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NEPHROLOGY FORUM

Infection-induced renal calculi

Principal discussant: DONALD P. GRIFFITH

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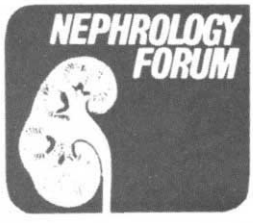

Case presentation

An obese, 49-year-old woman was admitted to the New England Medical Center (NEMC) because of nausea, vomiting, severe leg cramps, and intermittent dizziness for one week. In addition, she thought that her daily urine volume had been decreasing during the few days prior to admission. Mild hypertension had been treated for 5 years with a thiazide diuretic, but she had no history of urinary tract infection, renal calculi, hematuria, or analgesic abuse.

Physical examination revealed a blood pressure of 90/60 mm Hg and a pulse of 110 per minute in the supine position with marked orthostatic changes. The temperature was 36.5° C, and the respiratory rate was 28/min. She weighed 99.9 kg. Funduscopic examination revealed mild arteriolar narrowing and arteriovenous nicking. The lungs were clear. Cardiac, abdominal, pelvic, and neurologic examinations were unremarkable.

Laboratory findings revealed a hemoglobin of 16.1 g/dl, a hematocrit of 49%, and a white blood cell count of 23,800/mm^3 with 88% polymorphonuclear leukocytes; the platelet count was 687,000/mm^3. The serum sodium was 116 mEq/liter; potassium, 8.3 mEq/liter; chloride, 77 mEq/liter; total CO_2, 10 mm/liter; BUN, 192 mg/dl; serum creatinine, 8.8 mg/dl; serum calcium, 10.0 mg/dl; phosphorus, 12.9 mg/dl; uric acid, 16.5 mg/dl. Results of urinalysis revealed a specific gravity of 1.012, a pH of 7.5, and 3+ heme and 3+ protein on dipstick examination. Microscopic examination of the spun sediment revealed numerous red and white blood cells but no casts or renal tubular cells. The unspun urine sediment contained numerous gram-negative rods. The electrocardiogram revealed tall, peaked precordial T waves. A chest x-ray showed clear lung fields, and a plain film of the abdomen revealed massive bilateral staghorn calculi.

The patient was treated for hyperkalemia with an infusion of glucose, insulin, and sodium bicarbonate, and for volume depletion with intravenous saline. Peritoneal dialysis was initiated. Gentamicin and ampicillin therapy were begun for presumed gram-negative sepsis. Urine culture subsequently grew *Proteus mirabilis* sensitive to ampicillin, and gentamicin administration was discontinued. Blood cultures were negative. The patient's weight increased to 103.8 kg; the BUN fell to 86 mg/dl, and the serum creatinine decreased to 4.3 mg/dl over the next 36 hours. The BUN and serum creatinine fell to 25 mg/dl and 2.8 mg/dl respectively over the next week without additional dialysis.

A subsequent intravenous urogram disclosed that both kidneys were 18 cm in length and that both contained staghorn calculi. The ureters were not visualized but the contrast medium did reach the bladder. A renal echogram showed no ureteral obstruction, and a renal scan demonstrated good blood flow to both kidneys. A retrograde pyelogram revealed no evidence of stone or tumor in the ureters or the pelvis. During cystoscopy, the bladder mucosa appeared white and granular with cystic areas.

The patient was discharged 13 days after admission with a BUN of 18 mg/dl, a serum creatinine of 3.0 mg/dl; and a white blood cell count of 7000/mm^3; she was receiving only oral ampicillin. She was advised to return for evaluation but failed to do so until one year later at which time she was doing well. Urine culture at that time revealed greater than 100,000 col/ml of mixed fecal flora; the BUN was 63 mg/dl and the serum creatinine was 3.8 mg/dl.

Discussion

DR. DONALD P. GRIFFITH *(Associate Professor, Department of Urology, Baylor College of Medicine, Texas Medical Center, Houston, Texas)*: This patient has large, bilateral obstructing staghorn calculi. She also has acute and chronic pyelonephritis secondary to urea-splitting bacteria, probable pyonephrosis, and advanced renal failure. In many ways her renal disease parallels a malignant process: her disease is morbid, progressive, probably incurable, and life threatening. Some clinicians have referred to this condition as "stone cancer." This patient has infection-induced stones, but she may also have coexistent metabolic stones and anatomic abnormalities such as vesicoureteral reflux.

I am hesitant to discuss the management of this particular patient because therapy is greatly influenced by complicating factors (such as obesity and cardiopulmonary status), socioeconomic factors, and patient reliability. Clearly, however, this patient cannot be cured with medical treatment, and she is likely to receive only short-term palliation from antimicrobial agents. Without surgery, she will progressively lose renal function until she becomes a candidate for chronic dialysis or transplantation. The advanced nature of her renal failure reduces the outlook for successful surgical treatment of her stones. Surgical removal of all calculi from both kidneys with

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concomitant antimicrobial treatment, however, offers the potential for complete eradication of her urinary infection and for stabilization of renal function. If residual calculi remain postoperatively, persistent infection is virtually assured. But noncurative surgical treatment may offer significant palliation, particularly if recurrent stone formation can be retarded with long-term antibacterial therapy.

