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RECENT ADVANCES IN KNOWLEDGE  
RELATING TO THE FORMATION,  
RECOGNITION AND TREATMENT OF  
KIDNEY CALCULI\*

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I APPRECIATED tremendously your invitation to be present today, as well as your suggestion that the title of my remarks be, "Recent Advances in Knowledge Relating to the Formation, Recognition and Treatment of Kidney Calculi." It makes me think that perhaps I have had some influence in the elucidation of the etiology of renal stone. Unfortunately, the past few years have not allowed of further efforts in the research, and I am afraid we will have to spend a little time in reviewing the subject as studied by others, and balance their views against the theories and ideas propounded by me some years ago. As Hugh Cabot said before a group of urologists, "while cancer is our greatest problem, it belongs to all medicine, but kidney calculus is essentially a urological problem, and it belongs especially to urologists to solve."

Perhaps you will be interested in the way our work got started. Back in 1926 the American Association of Genito-Urinary Surgeons

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was meeting at Hot Springs, Va., and not being a golfer, I cornered your E. L. Keyes with some relevant questions and ideas, and it was his interested response that started the ball rolling. As the answers were not clear-cut, he suggested that we get pencil and paper and draw up specifications of what we knew and what we would like to know. Several other non-golfers joined us, and on the veranda of the hotel we gathered around a table and put down what was actually known. In so doing we found many things that were only roughly surmised, and these we proceeded to tear limb from limb. We ended with a clear estimation of what was trustworthy and what we actually did have to know and have to prove. Take, for instance, this statement by Howard A. Kelly, which is all that he could put down as fact in 1922 in regard to the etiology of renal stone formation: "The essential conditions which lead to stone formation in the kidney are imperfectly understood. Race, age, sex, habits, diet; none of them seems to play a great part." He then reports 30 cases, giving their stone characteristics, and describes each; the analysis of single, of multiple, of unilateral, of bilateral, of right-sided and of left-sided stones, and was "astonished to observe how closely his results agreed with those of other observers." Pages are devoted to age, to sex, to race, and to geographical locality, again with surprise at how closely his figures compare with others' reports, and he concludes with this statement under a heading, "Determining Factors": "The questions as to what determines the formation of stones in the kidney cannot be answered at the present time." (1922) Hinman (1935) says: "No more is known of what starts the mechanism of formation of stone than of the mechanism itself." A. J. Scholl (1936) says: "The etiology of urolithiasis is far from clear." And Hugh Young (1926): "The formation of stones in the urinary tract has long been a problem of the greatest interest and difficulty, both to pathologists and urologists. . . . while modern diagnostic methods have greatly improved the treatment. . . . yet the inability from which we still suffer, surely to prevent recurrences, makes the therapy of the disease unsatisfactory." And Keyes, in his *Urology* of 1917, frankly states, "The causes of stone formation are extremely obscure."

So in 1926, at the Hot Springs, we all placed our cards on the table face up, and the distressing ignorance was certainly stimulating. The question was asked, how does a stone start?; and all agreed: as a tiny crystal or a tiny cluster of crystals. But why is it not immediately

washed out of the pelvis? Perhaps some are; but some are not. Why? Where do they lodge, and why there? This constituted *problem number one*. The pelvic wall, simple and not undergoing any frequent pathologic change, was quickly ruled out; but keeping under suspicion the renal papilla. The *second problem* was the realization that stone may be composed of at least eight different salts, and the fact that they occur in urine that at one time is characteristically alkaline, and at another time highly acid, with all steps between. These facts do not help, except to exclude two often considered etiological factors, infection and stasis. *Problem number three* was the time factor, how long does a calculus take to grow to recognizable size? It is certain that a lot of them are found incidentally, and not until they start to pass, and cause ureteral blockage, do *clinically recognizable* symptoms develop. I watched one such over a period of four and one-half years, before an aeroplane trip caused dislodgement, followed by ureteral and kidney colic and, in seventy-two hours, the stone's expulsion! Diet is a frequent cause among theorists, but it falls far short of answering any of our problems, except perhaps that it plays a part in the stone's composition and which salt may predominate: this became *problem number four*. Why stone in one side at a time? There is no predominance, and while bilateral calculi are not unknown, bilaterality is rare in the majority of early cases. What causes the selection of one side, while the other remains in health, became *problem number five*.

