The medical management of stone disease

Introduction

Renal stone disease may present with pain and/or haematuria; the stone may pass spontaneously or may become arrested in the urinary tract, usually in the ureter, causing various degrees of obstruction and hydronephrosis. Alternatively, renal stones may be discovered accidentally, as a result of an abdominal radiograph, ultrasound examination, or CT examination. The surgical management of renal calculi has been transformed in the last decade by the introduction of percutaneous lithotripsy, extracorporeal shockwave lithotripsy, and improved endoscopic ureterolithotomy. As a result, the place of medical management in renal stone disease has been questioned, and the cost effectiveness of medical investigation and medical prophylaxis needs to be established. Nevertheless, effective preventative measures exist for most types of renal stone, and their appropriate application could prevent much of the morbidity associated with further episodes of spontaneous stone passage, as well as the costs and possible hazards of repeated lithotripsy.

At present, the first clinical stone attack (‘stone episode’) is usually unanticipated, and therefore prevention of the first stone is usually not an option. Metabolic investigation and prophylaxis are generally employed in patients who have already had one or more stone episodes. Rational prophylaxis, other than non-specific measures such as an increase in fluid intake, requires a knowledge of the composition of the stone. Therefore the opportunity to analyse a stone that has passed spontaneously or has been surgically removed, or the debris passed after extracorporeal shock-wave lithotripsy, should never be missed. The most common type of stone is composed of calcium oxalate (with or without calcium phosphate). Recommendations have varied as to whether patients should be subjected to a full metabolic work-up after a first stone, or whether this should be reserved for patients who have shown themselves to be recurrent stone-formers. In conditions such as cystinuria or primary hyperparathyroidism presenting with a stone, most physicians would agree that the condition is best diagnosed and treated without waiting for a further stone episode. In the case of the common ‘idiopathic’ calcium oxalate stone, whether or not to search for risk factors after the first stone has been controversial. There is a 40 to 60 per cent chance of a recurrence of stone within 10 years (Johnson et al. 1979; Sutherland et al. 1985; Uribarri et al. 1989). Whilst there may be economic and other reasons (Uribarri et al. 1989) for limiting the initial investigations, a recent provocative report (Parks and Coe 1994) has suggested that, at least in males during prophylactic treatment for calcium oxalate stones, relapses correlate with the number of pretreatment stones, which in turn depend largely on the period of observation before treatment. In other words, stones may beget stones, perhaps by leaving behind fragments which can act as nuclei for further stone formation, and therefore the results of prophylactic treatment may be better if risk factors are identified after the first episode, rather than after waiting for recurrences.

Stone composition

Renal stones may consist, in approximate descending order of frequency, of calcium oxalate (with or without calcium phosphate), uric acid, triple phosphate (or magnesium ammonium phosphate (struvite) with calcium phosphate), pure calcium phosphate, cystine, or, rarely, other materials including xanthine, dihydroxyadenine, ammonium acid urate, triamterene, or silica. If no stone is available for analysis, useful indirect information as to the probable composition of the patient’s stones can be obtained in other ways (see below).

Stone analysis

Several methods have been used for the analysis of stones or stone fragments. They are listed in Table 1.

Qualitative wet chemical analysis (Sutor et al. 1971) is commonly used in hospitals, but has several disadvantages. It requires at least 10 to 15 mg of material (although 5 mg may be sufficient for micromethods) and may yield false-positive or false-negative reactions; for example, a calcium oxalate–calcium phosphate stone may be identified only as calcium phosphate. In addition, rare constituents will not be identified. Schemes have been devised for quantitative wet chemical analysis (Rose 1982).

Crystallographic methods of analysis depend on the crystal structure of the stone components, and comprise optical and X-ray diffraction methods. Optical methods, using the polarizing microscope, recognize the crystal shape and determine the optical constants of the crystalline material (Prien and Frondel 1947). This technique is used by some commercial stone analysis laboratories. X-ray diffraction requires an X-ray source; a characteristic diffraction pattern is obtained for different stone materials. It requires only 2 mg of material (which is not consumed) and can be semiquantitative (Sutor 1982).

Thermogravimetric analysis requires expensive equipment and has some limitations; it has not been widely used (Rose and Woodfine 1976). Scanning electron microscopy also requires expensive equipment; it can identify stone components according to their crystal morphology, as well as determining the elemental composition of the material according to each element's characteristic X-ray emission, using X-ray spectrometers (Khan and Hackett 1986).

Stone analysis by IR spectroscopy is convenient, specific, and rapid, and can use crystalline or amorphous material which is compressed into a disc, usually with potassium bromide, for analysis (Gault et al. 1980). Individual compounds give characteristic spectra; the spectrometer can be coupled to a computer and software package that will identify calculus components either singly or in mixtures, including rare components such as xanthine, 2,8-dihydroxyadenine, or triamterene (Berthelot et al. 1987). IR spectroscopy can be made semi-quantitative (Gault et al. 1987).

Indirect evidence of stone composition

Where no stone has been retrieved for analysis, other information can be used to determine the probable nature of the stone(s).

Radiology

The X-ray appearance of the stone is of some value. Purine stones (uric acid, xanthine, 2,8-dihydroxyadenine) are radiolucent and appear as a filling defect on an excretory urogram. Calcium oxalate and phosphate stones are radio-opaque, typically somewhat more so than bone. Cystine and struvite stones are also radio-opaque, but somewhat less dense than bone. Both may form staghorn stones. Cystine stones are radio-opaque because of their sulphur content, and tend to be homogenous in appearance. Struvite stones are less homogenous and sometimes laminated.

Examination of urine for crystals

The examination of urine for crystals, preferably a fresh sample at body temperature, may provide useful information. The presence of uric acid or aggregated calcium oxalate crystals suggests that the stone may consist of uric acid or calcium oxalate respectively, while the characteristic hexagonal cystine crystals (Fig. 1) or 'coffin-lid' struvite crystals are diagnostic of cystinuria or of urinary tract infection with a urease-producing micro-organism respectively.

Urine pH

Determination of urine pH, preferably on a morning sample, may be of limited diagnostic value. It is usually in the range 5.5 to 6.5. A pH greater than 7.8 indicates infection with a urease-producing organism. A urine pH persistently greater than 7 suggests distal renal tubular acidosis, and a pH consistently less than 5.5 is associated with uric acid stones.

Other features from the history and physical examination

The patient’s history may suggest the nature of the underlying disorder. Many types of stones are familial, including those associated with cystinuria or idiopathic hypercalciuria. Occasional patients may be taking medications that predispose to particular types of stones, for example acetazolamide or triamterene. Other medical disorders may increase the risk of particular types of stone; for example, calcium oxalate stones may occur in the short-bowel syndrome, while uric acid stones are more frequent in patients with an ileostomy. The dietary history may reveal habits that may increase the risk of certain types of stones; however, patients should not be advised to change their diet unless analysis of the urine has demonstrated the presence of the relevant risk factor. For example, it is not rational to recommend a reduction in purine intake in a calcium oxalate stone-former unless hyperuricosuria has been demonstrated. Neither should dietary calcium restriction be advised in a stone-former in the absence of a specific indication, since a low calcium intake may actually increase the risk of calcium stones (Curhan et al. 1993).

Biochemical investigations

When the stone composition is known or suspected, appropriate investigations are required to identify risk factors for the formation of that particular stone type so that recommendations can be made regarding prevention of further stone episodes. For example, in the case of the common calcium oxalate–calcium phosphate stone, blood tests may be performed to identify underlying primary hyperparathyroidism, and urine may be collected for analysis for known risk factors, including hypercalciuria, hyperoxaluria, or hyperuricosuria, or a low urine volume or citrate content.

With respect to urine constituents, it is the concentration of substances such as calcium or oxalate that presumably determines the risk of crystal or stone formation; however, concentrations vary continuously during the day according to the rate of urine flow. Excretion per unit time is less variable, and the standard approach to identifying abnormal urinary excretions of solutes has been to determine their 24-h excretion. This may be rather inconvenient for patients; 24-h collections should be made while the patient is going about his or her normal activities, and consuming his or her usual diet. There is sufficient day-to-day variation in the output of many urine solutes that at least two 24-h collections should be analysed; some investigators have made the case for the analysis of three or more 24-h urine samples from each patient (Ryall and Marshall 1990; Coe et al. 1992). One 24-h urine sample may be collected during the working week, and another at the weekend when diet and activities may be markedly different.

A possible alternative to 24-h urine collections may be to collect a spot urine sample (from a single voiding) and then to use creatinine as a reference substance, expressing the output of solutes as a ratio with creatinine (Gokce et al. 1991). The reliability of this technique for estimating urinary uric acid and citrate has not been defined. A weakness of such use of spot urine samples is that it does not take account of variations in excretion through the day, for example in response to meals. The determination of urinary solute excretions from a spot urine sample according to the ratio with creatinine may be particularly useful in children, in whom
the collection of 24-h urines presents a greater problem than in the adult.

