

URIC ACID STONE DISEASE

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1. ABSTRACT

The trend in uric acid stone formation appears to be on the rise again throughout much of the world. This is thought secondary to diet, body habitus, and social reasons. Uric acid stone disease has a rich and fascinating medical history and probably is the oldest known stone disease. Uric acid stone disease is strongly linked to the purine metabolic pathway, and its treatment is primarily medical. Uric acid stone disease can be prevented and these are one of the few urinary tract stones that can be dissolved successfully. Surgical intervention with uric acid stone disease represents a failure of medical therapy and a whole host of modern, minimally invasive methods are available for treating patients with this disease. Finally, uric acid nephrolithiasis is associated with a variety of inborn errors of metabolism based on mutations of key enzymes in the purine metabolic pathways. This review of uric acid stone formation will start with historical consideration, review basic biochemistry, and physiology and then focus upon specific clinical scenarios. The discussions will be heavily referenced for those interested in greater details.

2. INTRODUCTION

Stone disease has afflicted humans since before recorded time. The first known stone, a bladder calculus, is well described in a 5th Century BC Egyptian youth of about 7 years of age. The stone was a mixture of uric acid and struvite. Uric acid was of primary interest to the founding fathers of chemistry.1). Urinary stones were quite common at the close of the 19th Century when the founders of chemistry were investigating basic chemical composition, so it is quite natural that they turned their attention to stone disease. Uric acid was the first urinary stone constituent that had been successfully identified.

Uric acid is the end product of human purine nucleotide metabolism. As such, uric acid is far from an ideal end product because it is poorly soluble. In excess, uric acid can precipitate as sodium hydrogen urate (common in joints and tissues) or as uric acid, sodium urate, or ammonium urate in the urinary tract. Man is continually on the precipice of crystallization and precipitation as the urine is relatively supersaturated with

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uric acid with an average of 600 mg/day. Human uric acid handling has become a complex physiologic issue. Humans lack the enzyme, uricase that nearly all other species have to oxidize uric acid into the more soluble allantoin.

Uric acid is a weak acid with the hydrogen atom at position 9 of the imidazole ring easily dissociated in the physiologic range ($pK_{a1} = 5.75$).

3. History of Uric Acid Chemistry

Uric acid stone formation represents one of the more fascinating enigmas of chronic human diseases. Hippocrates (460- 370 B.C.) noted the clinical features of gout, its hereditary nature and male predominance. Gouty tophi and uric acid bladder and kidney stones had been identified. Galenus (131- 201 A.D.) proposed relationships between gout and urolithiasis. Paracelsus (1493- 1541) believed stones were caused by dietary excesses.(2) Thomas Sydenham (1624-1689) suffered from kidney stones and gout. He hypothesized that specific increase in excretion of a kidney stone producing substance resulted in precipitates of stones. Sydenham's insight is shown as follows: "...the gout breeds the stone in the kidney of many subjects either (1) because the patient is obliged to lie long on his back, or (2) because the secretory organs have ceased performing their proper functions; else (3) because the stone is formed from a part of the same morbid matter." Sir William Osler (1849- 1919) followed in the lineage of great medical minds that suffered from urolithiasis. In his first edition of *The Principles and Practice of Medicine*, his *magnum opus*, Osler specifically refers to chemical varieties of calculi; "Uric acid, by far the most important, which may form the renal sand, the small solitary, or the large dendritic stones." (3)

The chemical composition of calculi parallels the infancy of clinical chemistry. One requisite of early chemists was the requirement of an abundant substrate. Calculus disease during the late 18th and early 19th Century was endemic and concurrent with the Industrial Revolution. Thus stones, particularly bladder calculi were readily available. In 1776, Karl Wilhelm Scheele (1742-1786) in seminal studies on bladder stones noted that though barely soluble in water, they turned litmus paper red and thus were acidic. Upon heating, the stones produced an odor of prussic acid. He gave the name lithic acid to the substance and thought that all urinary stones were of similar chemistry. Another chemist, T.B. Bergman (1734-1794) made similar observations. In 1795 George Pearson (1751-1828) presented an investigation of 300 stones from the collection of Mr. Heaviside. With exquisite attention to detail, he concluded that lithic acid is not present in the stone but was an oxide. Pearson suggested in his paper to change the name to uric acid. Pearson further points out that most stones do contain uric acid (194/200) but in varying concentrations. Antoine F. Fourcroy (1755-1809) also experimented upon a large number of uroliths and tended to agree with the misconceptions of Scheele. Fourcroy is considered the father of clinical chemistry. His insightful investigations included questioning whether uric acid was confined to humans, if uric acid existed outside of

the urine, how it was formed, if there was any left in the urine after stone precipitated, etc. He proposed and probably performed the first multi-center investigation of environmental and geographic regions to see if different stone types were seen in different areas. Fourcroy and his colleague, Nicolas Louis Vauquelin, not only expanded the chemical properties of uric acid, they identified the sodium and ammonium salts. Fourcroy also pursued the therapeutic possibility of dissolving such stones and commented that only pure uric acid stones should be capable of being dissolved.(4)

The rigorous method of experimental pursuit by these early investigators included experiments and dissection of various animal species. They noted that man was the only mammal to form uric acid stones. Pearson and Vauquelin could not find uric acid stones in large carnivores (lions and tigers). Fourcroy followed-up these observations by confirming a lack of uric acid stones in the horse, cow, rabbit, dog, cat, pig and rat.

William Hyde Wollaston (1766-1826) was another contemporary of these other investigators who also was interested in stone chemistry. Wollaston further refined chemical techniques to investigate the properties of uric acid, and also became an expert in crystallography. Wollaston was the first to identify cystine from the bladder of a 5 year old boy. He differentiated this stone from uric acid and correctly identified the first amino acid. He published the most significant work on urolithiasis up to this time in 1797; *On Gouty and Urinary Concretions*.(5) A contemporary of Wollaston was Alexander Marcet. He too was a physician and chemist, working in London and obtained calculi from Norwich Hospital. He was the first to discover xanthine stones. His book *An Essay on the Chemical History and Medical Treatment of Calculous Disorders* in 1817 was encyclopedic of the knowledge of stones at the time.(6) These were the pioneering fathers of calculous disease and serve a fitting introduction to the discussion of uric acid stone disease which first garnered attention of emerging science.

4.0. URIC ACID PHYSIOLOGY

4.1. Purine Metabolism

A huge literature is available regarding the physiology of purines and pyrimidines. These nucleic acid precursors form the foundations of understanding the physiology of this disease. In fact, if not for the lack of a single enzyme, uricase, human diseases such as gout and uric acid stone formation would not exist. As noted by our forefathers, among mammalian species, only humans and the great apes excrete uric acid as the end product of purine metabolism.(7) The net production of uric acid comes from two primary sources, dietary ingestion and the endogenous production via nucleotide synthesis (Figure 1). This process appears to be most active in liver cells but occurs in all living cells. The synthesis of purines is a sequence of 10 enzymatic steps by which small precursor molecules are placed into a purine ring synthesized on ribose phosphate. These small molecular species include glutamine, glycine, and formate to form 5-phosphoribosyl pyrophosphate (5-



Figure 1. Urinary uric crystals seen under regular microscopy.

RPP), the backbone of the molecule. This high-energy molecule is then involved in purine synthesis in two ways: it combines with L-glutamine and proceeds through *de novo* synthesis; or it participates in the salvage of purine bases, which can be reconverted to ribonucleotides. The enzymatic process of combining 5-PRPP and glutamine uses the enzyme 5-PRPP amidotransferase that is the major step in the pathway and subject of feedback control. Phosphoribosyl-n-amine is the highly labile amino sugar product of this reaction and it is converted to inosinic acid (IMP) in a series of 8 steps using glycine. There is little evidence that the intermediates along this pathway accumulate during synthesis. IMP can then be converted to adenylic acid (AMP) and/or guanylic acid (GMP), both of which are essential to DNA and RNA synthesis. Both AMP and GMP can feedback on the control of 5-PRPP amidotransferase limiting production. IMP can also be catabolized to inosine by a specific 5'-phosphomonoesterase and nonspecific acid and alkaline phosphates. This is a costly pathway in terms of energy utilized, requiring 6 moles of adenosine triphosphate (ATP) for generating one mole of inosinic acid, the first precursor. Purine interconversion is a built-in method of conserving energy and complexly allowing this pathway to reuse preformed purines. The hydrolysis of nucleoproteins and free purines from the diet can be reutilized in the formation of mononucleotides. This obviously is the result of the reversal of the reactions. The enzyme hypoxanthine-guanine phosphoribosyl-transferase (HPRase) catalyzes the transfer of ribose-5-phosphate from 5-PRPP to hypoxanthine and guanine to form IMP and GMP respectively. HPRase activity is also subject to negative feedback inhibition by IMP or GMP and APRTase activity is inhibited by AMP excess. There are hereditary syndromes of enzyme deficiency that can disrupt this reutilization pathway. Lesch-Nyhan syndrome is an HPRase deficiency associated with very high incidence of uric acid stones, interstitial nephritis, and neurological syndrome of choreoathetosis, mental retardation, spasticity, and self-mutilation. Enzyme deficiencies have been described for APRTase activity and the association of 2,8-dihydroxyadenine stone formations.

The last step in the production of uric acid involves xanthine oxidase degradation of hypoxanthine and

xanthine to uric acid. This enzyme is rather indiscriminate and acts upon a host of substrates. Liver and the small bowel have the highest concentrations of this enzyme but the kidney, spleen, skeletal muscle, and heart have activity. Hereditary deficiency in xanthine oxidase has also been discovered. These patients excrete xanthine and hypoxanthine as the end products of purine metabolism. Xanthine is less soluble in urine than is uric acid and these patients suffer from recurrent xanthine stone formation.

4.2. Crystalline Composition and Solubility

The primary determinant of uric acid solubility is the pH of the urine. At a pH of 5, uric acid solubility is 8 mg/dl; at a pH of 7.0 it is 158 mg/dl. The first pKa of uric acid is variously quoted from 5.35 to 5.75.(8) In a graph of the dissociation curve for uric acid, the urine pH on the abscissa, the percent of total uric acid as free undissociated uric acid on the ordinate, and a pKa of 5.57. At this point 50% of the total uric acid is free. The second dissociable proton has a pKa about 10.3 and is not normally clinically significant. The solubility of uric acid in urine is different than in water, being modulated by other ions. At a pH of 5.35, only 200 mg/L of urine can be present without exceeding supersaturation. When the urine pH is raised to 6.5, greater than 1,200 mg/L remains soluble.(9) Sodium concentration has a significant impact upon the solubility of uric acid. As sodium concentrations rise from 6 to 140 mEq/L this results in a 20-fold reduction in the solubility of sodium urate. Ammonium urate is also sparingly soluble with only 5.4 mg/dl at a pH of 7.4.

4.3. Supersaturation and Precipitation

The average adult consumes approximately 2mg of purine per kilogram of body weight, which results in 200-300 mg of urine uric acid daily. Endogenous production is also about 300 mg/day. Endogenous production comes from *de novo* synthesis and tissue catabolism and purine reclamation. In studies by Coe, uric acid excretion was estimated to be 5.6 mg/kg/day.(10) Dietary RNA purines contributed 50% and DNA 25% of the urinary uric acid.(11) Total uric acid excretion is about 600 mg/day for an average person. Excretion of xanthine and hypoxanthine is normally in the range of 5-10 mg/day.

