RECURRENT RENAL LITHIASIS

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With the modern facilities now available, an early and accurate diagnosis of urinary calculi may be established and surgical intervention instituted before the kidney has suffered irreparable damage. However, the recurrent formation of calculi following operation constitutes a major problem in urologic surgery and, in view of the frequency with which this occurs, the operative procedure, *per se*, must be considered as but one phase in the management of patients with calculous disease.

Numerous publications have appeared in the literature concerning the experimental production of urinary calculi, the etiologic factors associated with the formation of calculi, and refinements in operative technic, but the problem of recurrence and its prevention has only recently received attention. It is essential that intensive preoperative investigation be carried out to ascertain the etiologic factors associated with the formation of the primary calculus and that correction of the underlying factors be accomplished in order to prevent and minimize the formation of recurrent calculi. To better understand the problem, the present conceptions of calculous formation must be considered.

LESION OF THE PAPILLA

In 1912 at the meeting of the American Association of Genito-Urinary Surgeons, Caulk[1] reported a case of calcareous incrustation around one of the renal papillae and the next year, he[2] presented three additional cases in which a similar pathological process was found. Dr. Opie gave the following pathological description of the papillary lesion: "The section of the papilla with the incrustation showed that the tip of the papilla was covered with a homogeneous material, which took a deep blue stain of decalcified material. The tissue of the papilla was dense and fibrous and contained very few cells. The tissue in immediate contact with this mass has undergone hyaline degeneration. In this hyaline area, as the calcified mass is approached, numerous minute calcified granules are seen. Deeper into the substance of the papilla, the tissue is loose in texture and contains numerous blood vessels. There are also occasional collections of lymphoid cells. It was thought that the condition was due to primary necrosis of the papilla with a secondary deposition of calcium phosphate." The other cases Caulk reported included one of incrustation of the upper ureter, one of incrustation of calcium phosphate on the posterior wall of the kidney pelvis, and one of incrustation of the juxtavesical ureter. The incrustations from the posterior wall of the renal pelvis were composed of calcium phosphate with traces of

calcium oxalate. At this time Caulk raised the question as to the relationship of these lesions to calculous disease.

In 1936, Randall[3] also described a lesion of the papilla which he believed to be the initiating lesion of a renal calculus. This consisted of a sub-surface deposit of calcium and he traced from this the destruction of the covering mucous membrane and a deposit thereon of two types of urinary salts; namely, calcium phosphate and calcium oxalate. He stated that these salts appeared to be direct secondary deposits upon the calcium plaque once it was denuded of its epithelial covering. Investigation regarding the relationship of this lesion to infection, infarction, and avitaminosis is now in progress.

Infection

The relationship between infection and the formation of renal calculi has been stressed for a long time. Bartlett[4] in 1895 stated that two factors were associated with the formation of kidney stones, namely: (1) infection, and (2) stagnation. Brongersma's[5] statistics infer that recurrence following operation is usually due to infection. In aseptic cases, the incidence of recurrence was 3 to 6 per cent. Where a slight infection was present, the incidence was 27 per cent and 50 per cent where the infection was pronounced. Rovsing[6] in discussing Brongersma's paper stated that 68.18 per cent of all recurrences occurred when renal infection, either primarily or secondarily, was due to a urea splitting organism. It is of significance, however, that in 15.91 per cent of the cases, recurrences developed in sterile urine.

While attention has been directed in the last few years to the property of the proteus organism to split urea with the resultant formation of carbon dioxide and ammonia, it must be recalled that Brown and Earlam[7] have stated that 40 per cent of the Staphylococcus albus and 18 per cent of the bacilli infecting the urinary tract possess similar properties. It is necessary, therefore, not only to classify the infecting organism correctly, but it should be a routine procedure to determine if the organism has urea splitting properties.

While it may be true that infection plays a major rôle in influencing the formation of recurrent calculi, in view of the fact that many recurrences develop in the presence of sterile urine, further quest of the etiological factors is required.

