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THE PHARMACOLOGY OF RENAL LITHIASIS

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Although the history of pharmacologic intervention in patients afflicted with nephrolithiasis is a long one, many of the remedies employed probably have had a more soothing effect upon the conscience of the physician than on the colic of the patient. Striking exceptions have been the efficacy of penicillamine in the treatment of cystinuria and of allopurinol in the treatment of uric acid calculi. In recent years, however, significant advances have occurred in our knowledge regarding the pathogenesis of many (formerly) "idiopathic" cases of calcium stone formation. This, together with improved techniques for diagnosis, has led to several novel pharmacologic approaches to the treatment and prevention of calcium-containing stones. This review is concerned primarily with these newer aspects pertaining to calcium stone disease.

THE PRECIPITATION OF CRYSTALLOIDS

Three interrelated factors contribute importantly to the tendency for crystalloids to precipitate within the urinary tract (1). The first relates to the degree of supersaturation of the urine with respect to the constituents of the particular calculus. The second factor relates to the development of a nucleation site, either of an organic or heterologous inorganic nature, which can then promote the accretion of crystals from supersaturated urine. Finally, because the urine of many normal persons free of calculi is often supersaturated with respect to stone-forming crystalloids, inhibitors of crystallization and crystal aggregation could prevent or reverse a tendency toward stone formation. Although all three factors are important, different investigators usually have concentrated their efforts upon one aspect or the other.

Because the crystallization process is fundamental to the pathogenesis of any type of nephrolithiasis, a few prefatory remarks related to it are in order. Information regarding the tendency of a given crystalloid in solution to precipitate can be gained by a knowledge of its activity product (Figure 1). The activity product depends on

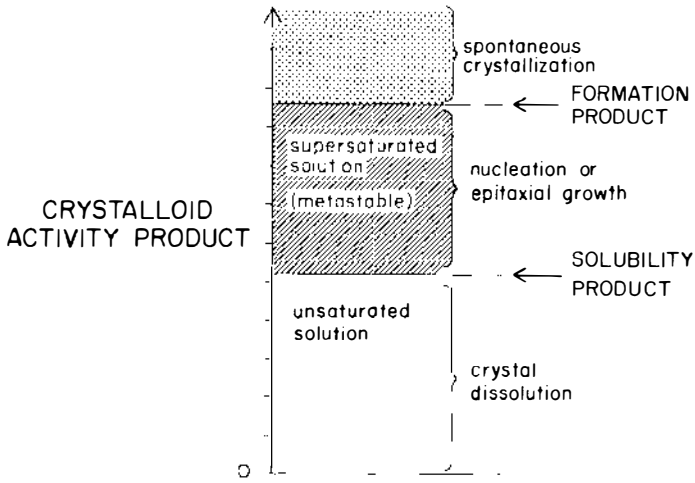

Figure 1 Qualitative representation of the solubility product and formation product, along a hypothetical crystalloid activity product axis (ordinate). Adapted from Pak (1, 23).

the concentrations and electrical charges of the crystalloid constituents, as well as upon the ionic strength of the solution. For example, computation of the activity product for brushite ($CaHPO_4 \cdot 2H_2O$) requires a knowledge of the calcium ion activity and of the monohydrogen phosphate ion activity; these activities are then multiplied to obtain the activity product. Similarly, one needs to know the calcium ion activity and the free oxalate ion activity in order to compute the calcium oxalate activity product. The activity product of monosodium urate is the activity of sodium times the activity of the monohydrogen urate ion. Although, in dilute solution, the activity is similar to the concentration, this does not hold for complex concentrated solutions such as urine. In practice, the activities of various ion species in urine are calculated utilizing computer programs after measuring the concentrations of many urinary constituents (2–4). The methods for computation of absolute ion activities involve the use of certain assumptions that may not be entirely valid. Finally, the computer programs utilize association constant data from various sources, some of which may be incorrect. Fortunately, certain ingenious approaches have permitted the expression of activity products in terms of solubility products, a procedure that cancels out many of the potential errors inherent in the calculation of absolute activities (4, 5). A knowledge of all complexing ion species is necessary, however, as has recently been shown in the case of calcium oxalate where certain soluble charged oxalate-cation species may form (5a).