Urinary excretion of uric acid and quantification of the amount varies upon the methods used to collect the specimens, upon the size and gender of the patient, the baseline renal function and dietary ingestion.(12) Urine collected and stored refrigerated, for example will have uric acid crystallize and precipitate at the bottom of the container, skewing measurements.(13) Dietary consumption of purine varies from day-to-day and from person-to-person. These fluctuations in dietary consumption translate to wide variations in urinary excretion of uric acid.(14) Looking more closely at 24 hour urine determinations, Pak in a series of 225 urolithiasis patients on random diets found by comparing two 24-hour urines, a high degree of correlation from one to the other.(15) Of these 225 patients, 27 were uric acid stone formers. Uric acid excretion was 609+/- 214 in the first sample and 597 +/- 203 in the second with a % concordance of 84.2, an r of 0.68 (p< 0.0001).(15) They

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did not break-out the 27 uric acid stone formers for separate analysis, however daily variation was substantial with the 95% confidence intervals (2 standard deviations) ranging from 101 to 1097 mg/day. Finally, other factors can affect urinary uric acid levels. This includes the ingestion of alcohol, long associated with gout and uric acid urolithiasis.(16) Fructose ingestion is another potential variable.(17) Obesity has long been linked to disorders of purine metabolism, both gout and uric acid stone formation.(18) A last consideration should be the ability of the intestinal microenvironment to process and catabolize purines. The gut microorganisms are capable of metabolizing purines and possess the enzyme uricase.(19)

5. CLINICAL CHARACTERISTICS

5.1. Clinical Presentation

As pointed out earlier, uric acid stone disease has been on the decline. Associated diseases of purine metabolism have been on the rise and at least one contemporary article suggests that uric acid stone disease may be back on the rise. In a review of 5477 stone patients in Japan, the incidence of uric acid stones was noted to rise to 7.2% between 1975 and 1993. This was an increase by 3.5 fold compared to the number of uric acid stones in 1975. These authors further noted that males were most commonly affected and hypothesized that gout, hyperuricemia and alcohol ingestion could account for these observations.(20) In another investigation of 652 stone patients, 36 had predominately uric acid stones (5.5%). The male to female ratio was 11:1 and the average age of the male uric acid patient was 49 +/-11 years. Serum uric acid levels were higher in males with pure uric acid stones. Those with pure uric acid stones and mixed stones were noted to have lower urinary calcium levels.(21) The prevalence of uric acid stone disease varies by location from a low of 2% in Texas to a high of 37.7% in Iran. It is well known that this variability by region is probably multifactorial with climatic, dietary, and ethnical influences all having some degree of influence.(22) One study that firmly places occupation and the hot environment as significant factors for uric acid stone prevalence comes from Borghi and colleagues. In a study of machinists at a glass plant, a high incidence of uric acid stones were noted in workers exposed to heat stress (38.8%). They next randomized 21 workers to heat exposure and 21 controls and found that uric acid concentration (722 +/-195 vs. 482 +/- 184 mg./L, $p<0.001$), specific gravity (1.026 +/- 4 vs. 1.021 +/- 6, $p<0.005$) and pH (5.31 +/- 0.28 vs. 5.64 +/- 0.54, $p<0.02$) respectively were all adversely affected.(23) Another epidemiologic study looked at 264 patients with pure uric acid stones and compared them to those patients presenting with other types of calculi. The patients with the uric acid stones were older men. They had comparatively lower incomes and spent less money on food but consumed more alcohol. The urinary pH was lower in this group but serum and urinary uric acid levels were not significantly different than the other stone formers. These authors concluded that alcohol again plays a significant role in uric acid stone disease and that these stones were more prevalent than suspected.(24)

5.2. Laboratory

Patients with uric acid stone disease represent the culmination of relatively intricate pathophysiology

involving purine metabolism. Radiolucent purine-derived stones include uric acid, uric acid dihydrate, ammonium acid urate, sodium urate monohydrate, xanthine, 2,8-dihydroxyadenine and oxypurinol. Chemical analysis and crystallographic evaluation of these stones is not adequate. False positives for uric acid are possible for the rarer types, particularly xanthine and 2,8-dihydroxyadenine stones. Infrared spectroscopy and/or x-ray diffraction techniques are far superior. Because of the clinical and genetic ramifications of purine metabolism deficiencies, children who present with a radiolucent stone should have mandatory stone analysis.

Serum chemistries and complete blood counts should be performed in all patients with a uric acid stone. Sodium, potassium and chloride can be altered by metabolic acidosis. Specifically, sodium and potassium serum levels can be decreased in patients with laxative abuse or chronic diarrheal syndromes. Serum CO_2 concentrations could be diminished in these patients with chronic metabolic acidosis. Serum phosphorus levels have had some utility in predicting tumor lysis syndrome and subsequent acute uric acid nephropathy. Higher serum phosphorus levels indicate a heightened risk of this preventable complication. Serum creatinine is important to estimate the baseline renal function and the BUN is helpful assessing the patient's fluid status. A complete blood count may identify hematologic disorders unknown to the patient presenting initially with a uric acid stone.

Serum uric acid levels should be quantified. It has been widely reported that serum uric acid concentrations are virtually nonexistent in patients with xanthinuria (below 2 mg./dL or $<119 \mu\text{mol}$). The most common potential association is with hyperuricemia and gout. Once these are excluded, idiopathic and inherited uric acid stone formers are sought. In addition, if a particular group of patients have gout, these patients will have higher serum uric acid levels. It has been estimated that only 1/3 of patients with uric acid stones have hyperuricemia.(25) Other series vary with ranges from 21 to 33%. One of the problems with serum determinations is that typically diet is not controlled nor is the 24-hour urine excretion known. Typically patients with either idiopathic uric stone disease or gout do tend to have higher serum uric acid levels. In gout patients with and without uric acid stone formation both tend to have higher serum levels than normals. Also, it can be noted that maximal serum uric acid values for gouty patients with stones are slightly higher than in those without stones.

Urine determinations are an essential aspect in the evaluation of gout and uric acid stone formation. Urinary values such as pH, specific gravity, and a complete urinalysis with appropriate cultures to identify urease-producing infections are essential. Twenty-four hour urine chemistry for uric acid levels is vital. Urine should not be preserved refrigerated, but rather with added acids to prevent bacterial overgrowth so as not to induce uric acid crystallization and spuriously low urinary levels. The ability of spot urine samples in predicting stone risk is uncertain.(26) The need to evaluate more than a single 24

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hour specimen is also controversial.(27) Over excretion is regularly sought in the expectation of finding those patients with hereditary underlying enzyme defects. The partial defects such as hypoxanthine guanine phosphoribosyl transferase (HPRT) might be discovered. The absence of HPRT leads to classic Lesch-Nyhan syndrome in children and over excretion of uric acid is typically severe. The partial impairments of this enzyme in Kelley-Seegmiller syndromes can be encountered as well. Other levels of purine metabolites such as xanthine, hypoxanthine, and 2,8-dihydroxyadenine can be measured with high definition liquid chromatography.

Low urine pH and a fixed acidification defect have long been known to affect uric acid stone formers. A very low 24-hour urine pH can be used to support the diagnosis of uric acid stones or crystalluria even without the actual stone analysis. Urine creatinine is required to insure that an adequate urine collection has been obtained. In patients with mixed stone disease a more extensive urinary chemistry panel is warranted. Also in patients with cystinuria, commonly uric acid levels will be significantly higher than normals and should be sought.

Low urinary volume is a consistent finding in some uric acid stone formers, especially patients with laxative abuse, chronic diarrheal syndromes, small bowel surgery, Crohn's disease, and some drug-related disorders. Low urine volumes can be secondary to poor oral intake, excessive gastrointestinal losses or both. Insensible losses also need to be considered for patients in a hot climate or performing heavy manual labor.

Hyperuricosuria can occur as a consequence to excess dietary ingestion, purine glutton. In gouty patients there is almost a linear increase in stone formation based upon the degree of hyperuricosuria. At levels above 1,000 mg/day about 50% of these patients will develop a uric acid stone. It is also known that 75% to 90% of gout patients have renal under excretion as a cause of their hyperuricemia. These patients have a reduced renal clearance of uric acid.(28) Stone disease activity thus correlates between the degree of hyperuricosuria and the degree of hyperuricemia (47% of gout patients with a serum uric acid level above 11 mg/dL).(29)

The final measurable variable in purine-related stone disease is those rare patients with enzyme abnormalities resulting in either overactive or deficient key enzyme activities. Both glucose-6-phosphate deficiency in type I glycogen storage disease and a superactive variant of glutathione reductase are rare conditions found in gouty patients and associated with overproduction of uric acid.(30,31) Phosphoribosylpyrophosphate synthetase mutations can occur with subsequent gout and uric acid stone production.(32) The enzyme amidotransferase exists in two forms, a smaller active and a larger inactive form. Mutations of this enzyme are known and the possibility of uric acid hypersecretion is possible.(33) Deficiencies, either complete or incomplete with the enzyme hypoxanthine guanine phosphoribosyl transferase (HPRT) lead to overproduction of uric acid by shutting down the

salvage pathways of purine metabolism. Likewise, deficiencies in the adenine phosphoribosyl transferase (APRT) enzyme can be complete or incomplete and leading to 2,8-dihydroxyadenine stone formation. Xanthine oxidase can be absent as in congenital xanthinuria or iatrogenically from allopurinol administration. A final method of increased renal urate clearance is a rare tubular defect called the "Dalmatian Dog Mutation" by Seegmiller. Stone formation is common.(34) These specific disorders will be discussed later, however some caveats are relevant. First, the pathophysiology of these disorders is still incompletely understood and many enzyme abnormalities have numerous genetic determinants. Second, red blood cell assays of these enzymes do not appear to be as reliable as fresh tissue assays using fibroblasts or small intestinal mucosa.

5.2. Radiographic Appearance

All purine-derived metabolic calculi are classically nonopaque, rendering them difficult to locate on conventional kidney-ureter-bladder (KUB) films. In perhaps the initial report on x-rays for the diagnosis of stone disease, the authors suggest that some stones might not be visible.(35) This feature, radio-lucency makes follow-up and secondary interventions difficult to monitor success or failure of therapy. Faintly opaque uric acid and 2-8 dihydroxyadenine calculi have been described, and the astute practitioner should be aware of this. In fact, larger uric acid stones have higher densities and are more likely to be faintly opaque. Tomograms are typically performed in following stone patients. These are of little practical aid in the follow-up or management of these patients. Intravenous urography (IVU) provides both functional information regarding the urinary tract as well as anatomical details regarding the stone and its effects within the collecting system. These calculi will be radiolucent and are not diagnostic for the stone type, but merely suggestive. The IVU is widely available and does provide functional information that aids in the management of these patients. Ultrasonography can usually identify uric acid stones and hydronephrosis when the stones are in the kidney. The limitation of this modality is when multiple stones are present and the presence or absence of ureteral stones. Ultrasonography is much more subjective in the presence of ureteral calculi. The computerized tomogram (CT Scan) is the gold standard for both diagnosis and follow-up of purine-derived metabolic calculi.

