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PRESIDENT'S ADDRESS
THE MANY ROLES OF OXALATE IN NATURE

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In my presentation I would like to share with you a small friend that occupied much of my time during the past forty years. The story has two sides, one good with which we will begin and the other evil that will develop as the story unfolds.

Oxalate (Figure 1) is a small organic compound that has a broad presence in nature. As is shown in Figure 2, oxalate may occur as an anion in biological solutions, as an acid, or combined with calcium as a sparingly soluble salt. It may precipitate in several crystalline phases, including calcium oxalate dehydrate (weddellite) and calcium oxalate monohydrate (whewellite). Examples of these crystalline phases are shown in Figures 3 and 4. Since much of this story has to do with the crystalline phases of calcium oxalate, some time needs to be spent considering the many features of this crystal system.

For crystals to form in biological fluids, the fluid must be supersaturated for the precipitating crystalline phase (1–2). Because of the complex nature of most biological solutions, the state of saturation is not dependent solely on the solute concentration for the precipitating crystals. Ionic strength, complexation and solution pH all influence the availability of ions and the state of saturation. Ionic strength is determined primarily by the monovalent ions present in the fluid and it influences the activity of a specific ion such as calcium or oxalate. As ionic strength increases, ion activity decreases, allowing more calcium and oxalate to be in solution without supersaturation.

Biological solutions contain substances that can complex or bind potential solute, effectively reducing their concentration in solution. For instance, citrate and phosphate bind calcium, magnesium and sodium bind oxalate. Removing solute in the form of soluble complexes reduces the free ion activity decreasing saturation of calcium oxalate. The pH of the solution influences the availability of these complexing substances, so solution pH also influences the state of saturation.

Summarized in Figure 5 is an overview of the states of saturation as they apply to biological solutions. In the calcium oxalate crystal system, starting with low concentrations of free ion activity of calcium and oxalate, the solution is undersaturated. If crystals are present, they can dissolve. As the free ion activity of calcium and oxalate increase,

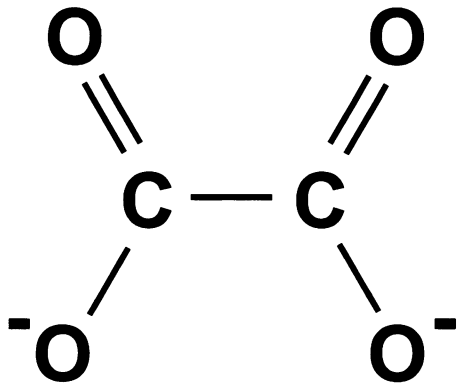

FIG. 1. Chemical structure of oxalate.

Terminology

Ca^{2+} —— calcium — cation

$C_2O_4^{2-}$ — oxalate —— anion

$H_2C_2O_4$ – oxalic acid – acid

CaC_2O_4 – calcium oxalate – salt

Crystals

$CaC_2O_4 \cdot H_2O$ – calcium oxalate monohydrate-whewellite

$CaC_2O_4 \cdot 2H_2O$ – calcium oxalate dihydrate-weddellite

FIG. 2. Forms of oxalate in nature.

the activity product increases until it reaches a well-defined point, the *solubility product* (K_{sp}). At K_{sp} the solution is saturated for calcium oxalate. If one continues to add solute, the solution becomes supersaturated until it reaches a less well-defined point, the *formation product* (K_{fp}). Above K_{fp} the solution is unstable for calcium oxalate, and spontaneous nucleation can occur. In the zone between *solubility product* and *formation product* the solution is supersaturated but metastable; there is the potential for heterogeneous nucleation and crystal growth. As illustrated in Figure 6, the amount of supersatura-

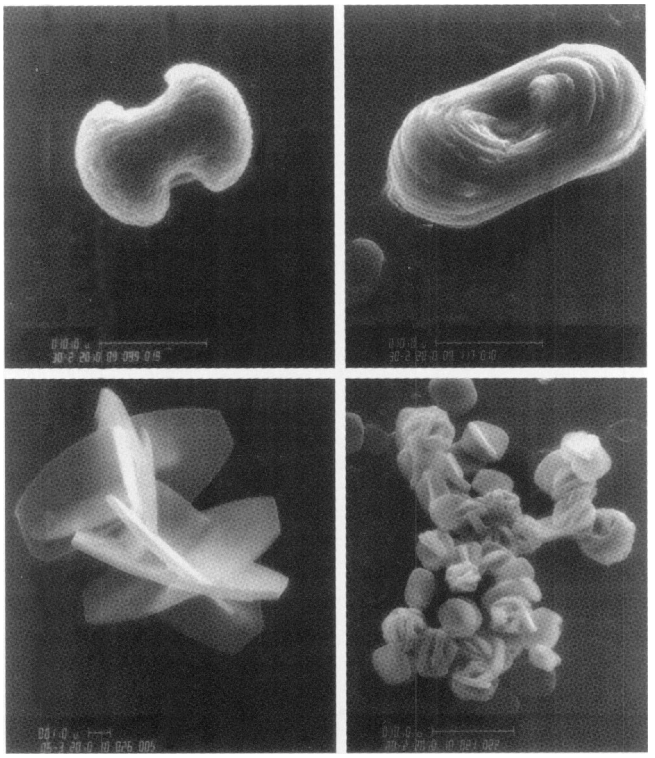

FIG. 3. Calcium oxalate monohydrate.

tion required for heterogeneous nucleation is much less than that required for homogeneous nucleation making it the principle form of nucleation involved in crystal formation in biological systems.

