THE CHEMICAL DISSOLUTION OF URINARY CALCULI BY IRRIGATION

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INTRODUCTION

During the past few years, many aspects of the treatment of urinary lithiasis have changed. Numerous clinical and experimental observations on the etiology of calculi have been made. Many of these recent observations are now being made use of in the treatment of urinary lithiasis and the prevention of recurrence following surgery.

Urologists have searched for years for a method of chemical dissolution of stones. During the past decade many efforts have been made to accomplish this. Surgeons are aware of the high mortality rate in the surgical treatment of urinary calculi. This is especially true in suprapubic surgery for stones. This fact has driven investigators constantly on in the search for a medical method of dissolving stones.

ETIOLOGY OF CALCULI

The relationship between urinary calculi and dietary deficiency has been reported by many men who based their deductions on the occurrence of definite "stone areas" throughout the world. The majority of people living in these "stone areas" were known to exist on diets poor nutritionally. (17). Following the world war there was a definite increase in the incidence of lithiasis in many parts of Europe. This increase was thought to be the result of the improper and inadequate diets during the war and post-war period.

Experimentally, the relationship between Vitamin A deficiency and calculous disease has been proved (15). Albino rats maintained on a diet deficient in Vitamin A develop bladder and renal calculi. In addition there is produced keratinization of the epithelium of the genito-urinary tract, urinary infection, and alkalinuria. All these conditions disappear when cod liver oil is added to the diet. The composition of stones produced experimentally by dietary deficiencies differs with the mineral content of the diets (16). In cases of urinary lithiasis studied at Higgin's Cleveland Clinic from 68 to 74 per cent gave biophotometric curves of Vitamin A deficiency.

Keyser (25) does not believe Vitamin A deficiency to be so important as an etiological factor as asserted by others. He points out that Vitamin A deficient diets used in producing calculi in experimental animals also produce changes in the cornea, respiratory tract, etc., which changes are almost never seen in patients with calculi in this country.

Urostatis is definitely associated with the formation of calculi. The importance of the time element in the precipitation of the insoluble salts of urine was shown by Holt (18). Hunner (20) showed that mechanical factors producing residual urine in the urinary tract were not only important in the etiology of renal and vesical lithiasis due to urostasis but also contribute to urinary infections.

Infection is known to be an etiological factor in the production of calculi. Bugbee (17) showed pyelonephritis had preceded stone formation in 23 of 29 cases of renal calculi reviewed by him. Urea splitting organisms are especially important as the urea is converted to ammonia, giving a basic reaction which favors the precipitation of calcium salts. Hyrntschak (19), Keyser (24), and others have produced calculi in experimental animals by injecting urea-splitting organisms intramuscularly. However, it was necessary to first produce stasis by partially tying off the ureters with silk sutures.

Focal infection is claimed by Rosenow and Meisser (17) to be a cause of lithiasis. They base their claims on an experiment in which they inoculated the pulps of the teeth of six dogs with streptococci isolated from the urine of patients with urinary lithiasis. Calculi developed in the dogs and the specific streptococci was isolated from the dogs' urine.

Barney and Mintz (14), Albright and Bloomberg (2), Barney and Sulkowitch (5), and others have stressed the association of renal lithiasis and hyperparathyroidism. These workers concluded that hyperparathyroidism is responsible for from 4 to 5 per cent of the cases of renal lithiasis; in almost 70 per cent of cases of hyperparathyroidism, stones are present; and in 38 per cent of the cases of hyperparathyroidism, the patients have pathological changes in the bones and urinary tract.

Griffin, Osterberg, and Braasch (13) and Higgins (17) have found hyperparathyroidism to be an etiological factor in urinary lithiasis in only 0.1 to 0.2 per cent of all cases. In view of the fact that workers specializing in the study of hyperparathyroidism (Albright, etc.) have more of these special cases referred to them, Higgins figures are more likely to be accurate.

Randall, in 1937, (33) pointed out that renal calculi in the absence of pelvic obstructions must have an initiating lesion in order to grow. He has found calcium plaques in renal papillae in about one-fifth of all post mortems made in a large series. Small stones growing from these plaques occurred in one-third of the calcified plaques found. The cause of this calcification of renal papillae is not known, but it may well be the initiating lesion for the formation of renal calculi.

Metabolic diseases such as gout, phosphaturia, or cystinuria, a disease of intermediate protein metabolism, are frequently associated with calculi (35). Calculi frequently follow recumbent diseases, orthopedic conditions, and diseases of bone (39). In these diseases there is decalcification of bone from disuse with consequent elevation of blood calcium. This results in hypercalcinuria which favors the precipitation of calcium salts from the urine.

FACTORS INFLUENCING THE SOLUBILITY OF THE SALTS OF URINE

Urine is a solution of many salts and organic materials. If these salts were present in water in the concentrations existing in urine, the solution would be supersaturated and precipitation would occur. An examination of the factors influencing the solubility of these salts may explain why in the urine of one person they remain in solution while in that of another they precipitate and form stones.

The compounds most frequently encountered in urinary sediments and concretions are the phosphate, oxalate, and carbonate of calcium, magnesium ammonium phosphate, uric acid, sodium urate, and ammonium urate (36).

From a table of solubility products the following figures may be obtained:

Compound.	Solubility product.
$Ca_3(PO_4)_2$	3.16×10^{-32}
$MgNH_4PO_4$	2.5×10^{-13}
Mg OH	1.2×10^{-11}
CaC_2O_4	2.6×10^{-9}
$CaCO_3$	9.3×10^{-8}
$CaHPO_4$	2.5×10^{-6}
$MgCO_3$	2.6×10^{-5}
MgC_2O_4	8.57×10^{-5}

The figures, however, apply to water solutions of the salts concerned and do not take into consideration the factors in urine which tend to keep the compounds in solution. However, the solubility products explain why these substances are more commonly found in stones.

Among the factors affecting the solubility of the above compounds is the acidity of the urine. Myers (36) found the degree of hypersaturation of relatively insoluble electrolytes in normal urine at various acidities to be:

Reaction pH	5.0	6.0	7.0	8.0
	Degree of supersaturation			
Secondary calcium phosphate	1/1.5	2	3.5	4.0
Tertiary Calcium phosphate	1/3	1.9	8.0	22.
Magnesium ammonium phosphate	1/5.6	1/1.3	7.5	5.6
Calcium Carbonate	1/132	1/13	1/1.3	7.7
Primary ammonium urate	1.5	2.2	2.3	1.8
Primary sodium urate	1.4		2.2	
Calcium oxalate	1.6		1.7	
Uric Acid	4.3		1/10	

the figures above represent the ratio of the solubility of the salts in urine as compared to water at the pH indicated.

Neutral salts such as sodium chloride greatly increase the solubility of calcium oxalate seven to eight times. It is well established that the solubility of a given salt may be markedly increased by the presence of other electrolytes in solution. Formation of soluble complex ions due to loose combination of the simpler ions is probably concerned in the phenomenon.

Holt (18) showed the solubility of $Ca_3(PO_4)_2$ to be enormously affected by neutral soluble salts and by the presence of insoluble salts of calcium such as the urate, carbonate, and perhaps also the oxalate. Sisk (36) proved that in normal urine, uric acid is twelve to seventeen times supersaturated on a solubility in water basis, but taking into account the acidity and neutral salt effect it is 4.3 to 0.1 supersaturated from pH 5.0 to 7.0, respectively. The system is complicated by the fact that the ionic strength of urine, and hence the solubility of the insoluble calcium salts in it, is subject to great variations.

Holt (15) also showed the phenomenon of delayed equilibrium to be a factor of considerable importance. The extreme slowness with which certain solutions of calcium phosphate approach equilibrium has been noted by many investigators. Delayed equilibrium causes $Ca_3(PO_4)_2$ precipitates to vary greatly in composition due to admixture with secondary phosphates.

Vergar (37) (cited by Snapper) was the first investigator to show the effect of the salts of organic acids on the solubility of certain insoluble calcium salts. He called this phenomenon the hydratropic effect and named these organic salts hydrotropic substances. Vergar's results showed that sodium salicylate increases the solution of calcium from calcium carbonate. Snapper then tried other organic salts. He showed that solutions of sodium salicylate, sodium benzoate, sodium hippurate, etc., dissolve more calcium oxalate than does water alone.

