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Cystinuria and its Treatment: 25 years Experience at St. Bartholomew's Hospital

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Summary: Cystinuria is an inherited condition affecting the active transport of the diamino acids cystine, ornithine, lysine and arginine across the renal tubule and the small intestine. The only clinical effect is the production of urinary tract stones and if these can be prevented the affected individuals can lead a normal life. In many people cystine stones can be dissolved and new stone formation prevented by a high fluid intake, but if this does not succeed regular treatment with penicillamine will do so. Although many side-effects have been described with penicillamine treatment it is rare for them to be severe enough to prevent its use in patients with cystinuria. Since the clinical effects of cystinuria can be prevented by either a high fluid intake or by penicillamine it is important to make the diagnosis in affected individuals as soon as possible and cystinuria should therefore be considered in all people (regardless of age) who form urinary stones.

INTRODUCTION

Cystinuria is an inherited disease (normally considered to be autosomal recessive) of amino acid transport which is known to affect both the small intestine and the kidney (McKusick 22010). When fully exhibited there is a transport defect of cystine, ornithine, lysine and arginine at both sites and, due to the insolubility of cystine, the patients suffer from recurrent urinary stones composed of cystine. These stones are radio-opaque and present similar symptoms and complications to those found with other urinary stones. The intestinal defect does not appear to result in any clinical symptoms even though lysine is an essential amino acid. The fact that there is no evidence of malnutrition in children with cystinuria may reflect the high level of lysine in milk, much of which will be absorbed even in the absence of an active transport mechanism for lysine, since it can be absorbed passively or actively as a dipeptide.

HISTORICAL SURVEY

The first description of a cystine stone was by Wollaston (1810) who analysed a glistening yellow bladder stone. He found this to be composed of an unusual

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substance which he called cystic oxide, since it came from the bladder. Later analysis showed this to be a sulphur-containing amino acid and so this stone ultimately gave its name, not only to cystinuria, but also to the amino acids cystine and cysteine. In 1817 Marcet showed that cystine stones also occurred in the kidney and suspected that the condition might be familial since two of his patients were brothers. Prout (1820) and Stromeyer (1824) observed cystine crystals in the urine of patients who formed cystine stones, and Prout postulated that excessive excretion of cystine was responsible for the crystalluria and stone formation. Prout (1823) also claimed that the disease was due to a local, functional disturbance in the kidneys.

In 1830 Berzelius realized that Wollaston's 'cystic oxide' was not an oxide and suggested altering the name to 'cystin'. The presence of sulphur was detected by Baudrimont and Malaguti in 1837 and by Thaulow in 1838, who was also able to calculate the correct molecular formula as $C_6H_{12}N_2S_2O_4$. In the next few years there was some confusion as to the true molecular formula of cystine which was confused with its reduction product cysteine by some authors (Gmelin, 1852; Cramer, 1865). However, Baumann (1883) not only confirmed the correct molecular formula of cystine but also showed that cystine was the disulphide oxidation product of cysteine which had a free SH group. He was only incorrect in suggesting that both the sulphur and the nitrogen atoms were attached to the same carbon atom. The correct structural formula was not elucidated until 20 years later when it was shown that the sulphur and nitrogen atoms were attached to different carbon atoms (Neuberg, 1902; Friedmann, 1903).

Toel in 1855, using gravimetric analysis, reported a cystine excretion of 1.2–1.5 g/24 h (5–6 mmol/24 h) in a cystinuric patient, which is very similar to the amounts found by present methods of analysis. Civiale (1838) was able to find 19 published cases, and Niemann (1876) reviewed the literature and gave details of 52 cases and also confirmed that the disease was familial in nature. Further clinical reviews have been carried out by Morner (1925), Renander (1941) and by Bostrom and Hambraeus (1964).