Lemann (1993) has reviewed some important aspects of the collection, preservation, and analysis of urine in identifying risk factors for nephrolithiasis. The normal values in Table 2 are taken from this paper.

Although it is customary to use certain defined normal limits (Table 2) to identify risk factors such as hypercalciuria, hyperuricosuria, or hypocitraturia, a note of caution is necessary. There are important geographical variations in the 24-h excretions of some of these solutes. For example, compared with the conventional normal ranges in the United States, the normal range for calcium excretion appears to be substantially higher in Europe (Ryall and Marshall 1990), while that of citrate is much lower in parts of South Asia (Talati, personal communication). Thus the identification of ‘abnormalities’ in stone-formers should be based on the determination of local normal ranges. However, in terms of interventions to modify stone risk factors, it is not the relationship to the normal range that matters, but rather the absolute risk of crystal formation, growth, or aggregation. For example, it may be beneficial to lower the urinary oxalate in a calcium oxalate stone-former in whom the 24-h urine value does not exceed the normal range. Unfortunately, it is not practical at present to determine parameters of crystal formation, growth, and aggregation on a routine basis which would permit the rational choice of stone prevention measures in each patient. Currently, it is usual practice for therapeutic efforts to be guided by the results of 24-h urine analyses, which are compared with accepted or locally determined normal ranges for each of the known risk factors.

The relevant investigations for each specific stone type are described in subsequent sections; some conditions may require additional special tests for their diagnosis, such as parathyroid hormone assay for primary hyperparathyroidism and urinary acidification tests for renal tubular acidosis.

Detailed investigation is not usually undertaken for the patient with a stone of unknown composition, except under special circumstances (e.g. the patient with stone disease in a single kidney). In such patients, particular attention should be given to stone analysis in any subsequent episode.

Medical management of specific stone types

Calcium stones

Calcium stones may consist of calcium oxalate, calcium phosphate, or a mixture of these salts. A knowledge of the proportions of oxalate or phosphate in a stone is of limited value in identifying the underlying cause of stone formation. However, pure calcium phosphate stones (which are rare) should suggest a disorder of urine acidification, particularly complete or incomplete distal (type 1) renal tubular acidosis (Gault et al. 1991).

Although a greater ratio of calcium phosphate to calcium oxalate may be present in the stones from some patients with primary hyperparathyroidism than in idiopathic calcium stones (Gault et al. 1987), the majority of stones in primary hyperparathyroidism consist of calcium oxalate (Parkset al. 1980).

The purpose of investigating the patient with calcium stone(s) is to identify underlying systemic or renal disorders (Table 3) which may require special treatment, and within the remaining group of ‘idiopathic’ calcium stone-formers, who constitute the majority of patients, to identify risk factors that may be amenable to modification with a view to reducing further stone formation (Table 4).

As discussed in the introduction to this chapter, there is controversy as to how extensively a patient should be investigated after the occurrence of a single stone known or suspected to be calcium oxalate (with or without...
calcium phosphate). It has been conventional either to undertake no investigations in the single stone-former (Ryall and Marshall 1990), or to perform a limited investigation (Tiselius 1994, Uribarri et al. 1989) which might include only a serum calcium to screen for primary hyperparathyroidism, and a serum creatinine and urine culture to rule out renal impairment and urinary tract infection. In addition, a diet history may be obtained to exclude obvious factors such as an excessive intake of calcium, vitamin D, or animal protein. If these contributing factors are excluded, non-specific advice may be given, such as to increase fluid intake to ensure a urinary output of at least 2 litres/day (e.g. eight 8 oz glasses of water, spaced evenly throughout the day) and to avoid an excessively high or low intake of calcium and a high intake of oxalate. Such patients may be monitored annually in order to determine whether their stone disease is active (Consensus Conference 1988).

As previously discussed, if ‘stones beget stones’ (Parks and Coe 1994) it may not be entirely rational to perform only limited investigations in the patient following a first stone episode; however, on average, only 50 per cent of first stone-formers have a recurrence within 10 years (Uribarri et al., 1989). Somewhat similar considerations apply to the patient with an accidentally discovered stone. In a recent study, 49 per cent of such patients became symptomatic within 5 years (Glowacki et al. 1992). In practice, in the developed world, patients come to a consultant or a stone clinic for a variety of reasons, including a personal desire to identify the cause of their stone formation, even if the recommended tests are relatively expensive. In contrast, in the developing world investigation is often limited by the extent to which the patient can afford the tests.

If cost is not the limiting factor, a reasonable panel of investigations for the recurrent (and perhaps the first) calcium stone-former is shown in Table 5.

The serum total calcium concentration, preferably corrected for the serum albumin or total protein (Nordin et al. 1989), provides the most practical screen for primary hyperparathyroidism. Most patients with stones and hypercalcaemia have primary hyperparathyroidism. The serum electrolytes may point to the diagnosis of complete (but not incomplete) distal (type 1) renal tubular acidosis in which hypokalaemia and a normal anion gap metabolic acidosis are usual. The urinary citrate, which is low in complete distal renal tubular acidosis, provides an alternative screening test for this disorder, but it is not invariably low in incomplete distal renal tubular acidosis. An increase in the urinary calcium, oxalate, or uric acid, and a decrease in urinary citrate or urine volume, are the usually accepted risk factors for calcium oxalate stones; these abnormalities may be idiopathic or may be indicative of specific underlying disorders (e.g. hyperoxaluria in bowel disease or hypocitraturia in renal tubular acidosis). The determination of urinary sodium and urea are optional, but may be helpful in identifying dietary habits contributing to abnormal stone risk factors. For example, an increased urinary urea indicates a high protein intake that may contribute to hypercalciuria, hyperoxaluria, hyperuricosuria, and/or hypocitraturia (Koket al. 1990), while a high sodium intake (and output) may exacerbate hypercalciuria (Breslauet al. 1982).

Primary hyperparathyroidism

Incidence and pathogenesis

Stone disease caused by primary hyperparathyroidism may be clinically indistinguishable from ‘idiopathic’ calcium stone disease. Occasional patients may have other clinical features suggestive of primary hyperparathyroidism, such as bone pain or symptoms of hypercalcaemia, but most patients with primary hyperparathyroidism and stones have only mild hypercalcaemia and are free of symptoms other than those due to the stones.
Approximately 7 per cent of stones are due to primary hyperparathyroidism. At the present time in the developed world about 7 per cent of patients with primary hyperparathyroidism present with stones (Halabe and Sutton 1992) and a very small proportion have clinical bone disease (osteitis fibrosa cystica), but the majority have non-specific symptoms and no clinical stone or bone disease. The usual method of identifying the 7 per cent or so of stone patients with primary hyperparathyroidism is by screening for hypercalcaemia; the majority of patients with stones and hypercalcaemia have primary hyperparathyroidism. Although occasional patients with primary hyperparathyroidism have intermittent or persistent normocalcaemia, they are sufficiently few that it is not recommended to search for primary hyperparathyroidism (e.g. by measuring the plasma parathyroid hormone) if the serum calcium is persistently normal. If the serum calcium is borderline, it should be repeated.

The total serum calcium is usually used for screening, preferably with a protein or albumin correction (Nordin et al. 1989); determination of the ionized calcium with a calcium electrode is becoming common in routine laboratories and may be helpful in diagnosing primary hyperparathyroidism (Ladenson 1991), but remains a more exacting analytical method than total calcium. In due course it may replace measurement of the total calcium concentration (Bowers et al. 1986).

Most patients with primary hyperparathyroidism and stones have hypercalciuria, which is often gross, despite only minimal or mild hypercalcaemia. Since parathyroid hormone promotes the tubular reabsorption of calcium, this is somewhat surprising and not fully understood. Unknown factors may inhibit tubular calcium reabsorption in this disorder, despite the presence of increased plasma parathyroid hormone (Gardin and Paillard 1984). The increased filtered calcium load is the main cause of the hypercalciuria in this condition.

The reasons for the very different clinical presentation of primary hyperparathyroidism, with classical osteitis fibrosis cystica, renal stones, or neither, are of interest (Halabe and Sutton 1992). Twenty years ago, in the developed world, roughly 50 per cent of patients with primary hyperparathyroidism presented with stones and 20 per cent with bone disease. Studies by Patronet et al. (1987) in Paris showed that bone disease was particularly prevalent in older patients (more often women) with lower glomerular filtration rates and nutritional vitamin D deficiency. Many of their patients were Arab immigrants from North Africa, whose skin is normally well protected from sunlight and whose diets are low in vitamin D. In contrast, patients with primary hyperparathyroidism presenting with stones had greater glomerular filtration rates and adequate vitamin D supplies, and therefore produced more 1,25-dihydroxyvitamin D (calcitriol) under the influence of parathyroid hormone. The increased calcitriol enhances the gastrointestinal absorption of calcium, and therefore causes more marked hypercalciuria.