The level of supersaturation for calcium oxalate in biological fluids can be estimated by several techniques. To date much of this work has been done with urine. Pak and Holt (3) reported a relatively simple method for estimating calcium oxalate saturation, that they termed the "activity product ratio". In this test, synthetic crystals of calcium oxalate are added to voided urine and incubated for a period of time. By measuring the concentration product (CP) before and after incubation, a ratio that estimates the level of supersaturation (CP before/CP after) is developed. A value of 1 represents saturation, a value greater than one is supersaturated, and a value of less than 1 is undersaturated.

A second technique uses an iterative computer program (EQUIL2) to estimate the state of calcium oxalate saturation (4). This method is more complex, but it provides a great deal more information about the state of saturation. The measurement of urine pH and the concentra-

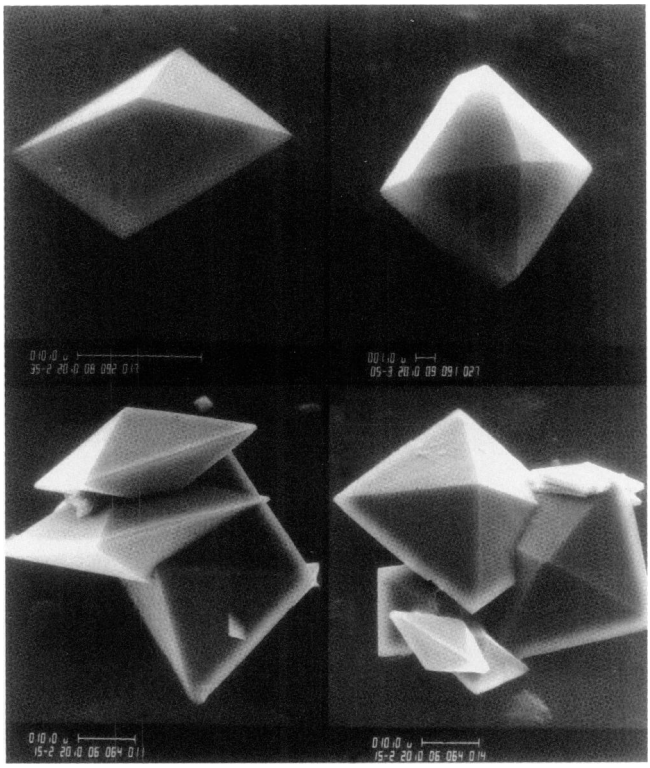

FIG. 4. Calcium oxalate dihydrate.

tion of the major ions, including sodium, potassium, chloride, calcium, magnesium, phosphate, sulfate, oxalate, citrate, urate and ammonium are required. These data are entered into the computer that allows the estimation of ionic strength, free ion activities, activity product and supersaturation for calcium oxalate. The relative supersaturation ratio is estimated by dividing the measured ion activity product by the thermodynamic solubility product. Again, a value of 1 represents saturation, a value greater than 1 is supersaturated, and a value less than 1 is undersaturated.

Wherever crystals are formed in biological fluids, substances may be present that can modify the crystal formation (5). At the meeting of this Association in 1958, Howard and Thomas (6) presented the now classic paper describing "good and evil" urine. They incubated rachitic rat cartilage with urine from 7 normal subjects and 12 patients with urinary calculi. Although the calcium phosphate product of the urine was much greater than necessary to mineralize the rachitic cartilage,

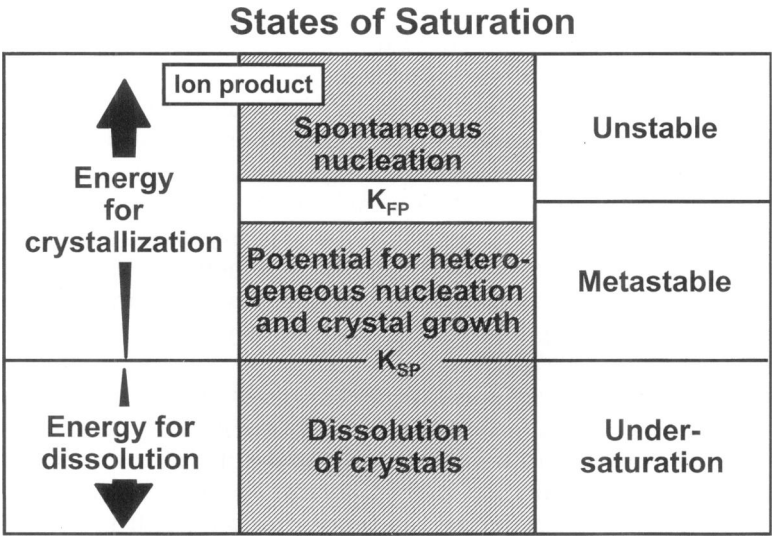

FIG. 5. States of saturation in biological fluids.