In 1908 Garrod postulated that cystinuria was due to a metabolic block and suggested that it was an inborn error of 'metabolism' leading to an overflow amino aciduria. However, this was incorrect since it is a transport defect, not an enzyme defect. Following this authoritative, but incorrect, classification there was little advance in our knowledge of cystinuria for another 40 years when, with the advent of better methods of amino acid analysis, it was shown that ornithine, lysine and arginine were also excreted in excessive amounts in cystinuria (Yeh *et al.*, 1947); Dent and Rose, 1951; Stein, 1951). Dent and Rose (1951) also showed that the plasma levels of these amino acids were normal and suggested that these structurally related amino acids, which each had two amino groups separated by four to six carbon or sulphur atoms (Figure 1), were re-absorbed by a common renal tubular mechanism which was defective in cystinuria. Ten years later in 1961 Frimpter showed that the mixed disulphide cysteine-homocysteine disulphide was also present in the urine of cystinuric patients, and in 1974 Cox and Cameron found excessive amounts of homoarginine in the urine of cystinuric patients. These two

amino acids have a similar structure to the previously described dibasic amino acids but these have two amino groups separated by seven carbon or sulphur atoms (Figure 1).

HISTORICAL REVIEW OF TREATMENT

Protein restriction: A low protein diet was suggested by Majendie in 1828 and again by Morner in 1925, but Dent and Senior in 1955 showed that the protein intake had to be reduced to 20 g/24 h in order to reduce the urinary cystine by 30%. The protein restriction must be severe, since to be effective it is necessary to reduce not only the cystine and cysteine but also the methionine in the diet and, if this is a diet containing natural protein, it would of necessity reduce other amino acids as well.

pH adjustment: In 1828 Majendie showed that cystine was most soluble in alkaline media and he also suggested that alkalis reduced cystine excretion. He probably reached this conclusion because he used cystine crystal formation in the urine as an indication of the total cystine excretion, but, although cystine crystal formation is reduced in an alkaline medium, the total cystine excretion is unchanged. On the other hand, Prout in 1825 and Venables in 1830 suggested treatment with dilute acids. In 1914 Klemperer and Jacoby again reported on the use of alkalis and showed the complete disappearance of cystine crystals by the administration of large amounts of alkali (6–8 g/day). However, none of these methods was sufficiently impressive for them to be adopted as a regular therapeutic regime in clinical practice. It was not possible to put treatment on a more reliable basis until accurate methods of amino acid analysis were developed. Dent and Rose (1951) were then able to demonstrate that the excessive urinary cystine was associated with normal blood levels and postulated that the disorder was due to a renal defect. They were also able to measure both the total urinary cystine and its solubility during different treatment regimes. In 1955 Dent and Senior showed that, although the solubility of cystine in urine varied with pH, the pH had to rise above pH 7.5 before a significant increase in solubility occurred. Initially they advocated treatment with alkalis but when they reviewed their patients 10 years later (Dent *et al.*, 1965) they reported that most of their patients found the amount of alkali unacceptable. This was because it meant an intake of 10–30 g sodium bicarbonate each day and they therefore no longer advocated its routine use.

High fluid intake: Although Bartels had recommended the administration of abundant fluids to reduce the urinary sediment of cystine in 1863, his suggestion was not generally accepted until after Dent and Senior's work in 1955, which showed that a high fluid regime (3–5 L/24 h) was successful, both in preventing new stone formation and in dissolving stones already present. However, to be effective it was essential to spread this intake evenly through the 24 h period so as to maintain a urinary output of at least 2 ml/min for each 4 h period and this included drinking two glasses of water on retiring to bed and two more glasses during the night at 02.00h. In spite of the inconvenience of this regime Dent *et al.* (1965) were able to