The calculation of activity products aside, a few generalizations can be made with regard to the tendency of crystalloids to precipitate (1, 6). When the activity product of the crystalloid in question reaches a certain value, nucleation or spontaneous crystallization ensues. The activity product at which precipitation begins to occur is termed the *formation product* (Figure 1). Once this formation product is reached

or exceeded and crystallization ensues, the activity product of the crystalloid will diminish as crystal accretion progresses. Finally, equilibrium will be reached between the crystalloid in solution and the solid phase. The activity product at which this equilibrium occurs is termed the *solubility product* (Figure 1). At activity product levels less than the solubility product, the solid crystalline phase will dissolve tending to reestablish equilibrium conditions. As long as the activity product remains less than the solubility product, crystal accretion cannot occur. The formation product, on the other hand, usually is considerably greater than the solubility product (Figure 1). At activity products between the solubility and formation products, the solution is termed *metastable.* In this metastable region, crystallization will not occur spontaneously, but may take place by epitaxial growth if a suitable nucleating site is placed in contact with the supersaturated solution.

CONDITIONS WITH INCREASED URINARY CRYSTALLOID CONSTITUENTS

Hypercalciuria

Hypercalciuria, whatever the cause, predisposes to calcium stone formation—most often oxalate but sometimes apatite, and infrequently, brushite. Because the intestinal absorption of calcium is regulated, the urinary calcium normally should remain relatively stable and reasonably independent of the dietary calcium intake (7, 8). The setting of an upper limit for normal calcium excretion has been problematic (9). Although the excretion of calcium by any one individual is likely to vary from day to day, the upper limit of normal for 24-hr urinary calcium in normal males is frequently set at 300 mg or 4 mg/kg body weight. More restrictive definitions have been proposed. For example, beneficial results have been claimed after decreasing urine calcium in "marginal hypercalciuric" nephrolithiasis patients with 24-hr urinary calcium excretions of 140 mg/square meter of body surface area (10). When hypercalciuria is accompanied by hypercalcemia, the differential diagnosis becomes that of hypercalcemia. Such diagnostic possibilities as primary hyperparathyroidism, sarcoidosis, hyperthyroidism, and neoplasia should be investigated.

The vast majority of patients with calcium-containing stones and increased urinary calcium excretion fall within the broad category of normocalcemic hypercalciuria. Normocalcemic primary hyperparathyroidism accounts for the hypercalciuria in a fraction of these patients (11–13). The diagnosis is best made by finding an elevated serum parathyroid hormone (PTH) concentration or urinary cyclic AMP excretion, which does not return to normal following calcium loading or normalization of the urinary calcium (14, 15). In this condition, a portion of the urinary calcium is derived from bone ("resorptive" hypercalciuria) (16). The treatment of choice is surgical. The syndrome may appear in certain postmenopausal women, probably as a consequence of the lack of estrogen antagonism against the bone-mobilizing action of PTH (17, 18). The signs of hyperparathyroidism in some members of this group (which may include many poor surgical candidates) may be controlled adequately with estrogen replacement (17, 18).

