for these infants to recompense for their restricted environment. Feeding the starved mind may, in the long term, be as important as feeding the starved body.

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Renal stone disease—investigative aspects

In Europe, renal stone disease affects between one and two children/million total population/year.¹ The disease is more prevalent in less industrialised countries where a high proportion of bladder stones are found,² Most patients present in the early years of childhood,³ usually with a urinary tract infection, abdominal pain, or haematuria.⁴ Although the majority have only one episode of stone formation,⁵ it is important to identify risk factors wherever possible because specific treatments can reduce stone recurrence and renal damage in those most at risk.⁶ ?

Aetiology

Renal stones result from the precipitation and growth of crystals within the urinary tract. Precipitation may be encouraged by an increased concentration of insoluble materials, a change in pH,⁶ or a reduction in concentration of one or more of the physiological inhibitors of crystal growth. The most important inhibitors are mucopolysaccharides, citrate, and pyrophosphate.⁸ ⁹ It is more difficult for crystals to form spontaneously than for material to precipitate on pre-existing crystals or other solid matter. This gives rise to the phenomenon of epitaxy where there may be an aggregation of material that is not necessarily the same as that of the original nidus.³

A variety of clinical disturbances can result in one or more of these conditions.

INFECTION
Within Europe the commonest identifiable factor is infection with urease producing organisms, proteus accounting for over 80% of cases.⁴ ¹⁰ Infection related urolithiasis is less common in the USA, where there is an overall lower incidence of stone disease.¹¹ The likely mechanism of stone formation is that ammonia, liberated from the action of urease on urea, increases urinary pH, decreasing the solubility of calcium salts and increasing the concentration of the ammonium ion which can precipitate with phosphate and magnesium (struvite). The majority of infection related stones consist of struvite with lesser amounts of calcium apatite (calcium hydrogen phosphate)⁷ and matrix material.

ANATOMIC ABNORMALITIES
Urolithiasis is associated with those developmental abnormalities of the urinary tract that result in urine stasis and lead to a greater risk of infection. These stones are predominantly calcium phosphate together with struvite.¹⁰

METABOLIC STONES
Children in whom a metabolic defect has been demonstrated are in the minority, 10 to 20% in Europe.¹ ¹¹ However this may well be an underestimate because not all children receive a metabolic evaluation.¹² The majority of those reported have idiopathic hypercalciuria,¹³ associated either with enhanced gut absorption, increased renal excretion, or enhanced mobilisation of calcium from bones as commonly occurs during prolonged immobilisation. Distal renal tubular acidosis can also lead to the formation of calcium stones. The combination of an increased urine pH, low citrate, and high calcium excretion enhances calcium precipitation.¹⁴ Diseases associated with hypercalcaemia rarely present with renal stones; they are more likely to lead to nephrocalcinosis.

The next most common metabolic cause of stones is cystinuria accounting for up to 2% of cases of urolithiasis.¹⁵ Cystinuria is a consequence of defective renal reabsorption of basic amino acids resulting in urinary concentrations of cystine that exceed its solubility. However not all individuals with the defect form stones, and not all the stones formed are pure cystine.¹⁶

Urate crystalluria and occasionally urolithiasis may be a complication of haematological tumours after chemotherapy. Hyperuricaemia may also be caused by a deficient activity of the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT). Complete deficiency gives rise to Lesch-Nyhan disease but partial defects have also been described.¹⁷ A deficiency of the next enzyme in the same pathway, xanthine oxidase, is responsible for the systemic accumula-
tion of xanthine that leads to xanthinuria. Another disorder of purine metabolism, adenosine phosphoribosyl transferase (APRT) deficiency, results in an increased excretion of 2,8-dihydroxyadenine. Evidence is accumulating to suggest that urolithiasis related to this defect is more common than was previously thought. The compound can be mistaken for urate during stone analysis and it will not be detected during urine analysis unless the appropriate chromatographic techniques are employed. Correct diagnosis is important because the treatment of the condition is different from that for hyperuricaemia. Alkalisation of the urine promotes the crystallisation of 2,8-dihydroxyadenine.

Oxalate is not an uncommon constituent of stones, but hyperoxaluria itself is not common. It may be due to one of two rare inherited disorders of metabolism, alanine: glyoxylate aminotransferase deficiency (hyperoxaluria type 1) or t-glycericaciduria (hyperoxaluria type 2). However it is more likely to be enteric in origin, caused either by enhanced intestinal absorption or dietary load. Malabsorption syndromes are associated with an increased absorption and excretion of oxalate due to the sequestration of calcium ions by unabsorbed fatty acids.

FACTITIOUS STONES
The possibility of factitious disease needs to be borne in mind. Although there are few data in the literature about its incidence, most paediatric departments have had experience of isolated cases of unidentifiable gravel being produced as evidence of urolithiasis. When stones are shown to be factitious, in an older child it is often the patient who is responsible for the story, but in young children the perpetrator is invariably a parent, usually the mother.