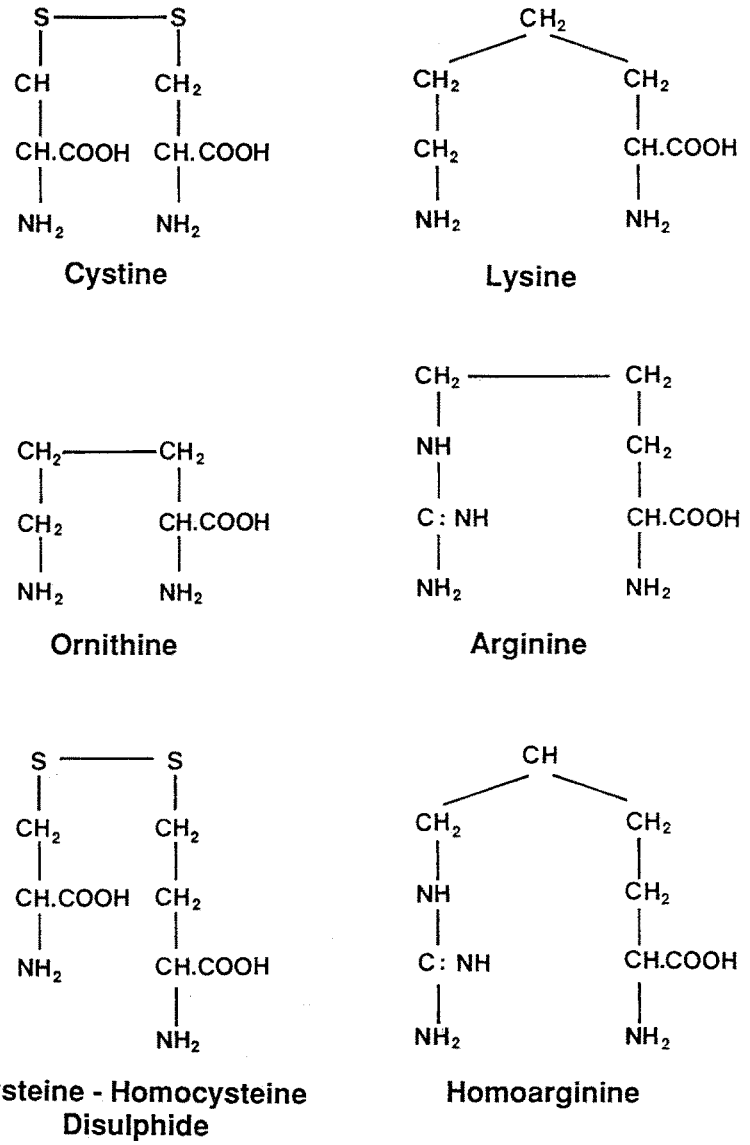

Figure 1 The structural formulae of the dibasic amino acids which are excreted in abnormal amounts in cystinuria. The figure shows the similarities in structure, each amino acid having at least two amino groups separated by 4–7 carbon or sulphur atoms

show in a 10-year follow-up that this treatment had been successful in 80% of their patients. However, other workers have not had such a high success rate; Harrison (personal communication, 1974), for example, claimed only a 25% success rate for the high fluid regime.

Penicillamine: Treatment of cystinuria with the sulphydryl amino acid penicilla-

mine was first suggested personally by Walshe in 1957, who had recently introduced it as a metal chelator in the treatment of Wilson's disease, but its clinical use had to await the work of Crawhall and his colleagues, who described their initial treatment of two cystinuric patients with D(−)penicillamine in 1963. They showed that, following the administration of penicillamine, the urinary 'free' cystine fell and could be reduced to levels below the concentration at which cystine precipitated. They also showed that the cystine was replaced by the mixed disulphide:

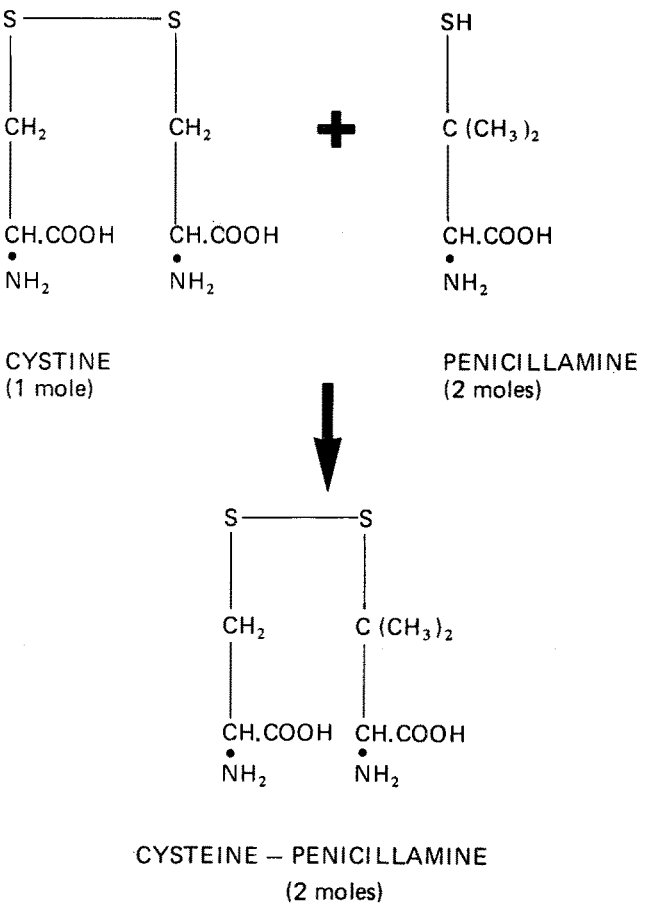

Figure 2 Formulae to show the combination of cystine with penicillamine to form the mixed disulphide: 'cysteine-penicillamine disulphide'