Intestinal hypercalciuria, a consequence of inappropriately increased enteric calcium absorption, may be diagnosed in a substantial percentage of patients with normocalcemic hypercalciuria (14, 19). Several years ago, the Leeds group observed that the urinary calcium varies much more directly with the dietary calcium intake in certain hypercalciuric patients than in comparable normals (7). The cause of the increased calcium absorption in intestinal hypercalciuria is presently unknown. Elevated plasma concentrations of 1,25-dihydroxyvitamin D, together with low plasma PTH values, have been reported in some hypercalciuric stone-formers (20, 21), suggesting that intestinal hyperabsorption may result from the actions of inappropriately elevated amounts of this active vitamin D metabolite. In patients with intestinal hypercalciuria, the serum PTH and urinary cyclic AMP, should be normal or depressed (14, 15, 19). Rational therapy for this condition includes some degree of restriction of the dietary calcium intake in many patients. In addition, cellulose phosphate, a nonabsorbable agent, which prevents calcium absorption by binding it in the intestine, appears to be the treatment of choice (22). The available data indicate that negative calcium balance does not develop during the administration of cellulose phosphate, at least in patients with intestinal hyperabsorption (23). Unfortunately cellulose phosphate currently is unavailable in the United States except as an investigational drug. Therefore, routine treatment is best accomplished by a combination of dietary calcium restriction and thiazide diuretic administration (see below).

Renal hypercalciuria constitutes a third type of normocalcemic hypercalciuria. In this condition, an increased calcium excretion may be ascribed to a defect in the renal tubular reabsorption of calcium (14, 19). The defective calcium reabsorption does not appear to arise from resistance to the renal tubular action of PTH to facilitate calcium reabsorption (24). Interestingly, in this syndrome, parathyroid stimulation occurs during hypercalciuria, and the serum PTH is elevated (19). Presumably the action of PTH to stimulate the renal biosynthesis of 1,25-dihydroxyvitamin D (25) may result in the intestinal absorption of sufficient additional calcium to offset the increment in renal calcium excretion and prevent negative calcium balance. The serum PTH usually returns toward normal upon amelioration of hypercalciuria (19). Thiazide diuretics are the treatment of choice for renal hypercalciuria. Under many types of experimental conditions, thiazides decrease the renal calcium-to-sodium clearance ratio (26, 27). Thus, during chronic thiazide administration, after sodium balance is achieved and the urinary sodium excretion has returned to control levels, calcium excretion is "reset" at a diminished rate. Animal experiments have indicated that this thiazide-induced dissociation between renal calcium and sodium reabsorption occurs within the distal nephron (28) and may be related to the distal delivery of bicarbonate (29). Although it formerly was believed that the presence of PTH is necessary for the hypocalciuric action of thiazides to occur, recent studies have indicated that PTH is not needed (30, 31). Thiazides are capable of normalizing the urinary calcium and decreasing the activity of calculus formation in most hypercalciuric stone-formers. Following the reports of Yendt and collaborators of the clinically beneficial effects of thiazides upon the activity of nephrolithiasis in these patients (32, 33), many other groups have experienced similar results.

The usual side effects of the thiazide diuretics such as electrolyte abnormalities, glucose intolerance, hyperuricemia, metabolic alkalosis, and postural hypotension due to volume depletion may occur. In addition, hypercalcemia has been reported as a consequence of thiazide therapy, although at least a substantial portion of the increase in serum calcium occurred within the protein-bound fraction (34). Rather variable histologic abnormalities of the parathyroid glands have been noted in some patients (35) and in dogs (36) receiving thiazide diuretics for prolonged intervals. Thus, there remains an aura of uncertainty surrounding a putative relationship between thiazides and the parathyroids (37–40). It seems most likely that hypercalciuric patients with occult parathyroid adenomas and relatively nonsuppressible PTH secretion should be optimal candidates to develop thiazide-induced hypercalcemia. Therefore, it is wise to monitor the serum calcium in hypercalciuric patients commencing thiazide therapy.

Hyperoxaluria

At least two types of inherited enzyme abnormalities leading to florid hyperoxaluria secondary to increased oxalate synthesis have been described (41). Clinically the disorders are characterized by calcium oxalate stone formation early in life, followed by renal and systemic oxalosis. The treatment of these patients is particularly vexing, but fortunately the number afflicted is small.