Confirmation of diagnosis

Other conditions that can cause hypercalcaemia and/or hypercalciuria with calcium oxalate–calcium phosphate stones include (rarely) sarcoidosis and possibly other granulomatous diseases, vitamin D excess, and the milk alkali syndrome. The characteristic combination of hypercalcaemia with an elevated plasma parathyroid hormone is required to make a definitive diagnosis of primary hyperparathyroidism. The newer intact parathyroid hormone assays (Nussbaum et al. 1987, Blind et al. 1988) are extremely reliable and less prone to interference from renal impairment than former assays. Only very rare cases of primary hyperparathyroidism have been reported in which the intact plasma parathyroid hormone is not greater than the normal range (Hollenberg and Arnold 1991). It is costly, and generally not useful, to measure the parathyroid hormone in a patient in whom the serum calcium is persistently normal. Familial hypocalciuric hypercalcaemia is another condition in which the serum calcium is elevated and the parathyroid hormone may be normal or elevated (Heath 1989). This condition is inherited as an autosomal dominant, does not cause renal calculi, and is now known to be due to a mutation of the parathyroid calcium receptor gene (Pollak et al.
Familial hypocalciuric hypercalcaemia is identified as a result of a positive family history, the absence of symptoms, and the typically rather low urinary calcium excretion (as compared with primary hyperparathyroidism).

Other laboratory characteristics of primary hyperparathyroidism, in addition to the increased serum and urinary calcium and the increased plasma parathyroid hormone, include hypophosphataemia (which is also seen in idiopathic hypercalciuria and therefore is of limited diagnostic value) and sometimes a mild hyperchloraemic acidosis. This last finding is sufficiently inconsistent that hyperchloraemia or a high chloride:phosphate ratio should now be discarded in favour of the use of improved intact parathyroid hormone assays for confirming the diagnosis of primary hyperparathyroidism.

**Treatment**

The treatment of choice for primary hyperparathyroidism with stones is generally surgical parathyroidectomy (Halabe and Sutton 1992). At the present time, attempts at parathyroid imaging prior to a first operation are generally not recommended (Doppman and Miller 1992). It is most important that the patient be referred to an experienced parathyroid surgeon. At surgery, the patient may have a single parathyroid adenoma (80 per cent) or parathyroid hyperplasia (10–15 per cent). Parathyroid hyperplasia should be suspected in familial hyperparathyroidism and in multiple endocrine neoplasia. Very rarely, a patient has parathyroid carcinoma; such patients usually have severe hypercalcaemia and bone disease. Following surgical parathyroidectomy the patient may have transient hypocalcaemia which may require treatment with calcium and/or vitamin D (Halabe and Sutton 1992). However, the hypocalcaemia is generally less severe in patients with stones than in those with parathyroid bone disease.

The results of surgery for primary hyperparathyroidism and stones are generally good. Most patients cease to form new stones (Halabe and Sutton 1992). However, an occasional patient continues to form stones after parathyroid surgery, and in such patients further investigation should be conducted to identify recurrent primary hyperparathyroidism or persistent hypercalciuria (Halabe and Sutton 1992).

If the patient with primary hyperparathyroidism is asymptomatic and has only a remote history of stone disease, and stone formation is apparently inactive, the question may arise as to whether surgery is really necessary or whether there is effective medical therapy that might suffice (Consensus Development Conference Panel 1991). In such patients it may be reasonable simply to follow the patient at regular intervals with repeated X-rays to determine the activity of the stone disease. With respect to medication, oestrogens may be helpful in women since they can lower serum and urinary calcium, although their effect on stone formation is uncertain (Marcus 1991). Alternative potential forms of medical therapy include bisphosphonates (Shane 1991), which can also lower serum and urinary calcium, and perhaps in the future the so-called calcimimetics, which are a new group of compounds (Steffey et al. 1993) that interact with the parathyroid cell calcium receptor to render it more sensitive to calcium so that parathyroid hormone is reduced and hyperparathyroidism potentially improved.

**Sarcoidosis**

Sarcoidosis affects calcium metabolism because the granulomas convert 25-hydroxyvitamin D to calcitriol in an unregulated fashion. Excess calcitriol causes enhanced intestinal calcium absorption, hypercalciuria, and, less frequently, hypercalcaemia. Most patients with sarcoidosis and stones have other clinical evidence suggestive of sarcoidosis, such as pulmonary involvement; even if the diagnosis is not clinically obvious, it should be suggested by the combination of an elevated serum calcium with a suppressed intact parathyroid
hormone as well as an elevated serum angiotensin-II-converting enzyme. Hypercalcaemia in these granulomatous disorders is treated with corticosteroids. The combination of hypercalcaemia with a suppressed parathyroid hormone also occurs in vitamin D intoxication and in humoral hypercalcaemia of malignancy (due to parathyroid-hormone-related peptide), in which stones rarely occur, perhaps in part because the condition is rarely very chronic.

**Medullary sponge kidney**

This disorder is dealt with in a separate section of this book (see also Chapter 17.4) It may cause nephrocalcinosis and stones, which may be associated with some of the same biochemical risk factors as are found in idiopathic calcium stone disease, including hypercalciuria and urinary acidification defects. It is diagnosed radiologically. However, it is not clear at present how important it is to make the diagnosis in stone patients, since the management of the stones involves the identification and correction of the same risk factors as in the idiopathic calcium stone-former.

**Renal tubular acidosis, calcium phosphate stones, and acetazolamide (see also Chapter 5.3)**

Of the several types of renal tubular acidosis, only classical distal (type 1) renal tubular acidosis is associated with stones (Brenner et al. 1982). The diagnosis of complete type 1 renal tubular acidosis should be suspected in a stone-former with the combination of a normal anion gap acidosis and hypokalaemia. These patients frequently have nephrocalcinosis as well as renal calculi, and invariably have hypocitraturia. Hypercalciuria is also a common feature; it may be the primary defect in some patients in whom hypercalciuria is believed to cause the acidification defect (Caruana and Buckalew 1988), whereas in other families the renal tubular acidosis is hereditary and the hypercalciuria is presumably secondary to the metabolic acidosis. Renal tubular acidosis may also be acquired, and is frequently associated with connective tissue diseases and hypergammaglobulinemia, particularly Sjögren’s disease. The treatment of complete renal tubular acidosis is with potassium alkalis, for example potassium citrate, in a sufficient dose (usually 1–3 mmol/kg body weight/day) to normalize the urinary citrate excretion. If the hypercalciuria persists despite this treatment, a thiazide diuretic may be added to lower the urinary calcium (Coe et al. 1992). The calculi in complete renal tubular acidosis contain a large proportion of calcium phosphate (Coe and Parks 1980).

Some patients with an impairment of urinary acidification are able to maintain a normal serum bicarbonate and a normal blood pH. This disorder has been called ‘incomplete’ distal renal tubular acidosis. The frequency of incomplete renal tubular acidosis among calcium stone-formers has ranged from 4 to 6 per cent (Preminger et al. 1985; Gault et al. 1991). In a large study, Gault et al. (1991) tested the hypothesis that acidification defects might be particularly frequent among calcium phosphate as opposed to calcium oxalate stone-formers. They found incomplete renal tubular acidosis, defined as a failure to lower urine pH to less than 5.25, in eight of 23 phosphate stone-formers but in no normal subjects or calcium oxalate stone-formers. In the calcium phosphate stone-formers with normal urinary acidification, risk factors (including hypercalciuria and hypocitraturia) were not different from those in calcium oxalate stone-formers. Hypocitraturia was not always present in the patients with incomplete renal tubular acidosis. Gault et al. (1991) suggested that prophylactic treatment for calcium phosphate and calcium oxalate stone-formers could probably be the same, except in the case of the patient with incomplete renal tubular acidosis and a normal urinary citrate excretion, in whom treatment with alkalis such as potassium citrate might worsen the stone disease by increasing urine pH.

Long-term acetazolamide treatment (usually for glaucoma) may be complicated by calcium-containing stones. Acetazolamide causes a metabolic acidosis which is associated with a very low urinary citrate excretion. The hypocitraturia is believed to be the main cause of stones in these patients. If stones are troublesome, the
acetazolamide needs to be replaced by alternative glaucoma therapy; unfortunately, alkali therapy, which would increase urinary citrate, may diminish the effectiveness of acetazolamide in lowering the intra-ocular pressure.