cysteine-penicillamine disulphide (Figure 2) which was much more soluble than the original cystine. Further work was reported by the same group in 1964 and soon confirmed by other workers (Lotz and Potts, 1964; King and Boyce, 1965). Within a few years dissolution of stones had also been reported in cystinuric patients taking penicillamine (McDonald and Henneman, 1965; Lotz *et al.*, 1965; Crawhall *et al.*,

1967; Frimpter, 1968). L(−)penicillamine and DL(−)penicillamine should not be used since L(−)penicillamine is more toxic than the D(−)penicillamine due to its effect on pyridoxine metabolism (Gibbs and Watts, 1969).

N-acetyl-D-penicillamine: *N*-acetyl-D-penicillamine was introduced by Stokes *et al.*, in 1968 (a,b) in the hope that it would have fewer side-effects than D-penicillamine, but a comparative study of the value of *N*-acetyl-D-penicillamine and D-penicillamine in the treatment of cystinuria showed that there was no significant advantage in the use of *N*-acetyl-D-penicillamine and that the incidence of side-effects was similar (Stephens and Watts, 1971).

TWENTY-FIVE YEARS EXPERIENCE AT ST. BARTHOLOMEW'S HOSPITAL

The quantitative data given below have mainly been obtained by studying 38 patients with cystinuria over the last 25 years at St. Bartholomew's Hospital and supplemented as indicated by data from the literature.

Clinical presentation

Cystinuria typically presents with the same symptoms and signs as other urinary tract stones. A total of 25% of patients present before the age of 10 years and a further 50% between the ages of 10 and 20 years. However, in spite of the fact that this is an inherited disorder, some 25% of patients do not present until after the age of 20 and some patients may reach old age before they get their first symptom

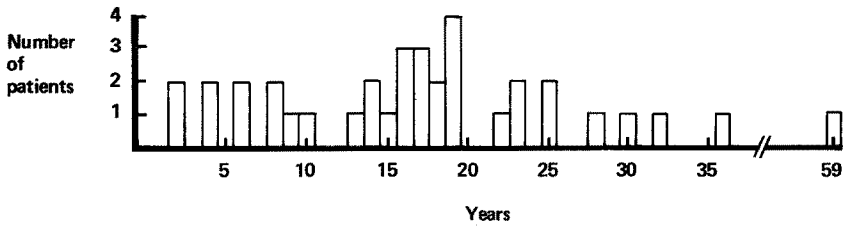

Figure 3 Histogram showing the age of these cystinuric patients when they had their first symptom of stone disease

(see Figure 3). Although most patients present with typical urinary colic, some present as acute right iliac fossa pain, similar to appendicitis and it is often only when the same pain recurs after appendicectomy that someone considers urinary tract stone disease as the cause of the pain. A few patients present as recurrent sterile cystitis and may have treatment for many years for apparent urinary tract infections before an alert microbiologist recognizes the typical hexagonal crystals in the urinary deposit and suggests cystinuria as a diagnosis. For these reasons there is often a long delay between the occurrence of the first symptom and the diagnosis (Figure 4) and in some people the symptoms only develop when they live in hot climates and become dehydrated.

