CHAPTER III

THEORIES OF UROLITHIASIS
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Crystallization and stone formation in urine involve a highly complex process, the true nature of which is still poorly understood. The great efforts dedicated to the research of this condition have furnished so far only accessory information and do not seem to have penetrated the core of the problem.

The theories of urolithiasis are classified and explained on basis of modern concepts of etiology. The Randall's and Vermeulen's theory are also described separately.

Randall's theory

Randall in 1937 described two kinds of calcific foci in the renal pyramids. Type I lesions were small calcified plaques located in the interstitial tissue beneath the surface epithelium of the renal papillae which gradually became exposed to the urine by the erosion of the epithelium overlying the plaque. Type II lesions consisted of calcific masses found in the terminal parts of the ducts of Bellini. The presence of Randall's plaques has been confirmed by many workers. They are believed to be the first or initiating lesion of many but not all calcium oxalate renal calculi. Microscopic calcific foci are frequently found at various sites in the normal kidney.
Vermeulen's Theory

The experiments carried out by Vermenlen indicate that the start of stones in a normal urinary system is intimately related to the renal papilla and the collecting ducts within it. A concept of embryogenesis is suggested in which the minute embryos first appear in the duct lumens in the papilla because this is the site where the urine finally attains its maximum concentration. Furthermore, the small size of the duct lumen also retards passage of the initially microscopic embryos and they thus have the opportunity to grow somewhat before discharge into the pelvis.

Most of the aborted embryos are expelled with the urine. Occasionally, retention by mere stagnation in the calyceal fornix may lead to development of a free stone. But more characteristically, embryo retention occurs at the duct ostium where the embryo grows into a small stone attached to the papillary surface. It subsequently, sloughs away (usually with fragmentation) and the fragments become secondary growth centres wherever they may lodge in the urinary system.

The stone process may be separated into two parts. The first phase requires more drastic supersaturation to trigger stone embryogenesis, but the triggering level needs be only a temporary episode. Thereafter, the second phase (continued growth of retained embryos) can proceed under urine conditions that are essentially normal.
Modern theories

Drach (1992) described the details of physicochemical principles involved in crystal formation and its growth.

It is necessary to explain some of the basic processes involved in crystallization in biologic system, renal anatomy and urinary excretion patterns of some substances to understand present theories.

1. Process of crystallization

To understand the process of crystallization, terms to be reviewed include saturation and the saturation concentration, supersaturation, solubility product, formation product, metastable region of supersaturation, crystal nucleation, crystal growth, crystal aggregation, epitaxy and zeta potential.

Saturation

If increasing amount of substances capable of crystallizing are added to pure water at a given temperature and pH eventually a high enough concentration is reached for crystal to form. When crystals begin to form, we say that the solution has become saturated with the substances when two or more substances are combined to form the crystal e.g. calcium oxalate, the level of saturation is governed by the product of the concentration of two or more substances. The point at which saturation is reached and crystallization begins is referred to as the "solubility product". It is defined as the product of the
molar concentration of the two substances at the point at which saturation is reached.

The pH and temperature are always specified for any crystallization process. Alteration in either factor may greatly alter the amount of substances or solute that may be held in the solution. Since urine varies widely in pH, this factor must be considered in any explanation of urolithiasis.

In urine, when the concentration of a substance reaches the point at which saturation would occur in water, crystallization does not occur as expected. Urine has the ability to hold more solute in solution than does pure water. Although all elements and molecules in urine are suspended in water, the mixture of many electrically active ions in urine causes interactions that change the solubility of their elements. In addition, many organic chemical molecules such as urea, uric acid, citrate and mucoprotein of urine all mutually affect the solubility of other substances. For example, citrate is known to combine with calcium to form a soluble complex. It therefore, prevents some calcium from combining with "oxalate" or phosphate and becoming crystalline. As a corollary to this statement, Elliot (1973), Finlayson (1974), Welshman and McGeown (1975), Schwille et al (1982), Menon and Mahle (1983) and Nicar et al (1983) have reported that deficiency of urinary citrate is one of the many factors found in the urine of stone formers.
Supersaturation

If a given amount of calcium and oxalate that would crystallize when placed in a solution of water at given pH and temperature is placed in urine, it will be held in solution. If the amount of calcium and oxalate is increased progressively in the same volume of urine at constant pH and temperature, the calcium and oxalate will stay in solution even though the solubility product has been exceeded. In doing this, we are actually creating supersaturation. This zone of supersaturation is called the metastable region.

