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Urease Stones*

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Summary. Urinary stones form as a consequence of urinary supersaturation. Supersaturation occurs as a result of elevated concentrations of urinary solutes. Dietary, metabolic, endocrine, hereditary, and infectious processes alter urinary solute concentrations. Struvite ($MgNH_4PO_4 . 6H_2O$) and carbonate-apatite [$Ca_{10}(PO_4)_6CO_3$] stones form in urine that becomes supersaturated as a by-product of the hydrolysis of urea by the bacterial enzyme urease. Urease-induced stones manifest primarily as branched renal calculi and as bladder calculi. Conventional therapy has usually consisted of surgical removal of the stone combined with a short course of antimicrobial therapy. Such treatment is curative in about 50% of cases. Recurrent stone formation and progressive pyelonephritis occur in those who are not cured. Adjunctive medical treatment with acetohydroxamic acid or hydroxyurea lessens the risk of calculogenesis and decreases growth of residual stones in patients who are not cured by conventional therapy. Patients with urea-splitting urinary infection and renal stones have a major life-threatening disease. The morbidity and expense that result from this disease are great. Long-term (perhaps lifetime) chemotherapy with antimicrobial agents and/or urease-inhibiting drugs combined with judicious and expert surgical intervention can be expected to significantly improve the plight of these unfortunate patients.

Key words: Staghorn calculi, Urea splitting organisms, Urease inhibitors.

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The association of urinary infection (putrefaction) and lithogenesis has been known since antiquity (1, 3). Marcet (1817) suggested that the evolution of ammonia during putrefaction alkalinized urine and that such alkalinization was "unavoidly attended by the precipitation of phosphates contained in urine" (3). Brown (1901) demonstrated the coexistence of "triple phosphate stones" and urea-splitting bacteria (2). Hagar and Magrath (1923) suggested that the bacterial enzyme urease was the biochemical basis of the urea-splitting reaction and thereby infection-induced stones (11). Bacteria apparently induce calculogenesis primarily, if not solely, by means of urease (10).

Urease is produced by all strains of Proteus species. A high percentage of Pseudomonas, Klebsiella, Providencia, Serratia and Staphylococcal strains also produce urease. E. coli, however, rarely if ever produces urease (7). Some strains of Mycoplasma pneumoniae also produce urease (12).

Most investigators agree that solute crystallization can occur only in the presence of supersaturation. Pathologically high urinary concentrations of OH^-, NH_4^+, and $CO_3^=$ are necessary to induce supersaturation with respect to struvite and carbonate-apatite. Pathological elevation of these ions to the degree required for crystallisation of struvite and carbonate-apatite can be achieved only by the hydrolysis of urea (Fig. 1). Pathologically elevated concentrations of calcium and phosphate will induce crystallisation of brushite ($CaHPO_4$) and hydroxyapatite [$Ca_{10}(PO_4)_6 . (OH)_2$] but will not crystallize carbonate-apatite.

Inhibition of the urea-splitting process by acetohydroxamic acid (AHA) or hydroxyurea (Fig. 2) which act as inhibitors of urease blocks pathological elevation of urinary OH^-, NH_4^+, and $CO_3^=$