Let me use this patient to initiate a review of infection-associated renal lithiasis. The association of stones and putrefaction has been known since Hippocrates, who cautioned his followers not to drain loin abscesses, but rather to leave such treatment to itinerant barber surgeons [1]. His admonitions probably resulted from the high mortality associated with the operation. In 1817, Marcet pointed out that "the alkalinization that attends putrefaction of urine unavoidably results in crystallization of dissolved urinary phosphates" [2]. Brown, in 1901, made clinical observations that supported Marcet's hypothesis [3]. Hagar and McGrath suggested in 1925 that urease was the biochemical basis for stone formation in infected urine [4]. In 1926, Sumner purified and isolated urease. He showed that urease was a protein and that it catalyzed the hydrolysis of urea. His discoveries ushered in the age of enzymology—an achievement for which he subsequently received a Nobel prize [5].

The pathophysiology of stone formation provides a rational basis for classifying patients with the combination of stones and infection. We recognize two distinct pathogenetic sequences: one in which infection is primary and stone formation is the secondary consequence, and another in which stone formation and urinary infection coexist as separate entities. I will refer to the first type as infection-induced stones and the second type as infection-associated stones.

The pathogenesis of infection-induced stones is well defined. Numerous observations have confirmed the historic concepts that bacteria induce crystallization of struvite ($MgNH_4PO_4$-$6H_20$) and carbonate apatite [$Ca_{10}(PO_4)_6C0_3$]. As shown in Figure 1, crystallization occurs as a consequence of the hydrolysis of urea by bacterial urease [6–9]. When urea is split in urine, an optimal milieu for precipitation is created: urinary pH is high (often 8 to 9), and the urine is rich in calcium, magnesium, ammonium, and phosphate. Figure 2 shows how these changes in urinary composition evolve as urea is hydrolyzed by the bacterial enzyme urease. It is primarily and perhaps only urease-producing bacteria that induce stone formation (Table 1). It should be pointed out that infection-induced stones can form primarily or secondarily upon preexistent metabolic stones. In fact, approximately 50% of patients with infection-induced stones have coexistent metabolic stones.

For completeness, let me mention infection-associated stones. These stones can have any chemical composition (calcium oxalate or cystine, for example). Infection occurs independently of the stone's presence. However, the foreign body acts as a nidus and harbors and perpetuates the infection. The bacteria have little or nothing to do with stone formation. The principal part of my discussion today will center around the problem of infection-induced stones.

Clinical manifestations. Patients with infection-induced urinary stones typically have branched renal calculi and urinary infection. Such stones may be found incidentally during evaluation of bacteriuria or cystitis. Conversely, the patient may present with acute pyelonephritis as the first manifestation; this was evidently the case in the patient presented today. The associated bacteriuria is usually, although not invariably, a urease-producing bacterial species. Occasionally, only a urease-negative bacterial species can be isolated from urine; however, a urease-producing bacterial species usually can be cultured from inside the stone. Such discrepancies probably are due to variations in in vitro bacterial growth when mixed cultures are present.

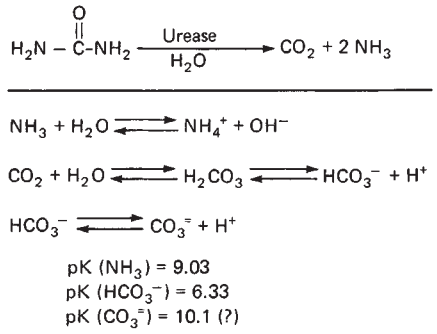

Fig. 1. *Hydrolysis of urea by the bacterial enzyme urease.*

Patients who are not cured by traditional medical and surgical treatment face a progressive clinical course such as that illustrated by the patient presented today. In fact, the consequences of this kind of stone disease are so serious that many urologists refer to it as "malignant stone disease" or even "stone cancer." Patients with disabilities—such as spinal cord injury or urinary diversion—who are particularly susceptible to urinary infection, are also particularly difficult to cure. The majority of deaths in paraplegic veterans of World War II and the Korean conflict occurred as a consequence of chronic urea-splitting pyelonephritis, recurrent renal calculi, and chronic renal failure [10].

Treatment with antimicrobial agents improves symptoms associated with acute pyelonephritis. Long-term oral treatment with antimicrobial agents is not very successful, however, in maintaining sterile urine when large renal calculi are present [11]. Persistent or recurrent infection is usually associated with stone recurrence, stone growth, or both.

Urease-producing bacteria often are associated with stones that contain a soft, mushy, gelatinous matrix [12, 13]. This matrix is composed of mucoproteinaceous debris that contains desquamated cells, leukocytes, and red cells. This matrix is radiolucent, but it can mineralize rapidly with calcium and magnesium phosphate (Fig. 3). The source of the matrix is unknown, but it may be derived from uroepithelial secretions.