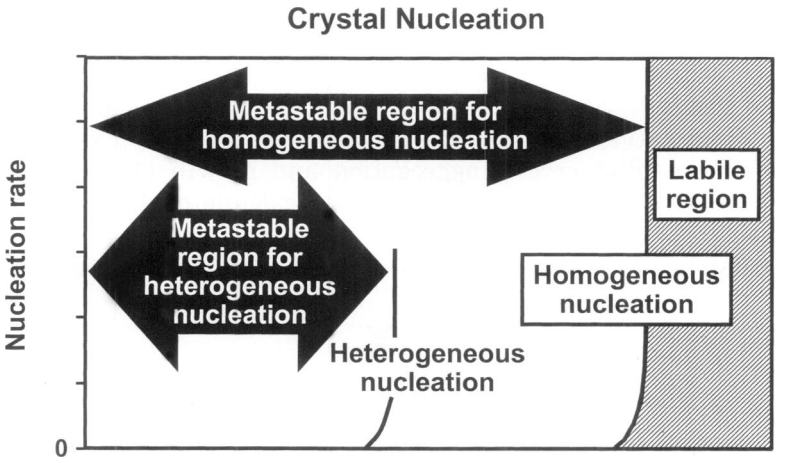

FIG. 6. Crystal nucleation rates are compared to the amount of supersaturation.

this calcification occurred with none of the urine from normal subjects and all of the urine from patients with urinary calculi. They termed normal urine "good" and stone-former's urine "evil" and postulated that some substance that inhibited crystal formation was absent or decreased in the patients with stones. These observations stimulated interest and research about substances that could modify crystal formation in biological fluids.

The modifiers of crystal formation in urine can be divided into three groups with some overlap. Inhibitors are substances that act at the crystal surface, most often interfering with active growth sites (7). Figure 7 shows a schematic drawing of a calcium oxalate microcrystal. On the surface is a dislocation or defect (X) where active crystal growth occurs. Nutrients are absorbed to the crystal surface (y) and migrate to the active growth site. Inhibitors attach to this site (X) and prevent the growth process. For the inhibition to be expressed, a crystal must be present. Typically these inhibitors act at extremely low concentrations. Examples in urine of inhibitors of calcium oxalate formation include citrate (8), pyrophosphate (9), glycosaminoglycans (10), RNA fragments (11) and acidic glycoproteins (12).

The second category of substances that modify calcium oxalate crystal formation are complexors that achieve their effect in solution by causing the formation of soluble complexes with calcium or oxalate. Figure 8 lists the many ion pairs that can occur in urine as soluble complexes effectively reducing the concentration and free ion activity of calcium and oxalate (4).

Promoters of crystal formation have been less well defined. Tamm-Horsfal mucoprotein (THM) at low concentration without polymerization acts as an inhibitor of calcium oxalate crystal formation. As the concentration of THM or the ionic strength of urine increases or as the pH of urine decreases, polymerization occurs, causing promotion of crystal formation (13). Glycosaminoglycans promote crystal nucleation, but inhibit crystal aggregation and growth (14,15). Various components of matrix also may promote calcium oxalate crystal formation.

Oxalate, in its several forms, is a common constituent of plants being

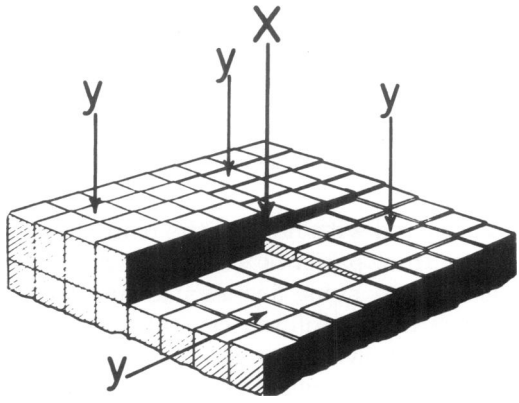

FIG. 7. Schematic drawing of urinary microcrystal.

Oxalate

KOx, CaOx, Ca_2Ox, $CaOx_2$, MgOx

Mg_2Ox, $MgOx_2$, NH_4Ox, HOx

Calcium

$CaPO_4$, $CaHPO_4$, CaH_2PO_4, $CaSO_4$, CaOx

Ca_2Ox, $CaOx_2$, CaCit, CaHCit, CaH_2Cit

CaPP, $CaCO_3$, CaHPP, CaOHPP, CaOH

FIG. 8. Potential ion pairs for oxalate and calcium in urine.

present in the majority of plant families (16). It can occur as oxalic acid, soluble salts of potassium, sodium and magnesium and as a sparingly soluble salt of calcium. When present as calcium oxalate, it can be as either of the crystalline phases of this salt. The amount of oxalate in plants can range from a few percent of dry weight up to 80% of the total weight of the plant as with some cacti (17). Oxalate is usually accumulated within the vacuoles of plant cells, although it may form within cell walls of some higher plants. Plant cells can have a very large amount of vacuolar space, often from 75 to 90% of cell volume, so there can be the potential for massive accumulation of oxalate. As much as 200 pounds of oxalate may accumulate in some large deciduous trees during a growing season.