It was also demonstrated by Medes (29) that urea increases the solubility of calcium oxalate and uric acid. The solubility of oxalates in urea rises continuously on increasing the amount of urea in the solution but the solubility of uric acid in urea rises until a 10 per cent solution is reached and then decreases. This decreased solubility is due to a reaction between urea and water by which water is made less available as a solvent. Urea as the unsaturated amide of carbonic acid combines with acids to form salt-like compounds, many of which are highly soluble. Urea also forms addition compounds with salts, probably through the residual valences of its nitrogen and oxygen.

However, the fact that so many practically insoluble substances are found in urine in supersaturated condition is only partly explained by the presence of hydrotropic substances. Lichtwitz (37) (cited by Snapper) demonstrated, by means of ingenious experiments, that many of the substances which,practically insoluble,remain in solution in urine,do so because of the presence of certain protective colloids, the composition of which is not definitely known. On the other hand, it is certain that mucin, and certain colloidal pigments such as urochrome, are labile colloids which precipitate easily, whereas nucleic acid and chondroitic sulphuric acid are stabile colloids, under the protective influence of which insoluble substances may remain in solution. Snapper (37) believes that when the labile colloids of urine preponderate over the stabile colloids, they precipitate forming a colloid nucleus for the precipitation of mineral salts and the formation of calculi.

The study of the complicated colloid frame, which exists in every stone, proves that the development of a calculus does not start with the formation of a crystalline precipitate. On the contrary, the central nucleus of a stone is formed by colloids. The nucleus consists usually of a minute mucin or fibrinogen particle, and occasionally a foreign body. This organic nucleus is then encrusted by one of the less soluble urine compounds. On this encrusted stone-nucleus a new colloid precipitation develops; this layer is encrusted again, and in this way the stone grows successively by precipitation of concentric colloid layers which are encrusted in due course of time. Therefore, the growth and devdopment of urinary calculi are bound to the formation of a colloid nucleus and a colloid frame.

A great deal of work has been done to determine the mode of action of urinary colloids. This field is in a state of great confusion at the present time. Ferguson (10) points out that irritation, trauma and infection which may be associated with the presence of urinary calculi increase the colloids in urine as a result of mucin, blood and pus formation. In clinical experience these factors aggravate stone growth. Also urines of patients with urinary calculi were compared with normal urine as to the colloidal protective properties of each group by the use of the gold number. By gold number is meant the amount of protective colloid that, when added to a standard gold solution, just fails to prevent a certain standard color change. The filtered urines from the calculi-formers exhibited higher gold numbers and hence greater protective colloid properties than normal urines. This contradicts the theory that lack of protective colloids in urine is a factor in calculus formation.

Newcomb (31) showed that the solubility of calcium oxalate in pure water is the same as a solution of urinary colloids abtained by dialysing urine. Also, upon dialysing urine the uric acid distributed itself evenly in the solution on both sides of the dialysis membrane showing uric acid is not firmly attached to the colloids. If normal urine is dialysed and the dialysate evaporated to the concentration of the original urine no precipitation occurs if the acidity is kept at, or restored to, its original value. He does not doubt that colloids exist in urine, but he does not believe that they have any considerable influence on the precipitation of such constituents as ordinarily go to form urinary calculi. However, the workers who believe in the colloid factors argue that it is not the amount of colloid present, but the degree of dispersion and specific nature that determines their ability to increase the solubility of insoluble salts.

Also it is known (36) that the absorption of colloids as foreign substances on crystal surfaces may retard further precipitation of the salt from a supersaturated solution. "Intermediate colloid stabilization" or the effect of colloids on the size and rate of settling out of crystals retards flocculation and inhibits precipitation.

Some dyes retard the precipitation of salts from supersaturated solutions. It is conceivable that the coloring substances present in urine may retard the precipitation of crystalloids.

It is certain that the precipitation of a substance will not take place unless the substance is supersaturated with respect to its solution. Co-precipitation causes urinary stones to generally consist of mixtures of substances. Thus when the principal substance precipitates out it tends to cause the other insoluble substances in urine to precipitate out in lesser quantities.

MEDICAL TREATMENTS IN URINARY LITHIASIS

The recent advances in the knowledge of the etiological factors of stone formation are now being used in the treatment of lithiasis.

In the past few years, the use of dietary methods in the management of urinary lithiasis has been stressed by Higgins (15). The dietary treatment is as follows:

1. High Vitamin A diet.
2. High acid-ashless diet.
3. Acidifying drugs by mouth.

Higgins' results show the dietary regimen to be most applicable (1) in the prevention of recurrent renal lithiasis, (2) in the prevention of the formation of urinary calculi in patients with orthopedic conditions, and (3) in the prevention of the formation of calculi in patients who pass stones at frequent intervals but in whom a calculus is not demonstrable in the kidney. The treatment should not be used if a calculus is producing obstruction and thereby causing renal damage or if a co-existing infection is present which cannot be eradicated because it is obvious that if the urine cannot be kept no benefit is likely to result.

The forcing of fluids is indicated for all kinds of stones. The more dilute the urine, the less chance there is for a precipitate to form. Albright (81) believes that there is no contraindication to having urine very dilute when one is trying to obtain a very acid urine. Forcing of fluids is also indicated for its mechanical flushing effect.

Albright begins his medical treatment by determining true nature of the stone. If no material is available for analysis, one has to try to arrive at the composition by circumstantial evidence such as the visibility of stones by x-ray, the dietary habits of the patient, the composition of the urine, the size of the stones, etc. Alkaline urine is indicated in cystine and uric acid stones.

In discussing the ingestion of ammonium chloride as an acidifying drug for urine, Albright (1) emphasizes its dangers in the presence of infection. The ammonia is converted to urea by the liver, thereby releasing hydrochloric acid for acidification. It reacts with buffers of the blood to form NaCl and to increase the ratios of buffer acids to buffer salts, thereby lowering the pH of blood according to Hasselbalch's equation. The blood acidosis is reflected in a lowered pH. The blood acidosis causes absorption of calcium and phosphate from the bones and their secretion in the urine. If urea-splitting organisms are present in the urinary tract, urea is split to ammonia and alkaline urine results, thereby tending to facilitate precipitation of calcium phosphate from the urine.

Higgins points out that the dietary treatment is recommended in only a limited group, that close co-operation between the physician and the patient is extremely important, that it is essential to know the pH of the urine from the kidney containing the calculus before treatment is instituted, and that it be checked at intervals while the patient is following treatment. Higgins' results show:

1. A group of 32 patients with calculi too large to pass spontaneously have responded favorably to dietary management.

2. A group of 79 patients who passed calculi at frequent intervals have been relieved of symptoms for a period of two years.

3. The incidence of recurrent calculus has been reduced from 16.4 to 4.7 per cent by addition of the dietary regimen to other therapeutic procedures employed in the past.

Snapper (37) believes that all factors which tend to stabilize labile colloids must help to prevent the formation of stones. The presence of salicylates, mandelates, hippurates, and other organic salts in urine may, by increasing the solubility of urinary colloids, exercise a prophylactic influence against the formation of stones. He showed that administration of sodium benzoate by mouth did (1) prevent stone formation in rats on a calcium carbonate rich diet, (2) stop phosphaturia in man, (3) diminish renal colic in patients. He believed that other more powerful stabilizers of the colloids of urine might be used for this purpose.

Chutes (3) does not question that an occasional calcium phosphate stone will disappear with Higgins' treatment, but considers that most stones fail to dissolve because the urine is very nearly saturated with calcium phosphate when it reaches the stone. The more acid the urine the more calcium and phosphate ions it will keep in solution, but as Albright has shown, the more acid the urine the more calcium and phosphate it already contains when excreted by the kidney. Chutes is of the opinion that if one could cause the patient to excrete an acid urine without at the same time increasing the calcium and phosphate in the urine, stones should dissolve readily. He believes the logical method lies in catheter irrigations with acids. Randall (17) has used phosphoric acid for lavage. This revived interest in the chemical dissolution of calculi. However, phosphoric acid is not theoretically a satisfactory acid to use because it supplies one of the end products of the reaction of dissolution and consequently tends to force the reaction in the wrong direction. Chutes (37) advocates the use of citric acid buffers for irrigation and lavage of calculi.