Ureteral obstruction is a relatively uncommon manifestation of infection-induced stones. When it is present, however, pyonephrosis and septicemia can occur. In such instances, immediate drainage of the pyonephrosis is warranted. The preferred method of drainage is either retrograde placement of ureteral catheters or percutaneous nephrostomy. Before and after drainage, concomitant therapy should include antimicrobial agents, intravenous fluids, and other adjunctive measures.

Treatment. Cure can only be achieved by the removal of all foreign bodies (calculi, matrices, and catheters) and by eradication of the infection [14]. Postoperatively, long-term antimicrobial therapy with agents known to be effective against the

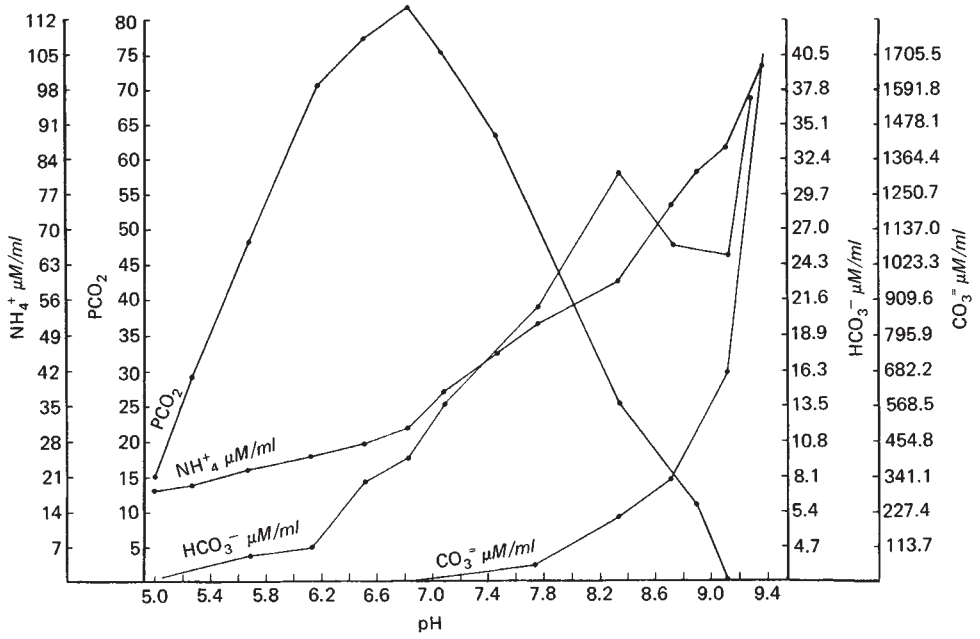

Fig. 2. *Changes in urinary solutes in sterile urine inoculated with bacterial urease.* Increases in alkalinity and solute concentrations brought about supersaturation with respect to calcium phosphate and magnesium ammonium phosphate. These substances crystallized rapidly. (Reproduced from Ref. 11.)

specific organism is needed in most cases to eradicate infection. Repeated urine cultures over many months are mandatory. Using "at home" culture techniques, patients can monitor the effectiveness of antimicrobial treatment themselves. These methods include Uricult (Medical Technology Corp., Hackensack, New Jersey) and Bacturcult (Wampete Corp., Cranberry, New Jersey 08512).

Operative removal of branched renal calculi requires that the surgeon have considerable urologic experience and expertise so that as much kidney tissue as possible can be preserved. Several adjunctive techniques are used, including renal hypothermia, intraoperative renal radiography, and intraoperative nephroscopy to facilitate removal of all calculous material. The details of such techniques have recently been reviewed [14].

Palliative medical treatment is warranted when stones cannot be eliminated completely or when infection persists even after all stones have been removed. Chronic antimicrobial therapy probably retards stone formation if it achieves sterile urine.

Penicillin has been advocated for *Proteus mirabilis* urinary infection because the drug concentration achieved in the urine exceeds the minimum inhibitory concentration of more than 90% of *P. mirabilis* strains [15]. Indeed, long-term, perhaps lifetime, treatment may sterilize the urine. Tetracycline has been advocated for suppression of urinary infection with pseudomonas species [16]. As with penicillin, achievable urinary concentrations of tetracycline inhibit most strains of pseudomonas. The benefit of antimicrobial agents such as sulfas, nitrofurantoins, and methenamine salts is undocumented.

Drugs that inhibit urease may retard growth of infection-induced stones. At present, however, no urease-inhibiting drugs have been approved by the Food and Drug Administration. Preliminary evidence suggests that concomitant treatment with antimicrobial agents and urease-inhibitor drugs may result in greater inhibition of stone formation than with either drug alone [17].

Kobashi, Hase, and Uehara showed in 1962 that the hydroxamic family of compounds effectively inhibited urease [18]. In 1970, Fishbein and Daly reported studies involving the structure, enzyme inhibitory potency, and relative toxicity of short-chain aliphatic hydroxamic acids [19]. They concluded that acetohydroxamic acid, more than any of the other hydroxamic acids tested, offered the greatest pharmacologic promise. Experimental studies show that urease inhibitors can prevent or retard infection-induced stone formation [8, 9, 20]. The efficacy of therapy depends on achievement of therapeutic urinary concentrations of the urease inhibitor. At least four compounds are undergoing evaluation (Fig. 4) [9, 17, 20–24].

