Contents

PART 1

WHAT IS XANTHINURIA AND HOW DO WE DIAGNOSE IT?

Dr Anne Simmonds

Xanthinuria simply means an excess of xanthine in the urine. But what is xanthine, where does it come from and how and why does it accumulate?

Xanthine is a purine, the immediate precursor of our old *"gouty friend"* uric acid. In humans and other primates uric acid forms the end-product of the breakdown of our purine nucleotides, whilst all other mammals break uric acid down further to a soluble compound, allantoin. Purine nucleotides are not only the chemical structures linked to pyrimidine nucleotides in the double helix of our DNA and RNA which not only form and express the genes controlling everything in the body, but also make up the largest single purine pool in our body, namely ATP. ATP is the vital energy-rich compound turned over daily during muscle work. Other nucleotides are also degraded to the corresponding base during the response of white blood cells to infection, or following the death of red blood cells, which have a short life span of 120 days.
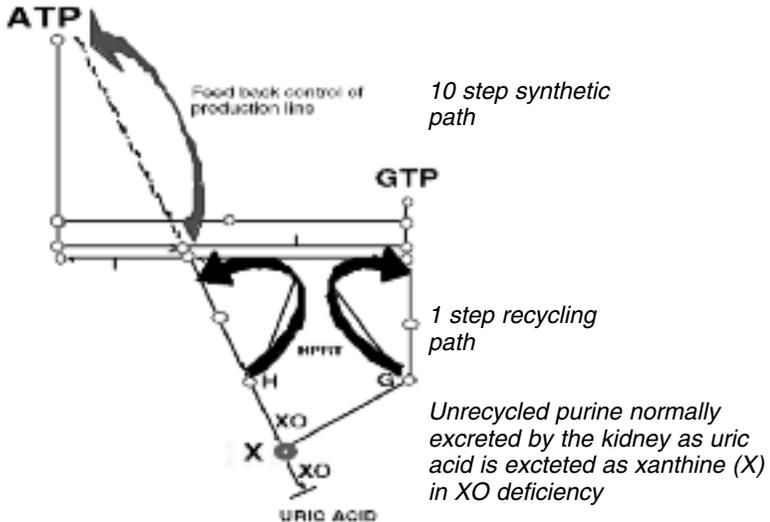
The concentration of xanthine in urine is normally extremely low because it is converted immediately to uric acid - the normal end-product of purine metabolism in humans as mentioned above - by the enzyme xanthine oxidase (XO). XO is found principally to the liver and intestinal lining in humans (unlike rodents where it is found in most tissues). The location in humans is considered to be of evolutionary origin, in that it helps protect us from foreign purine-like compounds in our diet by ensuring that after crossing our intestinal barrier dietary purines are already broken down to uric acid by XO when entering the blood stream.

Purines made within our body (endogenous purines) are used to supply our vital energy needs (ATP) and our genetic code (DNA). All are normally broken down to hypoxanthine (or guanine) and recycled, as shown in Fig 1. Endogenous purines, not recycled, are transported to the liver and thence degraded to uric acid that is excreted in the urine. This last step in the chain prior to uric acid formation is controlled by XO

(Fig 1). Consequently, when XO is defective as in a hereditary disorder, or ineffective for any reason, xanthine (X) accumulates in place of uric acid.

Role of XO in humans

10 step synthetic path

1 step recycling path

Unrecycled purine normally excreted by the kidney as uric acid is excteted as xanthine (X) in XO deficiency

There are three types of hereditary xanthinuria

Classical xanthinuria has two forms: An **isolated deficiency of XO (Type 1 deficiency),** or a **dual deficiency (Type 2),** in which a very similar enzyme, aldehyde oxidase (AOX), is deficient as well.

Both types are identical in terms of how they cause problems or come to notice, and are generally benign in terms of survival.

Severe life-threatening problems generally occur only in the rare **Type 3**, known as **Molybdenum co-factor deficiency,** where an additional enzyme - **sulphite oxidase** - is also inactive.