Dretler and Prien noted in 45 patients with 100% uric acid stones that on retrospective review almost 1/2 were apparent. They also appreciated that those larger than 2 cm. were more clearly identified.(36) Computerized tomography scans have become the gold standard for investigating radiolucent filling defects because it is non-invasive nature.(37) Some investigators strenuously support the ability of CT to provide density values (Hounsfield units) to correctly predict a stones composition, particularly uric acid. Mitcheson and investigators evaluated 80 urinary calculi with 3 specific parameters: absolute computerized tomography value, the difference between CT values measured at 2 different x-ray energies, and CT value-frequency histograms (pixel

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patterns). Uric acid stones were differentiated from all other stones at a significance level of $p < 0.001$. They established a minimal stone size for analysis of 5 mm.(38) CT scans might distinguish a density difference as small as 0.5% while plain x-rays require approximately 5% difference. The reported attenuation values for uric acid stones are from 346 to 400 HUs.(39) Another study of 102 chemically pure stones was scanned on a General Electric HiSpeed Advantage scanner (50 uric acid stones). Absolute CT values for uric acid stones were 409 ± 118 and using dual kilovolt CT values were 0 ± 41 HUs.(40) In a study of stone size and scan collimation, Saw and coworkers from Indianapolis noted that at 1-mm collimation, stone groups could be differentiated by attenuation. At wider collimation, attenuation became lower and discrimination was lost. By 10-mm collimation only some uric acid stones of about 6 mm could be predicted.(41) The primary problem with these studies, though well performed and comparative to other stones of known composition is that they were all done *in vitro* and any putative advantage to this technique would occur while the stones are still *in vivo*.

Moving to *in vivo* studies of uric acid stones, the CT method of identification is more tenuous. Motley and colleagues from San Antonio evaluated 100 patients on a GE High-Speed Advantage CT scanner prior to surgical intervention. There were 4 uric acid stones in their group and *in vivo* CT densities had a mean of 50 ± 24 (far less than previous studies reported *in vitro*). In addition, comparing calcium (87), uric acid (7), struvite (4) and cystine (2) the overlap of ranges precluded accurate identification.(42)

In conclusion, all methods of imaging play a role in the diagnosis and management of patients with uric acid stones. A regular radiograph may reveal no calculus or a faint trace of a stone. Ultrasound utilizes no ionizing radiation and can be helpful, but it is not a physiologic study and false negatives and positives are possible. Intravenous urography is more time consuming than CT scans but do provide function as well as anatomical details. Retrograde pyelography is even more invasive, however the urologist at times of intervention uses this routinely. CT scanning, as pointed out early by Resnick and colleagues clearly delineates radiolucent stones and is a non-invasive method to identify purine-based stones.(43) The primary problem with all imaging modalities is monitoring the outcomes of uric acid stone patients once a primary surgical intervention has been initiated. In this scenario, the urologist has placed hardware into the urinary collecting system and stone-free status cannot be readily confirmed. Even CT scans become less reliable with indwelling nephrostomy tubes or ureteral stints overlying potentially significant residual stones.(44)

5.3. Stone Disease and Gout

Stone disease and its relationship to gout have a long historical record as previously described. In the long-term studies by Dr. Ts'ai-Fan Yu, she noted that 22% of 2118 gouty patients gave a history of renal stones. She also observed that stone prevalence rose with the levels of

increasing uric acid excretion. The highest incidence was in patients excreting greater than 1,000 mg of uric acid daily on a purine restricted diet, 49%.(45) Most stone forming gout patients are men and the age of onset is about 36 years. Stones tend to occur before any systemic symptoms of gouty arthritis are evident (40%). In studies by Asplin and coworkers, about 75% to 90% of gout patients have renal under excretion as a cause of their hyperuricemia.(46)

5.4. Gout and Stone Disease

While arthritis is the most significant problem in patients with gout, renal disease remains the most frequent extra articular complication of this disease process. Significant impairment in renal function was historically reported in 40% of gouty patients prior to the introduction of allopurinol. Gouty nephropathy was seen clinically in the setting of prolonged hyperuricemia and correlated with the duration and magnitude of the disease. The kidneys in patients with gouty nephropathy were literally crystallized. Urate crystals were noted in the medulla or pyramids with significant giant cell inflammatory response.

5.5. Bowel Disease and Uric Acid Stone Formation

The incidence of uric acid stones is significantly higher than the normal population (5 to 10%), occurring in 20 to 30% of these patients. Surgery alters the relative distribution; the presence of an ileostomy adversely affects the stone prevalence as well as the number of patients that form uric acid stones (as high as 50%). The urine of these patients is low volume secondary to the gastrointestinal loss. Add an ileostomy and volume loss is even more pronounced. The average loss from pooled investigations of patients with an ileostomy is between 500 to 700 cc per day.(47,48) These same studies indicate that urine output is typically below 1 liter per day. More than 90% of ileostomy fluid loss is water. Compared to the normal adult loss in feces of less than 150 cc per day, this loss is significant.(48)

In more detailed investigations, Clarke and colleagues noted total body water was depleted by 11% in patients with an ileostomy.(48) Additionally, sodium is lost accounting for a 7% decrease as well as significantly lowered urinary sodium concentrations.(49) Despite evidence for sodium conservation in these patients, plasma aldosterone concentrations have been controversial in most series.(50,51) Kennedy and coworkers in a group of 39 ileostomists with proctocolectomy and less than 10 cm of terminal ileum resected plus an ileostomy showed a significant raised mean plasma aldosterone. Also, the plasma renin activity was increased, but not markedly so. They speculated that ileum adaptation might explain differences between studies.(47)

The second contributing factor increasing the risk of uric acid stone formation in patients with IBD is acidic urine. Since uric acid is a weak acid with its first dissociable hydrogen ion with a pK_a of 5.75, the urine's pH plays a significant role in stone risk. At a urine pH of 5, only approximately 100 mg/L of uric acid can be held in solution. Hydrogen ion excretion is known to be increased

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in IBD patients and markedly so in those with an ileostomy.(52) Unlike most uric acid stone formers without IBD, these patients have increased ammonium excretion in addition to titratable acid. This is thought to be secondary to intestinal loss of bicarbonate. This is again intensified in patients with active ileal disease and with ileostomies because the pH of ileal fluid is 7.0.(47)

There has been extensive investigation indicating that purine metabolism is not generally affected by IBD. The net excretion of uric acid is therefore not markedly higher than in normal patients. The water loss with subsequent lower urinary volume in addition to the lower pH drives the solubility product of uric acid into the high-risk range. Ileostomy patients excrete significantly more supersaturated urine for uric acid than controls and even more than most patients with uric acid stone formation without IBD.(52) A footnote at the conclusion of the discussion of inflammatory bowel disease and purine metabolism is necessary. A patient with ulcerative colitis and gout taking allopurinol at 600 mg/day was noted to have multiple recurrent radiolucent renal calculi. These were found to be the oxypurine metabolite of allopurinol, oxypurinol.

5.6. Catabolic States and Uric Acid Stone Disease

Hyperuricemic acute renal failure was first described by Bedrna and Polcak in 1929.(53) Even prior to this, Rudolph Virchow, in 1851 noted hyperuricemia and uricosuria complicating the course of leukemia.(54) Hyperuricemia can occur spontaneously secondarily to the rapid turnover of nucleic acids in patients with lymphomas and leukemias. It can also occur with the administration of chemotherapy leading to rapid cell destruction. There are two known mechanisms which increased urinary concentrations of uric acid can induce renal impairment. First is secondary to mechanical obstruction by large volumes of crystals or actual stones and the second is by the deposition of crystals in the intrarenal tubules. In the scenario of acute hyperuricemic nephropathy, the tubules, collecting ducts, pelvis and ureters can literally become blocked from deposition of uric acid crystals. Dunn and Polson in 1926 noted a severe selective damage to the ascending limb of Henle of rabbits given massive doses of lithium monourate.(55) In microdissections, it has been observed that a critical factor is the sudden precipitation of crystals in the collecting tubules.(56) The clinical manifestation is initial oliguria, progressing to anuria and rapidly rising serum creatinine. Although hyperuricemia is seen most commonly in association with acute and chronic leukemias, lymphomas, myeloma, and the myeloproliferative syndromes, there has been an association with nonhematologic malignancy such as breast, sarcoma and testicular cancers.(57)

Stones are noted with increased frequency in patients with myeloproliferative disorders, up to 40%. Other blood dyscrasias have been also noted to predispose to uric acid stone formation includes plasma cell dyscrasias, thalassemias, polycythemia, hemolytic anemia, and sickle cell anemia. Hyperuricemia and hyperuricosuria have been noted in patients with hyperthyroidism due to

Grave's disease.(58) Treatment of the catabolic turnover of purines in patients with these problems has been hydration, alkalinization and allopurinol. Doses beginning at 100 mg/day upwards to 1,000 mg/day have been reported to obviate the tumor lysis syndrome and prevent acute uric acid nephropathy. Uricosuric therapy using benzbromarone has also been effective. In an open-controlled, randomized trial over 24 weeks, serum uric acid lowering effects of daily allopurinol 100 mg with 20 mg of benzbromarone was compared to 300 mg of allopurinol. Both preparations led to decreases in serum uric acid levels to normal but the combination therapy was more pronounced.(59) Another comparative investigation confirms the efficacy of the uricosuric agent, benzbromarone over allopurinol in a crossover trial. The serum uric acid level was reduced from 9.89 +/- 1.43 mg/dl to 5.52 +/- 0.83 mg/dl and from 9.53 +/- 1.48 to 4.05 +/- 0.87 mg/dl by allopurinol and benzbromarone respectively (p<0.005).(60) In another long term investigation of allopurinol used intravenously in 1,172 patients treated in the United States as an adjunct to chemotherapy, 87% of adult patients normalized or improved elevated serum uric acid levels.(61) Another new uricosuric drug is CGS-12970, a thromboxane synthase inhibitor. 1-methyl-2(3-pyridyl)-1-indoleoctanoic acid is a reversible thromboxane synthase inhibitor that was tried in 20 healthy males receiving two doses 12 hours apart. Serum uric acid levels declined between 34% and 47% and urine uric acid levels fell between 28% and 134% within 12 hours of the first dose.(62) Finally, the ability of urate oxidase to catalyze the conversion of uric acid to the more soluble product allantoin has been therapeutically utilized to prevent tumor lysis syndrome. Rasburicase is a new recombinant form of urate oxidase available for clinical evaluation. A multi-institutional trial of rasburicase has been performed at 6 sites including 52 patients. The rasburicase versus allopurinol group experienced a 2.6-fold (95% CI: 2.0 – 3.4) less exposure to uric acid. Four hours after the first dose, patients randomized to rasburicase compared to allopurinol achieved an 86% vs. a 12% reduction in serum uric acid levels (p<0.0001).(63)

6. RARE DISORDERS OF PURINE METABOLISM

6.1. Xanthine Stone Disease (Xanthinuria)

Auscher and colleagues described a large kindred family with urolithiasis and gout.(64) These patients were noted to have an autosomal recessive pattern of xanthine oxidase deficiency. Serum and urinary uric acid levels were low and purine end-products, xanthine and hypoxanthine were elevated. These patients had little symptoms except for the formation of xanthine stones. There exist two inherited forms of xanthinuria. One is a deficiency in the enzyme xanthine dehydrogenase where the less soluble end product of guanylic acid breakdown, xanthine accumulates. Xanthine oxidase is a flavoprotein containing molybdenum. The other form of heritable xanthinuria is molybdenum cofactor deficiency presenting in infancy with microcephaly and severe CNS manifestations.(65)

The reported solubility of xanthine at pH of 5 is known to be 50 mg/L (compared to 150 mg/L for uric

Table 1. Guidance for consumption of purine containing food

High levels of purines Best To Avoid	Moderate levels of purines Eat Occasionally	Low levels of purines No Restriction
Liver	Asparagus	Carbonated drinks
Kidney	Beef	Coffee
Anchovies	Bouillon	Fruits
Sardines	Chicken	Breads
Herrings	Crab	Grains
Mussels	Duck	Macaroni
Bacon	Ham	Cheese
Scallops	Kidney beans	Eggs
Cod	Lentils	Milk products
Trout	Lima beans	Sugar
Haddock	Mushrooms	Tomatoes
Veal	Lobster	Green vegetables
Venison	Oysters	
Turkey	Pork	
Alcohol esp beer	Shrimp	
	Spinach	

acid).(66) In one study, only 30 to 40% of patients with xanthinuria formed radiolucent stones.(67) Screening laboratory studies indicate that the most common finding is a serum uric acid below 2 mg/dL or < 119 μ mol/L. In the United States, the incidence of xanthinuria is not known but from 1 in 6,000 to 1 in 69,000 has been suggested. Both types have been reported with similar distribution.(68)

More common, but still rare is the iatrogenic induction of xanthinuria by allopurinol administration. In particular, patients with uric acid overproduction such as those with Lesch-Nyhan syndrome or those with partial HGPRT deficiency can lead to overproduction of the oxypurines, xanthine and hypoxanthine.(69) Normally during allopurinol administration, the plasma levels of oxypurines remains between 0.5 and 2.0 mg/dL, well below the solubility limits. Patients with overproduction as noted earlier, and in some patients with myeloproliferative disorders can result in levels of xanthine above this limit.(70).