And so we discussed and wrote down our ignorance. No one of the five, or more, problems seemed insurmountable; yet our knowledge seemed to have taken off on any one of the various tangents, and investigators seemed in each case to have spent great effort to prove a pet theory in the face of self-evident facts to the contrary. It was illuminating to see how such a group could pool the resources of medical knowledge, and how easy it was to write the specifications of what we really wanted a research to bring out and to prove.

I got off to a poor start with the idea that we wanted to create lesions and then sit back and watch stones grow, but when insurmountable difficulties arose, and stones did not grow, I awoke to perhaps the most salient fact, that it was not given to us to imitate nature and make it fit into our preconceived ideas. It was then that we chose simply to study nature and to study what occurred, and I was glad to have recourse to a large amount of autopsy material. To be sure, we

changed some of our previously held ideas, such as the prescribed methods of examining kidneys, and we opened the pelvis first, searching for pathologic states. It bore fruit. We entered the field convinced by reasoning that we should find precalculus lesions and, secondly, that we should look and expect to find such a lesion on the renal papilla. That is a true precalculus lesion. Perhaps this is the one true fact that we have uncovered, and it is my sincere regret that stress of work and present shortages of personnel have temporarily stopped our further search as to cause and perhaps prevention.

*Etiology:* Now it has been said, when evidence appears to be confusing, that it is wise to make simple decisions, and that wise decisions must harmonize with the fundamental truths of human nature. Certain it is that the work on the etiology of stone has produced a very confused atmosphere; some of which bears little scientific fact, while some is entirely too ultra-scientific to be of clinical value. As we approach the problem, let us first make some simple decisions. First, let us restrict ourselves to the problem of renal calculus only, omitting all reference to ureteral and vesical calculus; second, let us restrict ourselves to a study of the early, the small, the simple, uncomplicated renal calculus. This I believe a wise decision, in order to avoid the confusing evidence and the conflicting ideas when more than one pathologic state is existent. This brings us directly to the study of what is known as the "primary renal calculus," and sets aside the "secondary calculi" where other possible conditions may have etiologic bearings.

Now may I make a few statements which I believe are axiomatic statements that are again wise decisions and do not bear refutation. The first negates what I have just said, for except as it is made to apply to the clinical picture alone, there is no such thing as a primary renal calculus, there is no such thing as "calculus disease," all books to the contrary, except as a clinical entity, there is no such clinical entity until a calculus attempts to pass and causes urinary stasis and renal colic, and I would be so bold as to say that near to 10 per cent, nay, even 15 per cent, of those here present in this room have today, now, the precursors that may later cause stone to develop in a kidney. I put it this way for I am most anxious to bring to your attention a second axiomatic statement, that renal calculus is, in the final analysis, and has to be, only a symptom; a symptom that takes its origin from some precursory pathology, and it is this precursory pathology to

which we must direct our attention when we wish to seek the real etiological reason in any given case.

Two additional axiomatic statements must be made to clear our picture further: The first is that these complicated crystalline calculi, while greatly differing in their chemical structure, the one from the next, are nevertheless composed under a single chemico-physical law governing all crystallization and are, without exception, composed of salts common to the urine of all mankind, with the rare and few exceptions, cystine and xanthin, in which cases they are recognized as the common and expected urinary products in those especial patients. The second statement worthy of comment and accentuation is the time-consuming interval during which growth of a calculus is gained. An interval frequently of months and of years is required for the slow crystallization and growth of a calculus, but most important of all is the recognition that this interval is one devoid of those clinical symptoms which we are most likely to attribute to the existence of a renal calculus. We must disassociate in our long-trained minds the clinical picture that springs into existence when those two words, renal calculus, are used, and then bring forward the pathologist's impersonal viewpoint when we start to search into the early stages of calculogenesis, for these early stages are themselves as impersonal and as non-clinical as the origin, the growth and the existence of a phlebolith.