Focal Infection

Diligent search for foci of infection is essential. The investigations of Rosenow and Meisser[8] demonstrate the relationship between the Strep-

tococcus and calculous formation. In 1921 they reported the results of a series of experiments in which the pulps of the teeth of six dogs were inoculated with Streptococci isolated from the urine of patients who had renal lithiasis. Calculi developed in the experimental animals and the Streptococci were isolated from the urine of the animals. Foci may be present in the teeth, tonsils, prostate, cervix, and bowel, all of which require examination.

Hyperparathyroidism

Publications by Barney,[9] Chute,[10] Albright, Baird, Cape, and Bloomberg[11] and others have focused attention on the relationship between hyperparathyroidism and the formation of renal calculi. Hunter[12] in 1931, in a review of a collected series of 32 cases of osteitis fibrosa in which there was evidence of hyperparathyroidism, noted the presence of renal calculi in 10 instances. Albright and Bloomberg[13] more recently reported 23 cases of hyperparathyroidism from the Massachusetts General Hospital and 15 of these patients had renal calculi.

During the past three years, we have made it a routine practice to study the serum calcium and inorganic phosphorus levels, blood phosphatase, and the excretion of calcium in the urine of all patients with renal calculi. A roentgenogram of the pelvis and tibiae is secured in each case. In more than 375 cases we have found only one instance of hyperparathyroidism. This patient, at the time of operation, was found to have a small tumor of one of the parathyroid glands and this was removed without difficulty. In the other cases, no evidence to indicate the presence of hyperparathyroidism was noted.

Vitamin A Deficiency

The results of experimental studies demonstrating the relationship between moderate or mild degrees of vitamin A deficiency extending over a long period of time and the formation of urinary calculi have been presented in previous publications.[14] In some articles appearing in the literature, it has been stated that a searching inquiry into the dietary habits has not indicated dietary or nutritional inadequacy. This is true in many instances; however, a dietary history is misleading and, by use of the biophotometer test, we have detected evidence of vitamin A deficiency when its presence was not suspected. Likewise, an adequate amount of vitamin A may be present in the diet but it may not be utilized properly. In several cases, we have elicited a definite history of night blindness which, as is well known, is associated with a pronounced deficiency in vitamin A. This observation simulates closely our experi-

mental observations in which a pronounced deficiency of vitamin A in the diet is not permitted, but rather a mild deficiency is allowed to extend over a long period of time.

In our series of patients with calculous disease, vitamin A deficiency has been present in 68 per cent of those who had the biophotometer test. Clinical data regarding vitamin A deficiency are gradually being accumulated. Jeghers[15] has found that "In a group of medical students, 35 per cent had low photometer readings and 12 per cent had clinical manifestations of the deficiency. The chief manifestations, in the order of their frequency, were night blindness, photophobia, dry skin, dry conjunctivae, blepharitis and follicular hyperkeratosis. The factors producing the deficiency were analyzed and showed that the skipping of meals and poor choice of foods were chiefly responsible. After dietary analyses it was concluded that 4,000 international units of vitamin A daily represent the minimal requirement for a healthy adult." The reports of Jeans,[16] of the University of Iowa, indicate that moderate or mild degrees of vitamin A deficiency are more prevalent than we have been led to presume. Studies of the seasonal fluctuation of the vitamin A content of various foods such as milk, cream, butter, and eggs have been made by the Ohio Experiment Station at Wooster, Ohio. Their results indicate the difficulty of determining whether or not a patient is securing adequate amounts of vitamin A even though a careful dietary history is taken.

Stasis

Attention also has been directed toward the possible relationship between the formation of renal calculi and stasis. Stasis, as we know, has a tendency to render urine alkaline and to induce precipitation of salts in an alkaline urine. Hunner[17] has stressed the importance of ureteral stricture with resultant stasis as an etiological factor in the formation of recurrent calculi. Since the advent of intravenous urography, pre- and postoperative evidence of stasis may be noted and corrective procedures employed to eradicate the causative factor instrumental in producing it. Certainly, intravenous urography should be employed in all cases of renal calculi to ascertain if stasis is present.

Metabolic Factors

Cystinuria: Calculi composed of cystine are an unusual type of stone. The association of cystinuria and cystine lithiasis has been stressed by Seegar and Kearns.[18] In a review of 181 collected cases of cystinuria, cystine calculi were noted in 124 instances.