Hydroxyurea, commercially available as an antitumor agent, has received little attention as a urease inhibitor. Preliminary clinical trials indicate, however, that its tendency to cause leukopenia and its weak urease-inhibiting properties limit its usefulness in patients with infection-induced stones [21].

Acetohydroxamic acid (AHA), which is weakly acidic (pK = 9.3) and is structurally similar to urea, forms a tight, noncompetitive, slowly reversible bond with urease. It also chelates iron. Highly soluble in water, AHA is distributed throughout body water and is rapidly and completely absorbed from the gastrointestinal tract [25]; 30% to 60% of the drug is excreted unchanged in urine. Urinary concentrations of AHA achievable by oral administration provide no significant antimicrobial activity. Approximately 10% of an oral dose of AHA is metabolized to acetamide, which is excreted in the urine, and another 10% of an oral dose is metabolized to carbon dioxide (Feldman S, Griffith DP, unpublished data). Protein binding has not been demonstrated. Renal failure results in an accumulation of AHA and perhaps also its metabolite acetamide. Research has shown

Table 1. Microbial species that produce urease[a]

Organism	Usually (> 90% of isolates)	Occasionally (5%–30% of isolates)
Bacteria		
	Gram-positive	
	Staphylococcus aureus	Staphylococcus epidermidis
	Micrococcus varians	Bacillus species
	Corynebacterium ulcerans	Corynebacterium murium
	Corynebacterium renale	Corynebacterium equi
	Corynebacterium ovis	Peptococcus saccharolyticus
	Corynebacterium hofmannii	Clostridium tetani
		Mycobacterium rhodochrous group
	Gram-negative	
	Proteus rettgeri	Klebsiella pneumoniae
	Proteus vulgaris	Klebsiella oxytoca
	Proteus mirabilis	Serratia marcescens
	Proteus morgani	Hemophilus parainfluenzae
	Providencia stuartii	Bordetella bronchiseptica
	Providencia rettgeri	Aeromonas hydrophila
	Enterobacter gergoviae	Pseudomonas aeruginosa
	Hemophilus influenzae	Pasteurella species
	Bordetella pertussis	
	Bacteroides corrodens	
	Yersinia enterocolitica	
	Brucella species	
	Flavobacterium species	
	Pasteurella aerogenes	
Yeasts		
	Cryptococcus	
	Rhodotorula	
	Sporobolomyces	
	Candida humicola	
	Trichosporon cutaneum	
Mycoplasma		
	T-strain mycoplasma	

[a] Analytab Products Inc., 200 Express Street, Plainview, New York 11803. Data from Cowan ST, Steele KJ: *Manual for the Identification of Medical Bacteria,* p. 238, Cambridge, Cambridge University Press, 1974; from Ford DK: Inhibition of growth of T-strain mycoplasmas by hydroxamic acids and by aurothiomalate. *Antimicrob Agents Chemother* 2:340, 1972; and from Seeliger HPR: Use of a urease test for the screening and identification of cryptococci. *J Bacteriol* 72:127, 1956. Reproduced from *Nephrolithiasis, Contemporary Issues in Nephrology,* vol. 5, edited by Fredric L. Coe, M.D., Barry M. Brenner, M.D., and Jay H. Stein, M.D. Copyright © 1980 by Churchill Livingstone. Reprinted by permission of Churchill Livingstone, New York.

AHA to be a weak teratogen in animals [26]. Although no carcinogenic activity has been demonstrated for AHA [27], acetamide is a weak carcinogen in mice [28].

We have given an oral dose of approximately 15 mg/kg/day of AHA to more than 70 patients in an effort to inhibit stone formation in the presence of an incurable urea-splitting infection. Details of the study have been reported elsewhere [24]. Virtually all patients sustained a reduction in ammoniuria and urinary alkalinity (Fig. 5). Stone growth was studied in patients treated with AHA (Group C), compared with the same patients before treatment (Group B), or after treatment (Group D). These patients also were compared with untreated controls (Group A). The AHA-treated group had statistically less stone formation than did any of the control groups (Figs. 6 and 7) (Griffith DG, unpublished data). Side effects consisted of gastrointestinal upset, malaise, phlebitis, tremulousness, loss of body hair, and a hemolytic anemia (Table 2). In most instances, the side effects did not warrant discontinuation of treatment, although we did sometimes reduce the dosage. In many instances, a cause-and-effect relationship between the reported symptoms and AHA treatment could not be definitely established. It is likely, however, that the hemolytic anemia, the tremulousness, the rash associated with alcohol ingestion, and the alopecia were drug induced. These abnormalities reversed when treatment was discontinued.

Urease-inhibiting drugs are not likely to dissolve large staghorn stones nor to replace surgical and antimicrobial therapy. Urease inhibitors seem best suited for long-term palliative treatment of the patient with recalcitrant urea-splitting infection, reasonably good renal function, and little or no obstruction to urinary flow. In such patients urease-inhibitors retard calculogenesis. It is likely that AHA will be ineffective in patients whose serum creatinine is greater than 2.0 mg/dl; also, the risk of side effects probably increases in patients with poor renal function. The ultimate role of urease-inhibiting drugs in the therapeutic armamentarium will be determined by clinical experience that seeks to balance the risks and benefits of treatment with the risks of the patient's disease.