Since alkalization has little affect upon the solubility of xanthine it adds little to the therapeutic regimen. High fluid intake is the key to therapy. Dehydration is to be avoided whenever possible. Low purine diet is effective (Table 1). There currently is no drug available that will reduce the risk of xanthine stone formation in these rare patients. In patients with iatrogenic allopurinol-induced xanthinuria, withdrawal of allopurinol is necessary.

6.2. 2-8 Dihydroxyadenine Stone Disease (APRT Deficiency)

The deficiency of adenine phosphoribosyl transferase (APRT) prevents the conversion of the adenine nucleotide to adenylic acid via the scavenger pathway. The result is increased production of the precursors 8-hydroxyadenine and 2,8-dihydroxyadenine (8-DHA and 2,8-DHA). This is a genetic disorder of metabolism localized to the long arm of chromosome 16. There currently is no evidence to suggest that heterozygotes get calculi or significantly excrete adenine, 8-DHA or 2,8-

DHA. There are reported patients with these calculi that have only partial APRT deficiency.(71,72)

The disease has been described in virtually all parts of the world now, but appears to be less frequent in the United States currently.(73,74) The disease was first described by Kelley and colleagues in 1968.(75) Stones are seen in these patients only because of the poor solubility of 2,8-DHA. Calculus formation and crystal nephropathy are primarily seen in children with this disease but adults can develop stones.(76-78) 2,8-dihydroxyadenine stone give a false-positive reaction to the colorimetric analysis for uric acid stones. Thus, infrared spectroscopy or x-ray diffraction analysis of these stones is mandatory. These stones are typically radiolucent making the differential diagnosis any of the purine-containing stones possible, but as with uric acid stones there are exceptions.(79) These patients tend to be well clinically, they do present with recurrent urolithiasis and occasionally crystal-induced nephropathy with no systemic symptoms of gout. This nephropathy can be very significant as demonstrated by a case of recurrent stones following a successful kidney transplant 23 years later.(80) Despite the absent or decreased APRT activity adenine can be catabolized to 8-DHA and 2,8-DHA making it a far different clinical problem than its counterpart salvage enzyme deficiency (HPRT) inducing the Lesch-Nyhan syndrome.

The clinical diagnosis of this rare syndrome includes a high degree of suspicion. Stone analysis with the appropriate methods (IR or XRD) is crucial. These stones tend to be grayish in color, not the golden-yellowish-brown of uric acid stones. The stones themselves crush easily and do not react with uricase. Once suspect, absence of erythrocyte APRT activity is confirmatory. Reports on the diagnosis by analysis of the urinary sediment, noting a significance of 2,8-dihydroxyadenine crystals has appeared. The crystals were brownish spheres noted in two family members of a symptomatic subject.(81,82) Therapy includes a high fluid intake. Diets low in purine are also utilized. Alkalization drug therapy has no therapeutic

benefit since 2,8-DHA solubility is not pH dependent in the physiologic range. Allopurinol does reduce the production of 2,8-DHA. At doses of 10 mg/kg/day, the elimination of 2,8-DHA has been noted.(83) Allopurinol dosing should be reduced in patients with renal impairment. In patients with high levels of excretion or with higher doses of allopurinol, oxypurinol stones can be induced. Shock wave lithotripsy has been used successfully in patients presenting with these stones.(84,85)

6.3. Lesch-Nyhan Syndrome (HPRT Deficiency)

In 1959 Catel and Schmidt first described an 18 month infant with hyperuricemia, hyperuricosuria and encephalopathy.(86) In 1964 Michael Lesch and William Nyhan described two brothers with a clinical syndrome of hyperuricemia, hyperuricaciduria, and severe neurologic dysfunction including choreoathetosis, mental retardation, and autodestructive behavior.(87) In 1966, the sex-linked inheritance of the syndrome became widely recognized. Seegmiller and colleagues demonstrated the following year that complete deficiency of hypoxanthine guanine phosphoribosyl transferase (HPRT) was the cause of the syndrome described by Lesch and Nyhan.(88) The prevalence of this disorder is from 1/100,000 to 1/380,000 live births. It affects all races. Much has been learned about this rare disorder characterized initially by excess uric acid in the urinary tract. Infants are often first noted to have orange crystals in the diapers, with subsequent stone formation and hematuria. The psychomotor elements of the syndrome become manifest within the first 3 to 6 months of life. A high serum uric acid level is typically what prompts more detailed testing, but some infants have borderline levels secondary to high renal clearances. In 1969, Kelley and colleagues described a partial deficiency of the HPRT enzyme in patients with gouty symptoms and uric acid stone disease without the neurologic stigmata of Lesch-Nyhan syndrome.(89)

A great deal of recent emphasis by researchers in this field are focusing upon the primary genetic etiology of this disorder.(90) The HPRT gene is located at the long arm of chromosome Xq26-27 and consists of 57 base pairs. Over 2,000 mutations are now known throughout this gene coding region from exon 1-9.(91) In addition, unexpected affected females have now been described.(92) There is evidence that a specific set of Alu repetitive units in DNA elements may be the basis of Lesch-Nyhan syndrome that can be traced phylogenetically through chimpanzee, gorillas and to humans.(93) Detailed gene analysis of Lesch-Nyhan variants have also been reported depending upon the severity of the neurologic presentation in four groups: group 1- normal development but HPRT deficiency, group 2- mild neurologic symptoms, group 3- severe neurologic deficiencies, and group 4- full blown Lesch-Nyhan syndrome.(94) In a review of genetic inherited mutations correlating to the severity of the disease, Jinnah and colleagues noted several points. The mutations are throughout the long arm of the Xq26 region, but some sites are "hot spots." Next genotype-phenotype correlations provide no indication of the specific mutation's location. Cases that are less severe (groups 1 and 2 from Puig) typically have mutations permitting some enzyme function.

Finally, knowledge of the mutations provides a rough guide of the phenotype.(95) As genetic knowledge advances; the hope for specific genetic interventions for this devastating disease may be possible. Adenovirus vector expressing the human HPRT cDNA has been used to transfect cells in culture, restoring purine metabolism.(96) In another attempt at somatic gene therapy, Palella and coworkers used a recombinant herpes simplex virus type I vector to transfect rat neuronal cells with human HPRT mRNA transcripts.(97)

There currently exists no great therapy for the neurologic manifestations of this disease; however, allopurinol can prevent the formation of uric acid crystalluria, nephrolithiasis and gouty arthritis associated with this syndrome. Starting doses are 10 mg/kg/day and adjusted to maintain high-normal serum uric acid levels. There have been reports of allopurinol therapy inducing xanthine and oxypurinol stones in these patients so response to the dose and monitoring are necessary. A high urinary output decreases both of these potential consequences of allopurinol therapy in patients with Lesch-Nyhan syndrome.

6.4. Oxypurinol Stone Disease

Allopurinol is an analog of hypoxanthine and it and its primary metabolite, oxypurinol inhibit the enzyme xanthine oxidase. Allopurinol blocks the conversion of hypoxanthine and xanthine to uric acid.(98) Associated with this blockage, the serum urate levels decline and urinary uric acid levels fall. Allopurinol has a short half-life of one to three hours but its active metabolite; oxypurinol persists much longer, 15 to 20 hours. Utilizing high-performance liquid chromatography, Safranow has demonstrated that oxypurinol could be found in 9 predominant uric acid stones in patients taking allopurinol.(99) Patients receiving allopurinol in higher doses can form oxypurinol stones. One patient with regional enteritis and recurrent uric acid stone disease treated with 600 mg of allopurinol daily began to develop small, soft, yellow stones shown to be oxypurinol.(100) Oxypurinol is not so soluble and it may precipitate in larger allopurinol dosages and if used over a long period of time.(101)

6.5. Ammonium Urate Stones

Four stone types of uric acid and urate are known: anhydrous uric acid (most common form), uric acid dihydrate (very unstable), ammonium acid urate, and sodium acid urate monohydrate. These latter two stone types are most commonly found in bladder calculi. The necessary condition to form ammonium acid urate calculi is a high concentration of ammonium. This can occur due to an intriguing number of mechanisms such as urinary infections, secondary to dehydration, starvation, acidosis, and excess of acid-forming foods.

6.6. Endemic Ammonium Urate Stones

Endemic bladder stone disease is reported primarily in children and has steadily declined in most Western countries. Its decline has been associated with a rise in living standards, particularly in urban centers. This

is paralleled by a rise in general nutrition. The types of endemic bladder stones depend upon the composition of the urine, which in turn, reflects the dietary consumption. Diets that are low in animal protein, calcium, phosphate, but high in cereal are acidogenic. This subsequently leads to urine with relatively high concentrations of ammonium and urate ions. This is the scenario where ammonium acid urate precipitation occurs.(102) In one recent investigation of children from Pakistan, peak age of stone formation in 1,440 children was 6 to 10 years for renal calculi and 1 to 5 years for bladder calculi (43% of renal and 38% of bladder stones). Bladder stones were more common prior to the mid 1980s in 60% of these children. The number of endemic bladder stones declined to 15% by the mid 1990s. Ammonium acid urate occurred in 210 children (27%). Diet, dehydration and poor nutrition were the main identified risk factors in these children.(103) In studies from Niger, India, South Africa, Australia's aboriginal children and Navajo Indian children reveal that 40% of endemic stones are nearly pure and almost 50% of the remaining had ammonium urate constituents.(104-108)

6.7. Other causes of ammonium urate calculi

Herring reported the incidence of these stones in the United States at 0.2%.(109) In a contemporary series from North America similar rates were reported from Canada and Cleveland, Ohio. 3.1% of stones contained some and 0.2% were predominantly ammonium acid urate.(110,111) The primary conditions associated with nonendemic ammonium acid urate stone are inflammatory bowel disease, laxative abuse, obesity and urease-producing urinary tract infections.(111) In a review of patients with AAU calculi, obesity and/or urinary tract infections accounted for the etiology of most of these stones. Patients with inflammatory bowel disease and laxative abuse had stones with the greatest proportion of ammonium urate.