Aside from the "primary hyperoxalurias," stones containing substantial amounts of calcium oxalate constitute about two thirds of the renal calculi in the United States (42). Although it seems surprising that our knowledge of the renal handling of oxalate is not extensive, this void stems largely from difficulties in the measurement of oxalate. Colorimetric procedures require a precipitation step, during which variable quantities of oxalate may be lost. One solution to this problem has been to add ^{14}C-labeled oxalate to urine as an "internal standard." A gas chromatographic technique has been utilized extensively in France (43, 44). Estimates of plasma oxalate concentrations have been obtained by systemically administering ^{14}C-oxalate and allowing sufficient time for its equilibration with the body oxalate pool (45–47). After equilibration the specific activity of labeled oxalate is assumed to be equal in plasma and urine, and oxalate may be measured chemically in the latter. The plasma oxalate values obtained by this method have been exceedingly low—on the order of a few μg/100 ml. An elevated blood oxalate concentration has been reported in a group of patients studied in Spain (47). Limited renal oxalate clearance data have indicated that oxalate may undergo net tubular secretion (45–47), but the details of its renal transport, including possible responsiveness to pharmacologic agents, are not yet well characterized.

A normal 24-hr urinary oxalate excretion appears to be something less than 50 mg. The Leeds group has reported that many calcium oxalate stone-formers have borderline-high urinary oxalate as well as calcium concentrations (3, 48). Presumably, this condition predisposes to intervals of urinary supersaturation, with consequent crystal formation and aggregation (48–51). Similar hyperoxaluric tendencies have been reported in series of nephrolithiasis patients from France (43, 44) and Spain (47). Unfortunately, the pathogenesis of this tendency toward increased urinary oxalate excretion in the usual nephrolithiasis patient is not known at present.

It may derive from an increase in oxalate synthesis or from an increase in the intestinal absorption of dietary oxalate. Oxalate absorption is inversely related to the dietary calcium intake (52, 53). The imposition of a low oxalate diet can result in an increase in the urinary calcium excretion (52). A simple explanation lies in the hypothesis that the calcium and oxalate that form (insoluble) calcium oxalate complexes in the intestine are unavailable for absorption. Thus, changes in the dietary intake of one of these ions will affect the intestinal absorption of the other in a reciprocal fashion.

Intestinal hyperoxaluria is a term applied to a syndrome of calcium oxalate renal lithiasis associated with intestinal disease or resection, chronic diarrhea, or other types of enteric malfunction (54). Daily urinary oxalate excretion in these patients is often greater that 100 mg. Although formerly it was thought that increased oxalate synthesis was responsible for intestinal hyperoxaluria, convincing recent evidence has demonstrated that the dietary oxalate accounts for most if not all of the increment in urinary oxalate excretion (55–57). The explanation for oxalate hyperabsorption probably is related to the concept that, in states of intestinal malfunction, increased amounts of fatty acids are available for complexing with calcium (56). Presumably, this results in decreased intestinal calcium oxalate complex formation, with a resultant increase in the availability of free oxalate for absorption. Therapeutically, dietary oxalate and fat restriction is a rational first step, but this often does not result in normalization of the urinary oxalate excretion. Cholestyramine, a nonabsorbable anion exchange resin, can result in oxalate retention within the intestine and subsequent reduction of the urinary oxalate (54). More recently it has been demonstrated that the feeding of calcium carbonate in patients with intestinal hyperoxaluria can result in a large decrease in urinary oxalate without increasing the urinary calcium (53, 58). By word of caution, it should be remembered that these patients also may have defects in calcium absorption which could explain their failure to develop hypercalciuria. In addition, aluminum hydroxide antacid preparations appear to be effective at binding oxalate within the gut and in reducing oxalate excretion (58). Although aluminum toxicity has been implicated in the pathogenesis of a bizarre neurologic syndrome occurring in patients with end-stage renal disease receiving chronic hemodialysis (59), aluminum has not been convincingly demonstrated as causative to most observers.