The oxalate in plants is a product of plant metabolism coming from glycolate, glyoxylate and/or ascorbic acid. Established reasons for plants to produce oxalate relate to the soil environment in which they grow and to the problems that this can cause in ion balance and calcium regulation (17). In the soluble phase of the vacuole, oxalate can charge balance for cations and positively charged amino acids stored in the vacuoles. These solutes are important for generation of positive internal hydrostatic pressure that is the physical force that allows plant cells to be rigid in the absence of any true skeletal structure. The total solute potential in the vacuole will produce an osmotic activity that can cause water to flow into the vacuole and lead to a positive hydrostatic pressure. The pressure is transmitted to the cytoplasm, and is balanced by an equal and opposite force from the elastic cell wall. To prevent dangerously high charge imbalance synthesis and transport of oxalate and other organic acids occurs. An example of this would be the halophyte plants such as *Halogeton* that grows in soils rich in sodium and potassium. This plant accumulates large amounts of sodium and soluble oxalate and will come up later in this presenta-

tion. This supports a role for oxalate in charge balance in plants specialized for growth in high salt environments. One might ask why oxalate instead of other available organic acids such as citrate or malate? In this setting, oxalate is more beneficial since in terms of carbon balance it provides the maximum charge balance capacity per carbon atom. It also is a more stable ion in terms of entry into biochemical pathways.

The second role for oxalate in plants, calcium regulation, is supported by physiological and biochemical data. Calcium enters the plant from the root zone in the supporting soil and is transported to various parts of the plant through its vascular system. Transport in the transpiration stream is driven by evaporation of water from the surface of the plant. As water is lost, the concentration of dissolved nutrients increases. With calcium this can become a significant problem. If the level of cellular calcium exceeds 10^{-6} to 10^{-8} M, it becomes toxic to the cells creating severe physiological problems relating to the role of calcium in signal transduction and biochemical regulation of cellular processes. According to Franceschi and Loewus (17) "calcium oxalate formation is not a simple precipitation phenomenon, but has been demonstrated to be a carefully regulated process involving coordination of cell growth and crystal growth, and production of specialized subcellular organelles. Formation of calcium oxalate and the specialized cells for this process can be induced by increasing calcium in the growth medium. With calcium limitation, calcium oxalate crystals can dissolve, providing calcium for plant growth and development. These observations indicate that calcium oxalate in many plants is produced in response to excess calcium and can be considered to be a high capacity mechanism for regulating calcium activity in tissues and organs."

Oxalate is commonly found associated with fungi, but in difference to higher plants where oxalate is intracellular, usually as soluble or sparingly soluble salts, fungi may actively secrete oxalic acid and calcium oxalate crystals are found in association with fungal hyphae (18). The crystals that form may develop within the fungal hyphae and then are expelled through the hyphae wall or they may form in the surrounding medium when oxalate comes into contact with calcium. Again the crystal formation removes calcium from the medium and protects the organism. Phytopathogenic fungi elaborate oxalic acid, pectic enzymes and cellulose that act together on the cell wall of plants during infection. Of the three factors involved in this process, it appears that pathogenicity is associated with oxalici acid production and not with the pectolytic or cellulolytic enzymes (17).

When one considers the amount of oxalate produced by plants and fungi, it is not surprising that bacteria also should be involved in the oxalate cycle. Allison, et al (19) made the following statement about bacteria and their role in the catabolism of oxalate. "As is true with other natural products, microbes that degrade products play an important role in the cycling of carbon. In the case of oxalate, its properties suggest that, were it not for microbial catabolism, its accumulation in large quantities might well be incompatible with life as we know it."

It would seem that oxalate is not a good choice of food for bacteria. It can be a strong acid or a sparingly soluble salt and it can act as an enzyme inhibitor and have other metabolic effects. Further, its digestion provides only a small amount of energy. Yet, there are a wide variety of bacteria that can and do use oxalate as a substrate. Anaerobic as well as aerobic bacteria are included (19). Some of the bacteria that can degrade oxalate are able to ferment many other substrates. Others depend upon oxalate for their existence. In this latter group are a genus and species, *Oxalobacter formigenes,* that can inhabit the rumen of sheep and cattle and the large bowel of man and other animals where their ability to destroy oxalate may be of considerable importance to the host (20).

Observations in Colorado in the spring when sheep were turned out to pasture were a stimulus to work that led to the isolation and understanding of *Oxalobacter formigenes* (21). If the sheep were left in the spring pasture with heavy exposure to *Halotegon,* many would die of renal failure secondary to renal deposits of oxalate. If instead, the sheep were allowed to be in the spring pasture for short periods each day with a gradual increase in the time in the pasture over a few weeks, there were no problems. Subsequent studies showed that during the winter on a low oxalate diet the sheep lost their flora of *Oxalobacter formigenes* that requires oxalate to be present in the diet to be maintained. When the sheep ate large amounts of *Halogeton,* they were presented with a diet rich in oxalate that was absorbed leading to the development of oxalosis. If the sheep were adapted to the pasture over a period of time, the flora of oxalate degrading bacteria were re-established and the sheep had no problems. This then represents the first example of the potentially evil side of oxalate.

In man and many animals, oxalate is an end product of glyoxylate metabolism. Its primary pathway of excretion is through the kidney. Oxalate is excreted into the urine with calcium, thus creating the potential for precipitation of the sparingly soluble calcium oxalate salt. In urine from normal subjects the ratio of calcium to oxalate is equal to or greater than 5:1 (calcium to oxalate). Since the stoichiometric rela-

tionship between calcium and oxalate in the two crystal phases is 1:1, and the greatest crystalline mass is produced when the crystal ingredients are at this ratio, increases in the urinary concentration of oxalate have a greater effect on increasing crystal formation than increases in calcium. When the urine becomes supersaturated with calcium oxalate, crystals can precipitate and urinary stones may form.