**Hyperoxaluria**

Hyperoxaluria in association with calcium oxalate stones can conveniently be divided into ‘mild idiopathic hyperoxaluria’, which is identified during metabolic screening of apparently idiopathic stone-formers and is considered below, and severe hyperoxaluria either due to primary (genetic) hyperoxaluria or secondary to extensive bowel disease (enteric hyperoxaluria). Hyperoxaluria may also result from ethylene glycol or methoxyflurane exposure, or very rarely from actinomycosis or pyridoxine deficiency, but these conditions are not known to be associated with stone formation. As discussed further in the section dealing with mild idiopathic hyperoxaluria, an increase in either the absolute urinary excretion of oxalate, or in the ratio of urinary oxalate to calcium, may increase the risk of calcium oxalate crystalluria or stones (Robertson and Hughes 1993).

**Primary hyperoxaluria**

At least two different enzyme defects can cause primary hyperoxaluria: type 1 results from a deficiency or mis-targeting of hepatic alanine-glyoxylate transaminase (AGT) (Danpure et al. 1994) and is associated with an increased urinary excretion of oxalate and glycolate, while type 1I results from deficiencies in glyoxylate reductase and glycerate dehydrogenase, and is associated with increased urinary glycolate and oxalate excretions (Mistry et al. 1988). In type 1 primary hyperoxaluria, calcium oxalate stone disease presents before 1 year of age in 15 per cent of patients, and before 5 years of age in 50 per cent; in a recent review 50 per cent of patients had endstage renal disease by the age of 15 years, and 80 per cent by the third decade (Latta and Brodehl 1990). Type 2 is rarer than type 1, and tends to follow a milder clinical course (Milliner et al. 1994).

Primary hyperoxaluria should be suspected in any stone-former with otherwise unexplained hyperoxaluria, and particularly in the patient in whom stone disease begins in childhood. If urinary glycolate excretion is also increased, type 1 primary hyperoxaluria is the most likely diagnosis. Mild late-presenting forms of the disease have also been described (Danpure 1991; Scheinman 1991; Irish and Doust 1992) and need to be distinguished from other pathophysiological forms of ‘mild idiopathic hyperoxaluria’ (Sutton and Walker 1994). The AGT gene has been cloned and sequenced, and the identity of some of the mutations in type 1 primary hyperoxaluria has been characterized (Danpure et al. 1994). In some patients the mutation leads to mis-targeting of the enzyme to the mitochondria rather than the normal location in the peroxisomes.

Pyridoxal phosphate is a cofactor for the enzyme alanine-glyoxylate transaminase. Some patients respond to pyridoxine with or without accompanying therapies including an increase in fluid intake, a low-oxalate diet, and magnesium and phosphate supplements (Milliner et al. 1994; Scheinman 1994). Milliner et al. (1994) have recently reported encouraging results from the long-term treatment of patients with primary hyperoxaluria with orthophosphate and pyridoxine; the treatment decreased urinary calcium oxalate crystallization and appeared to preserve renal function. The dose of orthophosphate used was 30 to 40 mg/kg body weight; in adults a reasonable dose is 0.5 g (as phosphorus) three or four times daily. The actuarial survival free of endstage renal disease was 96 per cent at 5 years and 74 per cent at 20 years.

When endstage renal disease supervenes, the outcome on dialysis is poor and organ replacement has been employed; renal transplantation alone gives disappointing results, with approximately 20 per cent patient
survival at 3 years (Broyer et al. 1990). Liver transplantation corrects the enzyme defect and has been successfully combined with renal transplantation in a few patients (Wattset al. 1987).

Type 2 primary hyperoxaluria is rarely diagnosed, since the determination of l-glyceric acid in the urine is not widely available; it may be more common than is generally recognized. None of five patients with type 1 primary hyperoxaluria progressed to renal failure during treatment with orthophosphate and pyridoxine (Milliner et al. 1994).

**Enteric hyperoxaluria**

Stone disease is an important complication of extensive bowel disease or resection; in patients with an intact colon, enteric hyperoxaluria and calcium oxalate stones may occur (Sutton and Walker 1994), while in patients with an ileostomy the stones more commonly consist of uric acid, secondary to the low urine volume and pH. Enteric hyperoxaluria results from the hyperabsorption of dietary oxalate because calcium in the gut lumen is preferentially bound to non-absorbed fatty acids, preventing the precipitation of insoluble calcium oxalate and leaving oxalate in the gut lumen free for absorption. There is also increased permeability of the colon to oxalate as a result of the increased delivery of non-absorbed bile salts from the ileum, and increased oxalate absorption probably occurs mainly in the colon.

Risk factors for calcium oxalate crystalluria and stone formation in these patients include low urine volume (secondary to diarrhoea), low urinary ionic strength (which decreases calcium oxalate solubility), and low urine citrate and perhaps magnesium, as well as the hyperoxaluria (Smith 1992). Calcium oxalate nephrolithiasis may be particularly troublesome following jejunal bypass surgery for obesity (Sutton and Walker 1994).

Many approaches have been suggested for stone prevention in enteric hyperoxaluria, but none has been subjected to rigorous prospective study (McLeod and Churchill 1992). Since the major source of the increased urinary oxalate is the diet, reduction of oxalate intake is rational. We have attempted to simplify recommendations for dietary oxalate restriction (Massey et al. 1993). However, the results of oxalate restriction tend to be poor; oxalate generation in the gut from precursors including protein (Hofmann et al. 1983) and possibly ascorbic acid (Zarembski and Hodgkinson 1969) may be important.

Reduction of steatorrhoea by reducing dietary fat or substituting medium-chain triglycerides may help to decrease urinary oxalate excretion (Andersson 1974). Several agents have been tried as luminal oxalate binders (Sutton and Walker 1994), including calcium and magnesium salts, organic marine hydrocolloid (Lindsjö et al. 1989), and cholestyramine. In jejunal bypass patients, we have been able to give 4 to 5 g/day of calcium as calcium carbonate with meals, with little increase in urinary calcium excretion and substantial reduction in urinary oxalate excretion (Walker and Sutton 1994a); other investigators have found calcium or magnesium supplements to be less effective (Barillaet al. 1978). Although organic marine hydrocolloid charged with calcium (Oxabsorb) was reported to lower urinary oxalate excretion (Lindsjö et al. 1989), we have found it to be no more effective than equivalent amounts of calcium given as calcium carbonate (Sutton and Walker 1994). Cholestyramine has been reported to reduce urinary oxalate excretion (Smithet al. 1972) or to have no useful effect. Attention should be given to other urinary risk factors including low urine volume, low citrate, and low magnesium.

A reasonable approach (McLeod and Churchill 1992) is to restrict dietary oxalate, treat the steatorrhoea and diarrhoea symptomatically, and give increased fluids (if tolerated) plus potassium citrate. If stones persist, calcium supplements may be given with meals and the effect on urinary oxalate and calcium excretion should be monitored. Finally, cholestyramine in a dose of 4 g four times daily or organic marine hydrocolloid...
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(Oxabsorb), three tablets three times daily, may be tried. In the jejunal bypass patient, refractory stones or oxalosis and renal impairment may eventually mandate reversal of the bypass.

Idiopathic calcium oxalate or mixed calcium oxalate–calcium phosphate stones

Laboratory investigation

Idiopathic calcium stone-formers are those patients in whom systemic or renal diseases causing stones, including primary hyperparathyroidism, primary and enteric hyperoxaluria, renal tubular acidosis, and sarcoidosis, have been excluded. In these patients, the stones consist predominantly of calcium oxalate. Known or suspected risk factors for calcium oxalate stones include low urine volume, hypercalciuria, hyperoxaluria, hyperuricosuria, or hypocitraturia. In addition, in recent years a number of macromolecular inhibitors of stone formation have been identified in the urine, including nephrocalcin (Coe et al. 1994), uropontin (Hoyer 1994), Tamm–Horsfall protein (Hess 1994), and crystal matrix protein (Stapleton and Ryall 1994). In the case of two of these inhibitors (nephrocalcin and Tamm–Horsfall protein), evidence has been presented to suggest that certain families may have a molecular defect in the inhibitor, perhaps underlying their stone formation (Coe et al. 1994; Hess 1994). In future, investigation of these and other inhibitors may become part of the metabolic screening of stone-formers, particularly those in whom the problem is familial. However, this is not practical at present and has not yet led to new forms of stone prevention.