Miscellaneous Urinary Solute Alterations

Phosphate-containing stones, brushite, apatite or struvite, may present different types of therapeutic problems. The crystallization of the latter two species is especially pH-dependent. Struvite is often associated with persistent urea-splitting gram-negative urinary tract infections. Aside from antibacterial therapy when appropriate, attempts often are made at urinary acidification. However, acidifying maneuvers which result in metabolic acidosis can elicit an increase in the urinary calcium excretion secondary to an inhibitory effect on the tubular reabsorption of calcium (60). In addition, very large pharmacologic doses of ascorbic acid, sometimes utilized as a urinary acidifying agent, may result in increased oxalate biosynthesis with consequent elevation of the urinary oxalate (61). Preliminary data have

indicated that the use of acetohydroxamic acid, a urease inhibitor, may provide a promising therapeutic approach in lithiasis patients with urea-splitting infections (62).

Another program utilized in the treatment of phosphate-containing calculi is essentially that of inducing phosphate depletion. This regimen utilizes oral aluminum hydroxide preparations in order to decrease intestinal phosphate absorption (63). With phosphate depletion, rapid hypophosphaturia occurs as a result of a sharp increase in the renal tubular reabsorption of phosphate (64), but this is accompanied by a reciprocal increase in calcium excretion (65), especially in women (66). A large portion of the increment in urinary calcium is derived from bone (67), and osteomalacia may result from severe phosphate depletion (68). Furthermore, phosphate depletion has other undesirable side effects including diminished phagocytic activity (69) and muscle dysfunction (70). Thus, probably the aluminum hydroxide regimen should be reserved for refractory cases, and then utilized with caution.

DISORDERS OF NUCLEATION INDUCTION

Crystal Nucleation by an Organic Matrix

As already mentioned, the presence of a nucleation site permits the precipitation of crystalloids at activity product values exceeding the solubility product but less than the level at which spontaneous crystallization begins to occur (i.e. the formation product). Work by Boyce and others has demonstrated that urine may contain mucoproteins which provide a nucleating function in urine supersaturated with crystalloids (71). One such substance, designated *matrix substance A,* has been implicated in the pathogenesis of nephrolithiasis in some patients (71). Unfortunately, little is known regarding the processes controlling the formation or excretion of such substances.

Pak's laboratory has demonstrated that collagen can provide the site for epitaxial growth of brushite ($CaHPO_4 \cdot 2H_2O$), a crystalline species which probably is transformed to apatite in alkaline solution (72). In addition, brushite has been implicated as a pathogenetic factor in the formation of other types of calcium-containing stones, as is discussed below (1, 16, 73, 74). The effects of various therapeutic regimens upon brushite activity product ratios have been delineated in detail in Pak's laboratory. For example, corticosteroid administration increases the brushite activity product ratio, whereas cellulose phosphate decreases it (23, 75). Surprisingly, administration of a thiazide diuretic, despite its hypocalciuric action, does not diminish the activity product ratio for brushite because of a concomitant increase in phosphate excretion (23, 76). Likewise, the administration of inorganic phosphate increases the brushite activity product ratio (75, 77).

Nucleation by Heterologous Crystals

It has been proposed that brushite provides a nidus for the epitaxial growth of other calcium-containing crystalline species in urine (1), but this view has been challenged (42). Although direct confirmatory evidence for it is lacking, the hypothesis has

many attractive features (1). In addition, many physiologic and pharmacologic influences upon brushite precipitation have been characterized extensively utilizing the assay system devised by Pak (23). For instance, the adequacy of a given type of therapy could be determined by measuring the activity product of brushite and determining its degree of proximity to the formation product. Despite these attractive features, confirmation of the therapeutic efficacy of this approach in a clinical setting is lacking at present. A somewhat similar type of in vitro assay system for calcium oxalate has been utilized in a clinical setting by the Leeds group with reportedly good results (5). A recent observation has been that seed crystals of apatite can induce the epitaxial growth of calcium oxalate monohydrate crystals from supersaturated calcium oxalate solutions (77a).