Questions and answers

DR. JOHN T. HARRINGTON: What specific surgical approach would you recommend in a patient such as the one presented

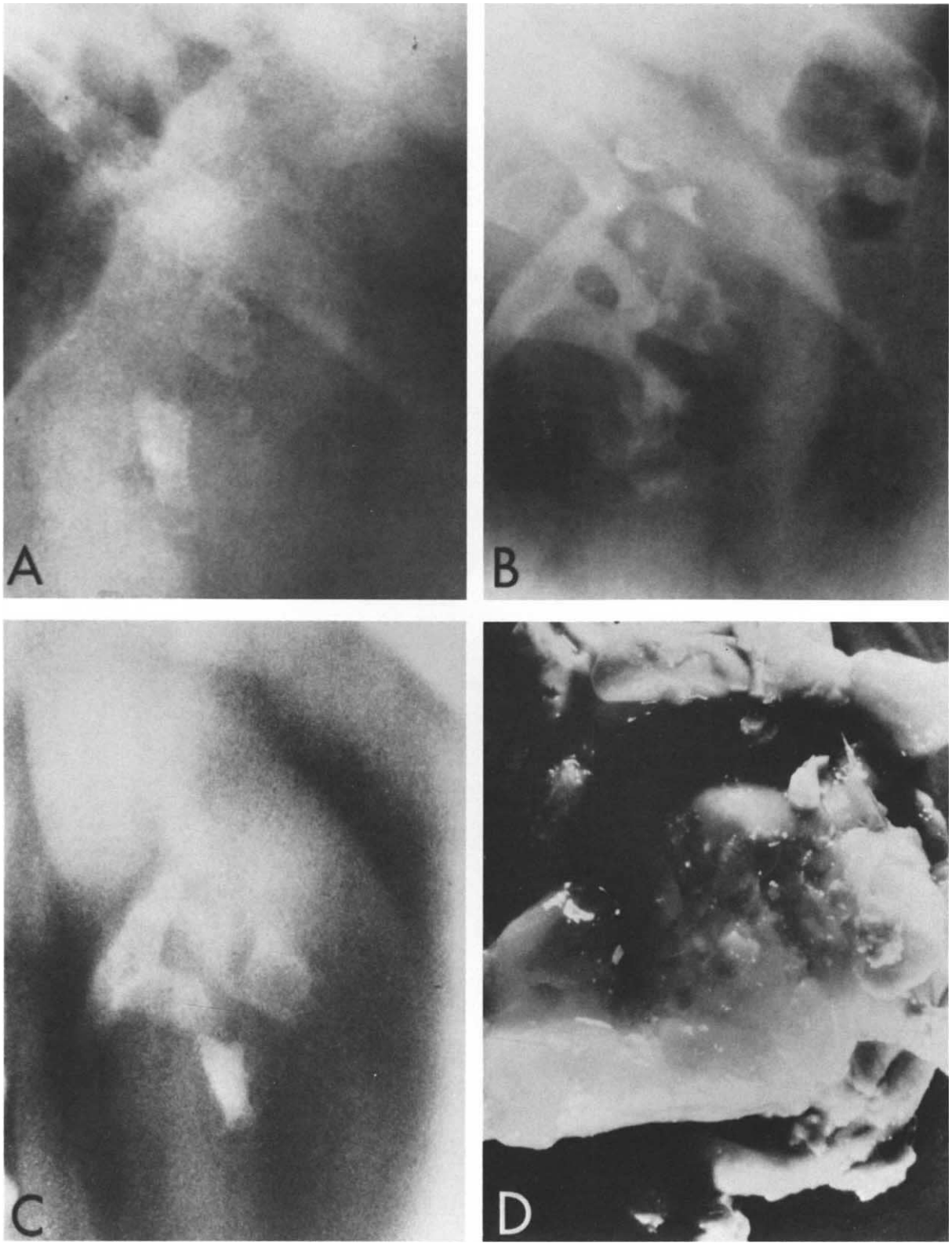

Fig. 3A. *A calyceal stone is present on plain film.* **B.** *A radiolucent cast of the pyelocaliceal system is apparent on the urogram.* (Reproduced from *Nephrolithiasis, Contemporary Issues in Nephrology*, vol. 5, edited by Fredric L. Coe., M.D., Barry M. Brenner, M.D., and Jay H. Stein, M.D. Copyright © 1980 by Churchill Livingstone. Reprinted with permission of Churchill Livingstone, New York.) **C.** *A staghorn stone is apparent on plain film 6 weeks after original plain film* (A). **D.** *A portion of the matrix concretion was subsequently recovered.* (Reproduced from *Nephrolithiasis, Contemporary Issues in Nephrology*, vol. 5, edited by Fredric L. Coe, M.D., Barry M. Brenner, M.D., and Jay H. Stein, M.D. Copyright © by Churchill Livingstone. Reprinted with permission of Churchill Livingstone, New York.)