Keyser (25), however, objects to the acid lavage treatment because clinically it is difficult to apply acid solutions on calculi for any length of time (in adequate concentrations) as ureteral or vesical spasm and irritation become intolerable to the patient after a short time. He states that the outer layers of calculi dissolve rapidly in "in vitro" experiments but as the inner layers are approached one reaches a point at which dissolution is greatly reduced or brought to a standstill.

SUMMARY OF ONE HUNDRED AND THREE CASES OF URINARY CALCULI

One hundred and three cases of urinary calculi taken from the records of the Multnomah hospital and the Outpatient Clinic of the University of Oregon Medical School were reviewed. The present system of filing cases in a record library began in 1931. The cases on record distribute themselves as follows according to the year they were seen:

1931	4
1932	12
1933	9
1934	18
1935	13
1936	13
1937	7
1938	14
1939	13
total	103

The ages of the patients were as follows:

ages	
0--10	2
11--20	7
21--30	15
31--40	8
41--50	19
51--60	21
61--70	21
71--80	8
81--100	2
	103

The age of the youngest patient was three years and of the oldest, 83. The average age was 46.1 years. The cases from 41--70 years, inclusive, comprise 58.3 per cent of the total. There were 77 males and 26 females in this series.

An attempt was made to classify the cases according to race and localities from which these patients were derived, but was impossible since the records were inadequately kept in this respect.

The anatomic classification was as follows:

	Right	Left	Bilateral
Renal	18	19	8
Ureteral	16	13	
Bilateral multiple, renal and ureteral	4		
Vesical	24		

Prostatic and Urethral 1

The procedures used in the treatment of these cases and the results obtained were tabulated. Palliative treatment was considered to be symptomatic treatment without attempt at direct removal of stones. The results of manipulative procedures used in efforts to remove the calculi are also stated. If the method was unsuccessful and other means of treatment were used, the case was classified accordingly and it is included under the other method or methods used for treatment with the results obtained.

Procedures	Number	Results: Cured	Improved	Unsuccessful	Fatal	% Mortality
Paliative	34	12	12	5	5	
Manipulative	18	9	6	3	0	
Pelviolithotomy	5	3	1	1	0	
Nephrotomy	3	1			2	
Nephrectomy	5	5				
Ureterolithotomy	10	10				
Litholopexy	5	2		2	1	
Perineal Vesicolithotomy	2	2				
Suprapubic Vesicolithotomy	18	13			5	27.8%
No treatment Silent stones	2					
Treatment refused	7					

The causes of death:

Hydronephrosis, pyonephrosis, and uremia.....3
Calculous anuria and uremia..................2

Post-operative shock........................2
Perforation of bladder......................2
Cardiac failure or terminal
    coronary thrombosis.....................2
Post-operative atelectasis..................1
Terminal bronchopneumonia...................1

The average urine output of all cases was tabulated. Two cases of calculous anuria were included. Albumin occurred in 69 per cent of all cases. Nearly all crystals seen were recorded as either calcium oxalate or calcium phosphate crystals. Pus was present in 63 per cent of the cases and hematuria in 35 per cent of the cases. As urine cultures were not taken on all patients no figures can be given. However, in thos cases where cultures were taken, B. Coli communis was the most frequent organism found, followed by staphylococcus albus and hemolytic streptococcus, respectively.

The associated findings in these cases were:

Pyelitis, pyelonephritis......22
Hydronephrosis................10
Stricture-ureteral.............6
          urethral.............6

Congenital anomalies, double
 ureters and pelvis, and ab-
 berent vessels................1
Nephroptosis...................3
Ureterocele....................1
Renal tuberculosis.............2
Benign prostatic hypertrophy..19
Foreign body (match)...........1

Discussion:

Joly (21-90) recorded the following classification of 636 cases of urinary calculi from the records of St. Peters Hospital in London:

Age	Renal	Ureteral	Vesical	Prostatic	Urethral
0-9	0	2	3	0	0
10-19	8	0	7	0	3
20-29	30	7	9	0	1

Age	Renal	Ureteral	Vesical	Prostatic	Urethral
30-39	43	7	34	0	5
40-49	47	9	48	6	9
50-59	25	3	90	11	7
60-69	8	3	122	14	7
70-79	4	1	54	3	2
80-	0	0	4	0	0
	165	32	371	34	34

An analysis of these figures shows that 64.3 per cent of stone cases occurred in individuals from the age group of from 40--69. This agrees with our figures that the preponderance of cases occurs in this age group.

A series of cases reported from the Mayo Clinic (21--91) also emphasizes this:

Age	Number
1--10	4
11--20	13
21--30	34
31--40	59
41--50	71
51--60	164
61--70	183
71--80	69
81--90	9
	606

According to July (21--90) renal calculi are slightly more common on the right side than on the left. Kimbrough (26--68) in a summary of 120 cases of renal and ureteral calculi gives the location as:

Right--50 Left--52 Bilateral--18

Renal--74 Ureteral--55

Stones in ureters and kidneys--9

Kimbroughs series shows no preponderance of cases on the right side. This coincides with our findings. Stevens (38) in a review of several published series of cases reported bilateral calculi to vary from 8 per cent to 20 per cent. Bilateral renal or renal-ureteral calculi occurred in 11.6 per cent of our series.

In the relatively small series of cases studied by the writer it is obvious that the removal of vesical calculi by suprapubic surgery results in a high mortality rate. This mortality rate is not unusual, as Joly (21--49) reports that in cases over 50 years of age the mortality amounts to 25.4 per cent. The usual mortality reported is about 6--8 per cent (22-360).

A collection of mortality rates for 1924 at the International Society of Urology reveals:

Pyelolithotomy------2.4%
Nephrolithotomy----10.3%
Nephrectomy--------8.4%

CONCEPT OF THE PROBLEM

Randall's introduction of phosphoric acid lavage for treatment of urinary calculi revived interest in the chemical dissolution of stones. Nearly all stones contain large quantities of calcium phosphates or triple phosphates. Therefore it is chemically unsound to use phosphoric acid for irrigation as it supplies one of the end products of the expected reaction and thus by common ion effect would tend to maintain a precipitate rather than dissolve it. In the presence of an alkalinizing infection the use of phosphoric acid may, certainly theoretically, contribute to stone deposition. This was indicated when a case, being treated by urologists of the County Hospital by Randall's method, failed to show dissolution of progress in this direction. At this same time Chutes, in an Urological Correspondence Club Letter to Dr. John Hand, had told of the use of neutral citrate solution in the dissolution of calculi. Judy (23) in his thesis (taken in the Department of Chemistry of the University of Oregon Medical School) showed that citric acid candies may be instrumental in producing dental caries. He demonstrated that the mineral salts of teeth or synthetic calcium phosphate (tertiary) are not dissolved appreciably in citric acid buffers at pH values above 5.1 to 5.2. The lower the pH of the solution the faster the rate dissolved. Teeth and calculi resemble each other closely. Each consists of an organic framework enmeshing calcium salts. The desirability of using a buffer solution of low pH for calculi dissolution was apparent from this work. For clinical use it was necessary to determine the lowest pH and highest buffer concentration well tolerated by patients when the solution is kept in contact with the bladder wall for considerable periods of time.

In the discussions on Randall's method of irrigating with one and two per cent phosphoric acid no mention is made of the pH of the solution or the effective pH maintained after it becomes mixed with urine.

A two per cent phosphoric acid solution was accurately prepared by titration to phenophthalein. The pH was determined by use of the Beckman pH meter. A portion of the solution was diluted to one per cent and the pH determined.

2% H_3PO_4 —pH 1.97

1% H_3PO_4 —pH 1.51

Keyser (25) attempted the use of malic acid, lactic acid, and other organic acids to lavage calculi. All of these unbuffered acids in the concentrations used have pH values below 2.4. These low pH values undoubtedly explain why Keyser stated that clinically it is inadvisable to introduce such acid solutions into the bladder for calculi dissolution because it is impossible for patients to tolerate them long enough for appreciable action to occur.

THEORETICAL FACTORS IN THE CHEMICAL DISSOLUTION OF URINARY CALCULI

In considering the dissolution of calculi, many factors must be considered. The first of these is the surface area involved. Multiple calculi offer a greater surface area than one single large calculus. Also as dissolution proceeds, the surface area becomes less and approaches zero as a limit. It is obvious that the dissolution will be proportional to the surface area exposed to the action of the acid buffers.