Urease-producing urinary tract infections are a prime importance in ammonium urate stone disease. These infections commonly result in stones of mixed composition with ammonium urate and magnesium ammonium phosphate hexahydrate (struvite).(112) The ureolytic infections can produce large amounts of ammonium resulting in alkaline urine. Of the 16 patients (36.4%) with documented urease-producing infections, Soble noted that only 19.9% of the stones volume was ammonium urate with the majority being struvite.(111)

Laxative abuse is another known risk factor producing AAU stones and it has been reported in patients with anorexia nervosa.(113) In a multi-institutional review of patients with laxative abuse and ammonium urate calculi, Dick and associates hypothesized that gastrointestinal loss of water and electrolytes causes volume depletion. Intracellular acidosis occurs with serum potassium and bicarbonate levels becoming slightly decreased.(114) Also noted was low serum magnesium levels secondary to gastrointestinal losses. The urine chemistries of this unique group of stone formers were obtained on laxatives. Urinary values for volume, citrate, sodium, potassium, magnesium, phosphorus and uric acid

were all reduced. Supersaturation for major crystal systems was calculated using EQUIL 2. It was noted that the negative affects of laxatives persisted for a few weeks after discontinuing these drugs. Studies by Teotia found that ammonium urate formed over a pH range from 6.0 to 7.5. Ammonium urate solubilizes nearly completely from the urine at a pH of less than 5.7.(115)

Clinically, most patients with laxative abuse are women although occasional males have been noted.(116) Sodium loss is the hallmark feature in these patients with urinary sodium typically below 10 to 15 mEq. per day. Phenolphthalein screens upon the urine of patients suspected with this syndrome can be performed. Other agents can cause this syndrome including bisacodyl, bisoxatin, danthron, oxyphenisatin and senna all capable of being identified in the urine of these patients.(117) These calculi are generally radiolucent. Rapid stone formation and encrustation of urinary stints has been reported.(118) Stones have been documented to regress if the offending laxative is removed and urinary chemistry returns to normal.(111,119) One final comment is necessary on ammonium urate stones in human deficiency virus infected individuals. In a review from a single center, 24 patients with acquired immunodeficiency disease (AIDS), all receiving protease inhibitors were noted to have urolithiasis. There were 2 ammonium acid urate stones in this group (8.3%) and these two unusual stones were 50% of those with indinavir calculi making these stones always a consideration in a patient presenting with HIV and a radiolucent stone.(120).

7. Therapy

The therapy of purine metabolic stone disease essentially mirrors that of uric acid, but some vital exceptions will be noted. The rare stone types xanthine and 2,8-dihydroxyadenine should both be considered if the right clinical circumstances are present. Stone analysis is the key to successful identification and knowledge of the serum uric acid level is crucial. Two methods of chemical analysis for purine-derived metabolic stones, the phosphomolybdate colorimetric test and the murexide test cannot discriminate uric acid from its precursors 2,8-dihydroxyadenine. Infrared spectroscopy and X-ray diffraction analysis are far more reliable methods of stone identification. With all purine-derived calculous patients some overall parameters should be utilized therapeutically. Hydration is the cornerstone of therapy. As the urinary volume increases, the supersaturation decreases. It is inexpensive and usually well tolerated. Dietary purine restriction is essential. The table lists foods high in purines, which should be avoided. Alcohol has usually been listed as a risk factor and should be avoided. All of the urologic methods that will be discussed are equally applicable to the rare purine stones: xanthine, 2,8-dihydroxyadenine, monosodium urate, and ammonium urate calculi. Shock wave lithotripsy can fragment these stones if they can be targeted at the F2 of the lithotriptors. All can be destroyed with ultrasonotrodes or the holmium:YAG laser.

7.1. Chemodissolution

There is little doubt that the primary method for treating patients with known uric acid stones is medical dissolution. The first pKa of this purine metabolite

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is 5.75 making manipulation of the urinary pH an easily accomplished therapeutic maneuver.(8) Increasing the urinary volume further enhances the therapeutic efficacy of alkaline medications. In addition, decreasing the oral purine load from dietary sources can effectively help manage patients, since 40-60% of excretable uric acid is derived from exogenous sources.(116) Sodium should be restricted as well during active therapy because the sodium salts of uric acid are less soluble than uric acid itself.(121)

The modern foundations for oral alkalinization therapy follow the principles outlined by Pak and colleagues for metaphylaxis of calcium stones.(122) Oral potassium citrate is the logical oral drug of choice since it does not involve the addition of sodium in the presence of a patient obviously supersaturating with uric acid.(123) Potassium citrate at doses from 30 to 80 mEq per 24 hours increased the urine pH from 5.3 to 6.19 and reduced new stone formation rate from 1.2 to 0.01 stones per year in patients with known uric acid lithiasis.(123) Unfortunately, potassium citrate is associated with a large number of side effects, predominately gastrointestinal upset.(124) To maintain the urine's pH from 6.0 to 6.5 often requires daily consumption of 30 to 60 mEq three to four times a day.(125) Preparations of potassium citrate vary from slow release wax matrix tablets (UroCit KTM, Mission Pharmaceuticals), to crystalline powder (Polycitra K CrystalsTM, Baker Norton Pharmaceuticals), to liquid (Polycitra KTM, Baker Norton Pharmaceuticals), to a simple pill (SlowK). If one variety fails another may be more tolerable to a given patient. In addition, the sodium or mixed sodium/potassium preparations may be a fall back alternative as is sodium bicarbonate.(126) Truly recalcitrant patients who cannot tolerate any of the aforementioned urinary alkalinizing medications can be placed on acetazolamide (DiamoxTM, 250 mg. at bedtime).(127) The role of the citrus fruit juices, orange and lemon, have been definitively documented enough to warrant their routine utilization. 1.2 liters of reconstituted orange juice increases urine pH from 5.7 to 6.5, and increases urinary citrate from 571 to 952 mg/d (equivalent to ingesting 60 mEq of potassium citrate).(128) Orange juice has no hypocalciuric effect and increases urinary oxalate excretion. Lemon juice on the other hand does not have these drawbacks but maintains the increased citrate load noted by Pak and colleagues.(129) The xanthine oxidase inhibiting drug, allopurinol, has no role in the acute management for dissolution.(123) Its use for decreasing supersaturation is widely recognized but it will not help dissolve a concretion that is already formed.

7.2. Prevention

Since most of the risk factors for uric acid precipitation are known, it would be prudent to devise methods that could be used to prevent these stones from recurring. This is particularly important because the natural history of uric acid stone formation generally is a more aggressive course than for idiopathic calcium stone formers. (Coe).

Potassium-containing oral alkalinizing agents have therefore assumed a greater role in the armamentarium for

prophylaxis. Compliance in the general stone population is known to be poor in long-term follow-up investigations. In one such study, Tiselius from Sweden noted that 62% of patients responding to a questionnaire reported compliance with citrate therapy.(130) In an intermediate follow-up study, Lee reviewed 493 patients with a 34.2% stone recurrence rate and only 49.3% remained on medical prophylaxis longer than 12 months.(131) An additional study on patients with surgically-active uric acid stones, all patients were either partially or totally non-compliant with oral alkaline therapy for a variety of reasons including lack physician-related information, concerns regarding possible side effects and medical neglect.(44) Drop out rates might also be contributed by the inconvenience of multiple, timed, daily dosings necessary with potassium citrate.(132)

For all of these reasons, it has become desirable to develop methods of decreasing the risk of new stone formation and minimizing the inconvenience to the patient. Therefore alkaline therapy strategies have evolved into dosing patients who are presently stone free with low doses of potassium citrate at bedtime. The rationale has been that the urine will become the most supersaturated with the decreased urinary volumes of the evening. In addition, acidity probably reaches its lowest point during sleep. The alkaline dose would therefore provide risk reduction at these key times. Some investigators have sought even lowering this dose to every other night suppression.

7.3. Surgical Therapy

Uric acid stone disease is predominately a medical condition, capable of being managed by chemodissolution and prevention. There are patients however that do present for surgical intervention. Classic indications for open stone surgery are evolving steadily with minimally invasive surgical procedures making these operations a thing of the past. In fact, every open operation now has its minimally invasive counterpart that can be done by those skilled in these techniques. The history of stone surgery is linked closely with the specialty of urology. Desnos describes in detail how itinerant lithotomists of centuries ago would treat predominately uric acid bladder stones.(133) In the past 20 years, the field of subspecialization, endourology might well relegate open stone surgery to the same historical status practiced by those vagabond surgeons.(134) Hippocrates' axiom for physicians to "...not cut on patients laboring from the stone..." might finally be achieved.

Looking closely at the indications for open stone surgery articles published just 2 years ago have to be seriously reconsidered. As new, less invasive techniques come to the forefront of therapy the old standards are always questioned. Paik and Resnick assess the trend to less aggressive surgical interventions in 2000. They suggest that there are diminishing indications for open stone surgery and list these as follows: complex stone burden, minimally invasive treatment failures, associated anatomic abnormalities, morbid obesity, comorbid medical diseases, concomitant open surgery and non-functioning lower poles.(135) The rate of open stone surgery at this tertiary care facility is quoted at 5.4%, quite high by most

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standards of other similar facilities both in the United States and abroad (0.7 to 2.4%).(136-138) In a retrospective review of stone surgery in Singapore, Sy and colleagues noted in 2,651 operations for patients presenting with urinary calculi, only 2% required open operations. They again noted indications for open operations as follows: complex stone burden requiring an anatomic nephrolithotomy and calicoplasty (15), 5 requiring pyeloplasty with pyelolithotomy, 18 ureterolithotomies and 11 nephrectomies for non-functioning kidneys with stones.(139)

Minimally invasive urologic surgery has seen three eras currently in modern urologic practice. In this, the third era of rapid procedural expansion almost every type of open urologic operation is being reproduced by its laparoscopic counterpart by pioneers in this field.(140) Currently, every indication discussed in the transitional papers on the role of open stone surgery are methodically being removed by laparoscopic centers.(141) Ureterolithotomy can be done laparoscopically with less post-operative discomfort to the patient.(142) Obesity has long been associated with an increased risk of both uric acid stone formation and failure of shock wave lithotripsy. Percutaneous ultrasonic nephrostolithotripsy can be very difficult in these patients as well. Endourologic innovations can successfully manage even massively obese patients.(143) Laparoscopic pyelolithotomy and concurrent pyeloplasty has been used successfully at the Johns Hopkins University in 19 patients with 20 involved kidneys. Immediate stone free status was achieved in 90% of these patients and 80% remain stone free at a mean follow-up of 12 months.(144) Of all the aforementioned indications noted for open stone surgery, only complex stone disease remains, but as with all things in medicine, just wait. Kaouk and colleagues at the Urologic Institute of the Cleveland Clinic Foundation have reported upon a porcine model of cooled, ischemic anatomic nephrolithotomy with synchronous repair of the calyces. Mean operative times were 125 minutes and the mean blood loss was 68 cc. in 8 animals.(145) Buoyed by their pre-clinical experiences, this same group has performed this rather remarkable procedure on 2 patients.(146) Despite all of the wondrous advances, the role of laparoscopic stone surgery will probably continue to decline to some small steady state because the urologic armamentarium has even less invasive alternatives.(147)

For large, symptomatic upper tract uric acid stones, percutaneous ultrasonic nephrostolithotripsy should be considered. Indications for intervention are large stone burdens and obstruction resulting in compromised renal function or symptoms (pain, bleeding or infection). There exist little or no data per se on the exact outcomes for patients with uric acid stones, but this type of concretion is easily fragmented with ultrasonic lithotrites.(148) Even in patients with staghorn uric acid stones filling all areas within the upper collecting system, successful debulking can be done with stone free rates from 42 to 96%. Combined "sandwich" strategies consisting of shock wave lithotripsy following percutaneous debulking and second look endoscopy further reduce the number and incidence of

residual fragments in active stone formers.(149) In addition, once nephrostomy tubes have been placed and the bulk of uric acid stone material has been removed, secondary direct chemodissolution can be performed. Almost any parentally available alkaline solutions can be used to successfully dissolve remaining uric acid debris. 2 ampules of sodium bicarbonate added to a liter of half-normal saline, the cardioplegic agents tromethamine and tromethamine-E (organic buffer with pH of 10.6) are usually available.(150)