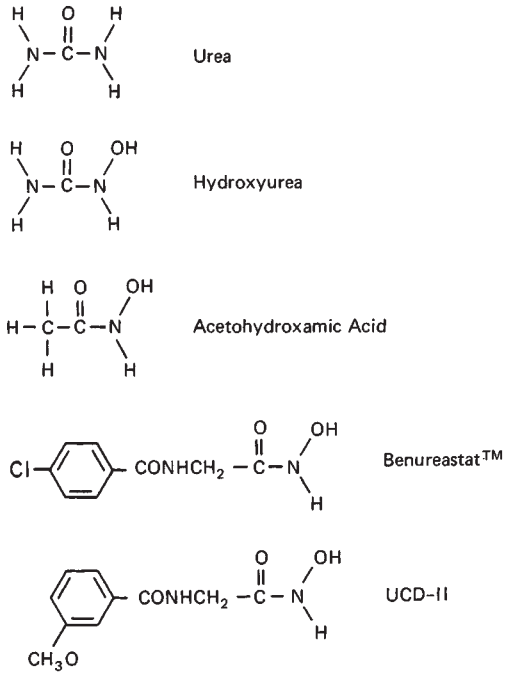

Fig. 4. *Molecular structures of urea and urease inhibitors.*

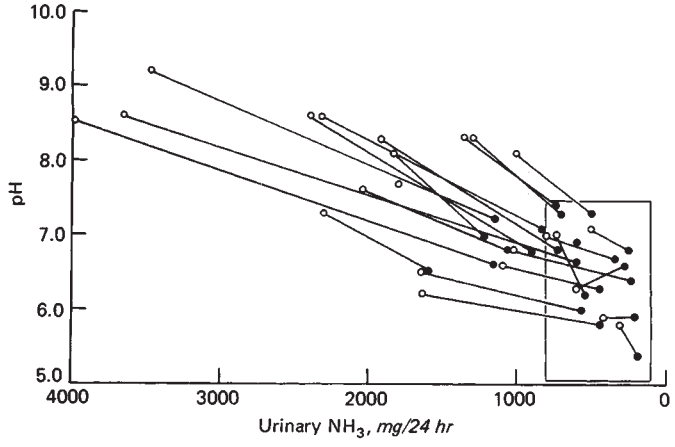

Fig. 5. *Changes in urinary pH and ammonia in 23 patients during long-term treatment with AHA at a dose of 1.0 g/day. Open circles* denote urinary pH and ammonia prior to AHA treatment. *Closed circles* denote urinary pH and ammonia while on AHA. *Rectangle* encloses ± SEM for ammonia and pH values in normal subjects (N = 20) with sterile urine. (Reproduced from Griffith DP, Gibson JR, Clinton CW, Musher DM: Acetohydroxamic acid: Clinical studies of a urease inhibitor in patients with staghorn renal calculi. *J Urol* 119:9–15, 1978; © The Williams and Wilkins Co., Baltimore.)

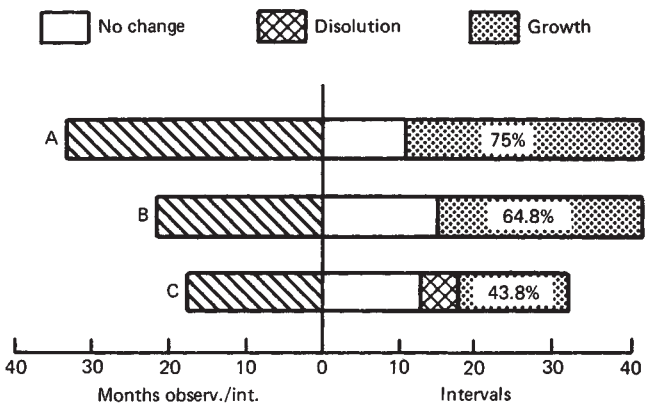

Fig. 6. *Incidence of stone growth in stone-containing kidneys.* Group A is untreated controls, Group B is pre-AHA treatment controls, Group C is AHA treatment group. N = 40, 42, and 32 respectively for Groups A, B, and C.

	x^2 *test*	*Statistical significance*	
A:B	t = 1.11	$P > 0.29$	Not significant
A:C	t = 7.31	$P > 0.007$	Significant
B:C	t = 3.10	$P > 0.07$	Significant
A + B:C	t = 6.50	$P > 0.10$	Significant

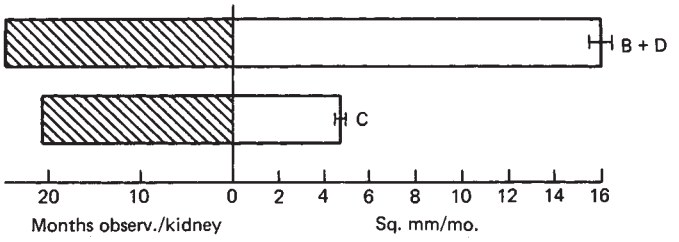

Fig. 7. *Stone growth rate in 40 patients paired against themselves.* Group B = Prior to AHA treatment; Group C = During AHA treatment; Group D = After AHA treatment; Wilcoxan signed rank test: Statistical significance t = 68.5, P = 0.001 highly significant

today who has a serum creatinine concentration of 2.5 to 3.0 mg/dl? Are any intraoperative strategies available today that were unknown, say, 10 years ago?