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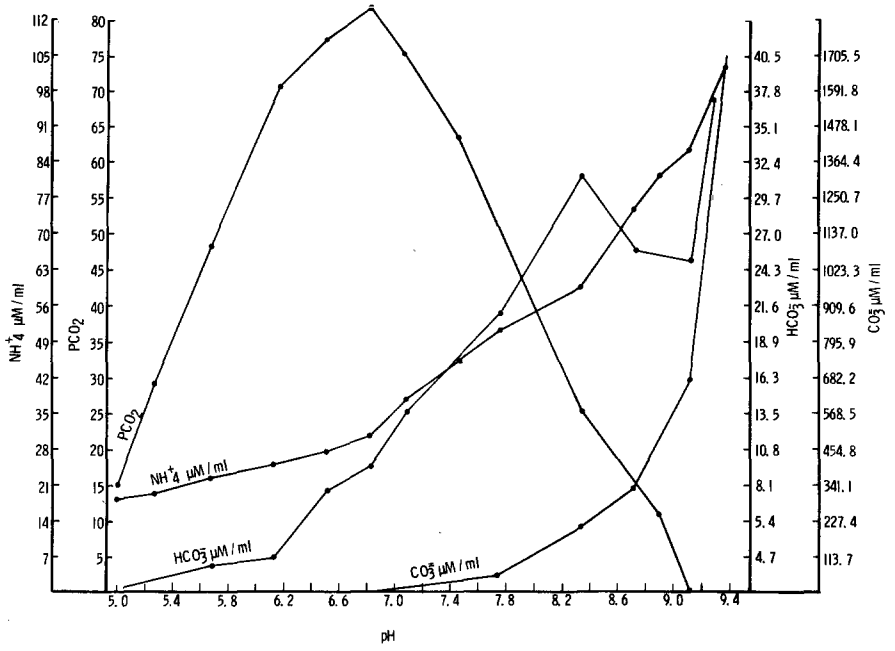
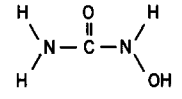
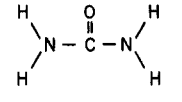


Fig. 1. Changes in solute concentration induced by the hydrolysis of urea. These changes occurred (during two hours at 37°C) in a beaker of human urine inoculated with jack bean urease. Similar experiments with Proteus bacteria and bacterial urease yielded similar results. The solute changes did not occur if the urine contained AHA


HYDROXYUREA


UREA

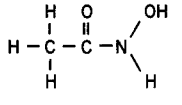

ACETOHYDROXAMIC ACID

Fig. 2. Molecular model of urea, hydroxyurea, and AHA

and effectively prevents precipitation of calcium phosphate and magnesium phosphate (Fig. 3).

The role of organic substances (matrix) in the pathogenesis of struvite and carbonate-apatite stones is incompletely understood. Poorly mineralised matrix concretions commonly occur in the presence of urea-splitting infection. It seems likely that infection-induced pyelitis and ureteritis cause a "weeping" of proteinacious debris from the urothelial surface. This material (so-called matrix) may obstruct portions of the collecting system and/or serve as a nidus for stone formation from the coexistent crystallization of struvite and carbonate-apatite. Figure 4 details a case that supports this contention.

CLINICAL MANIFESTATIONS

Urease-induced stones commonly manifest as matrix concretions in the renal pelvis, branched or staghorn renal calculi, or as bladder calculi. The renal calculi commonly cause caliceal obstruction, pyonephrosis, parenchymal atrophy, and chronic pyelonephritis. The bladder stones usually form around indwelling bladder catheters. Urease stones occasionally obstruct the ureter; in such circumstances, the patient commonly presents with life-threatening urosepsis.

Urease stones maybe composed primarily of carbonate-apatite or struvite. Both types of crystals, however, are invariably present. Urease stones may develop secondarily on a preexistent metabolic stone (Fig. 5). Urease stones are notoriously resistant to curative treatment. Total removal of all calculous material and matrix debris and eradication of urinary infection are required to effect a cure. Residual stones virtually assure persistent urea-splitting infection and the persistent infection results in a very high incidence of stone growth or stone recurrence. The