Ureteroscopy is even less invasive than percutaneous endorenal surgery, since small endoscopes can be passed retrograde via the body's naturally occurring openings. Ureteroscope manufacturing has improved to the point that diminutive instruments less than 3 mm. in diameter and excellent optics are available. Virtually every area within the kidney and ureter is thus amenable to this type of therapy. In addition, reports of urologic intervention with sub 8 Fr. (smaller than 3 mm. in diameter) flexible ureteroscopic laser lithotripsy being performed with the patients awake with intravenous sedation alone are beginning to be reported.(151) A whole host of energy-ablative technologies exist for ureteroscopic, intracorporeal lithotripsy.(152) The gold standard has become the holmium:YAG laser. The diminutive size, wide range of power and clinical effectiveness have made this modality the treatment of choice for urologist treating stones.(153) One harbinger of risk has been raised by Teichman regarding the laser light interaction with uric acid. Since the mechanism of action of holmium:YAG laser lithotripsy is a photothermal effect, breakdown products of uric acid include cyanide. Despite this potential, there have been no reported cases of cyanide toxicity to date using the holmium:YAG laser.(154)

Shock wave lithotripsy has been a well-established treatment for radiolucent or faintly opaque renal and ureteral calculi. Some uric acid stones appear to break up poorly but most series report significant fragmentation with this least invasive modality. Some interesting observations are apparent. First, it appears from studies *in vitro* that pretreating patients with uric acid stones increases the fragility of these stones and perhaps improves stone free status.(155) Detailed evaluations stone fragmentation in the past utilizing the Dornier HM-3 device shows fairly uniform fragmentation of uric acid stones suggesting disruption along concentric laminations within these stones.(156) Shock wave lithotriptors can focus radiolucent calculi at their F2 using either x-rays, fluoroscopy and/or ultrasound. Ultrasound focusing devices have an advantage since these stones are most commonly radiolucent. Intravenous contrast administration and retrograde contrast infusion have all been utilized to aid in targeting these stones for shock wave lithotripsy.(157-160) Treatment success has ranged from 76% to 82% stone free following these procedures. Retreatments are noted to be common in about 15% to 20% of patients possibly depending on the type of lithotripter utilized (more retreatments in the piezoelectric machines). Finally, the rarer xanthine and 2,8-dihydroxyadenine calculi can be treated effectively with shock wave lithotripsy.

8. CONCLUSIONS

Uric acid stone disease is an ancient medical condition. A lot has changed since Scheele and Pearson recognized it chemically. Currently there is much interest in the idiopathic uric acid stone formers and the possibility that this may represent more subtle presentations for inborn errors of metabolism. Since the purine metabolic pathways are so complex, involving regulatory and feedback mechanisms from both the salvage side and the *de novo* synthesis pathways this should be no great surprise. Genetic engineering may hold the future for the control of this disease. It is now known that the administration of recombinant urate oxidase to catalyze the conversion of uric acid to the more soluble product allantoin has been therapeutically utilized to prevent tumor lysis syndrome.(63) For the rarer types of purine-derived stones genetic alteration of the mutations causing these diseases might be possible. Medical therapy, both chemolysis and preventative are the hallmarks of therapy for this disease. For those patients failing this the endourologic armamentarium is rapidly expanding to the point that an open operation for uric acid stone disease should be almost anecdotal.

9. REFERENCES

- Moran,ME. Founding fathers of calculus chemistry. *J Endourol* in press
- Hall,MP: Paracelsus His Mystical and Medical Philosophy. The Philosophical Research Society, Los Angeles (1964)
- Osler,W Principles and Practice of Medicine. D. Appleton and Co., 765 (1892)
- Richet,G: The chemistry of urinary stones around 1800: A first in clinical chemistry. *Kid Inter* 48, 876-86 (1995)
- Wollaston,WH: On gouty and urinary concretions. *Philos Trans R Soc Lond* 87, 386-400 (1797)
- Rosenfeld,L: The chemical work of Alexander and Jane Marcet. *Clin Chem* 47, 784-92 (2001)
- Shattock,SG: On the microscopic structure of uric acid calculi. *Philos Trans R Soc Lond* 110-46 (1908)
- Finlayson,B, Smith,A: Stability of first dissociable proton of uric acid. *J Chem Engin Data* 19, 94-7 (1994)
- Coe,FL, Strauss,AL, Tembe,V, et al: Uric acid saturation in calcium nephrolithiasis. *Kid Inter* 17
- Coe,RL, Moran,E, Kavalach,AG: The contribution of dietary purine over-consumption to hyperuricosuria in calcium oxalate stone formers. *J Chronic Dis* 29, 793-800 (1976)
- Zollner,N, Griesch,A. Diet and gout. *Adv Exp Med Biol* 41, 435-42 (1974)
- Wortmann,RL, Fox,IH: Limited value of uric acid to creatinine ratios in estimating uric acid excretion. *Ann Intern Med* 93, 822-5 (1980)
- Yamakita,J, Yamamoto,T, Moriwaki,Y, Takahashi,S, Tsutsumi,Z, Hada,T: Effect of urine storage on urinary uric acid concentrations. *Ann Clin Biochem* 37, 355-9 (2000)
- Hesse,A, Siener,R, Heynck,A, Jähren,A: The influence of dietary factors on the risk or urinary stone formation. *Scanning Microsc* 7, 1119-27 (1993)
- Pak,CYC, Peterson,R, Poindexter,JR: Adequacy of a single stone risk analysis in the medical evaluation of urolithiasis. *J Urol* 165, 378-81 (2001)
- Faller,J, Fox,IH: Ethanol induced alterations in uric acid metabolism. *Adv Exp Med Biol* 165, 457-62 (1984)
- Raivo,KO, Becker,MA, Meyer,W, Greene,ML, Nuki,G, Seegmiller,JE: Stimulation of human purine synthesis *de novo* by fructose infusion. *Metabolism* 24, 861-9 (1975)
- Matsuura,F, Yamashita,S, Nakamura,T, et al: Effect of visceral fat accumulation on uric acid metabolism in male obese subjects: visceral fat obesity is linked more closely to overproduction of uric acid than subcutaneous fat obesity. *Metabolism* 47, 929-33 (1998)
- Sorensen,LB, Levinson,DS: Origin and extrarenal elimination of uric acid in men. *Nephron* 14, 7-20 (1975)
- Okabe,H, Hosoya,T, Ichida,K, Tabe,A, Saji,M, Hikita,M, Sakai,O: An epidemiologic study on pathogenesis of uric acid urolithiasis. *Ryumachi* 35, 773-9 (1995)
- Ito,H, Kotake,T, Nomura,K, Masai,M: Clinical and biochemical features of uric acid nephrolithiasis. *Europ Urol* 27, 324-8 (1995)
- Halabe,A, Sperling,O: Uric acid nephrolithiasis. *Min Electrol Metab* 20, 424-31 (1994)
- Borghi,L, Meschi,T, Amato,F, Novarini,A, Romanelli,A, Cigala,F: Hot occupation and nephrolithiasis. *J Urol* 150, 1757-60 (1993)
- Zecher,O, Pfluger,H, Scheiber,V: Idiopathic uric acid lithiasis: epidemiologic and metabolic aspects. *J Urol* 128,1219-23 (1982)
- Mueller,SR, Sears,B: The problem of the nonopaque urinary tract stone. *J Urol* 67, 832 (1952)
- Simkin,PA, Hoover,PL, Paxson,CS, Wilson,WF: Uric acid excretion: quantitative assessment from spot, midmorning serum and urine samples. *Ann Intern Med* 91, 44-7 (1979)
- Boisson,RC, Eynard,JC, Crozier,M, Grafmeyer,DC: French experience of quality assessment of quantitative urinary analysis. *Clin Chem Acta* 297, 285-95 (2000)
- Lanthem,W, Rodman,GP: Impairment of uric acid excretion in gout. *J Clin Invest* 41, 1955 (1962)
- Yu,TF, Gutman,AB: Uric acid nephrolithiasis and gout. Predisposing factors. *Ann Intern Med* 67, 1133 (1967)
- Holling,HE: Gout and glycogen storage disease. *Ann Intern Med* 58, 654 (1963)
- Long,WK: Glutathione reductase in red blood cells: variant associated with gout. *Science* 155, 712 (1967)
- Sperling,O, Persky-Brosh,S, Boer,P, deVries,A: Human erythrocyte PRPP synthetase mutationally altered in regulatory properties. *Biochem Med* 7, 389 (1973)
- Holmes,EW, WyngaardenJB, Kelley,WN: Human glutamine phosphoribosylpyrophosphate amidotransferase: two molecular forms inconvertible by purine ribonucleotides and phosphoribosylpyrophosphate. *J Biol Chem* 248, 6035 (1973)
- deVries,A, Sperling,O: Inborn hypouricemia due to isolated renal tubular defect. *Biomedicine* 30, 75 (1979)
- Macintyre,J, Glasg,CM: Reontgen rays. Photography of renal calculus; description of an adjustable modification in the focus tube. *Lancet* July 11, 418 (1896)
- Dretler,SP, Prien,EL,Jr: Uric acid radiodensity: a matter of size and form. *J Urol* 149, 253A (1993)
- Fielding,JR, Steele,G, Fox,LA, Helles,H, Loughlin,KR: Spiral computerized tomography in the evaluation of acute