Montaigne made the following classic observations about his urinary stones: "I feel everywhere Men tormented with the same Disease; and am honour'd by the fellowship, for as much as Men of the best Quality are most frequently afflicted with it; 'tis a noble and dignified Disease. And were it not a good office to a man to put him in mind of his end? My kidneys claw me to purpose."

Figure 9 presents the composition of 4525 consecutive urinary stones analyzed in the Mayo Clinic Stone laboratory from September 1971, through August 1976, prior to Electracorporeal Shock Wave Lithotripsy. Of these stones, 58.8% were calcium oxalate and another 11.4% were calcium oxalate mixed with calcium phosphate. Thus, slightly more than 70% of the stones analyzed contained calcium oxalate. These data are similar to other large series of stone analyses (22,23). In this presentation of the problem of the formation of calcium oxalate stones within the urinary tract, I will limit my discussion to those conditions that are associated with an increased urinary excretion rate of oxalate with hyperoxaluria.

In 1966, Wyngaarden and Elder (24) roughly quantitated the sources of oxalate found in urine. They estimated that 40% came from glycine through glyoxylate, 40% from ascorbic acid, 10% from other endoge-

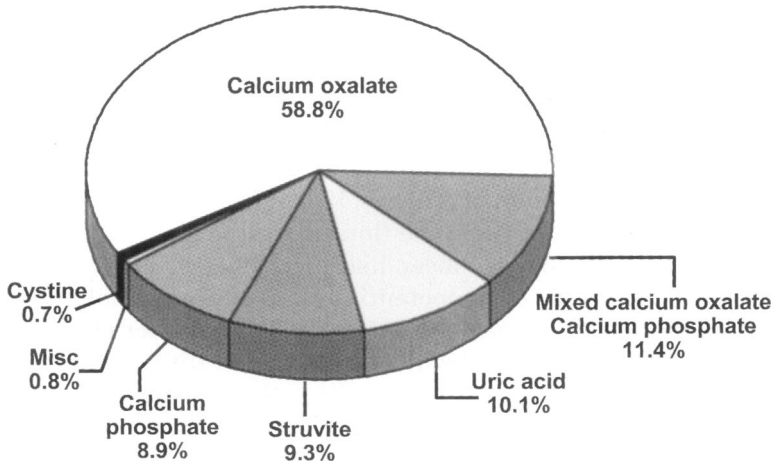

FIG. 9. Crystalline composition of urinary stones.

nous precursors of oxalate and 10% from diet in normal subjects. This estimate suggested that the dietary contribution of oxalate was fixed and represented a small amount of oxalate excreted in urine (<0.046 mmol/24 hours). Other observations in man suggest that urinary oxalate is inversely related to the dietary intake of calcium. Zarembski and Hodgkinson (25) examined this relationship and noted a significant increase in the urinary excretion of oxalate in patients with idiopathic calcium oxalate urolithiasis who were given a low calcium diet. Further, this increase was magnified when oral EDTA was added to the low calcium diet. They noted a 56% increase in oxalate excretion with low calcium and an 86% increase in oxalate excretion when EDTA was added. Hesse et al. (26) observed hyperoxaluria in 52.7% of men (n = 74) and 18.8% of women (n = 32) with urolithiasis on a free diet. When these same subjects were placed on a standard diet with 100 g of protein, 1 g of calcium and 100 mg of oxalate, hyperoxaluria was observed in only 18.9% of the men and 6.3% of the women. Clearly, the most common variables in the urinary excretion of oxalate are diet and the intestinal absorption of oxalate that will be discussed in more detail subsequently.

There are three groups of disorders complicated by the formation of calcium oxalate urinary calculi that can be associated with hyperoxaluria. These include the syndrome of idiopathic calcium oxalate urolithiasis, enteric hyperoxaluria and primary hyperoxaluria. Idiopathic calcium oxalate urolithiasis is associated with a group of disorders that affect the composition of urine leading to stone formation (27–29). One or more of these disorders may be present in a patient forming stones. Hyperoxaluria is one of these urinary disorders that may be present in 15 to over 50% of these patients. Potential causes of the increased urinary excretion of oxalate include diet as previously outlined, membrane transport and increased endogenous production of oxalate. Baggio et al. (30) reported the increased uptake of oxalate by the red blood cell membrane in a subset of patients with idiopathic calcium oxalate urolithiasis. Oxalate absorption from the intestine of five of these patients was increased in the first four hours following the ingestion of oxalate. Studies of oxalate transport in patients with idiopathic calcium urolithiasis have identified an abnormality in tubular handling of oxalate by the kidney (31,32). Both groups noted a reduction in plasma oxalate and an increase in fractional excretion of oxalate. It is attractive to consider a primary transport defect of oxalate in a subset of these patients, yet, detailed studies in an appropriate subset of patients are needed to confirm the presence and define the mechanism of these possible membrane defects.