Many old observations in the renal lithiasis field indicate that stones containing predominantly calcium oxalate may have a central core of uric acid or urate (78). Recent studies, by Coe (79) and Pak (80), have indicated that monosodium urate can act as a nucleator for calcium oxalate. Crystalline monosodium urate, when added to supersaturated calcium oxalate solutions in vitro, initiated calcium oxalate crystallization and increased its rate of precipitation (79, 80).

In a clinical experience with a large group of patients with recurrent calcium-containing stones, Coe & Kavalach found that hyperuricosuria was present in more than one third (81). The etiologies of the hyperuricosuria seemed diverse. Some patients with hyperuricemia and hyperuricosuria probably suffered from urate overproduction secondary to increased de novo purine biosynthesis. Others gave a dietary history of excessive purine ingestion. In the remainder, no cause for the hyperuricosuria could be identified. In these patients, the urinary uric acid excretion was shown to be exceptionally responsive to dietary purine loading (81), a type of response which had been noted previously in unilaterally nephrectomized renal transplant donors (82). Although control studies have not been done, preliminary data have indicated that the use of allopurinol in hyperuricosuric oxalate stone-formers affects the activity of the process favorably (10, 81, 83). Coe's laboratory also has found that some patients with recurrent calcium oxalate calculi demonstrate both hyperuricosuria and hypercalciuria. The treatment of those patients with both thiazide diuretics and allopurinol has seemed beneficial (10).

The observation that monosodium urate may act as a nidus for the precipitation of calcium oxalate probably provides an explanation for the old observation that the incidence of calcium-containing kidney stones is increased in patients with gout (84, 85). The fact that crystalline monosodium urate, rather than uric acid, is the offending species is a point of considerable interest and may give rise to some therapeutic dilemmas. Uric acid has usually been considered as the crystalline species which precipitates within and occludes the renal tubules of patients with uric acid nephropathy (86), whereas monosodium urate precipitation occurs within the renal medullary interstitium in gout (86). The solubilities of uric acid and monosodium urate are pH-dependent, but in opposite directions. The solubility of uric acid increases sharply with pH, whereas that of monosodium urate decreases with increasing pH (87–89). Furthermore, an increase in the sodium concentration

will decrease the apparent solubility of urate (i.e. by increasing the activity product of monosodium urate) (88, 89). Traditionally, sodium bicarbonate, citrate, or other alkalinizing salts have been utilized to increase the urinary pH in gouty patients with hyperuricosuria and histories of uric acid stones. Such alkalinizing measures in the presence of hyperuricosuria might result in exceeding the formation product of monosodium urate with the resultant formation of a nidus which could promote the deposition and epitaxial growth of calcium oxalate crystals in patients whose urine happened to be supersaturated with respect to the latter crystalloid.

Another potential therapeutic dilemma may arise with the utilization of certain uricosuric natriuretic pharmacologic agents currently being introduced. One such agent, known generically as ticrynafen in the United States and as tienilic acid in Europe, manifests a uricosuric potency exceeding that of probenecid and a natriuretic potency similar to chlorothiazide (90). Whether the use of such an agent would predispose to the formation of calcium oxalate calculi as an indirect consequence of increasing the monosodium urate activity product in urine will have to be determined experimentally (91).

INHIBITORS OF CRYSTAL FORMATION AND GROWTH

Considerable effort has been expended in the identification of organic and inorganic urinary constituents that inhibit the calcification process (92, 92a, 92b). Urinary citrate may diminish somewhat the tendency for calcium stones to form because of its ability to chelate calcium (93). In renal tubular acidosis, the excretion of citrate is diminished because of systemic and probably intracellular acidosis (94), and a diminished urinary citrate has been implicated as a pathogenetic factor in the tendency for some patients with renal tubular acidosis to form calcium-containing stones. The correction of acidosis may ameliorate their tendency toward calcium stone formation (95). However, it is not clear how the administration of alkalinizing salts could correct the stone-forming tendency in patients with *latent* renal tubular acidosis who suffer from nephrolithiasis in the absence of systemic acidosis (95). A diminished urinary citrate probably also partially explains the stone-forming tendencies of patients receiving acetazolamide chronically (96). Stone-forming patients with renal tubular acidosis sometimes are hypercalciuric (95). This may occur because of an inhibitory action of metabolic acidosis upon renal tubular calcium reabsorption (60). In addition, some hypercalciuric patients with renal tubular acidosis have demonstrated intestinal hyperabsorption of calcium (97).