The second factor is the time element. It is readily understood that the amount of stone dissolved will be proportional to the time the calculus is exposed to the acid buffer. Thus a continuous irrigation would naturally give a greater time factor than a single irrigation taken three times daily.

The third factor is the pH and concentration of the acid buffer used. The lower the pH of the solution in contact with the salts of calcium, the faster the dissolution takes place. This refers, of course, to the effective pH in contact with the stone. Now the effective pH is the result of the mixture of urine and the irrigation fluid. This reaction and concentration depend on the buffers present in the urine, and the pH and concentration of the irrigation buffer used together with the relative quantities of urine and buffers which mix in the bladder. Also, as the salts of the stone go into solution the pH tends to rise. The lowest pH with the highest buffer concentration which can be tolerated by the patient should be most effective for clinical use.

The fourth factor is the specific properties of the acid itself. Ideally an acid for use as an irrigation fluid for dissolution of urinary calculi should form a very soluble calcium salt which does not ionise to any appreciable extent, thus removing the chances of reprecipitation following solution of the salt of the stone.

The fifth factor is the stone itself. The solubility of the salts found in stones is different for each compound. Oxalates are more difficult to dissolve than phosphates. Each stone has a different chemical compound. Also the colloids binding the stone together play a considerable part in the dissolution. Each stone may differ in this respect also. Thus some stones will dissolve easier than others.

Time of irrigation, pH and concentration of buffered acids, and the specific properties of the acid used are factors which may be readily controlled. The problem of the dissolution of calculi is largely concerned with these factors.

EXPERIMENTAL PROCEDURES

The chemical dissolution of vesical calculi was studied by clinical and laboratory methods. In the clinical studies, the cases were treated by bladder irrigations. Essentially three types of irrigations were used. These will be discussed later in detail. In each case the total 24 hour urine was collected with the irrigation fluid. Creatinine determinations were run from time to time to check on the accuracy of urine collection. Total calcium, phosphate, uric acid and oxalate determinations were made on the samples. Because of daily variation in the excretion of these substances, generally ten samples were collected. For each buffer used (of definite pH and concentration) the total and average excretion of the above substances for the period of irrigation was calculated. The theory was that any amount of substance dissolved from the calculi by the buffer would increase the total excretion by that amount,and thereby a comparison of buffers could be obtained. The progress of each case was also followed by radiograms.

The method first used for calcium determinations was a modification of McCrudden's (26). Two hundred cubic centimeter centrifuge tubes were used to eliminate the filtration of urine. The method proved cumbersome, and the Clark and Collip modification of the Kramer and Tisdall method (8) was adopted. We further modified this method for urine determinations by acidifying to congo red in order to bring all calcium phosphate into solution and readjusting the pH to around neutrality with sodium acetate buffer.

In the modified procedure the urine was acidified to congo red, filtered, 10 cc. pipetted into a 15cc centrifuge tube, followed by the addition of 2 cc of 4% ammonium oxalate and 3 cc of 10% sodium acetate. From this point the procedure was that of Clark and Collip referred to above. This method gave satisfactory results on known calcium solutions and on urine. The values by it are not influenced by the presence of citrates.

Phosphates were determined by the method of Fiske, and Subbarow (11-375). The presence of large amounts of citrate ion interfere with this method and to obviate this in our work the samples were wet ashed to destroy organic matter.by the perchlorate method of Gevirts.

The determination of uric acid was carried out by the direct colorimetric method originally described by Benedict and Franke (6).

Dakin's modification (9) of the Salkowski-Autenrieth and Barth method for the determination of oxalates was used.

Hippuric acid was determined by the method of Griffith (14) using the simplified micro-Kjeldahl apparatus of Scott and West (34). Where analysis of stones was necessary the procedures of Newcomb (32) for sampling and wet ashing were used, then aliquot parts of the solution were taken for the separate determinations using the methods described above.

The Folin colorimeteric method for creatinine was used to make sure that total twenty-four hour urine samples were received. This was found to be invaluable in keeping a check upon the completeness of collection by the nurses.

All buffers used in the clinical and "in vitro" experiments were brought to the proper pH by use of sodium hydroxide. The pH in all cases was determined by use of the Beckman pH meter.

IRRIGATION METHODS

Three methods of irrigation were used throughout the clinical experiments. The first procedure was intermittent irrigation. This was carried out with an ordinary urethral catheter in place, connected with a reservoir of buffer suspended over the patient's bed. 50 cc. of the buffer was injected three times daily and held for one hour by a clamp placed on the end of the catheter. This had the disadvantage of giving only three hours of contact between calculi and buffer per day.

The second method of irrigation employed a continuous irrigator developed in our laboratory (see figure). The Murphy drip allows accurate control of the amount of buffer flowing per minute. The Bunsen check valve prevents rise in intravesical pressure from pushing urine up into the reservoir. A double F 24 catheter is used, one tube serving as the inflow, the other as the outflow. The height of the side arm above the bladder controls intravesical pressure and the quantity of fluid in the bladder. The air vent is placed near the side arm to prevent siphoning. This apparatus permits continuous irrigation without sudden changes in intravesical pH. The contents of the bladder and its pressure do not vary greatly during irrigation. The incoming buffer is mixed with the urine by the circulating action of the tip of the double catheter. The irrigator is simple in operation; permitting variation in rate of flow and intravesical pressure at will.

The Munro tidal wave apparatus (30) was also tried. Due to the rapid changes in intravesical pH caused by the sudden filling of the bladder during the positive pressure phase, more vesical irritation and spasm were caused by this irrigator than by the apparatus described above.