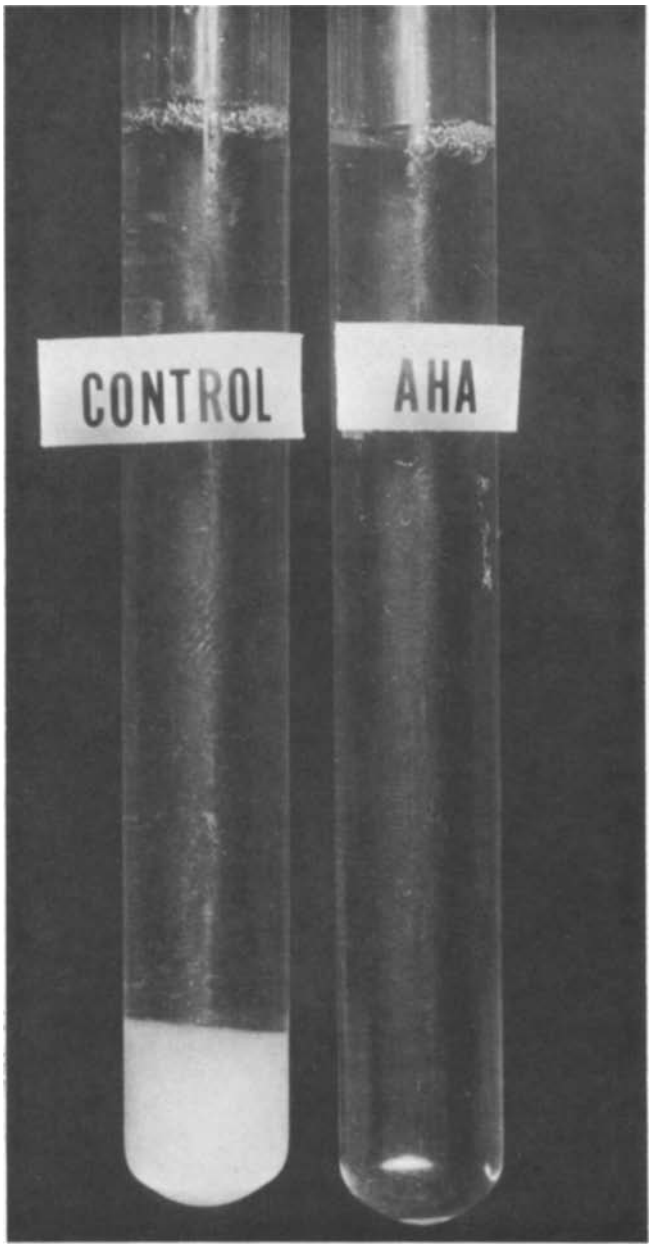


Fig. 3. Urease-induced crystallization of struvite and apatite. Both tubes initially contained human urine at pH 5.5. AHA was added to one tube, and one tube served as a control. Proteus mirabilis (10^6 colonies/ml) was added to both tubes, which were maintained at 37°C. This photograph was taken after 24 hours of incubation, at which time there were 10^9 colonies of P. mirabilis in both tubes. The precipitate in the control tube (left) was composed of struvite and carbonate-apatite crystals and amorphous calcium phosphate

true incidence of stone recurrence in patients with persistent postoperative urea-splitting infection is unknown. A recent review of published renal lithotomy series suggests that chronic infection persits postoperatively in about 40% of cases and that recurrent stones develop within six years in about 30% of case (7). If recurrent stones develop only in those patients with persistent postoperative infection, then the incidence of stone recurrence in patients with persistent postoperative infection may be as high as 70-80%.

Patients treated medically fair no better and perhaps have a more morbid prognosis than those treated surgically. Fifty percent of those treated medically ultimately lose kidneys (14,16). The persistent, progressive nature of this morbid and sometimes life-threatening disease has prompted some clinicians to refer to urease stones as "stone cancer."

COMBINED MEDICAL-SURGICAL THERAPY

Recent clinical investigations suggest that urease-inhibiting drugs may be useful adjunctive chemotherapeutic agents in patients in whom conventional therapy has failed to effect a cure. Acetohydroxamic acid and hydroxyurea effectively inhibit bacterial urease in urine (8,15). These agents reduce pathologically elevated levels of urinary pH and ammonia and thereby reduce urinary saturation with respect to struvite and carbonate-apatite. Long-term treatment with AHA retards growth of existing stones and prevents new stone formation in patients whose chronic urea-splitting infection is recalcitrant to eradication (9) (Fig. 6). In rare indstances, stone dissolution has occurred in patients receiving AHA and/or hydroxyurea (9,15).

These drugs are more efficacious in preventing stone growth or stone recurrence when there is minimal obstruction and stasis within the urinary collecting system. AHA improves urinary chemistry minimally in the presence of segmental or generalised pyonephrosis. Therapeutic concentrations of AHA (10-70 μg/ml) are achieved in urine only if renal function is reasonable (i.e., glomerular filtration rate of approximately 30 ml/min).

