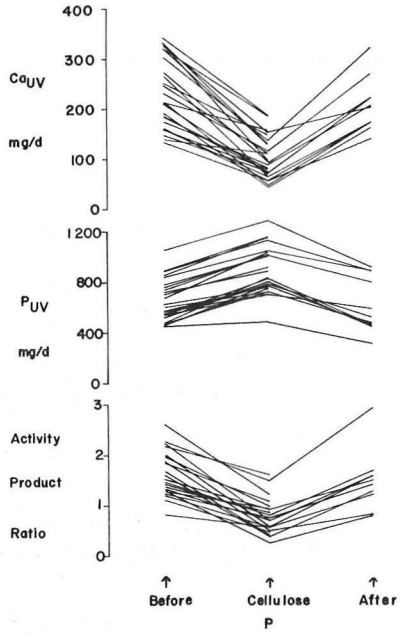


Figure 15.

The effect of long-term treatment from 0.6 years to 4 years with cellulose phosphate in 11 patients with idiopathic hypercalciuria is shown here[37] (Figure 16). Numbers below the block represent duration of treatment in years when the determinations were made. Before treatment, urinary calcium exceeded 200 mg/day and urine specimens were supersaturated with respect to brushite. During treatment, urinary calcium was less than 200 mg/day and urinary activity product decreased, usually to undersaturation. During three years prior to institution of therapy, these 11 patients passed 214 stones, or 6.5 stones per year. During 27 cumulative years of treatment 11 stones were passed spontaneously, or 0.4 per year. During treatment, they have been essentially symptom-

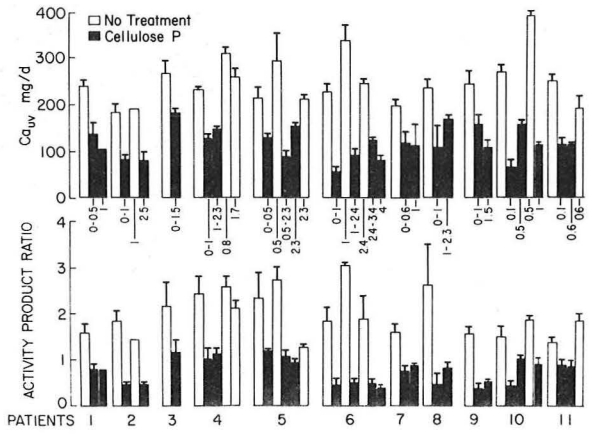


Figure 16.

free and have not required operations for removal of stones. No significant side-effects have been noted. Density of bone, plasma concentration of parathyroid hormone and serum and urinary trace metals have not changed significantly or have remained within the normal limits.

The mechanism of action of cellulose phosphate is now well known.[55] It is an ion-exchange resin where the phosphate is attached to cellulose by an esther linkage. When it is given orally, it binds calcium as it has a high affinity for the calcium ion. Since it is non-absorbable, it and the bound calcium are excreted in the feces. Extensive studies from both here and abroad indicate that the calcium balance does not turn more negative during cellulose phosphate therapy: the increase in fecal calcium is usually exactly compensated by a decrease in urinary calcium. This drug should be particularly useful in patients with hypercalciuria resulting from an intestinal hyperabsorption of calcium. When the treatment has been carefully monitored to bring the calcium absorption and hence urinary calcium to the normal range but not below it, few if any side-effects have been encountered.

PRACTICAL ASPECTS

We shall now consider the practical problem of evaluation and management of patients with a history of recurrent passage of renal stones. Approximately 80% of all stones are believed to be calcium stones, with which we are concerned here. Of those with calcium-containing renal stones, approximately 25% are considered to be the result of primary hyperparathyroidism. Usually, the diagnosis of primary hyperparathyroidism in patients with hypercalcemia is not too difficult. However, such is not the case in patients who are normocalcemic or only slightly hypercalcemic. We have therefore devised a relatively simple 4-day protocol for the evaluation of parathyroid function.

EVALUATION OF PARATHYROID FUNCTION

The patients are placed on a synthetic diet containing 400 mg calcium per day over a 4-day period (Figure 17). Note that contents of calcium and sodium, two major determinants of renal excretion of calcium, are fixed. Urine is collected daily for phosphorus, calcium, and cyclic AMP. Blood is obtained for calcium, phosphous, alkaline phosphatase and parathyroid hormone. On Day 3, the patient undergoes measurement of intestinal calcium absorption and bone mineral density by I-125 photon absorption. On Day 4, the patient undergoes the calcium infusion test.[56] Patients with hyperparathyroidism demonstrate an elevated plasma concentration of parathyroid hormone and urinary cyclic AMP,[57] and a decrease in urinary phosphorus during latter half of the infusion day of less than 29%. In addition,

SYNTHETIC DIET

DAILY COMPOSITION

calories	1500	Ca	400 mg
fat	51 g	Mg	213
CHO	195 g	P	800
prot	63 g	Na	100 mEq
Ash	neutral	K	60

Figure 17.

urinary calcim excretion is frequently greater than the amount of calcium absorbed from the gastro-intestinal tract,[58] and the density of bone often is low.[59]

This evaluation also allows an assessment of the extent to which the state of hyperparathyroidism is being deleterious to the patient. Decision on parathyroid exploration is based on whether the patient presents the following features: reduced creatinine clearance, reduced density of bone, urinary calcium exceeding absorbed calcium, urine specimens which are supersaturated or oversaturated with respect to brushite, and history of renal stones, bone disease or peptic ulceration. When the patient presents none of these findings, there is seldom a need for parathyroid exploration.