Gout is another metabolic condition in which an excess of crystalloids may appear in the urine, microscopic examination of the urinary sediment revealing the presence of uric acid crystals and urates. Not only may calculi composed of uric acid be produced, but the patient may experience attacks of colic as showers of uric acid crystals are passed. Gout, however, need not be present for uric acid calculi to form. The amount of uric acid eliminated daily in a normal individual varies largely according to the individual diet. Normally, 0.3 to 1.2 gm. are excreted in 24 hours.

Phosphaturia: Temporary phosphaturia may be caused by eating foods containing an excess of alkaline ash, such as large quantities of citrous fruits. Permanent infected phosphaturia is associated with the presence of an organism that has the power of splitting urea, rendering the reaction of the urine strongly alkaline and this is frequently associated with recurrent formation of calculi. Permanent noninfected phosphaturia is said to be associated with alteration in function of the large bowel.

Oxaluria: Oxaluria has been stated by Neville[19] to be associated with a deficiency of vitamin B in the diet. However, an excessive intake of food having a high oxalic acid content may be associated with elimination of more than the normal amount of oxalates in the urine with resultant oxaluria.

Xanthin calculi: Urinary calculi composed of xanthin are of rare occurrence. Kretschmer[20] in 1937 collected a series of 15 cases and added one of his own. Mathews[21] has stated that the most important purine found in the human urine is uric acid, but there are present also from 30 to 50 mg. of purine bases, xanthin, hypoxanthin, guanine, and adenine. He estimates that from 16 to 60 mg. of purine bases are eliminated in the urine daily as the purines are the end products of the metabolism of the nucleins. An excessive intake of food high in purine content may be elicited by a careful dietary history in such instances.

Trauma

Statistics have indicated that recurrences following nephrolithotomy are more frequent than when the simpler procedure of pelviolithotomy is employed. In 1915 Cabot and Crabtree[22] reviewed a series of cases at the Massachusetts General Hospital and found an incidence of 56 per cent recurrence following nephrectomy and 51 per cent following pyelotomy. Braasch and Foulds[23] in 1924 estimated a recurrence of 10.79 per cent. They stated a recurrence of 11.85 per cent followed pyelotomy and 24.03 per cent followed nephrolithotomy.

Certainly, a minimum of trauma should be inflicted during the surgical procedure. As evidence of the danger of trauma, we have seen cases in which, when a recurrent stone was carefully sectioned, a blood clot was found to be the nucleus.

Type of Stone

The removal of a branched calculus extending into the calices is more prone to be followed by a recurrence than when the stone is confined to the pelvis of the kidney itself. This may be due to injury of the calix or the infundibulum in the removal of the calculus or a small fragment of the calculus may be broken off and this acts as a nucleus for secondary formation of a calculus. It is also true that the removal of small multiple stones is followed by a recurrence far more frequently than when a small, solitary stone is removed. A small calculus may not be demonstrable on the roentgenogram and thus may be overlooked, but with a suction apparatus which we use, minute calculi have been removed on several occasions when their presence was not suspected previously.

In a similar manner, stones of a soft consistency are more prone to be followed by a recurrence, possibly because sand remains to act as a nucleus for secondary formation of a stone. Thorough lavage of the pelvis and calices after removal of a calculus eliminates this possibility.

Surgical Aspects for Prevention

As stated previously, we believe the surgical procedure which is accompanied by a minimum of trauma to the kidney is preferable. In an attempt to deliver the kidney, handling it or traumatizing the renal parenchyma by manipulating the kidney is unnecessary as a routine procedure. The operation is preferably carried down to the renal pelvis which is exposed by means of flexible retractors and the calculus is removed without delivering the kidney.

In instances in which there is no renal infection or if infection is not pronounced, the incision in the renal pelvis should be closed with fine catgut sutures passing through only the outer layers of the pelvis and not through the mucosa where it might be retained and act as a nucleus for recurrent formation of a calculus.

Joly[24] has stated that even temporary leakage of urine increases the risk of recurrence of stone and should be avoided if possible. He further states that if the kidney has been drained, it is usually found to be infected with Staphylococcus albus. Rovsing[6] also stated that urinary leakage of only a few days' duration was sufficient to infect the kidney. In cases in which a more pronounced infection is present, pelvic drain-

age may be necessary for thorough drainage and irrigation to eradicate the infection.