Patients inheriting xanthinuria Types 1 or 2 can present at any age from a few months to more than 70 years. Presentation is usually with xanthine stones, xanthine crystals in the urine or acute kidney failure. Unrecognised any of these can lead to end-stage renal disease, with perhaps a need for dialysis treatment, surgical removal of a kidney or even death. Conversely, at least 50% of xanthinuric subjects may remain asymptomatic throughout life.

Why do such serious kidney problems sometimes arise in hereditary XO deficiency? The basic problem is that xanthine is even more insoluble than uric acid in body fluids, including urine. Moreover, unlike uric acid, whose solubility can be increased ten-fold by making the urine more alkaline, xanthine solubility is not altered by this manoeuvre. Another difference is that xanthine, again unlike uric acid, is also cleared very effectively by the human kidney into the urine. As a result plasma levels are very low and urine levels are correspondingly high, which increases the tendency for xanthine stones to form in the kidney or urinary tract.

Fig 2

Interestingly, xanthine was first reported as the component of a human kidney stone by a Swiss chemist, Marcet (Fig 2), working at Guy's Hospital in 1817, and these stones are still in the Gordon Museum at Guy's. In 1838 two German chemists (Wöhler and Liebig) reportedly obtained the "larger half" of one of these stones and compared it with uric acid. They suggested it was a close relative with one less oxygen atom - normally a minor constituent of urine, which under some unusual circumstance had given rise to a calculus! Thus xanthinuria was first proposed.

The next report of severe xanthine stone formation was in the kidneys of sheep in New Zealand's South Island in the 1930's. The cause here was found to be a deficit in the local soil of the vital trace element - Molybdenum (Mo). As we will hear later, Mo is an essential co-factor for XO. Deficient functioning of XO in the absence of Mo in the diet, thus explained the accumulation of xanthine instead of uric acid (or in the case of the sheep, instead of the more soluble allantoin, because unlike humans, all other mammals possess the enzyme uricase and thus escape the problems excess uric acid causes).

The first case of xanthinuria in Man was reported a quarter of a century later in London by the clinicians Dent & Philpott (1954). They treated a 4 year old girl, who passed a kidney stone weighing 1g, and subsequently found it to consist of pure xanthine. Xanthinuria was thus the first genetic disorder of purine metabolism ever found and preceded the recognition of the next genetic metabolic purine disorder- the

devastating Lesch-Nyhan disease (LND, reported in 1964) - by ten years. As PUMPA members may recall, LND was the subject of our first booklet in this series.

Diagnosis and treatment.

Absolute confirmation of a defect in XO would require the removal of tissue to analyse the enzyme's activity. Since the enzyme is, in humans, only found the intestinal lining, or in the liver, an intrusive biopsy (surgical or needle removal) is needed but rarely if ever done: diagnosis usually depends on the findings of a low to absent uric acid in plasma and urine, replaced in the urine by xanthine (and to a lesser extent by the closely-related hypoxanthine) in a ratio of approximately 4:1. The preferential accumulation of xanthine results from the extensive removal by recycling of hypoxanthine by the enzyme HPRT, as already mentioned, for which xanthine in not a substrate (Fig 1).

Pitfalls in diagnosis can be caused by bacterial infection which can result in significant uric acid being found in the urine due to degradation of xanthine to uric acid. Measurement of both plasma and urine uric acid is thus essential.

THE CLINICAL CONSEQUENCES OF XANTHINURIA

Prof J Stewart Cameron

We have heard that a deficiency of xanthine oxidase (XO) in humans, whether hereditary, or as a result of treatment with allopurinol or similar drugs (as we describe later) results in the accumulation of xanthine, not uric acid as the end-product of purine metabolism. The resulting problems are due to the high clearance of xanthine by the kidney (up to 100%, see Fig 3) compared with uric acid, which as mentioned in our FJHN booklet, is largely reabsorbed in the tubule, with only around 10%being excreted in the urine.