Adjunctive treatment with AHA and/or hydroxyurea (with or without concomitant antibiotics) is likely to be most effective in preventing stone growth and/or stone recurrence in patients whose obstructive uropathy has been surgically relieved and whose infection persists postoperatively. An illustrative case is depicted in Figure 7.

Both AHA and hydroxyurea inhibit DNA synthesis and depress bone marrow. Both are teratogenic in high doses. AHA has induced a haemolytic anaemia in about 10% of patients treated to

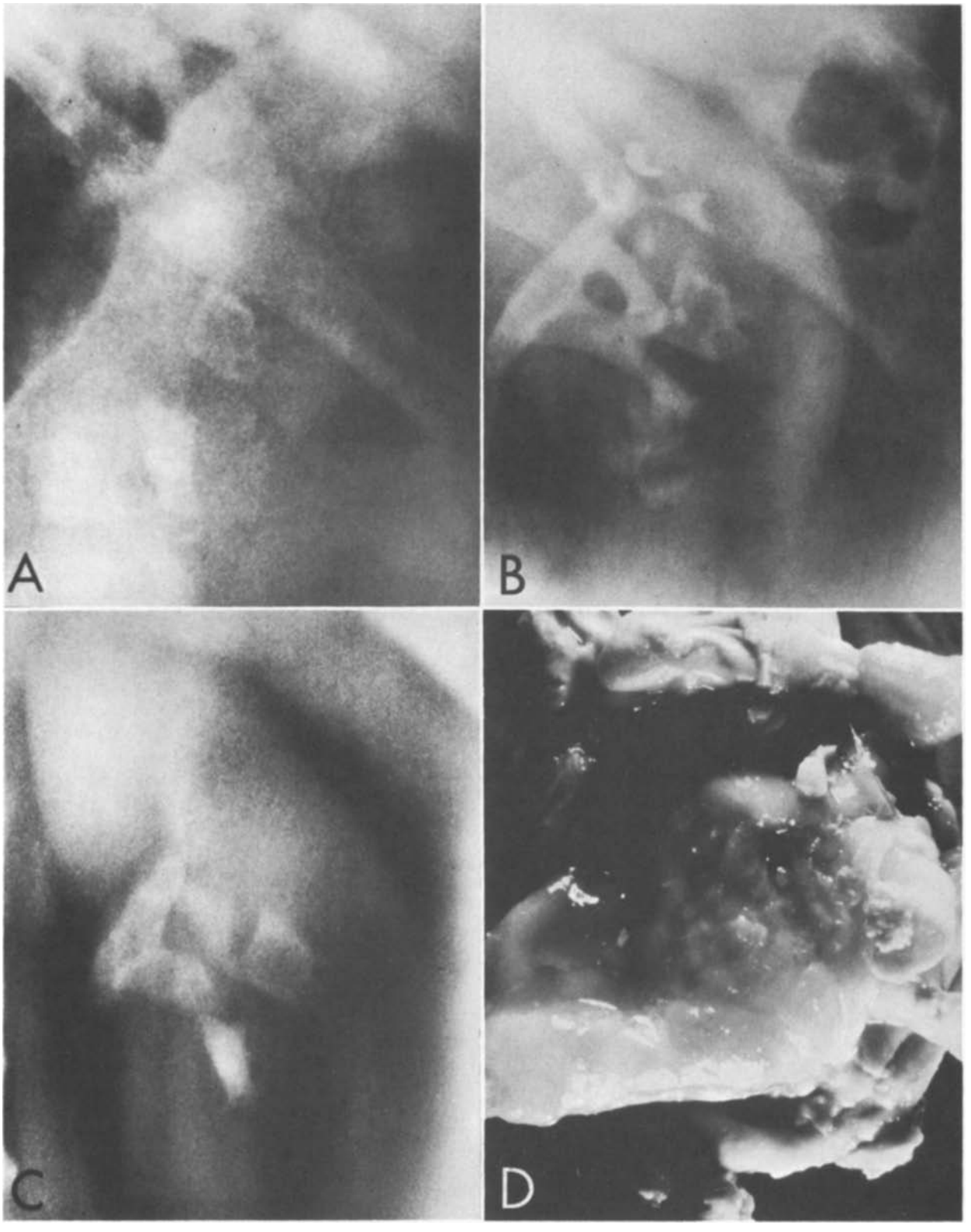


Fig. 4. Rapid crystallization of a matrix concretion. P. F., a 42-year-old female, presented with a Proteus urinary infection, an opaque lower