A reasonable schema for the laboratory investigation of the patient with idiopathic calcium stones is shown in Table 5. Ideally these tests, as well as a record of food intake or a diet diary (which can be obtained and analysed by the clinic dietitian), should be completed before the patient's first visit to the consultant or the stone clinic. This ensures that the patient has not modified his or her dietary or other habits as result of advice from the physician, dietitian, or others before collecting the 24-h urine samples. This approach also allows the physician to focus questions according to demonstrated risk factors; there is likely to be little benefit in taking a detailed dietary history in a calcium stone patient whose 24-h urine analysis shows consistently normal values for calcium, oxalate, uric acid, and citrate. The results of these tests will also help to identify underlying systemic or renal disorders. After these have been excluded, the patient may be classified as an 'idiopathic' calcium stone-former. In the remainder of this section, an approach to this important group of patients will be further discussed according to whether the patient has one or more of the following risk factors:

- hypercalciuria
- hyperoxaluria
- hyperuricosuria
- hypocitraturia
- low urine volume
- no identified risk factors

Hypercalciuria

The upper limit of normal for the 24-h urinary calcium excretion is commonly taken to be 6.25 mmol in females and 7.5 mmol in males, or greater than 4 mg/kg in patients of either gender. Patients with calcium excretions in excess of these values may be defined as having hypercalciuria. However, the risk of stones may also vary with urinary calcium excretion within the normal range as well as at 'hypercalciuric' amounts (Wasserstein et al. 1987; Robertson et al. 1978), and therefore it may not be rational to restrict treatments aimed at lowering urinary calcium only to patients whose values exceed an 'upper limit of normal'. Nevertheless, most
physicians choose to intervene when 24-h calcium values exceed 6.25 mmol in females or 7.5 mmol in males.

Hypercalciuria is one of the most common findings in calcium stone-formers, being reported in over 50 per cent of patients (Coe et al. 1992). Idiopathic hypercalciuria may be inherited as an autosomal dominant trait (Coe et al. 1979; Mehes and Szeliid 1980). The pathophysiology is considered elsewhere (Breslau 1994), but there are some families in whom hypercalciuria is associated with distal renal tubular acidosis (Caruana and Buckalew 1988), and others in whom there is marked hypophosphataemia as well as family members (perhaps those with a double dose of an abnormal gene) who may have hereditary hypophosphataemic rickets with hypercalciuria (Tieder et al. 1987). In idiopathic hypercalciuria as a whole, the serum phosphorus tends to be low, which may lead to confusion with primary hyperparathyroidism, but the serum calcium is (by definition) normal in idiopathic hypercalciuria and generally elevated in primary hyperparathyroidism.

In most cases, idiopathic hypercalciuria appears to result from intestinal calcium hyperabsorption (so-called absorptive hypercalciuria) and there is a tendency for bone density to be slightly low. Serum calcitriol is normal or increased. At present, the hypothesis that best explains this combination of findings is as follows. Either elevated absolute concentrations of calcitriol or increased sensitivity to calcitriol, possibly due to an increase in calcitriol receptors in gut (Xiao-Quiang et al. 1993) and bone (Stathopoulos and Bushinsky 1992), cause increased intestinal calcium absorption and increased skeletal resorption, particularly when the dietary calcium intake is low (Lemann and Gray 1989).

In those patients whose serum phosphorus is low, hypophosphataemia may be the stimulus for the increased production of calcitriol, and treatment with phosphate may be an attractive option (Breslau 1994; Breslau et al. 1995).

In a minority of patients, hypercalciuria may result from a defect in renal tubular calcium reabsorption (so-called renal hypercalciuria), rather than being due primarily to increased intestinal calcium absorption (Breslau 1994). Such patients would be expected to have an increased urinary calcium excretion after fasting, and a tendency to a low serum ionized calcium and an increased plasma parathyroid hormone. There may be a secondary increase in intestinal calcium absorption due to enhancement of calcitriol production by parathyroid hormone. Increased plasma parathyroid hormone is not commonly found in idiopathic hypercalciuria. When the urinary calcium excretion is abnormally elevated after fasting, it may result from increased skeletal resorption rather than a renal calcium 'leak' (Sutton and Walker 1986).

From a practical viewpoint, the question arises as to whether attempts to differentiate so-called renal and absorptive idiopathic hypercalciuria lead to the identification of separate disorders requiring different therapy. In theory, a low-calcium diet or a calcium-binding agent such as cellulose phosphate might be appropriate for the treatment of a primary intestinal hyperabsorptive defect, whereas an agent enhancing renal tubular calcium reabsorption, such as a thiazide diuretic, might be preferable for a primary renal calcium leak (Coe et al. 1992; Breslau 1994). However, although avoidance of a high calcium intake seems prudent (not more than 1000 mg/day), a low calcium intake is not advisable, partly because it may cause increased bone resorption and ultimately osteoporosis (Coe et al. 1982) and partly because a low-calcium diet may actually increase the risk of stones, perhaps by enhancing intestinal oxalate absorption (Curhan et al. 1993). Preminger and Pak (1986) have reported that the beneficial effect of a thiazide diuretic in so-called absorptive hypercalciuria may wane after several years. Despite this as yet unconfirmed observation, the author's view is that there is little practical merit in subdividing idiopathic hypercalciuria into different putative pathophysiological types, and that an appropriate therapeutic approach is first to correct dietary factors that may be enhancing urinary calcium excretion (including a high calcium intake or an excessive intake of salt, protein, or vitamin D) and, if that does not correct the hypercalciuria, to use one of the pharmacological alternatives which might consist of a thiazide diuretic, potassium citrate, or potassium phosphate.
Patients with idiopathic hypercalciuria excrete abnormally large amounts of calcium in the urine at any level of dietary calcium intake. There has been considerable interest in dietary factors that may influence the urinary calcium excretion (Goldfarb 1988; Jaeger 1994), including a high salt intake (Breslau et al. 1982) and a high protein intake (Kok et al. 1990), or an abnormally high intake of vitamin D. In addition, excessive dietary calcium ingestion may contribute to hypercalciuria.

With respect to salt intake, the author’s approach is to determine the urinary sodium as well as the calcium content in the 24-h urine collection at the time of the metabolic work-up. In addition, the clinic dietitian obtains an estimate of dietary sodium intake. If the patient has hypercalciuria and urinary sodium excretion is greater than 100 mmol/day, he or she is advised to limit the salt intake to 100 mmol/day or less. After 1 month, the 24-h urinary sodium and calcium excretions are rechecked. In some patients, this reduction in salt intake may correct the hypercalciuria. There may be a subgroup of stone patients with an undue sensitivity to the hypercalciuria-inducing effect of a high salt intake (Goldfarb 1988). As well as directly inducing hypercalciuria, a high salt intake may blunt the effect of thiazide diuretics to lower the urinary calcium excretion. In such patients salt restriction may render a patient normally responsive to the hypocalciuric action of the thiazide diuretic. A high salt intake may also contribute to hypocitraturia (Pak 1994).

A similar approach may be used with respect to the dietary protein intake. If hypercalciuria is present and the dietitian’s review suggests a high protein intake, particularly if the urea content in the 24-h urine confirms a high dietary protein intake, patients with a daily protein intake greater than 1.0 g/kg body weight may be counselled to reduce their protein intake to 1.0 g/kg or less.* Again, this may correct hypercalciuria in some patients. As with sodium, some stone patients may have an abnormal sensitivity to the hypercalciuric effect of protein (Goldfarb 1988). Various mechanisms have been postulated to account for the hypercalciuric effect of protein, including the effect of sulphate derived particularly from animal protein metabolism (Breslau et al. 1988), as well as the effects of the increased net acid production from protein, leading to a mild chronic metabolic acidosis which may enhance skeletal resorption (Lemann et al. 1986) and inhibit tubular calcium reabsorption as well as lowering urinary citrate excretion (Goldfarb 1988).

*Protein intake is calculated from urea excretion. The relationship is not strictly linear since part of the protein nitrogen intake is excreted as non-urea urinary nitrogen and faecal nitrogen. These add up to an average of 31 mg/kg/24 h (Maronie et al. 1985) and do not change appreciably with protein intake. A 70-kg man on a diet of 1 g/kg/24 h will excrete 11.2 g of nitrogen, of which 2.2 g will be non-urea urinary and faecal. The remaining 9 g will appear as urinary urea (about 320 mmol/24 h). A similar calculation must be performed for each patient to judge total protein intake. However, changes in protein intake (in the range of interest in stone disease) are wholly reflected in urea excretion. For any subject a change in protein intake of 10 g/24 h causes a change in urinary urea excretion of about 57 mmol/24 h.

With regard to vitamin D, supplements should obviously be avoided in patients with idiopathic hypercalciuria and stones. A calcium intake in the range of 800 to 1000 mg/day is recommended. A high calcium intake may increase calciuria, while dietary calcium restriction may have adverse effects on bone (Fusset al. 1990) and may increase the urinary oxalate excretion (Zarembski and Hodgkinson 1969).

