5

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NEPHROLITHIASIS

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CHURCHILL LIVINGSTONE

Nephrolithiasis

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Preface: Four Questions

After a serious falling out with his father-in-law, David, who was to do so many things well, showed that he had a gift for research. Fleeing from Saul, he and his small band of warriors paused to aid Keilah, a city besieged by Philistines, and after he had rescued it, he settled down within its walls, for a brief rest.[1] Naturally, word got out about his whereabouts, and rumors arose that Saul was on his way, with 10,000 men, to get him. David needed to know if the rumors were true and if he had to get back on the road; he couldn't afford to find out by waiting until Saul might arrive, so he instituted a research effort.

Now at that time some people could bypass all of the cumbersome methods we use and talk directly to God; no research grant was needed, no laboratory space, nothing but a good question. But a good question was important. The God of David, Saul and Samuel was impatient, temperamental, and burdened by many concerns and was known to respond very indirectly on occasion, so the question had to be important, clearly stated, and easily answered by "yes" or "no." David wasted no time on preliminaries. He called to God[2] and asked: "Will Saul come down, as thy servant hast heard? O Lord God of Israel, I beseech thee, tell thy servant." And the Lord said, "He will come down." He then asked the perfect, and not obvious, next one: "Will the men of Keilah deliver me and my men into the hand of Saul?" And the Lord said: "They will deliver thee up." David eventually did well in his career, and first-class research was a critical steppingstone to his getting a serious administrative position.

If we had the ear of the Lord, what should we ask about kidney stones? I maintain that it would be all right to ask about them, even though they are not a deadly disease, nor, like the fate of David, part of a holy story, because many suffer and we physicians have a right to inquire on their behalf. But we should try to emulate the clarity of David before we frame our questions. David didn't say so, but he probably thought his questions through and assigned priorities before beginning his experiment, and I believe he followed only a few principles, which apply well to stones. First, the research concerned only immediate survival, not long-term insight, because of the nature of the problem. Second linked to immediacy, his questions about mechanisms were limited to those that might influence treatment: e.g., will Saul come down? Will they deliver me up? He could have tried to ask why Saul was so vengeful, hoping that fundamental insights into pathogenesis would lead to the most effective remedies for his problems, but he reasoned that the problem itself, i.e.,

Saul, was not necessarily going to persist indefinitely and that effective short-term solutions were good enough. He probably also decided that even if he knew why Saul was angry the knowledge would not lead to any improved method for curing his present dilemma.

All of this could be said about stones. They probably do illustrate the breakdown of mechanisms that normally control and modulate the solubility of alkaline earth salts in urine, but the problem of interest in clinical research is their prevention and dissolution. We have very promising remedies at hand, as David did. We suspect that calcium stones were not very common a century ago, and therefore may become uncommon again, as our diets or lifestyles or environment change; since they may not persist indefinitely, effective short-term remedies may be good enough. Furthermore, we have no reason to believe that deeper insights into pathogenesis will necessarily disclose improved methods of treatment.

The most common putative cause of calcium stones, idiopathic hypercalciuria, illustrates the analogy particularly well. Thiazide diuretic agents lower urine calcium in people with hypercalciuria, and seem to prevent recurrent stones. But some people, perhaps a majority, have hypercalciuria because of intestinal calcium overabsorption that persists during thiazide treatment (see Ch. 5). In other words, the drug may close the drain but not the faucet, and calcium may accumulate in the body. Because of this, doctors may have to distinguish "absorptive" hypercalciuria, which may not be best treated with thiazide, from the other form, which is due to defective renal calcium reabsorption and is ideally treated with thiazide. It is difficult to do this, and possibly uncertain, as well, and it will be an expensive and confusing experience in practice. Above all, it may be unnecessary. Thiazide may not be unsafe in absorptive hypercalciuria. I would ask, if I could: "If I give a thiazide diuretic agent to someone with absorptive hypercalciuria, and he takes it, even for years, will he be harmed?"

It is also true that at least 20 percent of people who form calcium stones have no obvious metabolic disorder at all (see Ch. 8). Seemingly, they cannot eliminate even normal amounts of calcium in their urine without some of it forming crystals with oxalate and phosphate. If these people excreted less calcium they probably would form fewer stones, because if they excreted no calcium they certainly would form no stones and the only uncertainty is whether thiazide lowers urine calcium enough. Yendt[3] and I[4] both have found that thiazide seems to protect these patients from stones, but neither of us has studied the issue very well. I would gladly use up one of my questions on the matter and ask: "If I give a thiazide diuretic to someone who forms stones yet is not hypercalciuric, nor abnormal in any discernible way, and he takes it for years, will his stones come back?"