Among those with hypercalcemic primary hyperparathyroidism and stones, parathyroidectomy usually leads to cessation of stone formation. Several workers have reported a virtual "cure" of renal stone disease when patients with "normocalcemic hyperparathyroidism" and stones are subjected to surgical parathyroidectomy.[59,60] These patients probably had primary hyperparathyroidism, as their parathyroid function was not suppressed by an induced hypercalcemia. However, in those patients with hypercalciuria and renal stones in whom hyperparathyroidism is secondary to the defective or impaired renal tubular reabsorption of calcium, parathyroidectomy is clearly contraindicated. In them, treatment with thiazide may be considered, as it has been shown to decrease parathyroid hormone secretion.[49]

INTESTINAL CALCIUM HYPERABSORPTION SYNDROME

The remaining patients with normal parathyroid function probably comprise approximately 75% of the cases of calcareous renal stones. In our experience the majority of these patients have hypercalciuria and intestinal hyperabsorption of calcium.[58,62] There is some evidence that hypercalciuria is secondary to an intestinal hyperabsorption of calcium. It is perhaps more appropriate to describe this condition as absorptive hypercalciuria rather than as idiopathic hypercalciuria. The characteristic features of this condition are: (1) Hypercalciuria (urinary calcium exceeding 200 mg/day on an intake of 400 mg/day), (2) calcium absorbed from gut exceeding urinary calcium,[58] (3) normal bone density, and (4) normal parathyroid function as evaluated by plasma PTH, urinary cAMP, and calcium infusion test. In these patients, the treatment of choice is cellulose phosphate since it specifically inhibits the intestinal absorption of calcium. The success of cellulose phosphate therapy without a significant stimulation of parathyroid function or an alteration of calcium balance further confirms the concept that the primary defect in these patients is the intestinal calcium hyperabsorption. Since cellulose phosphate is not yet available for general use in the United States, thiazide diuretics probably represent the best of the available drugs. Orthophosphate may be used if thiazides are ineffective, provided the treatment is carefully monitored for potential side-effects.

The remaining patients with calcareous renal stones are usually those with urinary tract infections with urea-splitting organisms, renal tubular acidosis, and with bone wasting diseases, such as osteoporosis, osteolytic metastases, and Cushing's syndrome. Conditions characterized by hyperoxaluria are rare. Treatment should be directed at the primary disorder, as for example, correction of acidosis by bicarbonate therapy. Too often, however, it is not possible to correct or treat adequately the primary disorder. Many of us have experienced frustration at attempting to treat urinary tract infection in the presence of renal stones or in attempting to control stone formation resulting from chronic steroid therapy in a patient who must continue to receive them for his primary condition.

A new drug may be available which may portend great promise in the management of these difficult cases. This drug is diphosphonate, a synthetic analogue of pyrophosphate. Unlike pyrophosphate, however, diphosphonate is not hydrolyzed in vivo. It is absorbed from the gut and excreted in the urine in an unaltered form. Our initial studies indicate that as little as 0.5 mg of this compound as phosphorus per liter of urine effectively inhibits the nucleation and crystal growth of brushite and calcium oxalate in vitro. Studies by Fraser[63] and associates have already shown that it inhibits the formation of bladder stones in the rat (Figure 18). It is perhaps appropriate that we end end this medical grand rounds in this high note of promise. We may finally have left the era of Frere de Beaulieu and have reached a more exact understanding of the pathogenesis and treatment of calcareous renal stones.

Regimen	Predominant Stone Type	Dose of EHDP (% of the drinking water)	Weight of stones of proven composition (mg)
B Vitamin D_3 10000 i.u./week	$CaHPO_4, 2H_2O$	0	72.8 ± 9.0(33)
		0.0025	70.1 ± 8.8(18)
		0.05	63.0 ± 8.7(19)
		0.5	22.1 ± 5.3(11)**
C 1% Ethylene glycol	Calcium oxalate H_2O and $2H_2O$	0	24.8 ± 1.8(32)
		0.0025	19.1 ± 1.5(17)*
		0.05	18.2 ± 1.7(15)*
		0.5	15.6 ± 1.3(14)**

* and ** denote difference from control (no EHDP) significant at 5% and 1% level, respectively.

Figure 18.

In summary:

(1) Majority of calcareous renal stones are of calcium phosphate origin.

(2) Brushite probably represents crystal nidus for above stones.

(3) Stones form when urinary state of saturation with respect to brushite (activity product ratio) exceeds the metastably supersaturated state (formation product ratio).

(4) Formation of stones may be prevented by measures which lower the activity product ratio or increase the formation product ratio of brushite.

   (a) Orthophosphate invariably increases the activity product ratio and usually raises the formation product ratio.

   (b) Thiazide diuretic usually decreases activity product ratio and increases the formation product ratio.

(c) Cellulose phosphate decreases the activity product ratio.

(5) Preferred treatment is

(a) Parathyroidectomy in hypercalcemic primary hyperparathyroidism.

(b) Thiazide diuretic in normocalcemic hyperparathyroidism secondary to "renal leak" of calcium.

(c) Cellulose phosphate in intestinal calcium hyperabsorption syndrome with normal parathyroid function.

(6) Diphosphonate may be useful in nephrolithiasis assocaited with urinary tract infection, renal tubular acidosis, chronic steroid therapy, and "bone-wasting" diseases.

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