If these simple dietary measures (one or more of which may be introduced at the time of the patient’s initial visit to the stone clinic) fail to correct the hypercalciuria and the patient is actively forming stones, additional pharmacological measures are required. The usual choice is a thiazide diuretic, which directly promotes renal tubular calcium reabsorption and may have beneficial long-term effects on the skeleton (Wasnick et al. 1983; Coe et al. 1988).
As already noted, a thiazide diuretic may be relatively ineffective in lowering the urinary calcium excretion in the presence of a high salt intake, and therefore if the 24-h urinary sodium excretion is greater than 100 mmol/day, advice to limit salt intake should accompany the introduction of the drug. Thiazide-induced hypokalaemia should be avoided since it may cause hypocitraturia (Pak et al. 1985). Various thiazide-like diuretics have been used, including chlorthalidone, for which a placebo-controlled prospective study has shown that a dose of 25 mg/day is as effective as 50 mg/day in reducing stone recurrences (Ettinger et al. 1988). Chlorthalidone has also been shown to improve calcium balance (Coe et al. 1988). Thiazides have been shown to reduce stone recurrences by about 60 per cent (Laerum and Larsen 1984; Ettinger et al. 1988). However, thiazides have a number of possible long-term side-effects, including adverse effects on lipids and potassium depletion. Indapamide, in a dose of 2.5 mg/day, may lower urinary calcium excretion to an extent similar to 50 mg/day of hydrochlorothiazide but with less adverse effects on cholesterol and urate. A recent study has suggested that indapamide may reduce stone recurrences (Borghini et al. 1993).

Other drugs that may be useful in the treatment of the patient with idiopathic hypercalciuria include potassium citrate, 60 to 80 mEq/day, which (unlike sodium citrate) may lower urinary calcium excretion (Sakhaee et al. 1983) as well as increasing urinary citrate excretion. Neutral phosphate has been used for many years, but has not been subjected to randomized placebo-controlled prospective studies (Coe et al. 1992). Its postulated beneficial effects include a decrease in urinary calcium excretion (Insogna et al. 1989), an increase in urinary pyrophosphate (an inhibitor of uncertain importance), and an increase in plasma phosphate, which in turn downregulates calcitriol production. However, the sodium in neutral sodium phosphate may tend to increase the urinary calcium excretion, and therefore a new preparation of neutral potassium phosphate (UroPhos-K) may have advantages (Breslau 1994). This agent is currently undergoing trials and may prove to have an important place in the treatment of patients with idiopathic hypercalciuria. Phosphate therapy may be particularly beneficial in patients in whom idiopathic hypercalciuria is associated with hypophosphataemia.

Cellulose phosphate, by binding calcium in the gut, can produce appreciable lowering of the urinary calcium excretion (Coe et al. 1992). It was extensively used in the past in Europe, but is not widely available now. Its effect is equivalent to a very low calcium intake, and as a result it may increase the urinary oxalate excretion as well as possibly having adverse long-term effects on the bone. In addition, it binds magnesium and may lead to magnesium deficiency. It is no longer recommended for stone prevention.

Although these approaches to the correction of idiopathic hypercalciuria tend to be restricted to patients with urinary calcium values above the somewhat arbitrarily defined upper limit of normal, it may also be useful to lower the urinary calcium excretion in idiopathic calcium stone-formers with frequent recurrences, even it is not above the normal range. Potassium citrate, a thiazide diuretic, or neutral potassium phosphate might be considered in such patients if other measures have not led to a cessation of stone formation. However, no controlled studies have been undertaken to prove the efficacy of such therapy.

Hyperoxaluria

Until recently, the laboratory determination of oxalate in the urine has often been poorly performed (Kasidas 1988). With the introduction of commercial kits as well as other methods, such as high-pressure ion chromatography, satisfactory urinary oxalate analysis is now widely available. The upper limit of normal for 24-h urinary oxalate excretion in the adult is approximately 4 mg or 460 μmol. As in the case of calcium, it may sometimes be advantageous to lower the urinary oxalate excretion, even when it does not exceed the upper limit of normal. Robertson and Hughes (1993) have presented evidence that calcium oxalate crystalluria is maximal at a molar ratio of urinary oxalate to calcium of about 1.0. The ratio in normal urine is about 0.1, but
may be greater as a result of an increase in oxalate, a decrease in calcium, or both. A reduction in the ratio of urinary oxalate to calcium may be beneficial, even when the product of calcium and oxalate in the urine is unchanged. Thus the lowering of oxalate may offer particular advantages. The reported incidence of hyperoxaluria in idiopathic calcium oxalate stone-formers has varied widely from 8 per cent to 50 per cent (Sutton and Walker 1994). Pathophysiological mechanisms for this mild hyperoxaluria may include a high dietary oxalate intake, enhanced intestinal oxalate absorption, which may be either primary (Borsatti 1991) or secondary to a low dietary calcium intake, a renal oxalate leak, or enhanced oxalate production from precursors such as ascorbic acid or protein (Sutton and Walker 1994). Finally, among these patients may be an occasional individual with a mild late-presenting form of primary (hereditary) hyperoxaluria. Edwards and Rose (1991) have described a group of patients with pyridoxine-responsive hyperoxaluria in whom there appears to be impaired phosphorylation of pyridoxine to pyridoxal phosphate, the cofactor for the enzyme alanine-glyoxalate transaminase which is defective in type 1 primary hyperoxaluria.

Glycolate is in equilibrium with glyoxylate, the immediate precursor of oxalate in the metabolic pathways from several amino acids including glycine, serine, and hydroxyproline. The pathways from ascorbate and tryptophan do not proceed through glyoxylate. The measurement of glycolate may be useful in determining the cause of hyperoxaluria (Wandzilak et al. 1991; Marangella et al. 1992). However, this assay is not widely available (Scheinman 1994). At the present time the pathophysiology of mild idiopathic hyperoxaluria is uncertain (Sutton and Walker 1994), but there is evidence against either primary hyperoxaluria or a renal oxalate leak as the major mechanism, and there is limited evidence to support the existence of increased production from protein (Holmes et al. 1993). Lemann et al. (1994) have recently suggested that the major determinant of urinary oxalate excretion among healthy adults is body size, presumably reflecting variations in endogenous oxalate synthesis with lean body mass.

It has been known for many years that a low-calcium diet increases urinary oxalate excretion (Zarembski and Hodgkinson 1969); hence a controlled increase in calcium intake should be tried in a patient with a normal or low urinary calcium excretion and high urinary oxalate excretion, and may be very effective in reducing the excretion of oxalate with little or no change in urinary calcium (Walker and Sutton 1994b). If a reduction in dietary calcium is advised for stone prevention, dietary oxalate should also be reduced to curtail secondary increases in urinary oxalate. In patients with hyperoxaluria, and evidence from dietary review or from the urinary urea excretion of a high protein intake, a reduction in protein intake to less than 1.0 g/kg/day is advised.

The relationship between dietary ascorbic acid and urinary oxalate is controversial. Ascorbate can be non-enzymatically converted to oxalate, particularly under alkaline conditions. This can occur in the urine after voiding, unless precautions are taken to prevent it, and therefore misleading results may be obtained in studies of the effect of dietary ascorbate on oxalate excretion. In studies in which appropriate precautions were taken, no effect of up to 4 g/day of ascorbate on urinary oxalate was observed (Fituri et al. 1983). However, occasional patients may be unduly sensitive to the effect of ascorbic acid in increasing oxalate excretion. Non-enzymatic conversion of ascorbate to oxalate may also occur in the intestinal lumen, with subsequent absorption of the oxalate and excretion in the urine. Chalmers at al. (1986) presented data suggesting that the intestinal absorption of hydroxycarboxylic acids (including ascorbate and citrate) may be impaired in stone-formers, which could lead to increased conversion of ascorbate to oxalate in the intestine and therefore to increased urinary oxalate excretion.

Another proposed mechanism for hyperoxaluria is decreased bacterial oxalate degradation in the gut, which is normally carried out by the organism Oxalobacter formigenes for which oxalate is the sole energy source. However, there is as yet only preliminary evidence to suggest that reduced oxalate degradation contributes to idiopathic hyperoxaluria and stones (Kleinschmidt et al. 1994).
Although pyridoxine deficiency can cause hyperoxaluria, perhaps by decreasing the activity of the enzyme alanine-glyoxylate transaminase, there is no clear role for pyridoxine deficiency in idiopathic hyperoxaluria or stone disease.

Sutton and Walker (1994) have proposed a practical approach to the management of mild idiopathic hyperoxaluria. If urinary glycolate excretion is also increased, possibilities include increased endogenous oxalate production, including variants of type 1 primary hyperoxaluria as well as pyridoxine deficiency. If glycolate cannot be determined, a first step is to reduce dietary oxalate. If dietary calcium is low and urinary calcium is normal or low, dietary calcium can be cautiously increased (for example by the administration of 250 mg calcium as calcium carbonate twice daily with main meals). This dose can be adjusted according to the urinary calcium and oxalate results. If hyperoxaluria persists, other potential precursors, including protein, ascorbic acid, and xylitol, should be moderated. Xylitol is used as an artificial sweetener and has recently been shown to be a potential source of urinary oxalate (Nguyen et al. 1993). If these measures fail, and particularly if the excretion of glycolate as well as oxalate is increased in the urine, a trial of pyridoxine is warranted. Administration of pyridoxine will correct deficiency and may also improve type 1 primary hyperoxaluria (Edwards and Rose 1991; Milliner et al. 1994). A dose of 10 mg/day of pyridoxine may be tried for 2 to 4 weeks; if this is ineffective, the dose can be increased to 100 mg/day and subsequently to 500 mg/day.