Cystinuria is an uncommon, but not a rare cause of urinary stone disease, since

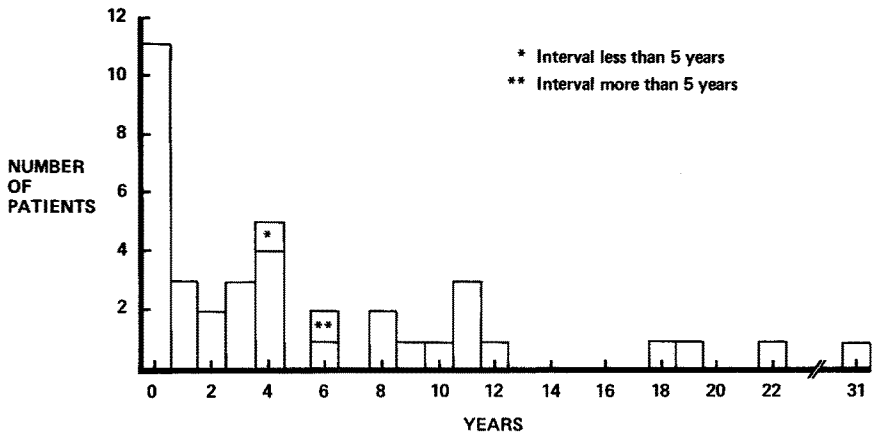

Figure 4 Histogram showing the time interval between the first symptom of stone disease and the diagnosis of cystinuria

it is said to occur in 1 in 20 000 of the population and accounts for approximately 2% of urinary stones (Herring, 1962; Gaches *et al.*, 1975; Williams and Chisholm, 1976). Since many casualty departments see at least two cases of urinary tract stones every week, most casualty departments will see a case of cystinuria at least once a year, although the diagnosis is frequently missed, because no one thinks of the diagnosis and hence no one does the appropriate tests. In 1966 Crawhall and colleagues tested 1060 patients attending a general medical outpatient clinic and found five who excreted excessive amounts of cystine in their urine. Harris (1955a,b) showed that 'completely recessive' cystinurics are twice as common as incompletely recessive (and hence detectable) cystinurics and the combination of these two sets of data would indicate an incidence of 1 : 18 000 in that population. The best screening test is the nitroprusside test, described by Brand in 1930. This only requires a few drops of unacidified urine and will rarely give false-positive or false-negative results, unless the urine is extremely dilute or acidified, which would then result in a false-negative result. For these reasons it is usually recommended that an unacidified early morning urine specimen is used for this test. False-positives can occur if the patient is receiving very large doses of penicillin or penicillin-like antibiotics (D. Perrett, 1989, personal communication) in homocystinuria, or if there is a high concentration of urate in the urine. Confirmation of the diagnosis requires qualitative amino acid chromatography to show the excessive excretion of the diamino acids, cystine, ornithine, lysine and arginine. Quantitative amino acid analysis is unnecessary for the diagnosis of cystinuria, but can be very useful in assessing the appropriate dose of penicillamine, and, since penicillamine can be quantitated, it is also a useful technique to assess patient compliance with their medication regime.

Cystine stones are typically golden yellow in colour and may vary in size from gravel weighing a few milligrams up to staghorn stones weighing up to 65 g. Analysis of stones in cystinuric patients shows most to be composed almost entirely of

cystine, but some cystinurics may have a second cause such as infection, leading to triple phosphate stones or idiopathic hypercalcuria leading to calcium stones.

Cystine stones are radio-opaque and have a similar X-ray density to triple phosphate 'infective stones'. They have been well described as being of ground glass appearance or of similar appearance to that produced by a piece of chalk wiped sideways across a blackboard. We now know that the radiodensity is related to the third power of the atomic number of the elements comprising the stone

Table 1 Comparative attenuation of substances to X-rays

Substance	$\bar{Z}$	$\bar{Z}^3$	$\bar{Z}^3$ *relative to water*
Fat	6.0	216	0.53
Uric acid	6.9	329	0.81
Water	7.4	405	1.00
Muscle	7.7	457	1.13
$Mg(NH_4)PO_4.6H_2O$	9.6	883	2.18
$MgHPO_4.2H_2O$	10.7	1241	3.06
Cystine	10.8	1260	3.11
$Ca(COO)_2.2H_2O$	12.5	1936	4.78
$Ca(COO)_2.H_2O$	13.5	2474	6.11
Bone	13.8	2628	6.49
$CaHPO_4.2H_2O$	13.9	2673	6.60
$CaHPO_4$	15.0	3338	8.24

The radiodensity is proportional to the cube of the effective atomic number ($\bar{Z}$). Effective atomic numbers ($\bar{Z}$) for fat, muscle and bone at 40 keV are taken from White (1977) and White and Fitzgerald (1977). The remainder were calculated from the formula by White (personal communication)

(Table 1) and hence it is the sulphur in cystine which results in the radiodensity. Unfortunately some urology and radiology textbooks incorrectly describe cystine stones as being radiolucent and this has led to many missed diagnoses. Some such textbooks have even stated that any density present is due to 'contamination with sulphur'. However, it is hard to accept that constituent parts of a molecule should be classified as contamination!