At least an equal percentage of stoneformers is hyperuricosuric but otherwise normal, and if one detects their hyperuricosuria and treats it their stones do not normally recur (see Ch. 6). But it is not easy to do this. Urine uric acid can be measured reliably only by using uricase; widely available automated

methods, designed for serum, may give misleadingly high values. Allopurinol causes drug allergies in some people, usually benign but occasionally very serious. What if thiazide could do as well by reducing urine calcium and therefore supersaturation with respect to calcium oxalate? Unselective treatment is less interesting than what we now do but would be more widely used, and the chance for error due to laboratory problems would be reduced. Suppose I asked: "If I give a thiazide diuretic agent to someone who forms stones and is hyperuricosuric but otherwise normal, and he takes it for years, will his stones come back?"

I think David would not have been altogether dissatisfied with my questions. If all three were answered by "no," as they probably would be, we could dispense with most of the diagnostic effort in nephrolithiasis. We would look for primary hyperparathyroidism, renal tubular acidosis, intestinal diseases that cause hyperoxaluria or acidic urines, and for uric acid, cystine and struvite stones (see Ch. 1, 4, 7, 9, 10, and 11), which require selective treatment, and for the 80 percent of patients in whom none of these were present prescribe a thiazide diuretic agent. We proceed in an analogous way for hypertension, about whose pathogenesis we are surprisingly ignorant, and by such prescribing save many lives. Why not consider the same tactic for stones?

One question remains to be put, for I have reserved four for this occasion and have used up only three. There is little doubt that the fourth should be used to substantiate a hidden assumption about stone disease that makes it, in my mind at least, a threat more like that of Saul to David than like idolatry to monotheism: its transience. Some people who have studied the matter believe that kidney stones were rare no more than one or two centuries ago, and may come and go, in long cycles.[5] Isn't this a critical issue? Renal stones are not very interesting in themselves; understanding them, even completely, probably will not enrich the intellectual life of mankind. They are important only because they occur and we wish they would not; if stones are merely a transient plague, using the simplest means to suppress them probably is the best tactic we physicians can pursue. We can reserve our deeper inquiries for more enduring and more beautiful questions. Furthermore, if transient, they must arise more because of our habits and diets than our essential selves, and solutions should, perhaps, be sought in such homely matters as nutrition rather than divalent mineral metabolism. So I would ask if I could: "Were kidney stones really rare, two hundred years ago, not only here but throughout the world?" I suspect they were.

Whether or not David would have approved of my research proposal really matters to me because he was the very model of a clinical investigator. His questions were pertinent to the solution of the most important problems that affected people in his time, and he sought answers to them by going as directly as he could to the proper source of information. Do we usually do as well as he? In stone research, I think not. Most of us, probably, would have become entangled in the complexities of why Saul was vengeful, and not have focussed on the really important issue of how to prevent a catastrophe even without

understanding why it was going to occur. Clinical investigators need to be like David if they want to protect people from trouble; they must devote themselves to action, not merely to inquiry for its own sake. So I propose a test we all can use to tell if our questions are up to his standards. I will call it David's test, in honor of a man who, had he lived in our age and become a physician, would have given the best presidential address the Society for Clinical Investigation has ever heard. The test resides in a bit of doggerel verse, to make it easier to remember:

If you would like to do research
And your career enhance, sir;
Only ask questions that God should be asked,
And ones that God can answer.

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Contents

1

Clinical stone disease

FREDRIC L. COE

The subsequent chapters in this book each concern aspects of stone disease that are controversial or could benefit from a fresh presentation; this one, however, has an integrative purpose. It is designed to introduce the problem of stone disease in its clinical perspective and to communicate the gist of this particularly technical field to the physician. It is deliberately incomplete, as it leaves the details of pathogenesis and treatment to be found in the individual chapters, but it makes clear the underlying framework of our current understanding of stone disease and the importance of the specific topics that follow it. References are provided only for the few topics for which specific references are not given in subsequent chapters.

TYPES OF STONES AND THEIR CAUSES

Renal stones are composed of calcium salts, uric acid, cystine, or struvite ($MgNH_4PO_4$) (Table 1.1). Each type of stone has its own group of causes, for the most part, and presents special problems of treatment. However, all four types share in common a pathogenesis that is based upon excessive supersaturation of the urine with a poorly soluble material, perhaps modified, at least in the case of calcium stones, by the presence or absence of crystallization inhibitors and sources of seed crystals. In addition, as Mandel (Ch. 3) makes clear, stones are often admixtures of crystals, for reasons that are not fully clear.