Magnesium oxide has been utilized therapeutically in calcium stone-formers with variable results. Magnesium in high concentration appears to inhibit the crystal growth of calcium oxalate (98, 99). Nevertheless, the diarrhea caused by this and other magnesium-containing compounds sharply curtails their usefulness by forcing limitations on dosage. Methylene blue also has been administered in small doses as a precipitation inhibitor (100, 101). Supplemental ascorbic acid is given in order to avoid the depletion of its body stores. Although patients receiving methylene blue invariably are impressed by the bluish-green color imparted to their urine, a definite

salutory effect of methylene blue upon the natural history of stone disease has remained unproved.

Inorganic phosphate has been utilized as a therapeutic agent in patients with calcium-containing stones, with some success at modifying the natural history of the disorder (102, 103). As mentioned earlier, phosphate administration results in an increase in the urinary brushite activity product (23, 75, 77). However, this is offset by the induction of an even greater increase in the formation product for brushite after phosphate administration (75, 77). The salutory effect of phosphate in stone patients has been ascribed to an increase in the urinary pyrophosphate excretion (104, 105). Pyrophosphate has been demonstrated to function as an inhibitor of crystallization and of crystal growth (105). Diarrhea, abdominal cramps, or even constipation are unpleasant side effects of inorganic phosphate administration, but fortunately are short-lived in many patients and often are ameliorated if neutral phosphate is taken in multiple small doses with food. Although phosphate administration does result in an increase in the urinary brushite formation product (75, 77), it probably is unwise to administer phosphate to patients whose calculi contain phosphate as a predominant constituent. The available data indicate that chronic phosphate administration does not elevate the plasma PTH (105a).

Unfortunately, pyrophosphate cannot be administered orally because it is hydrolyzed in the gut. However, the diphosphonates, analogues of pyrophosphate with a carbon atom instead of oxygen bridging the two phosphorus atoms, may be administered orally. The properties of these diphosphonates vary with the nature of the substituents bonded to the carbon bridge. EHDP® (ethane hydroxydiphosphonate) has exhibited a salutory influence on calculus formation in a rat model (106), and also appears to be a highly effective inhibitor of phosphate and oxalate precipitation in crystallization systems in vitro (107–109). EHDP diminishes the renal clearance of phosphate and readily elicits hyperphosphatemia (110). In addition, it interferes with the intrarenal formation of 1,25-dihydroxyvitamin D (111). Finally, EHDP facilitates bone demineralization (111–113). Preliminary studies have suggested a beneficial effect of EHDP on calcium oxalate crystal aggregation in stone-formers (114). Currently, clinical trials of EHDP in nephrolithiasis patients are in progress within the United States but the complete results are not yet generally available (1). Because of its multifactorial toxic potential, it would seem that EHDP is not the ideal agent for the treatment or prevention of renal stones. On the other hand, some other diphosphonate could conceivably provide a better solution for nephrolithiasis patients.

In summary, this review mentions some of the newer (and older) notions regarding the pathogenesis of various types of calcium-containing stones, as well as any currently available or potential pharmacologic interventions which may prove effective. It should be evident that a pharmacologic panacea has yet to be delineated. On the other hand, therapy directed toward decreasing the urinary activity products of crystalloids and eliminating nucleating sites, as well as increasing the concentrations of inhibitors of crystallization in urine, may lead to a more rational and effective pharmacologic assault upon the renal lithiasis problem.

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