And finally, I wish to make the most positive axiomatic statement of all, one on which I feel the most emphatic, and one to which we must turn and must understand, if the science of reason and logic is to prevail, and the problem of the etiology of primary renal calculus is to be solved. This statement is that there has to be a precalculis renal lesion, an initiating lesion, a true pathologic condition existing in the kidney pelvis before the first microscopic crystal of a future calculus is laid down upon it as the necessary and essential nidus. Please grasp firmly upon the statement, a calculus has to be but the symptom of a pre-existent pathologic lesion!

So with these basic, truly axiomatic facts at hand, let us look at our problem and analyze what we can from our knowledge of today. Let us forget, for the moment, the picture in our clinically trained minds and our roentgenologically trained eyes and go back-stage, away from the actor who has been strutting these centuries before the foot-lights, and try to see and reason out what "makes the thing work."

That then will be the etiology.

I do not want to confuse the picture. I truly want to simplify it, even if I open myself, in the discussion, to heinous errors.

Let us look at the thoughtful and very acceptable theories that have been presented and well defended as the possible cause of renal calculus, and let us try to fit them into our need for a pre-calculus lesion and nidus:

*Hyperexcretion:* Probably the largest single factor that can be held responsible is the condition in which the kidney is putting out a urine overloaded with a single excretory salt. The simplest example is the hereditary cystinuric; right after him comes the patient suffering from hyperparathyroidism and eliminating hypercalcinuria; and third comes the experimental animal overfed with oxamid and excreting a hyperoxaluria. There is no essential difference between these three. The cystinuric is our perfect experimental animal, and from him we should get valuable evidence. In order to prove one of our axiomatic statements, let me ask, why do only 2.7 per cent (Hinman says 3 to 5 per cent) of the recognized cystinurics develop stone, and why does he first form a stone in only one kidney and in only one calyx of that kidney? Do we need more to make us think that there must be a reason at that point, that there must be a precalculus lesion, yes, a *precalculus* lesion? The initiating lesion! And from this I believe we are on perfectly safe ground to reason by analogy into and through the hyperparathyroid and oxamid groups, noting in passing that each group entails the same etiological and pathological sequences, but each working with a different salt. The first forms a cystine stone, the second forms a calcium phosphate stone, and the third forms an oxalate stone.

Do bear with me. There are a lot of complicating factors and unexplained observations. Let me give you an example. We had a lad of eleven years, an hereditary cystinuric, with a large single stone in his right kidney which was surgically removed and a nephrostomy drainage placed. Apparently it was a perfect differentiating state, for his nephrostomy drainage equalled his left kidney's voided urine. Dr. Andrews of the Department of Physiological Chemistry was interested, and for twelve days we continued the separate collection of each kidney's daily excretion, running as high as 480, 940 and 1050 cc. from the operated side alone. Imagine our surprise when it was observed that the unoperated left kidney continued to put out a cystinuric urine, and the oper-

ated right kidney drainage (this the kidney which had made a cystine stone) was totally free of any cystine! That the observation was perfectly balanced and repeatedly proven I need hardly say (see *J. Urol.*, 37: May, 1937, p. 655). Other excretory products were equally eliminated, but cystine was totally absent from the operated side. The fistula was allowed to heal and the boy was kept under repeated observations, and seven months later a cystoscopic differential catheterization proved that both kidneys were excreting a urine containing an equal and equivalent amount of cystine. We cannot yet explain this anomalous and confusing observation.