Nephrolithotomy is employed in cases in which pyelotomy does not seem feasible. When a calculus is confined to a calix and the infundibulum is too narrow to permit its extraction through the pelvis, a localized nephrolithotomy is employed. This procedure should, however, always be as conservative as possible. In the removal of a staghorn stone, nephrolithotomy may be necessary and I believe adequate drainage should be instituted in such cases.

A heminephrectomy may be the preferable procedure in some instances in which a calculus is confined to a dilated calix. In the presence of a stricture of the infundibulum with infection, the latter can only be eradicated by this procedure and fewer recurrences will follow this method than if a localized nephrotomy is employed. After removal of the calculus, the calices and pelvis are thoroughly lavaged with saline solution and a suction tube is placed in the calices and pelvis to remove any remaining debris.

When small calculi are being removed, a roentgenogram of the exposed kidney is advisable to locate a small calculus which might be overlooked and produce a false recurrence.

Postoperative Routine

Elimination of stasis: If the postoperative urogram which is secured in all cases reveals evidence of stasis, ureteral dilatation and lavage of the renal pelvis is advisable. I believe this is essential. At the time of dilatation, specimens of urine may be secured from the kidney for culture and determination of the pH.

Eradication of infection: As stated previously, it is extremely important not only to classify the organism but also to determine if the organism possesses urea splitting properties. We attempt to eliminate the infection if possible before the patient is dismissed from the hospital, utilizing the period of convalescence for this purpose. If the organism is of the colon group, we find now that the infection may be eradicated by mandelic acid therapy rather than the ketogenic diet which we formerly employed. We have also used mandelic acid in combination with the ketogenic diet. Mandelic acid therapy should not be employed indiscriminately and the contraindications to its use, such as impaired renal function which leads to acidosis, have been cited previously in the literature. Limitation of fluids and a careful check of the pH of the urine are essential to satisfactory results with mandelic acid.

In the presence of the group of colon bacilli that split urea with the

formation of carbon dioxide and ammonia, we have usually been able to acidify the urine by use of acidifying agents. This is in contrast to the proteus group in which I have been unable to acidify the urine by the ketogenic diet, the acid-ash diet, or acidifying agents. Obviously, if the pH of the urine cannot be shifted from the alkaline to the acid side, the acid-ash diet routine is not efficacious. Likewise, it may be impossible in this group to acidify the urine by administration of ammonium chloride. As the ammonia is synthesized in the body, urea will be broken down by the proteus organism into ammonia. It leads to blood acidosis, causing increased elimination of calcium and phosphorus in the urine which, being alkaline and at a point at which the phosphates and carbonates in the urine are precipitated, may lead to enlargement of the calculus. Individualization of the patient is obviously necessary. I have found the proteus infection extremely difficult to eradicate and the use of vaccine therapy, mandelic acid, prontosil, and other drugs have usually been followed by poor results. For treatment of the staphylococcus group, salvarsan in addition to other medication is employed. It is important to eliminate the infection if possible before the patient leaves the hospital. In this way, close supervision can be kept and then either the acid-ash or alkaline-ash diet may be started.

In view of Rosenow's and Meisser's work,[8] a careful check of foci of infection is essential and, if such are found, they should be eradicated, tonsils, teeth, prostate, cervix, and bowel being carefully studied.

Treatment of hyperparathyroidism: If clinical investigation has demonstrated the presence of hyperparathyroidism, correction is obviously necessary to prevent a recurrence. In the one case in which we have seen coexisting renal calculi and hyperparathyroidism, the patient's general condition and renal function were such that we were able to remove the adenoma of the parathyroid gland before attacking the kidney problem. Each patient must be studied carefully to ascertain which problem should receive priority in treatment.

Vitamin A deficiency: Vitamin A in large doses is administered postoperatively for two reasons: (1) to correct vitamin A deficiency if it be present and (2) for its specific effect on epithelial structures.