Hyperuricosuria

The currently accepted upper normal limit for the urinary excretion of uric acid is 800 mg/day for men and 700 mg/day for women. Although the mechanisms through which hyperuricosuria may potentiate calcium oxalate stone formation are disputed (Coe et al. 1992; Grover and Ryall 1994), there is reasonably clear evidence that the correction of hyperuricosuria reduces the risk of recurrence of calcium oxalate stones (Ettinger et al. 1986). In this circumstance, hyperuricosuria is probably mainly of dietary origin and related to a high intake of purine, particularly in fish, meat, and poultry. If the dietary history confirms that the hyperuricosuric stone-former (often an affluent middle-aged male) does indulge in such dietary excesses, an attempt may be made to correct the hyperuricosuria by reducing purine intake. This is often not particularly successful, and the alternative is the use of allopurinol in a dose of 200 to 300 mg/day, which has been shown to be effective in reducing both uric acid excretion and calcium oxalate stone recurrence (Ettinger et al. 1986).

Hypocitraturia

Citrate has been recognized as being of potential importance in the pathogenesis of urinary calculi for decades. However, there has recently been a major resurgence of interest in the relationship of citrate to stones, much of it stimulated by the work of Pak and his colleagues (Pak 1994). A low urinary citrate excretion may predispose to calcium stones through at least two mechanisms: citrate forms soluble complexes with calcium, which render the calcium unavailable to precipitate as calcium oxalate or calcium phosphate; in addition, citrate can function as a potent inhibitor of the aggregation of calcium oxalate crystals (Kok et al. 1986), a process which is believed to be an important step in stone formation. Several of the macromolecular inhibitors of stone formation also function, at least in part, as aggregation inhibitors. Tamm–Horsfall protein has potentially important interactions with citrate, whereby a low citrate concentration may encourage the self-aggregation of the protein, leading to its functioning as a promoter rather than an inhibitor of stone formation (Hess 1994). This may be an important mechanism through which urinary citrate normally protects against stone formation.
The normal range for urinary citrate is wide (e.g. 1–5.8 mmol/day in men and 2–6.5 mmol/day in women (Lemann 1993)). An empirical lower normal limit of 1.5 mmol (320 mg) per day has been accepted by Pak and colleagues (Pak 1994). They and others report an incidence of hypocitraturia of 19 to 63 per cent in patients with nephrolithiasis. As with other risk factors for calcium stones, it may sometimes be advantageous to increase the urinary citrate excretion in patients with refractory stone disease, even if the baseline level of citrate excretion is not less than the normal range. However, responses to citrate therapy may be superior in patients with initial hypocitraturia (Pak 1994). The urinary excretion of citrate in health appears to be mainly determined by the patient’s diet, being directly related to net alkali absorption (Sakhaee et al. 2019). In stone patients with hypocitraturia, a decrease in net alkali absorption is the usual cause of the low citrate excretion and is related to a high animal protein intake (Kok et al. 1990), but other factors may contribute, including a high sodium intake (Sakhaee et al. 1991) and a low vegetable fibre intake (Hess et al. 1994). Abnormal renal handling of citrate may be present (Pak 1994).

In the hypocitraturic patient, the treatment of choice is potassium citrate in a dose of 40 to 60 mEq/day, conveniently given as Urocit-K, which has recently been shown in a prospective placebo-controlled study to reduce stone recurrences significantly (Barceloet al. 1994). A new medication, potassium-magnesium citrate, has been developed (Pak 1994) which is convenient to take and increases the urinary excretion of magnesium as well as citrate. Although magnesium has been considered to be an inhibitor of stone formation, the role of hypomagnesiuria in idiopathic calcium stone disease is unclear. Hypomagnesiuria and hypocitraturia frequently coexist in stone patients (Pak 1994). A magnesium preparation such as potassium-magnesium citrate or magnesium oxide may merit a trial in patients who are refractory to other treatments and in whom the urinary magnesium excretion is low.

Urine volume

It is probably advantageous to increase urinary volume in all recurrent stone-formers despite the theoretical risk that the concentration of inhibitors is reduced. A low urine volume may be the only identifiable risk factor in some idiopathic calcium stone patients. Such patients often have an aversion to water; for example some young women feel ‘bloating’ after drinking water. These patients need to be encouraged to increase their water intake gradually, with the aim of eventually achieving a target urinary volume of at least 2 and preferably 3 l/day. Alternatives to water may include fruit juices such as orange juice, which may also increase citrate excretion but modestly increase oxalate excretion (Wabner and Pak 1992). Soft drinks containing phosphoric acid may be less effective for stone prevention (Shuster et al. 1992), and intake should probably be restricted to less than 1 litre per week.

The patient with no identifiable risk factors

There remains a group of idiopathic calcium stone-formers in whom none of the traditional risk factors are positive. It is among such patients, particularly those where other family members are affected with stone formation, that it seems appropriate to seek defects in the newly recognized macromolecular inhibitors. Unfortunately, the techniques for identifying such abnormalities are not generally available and there are no forms of specific treatment. However, it seems reasonable to hope that the further study of these interesting proteins may not only provide information that helps to explain the pathophysiology of many apparently idiopathic stones, but may also lead to new methods of stone prevention. In the meantime, in the recurrent calcium stone-former without identifiable risk factors it may be appropriate to increase fluid intake, moderate dietary salt, protein, and oxalate, and perhaps add potassium citrate therapy.

Prevention of stone recurrence after lithotripsy
Small stone fragments are frequently left behind in the collecting system after extracorporeal lithotripsy. They may be too small to be visualized by plain radiography or ultrasound. Guidelines for continuing medical prophylaxis after extracorporeal lithotripsy have not been developed. Cicerello et al. (1994) have shown that citrate therapy improved the stone clearance rate at 6 and 12 months in patients with infection stones and with sterile calcium stones. Fine et al. (1995) have also demonstrated the efficacy of medical therapy following extracorporeal lithotripsy, whether or not residual stone fragments can be detected.

**Uric acid stones**

The prevalence of uric acid stones varies widely across the world from 2.1 per cent in Texas to 37.7 per cent in Iran (Halabe and Sperling 1995), perhaps reflecting ethnic, climatic, and dietary differences. The major risk factors for uric acid stone formation are a low urine pH (pK_a for uric acid is 5.35), low urine volume, and hyperuricosuria. In the patient with hyperuricosuria, contributing factors may include a high dietary purine intake, gout, haemopoietic malignancies, haemolytic disorders, and abnormalities of purine synthetic enzymes (HGPRT deficiency or PRPP synthetase overactivity (Halabe and Sperling 1994)). Investigation of the patient in whom uric acid stones have been confirmed, usually by stone analysis, and who has no obvious underlying cause should include determination of the 24-h urinary uric acid and the urine pH. The latter can conveniently be monitored by giving the patient nitrazine pH test paper to check and record the pH of urine at each voiding for a period of 24 to 48 h. Typically, the urine pH is persistently low in the uric acid stone-former (usually 5.5 or below). The impact of pH on uric acid solubility is such that, irrespective of the presence of hyperuricosuria, the urine is unlikely to be saturated at a pH greater than 6.5. In 50 per cent of patients with uric acid stones, the fasting urine pH is less than 5.0, whereas this is the case in only 15 per cent of normal subjects (Halabe and Sperling 1994). The reason for this persistent aciduria is not certain. It may relate to diet, but there may also be a defect in the urinary buffering of hydrogen ions, for example as a result of reduced ammonia production. Persistent aciduria and uric acid stones may also result from a mild chronic metabolic acidosis, for example due to chronic diarrhoea in Crohn’s disease and in the patient with an ileostomy.

The treatment of the uric acid stone-former should rarely need to be surgical, since uric acid stones can usually be dissolved in situ (Chugtai et al. 1992). The prevention or treatment of uric acid stones should include an increase in fluid intake, to achieve a urine volume of at least 2 l/day, and the administration of alkali, for example as potassium citrate or potassium bicarbonate, preferably in an amount sufficient to increase the urine pH to above 6 to 6.5 for at least part of the day. The intelligent and motivated patient can determine the amount of alkali (e.g. potassium citrate 20 mEq three times daily) that is needed to achieve this result. Sodium alkalis may be less effective, since they may increase calcium excretion and lead to the superimposition of calcium stones on uric acid stones. If urinary alkalinization fails to prevent stones or hyperuricosuria is marked, treatment may also be directed at reducing uric acid excretion. This can be achieved by dietary purine restriction and, if necessary, the addition of allopurinol, which inhibits the enzyme xanthine oxidase which catalyses uric acid production from hypoxanthine and xanthine.