But these vagrancies must not be allowed to disturb our study of simple facts, for there has to be a large group of related and, at times, significant factors in our completed study. They are like the artist's gifted brush strokes that paint the background to the portrait, real, necessary, positive strokes, but we must not let them carry our attention away from the essential subject. Such is but one of the vagrancies that has helped to confuse the study in the past, and must be set aside, for the moment, in our effort to simplify the problem and cover the majority of ordinary cases.

Let us pass from the aforementioned studies, the simple, physiologic and hereditary cystinuric, the pathologic and acquired hyperparathyroidism, and the experimental, overdosed oxaluric animal; pass on to another theoretical cause and gaze on it with the same background as the foregoing; i.e., the theory of the role of hypovitaminosis A, which today includes the entire role of dietary causes. Such hypovitaminosis is accompanied by two (really three) urinary changes: (1) a consistent alkaline urine reaction, (2) a disturbance in the normal calcium-phosphorus ratio and a distinct phosphaturia, and (3), if you will, early urinary tract infection. I would like to limit this phase of our subject to the simple chemical disturbance in the urine and place these cases in the group of hyperexcretion, as seen in the cystinuric, the hyperparathyroid and the oxamid-fed animal; but other factors enter, and I wish to use them in the role in which they appear as vagrancies to the composite whole, and as factors in stone's occurrence and growth. I refer to the degenerative changes in the epithelium of the urinary tract under vitamin A deficiency, changes even to desquamation, and to the early spontaneous infection of the highly alkaline urine. Both of these coincidental factors can be recognized as contributory to crystalliza-

tion and, hence, to calculus formation. In fact, Higgins (1935) reported the interesting observation that acidification of the urine by drugs decreased the incidence of stone in animals on vitamin A deficient diets. I believe that the work on hypovitaminosis, and it is practically all animal experimentation, and devoid of human clinical studies or proof, is but another phase of an hyperexcretory state, plus local urinary tract damage, wherein such damage enters to act as the nidus about which the disturbed urine is given a chance to crystallize and form stone.

And now we are left with two further problems to elucidate and to correlate with both fact and theory in the etiology of calculus. The first is the individual who forms pure uric acid (or urate) stone, and the same in regard to the growth of pure oxalate stone; while the second problem is the role of infection.

It is difficult to make the uric acid-urate problem as plain and as simple as the previous cystine story, unless one be allowed to reason by analogy. It appears to be a complete reversal of the hyperparathyroid and the hypovitaminosis problems, as an extremely acid urine is characteristic of these uratic cases, and it is my belief that again a metabolic disturbance, probably in protein metabolism, and perhaps of liver origin, is fundamentally at fault. Certain it is that these patients who continue to pass uric acid stones (I have one who has passed 33 calculi, and another 58) constantly void a urine with a pH of 5.2 or lower, and while they frequently have attacks on first one side and then the other, I have been completely unable to demonstrate, on exhaustive studies in several such, any one thing that suggested correction; and they live happily and they form no more stones as long as the urinary pH is kept between 6.0 and 7.0.

The oxaluric also lacks all explanation as to why he so crystallizes his calculus. What we know is that it is rather characteristically single, is rarely a repeater, is extremely slow-growing and in the kidney is usually small. We know nothing that is associated with the state that bears any possible etiological significance, except that oxaluria is not a rare clinical observation, and the probable relationship to ingestive, digestive and eliminative irregularities, plus the high concentration of oxalates in certain foods.

It is my firm conviction, from the foregoing facts, that an hyperexcretory state, either periodic or constant, rules the chemical type of stone that will form, but truly plays no causative part in deciding where



or when a calculus will appear.