- flank pain: a replacement for intravenous urography. *J Urol* 157, 2071-3 (1997)
38. Mitcheson,HD, Zamenhof,RG, Bankoff,MS, Prien,EL: Determination of the chemical composition of urinary calculi by computerized tomography. *J Urol* 130, 814-9 (1983)
39. Federle,MP, McAnich,JW, Kaiser,JA et al: Computed tomography of urinary calculi. *Am J Roentgen* 136, 255 (1981)
40. Mostafavi,MR, Ernst,RD, Saltzman,B: A accurate determination of chemical composition of urinary calculi by spiral computerized tomography. *J Urol* 159, 673-5 (1988)
41. Saw,KC, McAteer,JA, Monga,AG, Chua,GT, Lingeman,JE, Williams,JC Jr: Helical CT of urinary calculi: effects of stone composition, stone size, and scan collimation. *Am J Roentgen* 175, 329-32 (2000)
42. Motley,G, Dalrymple,N, Keesling,C, Fischer,J, Harmon,W: Hounsfield unit density in the determination of urinary stone composition. *Urology* 58, 170-3 (2001)
43. Resnick,MI, Kursh,ED, Cohen,AM: Use of computed tomography in the delineation of uric acid calculi. *J Urol* 131, 9-10 (1984)
44. Moran,ME, Abrahams,HM, Burday,DE, Greene,TD: Utility of oral dissolution therapy in the management of referred patients with secondarily treated uric acid stones. *Urology* 59, 206-10 (2002)
45. Yu,TF: Nephrolithiasis in patients with gout. *Postgrad Med* 63, 164-70 (1978)
46. Asplin,J: Uric acid stones. *Semin Nephrol* 16, 412-24 (1996)
47. Kanaghinis,T, Lubran,M, Coghill,NF: The composition of ileostomy fluid. *Gut* 4, 322-38 (1963)
48. Clarke,AM, Chirnside,A, Hill,GL, Pope,G, Stewart,MK: Chronic dehydration and sodium depletion in patients with established ileostomies. *Lancet* 2, 740-3 (1967)
49. Turnberg,LA, Morris,AI, Hawler,PC, Herman,KJ, Shields,RA, Horth,CE: Intracellular electrolyte depletion in patients with ileostomies. *Gut* 19, 563-8 (1978)
50. Isaacs,PET, Horth,CE, Turnberg,LA: The electrical potential difference across human ileostomy mucosa. *Gastroenterol* 70, 52-8 (1976)
51. Clarke,AM, McKenzie,RG: Ileostomy and the risk of uric acid stones. *Lancet* 2, 395-7 (1969)
52. Bambach,CP, Robertson,WG, Peacock,M, Hill,GL: Effect of intestinal surgery on the risk of urinary stone formation. *Gut* 22, 257-63 (1981)
53. Bedrna,J, Polcak,J: Akuter Harnleiterverschluss nac Bestrahlung chronischer Leukamien mit Rontgenstrahlen. *Med Klin* 25, 1700-1 (1929)
54. Talbott,J: Gout and blood dyscrasias. *Medicine* 38, 173-205 (1959)
55. Dunn,JS, Polson,CJ: Experimental uric acid nephritis. *J Pathol* 29, 337-52 (1926)
56. Epstein,FH, Pigeon,G: Experimental urate nephropathy: studies of the distribution of urate in renal tissue. *Nephron* 1, 144-57 (1964)
57. Perry,MC, Hoagland,HC, Wagoner,RD: Uric acid nephropathy. *JAMA* 236, 961-2 (1976)
58. Sata,A, Shirota,T, Komiya,I, Aizawa,T, Takemura,Y, Yamada,T: Hyperuricemia in patients with hyperthyroidism due to Grave's disease. *Metabolism* 44, 207-11 (1995)
59. Berg,H: Effectiveness and tolerance of long-term uricosuric treatment. *Z Gesamte Inn Med* 45, 719-20 (1990)
60. Hanvivadhanakul,P, Akkasilpa,S, Deesomchok,U: Efficacy of benzbromarone compared to allopurinol in lowering serum uric acid level in hyperuricemic patients. *J Med Assoc Thai* 85, S40-7 (2002)
61. Smalley,RV,Guaspari,A, Haase-Statz,S, Anderson,SA, Cederberg,D, Hohnaker,JA: Allopurinol: intravenous use for prevention and treatment of hyperuricemia. *J Clin Oncol* 18, 1758-63 (2000)
62. Saris,SD, Piraino,AJ, Morgan,JM, Hirschhorn,WL, Meidl,E, Schaffer,AV: Uricosuric effect of CGS-12970, a new thromboxane synthase inhibitor. *Clin Pharmacol Ther* 54, 65-9 (1993)
63. Goldman,SC, Holcenberg,JS, Finklestein,JZ, Hutchinson,R, Kreissman,S, Johnson,FL, Tou,C, Harvey,E, Morris,E, Cairo,MS: A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. *Blood* 97, 2998-3003 (2001)
64. Auscher,C, Pasquier,C, DeGery,A et al: Xanthinuria: study of a large kindred with familial urolithiasis and gout. *Biomedicine* 27, 57-9 (1977)
65. vanGennip,AH, Mandel,H, Stroomer,LEM: Effects of allopurinol on the xanthinuria in a patient with molybdenum cofactor deficiency. In *Purine and Pyrimidine Metabolism in Man*. 8, 375-8 (1995)
66. Klineberg,JR, Goldfinger,SE, Seegmiller,JE: The effectiveness of the xanthine oxidase inhibitor allopurinol in the treatment of gout. *Ann Intern Med* 62, 639-47 (1965)
67. Strauven,P, Hesse,A, Thon,A, Behrendt,H: Xanthinuria with nephrolithiasis in infancy. *Akt Urol* 20, 218-22 (1989)
68. Diven,SC: Xanthinuria. <http://author.emedicine.com/PED/topic2452.htm>
69. Volpe,P, Peyrottes,A, Lammle,M, Saquet,D, Choquet,C: Xanthine urinary calculus in a patient with Lesch-Nyhan syndrome. Apropos of a case. *Prog Urol* 7, 74-7 (1997)
70. Potter,JL, Silvidi,AA: Xanthine lithiasis, nephrocalcinosis, and renal failure in a leukemia patient treated with allopurinol. *Clin Chem* 33, 2314-6 (1987)
71. Suzuki,K, Kobayashi,S, Kawamura,K, Kuhara,T, Tsugawa,R: Family study of 2,8-dihydroxyadenine stone formation: report of two cases of a compound heterozygote for adenine phosphoribosyltransferase deficiency (APRT*J/APRT*Q0). *Int J Urol* 4, 304-6 (1997)
72. Takeuchi,H, Kaneko,Y, Fujita,J, Yoshida,O: A case of a compound heterozygote for adenine phosphoribosyltransferase deficiency (APRT*J/APRT*Q0) leading to 2,8-dihydroxyadenine urolithiasis: review of the reported cases with 2,8-dihydroxyadenine stones in Japan. *J Urol* 149, 824-6 (1993)
73. Simmonds,HA: 2,8-dihydroxyadenine lithiasis. *Clin Chem Acta* 160, 103-8 (1986)
74. Witten,FR, Morgan,JW, Foster,JG, Glenn,JF: 2,8-dihydroxyadenine urolithiasis: review of the literature and report of a case in the United States. *J Urol* 130, 938-42 (1983)
75. Kelley,WN, Levy,RI, Rosenbloom,FM, Henderson,JF, Seegmiller,JE: Adenine phosphoribosyltransferase deficiency: a previously undescribed genetic defect in man. *J Clin Invest* 47, 2281 (1968)

76. Lamontagne,AE Jr: 2,8-dihydroxyadenine urolithiasis: report of a case in a woman in the United States. *J Urol* 142, 369 (1989)
77. Usenius,JP, Ruopuro,ML, Usenius,R: Adenine phosphoribosyltransferase deficiency: 2,8-dihydroxyadenine urolithiasis in a 48-year-old woman. *Br J Urol* 62, 521-4 (1988)
78. Greenwood,MC, Dillon,MJ, Simmonds,HA, Barratt,TM, Pincott,JR, Metreweli,C: Renal failure due to 2,8-dihydroxyadenine urolithiasis. *Eur J Pediatr* 138, 346-9 (1982)
79. Yagisawa,T, Yamazaki,Y, Toma,H, Kamatani,N: Radiopaque 2,8-dihydroxyadenine lithiasis. *Int Urol Nephrol* 31, 141-3 (1999)
80. Glicklich,D, Gruber,HE, Matas,AJ, Tellis,VA, Karwa,G, Finley,K, Salem,C, Soberman,R, Seegmiller,JE: 2,8-dihydroxyadenine urolithiasis: report of a case first diagnosed after renal transplant. *Q J Med* 68, 785-93 (1988)
81. Konishi,N, Takeshita,K, Yasui,H: A case of adenine phosphoribosyltransferase (APRT) deficiency discovered by urine examination. *Nippon Jinzo Gakkai Shi* 36, 1191-5 (1994)
82. Terai,C, Hakado,M, Yamanaka,H, Kamatani,N, OKai,M, Takahashi,F, Kashiwazaki,S: Adenine phosphoribosyltransferase deficiency identified by urinary sediment analysis: cellular and molecular confirmation. *Clin Genet* 48, 246-50 (1995)
83. Kambayashi,T, Nakanishi,T, Suzuki,K, Fujita,K, Tajima,A, Kawabe,K: Two siblings with 2,8-dihydroxyadenine urolithiasis. *Hinyokika Kiyo* 40, 1097-1101 (1994)
84. Thomas,J, Conort,P, Fompeydie,D, Bellin,J, Rechke,JP, Arvis,G: A case of lithiasis caused by 2,8-dihydroxyadenine. Evolutionary characteristics. Therapeutic problems. *J Urol (Paris)* 102, 161-7 (1996)
85. Coupris,L, Champion,G, Duverne,C, Varlet,F, Ratajczak,A: 2,8-dihydroxyadenine lithiasis. 2 new pediatric cases of an unknown metabolic deficit. The use of extracorporeal lithotripsy. *Chir Pediatr* 31, 26-31 (1990)
86. Catel,W, Schmidt,J: Über familiäre gichtische Diathese in Verbindung mit zerebralen und renalen Symptomen bei einem Kleindind. *Deutsche medicin Woch* 84, 2145-7 (1959)
87. Lesch,M, Nyhan,WL: A familial disorder of uric acid metabolism and central nervous system function. *Am J Med* 363, 561-4 (1964)
88. Seegmiller,JE, Rosenbloom,FM, Kelley,WN: Enzyme defect associated with a sex-linked human neurological disorder and excessive purine synthesis. *Science* 155, 1682-4 (1967)
89. Kelley,WN, Greene,ML, Rosenbloom,FM, Henderson,JF, Seegmiller,JE: Hypoxanthine-guanine phosphoribosyltransferase in gout. *Ann Intern Med* 70, 155-60 (1969)
90. Augoustides-Savvopoulou,P, Papachristou,F, Fairbanks,LD, Dimitrakopoulos,K, Marinaki,AM: Partial hypoxanthine-guanine phosphoribosyltransferase deficiency as the unsuspected cause of renal disease spanning three generations. *Pediatr* 109, E17 (2002)
91. Mak,BS, Chi,CS, Tsai,CR, Lee,WJ, Lin,HY: New mutations of the HPRT gene in Lesch-Nyhan syndrome. *Pediatr Neurol* 23, 332-5 (2000)
92. DeGregorio,L, Nyhan,WL, Serafin,E, Chamoles,NA: An unexpected affected female patient in classical Lesch-Nyhan family. *Mol Genet Metab* 69, 263-8 (2000)
93. Martinez,J, Dugaiczky,LJ, Zielinski,R, Dugaiczky,A: Human genetic disorders, a phylogenetic perspective. *J Mol Biol* 308, 587-96 (2001)
94. Puig,JG, Torres,RJ, Mateos,FA, Ramos,TH, Arcas,JM, Buno,AS, O'Neill,P: The spectrum of hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency. Clinical experience based on 22 patients from 18 Spanish families. *Medicine* 80, 102-12 (2001)
95. Jinnah,HA, DeGregorio,L, Harris,JC, Nyhan,WL, O'Neill,JP: The spectrum of inherited mutations causing HPRT deficiency: 75 new cases and a review of 196 previously reported cases. *Mutat Res* 463, 309-26 (2000)
96. Southgate,TD, Bain,D, Fairbanks,LD, Morelli,AE, Larregina,AT, Simmonds,HA, Castro,MG, Lowenstein,PR: Adenoviruses encoding HPRT correct biochemical abnormalities of HPRT-deficient cells and allow their survival in negative selection medium. *Metab Brain Dis* 14, 205-21 (1999)
97. Palella,TD, Hidaka,Y, Silverman,LJ, Levine,M, Glorioso,J, Kelley,WN: Expression of human HPRT mRNA in brains of mice infected with a recombinant herpes simplex virus-1 vector. *Gene* 80, 137-44 (1989)
98. Yu,TF, Gutman,AB: Effects of allopurinol (4-hydroxypyrazolo-(3,4-d) pyrimidine) on serum and urinary uric acid in primary and secondary gout. *Am J Med* 37, 885-98 (1964)
99. Safranow,K: Identification and quantification of purine derivatives in urinary calculi as markers of abnormal purine metabolism by using high-performance liquid chromatography (HPLC). *Ann Acad Med Stetin* 46, 35-49 (2000)
100. Stote,RM, Smith,LH, Dubb,JW, Moyer,TP, Alexander,F, Roth,JL: Oxypurinol nephrolithiasis in regional enteritis secondary to allopurinol therapy. *Ann Intern Med* 92, 384-5 (1980)
101. Landgrebe,AR, Nyhan,WL, Coleman,M: Urinary tract stones resulting from excretion of oxypurinol. *N Engl J Med* 292, 626-7 (1975)
102. Robertsson,WG: Renal stones in the tropics. *Semin Nephrol* 23, 77-87 (2003)
103. Rizvi,SA, Naqvi,SA, Hussain,Z, Hashmi,A, Hussain,M, Zafar,MN, Sultan,S, Mehdi,H: Pediatric urolithiasis: developing nation perspectives. *J Urol* 168, 1522-5 (2002)
104. VanWaeyenbergh,J, Vergauwe,D, Verbeek,RM: Infrared spectroscopic analysis of endemic bladder stones in Niger. *Eur Urol* 27, 154-9 (1995)
105. Teotia,M, Rodgers,A, Teotia,Sp, Wandt,AE, Nath,M: Fluoride metabolism and fluoride content of stones from children with endemic vesical stones. *Br J Urol* 68, 4258-9 (1991)
106. Beukos,GJ, deBruijn,H, Vermaak,WJ: Effect of changes in epidemiological factors on the composition and racial distribution of renal calculi. *Br J Urol* 60, 387-92 (1987)
107. Wisniewski,ZS, Brockis,JG, Ryan,GD: Urinary bladder stones in aboriginal children. *Aust NZ J Surg* 51, 292-5 (1987)
108. Borden,TA, Dean,WM: Ammonium acid urate stone in Navajo Indian children. *Urology* 14, 9-12 (1979)
109. Herring,LC: Observations on the analysis of ten thousand urinary calculi. *J Urol* 88, 545 (1962)