caliceal stone (A, plain film) and an associated matrix stone (B, excretion film). Within 6 weeks the matrix was a rapidly mineralizing staghorn (C, plain film). After 6 weeks of sterile urine (while on culture-specific antibiotics), a portion of the poorly mineralized matrix (D) was passed spontaneously. The concretion was composed of mucoproteins, cellular debris, and struvite and carbonate-apatite crystals

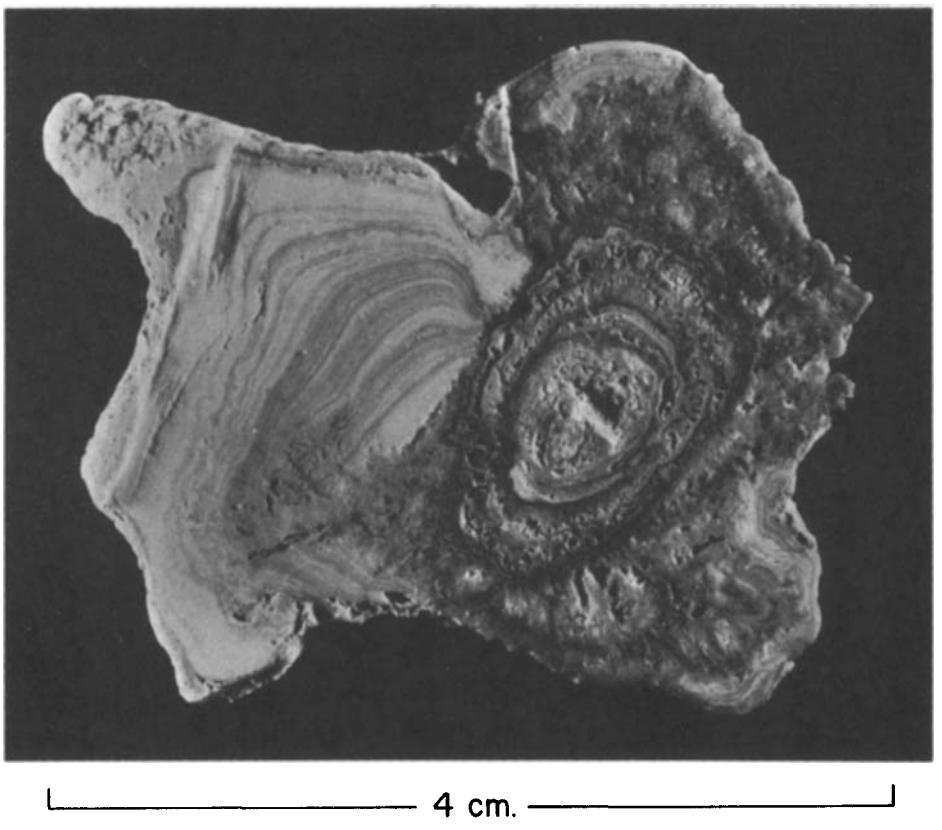


Fig. 5. Cross-sectional surface of a staghorn calculus. The right side of the stone is composed of calcium oxalate and hydroxyapatite (i. e., a metabolic stone). The left side is composed to struvite and carbonate-apatite (i. e., an infection stone)