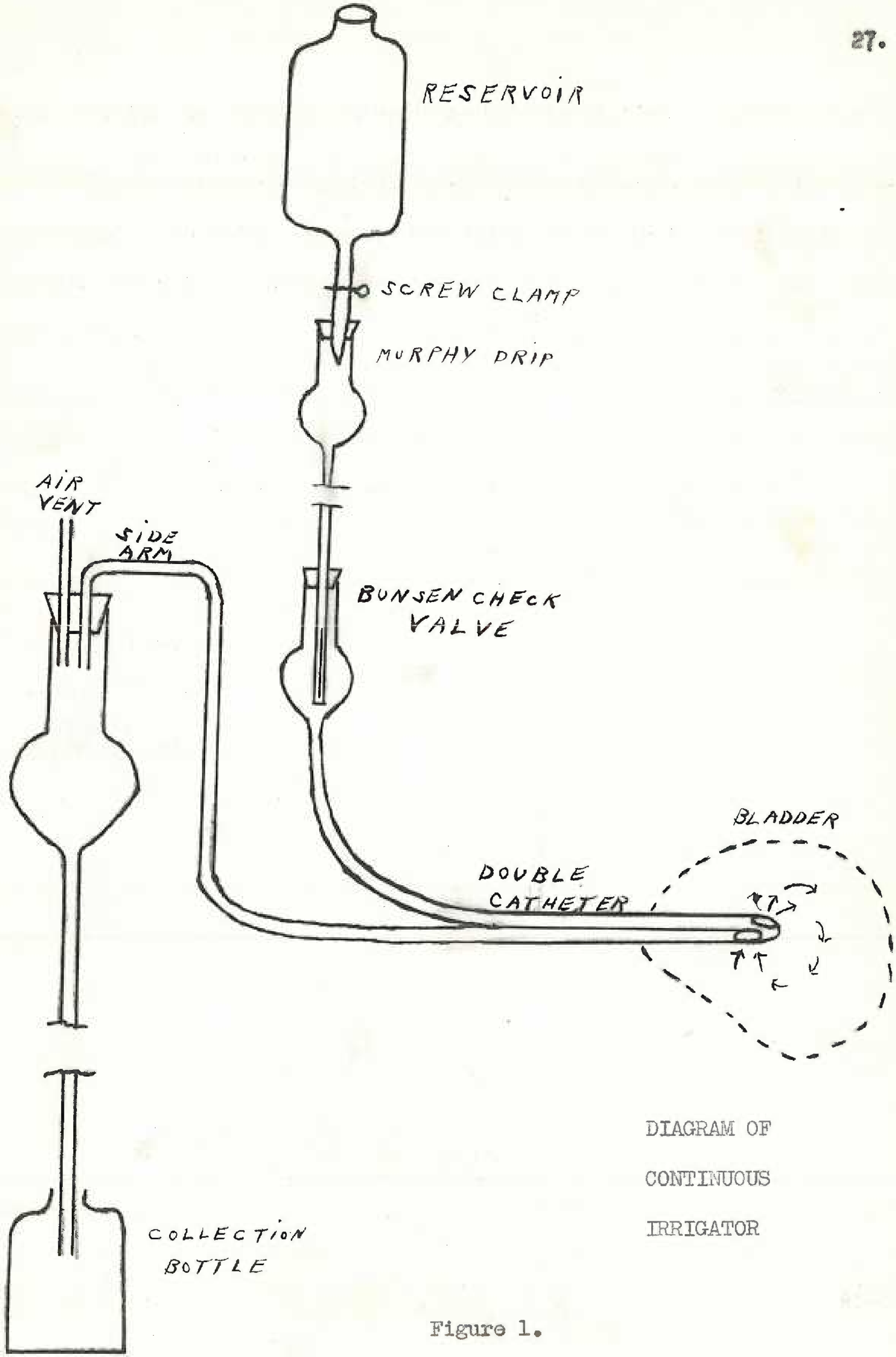


DIAGRAM OF

CONTINUOUS

IRRIGATOR

Figure 1.

CLINICAL DISSOLUTION OF VESICAL CALCULI. REPORT OF CASES.

CASE I.

#39275.

J. T., a 57 year old white male, entered Multnomah County Hospital with the chief complaints, (1) low back pain, and (2) difficulty in passing urine for about the past six years. The difficulty was mainly on starting the stream. The stream progressively became smaller. For the last three months the patient had had more trouble than previously. There had also been some burning on urination and he had a low backache for the last week before admission. There had been times when the patient's stream shut off abruptly while urinating. The patient had epileptic seizures for the past forty years. During the last six years he had taken phenobarbital, grain 1 1/2 to 3, daily, and had no attacks. History by systems was essentially negative.

Physical examination revealed an area of bladder dullness after urination. Rectal examination gave evidence of slight hypertrophy of the prostate. Otherwise physical examination was negative except for the absence of the right eye.

Laboratory examination revealed: Urine on all occasions showed from one plus to two plus albumin, occasional triple phosphates, and pus cells ranging from one to two plus. Occasional red cells were found in a majority of samples. Blood examination was negative except for a sedimentation rate of 35/81. Blood calcium was 8.7 mg., blood phosphate 3.4 mg., B. U. N. 13, alkali reserve 80, and P. S. P. 65%. Serology was negative.

A radiogram of the bladder area, taken on 3/29/39, had revealed in the bladder area at least seven densities, the largest of which measured slightly over two centimeters in diameter (see Figure 2), on 4/25/39. a cystoscopic examination showed many large white stones.

Treatment and Progress: Bladder irrigations with 1 per cent phosphoric acid were begun. On 5/5/39, the bladder irrigations were changed to 2 per cent neutral sodium citrate using 50 cc. three times daily. On 5/9/39, acidifying mixtures were begun. Forty drops each of phosphoric acid and hydrochloric acid with water as necessary to dilute were given orally three times daily.

On 6/5/39, a radiogram of the bladder area revealed no change in the size or number of stones.

Because of the lack of progress, aid of the Department of Biochemistry was requested. On June 15, the bladder irrigations were changed to 0.2 molar citrate buffer of pH 4.0. This was continued until June 30, when irrigation by neutral citrate was again used in order to obtain control samples for analysis. An x-ray on the 19th of June gave the impression that the stones were slightly smaller than in previous films. After ten days on neutral citrate irrigations, another x-ray was taken, but no change was noted.

On July 10, irrigation with 0.4 molar citrate buffer, pH 3.5, was started. After two days this was discontinued because of bladder irritation and the solution changed to 0.2 molar citrate buffer, pH 3.5, which was continued until July 21. The irrigations were now changed to 0.4 molar citrate buffer, pH 4.0, but the buffer caused irritation. This buffer was then diluted to 0.3 molar, pH 4.0, on July 27 and continued with only slight burning sensations during irrigations. A radiogram on July 24, showed considerable decrease in size but no change in the number of stones. The 0.3 molar citrate buffer pH 4.0 was continued for four days from July 27 to July 31. An x-ray at the end of this time showed the stones to be much smaller and not so numerous.

On August 1, a litholopaxy and a transurethral prostatic resection was done. The stones were very soft and crushing was relatively simple. Litholopaxy was done as the resection of the prostate was necessary and by this means a small sample of the stone was collected.

The stone gave the following analysis:

Calcium--------10.7%	$CaHPO_4 \cdot 2H_2O$ (Calculated) 46.0%
Phosphorus----15.2%	PO_4 (Calculated) 38.7%

The phosphorus content of the stone was equivalent to 84.3% $CaHPO_4 \cdot 2H_2O$, considerable of which was probably present as a result of the action of acid upon $Ca_3(PO_4)_2$ present in the stone originally. The calcium content of the stone was equivalent to only 46% $CaHPO_4 \cdot 2H_2O$. Apparently a considerable part of the phosphates present must have been in other forms such as magnesium ammonium phosphate. This may be considered primarily a phosphate stone.

Total calcium was determined on the 24 hour urines (plus irrigation fluid) during the experimental periods. The results were as follows:

Buffer Used	No. of Samples	Daily Calcium Average mg.
Neutral Citrate	10	211
0.2 Mol. Cit. pH 3.5	10	240
0.3 Mol. Cit. pH 4.0	5	272

(All calcium figures are computed and expressed as elementary calcium).

Conclusions:

1. A case with multiple vesical calculi composed mainly of phosphates showed progressive dissolution under irrigation with various citrate buffers.

2. Calcium determinations proved 0.3 molar citrate buffer, pH 4.0, to be most satisfactory for the dissolution of these particular stones.

3. No progress was noted with irrigations by Randall's phosphoric acid method.

4. Radiographic evidence agreed roughly with the chemical evidence, from calcium determinations, but the chemical evidence gave a more accurate indication of the progress made.

5. 0.4 molar citrate buffers, pH 4.0 and pH 3.5 were not well tolerated. This was probably related to their hypertonicity.

6. 0.2 molar citrate buffers, pH 4.0 and pH 3.5 were tolerated. 0.3 molar buffer, pH 4.0, caused some irritation but could be used over an extended period of time. It was the most efficient compromise of pH and molarity studied in this case.