**Other purine stones**

**Xanthine**

Xanthine stones, which are radiolucent, may occasionally result from the therapeutic use of allopurinol. They also occur in hereditary xanthinuria which is characterized by abnormally low serum and urinary uric acid. There may be associated xanthinuric myopathy. Xanthine is extremely insoluble in the urine, and therefore the effect of increased urine volume in preventing these stones is relatively modest. Purine intake should be limited, and allopurinol may be administered to block the residual oxidation of hypoxanthine to xanthine, thus
reducing xanthine excretion (Rose 1992).

**8-Dihydroxyadenine**

2,8-Dihydroxyadenine stones may be more common than currently suspected. They result from a deficiency in the enzyme APRT, inherited as an autosomal recessive trait (Simmonds et al. 1976). If chemical stone analyses are used, 2,8-dihydroxyadenine will be misidentified as uric acid. The use of the enzyme uricase or IR analysis allows reliable identification. Urinary 2,8-dihydroxyadenine can be measured by high-pressure liquid chromatography. Treatment of these stones is with a high fluid intake and allopurinol.

**Ammonium acid urate**

Ammonium acid urate is an important constituent of endemic bladder stones in the developing world. In addition, ammonium acid urate stones have recently been described as a complication of laxative abuse and intestinal resection (Dick et al. 1994).

**Cystine stones**

Cystine stones may be identified by stone analysis, or may be suspected as a result of a family history, presentation at an early age, or the presence of the characteristic hexagonal cystine crystals in the urine (Sakhaee 1994) (Fig. 1). Cystinuria can be confirmed by measurement of the 24-h urinary cystine excretion. The stones are radio-opaque (Fig. 2) and may be of large size or even staghorn configuration (Fig. 3). The genetic defect has recently been identified (Calonge et al. 1994; Praset et al. 1994). The gene resides on chromosome 2. The urinary cystine excretion is normally 30 mg/day; cystinurics excrete 400 to 3600 mg/day. The solubility of cystine is about 250 mg/l in urine; therefore treatment is aimed at reducing the free cystine concentration to less than this, and includes an increase in urine volume by increasing fluid intake. For example, if the urinary cystine excretion is 500 mg/day, a urine output of 2 l/day should be sufficient to prevent stone growth or new stone formation. A high fluid intake alone can cause stone dissolution in cystinuria. the usual target is a urine volume of at least 3 l/day. Urine alkalinization is generally recommended, but increasing the urine pH has only a modest effect until it exceeds 7.0, and this is difficult to achieve and may increase the risk of superimposed calcium phosphate stones. Potassium citrate 60 mEq/day has been recommended (Sakhaee 1994), but its value has not been proved.

If increased urine volume and treatment with alkalis does not prevent stone formation, a chelating agent that increases cystine solubility is required. Available compounds include penicillamine, mercaptopropionylglycine, and captopril (Sakhaee 1994). The original chelating agent was penicillamine, which is effective but unfortunately has undesirable side-effects including blood dyscrasias and nephropathy. Pak and colleagues (Sakhaee 1994) have suggested that the dose can be based on the 24-h urine cystine output and urine volume. It is assumed that each litre of urine can hold a 250-mg dose of cystine in solution, and that each 250 mg of penicillamine lowers the urinary free cystine by 100 mg. For example, if urine cystine is 1200 mg and the urine volume is 3 litres, the amount of cystine to be dealt with by penicillamine is 1200/3×250 =450 mg, which requires four to five penicillamine tablets daily. It is recommended that patients being treated with penicillamine also receive pyridoxine 50 mg/day, since penicillamine may cause pyridoxine deficiency. Penicillamine-treated patients should have regular monitoring of their blood count as well as their urine for protein. Mercaptopropionylglycine (Tiopronin) may be somewhat less toxic than penicillamine (Sakhaee 1994). It has an equivalent hypocystinuric effect to penicillamine, but needs to be discontinued less frequently for toxic effects. Another (third-generation) chelating agent is currently undergoing trials (Sakhaee 1994).
Encouraging results have recently been reported with the use of captopril, which also chelates cystine and renders it more soluble (Sloand and Izzo 1987; Perazella and Buller 1993). Surprisingly, captopril doses of 75 to 100 mg/day have been reported to lower cystine by 70 to 90 per cent, an effect much greater than would be predicted from its cystine-binding activity. Therefore captopril may be working in some other (additional) manner. Further studies are required, and if these effects are substantiated, captopril may have a useful role since it is generally less toxic and better tolerated than other available agents.

Since cystine stones do not fragment as readily as other types of stones with extracorporeal shock wave lithotripsy, medical prophylaxis is particularly important. Without stone prevention, such patients can progress to endstage renal disease as a result of repeated stone episodes. A decrease in sodium excretion has been reported to reduce urinary cystine; therefore sodium restriction may be beneficial (Jaeger et al. 1986). Attempts to decrease urinary cystine by dietary restriction of cystine and its precursors, including methionine, have not proved to be practical.

Struvite stones

Struvite (magnesium ammonium phosphate) stones result from urinary tract infection with urease-producing organisms, which produce an alkaline urine with a high ammonium content. As a result, the urine is supersaturated with magnesium ammonium phosphate.

The stones consist of struvite plus carbonate apatite; they are radio-opaque and are often large or of the staghorn type. They can grow very rapidly. They often occur in anatomically or physiologically abnormal lower urinary tracts, for example in patients with paraplegia and bladder paralysis. Struvite stones may also occur secondary to other metabolic stone disease if the kidney becomes infected with urease-producing organisms. In part because the organisms reside within the stones, they may be difficult or impossible to eradicate with antibiotics, though antibiotic treatment may slow stone growth (Griffith 1978). Proteus mirabilis is the most common of these organisms, but many other bacteria, including Ureaplasma urealyticum (Hedelin et al. 1984), may occasionally produce urease. An inhibitor of the enzyme urease (acetohydroxamic acid) is effective in reducing urinary pH and ammonia (Williams et al. 1984) but has unacceptable side-effects. Other less toxic analogues are being sought.

In addition to appropriate antibacterial agents (based on urine culture), other treatments include the removal of large stones by percutaneous lithotripsy and the use of extracorporeal lithotripsy, as well as chemolysis with hemiacidrin (Dretler 1994). Subsequent stone-free rates are greatest if all fragments are removed with the initial therapy (Beck and Riehle 1991). Potassium citrate may help to prevent the growth of residual stone fragments (Cicerello et al. 1994).

Silica stones

A small number of cases of silica stones have been reported in patients taking silica-rich medications such as magnesium trisilicate. These stones are only poorly visible on plain radiographs; they can be identified by IR spectroscopy. The treatment is to withdraw the silica-rich medication (Haddad and Koyyomdjian 1986).

Triamterene stones

Triamterene has been found in large numbers of renal calculi analysed by a commercial laboratory (Ettinger et al. 1981). However, only a third of these stones were composed entirely or almost entirely of triamterene. A
specific lithogenic role for triamterene remains unproven (Woolfson and Mansell 1991).

Summary

The various medical treatments for stone disease are summarized in Table 6.

Stones in childhood

Bladder stones were common in European children until the nineteenth century, but they are now rare. However, they remain common in parts of Asia and some areas of Africa. They consist of ammonium urate, which forms the nidus of nearly all such stones, with a variable amount of calcium oxalate (Vanwaeyenbergh et al. 1995). They have been attributed to a high-vegetable low-phosphate diet which causes an alkaline urine with high ammonium urate content (Dick et al. 1994). Public health measures which have been suggested to prevent the disease include promoting early introduction into the diet of milk, other high protein foods, and locally available supplements which the vulnerable population can afford (Suphiphat et al. 1993). Orthophosphate is given orally to prevent recurrence after stone removal.

Upper urinary tract stones are uncommon in children. In European patients they usually consist of struvite and are related to infection with urease-producing bacteria in an often congenitally abnormal urinary tract. Elsewhere, stones in children are most commonly calcium oxalate or uric acid. Hereditary metabolic disorders, including cystinuria, hyperoxaluria, disorders of purine metabolism, and rare conditions such as X-linked recessive nephrolithiasis (Frymoyer et al. 1993), should be particularly suspected in children. Hypercalciuria also occurs in childhood nephrolithiasis as well as in association with haematuria, and can be treated with thiazides. However, adverse lipid effects may occur, and hence risks and benefits should be carefully considered before starting long-term treatment of children with thiazide diuretics (Reusz et al. 1993).

References