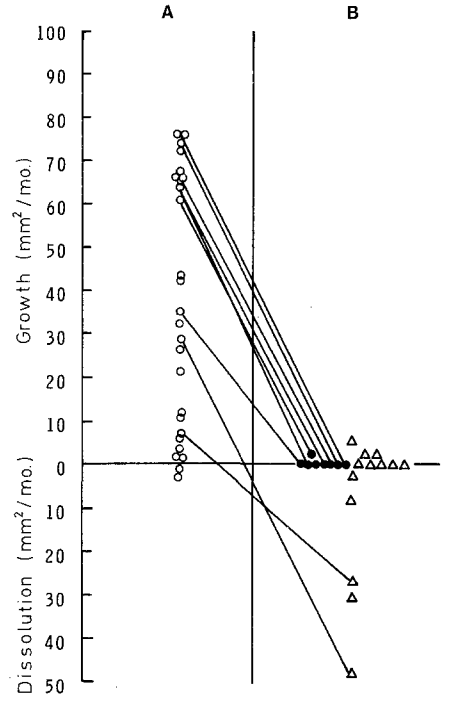


Fig. 6. Stone growth/dissolution rate in patients with branched renal calculi and resistant urea-splitting infection. Growth/dissolution rates were determined by measuring the stone's area with a planimeter and dividing the change in stone size by the number of months between sequential radiographs. All observations were for 6 months or longer. Group A patients were treated unseccessfully (i. e., urine remained infected) with antibiotics. Group B patients (also infected) were treated with AHA. Lines connect patients who were observed during both control (Group A) and AHA (Group B) treatment periods. ● = stone free but chronically infected postoperatively. O and △ = non-operated patients with renal stones and chronic resistant urea-splitting infection

date (9). The anaemia is dose related and reversible. A reversible thrombophlebitis has occurred in four patients treated with AHA; all had pre-existent varicosities in their lower extremities. Deep vein thrombosis has occurred in one patient. Embolic phenomena have not occurred. All patients improved following cessation of treatment with AHA and institution of appropriate medical therapy. Treatment with AHA has been re-initiated in all but two patients; none has developed recurrent problems.

Hydroxyurea is available clinically to treat neoplasms – notably melanoma, chronic myelocytic leukemia and metastatic ovarian carcinoma. Bone marrow suppression by hydroxyurea is dose related and reversible. Leukopenia is the primary manifestation of this toxicity (4).

Clinical comparisons of the relative safety and efficacy of hydroxyurea and AHA have not, to my knowledge, been reported. In vitro com-