IDIOPATHIC STONES
There will be a number of patients in whom no risk factors for their stones can be found.

Investigation strategy
Wherever possible all children presenting with signs and symptoms or urolithiasis should receive an abdominal plain film x ray and ultrasound. The vast majority of stones, including cystine, are radio-opaque, but purine stones are radiolucent. If stone disease is confirmed then investigations should be carried out as follows.

1. Blood chemistry should be examined for evidence of recognisable risk factors, that is immobilisation, persistently low urine volume, excessive animal protein, salt or vitamin D in the diet, clinical disorders associated with renal tubular acidosis, ketogenic diet for epilepsy or chemotherapy.

The possibility of a urinary tract infection should be investigated. Metabolic investigations should not be undertaken until any infection has been treated. Some compounds, notably amino acids, may be metabolised by infective organisms. However it is important not to neglect a metabolic evaluation because metabolic disturbances may lead to urinary tract infection. The finding of a metabolic disturbance in children presenting with anatomic or infection related stones is not uncommon. The major difficulty is in deciding how thorough the metabolic investigation should be in each case. This should be influenced by such factors as stone recurrence, positive family history, consanguinity, or the presence of radiolucent stones.

The straightforward tests should certainly be performed in every case. A reasonable protocol would be as follows, with the child maintaining their usual diet.

(1) Collect a blood sample for the measurement of calcium, albumin, urate, phosphate, and creatinine. The calcium result should be adjusted for any abnormality in the albumin concentration.

(2) Collect a spot urine sample from the second voiding of the day, that is after the overnight urine has been discarded. Request the analysis of calcium, oxalate, cystine (amino acids), urate, creatinine, and pH. If the pH is found to be less than 5.5 then renal tubular acidosis can be excluded. The laboratory should test the sample, with a dipstick, for the presence of ketones. Any ketotic sample should be discarded because ketones interfere with the analysis of creatinine. Samples from later in the day should not be used due to the postprandial increase in creatinine excretion that may occur. Timed urine collections are no longer necessary as reliable reference data are now available for the excretion of metabolites related to creatinine. There are obvious difficulties in making accurate timed collections from children. They are not only inconvenient but incomplete samples will lead to erroneous results.

There does not appear to be an age related trend in calcium excretion, but the distribution of values within an age group is logarithmic. The 97th centile for all ages was recently reported to be 0.69 mol:mol creatinine. In the majority of cases serum calcium will not be abnormal, in which case further investigations into the aetiology are not clinically useful as they will not influence treatment. The excretion of both urate and oxalate does vary with age, decreasing throughout childhood (table). Disorders of purine metabolism are usually indicated by elevated serum and urine urate, but very low concentrations are observed in xanthinuria. A disorder of purine or pyrimidine metabolism should be suspected if any of these conditions are observed or if stone analysis reveals the presence of urate or 2,8-dihydroxyadenine or if the stones are radiolucent. The local laboratory should then send samples to a laboratory with proved expertise, for example the purine research laboratory at Guy’s Hospital in London.

In circumstances where oxalate excretion is found to be raised a sample of urine should be sent to a specialist laboratory for the analysis of glyoxyllic and glyceric acids. The presence of either of these metabolites in increased amounts will differentiate between a primary inherited metabolic disorder and a secondary cause. It should be noted that hyperoxaluria may be missed if the patient has renal impairment because oxalate excretion decreases as renal function deteriorates.

Cystinuria should be tested for by a chromatographic examination of urine which need not be quantitative. Although the cyanide/nitroprusside spot test is often advocated as a screening test it can be unreliable, particularly if the unstable reagents are not prepared regularly.

Urine microscopy is of limited value. The presence of typical cystine crystals is specific to cystinuria, but they are observed in only 20% of cystinurics.

There is at present no clinical value in measuring the urinary excretion of stone inhibitors. Although there is scientific evidence linking a decrease in their excretion or an
imbalance to an enhanced tendency to form stones, there is little evidence yet that therapeutic intervention is of benefit.

**STONE ANALYSIS**

The general appearance of stones should be noted. Cystine stones are typically golden yellow and waxy, urate stones are yellowish and hard, 2,8-dihydroxyadenine stones are pale grey and friable, and xanthine stones are brownish and friable. Chemical analysis should be performed wherever possible because vital clues may be gained, especially for purine or factitious stones. However results should be interpreted with caution, because they may be misleading or even unhelpful due to heterogeneity of stone structure or secondary infection.

In general the results of urine analyses are more reliable for identifying metabolic disturbances. These defects are unlike some other inborn errors of metabolism where metabolite production remits and relapses. If an inborn error of metabolism is diagnosed, other family members should be tested for the abnormality. They may well be asymptomatic but nevertheless at risk of urolithiasis.

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