Radiogram of Bladder

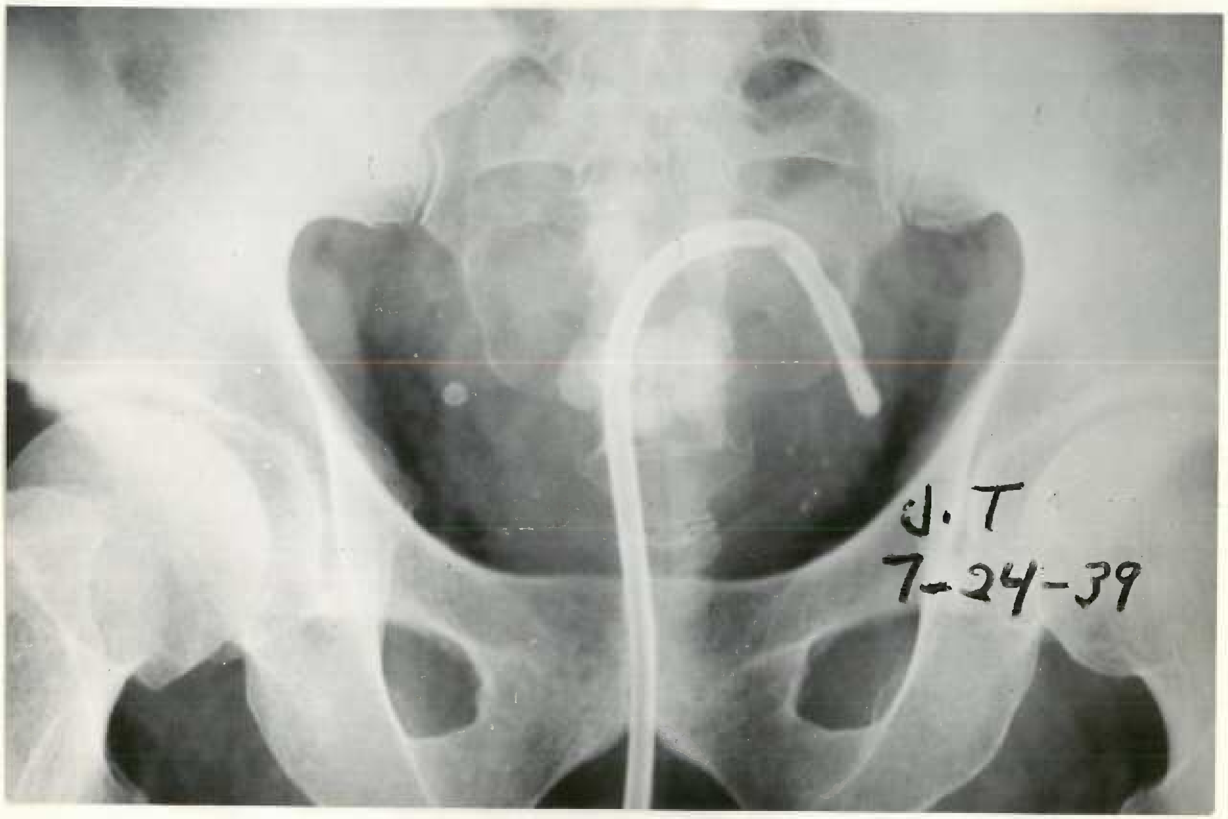
Before Treatment

Figure 2.

Radiogram before treatment with citric acid buffers. No Change is noted as compared to previous film. The patient had been treated with Randall's 1% phosphoric acid lavage.
Figure 3.

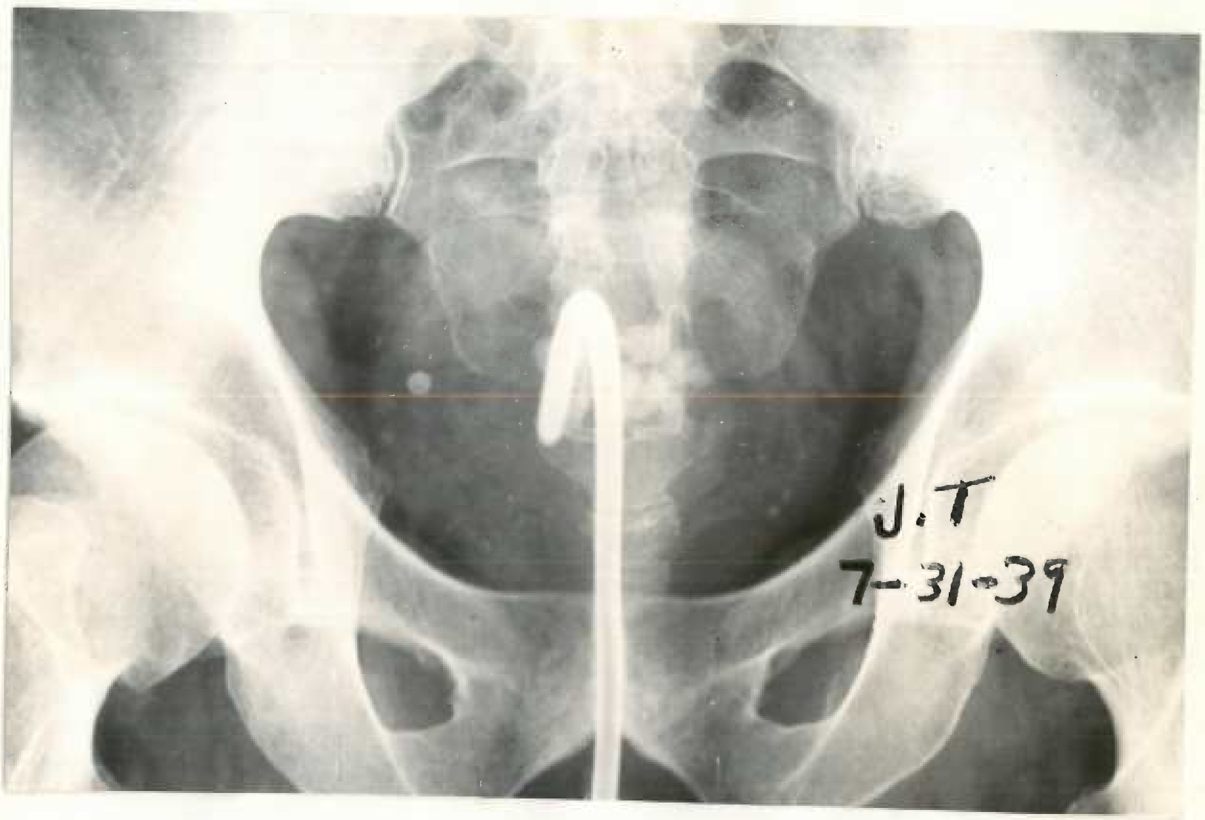
This radiogram showed some dissolution with 0.2 molar citrate irrigations at pH 4.0.

Figure 4.



Considerable decrease in the size of the stones is noted.

Figure 5.



The radiogram showed rapid dissolution as compared to the previous radiogram, after one week of irrigation with 0.3 molar citrate buffer, pH 4.0.
Figure 6.

CASE II

#79984

G. T., a 62 year old white male, was first seen in the Urology clinic in August, 1937, at which time his chief complaint was incontinence of urine. Two years previous to this time he had had a two stage suprapubic prostatectomy following which he had repeated soundings. When first seen in the clinic, sounds could not be passed. However, following dilatation with filiforms and metal followers, sounds could be passed and cystoscopy done. At cystoscopy recurrent hypertrophy or incomplete enucleation was seen. What appeared to be diverticulation of the prostatic urethra was present.

The patient progressed well on occasional soundings and bladder irrigations until the latter part of July, 1939, when it became difficult to pass sounds. Finally filiform sounds and metal followers were passed which grated in the prostatic urethra. A radiogram of the bladder taken at this time revealed multiple vesical calculi, one of which appeared to be impacted in the prostatic urethra.

The patient was admitted to Multnomah County Hospital on 9-25-39. Physical examination revealed no findings other than those discussed above. Urine showed a one plus albumin, calcium phosphate crystals, pus, and bacteria. Blood was essentially negative. Serology was negative.

From October 2 to 11, ten 24 hour control samples were collected. Throughout this case total calcium, phosphorus, and urates were determined. A single oxalate determination was done giving a figure of 25.8 mgms. of oxalate in the total 24 hour urine sample. Because of the difficulty in running oxalates this procedure was abandoned.

On October 12th, a retention catheter was placed and the patient was irrigated with 1-5000 potassium permanganate to control his infection and lessen vesical irritability. On October 24th intermittent irrigation was begun with 0.2 molar citrate buffer, pH 5.0. It was decided to lower the pH in a step-wise fashion in order to find the critical pH for the dissolution of stones in vivo. This was carried out with 0.2 molar citrate buffer lowering the pH 0.5 of a unit at the end of each ten days. When the samples for 0.2 molar buffer, pH 3.5, had been collected it was decided to use the continuous irrigator developed by this laboratory. Accordingly the apparatus was set up and started on December 14th. However, due to trouble with the irrigator no collection of samples was made until December 23rd. The irrigations were continued until January 3rd when the solution was changed to 0.4 molar citrate buffer, pH 4.0, and continued until the 14th of January. With 0.2 molar citrate buffer, pH 3.5, the intravesical pH was 4.7 while with 0.4 molar buffer, pH 4.0, the pH fell to 4.3-4.4 due to the increased capacity of the buffer.

Cystograms taken on 1-9-40 showed that one of the three calculi, present throughout on the series of plates made of the patient, had disappeared. Subsequent x-rays showed progressive dissolution and decalcification to be taking place while on the citrate buffer. (See plates.)

On January 14th irrigations with 0.2 molar acetic acid pH 3.0 were tried. After twenty-eight days this was discontinued since no evidence of dissolution was noted from the calcium determinations during this series.

The irrigations were then continued with 0.2 molar citrate buffer, pH 3.5, until 3-4-40. At this time a small piece of stone was passed and because an ex-ray taken previously revealed only one small density it was felt that the patient had been cured.