DR. GRIFFITH: As a rule, I would operate first on the kidney that is going to have the least benefit—in this case, the right kidney, which may have xanthogranulomatous pyelonephritis. If there is little improvement of renal function, the patient hasn't lost very much. If improved function results from the operation, the margin of safety is improved as I operate on the better kidney. Complete mobilization of the kidney will be required, and this is likely to require an incision at the eleventh rib. I would try to remain extrapleural, but there is high probability that the pleural space will be entered. A pyelolithotomy is unlikely to yield all of the stones. Therefore, I would perform a nephrolithotomy through the parenchyma. I also would utilize renal ischemia and hypothermia. Recently I have been inserting ureteral catheters preoperatively and instilling a coagulum composed of cryoprecipitate, thrombin, and calcium into the pyelocalyceal system. Often the soft, mushy, poorly mineralized matrix, an integral component of these stones, becomes trapped in this gelatinous coagulum. This method assists in the removal of debris. Before completing the procedure, I would take intraoperative radiographs to be sure that all of the stone had been removed. Finally, I would leave a nephrostomy tube in the kidney and would use the tube postoperatively to measure renal function and to lavage the pyelocalyceal system with an acidic stone solvent. After a few weeks I would approach the left kidney if the patient had done well.

DR. HARRINGTON: Dr. Meares, you have had an opportunity to examine this patient. Taking into account her weight of 100 kg and the complexities of this exceedingly difficult case, what

Table 2. Possible side effects of acetohydroxamic acid therapy[a]

	% Patients
Headache	75
Gastrointestinal upset	50
Anemia (mild)	17
Phlebitis[b]	13
Loss of hair	10
Rash with consumption of alcohol	8
Tremulousness	4
Anemia (severe)	3
Pulmonary emboli[b]	1.4

[a] Seventy-six patients were treated for 1309 patient months [23].
[b] Phlebitis was endemic in the study population, which contained a large population of patients with spinal cord injury. A cause-and-effect relationship with AHA treatment is doubtful.

are your thoughts and how do you manage patients with staghorn calculi?

DR. EDWIN M. MEARES, JR. *(Chairman, Department of Urology, NEMC):* When I saw her initially I thought the right kidney was not operable because I too believed it demonstrated xanthogranulomatous pyelonephritis. In such cases the dense inflammatory tissue surrounding the kidney often makes performance of anatrophic nephrolithotomy impossible. We had planned to explore the left kidney, provided the patient lost sufficient weight to make a transpleural approach unnecessary. Her body habitus was such that I believed the only way one could safely approach that kidney—mobilize it completely and obtain control of its blood supply—was through a thoracoabdominal incision. Although I use this approach routinely for large renal tumors, in this patient I did not want to risk a chest infection due to proteus and death from complications of surgery. Our plan was to manage her as an outpatient with diet and antibiotics in the hope that she would lose about 50 pounds; then we would operate. Unfortunately, she gained weight on this diet. Although I agree with Dr. Griffith that this patient's chances of surviving for very long without successful stone removal or dissolution are not good, I finally decided that she was not sufficiently motivated to lose the necessary weight to allow us to undertake surgical intervention safely.

My surgical technique in managing staghorn calculi is similar to the approach described by Dr. Griffith. The operation was popularized by Dr. William Boyce at Bowman Gray and usually is referred to as an anatrophic nephrolithotomy. The kidney is mobilized completely, the renal artery controlled, and the kidney cooled. A non-crushing vascular clamp is placed across the artery (the vein is usually left open); a nephrotomy incision allows the surgeon wide access to the renal pelvis and calices through the parenchyma with minimal blood loss. With renal hypothermia one can keep the renal artery clamped continuously for more than an hour. We always leave a nephrostomy tube in place to irrigate the kidney postoperatively with Renacidin® solution. In our experience, postoperative irrigation is an extremely important component of any operation on a staghorn calculus. Almost always, little fragments of stone that one cannot see on x-ray film are left attached to the urothelium and papillae following nephrolithotomy. This will cause the operation to fail because these infected particles serve as a nidus for re-formation of the staghorn.

DR. HARRINGTON: Dr. Griffith, would you comment about Renacidin®? What are your indications for its use?

DR. GRIFFITH: We use Renacidin® commonly but not routinely. If the stone is hard and can be removed intact without fragmentation, I do not use a nephrostomy tube or irrigation. If the stone is mushy, or if it is fragmented during extraction, I irrigate postoperatively with Renicidin® through a nephrostomy tube.

DR. JERRY BLAIVAS *(Department of Urology, NEMC):* If the decision in this case was to remove the stones on the left side only, would you think it important to remove the right kidney to lower the likelihood of recurrent proteus infection?

DR. GRIFFITH: Yes.