I have attempted to clear the picture of etiology as it may be related to four of the theories advanced, and now we come to the last; i.e., the role of infection. I do not wish to attempt an analysis of the voluminous literature that has developed, but only to point to the failure of this theory to meet the requirements necessary to a factual answer. First, let me refer to the microscopic observations on human kidneys studied in our autopsy series. In 65 of them actual calculi were present, and in 227 cases papillary calcification was observed; but in only 17 out of these 292 could we demonstrate, on microscopic study, actual evidences of infectious reactions to be associated therewith. I mean the observation of organisms, of round cell exudate and of necrosis, the picture of infectious activity as ordinarily understood and observed was absent. Second is the wide variety of organisms as observed by reporters, we having recorded 15 different organisms in 39 clinical cases. And third is the high percentage of reported sterile cases in series which the reporter himself was anxious to prove infectious, a percentage of even one-third of the cases studied. We have regularly cultured the pelvic urine at operation, not depending on catheter culture, and feeling sure, especially in obstructed cases, that with such a foreign body present the occurrence of an active infection would surely heighten and augment any bacterial process above it. We have reported an analysis of seventy-five such cases, selecting only the simple ones and omitting the evident, drastic cases of calculous pyonephrosis of long standing. In thirty-six instances, or 48 per cent, such cultures of pelvic urine were sterile, though urinary obstruction from ureteral blockage by stone was present in practically every one. A very recent case records the point at issue: a twelve-year-old child with a single stone in each side. Our studies showed a pea-sized calculus almost completely blocking the left ureter, with a rapidly developing hydronephrosis behind it; while on the right was a pelvic calculus, four times as large, but without gross obstruction. One might ask which side would be most likely to be infected? There had been no cystoscopy and no ureteral catheterization. I removed the left ureteral calculus, and released a gush of clear urine whose culture was sterile. I then removed the right renal calculus at the same operation, and found a heavy, purulent urine whose culture showed non-hemolytic *Staphylococcus albus*. If our theorizing in regard to the role of infection as a cause of calculus has been willfully dis-

torted by us, don't let us try to distort the truth of facts; for here, in the same patient, at the same time, one side is infected and the other, sterile, with the sterile side suffering the greater insult and damage.

To me these negative evidences speak much louder than the mere finding of an infection in the presence of a stone, especially when we know that such a stone has been relatively long resident in the kidney, and has only recently played an active part in a drastic obstructive uropathy. Perhaps I can stimulate further investigation by being disagreeable and simply saying that local infection does not, or only very rarely can, play any part in primary stone formation, and then hope that some one will promptly jump into the problem and succeed in proving, even to me, how local infection can and does cause primary calculus formation. Watch, please! I'm choosing my words, and do not want to infer "never," for again in creep those vagrancies which all medicine is trained to expect and to accept, but I am sure of my ground in the greater majority. And before dismissing the subject of infection, I want to tell you, again very bluntly, that I believe the products of infection, the toxins of distant infection, of chronic focal infection, of chronic infectious processes, and perhaps of other degenerative processes, do play a very active part in creating renal damage and papillary pathology, which assumes its position as the most important missing link in the origin and growth of a crystalline calculus.

I will show this pathology to you in lantern slides shortly, where I am sure you will be impressed by the clear-cut evidence and be better able to appreciate this simplification of an erstwhile complex problem. I hope you will perhaps even agree with me that, after all, only two essential conditions are necessary, but each necessary, in order that a renal stone may originate: first, a primary tissue damage, and second, a permanent, or transient and oft repeated, hyperexcretory state.

*Treatment:* There is little I can add to the subject of treatment, except to express my own handling of these cases. It has been a pleasure to have lived through the period when nephrolithotomy gradually gave way to pyelolithotomy. The elder surgeons used, almost routinely, to plunge through the renal cortex for a bloody extraction of a calculus, and left further damage with gross mattress suturing to control the active bleeding. The simple exposure of the pelvis, and, if need be, the proper enlargement of the pyelotomy into the parenchyma in cases of large stone, has much to commend it. I imagine this change has followed

the making of earlier diagnoses and, therefore, the removal of smaller calculi. This has been recently brought home to me in reviewing my teaching slides, and finding those of twenty and twenty-five years ago demonstrating conditions we rarely see today, all picturing much grosser surgical conditions. The closure of such an incision (pyelotomy) had best be left to nature, and unless unusually large, no sutures are used and no foreign material introduced, even ties, for I coagulate with electricity all bleeding points. If stitching be necessary, we use 000 and 0000 plain catgut and keep it entirely outside of the urinary passageway.