Scattered reports have identified a group of patients with idiopathic calcium oxalate urolithiasis with mild hyperoxaluria and an increase in the urinary excretion of glycolate consistent with endogenous overproduction of oxalate (33). The abnormality appeared to be corrected with oral pyridoxine in some of the patients. Although some have suggested that this may be some mild form of primary hyperoxaluria, an enzyme defect has not been demonstrated and careful studies are needed in a group of these patients to define the cause of the mild hyperoxaluria. Treatment of these patients involves high fluid intake and adjustment of diet. If needed, orthophosphate, potassium citrate, Mg(OH) or MgO or pyridoxine may be added to the treatment program (27).

Enteric hyperoxaluria secondary to malabsorption was first described in a small group of patients who had had a substantial portion of their small bowel resected and subsequently began to develop recurrent calcium oxalate stones in the urinary tract (34). Since then it has become apparent that a number of factors play a role in the stone formation in patients with enteric hyperoxaluria (35–39). The hyperoxaluria invariably associated with this condition reflects hyperabsorption from the intestinal tract and is not the product of excessive endogenous oxalate production. Three factors are involved in the hyperoxaluria. The first, dietary oxalate, is self evident. The second involves fatty acids that are malabsorbed. These form soaps with calcium, decreasing the availability of calcium in the intestinal tract for binding dietary oxalate and thus increasing the bioavailability of oxalate for absorption. The third factor relates to the malabsorption of bile acids and fatty acids that increase the colon's permeability to oxalate.

The second set of abnormalities is more general, but also relates directly to intestinal malabsorption and promotes urinary stone formation. Water is malabsorbed, decreasing urine volume. Electrolytes including sodium, potassium, and chloride are malabsorbed, decreasing ionic strength. If potassium deficiency occurs, it will be associated with intracellular metabolic acidosis, that will markedly reduce the urinary excretion of citrate. Magnesium malabsorption occurs, decreasing this important complexor of oxalate in urine. If magnesium depletion occurs, it will be associated with hypokalemia, intracellular metabolic acidosis, and hypocitric aciduria. Malabsorption of protein, phosphate, and sulfate decreases these important complexors of calcium. Also, the concentration of the inhibitor of calcium oxalate crystal formation, pyrophosphate, in urine is proportional to phosphate excretion. Finally, there is bicarbonate loss with development of a mild

compensated metabolic acidosis that is accompanied by hypocitric aciduria. All of these abnormalities may contribute to stone formation. At times patients are seen who are actively making calcium oxalate stones, but who do not have hyperoxaluria with their malabsorptive state; instead the other factors described above are responsible for the stone formation. Data from normal subjects and patients with enteric hyperoxaluria and primary hyperoxaluria clearly illustrate the effect of these abnormalities on the state of calcium oxalate saturation (Table 1). The calcium concentration is the same in each group. The oxalate concentration is significantly greater in both patient groups, but it is twice as great in the patients with primary hyperoxaluria when compared with the patients with enteric hyperoxaluria. Yet, supersaturation is significantly greater in the patients with enteric hyperoxaluria. This is due to the other abnormalities in the urine of the patients with enteric hyperoxaluria and their effect on complexation, ionic strength, and PH in the urine.

Significant calcium oxalate urolithiasis may occur in some of these patients with intestinal malabsorption. The patient whose KUB roentgenograms (Figure 10) illustrates bilateral calcium oxalate renal calculi had a portion of his small bowel resected due to regional enteritis. He had no previous history of urinary calculi. During the year following the surgery the massive stone formation occurred. The stones were removed surgically and a medical program based on the principles outlined below prevented recurrence of the stone formation.

Treatment of these patients is usually staged (Table 2) and begins by correcting the hyperoxaluria. A diet containing minimal oxalate, 50 gm

TABLE 1
Hyperoxaluric States

Mole/Mole Creatine	Normal Subjects n = 16	Enteric Hyperoxaluria n = 15	Primary Hyperoxaluria n = 12
Calcium*	0.32 ± 0.03	0.33 ± 0.05	0.34 ± 0.06
Oxalate†	0.03 ± 0.003	0.11 ± 0.01	0.22 ± 0.05
Magnesium*	0.5 ± 0.03	0.2 ± 0.04	0.6 ± 0.05
Citrate*	0.3 ± 0.03	0.08 ± 0.02	0.3 ± 0.08
Phosphate*	2.7 ± 0.2	2.0 ± 0.1	3.1 ± 0.3
Pyrophosphate*	0.0033 ± 0.0005	0.0013 ± 0.0003	0.0042 ± 0.0001
Sulfate*	1.4 ± 0.1	0.8 ± 0.1	1.4 ± 0.2
Potassium*	7.0 ± 0.5	4.0 ± 0.6	7.9 ± 0.7
Supersaturation† CaC_2O_4	2.45 ± 0.6	11.23 ± 1.4	7.61 ± 0.8

* = Enteric Hyperoxaluria is significantly different from the others.
† = Each group is significantly different from the others.