During the past three years, in several instances at the time I removed a calculus from the renal pelvis, I excised for pathological examination a small portion of the pelvis contiguous to the calculus. In the majority of cases, microscopic examination revealed denudation of the epithelium and ulceration extending through the mucosa. This is undoubtedly due to trauma from the calculus. The ulcerated area is frequently covered with adherent granular debris and calcific deposits which may act as a nucleus for secondary stone formation. Certainly, from this

site, colloid (fibrin) is produced which will serve to bind together whatever salts are being precipitated, dependent on the pH of the urine. Thus I believe vitamin A is of value to promote rapid healing of this ulcerated area even in cases where the biophotometer test gives normal results.

Dietary Adjustment

As stated previously, experimental evidence led us to believe that the incidence of the formation of recurrent calculi could be minimized by a carefully planned dietary regimen which would be utilized to control the pH of urine. Although it has been our observation that the majority of recurrent calculi are composed of salts which are precipitated in an alkaline urine, special attention must be directed to the cases in which the calculi are composed of cystine, uric acid, and xanthin, i. e., salts which are precipitated in an acid urine, as well as those composed of oxalates, a salt which is precipitated in a wide range of urinary reactions.

In our experience, the initial dietary control requires or at least is better managed if the patient is hospitalized, the cooperation of the Dietetic Department being essential. When the acid-ash diet is utilized, an initial diet with an excess acid-ash of 17.3 cc. is prescribed. The various constituents of the diet, i. e., the proteins, fats, and carbohydrates, are varied daily until the pH of the urine secured by catheterization of the ureters is maintained at 5.2 to 5.5. This may necessitate increasing the acid-ash content of the diet to 28 or 30 cc. and, in some cases, additional acidification by ammonium chloride may be necessary. Obviously, if the pH of the urine cannot be shifted to the acid side by the diet, as in many cases of proteus infection, satisfactory results cannot be anticipated. Ammonium chloride is administered in the form of enteric coated tablets (7½ grains). If the proteus infection cannot be eradicated, the pH of the urine in the majority of cases cannot be maintained at 5.2 to 5.4 and precipitation of the alkaline salts will continue.

In addition to the acid-ash diet, if the calculi contain traces of oxalates, it is advisable to restrict foods having a high oxalic acid content, substituting those containing little or no oxalic acid. As suggested by Snapper[25] it is well to attempt stabilization of the colloids of the urine by the administration of sodium benzoate in the group of patients who have calculi composed of oxalates, in view of the fact that these salts precipitate in a wide range of urinary reactions. At the present time, we are giving from 1 to 2 gm. sodium benzoate three times a day. As a general rule, the patients consume a sufficient amount of glycocoll that the resultant formation of hippuric acid from the benzoic acid occurs. Snapper has also recommended supplying additional glycocoll by having the patient eat every day soup extracted from calf bones. In cases

in which the calculi are composed of uric acid, the alkaline-ash diet is utilized. The basic diet then has an excess alkaline-ash of 17.3 cc., the contents of the diet being varied daily until a pH of 5.4 to 5.6 is maintained. Care must be exercised that the pH is not shifted too strongly to the alkaline side, as precipitation of phosphates and carbonates must be avoided. In this group, a purine-free or low purine content of the diet is necessary. A similar diet is utilized for calculi composed of cystine or xanthin.

It does not suffice merely to prescribe a list of foods having an excess of alkaline- or acid-ash. The diet must be prescribed as carefully as that which would be instituted for a patient with diabetes. It has been found necessary to alter the diet from time to time in order to maintain the pH at the correct level. The patient makes daily determinations of the pH and these are recorded and presented to the physician at frequent intervals. The diet may then be adjusted or the medication altered. If this is not carefully observed while the patient is under dietary management, failures are bound to ensue and beneficial results will not be obtained.

In conclusion, the management of patients with calculous disease requires intensive study, diligent observation, and a conscientious and judicious postoperative routine. Since adding our dietary program to the other procedures used postoperatively following removal of renal calculi, we have reduced the incidence of recurrence from 16.9 per cent to 4.6 per cent, recurrences having developed chiefly in the group of patients in whom the pH of the urine could not be controlled successfully. If satisfactory treatment for the proteus organisms can be attained eventually, the incidence of recurrence can be reduced to a minimum.

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