The patient was discharged and told to return to the Urology department of the Outpatient clinic for cystoscopy. Upon cystoscopy, however, a small stone about the diameter of an F 30 catheter was seen. The patient is to be re-admitted to the hospital as soon as bed space will permit in order to complete the dissolution.

The results of the determinations on the 24 hour urines (plus irrigation fluid) during the experimental periods follow:

Buffer Used	No. of Samples	Daily calcium average (mg)	Daily phosphorus average (gm)
Control	10	44.9	.91
I. Intermittent Irrigation			
0.2 Mol. Cit. pH 6.0	8	48.7	.86
0.2 Mol. Cit. pH 5.5	8	49.6	.88
0.2 Mol. Cit. pH 5.0	8	47.4	1.17
0.2 Mol. Cit. pH 4.5	18	44.6	.93
0.2 Mol. Cit. pH 4.0	11	40.8	1.30
0.2 Mol. Cit. pH 3.5	8	51.7	1.29
II. Continuous Irrigation			
0.2 Mol. Cit. pH 3.5	8	56.6	.94
0.4 Mol. Cit. pH 4.0	8	48.8	.76
0.2 Mol. Acetic Acid pH 3.0	8	35.7	.59

No relation was noted between uric acid and phosphorus excretion. However, the calcium values show that continuous irrigation was more effective than intermittent. No appreciable increase in calcium excretion was noted until a pH of 3.5 was reached. In the continuous irrigator this buffer gave an effective bladder pH of 4.7. The 0.4 molar buffer, pH 4.0, gave a lower intravesical pH but did not cause so much calcium dissolution. This was due to the fact that the patient could not tolerate the irrigation over as long a period of time with this buffer as he could with the buffer of lower concentration. Acetic acid buffers were not effective.

Conclusions:

1. Continuous irrigation gave faster dissolution with less irritation than did intermittent irrigation.

2. 0.2 molar citrate buffer, pH 3.5, with an intravesical pH of 4.7 gave an appreciable increase in the daily average calcium excretion.

3. 0.2 molar citrate buffer, pH 3.5, was more effective than 0.4 molar citrate buffer, pH 4.0, with continuous irrigation since it could be used for longer periods of time without irritation.

4. Acetic acid was not effective in the dissolution of calculi in vivo.

Radiogram of the bladder before treatment.
Figure 7.

The radiogram showed dissolution was taking place as compared to previous film. One stone has disappeared.

Figure 8.

This radiogram showed further dissolution of the stones.

Figure 9.

One stone remained after a week of irrigation with citrate buffer.

Figure 10

A single stone was present behind the pubis.
Figure 11.

CASE III

R. C., a private patient of Dr. John Hand, had bilateral renal staghorn calculi. These were producing no obstruction on either side. It was decided to try this patient on a dietary regimen and phosphoric and hydrochloric acid by mouth. Also, hippuric acid was given in one gram quantities once per a day. Control samples of urine were first taken. Later, while hippuric as the only acid was given, other urine samples were collected. No significant change in calcium phosphorus, or uric acid excretion was noted. However, the total average hippuric acid excretion increased from the control level of 1.31 grams to 2.30 grams daily. The results show hippuric acid to be readily absorbed from the intestine and quantitatively excreted in the urine.

Conclusions:

1. No change in calcium, phosphate, or uric acid excretion was noted when hippuric acid was given orally.

2. Hippuric acid administered orally was readily absorbed and readily absorbed and excreted in the urine quantitatively.

CASE IV

#106240

N.S., a 62 year old male, was admitted to Multnomah County Hospital on 1-28-40, with bloody urine as the chief complaint. He had had urinary difficulty for the past three years consisting of dribbling, diminution of stream, and sudden stoppage of urine. For several weeks before admission, he had hematuria and a burning sensation upon urination. He also had an indirect inguinal hernia and positive serology. Urine showed two plus R. B.C. and positive culture for gram positive cocci.

Sulphanilamide reduced the frequency of urination and the accompanying burning and pain. Cystoscopy and radiography revealed a calculus about the size of a small egg. Marked cystitis and benign prostatic hypertrophy of the median and lateral lobes were present. The patient refused surgery and dissolution was attempted by irrigation.

On 2-11-40, the patient was placed on an acid ash high vitamin A diet and fifteen grains of ammonium chloride were administered five times daily. Two days latera Munro tidal wave irrigator (30) with a single French 18 catheter was set up. Irrigations were begun with 0.2 Molar citrate buffer, pH 4.0, and continued for ten hours daily for two days when gross blood suddenly appeared in the outflow tube of the apparatus. There was also extreme pain, swelling, and edema of the penis due to catheterization. The catheter was removed. It was felt that it might be better to use the continuous irrigation apparatus as this had proved satisfactory in previous cases.

On 2-21-40, the anterior urethra was dilated with F24 and F 26 metal sounds in order to insert an F 24 double catheter. The dilatation was necessary because of a stricture in the anterior urethra. This caused a fever of 104°, which subsided by use of sulphanilamide. Irrigations were carried out for two days with the continuous double catheter irrigator using a 0.2 Mular citrate buffer, pH 3.5. At 5 P.M. on the second day gross hematuria developed due to cystitis and ulceration secondary to the stone present. The irrigation was stopped and the hematuria promptly subsided. Fluids were forced and supportive treatment given. Irrigations were again instituted for three days when gross hematuria again developed. In view of the continued hematuria and apparent toxic condition of the patient it was felt that he was not a suitable risk for irrigative treatment. The patient was given supportive treatment.

On 3-2-40, a suprapubic vesicolithotomy was performed.

Conclusions:

1. The appearance of hematuria constitues a contraindication to irrigative treatment.

2. The disadvantage of the continuous double catheter irrigator lies in the fact that the smallest double catheter made is F 24.