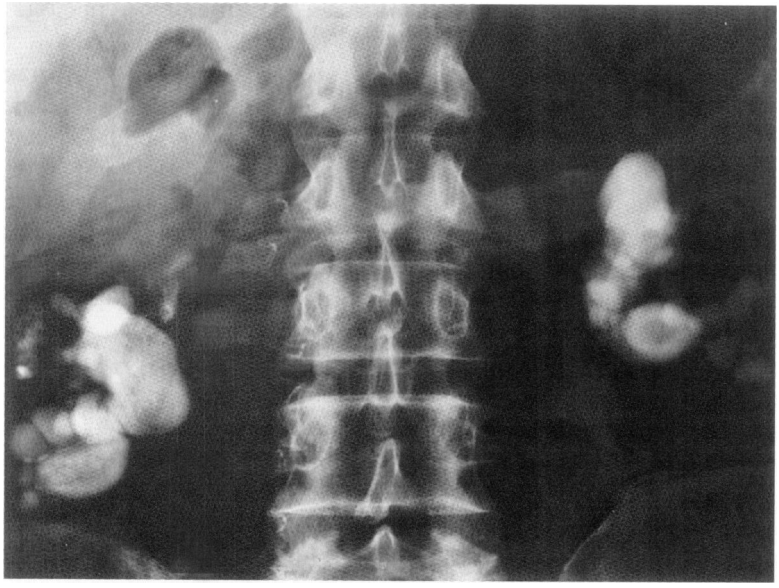

FIG. 10. KUB roentgenogram of a patient with enteric hyperoxaluria.

TABLE 2
Treatment of Patients with Enteric Hyperoxaluria

Increase fluid intake
Diet—low oxalate 50 gm fat (if fatty acid malabsorption) 1 gm calcium
Cholestyramine—4 gm qid (if bile acid malabsorption)
Alkali—NaK citrate 30 mEq tid to qid
Magnesium—usually needs to be given IM
Allopurinol—300 mg qd

of fat, and 1 gm of calcium is ideal. By reducing the fat, the fatty acid malabsorption will be reduced, leaving more calcium available to complex with the small amount of oxalate remaining in the diet. Patients like this diet, since it will have a dramatic beneficial effect of their diarrhea. This diet also results in better generalized absorption with an increase in water absorption and urine volume. In patients who have bile acid malabsorption, cholestyramine will be beneficial in decreasing diarrhea, increasing urine volume, and correcting in part

the increased permeability to oxalate in the colon. Alkali and electrolyte replacement as sodium potassium citrate can provide significant benefit increasing the citrate excretion in the urine. Oral replacement of magnesium is difficult because of the malabsorption. When required, magnesium is best given intramuscularly. Allopurinol would need to be considered if the stones formed also contained uric acid.

Our last disorder associated with hyperoxaluria is the syndrome of primary hyperoxaluria (PH) that includes two enzyme deficiencies at this time (40,41). PH1 is due to a deficiency of alanine:glyoxylate aminotransferase (AGT) that is normally located within the peroxisomes of the liver cells. This enzyme catalyses the transamination of glyoxylate to glycine using pyridoxal-5-phosphate as a co-factor (42). In the absence of AGT, glyoxylate is either oxidized to oxalate within the peroxisomes or diffuses across the peroxisomal membrane into the cytosol, where it is oxidized to oxalate or reduced to glycolate. These products are excreted by the kidneys and become the markers for PH1 as hyperoxaluria and hyperglycolic aciduria. Approximately two thirds of these patients have a deficiency of AGT. The other one third have a unique trafficking defect with about 90% of the AGT mislocated in the mitochondria where it is ineffective (43).

In PH2 there is a deficiency of glyoxylate reductase/D-glycerate dehydrogenase in liver cells with an increased production of oxalate and L-glycerate that is excreted in the urine to become markers for the disease (44,45). Both of these disorders are rare, but PH2 appears to be much more so. The severity of disease expression is greater in PH1 than in PH2. This may relate to greater oxalate excretion and lower concentrations of urine citrate and magnesium in patients with PH1 (46). Transmission of these enzyme disorders is by an autosomal recessive inheritance pattern with no recognizable biochemical abnormalities in the heterozygote.

Primary hyperoxaluria in its untreated state is the most malignant of the conditions complicated by urolithiasis. In 1964 Hockaday et al. (47) summarized 64 cases from the world's literature that they consider consistent with the diagnosis of PH. In 40 patients, by the age of 4, symptoms or signs of the disease had appeared: 28 patients had died of their disease by the age of 20, and only two lived past the age of 40. An example of the type of stone formation that can occur is shown in Figure 11. The natural progression of the disease in the untreated patient is to move from stone formation to nephrocalcinosis to renal insufficiency. The endogenous production of oxalate persists, and in the face of renal insufficiency, plasma oxalate increases, leading to generalized oxalosis as calcium oxalate is deposited throughout the