Fig 3

XANTHINE HANDLING BY THE HUMAN KIDNEY
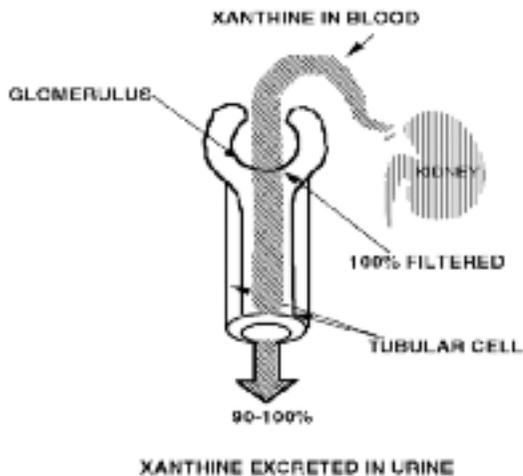
Xanthine thus is present at high concentration in the ureters and urine, and because of its poor solubility precipitates out readily, especially in hot climates where urine volumes are small and urine very concentrated. The high clearance of xanthine, compared with uric acid, explains the presence in the urine in excess of this highly insoluble purine, resulting in very low plasma levels.

In the case of the four year old girl, diagnosed in London, mild reduction in kidney function and "clubbing" (blunting) of the calyces draining from the kidney was noted

at the time of diagnosis. Fortunately the damage to the kidneys had progressed no further in several later reports, due to the maintenance of a high fluid intake. **Thus XOD is not a potentially serious disorder if diagnosed sufficiently early** and a high fluid intake is maintained. Although the problems associated with xanthine accumulation almost always lie in the kidneys or urinary tract, very high concentrations in the blood occasionally may lead to joint or muscle problems from deposition of xanthine at these sites.

A classic example of the additional role of climate in the formation of poorly soluble purine end products is a patient from the Mediterranean area, who lost a left kidney in Lebanon because of kidney stones - the composition of which was not determined at the time. A subsequent occurrence of renal colic in Britain led to a further admission to a Renal Unit and the passing of stones by the remaining kidney, at which time a very low, not high, plasma uric acid was noted. The stones when analysed at Guy's were found to consist of pure xanthine, not uric acid. Sadly, renal failure was already very severe and despite haemodialysis the patient did not survive, underlining the importance of early diagnosis of xanthinuria.

Although 50% of xanthinuric patients are asymptomatic and xanthinuria is relatively benign, the above case demonstrates that it can be a potentially fatal disorder if not recognised and treated early. Although xanthinuria may come to attention later in life, even old age - or not at all - in 40% problems become evident in childhood. These include pain from passing stones (renal colic), obstruction, infections, blood in the urine, or just general irritability and ill-health.

As noted above, confirmation of the enzyme defect would require intrusive intestinal or liver biopsy, and is rarely, if ever, done. Consequently, diagnosis depends on the finding of xanthine replacing uric acid in the urine. A high fluid intake and low purine diet is the only treatment. Presentation after dehydration (e.g. diarrhoea), infection, or intense physical activity is common. Vigorous exercise should be avoided. An internationally competitive German cyclist found to be xanthinuric overcame his problem by carrying bottles of water which he drank at intervals en route.

Fig 4.

HOW IS XANTHINURIA INHERITED?

Prof J Stewart Cameron

Our DNA is arranged in chromosomes within the nucleus of our cells. Each chromosome has one copy - a pair. This DNA within each cell forms part of a huge set of messages within a giant library of 'books' (chromosomes) containing three billion "letters" (purine and pyrimidine bases) - about a billion "words" in total, which form the long strings which make up each chromosome. Along this string of DNA are found approximately 24,000 messages, or genes, each of which is the instruction for making a particular protein. The gene coding for the protein of XOD is found on the short arm of chromosome 2 (at 22p23), out of the 23 pairs of chromosomes we all have (see *Marinaki* below for details).

