Medical Management of Stone Disease*

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The purpose of this review is to try to take a practical approach toward the management of patients with renal calculous disease. This will be a personal approach; I will, however, try to avoid injecting my prejudices and research interests. I want to show that proper management can be achieved even in the most unsophisticated environment.

Clinical Evaluation. It is often true that the first evaluation is the most important in giving a clue to underlying cause. Therefore, every effort must be made to avoid failure and thus discourage both clinician and patient. Patients with renal stones generally seek help when they are experiencing symptoms which may be due to partial obstruction with loss of appetite and perhaps partial dehydration. This is not the time to investigate one's patient as the underlying metabolic disorder may be completely obscured. Thus, delay until the patient has resumed his normal state is important.

I do not believe that it is worthwhile in this area to submit a patient to an evaluation who has passed and/or made a single stone. We live in a stone belt. In this area, 80% of the patients who have made only one stone will not make another. In the remaining percentage of patients who have made one stone, there is nearly an 80% chance that they will make another within a year. As yet we have no test available to us that will allow us to distinguish the true stone former.

A careful history must probe for previous episodes and associated conditions such as urinary infections, excessive dehydration, diarrhea, fractures with prolonged immobilization, high alkali, Vitamin D or milk intake. Certain drugs, for example Diamox® and steroids, are associated with stone formation. A family history of calculi is often present and may be so prominent, as in cystinuria or oxaluria, that the patient already knows the diagnosis.

A careful urinalysis with recording of the pH, crystal content, and presence of bacteria is still the best single test in the management of these patients.

The following laboratory evaluations are important and can be done while in the hospital or as an out-patient:

1) Urine for culture and sensitivity.
2) Urine for cyanide-nitroprusside test (screening for cystine).
3) Teach the patient to test the pH of every voided specimen of urine with nitrazine paper (Lilly Company).
4) Three determinations of serum calcium, phosphorus, uric acid, and creatinine and additional routine determinations of total protein, albumin, alkaline phosphatase, and electrolytes.
5) Three 24-hour urines for calcium, phosphorus, magnesium, uric acid, and creatinine.
6) Analysis of stones should include x-ray diffraction or crystallographic analysis which is readily available. This is very important because, at this time, medical management is directed toward the crystalline components.
7) Plain film of the abdomen with an intravenous pyelogram. The roentgenographic appearance of calculi with particular attention to the position in the parenchyma or collecting system and also evidence of layering of calcium over a possibly radiolucent nidus are most important in arriving at the diagnosis for a specific cause of a stone and thus planning the therapy. It goes without saying that it is necessary to exclude all forms of obstruction, and at-

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tention should be paid to whether there is parenchymal calcification which can take various forms. A peppering of small calculi outlining the renal papilla often suggests renal tubular acidosis; however, if this is confined to only one papilla then one would think more of a medullary sponge kidney. If there is evidence of infection of the urinary tract, then I believe that a voiding cystourethrogram should always be carried out to detect the presence of vesicoureteral reflux.

Calculi.

Uric Acid Calculi. In this area, uric acid calculi make up 15% of all calculi seen. They are the only truly radiolucent stones and are not necessarily associated with hyperuricemia and hyperuricosuria. They are most often associated with excretion of unusually acid urine and repeated bouts of dehydration. One may see these types of stones in patients with chronic diarrhea. Certain cytotoxic drugs, particularly those used in the treatment of lymphomas and leukemia, the thiazides, salicylates, and steroids will cause uricosuria, and in the presence of low urinary pH, uric acid stones can form.

Patients will respond very rapidly to a program of high urinary output and alkalization. The patient must continually check his urine, particularly the morning specimen, and adjust the dosage of bicarbonate so that the pH is above 6.0.

In some patients it may be necessary to add allopurinol to the regimen, and the dosage will vary from 100–800 mg daily. This potent enzyme inhibitor will prevent further uric acid calculi formation, but there is the theoretical possibility of xanthine stone formation so alkalization must be continued to prevent this possibility.