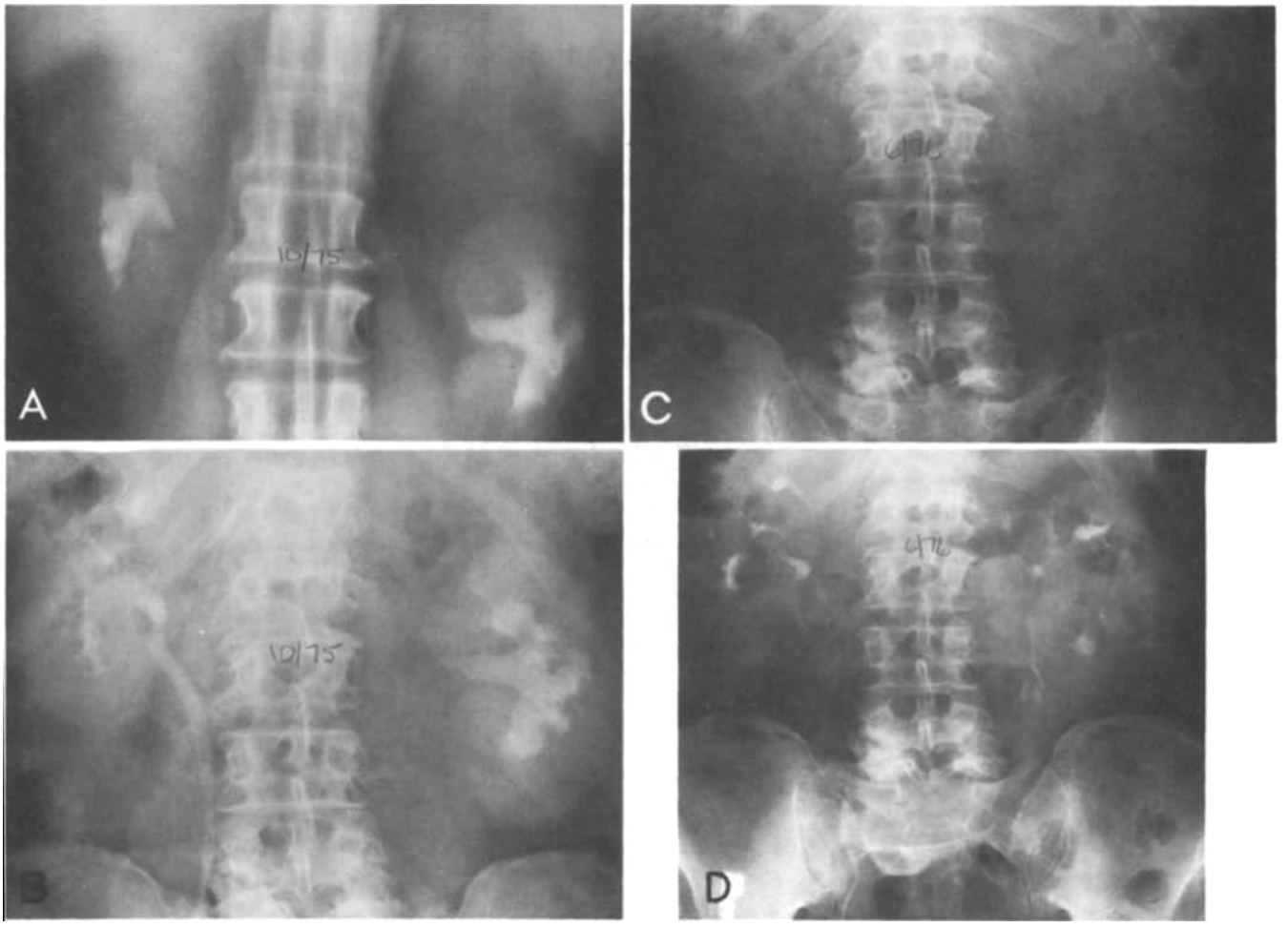


Fig. 7. Surgery and adjunctive chemotherapy. W. M., a 66-year-old male, presented with bilateral staghorn calculi (A). There was no visualization of the left collecting system on excretory urography (B). Fourteen months earlier a staghorn calculus was removed from the left kidney. A stone fragment was left behind and the chronic Proteus infection persisted. The right kidney contained no stones at this time. Following bilateral nephrolithotomies, both kidneys were stone free (C) and functioning (D) but the Proteus infection persisted. He has been maintained on AHA for all but four months (terminated because of transient phlebitis) of the past three years. A small caliceal stone (too small to illustrate) developed while the patient wias off of AHA. There has been no growth of the stone since reinstitution of AHA (1 1/2 years)

parisons suggest that AHA is a considerably more potent inhibitor of urease than hydroxyurea (5, 6). Experimental studies have shown that AHA is approximately one tenth as cytotoxic as hydroxyurea (13).

CONCLUSION

The hydrolysis of urea by the bacterial enzyme urease is the primary biochemical reaction responsible for the crystallization of struvite and carbonate-apatite. Urease stones manifest clinically as staghorn renal calculi and/or bladder stones associated with indwelling catheters. Curative treatment is attendant upon elimination of the stone and eradication of the urinary infection. Failure to achive these goals results in a high incidence of recurrent calculogenesis and repeat operative procedures.

A combined medical and surgical approach similar to that utilised for the treatment of malignant disease is likely to produce a more satisfactory therapeutic result than either medical or surgical treatment alone.

Comprehensive patient education and long-

term (perhaps lifetime) bacteriologic and radiographic follow-up coupled with long-term treatment with urease-inhibiting drugs with or without concomitant antimicrobial agents can be expected to reduce the morbidity and mortality currently associated with urease-induced urolithiasis.

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