Fig 5

XOD PASSES VIA BOTH PARENTS TO 1 IN 4 OF THEIR CHILDREN
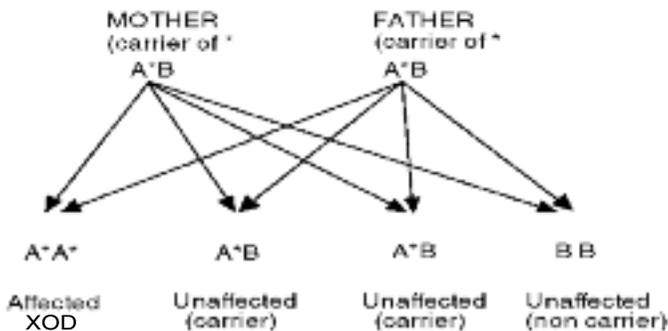
One gene in each pair of genes in every cell of every tissue in all of us comes from our mother, the other from our father. In XOD a person with one chromosome bearing the defect (Figure 4) and one normal chromosome will be a carrier, capable of passing on the defect, but without any problems themselves. However, if two carriers have children, there is the possibility that some children may receive **two** copies of the defective gene (one from each parent) and thus be unable to make normal XO, thereby inheriting XOD. The chance of any one child doing this is one in four, whilst the chance of being a carrier like their parents is one in 2. Thus xanthinuria is called a "recessive" disorder: there may be a history of previously

affected individuals in the family, but there may not be, especially as there is about a 30% possibility that the defect on one of the two chromosomes in the cells of either parent is a random alteration in the DNA - a new mutation.

Thus also, if an individual who has xanthinuria has children with a normal partner, half their children liable to be carriers. But if they are unlucky and have another carrier for xanthinuria as partner, one quarter of their children could have the disease (Fig 5).

HOW DO WE DIAGNOSE XANTHINURIA IN THE LABORATORY?

Prof David Perrett

Humans frequently form renal calculi. They can occur at any age and are particularly associated with kidney infections, and of course dehydration. To date over 200 different chemical compounds have been found in renal stones. The vast majority of renal stones (99%) are mixtures of inorganic compounds such as calcium and in chemical terms, similar to the fur inside kettles. For over 200 years the commonest method to determine the chemical nature of a stone was to grind it up and then use commonplace chemical analysis procedures such as simple colour test for salts etc. Unlike inorganic materials, stones made of organic matter, such as uric acid or xanthine, entirely burn away in a flame. Further tests can help distinguish which material they are made of. One of these tests is the Murexide test. Murexide is a purple compound discovered by Karl Scheele (1742-1786) in Sweden in 1776. He obtained uric acid from human calculi, hence his name for it: lithic acid (Greek: *lithos* = stone). Murexide is formed by treating uric acid successively with nitric acid and ammonia. If the stone is urate then the residue turns purple (Murexide). As Marcet found in 1817 if a stone contains xanthine then the residue turns red, but only on warming.

Xanthinuria was not only the first genetic purine disorder ever recognised, it was also the first genetic purine disorder to be diagnosed in the 1950's using the then new technique of paper chromatography by Dent & Philpott. A later diagnosis used the developing technology of Mass spectrometry. The diagnosis was made at St Bartholomew's Hospital in London by Richard Watts and staff when studying an athlete who had developed muscle cramps. The crystals found in the muscle at biopsy were examined and confirmed to be xanthine using an early prototype mass spectrometer, which filled the whole laboratory. Actually, xanthine crystals in muscle and muscle problems are rare in xanthinuria.

Considerable advances have taken place since then in the way purines such as xanthine, can be measured in the laboratory. Modern techniques now enable patients to be diagnosed speedily from the unusually high levels of xanthine excreted in their urine, compared with the low levels of uric acid, in their plasma. Paper chromatography has now been replaced by high performance liquid chromatography (abbreviated HPLC), and reversed phase liquid chromatography. These are accurate

automated instruments able to separate and quantify the large numbers of compounds in blood and urine. The first HPLC systems were developed in the early 1970's. Their sensitivity enabled the recognition of many more genetic purine disorders and started a boom in their diagnosis. The number of disorders now recognised is 29, some of which have been the focus of earlier PUMPA seminars. HPLC measurements in urine which will detect not only xanthinuria, but also any one of the 29 genetic metabolic disorders of nucleotide metabolism now known and in 30 minutes or less.

Mass spectrometers have also advanced considerably and are now small compact instruments. In addition they can be linked to HPLC systems. Other methods and machines have also been developed for identifying and diagnosing genetic disease. These range from Nuclear Magnetic resonance (NMR) instruments to molecular biological procedures.