The amount of substances in urine can be increased to a point at which urine will no longer hold it in solution. Then spontaneous nucleation of the crystals begins. The area of supersaturation between the solubility product and spontaneous urinary crystallization is the metastable region for a given substances.

The point at which spontaneous nucleation of crystals occurs is known as the formation product (FP) for urine. This means that although urine contains multiple and complex solubilizing factors for that particular crystal, the amount of substance in urine may eventually become so great that it is capable of crystallizing inspite of the solubilizers and inhibitors that are present (Fleisch, 1965; Walton, 1965; Dyer and Nordin, 1967; Lonsdale, 1968 a,b; Hodgkinson and Nordin, 1971; Mullin, 1972; Finlayson, 1974; Thomas, 1974; Williams, 1974 a,b; Breslan and Pak, 1980).
Electrical attraction or repulsion of ions in biologic solution is also involved in the stone forming crystallization process. Rollins and Finlayson (1973) studied electrical fields of urine-like solutions and the effects of various additives on the electrical attraction of urinary substances. This type of biologic electrical activity is called Zeta Potential (Gardner, 1969).

**Crystal Nucleation**

Nucleation of crystals occurs when active ions and molecules in a solution no longer flow randomly in a completely dissociated fashion, but cluster together closely enough to form the earliest crystal structure that will not dissolve.

**Crystal Growth**

Once nucleation has occurred in the complex solution like urine, certain nuclei may continue to grow if the urine remains supersaturated. Not only will such nuclei continue to grow in the zone above the formation product (the zone that permits spontaneous nucleation), they will continue to grow even if the saturation of urine falls into the metastable zone between solubility product and formation product. The concept of increasing the urine concentration to the level where the formation product is exceeded is critical to certain theories of urinary stone formation in which homogenous nucleation is a critical event. In other theories, however, saturation is required only to the range of metastable supersaturation, it is postulated that adequate heterogenous
nuclei are already created by biologic processes in the kidney (Randall, 1937; Carr, 1969; Drach and Bayle, 1972; Malek and Boyce, 1973).

These two concepts of nucleation may be further separated into free particle theory and the fixed particle theory (Finlayson and Reid, 1978). In free particle nucleation, multiple crystals are formed simultaneously in the upper urinary system when the formation product of a substance is exceeded. One concept of free particle nucleation also allows for the fact that urine probably contain multiple previously formed microliths in the kidney papillae that are subsequently excreted and may then serve as nuclei for other ions. In the theory of fixed particle nucleation, it is suggested that because of excessive concentration of certain ions in certain areas of kidney precipitation of crystals or spherules may occur in the renal papillae either within the tubular lumina or beneath the surface of the papillae (Randall, 1937; Vermenlen and Lyon, 1968; Drach and Boyce, 1972; Malek and Boyce, 1973; Finlayson and Reid, 1978; Resnick et al, 1978; Resnick and Boyce, 1978; Haunmann et al, 1980). These particles remain 'fixed' and serve as nuclei for further growth.

**Crystal Aggregation**

If multiple nuclei and crystals are formed spontaneously and float freely, these nuclei become active kinetically and bounce about in the urine. Under certain conditions, however, these nuclei can grow and
may come close enough to each other to be bound together by various chemical forces. Therefore, nuclei or larger growing crystals may aggregate to form larger crystal masses. They may add additional crystals to their surfaces by the process of aggregation or they may grow by adding new crystal mass to their surfaces.

**Epitaxy**

If a crystal has a pattern or organization of ions that is regular and predictable, this structure is called lattice. This surface lattice may resemble very closely that of a second but different type of crystal. Depending upon the closeness of resemblance the second type of crystal mass may actually be able to grow upon the surface of the first. This is called epitaxy.

The degree to which epitaxy may be important in the formation of a particular crystal depends upon the relationship between the amount of supersaturation for that crystal and that for the crystal that forms on its surface by epitaxy.

**Modern Theories**

1. **Supersaturation / Crystallization**

Uric acid and cystine calculi are formed when urine is acidic due to oversaturation with uric acid or cystine. Magnesium ammonium phosphate (struvite) calculi form whenever the product of the concentration of these ions exceeds the saturation product and when the urine remains
alkaline for long periods of time. Therefore, three of the five major types of urinary calculi can be explained primarily by this first theory of stone formation - supersaturation of urine with a substance that can crystallize in urine at a given pH.