At present, it is possible to completely prevent uric acid calculi. Surgery should play a minimal part in the management of these patients even when stones are present in the urinary tract. It has long been known that high output of alkaline urine will sometimes dissolve these stones. The introduction of allopurinol to the armamentarium has provided some dramatic cures. I have five patients in whom uric acid staghorns have completely dissappeared after an average of six months.

Cystine Calculi. The diagnosis of this familial disease will usually follow from the routine testing noted above and the finding of hexagonal crystals in acid urine. One should stress again that these stones are radio-opaque because of their 27% content of sulphur and that they have a typical ground glass appearance.

At the Medical College of Virginia, we have an unusually high incidence of cystine stones because of the presence of this inherited metabolic disease in the Chickahominy Indians. Usually, the incidence is only 0.5–1% of all stones.

Therapy is directed toward maintaining the urinary volume in excess of 2,500 ml per day, including an intake of at least 500 ml of fluids in the mid-sleep hours. The urine is maintained alkaline, and the patient is instructed to check his urine and adjust the dosage of his alkalizing medication in order to keep the pH of the urine above 6.5. If the patient follows such a regimen conscientiously, the solubility of cystine in urine will increase and further stone formation may not occur. This can readily be checked by routine urinalysis. Patients who are unsuccessful in such therapy may require the addition of D-penicillamine to the treatment program. This drug is given in dosages of 1–4 g per day guided by the screening tests for cystine (nitroprusside tests).

D-Penicillamine is not completely without its complications; a rash may occur but can be abated by stopping the medication for two weeks and then resuming it by gradually increasing it from 250 mg per day to the required daily dose. Nephrotic syndrome has occurred and requires cessation of the therapy along with prolonged medical observation. There is an increasing number of reports of patients losing their sense of taste while on this drug.

Reappearance of the stones or failure of the stones to dissolve might imply failure of therapy. On several occasions, however, we have found that this was due to the production of stones of other chemical makeup; therefore, these patients must be very carefully followed and watched in case such an event occurs.

It is extremely important when treating these patients with penicillamine to keep the dose as low as possible, that is, to keep the urinary cystine level below 250 mg per day by the minimum dose of D-penicillamine possible. It is conceivable, and we have seen it here on two occasions, that prolonged high doses of penicillamine will interfere with collagen maturation and thus give rise to bruising and striae formation; great care must be exercised in the management of these patients.

Calcium Calculi. The stones that contain calcium are found in a wide spectrum of conditions that can be broken down into individual management problems once the proper diagnosis has been made. The principal breakdown is into those patients with or without infection. One should not lose sight of the fact that many so-called infectious stones may have had as a nucleus an uninfected stone so one should adjust the therapeutic attack accordingly.

Triple Phosphate Calculi. Stones associated with infection imply the presence of stones containing varying amounts of calcium magnesium ammonium phosphate. Their roentgen appearance is variable as they may have a high content of so-called matrix. Therapy is directed toward eliminating the infection. It is essential to correct obstruction, diabetes and hyperparathyroidism, and to remove all foreign bodies; otherwise, any therapy directed toward the infection will be doomed to failure.

Appropriate antibiotic therapy must be intensive and often prolonged until the urine is sterile and stays that way. Acidification of the urine is certainly very helpful. A regimen using methenamine and ascorbic acid is helpful. We have found that in some patients methylene blue will lower the urinary pH, and it seems to prevent organization of the matrix and prevents it from binding the calcium ions.

Oral use of magnesium or phosphates is contraindicated. If one can lower the urinary phosphorus by use of a low phosphorus-containing diet and Basaljel®, then success has been achieved. It is often extremely difficult to insure that patients remain on this regimen, however, and I no longer use it except with very compulsive patients.

I believe it can rarely be said that a stone is purely secondary to infection.