In ureteral calculus two things stand out: First, the simplicity and ease of ureterolithotomy in the upper two-thirds of the ureter; and I am quite positive and adamant in my preference for surgery as against instrumental efforts in such high ureteral calculi. Second, in the lower third of the ureter the picture changes, and instrumental manipulation is the first choice, but only under quite limited and strict rules for the game. We were joking only a few weeks back about our apparent proficiency in cystoscopic removal of low ureteral stones, and it started an analysis as to why we were so successful that we were listing a stone's *removal* almost as casually as though it were the appendix. We use the Howard corkscrew and the Johnson basket, being sure that each instrument is in perfect condition, especially the latter. We demand hospitalization and operating room surroundings. But probably the most important of all is the routine use of spinal anesthesia. I want the complete anesthesia and the perfect relaxation that it produces, and I believe a fair proportion of our success is due to its consistent use. Too often I feel we mistake analgesia for anesthesia in lots of our work, and in these cases I want the complete relaxation of all muscular activity that spinal anesthesia gives. I strive for that condition delightfully expressed by Jonesco as "abdominal silence" and "postmortem relaxation."

*Prevention:* As we approach a better understanding of the cause of stone, we naturally look for a better ability to control its occurrence. Let me outline briefly what our knowledge allows us to demand today: First, a prompt stone analysis; and we need improvement in this problem. There is rarely a truly pure stone, and when 90 per cent of a stone is of one salt, it should be considered pure for that alone. Recent chemical testing that has been advanced is too refined, perhaps too delicate, for certainly, unless a distinctly laminated calculus is present (and I am dealing principally with the small calculi where such is rare), one

cannot expect acid and alkaline salts to be alternately deposited; yet such a report is quite within reason with a recently published technique. If uric acid is the salt, let me urge a careful metabolic study, looking for the as yet undisclosed secret, and the giving to the patient of citro-carbonate, or a similar drug, to find the dose that will raise the urinary pH to 6.0 and keep it thereabouts. The oxalate stone is likewise a difficult problem, where to me dietary regulation is a poor crutch to depend upon, and where moderate alkalinization may be tried. But I believe that in both of these salts the clearing up of all focal infections and the regular ingestion of at least 2,000 cc. of water daily are paramount. The calcium phosphate stone makers are to be studied to insure a well balanced diet, and are to be especially tested for hyperparathyroidism, and if the latter is positive, or even suggestive, exploration of the neck is urged. The taking of large quantities of water daily is perhaps the surest answer to our question of prevention, for given a dilute urine, there is little likelihood of sufficient concentration for any salt to be deposited as crystals, whether there be a nidus or not.

I believe we have a much better control today than even a decade ago, and probably a much more coöperative group of patients; but there is yet a great deal of work to be done, with, let us hope, a constant clarification of the problem and its complicated pathologic state.

#### CONCLUSIONS

Certain axiomatic statements can now be made in regard to calculogenesis. In this brief paper we have touched upon the five general theories of stone's formation, avitaminosis A, hyperparathyroidism, infection, colloidal imbalance and stasis, and none gives us a truly complete answer. Stone is now considered only a symptom in a very much broadened problem, and the answer is not so simple. We want, and must have, a common denominator for stone's origin, something which will act as a nidus to which the earliest crystal (be it what it may) can be attached; and for this we must go back beyond the occurrence of a visible calculus. As contributory factors we now know, not only that certain metabolic, dietary, infectious and pathologic conditions can produce the renal damage, but that, with such, also must occur the hyperexcretion of certain urinary salts, actually in supersaturation, verging on precipitation; and when these two conditions meet in the renal calyx, crystals are deposited, to grow into a primary renal calculus.