110. Pichette,V, Bonnardeaux,A, Cardinal,J, Houle,M, Nolin,L, Boucher,A, Ouimet,D: Ammonium acid urate crystal formation in adult North American stone-formers. *Am J Kidney Dis* 30, 237-42 (1997)
111. Soble,JJ, Hamilton,BD, Stroom,SB: Ammonium acid urate calculi: a reevaluation of risk factors. *J Urol* 161, 869-73 (1999)
112. Kohn,M, Bolle,JF, Reverdin,NP, Susini,A, Baud,CA, Graber,P: Ammonium urate urinary stones. *Urol Res* 14, 315-8 (1986)
113. Komori,K, Arai,H, Gotah,T, Imazu,T, Honda,M, Fujioka,H: A case of ammonium urate urinary stones with anorexia nervosa. *Hanyokika Kyo* 46, 627-9 (2000)
114. Dick,DM, Lingeman,JE, Preminger,GM, Smith,LH, Wilson,DM, Shirrell,WL: Laxative abuse as a cause for ammonium urate renal calculi. *J Urol* 143, 244-7 (1990)
115. Teotia,M, Sutor,DJ: Crystallisation of ammonium acid urate and other uric acid derivatives from urine. *Br J Urol* 43, 381 (1971)
116. Low RK, Stoller ML: Uric acid-related nephrolithiasis. *Urol Clin NA* 24, 135-148 (1997)
117. LaRusso,NF, McGill,DG: Surreptitious laxative ingestion. Delayed recognition of a serious condition: a case report. *Mayo Clin Proc* 50, 706 (1975)
118. DeWolff,FA, deHass,EJM, Verweij,M: A screening method for establishing laxative abuse. *Clin Chem* 27, 914 (1981)
119. Wu,WJ, Huang,CH, Chiang,CP, Huang,CN, Wang,CN: Urolithiasis related to laxative abuse. *J Formos Med Assoc* 92, 1004-6 (1993)
120. Nadler,RB, Rubenstein,JN, Eggener,SE, Loo,MM, Smith,ND: The etiology of urolithiasis in HIV infected patients. *J Urol* 169, 475-7 (2003)
121. Sakhaee K, Nicar M, Hill K, Pak CYC: Contrasting effects of potassium citrate and sodium citrate therapies on urinary chemistries and crystallization of stone-forming salts. *Kid Int* 24, 348-352 (1983)
122. Nicar,MJ, Hill,K, Pak,CYC: Inhibition by citrate of spontaneous precipitation of calcium oxalate, in vitro. *J Bone Min Res* 2, 215-220 (1987)
123. Pak,CYC, Sakhaee,K, Fuller,C: Successful management of uric acid nephrolithiasis with potassium citrate. *Kid Int* 30, 422-428 (1986)
124. Sharma,SK, Indudhara,R: Chemodissolution of urinary uric acid stones by alkali therapy. *Urol Int* 48, 81-86 (1992)
125. Rodman,JS: Prophylaxis of uric acid stones with alternate day doses of alkaline potassium salts. *J Urol* 145, 97-99 (1991)
126. Kursh,ED, Resnick,MI: Dissolution of uric acid calculi with systemic alkalization. *J Urol* 132, 286-7 (1984)
127. Freed,SZ: The alternating use of an alkalinizing salt and acetazolamide in the management of cystine and uric acid stones. *J Urol* 123, 96-9 (1975)
128. Wabner,CL, Pak,CYC: Effect of orange juice consumption on urinary stone risk factors. *J Urol* 149, 1405-1408 (1993)
129. Sletzer,MA, Low,RK, McDonald,M, Shami,GS, Stoller,M: Dietary manipulation with lemonade to treat hypocitraturic calcium nephrolithiasis. *J Urol* 156, 907-909 (1996)
130. Jendle-Bengton,C, Tiselius,HG: Long-term follow-up of stone formers treated with low dose of sodium potassium citrate. *Scand J Urol Nephrol* 34, 36-41 (2000)
131. Lee,YH, Huang,WC, Tsai,JY, Huang,JK: The efficiency of potassium citrate based medical prophylaxis for preventing upper urinary tract calculi: a midterm followup study. *J Urol* 161, 1453-7 (1999)
132. Cramer,JA, Mattson,RH, Prevey,ML, Scheyer,RD, Ouellete,VL: How often is medication taken as prescribed? A novel assessment technique. *JAMA* 261, 3273 (1989)
133. Desnos,E: L'histoire de l'urologie. In Murphy,LJT. The History of Urology, Charles C. Thomas, Springfield (1972)
134. Auge,B, Preminger,GM: Surgical management of urolithiasis. *Endocr Metab Clin NA* 31, 1065-82 (2002)
135. Paik,ML, Resnick,MI: Is there a role for open stone surgery? *Urol Clin NA* 27, 323-31 (2000)
136. Paik,ML, Wainstein,MA, Sprinack,JP, Haupel,N, Resnick,MI: Current indications for open stone surgery in the treatment of renal and ureteral calculi. *J Urol* 159, 374-9 (1998)
137. Downey,P, Tolley,D: Contemporary management of renal calculus disease. *J Royal Coll Surg Edinburgh* 47, 668-75 (2002)
138. Mattanga,BR, Assimos,DG: Changing indications of open stone surgery. *Urology* 59, 490-3 (2002)
139. Sy,FY, Wong,MY, Foo,KT: Current indications for open stone surgery in Singapore. *Ann Acad Med Singapore* 28, 241-4 (1999)
140. Das,S: Urologic laparoscopy: the future is now. *Urol Clin NA* 28, 1-3 (2001)
141. Ramkumar,S, Segura,JW: Laparoscopic surgery for urolithiasis: pyelolithotomy, caliceal diverticulectomy, and treatment of stones in a pelvic kidney. *J Endourol* 14, 829-32 (2000)
142. Skrepetis,K, Doumas,K, Siakfas,I, Lykourinas,M: Laparoscopic vs. open ureterolithotomy. A comparative study. *Eur Urol* 40, 32-6 (2001)
143. Hofmann,R, Stoller,ML: Endoscopic and open stone surgery in morbid obese patients. *J Urol* 148, 1108-11 (1992)
144. Ramakumar,S, Lancini,V, Chu,DY, Parsons,JK, Kavoussi,LR, Jarrett,TW: Laparoscopic pyeloplasty with concomitant pyelolithotomy. *J Urol* 167, 1378-80 (2002)
145. Kaouk,JH, Gill,IS, Desai,MM, Banks,KW, Raja,SS, Skacel,M, Sung,GT: Laparoscopic anastrophic nephrolithotomy: feasibility study in a chronic porcine model. *J Urol* 169, 691-6 (2003)
146. Gill,IS, Kaouk,JH, Desai,MM, Desai,M: Laparoscopic anastrophic nephrolithotomy: initial clinical experience. Unpublished data
147. Abrahams,HM, Meng,MV, White,MD, Moran,ME, Stoller,ML: The role of laparoscopy in treating urolithiasis. *Precis Western Section, AUA* 193 (2002)
148. Moran,M.E., Abrahams,H.M.: Ultrasonic Lithotripsy, In Khoury,S and Segura,J (Eds.) 1st International Consultation on Stone Disease (2001)
149. Stroom,SB, Geisinger,M, Risius,B, Zelch,MG, Siegel,S: Endourologic "sandwich" therapy for extensive staghorn calculi. *J Endourol* 1, 253 (1987)
150. Sadi,MV, Saltzman,N, Faria,G, Gettes,RF: Experimental observations on dissolution of uric acid calculi. *J Urol* 134, 575-9 (1985)

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151. Moran,ME: Ureteroscopic holmium:YAG laser lithotripsy utilizing I.V. sedation: preliminary experience in 40 consecutive patients. *J Urol* 169, 490-1 (2003)
152. Zheng,W, Denstedt,JD: Intracorporeal lithotripsy: update on technology. *Urol Clin NA* 27, 301-14 (2000)
153. Teichman,JM, Vassar,GJ, Bishoff,JT: Holmium:YAG lithotripsy yields smaller fragments than lithoclast, pulsed dye or electrohydraulic lithotripsy. *J Urol* 159, 17-23 (1998)
154. Chan,KF, Vassar,GJ, Teichman,JM, Glickman,RD, Weintraub,ST, Welch,AJ: Holmium:YAG laser lithotripsy: a dominant photothermal ablative mechanism with chemical decomposition of urinary calculi. *Las Surg Med* 25, 22-37 (1999)
155. Heimback,D, Jacobs,D, Muller,SC, Hesse,A: Influence of alkaline solutions on chemolysis and lithotripsy of uric acid stones. An in vitro study. *Eur Urol* 38, 621-6 (2000)
156. Khan,SR, Hackett,RL, Finlayson,B: Morphology of urinary stone particles resulting from ESWL treatment. *J Urol* 136, 1367-72 (1986)
157. Netto,NR Jr, Claro,JFA, Cortado,PL: Extracorporeal shock wave lithotripsy of radiolucent urinary calculi using the Siemens Lithostar Plus. *J Urol* 148, 112-3 (1992)
158. Royce,PL, Fuch,GJ, Lupu,AN, Chaussy,CG: The treatment of uric acid calculi with extracorporeal shock wave lithotripsy. *Br J Urol* 60, 6-9 (1987)
159. Kumar,S, Srinivasan,V: Extracorporeal shock wave lithotripsy for radiolucent stones. *J Natl Med Assoc* 84, 797-9 (1992)
160. Dore,B, Grange,P, Aubert,J: Effect of the chemical nature of urinary calculi on the results of extracorporeal shock wave lithotripsy. *Ann Urol (Paris)* 19, 209-12 (1991)

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