2. Inhibitor lack

The supersaturation alone does not completely explain even three types of calculi and certainly not calcium phosphate or calcium oxalate stone formation. Many normal persons have supersaturation of substances in urine. They will form crystals, but the crystals remain small and are passed easily.

The inhibitors which prevent or at least limit crystal growth and aggregation in normal urine must be playing important role. Neither the supersaturation theory nor inhibitor theory can stand alone. It seems necessary to combine both to have a cogent theory of stone formation. Robertson and colleagues (1976) have postulated such a theory for calcium oxalate lithiasis. It suggests that stone formers show greater supersaturation and less inhibition of crystallization.

3. Matrix initiation

Matrix may inhibit crystal growth, interfere with crystal aggregation and even enhance stone growth. The uromucoid of normal person is possibly the inhibitor of crystallization and stone formation. While the matrix of stone formers represents uromucoid with some qualitative
defect that alters its ability to inhibit crystallization or even causes it to promote stone formation.

4. Intranephrotic and fixed nucleation

This theory states that the major process that ultimately leads to stone formation is aggregation of small crystals formed previously in the kidney. Some investigators believed that the initial nucleation and growth of nuclei and crystals begin in the renal (intranephrotic) tissue; while others believe that the process begins freely in renal tubular urine.

The proponents of the intranephrotic theory believe that disease begins within the renal tubular cell. Excretion of multiple calcified nuclei from these cells into the urine allows growth of crystals in the previously supersaturated urine.

5. Extranephrotic and free particle nucleation

This theory reports that the stone formation takes place in urine. The arguments of proponents of this theory can be separated into three major divisions. There are those who believe that urinary supersaturation with a given element results in spontaneous crystallization of that element. Since the crystal growth in urinary solutions does not proceed rapidly enough to postulate formation of a single large mass that obstructs the bladder or ureter (Finlayson and Dubois, 1973; Miller et al, 1977), concepts of aggregation or
agglomeration of spontaneously nucleated crystals must be prepared to explain formation of larger mass. It is known that crystal inhibitors are present in urine and they affect the surfaces of crystals and prevent them from aggregating or from growing larger.

6. Final Theory

This final theory of urolithiasis is an attempt to combine all the elements discussed earlier.

a) The renal function must be adequate for the excretion of excess amount of crystallizable substances. The excess excretion is the result of some defect in renal tubular function (e.g. cystinuria).

b) The ability of the kidney to excrete an excessive amount of a given substances at a pH that allows precipitation of that substance.

c) The urine must have a complete or relative absence of a number of inhibitors of crystallization.

d) The crystal mass must reside in the urinary system for a time sufficient to allow growth or aggregation of the crystal mass to a size large enough to obstruct the urinary passage. The stasis may have an important part in the genesis of urinary calculi.

Inhibitors of crystallization

Elliot (1983) studied calcium oxalate solubility in urine and pointed out that the solubility of calcium oxalate in urine is not greatly
different in stone patients from that in normal persons. On the other hand, Robertson and Peacock (1972) have shown that calcium stone formers tend to excrete considerably more oxalate and calcium than do normal persons. But they also showed moderate overlap in the degree of saturation between normal and stone forming groups. Many cystinurics do not form calculi. Therefore, inspite of the fact that these people have an excessive amount of cystine in their urine, for some reason, they do not develop the process of crystallization. Many investigators discussed the role of crystallization inhibitors in stone formers and normal individuals. Inhibitors may be classified as organic or inorganic.

**Organic inhibitors**

The organic inhibitor is the peptide inhibitor first described by Howard et al (1967) and studied extensively by Robertson et al (1969) and Smith et al (1969). This low molecular weight peptide enables the urine to hold in solution considerably greater amount of calcium than is possible when it is absent. Later Barker et al (1974) indicated that most inhibition that they found in urine could be accounted for by the polyelectrolyte interactivity of the multiple ions of urine. More recently, higher molecular weight glycoproteins have been shown to inhibit calcium oxalate crystallization (Drach et al, 1983 and White et al, 1983).
Nakagawa and associates (1987) described an agent, nephrocalcin, which inhibits growth of calcium oxalate crystals and may be deficient in those who form stones.