Quantitative aspects of supersaturation and its measurement in simple solutions and urine are very complex, technically and conceptually (Ch. 2), but the intuitive notion is not. Any solid phase, for example calcium oxalate monohydrate, the most common form of calcium oxalate found in stones, will dissolve

Table 1.1 Types of stones and their general causes

Stone type and general causes	Percent of all stones[a]
Calcium (oxalate or phosphate)	70.6[b]
Hypercalciuria	
Hyperuricosuria	
Hyperoxaluria	
High urine pH	
Low urine volume	
Uric acid stones	5.4
Low urine pH	
Hyperuricosuria	
Low urine volume	
Cystine stones	3.5
Cystinuria	
Struvite stones	21.5
Urinary infection with bacteria that possess urease and cause the combination of high pH and high NH_4^+ concentration	

[a] Taken from reports of 1,870 stones, reported from four series (Nordin & Hodgkinson, 1962; Lagergren, 1956; Melick & Henneman, 1958; Prien, 1949).

[b] 63.2% are calcium oxalate, alone (25.4%) or admixed with calcium phosphate (37.8%).

to some extent in water. As it dissolves, the concentrations of calcium and oxalate ions in the water rise until a critical point is reached, at which the product of the calcium and oxalate ions is sufficient to produce growth of the solid phase at the same rate that the solid phase can dissolve; thereafter, no decrease in the mass of calcium oxalate monohydrate occurs. The ion product at this critical equilibrium point is called the equilibrium solubility product. Supersaturation means that the ion product in solution exceeds the solubility product, and undersaturation means the ion product is below it. By definition, a solution will support the growth of any solid phase with which it is supersaturated until the equilibrium solubility product is reattained; likewise, crystals will dissolve in an undersaturated solution.

Although crystals will grow in a supersaturated solution, such a solution need not produce new solid phase de novo even if the ion product is appreciably above the solubility product for a given solid phase. There is an ion product, called the formation product characteristic for a given solution and temperature, at which solid phase will begin to appear; the range of supersaturation between the solubility and formation products is called the metastable zone. As an example, the metastable zone for calcium oxalate monohydrate in water at 37° C extends from the solubility product to an activity product that is 8 times the solubility product. The other stone-forming substances each have individual and generally different ranges of metastability.

In the metastable zone, the presence of heterogeneous nuclei can come to play a critical role in the production of a solid phase. For example, if certain kinds of crystals other than calcium oxalate are added to a metastably supersaturated calcium oxalate solution, calcium oxalate crystals may begin to grow

on its surface, as though crystals of calcium oxalate itself were present, and a solid phase can be produced even though the formation product is never achieved. The ability of one crystal to act as a seed nucleus for another depends in large measure upon the similarity of their structures. In the case of the stone-forming crystals, present data on structure are not yet complete (see Ch. 3), but examples of heterogeneous nucleation are well known. A particularly good example is nucleation of calcium oxalate monohydrate by seeds of sodium hydrogen urate or of uric acid. Thus far, heterogeneous nucleation has been invoked to explain only one form of stone disease, calcium oxalate stones in hyperuricosuric patients (Ch. 6); even in this case, it has not been established securely.

Measurement and prediction of saturation are complicated in a polyelectrolyte solution, like urine, by the fact that ions, such as calcium, oxalate, phosphate, and urate each react and form complexes not with any one specific ion, but with many ions at the same time. For example, in urine, calcium forms soluble complexes with phosphate and with oxalate; one-half of urine calcium may react with citrate ions. As a result of this sharing or competition of ligands for one another, the effective ion product available to promote calcium oxalate crystal formation, which is the product of the chemical activities of the calcium and oxalate ions, is generally much less than the product of the total concentrations of the two substances. In order to calculate saturation with respect to any one solid phase, all of the sharing of the ions that enter into that phase must be accounted for so that the fractions of the ions available for creation of the particular solid phase can be calculated. As an alternative, one can assess the ability of the solution to cause growth or dissolution of a given solid phase and use the extent of either as an index of saturation.

Although not as well studied as saturation, inhibitors of the growth of calcium oxalate and calcium phosphate crystals are present in urine and may be an important defense against stone formation (see Ch. 2). The best characterized of these is inorganic pyrophosphate, which is probably more important for calcium phosphate than calcium oxalate crystals. The others, which are macromolecules, are glycoproteins or, perhaps, polysaccharides and are most important for calcium oxalate crystals. These inhibitors slow crystal growth and raise the degree of supersaturation required to initiate the formation of solid phase; in other words, they widen the metastable zone. As an example, the calcium oxalate monohydrate formation product in normal urine is about 12 times the solubility product, compared to 8 times the solubility product in a simple salt solution.