DR. HARRINGTON: What about using Renacidin® preoperatively?

DR. GRIFFITH: We have had no experience with this approach. Drs. Dretler, Pfister, and Newhouse from the Massachusetts General Hospital recently reported a favorable experience with percutaneous lavage of staghorn calculi using Renacidin® [29]. Dr. Heaney was on the staff at the M.G.H. during that time and might be able to provide more information.

DR. JOHN A. HEANEY *(Department of Urology, NEMC):* One of the problems with these patients was that although we could remove the radiologically obvious stone, we sometimes were unable to remove the matrix. Two of our patients at Tufts had stones on one side that we thought we could remove surgically, but each had a stone on the other side, in a kidney previously operated on, that we thought would be exceedingly difficult to approach surgically. We have a follow-up of one year on one patient in whom we completely dissolved the stones on the previously operated side with percutaneous nephrostomy and Renacidin® only. There are selected instances in which percutaneous stone dissolution can be accomplished, but we must keep in mind that stone dissolution with these methods is often complicated by recurrent infection and pain. Weeks of hospitalization may be required in patients in whom the expeditious surgical removal of the calculus or kidney would have the patient out of the hospital in 10 days.

DR. HARRINGTON: I believe that there are other ways of breaking up staghorn calculi, such as ultrasonic destruction of the stone. Could you comment on this new approach, Dr. Griffith?

DR. GRIFFITH: New technology is being developed in Europe that may permit "in situ" stone disintegration utilizing hydrodynamic shock waves without surgery [30, 31]. Another European approach utilizes operative nephroscopy combined with electrohydraulic lithotripsy [32]. Both of these approaches appear promising but are still investigational.

DR. JAMES STROM *(Renal Service, St. Elizabeth's Hospital, Boston, Mass.):* What are your usual indications for surgical therapy in patients with staghorn calculi? Because recurrent stones are common even with good surgical therapy and because one occasionally can sterilize the urine with antibiotics, some nephrologists simply treat with antibiotics and follow the patient carefully. If the urine is sterilized and if there isn't progressive renal insufficiency, surgery is not used. What do you think of that approach?

DR. GRIFFITH: I believe the approach to cancer treatment is analagous. If a patient presents with a malignant disease, do

you offer curative therapy, or do you offer palliative therapy?

DR. STROM: What I'm asking is how do you know whether you're dealing with "malignant stone disease"?

DR. GRIFFITH: All infection-induced stones are a potentially malignant disease. I believe that all patients with renal stones and a chronic urea-splitting urinary infection should be offered curative surgical treatment if they are reasonable candidates for operation.

DR. MEARES: I would like to add a comment. I believe that the cure rate following surgical treatment of staghorn calculi in the usual patient, not the patient presented, is probably much higher than 80% when the procedure is performed correctly. I believe that it is not in the patient's best interest to treat by medical suppression a condition that can be cured about 90% of the time by an operation in which the risk of death or loss of kidney function is very low.

DR. GRIFFITH: I agree.

DR. BARRY STRAUBE *(Renal Fellow, NEMC):* You commented that some staghorn calculi originate from a calcium oxalate stone or uric acid stone. Do you recommend thiazide or allopurinol therapy in these patients?

DR. GRIFFITH: Appropriate medical therapy is warranted and may consist of dietary alterations, drug treatment, or both. Stone analysis and biochemical evaluation of blood and urine should point the way toward appropriate medical treatment. I favor postoperative biochemical evaluation. The Mayo Clinic has reported a 50% incidence of underlying metabolic stones in patients with infectious stones [33]. Drs. Boyce and Resnick recently reported a 50% incidence of mixed stones in a series of patients with staghorn calculi [34]. Interestingly, preoperative metabolic studies had detected essentially nothing other than infection to account for the stones. When the metabolic studies were repeated postoperatively after the urine had been rendered sterile, a high incidence of hypercalciuria and hyperuricosuria was found. These findings probably can be explained by the improvement in renal function consequent to elimination of stones and infection.

DR. ANDREW LEVEY *(Renal Service, NEMC):* You have clarified the pathogenesis of the infection-induced stone. Would you speak for a moment on what causes infection-associated stones? Do the bacteria in urine nucleate stones in patients whose urine is already supersaturated with minerals such as calcium or urate, or do stones allow a nidus of bacterial infection to persist?

DR. GRIFFITH: I believe that urinary infection and stones are separate entities. Sometimes they coexist in the same patient. A stone that becomes infected can harbor and perpetuate the infection, but the stones themselves do not cause infection. Only urease-producing bacteria cause calculogenesis.

DR. STEVEN ZELMAN *(Renal Fellow, NEMC):* You have shown that AHA reduces both the urinary pH and the ammonium concentration, presumably as a result of a reduction in urease activity. If antibiotics are suppressing bacterial growth and urease production, what additional benefit does AHA provide?

DR. GRIFFITH: If sterile urine can be achieved with antibiotics, AHA may not be needed. If consistent sterility cannot be achieved, then concomitant treatment (with antibiotics and AHA) is likely to reduce the quantity of urease and block the urease that is produced.

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