Other organic inhibitors may be present. Matrix (uromucoid) may have the ability to inhibit the formation of urinary calculi. The particular types of matrix may be more active in coating the surface of crystals. This may be particularly true when crystals reach a certain size. Matrix coating may inhibit stone formation by producing surface (Zeta potential) charges that prevent further depositing of crystal or that inhibit aggregation.

Other organic substances have some importance in the inhibitory processes of urine (Angel and Resnick, 1989). Amino acids, specifically alanine, may be important in improving the solubility of calcium substances (Elliot and Busebío, 1967 and Chow et al, 1973).

Urinary citrate is found to be decreased in patients with stone disease (Miller et al, 1958; King, 1967; 1971; Elliot, 1973 a; Finlayson, 1974; Williams, 1974 a, b; Welshman and McGeown, 1976). Urea increases the solubility of some components of urine especially uric acid (Porter, 1966) but it does not seem to influence calcium precipitation (Finlayson et al, 1972).

Inorganic inhibitors

The inorganic inhibitors include phosphate especially pyrophosphate (Fleisch and Bisaz, 1964; Drach et al, 1983). The action of phosphate
as a crystal poison of calcification has been known for many years. Simkiss (1964) reviewed the multiple effects that phosphates may have upon calcifying biologic systems and found that orthophosphate do not have a direct effect on urinary stone formation of calcigerous type. In fact, administration of orthophosphates to patients who have a tendency towards phosphate stone can actually increase the rate of stone formation.

Magnesium, a divalent cation tends to increase the solubility of calcium, phosphate and perhaps oxalate (Moore and Gowland, 1975). A high calcium/magnesium ratio has been implicated as one of the causes of calcigerous renal calculi (King, 1967; Oreopoulos et al, 1975).

Some trace elements are reported to have inhibitory actions. Zinc is most frequently mentioned of these substances (Elliot and Eusebio, 1967; Elliot and Ribeino, 1973).

A urinary detergent and urolithiasis

Charlton (1989) gave an idea about the urinary detergent in his review article. This idea was conceived by the correlation of various scientific works described in his review article. He quoted the work of Kohri et al (1987) who showed that thiazides reduced urinary calcium excretion for 3 months but that at 6 and 12 months; the levels reverted to the pretreatment values. In a carefully supervised group of 124 stone formers with idiopathic hypercalciuria studied at
the Institute of Urology in London, Marickar and Rose (1985) found that the urinary calcium was brought into normal range, yet over one-half continued to develop new or larger calculi. It follows that there must be other unidentified factors which are partly responsible for the continued urolithiasis and a possible explanation for this lies in the urinary mucopolysaccharides (colloids). These are also known as glycosaminoglycans and are said to inhibit the crystallization of urinary calcium salts. It is more logical to think of these macromolecules in terms of size and that for a given volume of these substances, the smaller the aggregates, the greater the surface area available for the adsorption of crystalloids. It is through this mechanism that there exists a urinary detergent activity.

Urinary macromolecules are constituents of normal urine (about 470 mg daily; King et al, 1958). It has been shown that the urinary macromolecules are substrates of plasmin (the active fibrinolytic enzyme) and this results in the larger macromolecules being disaggregated into smaller particles which result in a relative increase in the surface area (Charlton, 1969). The colloids are negatively charged and adsorb on to their surfaces, cations such as calcium. The greater the subdivision of the macromolecules, the greater the surface area available for the absorption of calcium. This explains the phenomenon of the metastable zone present in normal urine; whereby the solubility product of calcium and oxalate are exceeded, yet nucleation and crystallization do not occur, since the
chelation of these inorganic ions avoids supersaturation and concrement formation. It has been shown that in stone formers, all of the urinary macromolecules are larger than 50,000 daltons (Drach et al, 1982), whereas, in the normal individual, two-thirds of the total macromolecules are smaller than 30,000 daltons. The presence of larger colloids in urine suggests decrease in urinary fibrinolytic activity. Charlton and Osmond (1986) found two-thirds of 188 patients withcalculi disease in whom the urinary fibrinolytic activity decreased as compared with control.

Boyce and King (1959) stated that the mucosubstances were an essential ingredient in the genesis of stone formation and formed the skeletal framework on which the crystalloids adhered.

In the case of the vascular system, thrombi and fibrinous clots are digested by the proteolytic enzyme plasmin. In the urinary tract, blood clots are dispersed by urinary fibrinolytic activity and it seems responsible for attempting to prevent the formation of potential obstructing agent such as stones.