Despite the genuine difficulties of its measurement and the modulating effects of inhibitors and heterogeneous nuclei, excessive supersaturation has been documented as a feature of urine from stone formers (Ch. 2) and probably is the central factor in stone genesis. Furthermore, the reasons for excessive supersaturation are usually excessive excretion of an insoluble material, an abnormal urine pH (Table 1.1), or low urine volume. Except for a few entries, the link between the causal factors shown in Table 1.1 and the production of

stones is clear. Hyperuricosuria appears to cause calcium oxalate stones (Ch. 6) by promoting the formation of a solid phase of monosodium urate or uric acid that either provides seed nuclei for calcium oxalate to grow upon (see Ch. 3) or adsorbs inhibitors of calcium oxalate crystal growth (Ch. 2) and thereby deprives the urine of what appears to be an important defense against stone formation. High urine pH, from diet or antacids, raises the urine concentration of $HPO_4^=$ and $PO_4^{\equiv}$, and it is these 2 forms of phosphate that combine with calcium to form brushite ($CaHPO_4$) or apatite crystals. Low urine pH predisposes to uric acid stones by increasing the concentration in urine of undissociated uric acid (pK 5.47) at the expense of urate (Ch. 9). Finally, by releasing NH_3 from urea, bacteria that possess urease raise the pH of the urine and simultaneously increase the concentration of NH_4+ so that struvite crystals can form (Ch. 11). Thus far, there are no fully documented instances in which reduced crystal growth inhibitors have been the putative cause of stones, and, except for hyperuricosuric calcium oxalate nephrolithiasis, none in which heterogeneous nucleation has been suspected to be causal.

In the case of calcium oxalate stones, which are the overwhelming majority, the individual causes of hypercalciuria, hyperuricosuria, hyperoxaluria, elevated urine pH, low urine volume, and low urine citrate comprise the list of specific diseases that are thought to be responsible for stone disease (Table 1.2) and whose detection and treatment are the main goals of the clinician. Although Table 1.2 is by no means an exhaustive one, from a practical point of view it is sufficient. Idiopathic hypercalciuria alone accounts for over 30 percent of cases, and hyperuricosuria 15 percent more. The exact frequency of low urine volume as a main or sole cause of stones is unknown, at least in the temperate zones, but probably is low, even though low volumes may commonly play a contributory role. Primary hyperparathyroidism accounts for between 5 and 7 percent of calcium stones, and all of the other causes are even less common. If one considers Table 1.2 in its entirety, very few patients will be less than fully evaluated.

NATURAL HISTORY OF STONE DISEASE

The direct clinical consequences of stones are urinary tract obstruction, pain, and bleeding. Infection often accompanies stones as a cause of the struvite variety and a complication of the obstruction, surgery, and urologic instrumentation that all stones may engender. Loss of kidney function occurs mainly because of damage to kidney tissue from infection or chronic obstruction, scarring from pyelolithotomy, or deliberate surgical removal of kidney tissue that has been badly damaged by prior obstruction, infection or surgical accident, or sacrificed to control bleeding during surgery for stone removal.

Obstruction is the primary problem caused by stones, and in its most typical form it occurs acutely, as a stone attempts to traverse the ureter. All but struvite stones seem to form on the surfaces of the renal papillae, and as long as they remain in place they cause, at most, hematuria, which usually is asymp-

Table 1.2 Specific causes of calcium stones

Oversaturation
- Hypercalciuria
  - Idiopathic
  - Primary hyperparathyroidism
  - Renal tubular acidosis
  - Immobilization
  - Paget's disease
  - Sarcoid
  - Hyperthyroidism
  - Vitamin D and calcium excess
  - Cushing's disease
- Hyperoxaluria
  - Ileitis
  - Jejuno-ileal bypass
  - Ileal resection
  - Dietary oxalate excess?
- Low urine volume
  - Habitual
  - Cultural
  - Ileostomy
  - Colostomy
  - Diarrheic states
  - Hot/dry environment
- Elevated urine pH
  - Renal tubular acidosis
  - Alkali excess
- Low urine citrate
  - Renal tubular acidosis
  - Intestinal disease

Heterogeneous nucleation
- ?Hyperuricosuria
  - Dietary
  - Uric acid overproduction

Reduced inhibitors
- ?Hyperuricosuria

tomatic. However, when they break loose and are carried into the ureter, they can cause sudden, severe pain, due to acute obstruction, hematuria, and partial or complete cessation of urine flow.

The pain of stone passage, called renal colic, appears abruptly in the flank, loin, groin, pelvis, or even the testicle or vulva, on one side. Bretland (1972) has provided a very fine review of this symptom. Flank or loin pain always reflects an upper ureteral obstruction; pain that begins in the flank but then migrates downward generally reflects a stone that has come to lodge in the last one-third of the ureter. A stone at the ureterovesical junction causes urinary urgency, frequency, and dysuria and is easily mistaken for cystitis or prostatitis. The character of the pain from ureteral obstruction is a steady ache or tearing sensation that is localized on the body surface only poorly and mainly