Clinical management

The only clinical symptoms of cystinuria are those which result from urinary tract stones. The management of acute situations, such as urinary tract pain and/or obstruction, is the same as for all other urinary tract stones. If pain is present it must be adequately controlled, if obstruction is present it must be relieved. However, if there is neither pain nor acute obstruction there is no urgency to pursue active treatment and an individual treatment regime can be planned and agreed for each patient.

If no stones are present, then the only requirement is to keep the urine dilute enough so as to ensure that the cystine stays in solution. Some patients, probably about 50%, can drink sufficient water at regular intervals throughout the day and

night to achieve such a dilute urine. Dent and Senior (1955) and Dent *et al.* (1965) showed that an intake of 2 ml per minute (approximately 1 pint) over each 4-h period was an adequate amount for most individuals. Although many individuals can achieve this for part of the day, many cannot maintain it on a regular basis and therefore form cystine stones or gravel or crystals. In these cases other measures need to be tried and penicillamine should be considered, since it can combine with cystine (Figure 4) and make it about 50 times more soluble so that the cystine no longer precipitates and forms stones. In many individuals a satisfactory regime is water-based fluids during the daytime, combined with penicillamine (500–1000 mg) on retiring to bed in the evening. In a few people a more active regime is required and this is also needed if stones are present. In these situations 500–1000 mg of penicillamine 8-hourly, associated with whatever oral fluids the patient can manage, will usually prove satisfactory. Such a regime can prevent new stone formation and in many cases it will also dissolve stones already present. When treating patients prophylactically it is helpful to aim for a urinary concentration of 'free' cystine of 300 mg/L (or 1.25 mmol/L). If the aim of treatment is to dissolve stones then a urinary 'free' cystine concentration of 200 mg/L (0.8 mmol/L) should be the goal.

Treatment failures are uncommon with penicillamine therapy and are usually due to lack of compliance on the part of the patient. Apparent failures can occur if a patient also has another cause for urinary stones such as infection or idiopathic hypercalcuria since, although the penicillamine therapy can successfully control the cystinuria, it can do nothing for the triple phosphate infective stones or calcium stones.

Like penicillamine treatment in Wilson's disease, but unlike penicillamine treatment in rheumatoid arthritis, there seems to be no advantage in introducing penicillamine slowly and a dose of 3 g per day can be reached within 2–3 weeks or even on the first day or two of treatment. If the dose is gradually increased every 2–3 days and the urine is analysed quantitatively for cystine, it is possible to select the dose of penicillamine that is most appropriate for each individual patient. However, in view of the chemical similarity between penicillamine and cystine and the fact that mixed disulphides such as cysteine-penicillamine disulphide will also be present in the urine, the only analytical technique that is suitable for monitoring the free cystine in the urine is column chromatography (such as HPLC or an amino acid analyser). This analyser will also need a suitable buffer gradient to ensure the adequate separation of these similar disulphide compounds, because it is only the free cystine that needs to be quantitated. Most colour reagents will react in a similar fashion with cystine, cysteine-penicillamine and penicillamine disulphide. However, for most patients the penicillamine dose can be judged arbitrarily, but if an adequate clinical result is difficult to achieve, quantitation of the cystine, cysteine-penicillamine and penicillamine can be very helpful, since it will sometimes indicate that a patient is not taking the prescribed dose. Similar analysis is also useful to decide the minimum useful dosage, especially if a patient is experiencing adverse reactions to the penicillamine.

If patients take penicillamine regularly 1 g three times per day they will take approximately 1 kg each year, so that in a lifetime they are likely to have ingested