A decrease in the production of plasminogen activator has been noted when the circulating triglycerides (Glas-Greenwalt et al, 1984) and cholesterol levels are raised; demonstrating that the activity and function of the vascular endothelial cells are modified by the blood constituents flowing over them. The change in dietary pattern to high protein and fat intake in blacks reflected in the increasing incidence
of ischemic heart disease which may also be responsible for the observed changes in renal stones. The Bantu living in South Africa are remarkably free from cardiovascular disease and the blood fibrinolytic activity of the male Bantu is greater than that of his Caucasian counterpart (Walker, 1961). When the former becomes westernised, the prevalence of heart disease rises with relative decrease in circulatory fibrinolytic activity (Meade et al, 1978). Similarly, renal stone disease is virtually unknown in the Bantu living in South Africa (Vermooten, 1941). When member of the race migrates to the United States, their successors (the American negro) form renal stones as frequently as the rest of the American population (Dadson and Clark, 1946). Since it is not possible for a genetic mutation to become established in a large cohort within a few generations, these changes must be attributable to altered environment and/or diet.

The author finally suggested that to prevent further stone formation, raise the lowered urinary fibrinolytic activity to its normal effective detergent level by using an appropriate fibrinolytic enhancer such as an anabolic steroid (Walker and Davidson, 1978) or a biguanide (Hocking et al, 1967).

Relationship between time allowed for crystal growth and size of passages

Normal urine is not a static solution. It flows continuously and new solutes are continuously excreted. Therefore, crystals may form best at
the point of greatest supersaturation of urine, usually the renal papillae (Vermenlen and Lyon, 1968; Jorden et al, 1978 and Hantman et al, 1980). As soon as these crystals form, they can flow within 3 to 5 minutes into renal pelvis, down the ureter and into the bladder, where they remain for a period of approximately 3 to 6 hours. Transit time of urine from the normal kidney to the normal bladder is estimated to be from 5 to 10 minutes.

The lumen of the nephron is smallest at the level of collecting duct, where its diameter is 50 to 200 micrometers. Anatomically, this portion occurs in the renal papillae (Finlayson, 1974). If the crystal does not have time to grow large enough to obstruct any renal tubule, it then passes into ureter, where the minimum diameter that can cause obstruction within 10 minutes is approximately 2 mm. (This statement is a clinical observation based on the fact that the majority of urinary calculi that cause symptoms are greater than 2 mm. in diameter (Lohtonen, 1973; Sutor and Wooley, 1975 and many others). After the crystal has reached the bladder, it may still grow and may achieve a size that exceeds 6 mm. in diameter, such a crystal could still be voided through the urethra without difficulty.

To summarize this theory, urinary crystals form in the small lumen of the renal tubule and progress through the renal pelvis to the ureter, into the bladder and out the urethra. Even if crystals grow as they progress through the urinary tract, they are able to pass because the conduits become progressively larger towards the outside.
For a urolith to achieve adequate size within brief period of time in transit from kidney to bladder, the supersaturation of urine is so great that the crystal will grow very rapidly into a structure that can pass no further through the system. To try to avoid this problem, the urinary tract is anatomically constructed like an inverted cone. The diameter is smallest in the renal tubule then become progressively larger. But if a particular crystal becomes stuck, growth can continue for long period of time whenever urinary supersaturation or aggregation of new crystals occurs. If somehow the crystal mass becomes lodged in the renal papilla or tubule it is no longer able to move through the system. It resides at that point and continues to grow in supersaturated urine. Intermittent layered growth of stones has been reviewed by Lonsdale (1968a). If the crystal breaks off or breaks away from the renal papilla when it is smaller than the size required to obstruct the ureter, it will pass through the system without causing symptoms. But if it attains a diameter of greater than approximately 2 mm., it may pass into ureter and create urinary obstruction. Then it becomes a symptomatic urinary calculus.

A calculus of 2 to 3 mm. may pass through the ureter and into the bladder with relatively few symptoms. But let us suppose it enters a bladder in which there is obstruction of the urinary outlet (this occurs especially often in males, bladder calculi are extremely rare in females). If because of prostate obstruction or a narrow bladder neck,
the stone cannot enter the urethra but remains in the base of the bladder or in a diverticulum, it can then continue to grow whenever the urine is supersaturated with the substances that created the stone. Such stones may achieve enormous size, the largest reported weighing over 1 kg. (Becher et al, 1978).