Calcium Oxalate and Calcium Phosphate. Prior to discussion of the management of these common stones, a few general observations should be made. Pure calcium phosphate stones are most commonly found in association with metabolic diseases; for example, hyperparathyroidism, renal tubular acidosis, immobilization syndrome, and stones associated with the hypercalcemia of malignant disease and sarcoidosis; a more intensive investigation by a metabolic unit is indicated. Many patients will alternate calcium oxalate and phosphate stones, presumably due to the variation in urinary pH, as calcium phosphate precipitates at high urinary pH. Hyperoxaluria should be suspected in children or young patients with recurrent stone formation.

Calcium oxalate and/or phosphate calculi represent a disease complex which has many factors associated with it, and therefore, it seems that one should direct attention and therapy toward the most prominent biochemical abnormality that the preliminary investigation turns up; always remember that continuous monitoring and flexibility are essential.

Hypercalciuria. There is still considerable controversy as to the best therapy for this common problem. The following therapies are recommended:

Thiazides. If given in a dosage of 500 mg twice daily, they will reduce the urinary calcium and elevate the magnesium. There are certain side effects, however, which may be potentially harmful. Metabolic acidosis and potassium deficiency have been reported. Citrate excretion is practically abolished and hyperuricemia may occur. Rarely, this will cause hypercalcemia unmasking that group of people who exhibit normocalcemic hyperparathyroidism. All of these patients must be warned to keep their sodium intake low, or the effect of the thiazides will be nullified. It is questionable whether this form of therapy should be combined with the phosphate type as there exists the potential of exacerbating the renal damage that can occur from phosphate ingestion.

Neutral Orthophosphate. In 1958 and 1959, Drs. Howard and Thomas made a crucial observation concerning "evil urine" and its ability to calcify rachitic rat cartilage while good urine would not do this. This led to the discovery that neutral orthophosphate taken orally will consistently lower urinary calcium and convert evil to good urine. Subsequent work by others in the field has confirmed that a dosage of 1.3–1.5 g per day is sufficient to stop stone formation. Unfortunately, this dosage is sometimes limited by the diarrhea which may occur.

Uricosuria. There is a group of patients whose only detectable metabolic abnormality was a relative uricemia and uricosuria. Interestingly, these patients often belong to the so-called "young executive stone former." It has been possible to control their oxalate stone formation with a low dosage of allopurinol (50 mg) and alkalization.

Calcium/Magnesium Ratio. There is a group of stone formers who have a ratio of these ions to each other greater than three and who appear to benefit from magnesium oxide therapy usually administered as Milk of Magnesia® tablets. I should stress that some workers have not been able to demonstrate these differences so that if one uses

this therapy, very careful monitoring and study is essential.

Lack of Detectable Abnormality. There is a group of people in whom there is no detectable abnormality on the biochemical survey. A variety of therapeutic approaches is currently under study.

Dr. Prien is presently conducting a study on the effect of magnesium oxide (300 mg per day) and pyridoxine (10 mg per day) in the management of recurrent stone formers. He will provide the protocol and therapy in return for follow-up results.

Studies on methylene blue by Boyce and by Smith have been reported previously. At this time, methylene blue (65 mg three times a day) would seem to be effective in preventing the formation of stones in uninfected calcium oxalate stone formers. I admit that it may also be helpful in "urine watchers" in that they will tend to keep up an adequate fluid intake.

Discredited Therapy. Aspirin, hyaluronidases, and cranberry juice have fallen into disrepute as forms of therapy.

General Measures. As has been indicated, each patient will require individualized therapy. It is extremely important to be prepared to evaluate patients continually as to their response to a particular therapy and, if necessary, to shift to another.

Dietary therapy is not emphasized; however, all patients are instructed in a simple low calcium diet. There are a few people who can remain on diets and successfully reduce the urinary calcium levels. All patients are taught to measure their urine volume and to aim to maintain an output above 100 ml in one hour. It is probably wise to advise patients to avoid excessive consumption of soft drinks, since a carbohydrate load has been shown to induce hypercalciuria of frightening proportions. I believe the intelligent participation by a patient in his medical management is probably the single most important facet in the management of recurrent urinary calculi.

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