70 kg of penicillamine. It is therefore not surprising that there is a significant incidence of side-effects. Although side-effects are common with penicillamine therapy, they are rarely severe enough to warrant withdrawal of treatment when penicillamine is used in the treatment of cystinuria. When penicillamine is used in the treatment of rheumatoid arthritis, side-effects appear to be both more common and more serious, than when penicillamine is used in the treatment of cystinuria or Wilson's disease. When penicillamine is used in the treatment of cystinuria in the dose regime suggested above, it is common for patients (approximately 25%) to get a morbiliform rash, often associated with mild pyrexia, 10–14 days after commencing treatment. This rash is not an indication for withdrawal of treatment and will usually disappear within 2–3 days, even if treatment is continued at the same dosage. In a few patients the rash will be urticarial and it is then usually necessary to withdraw treatment for a few days until the rash has disappeared. In this situation treatment can usually be recommenced under steroid cover, which itself can be withdrawn within 2 weeks, without recurrence of the rash. About 20% of patients will get a later rash and although many different late rashes have been described, the commonest one is usually termed penicillamine dermopathy, although it has been called epidermolysis bullosa and in this group of patients occurred 2–15 years after starting treatment. It did not appear to be related to the dose of penicillamine. This rash is not an indication for withdrawal of treatment with penicillamine and some patients have had the rash for several years before commenting on it to a doctor. This rash may regress or even disappear completely either if the penicillamine is continued or if it is stopped.

Proteinuria is common and occurs in approximately 25% of cystinurics treated with penicillamine. From a clinical point of view it is useful to subdivide patients with proteinuria into three groups; mild, those with less than 1 g/24 h; moderate, those with 1–5 g/24 h and severe, those with more than 5 g/24 h. In the group of patients studied it is interesting that if a patient was found in one of these groups the proteinuria has never developed into one of the more severe groups. Proteinuria of less than 1 g/24 h was associated with urinary tract infection or stone. Proteinuria between 1 and 5 g/24 h appears to be associated with the penicillamine therapy and usually remains at a similar level as long as the penicillamine is continued and does not appear to be associated with any long-term clinical harm. Severe proteinuria has occurred in four patients (11–19 g/24 h) and in two of them it was associated with a nephrotic syndrome. In all four patients the penicillamine was discontinued and in all four patients the proteinuria disappeared over a period of several months. It is thought that proteinuria of more than 1 g/24 h is due to an immune mechanism. But it is interesting that, after 2 years without penicillamine, the patient who had had 19 g/24 h proteinuria was restarted on penicillamine and this patient has since had penicillamine at a dose of 2 g/24 h for 5 years and does not have any proteinuria (when he developed massive proteinuria his dose of penicillamine had been 3 g/24 h). We therefore believe that it is reasonable to continue penicillamine treatment unless the proteinuria is more than 5 g/24 h and several patients have now been maintained on this regime for several years, in spite of continuing to excrete protein in the 1–5 g/24 h range.

No serious haematological side-effects have been noticed in this group of patients treated with penicillamine, but in one patient the platelet count fell to 100×10^9/L 10 days after starting penicillamine. However, it returned to the normal range the next day without any change in penicillamine dosage.

Other thiol drugs may be useful as an alternative to penicillamine and 2-mercaptopropionyl glycine (Thiola®) is an example of such a drug. Initial reports suggested a low incidence of side-effects, but it has since been shown to have similar side-effects to penicillamine and it is likely that all thiol drugs will have similar side-effects.

If medical treatment fails or if stones are present and it is thought that it will take too long to dissolve them, then surgical treatment should be considered. Traditional surgical procedures can be used to remove cystine stones, but the recent introduction of percutaneous and extracorporeal lithotripsy has simplified the procedure, in the same way as it has for patients with other types of urinary stone disease. This is a relatively new technique and different surgeons have had different degrees of success with this technique. One explanation of some of the difficulties encountered may be the regular crystal structure of pure cystine stones. Since cystinuria is due to an inherited transport defect in the renal tubule, a successful renal transplant would result in a permanent 'cure' of the condition, as long as the patient also undergoes a bilateral nephrectomy.

CONCLUSION

Although cystinuria is an inherited condition, there is considerable variation from one patient to another of both the age at which the first symptom occurs and of the frequency at which the stones and gravel develop. If stone formation can be prevented the affected individuals can expect to have a normal life. A large proportion of affected people can prevent stone formation by maintaining a regular, high fluid intake of approximately 1 pint every 4 hours but others require more active treatment. Oral D(−)penicillamine is a satisfactory way of preventing stone formation if a high fluid intake is unsuccessful or in those people who find that they cannot maintain a high fluid intake. Penicillamine therapy is often associated with side-effects but it has now been used in the treatment of cystinuria for more than 25 years so that both the incidence of side-effects and their management is reasonably well documented. As with other urinary tract stones, surgical treatment and lithotripsy are sometimes indicated and in the future renal transplantation may be considered in exceptional cases since bilateral nephrectomy together with successful renal transplantation would result in a 'cure'.

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