3. It was undoubtedly a mistake to dilate the urethra in order to place the double catheter.

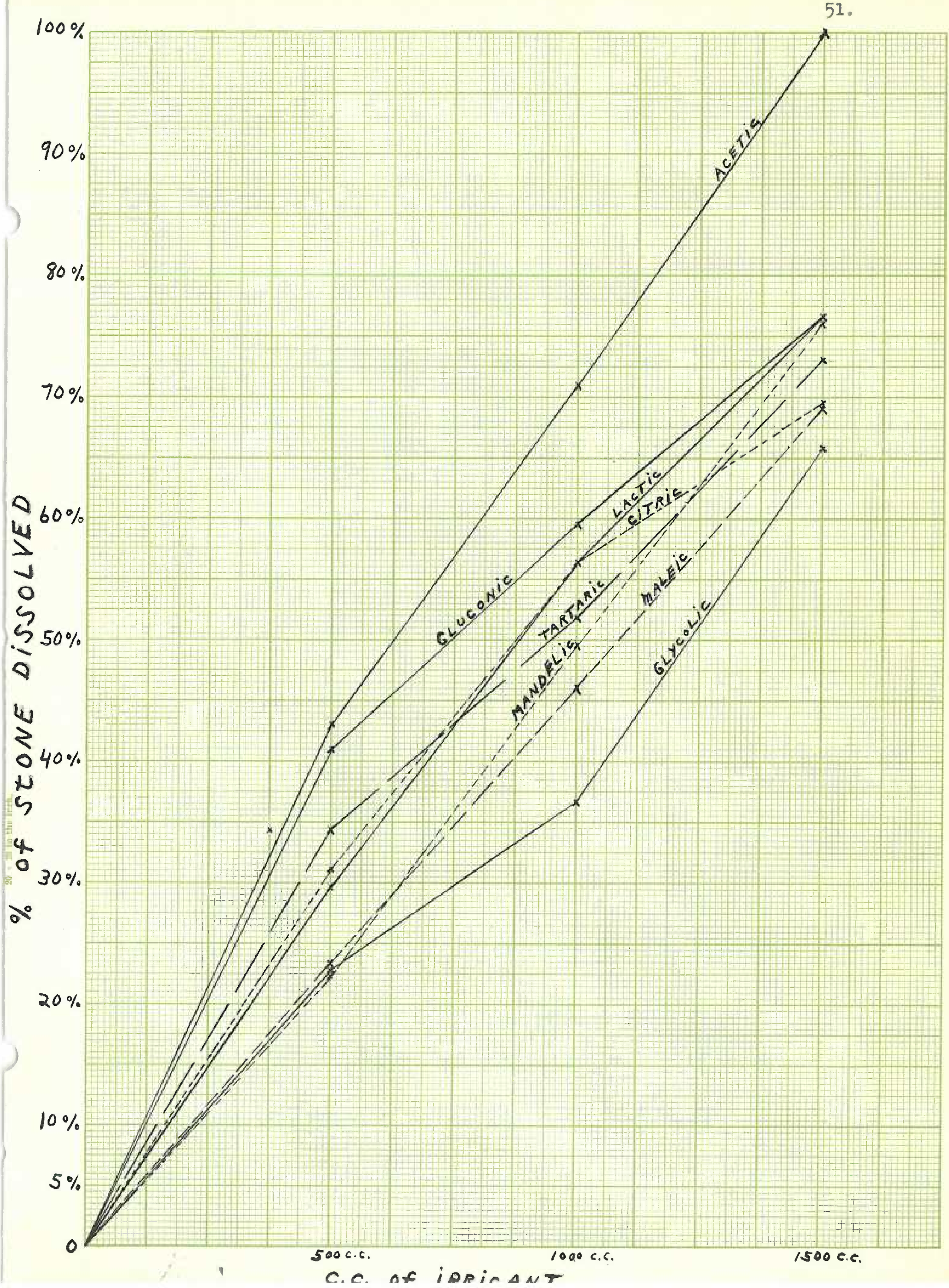
"IN VITRO" DISSOLUTION OF CALCULI WITH VARIOUS ORGANIC ACIDS

A single calcium phosphate stone was broken into several small pieces each weighing from 500 to 600 mgm., and with similar surface areas. Each stone was placed in a tube and so arranged that it could be bathed by any desired buffer solution from below, the excess solution running over through a side arm into a receptacle. Each of the organic acids tried was 0.1 molar, pH 4.0. Each acid was run into the tube at a constant rate of 50 cc. per hour and was collected in consecutive 500 cc. samples. The tubes were immersed in a constant temperature bath at 37.5° centigrade. Calcium determinations were run on the first three 500 cc. samples and on the remainder of the stone in each case.

Sample No.		Acid used	Total calcium in stone*	Total calcium dissolved (mg)	Total % stone calcium dissolved
I	1	Mandelic	117	26	22.4
	2			32	49.6
	3			31	76.1
II	1	Lactic	64	19	29.7
	2			17	56.3
	3			13	76.6
III	1	Glycolic	79	18	22.8
	2			11	36.7
	3			23	65.8
IV	1	Citric	99	31	31.2
	2			25	56.4
	3			13	69.5
V	1	Acetic	100	43	43.0
	2			28	71.0
	3			29	100.0
VI	1	Maleic	179	42	23.4
	2			41	46.1
	3			41	69.0

*Total calcium in the stone was calculated from the total calcium in each sample plus the calcium in the undissolved portion of the stone.

VII	1	Gluconic	334	137	41.0
	2			62	59.6
	3			57	76.7
VIII	1	Tartaric	297	95	34.3
	2			55	52.8
	3			60	73.0



100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
5%
0
% of STONE DISSOLVED
ACETIC
LACTIC
CITRIC
GLUCONIC
TARTARIC
MALEIC
MANDELIC
GLYCOLIC
500 c.c.
1000 c.c.
1500 c.c.
C.C. of IRRIGANT

Acetic acid is seen to be the most efficient buffer in "in vitro" experiments. This is not in accord with our "in vivo" findings. This lack of agreement between the "in vitro" and "in vivo" work is probably due to the appreciable ionisation of calcium acetate. In the bladder this ionization allows secondary precipitation to take place, thereby counteracting the dissolution which takes place by reason of the low pH. In the test tube, however, the calcium and phosphate concentrations in solution are low and this does not occur, thus allowing dissolution to take place.

Gluconic acid appears to be an excellent substance buffer with which to attempt dissolution. Little difference was found between the other acids with respect to their capacity to dissolve stones in "in vitro". A serious fault with the above experiments is that the surface area of the stone exposed to the acids varied considerably in different experiments. Attempts are being made to obviate this difficulty.

SUMMARY

The etiology of urinary lithiasis is reviewed. Among the factors considered are Vitamin A deficiencies, urostasis, infection (especially with urea-splitting organisms), focal infection, hyperparathyroidism, calcification of plaques in the renal papillae, metabolic diseases and orthopedic conditions.

The factors concerned with maintaining the insoluble salts of clacium in solution in urine are considered. A consideration of solubility products explains why certain calcium salts are more often the prindpal constituents of calculi. Among the factors affecting the solubility of these compounds are the relative concentrations of the substances excreted, the acidity of the urine, the simultaneous presence of organic hydrotropic substances such as hippuric acid, and the effect of urea. The part that urinary colloids play in the solubility mechanisms of difficultly soluble salts of urine is discussed.

The application of these recent advances to the medical treatment of urinary lithiasis is discussed. A summary of one hundred and three cases of urinary lithiasis taken from the records of Multnomah Hospital and Outpatient clinic of the University of Oregon Medical School is included. A consideration of these cases emphasizes that urinary lithiasis is predominately a disease of middle age as nearly two-thirds of all these cases occurred in the age groups from 41 to 70 years. The marked mortality rate of suprapubic surgery is emphasized.

Randall's introduction of phosphoric acid lavage for the treatment of urinary lithiasis revived interest in the chemical dissolution

of stones. Irrigation is considered to be the logical method for the medical dissolution of urinary calculi. The use of Phosphoric acid is theoretically erroneous. The use of citric acid was suggested by Chutes. The work of Judy upon the effect of citric acid candies on teeth also suggests this.

Keyser's objection to irrigations with these acids is that they are too irritating when used over long periods of time. It was determined that the 1% phosphoric acid used by Randall has a pH of 1.51, which explains why this solution is irritating to the bladder wall and ureter when used for irrigation.

The theoretical considerations for the dissolution of stones is discussed. The factors considered are surface area, pH, concentration and specific properties of the buffered acid used, the time of irrigation, and the inherent nature of the stone itself.

In the clinical experiments three cases of vesical calculi were treated by use of citric acid buffer lavage varying the pH, concentration and method of irrigation to determine the most effective conditions for dissolution. The cases were carefully controlled and progress followed by calcium and phosphorus excretions in the total 24 hour urine plus irrigation fluid, and by radiograms taken at periodic intervals. Three methods of irrigation were used. These consisted of intermittent lavage, continuous irrigation with an apparatus developed in our laboratory, and tidal wave irrigation.

Continuous irrigation proved to be the most effective. The continuous irrigator gave the least amount of irritation and was relatively simple in operation. The Munro tidal wave apparatus gave a great deal of irritation due to the sudden changes of intravesical pH. The intermittent lavage was ineffective as it did not give sufficient irrigation time.

Two cases of multiple vesical calculi showed progressive dissolution with citrate buffer lavage. The calculi from one of the cases consisted mainly of phosphates. No progress was noted with irrigations by Randall's phosphoric acid method or by acetic acid lavage. 0.2 molar citrate buffer, pH 3.5, was the most effective buffer tried with continuous irrigation. 0.3 molar citrate buffer, pH 4.0, was the most effective buffer used with intermittent irrigation.

Radiographic evidence agreed with the chemical evidence but is less accurate as an index of day to day progress than calcium and phosphoric determination.

In one clinical case, continuous hematuria forced a discontinuance of the irrigative treatment. Continuous hematuria constitutes a contraindication to irrigative treatment. The disadvantage of the continuous irrigator was shown in this case when the urethra was dilated to place the smallest double catheter made, a French 24 caliber. Following the dilatation the patient's course was very stormy.

In the in Vitro experiments acetic and gluconic acids proved to be the most efficient. This does not agree with in Vivo results since acetic acid was not effective in clinical experiments. More accurate methods of controlling surface area and other factors are necessary before in Vitro and in Vivo results will agree.

While it is realised that acid buffer lavage is by no means perfected, it seems reasonable that it may be used to reduce large vesical stones to a size suitable for litholopaxy. Combined with trans-urethral resections for prostatic hypertrophy and litholopaxy it might largely eliminate the suprapubic vesicolithotomy and its attending mortality rate.

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