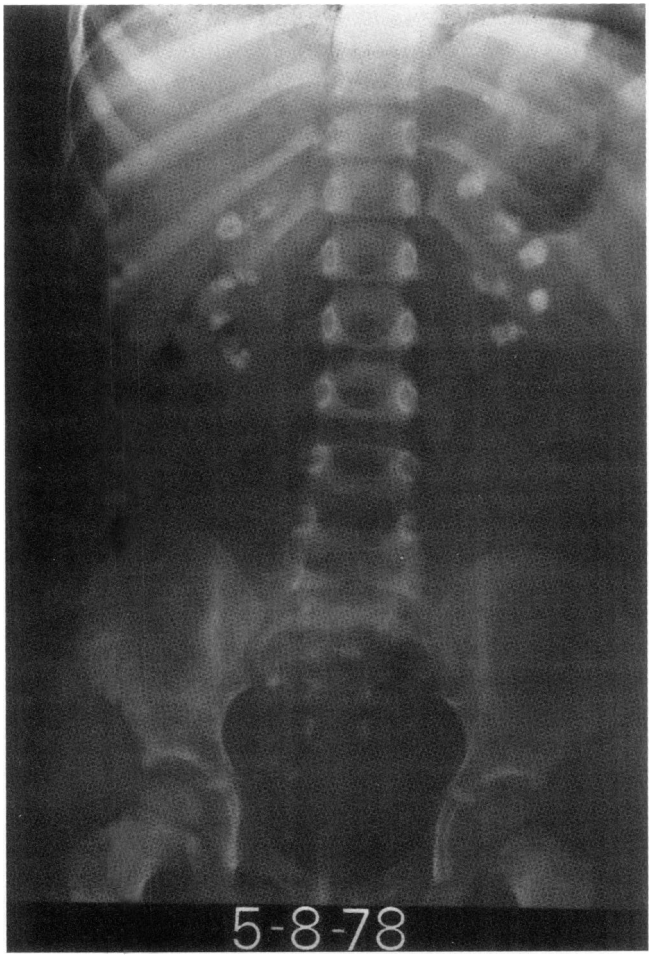

FIG. 11. A KUB roentgenogram illustrates the massive collection of stones in the kidneys and right ureter that can occur in a 5 year-old boy with Type 1 primary hyperoxaluria.

body. This deposition of calcium oxalate outside the kidney often is seen first in the blood vessels and bone marrow. Bone deposition is common in the later stages of the disease. An example of the extent of the oxalosis that can occur is illustrated in Figure 12.

Medical treatment of patients with PH has met with some success (48). Pyridoxine is a co-enzyme in the conversion of glyoxylate to glycine and in patients with PH1 30 to 50% of the patients treated with pyridoxine will have a significant reduction (>60%) in their urinary excretion of oxalate. The other approach to treatment affects the phys-

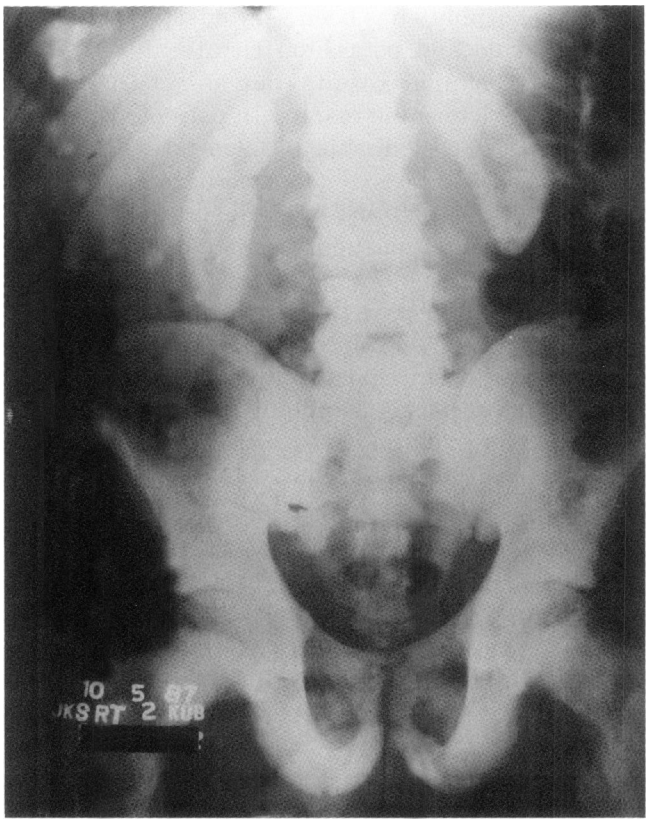

FIG. 12. The KUB roentgenogram illustrates the oxalosis that can occur in patients with primary hyperoxaluria and renal failure. A bone biopsy showed only calcium oxalate monohydrate by x-ray defraction. No hydroxyapatite was present. Also, the kidneys are calcified. Patient is a 28 year-old white male who had made no urine for 7 years while on dialysis.

ical/chemical factors in urine that control solubility and crystal formation. The first approach to this was with oral orthophosphate. In 1971 at this Association meeting, Dr. Thomas (49) reported the beneficial effects of oral orthophosphate in patients with recurrent calcium oxalate urolithiasis. Their urine that had been evil became good and they stopped forming stones. Frederick et al. (50) took this clue and treated two patients with PH with the program with encouraging results. Later it was suggested that pyridoxine should be combined with orthophosphate to obtain the benefits of both treatment programs (51). Subsequent studies have confirmed the benefit of this program in patients with PH1 (48). Patients with PH2 will not respond to pyri-

doxine, but orthophosphate has been very effective. Magnesium oxide, magnesium hydroxide and potassium citrate all have been used in attempts to achieve similar results, but as yet there have been no long-term studies to determine results. In patients with PH and renal failure dialysis has proved unable to keep up with the endogenous production of oxalate and renal transplant has often only been of temporary value. The availability of organs and the potential complications of long-term immunosuppression make the combination of liver/kidney transplantation one potential approach to management, but perhaps only a step to gene therapy in the future.

Although we look at the evil side of my friend oxalate because of the problems that it can cause in man, in nature there is much more good about oxalate. Just consider we and our animal friends might not be here if it were not for oxalate. Be that as it may, oxalate has been a good friend that has opened for me many exciting challenges and adventures over the years.

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