However, for investigators in remote areas where expensive techniques may not be available, the first suspicion of xanthinuria in a patient with appropriate symptoms is the almost complete absence of uric acid from the blood or urine during routine hospital laboratory testing.

The absence of uric acid from both plasma and urine is the important clue. However, investigators need to be aware of the all the possible pitfalls. The urine must be warmed and shaken and examined carefully to ensure xanthine has not precipitated out. Severe bacterial contamination of the urine can also result in very low urinary uric acid levels. Consequently, plasma uric acid must be measured as well as urine uric acid, to confirm the near absence of uric acid in both. If possible, its replacement by xanthine should be confirmed by the above methods to establish the diagnosis of xanthinuria.

THE MOLECULAR DEFECT IN HEREDITARY XANTHINURIA

The human gene coding for xanthine oxidase (XO) has been mapped to the short arm of the second of our 23 pairs of chromosomes, namely chromosome 2p22-p23. However, what is called "genetic heterogeneity" has been demonstrated in xanthinuria based on the ability, or inability, of patients with XO deficiency to convert

the gout drug allopurinol to oxipurinol (see *Simmonds* below).

Patients with Type 1 XO deficiency are able to convert allopurinol to oxipurinol, whilst Type 2 patients cannot. This difference relates to the presence of a similar enzyme, called aldehyde oxidase (AOX) in Type 1 patients (up to 50% of cases). The remaining 50% are unable to convert allopurinol to oxipurinol, because they lack both AOX and XO and are classified as having Type 11 XO deficiency

Children inheriting a third type of xanthinuria, called molybdenum cofactor (MOCO) deficiency, by contrast, usually present neonatlly with severe neurological deficits, as well as kidney stones or gravel etc. Such cases have a combined deficiency of the enzymes, **sulfite oxidase**, xanthine oxidase and aldehyde oxidase. MOCO deficiency is usually a fatal neurological disorder and likewise has an autosomal recessive mode of inheritance. However, it is important to note that a family with much milder symptoms, presenting only in a girl at 5 years of age, has been reported in the UK.

Xanthinuria types I and II are both rare recessive disorders. The combined incidence has been reported to be between 1/6,000 and 1/69,000 people, being much higher around the Mediterranean due to the arid climate, as mentioned earlier.

IATROGENIC, OR MEDICALLY-INDUCED, XANTHINURIA

Anne Simmonds

The culprit in drug-induced xanthinuria is the anti-gout drug allopurinol, mentioned above. Allopurinol was first developed by Nobel Prize winners Gertrude Elion and George Hitchings as an anticancer drug, but reportedly 'flunked its clinical trials', and was put away on the shelf. Fortunately, it was noted, at that time, that allopurinol reduced the concentration of uric acid in the blood, and it was later retrieved for use in patients given other anticancer drugs that produced sharp increases in uric acid as a result of cell breakdown. Success in these patients resulted in the first clinical trials in subjects with hyperuricaemia associated with severe renal disease in the mid 1960s and subsequently in patients with intractable gout in the early 70s. Allopurinol has proved to be a very safe drug and is now sold around the world by the ton as the treatment of choice for gout. Reported side effects are extremely rare.

How allopurinol works

Allopurinol has a very similar chemical structure to that of hypoxanthine, with just a minor rearrangement of carbon and nitrogen atoms, as shown in Fig 6.

Fig 6

ALLOPURINOL   HYPOXANTHINE   XANTHINE   URIC ACID
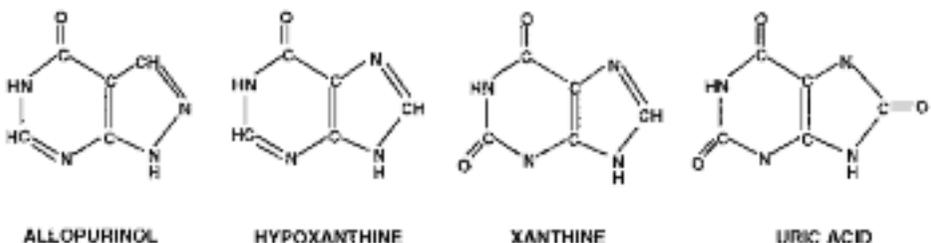
It is thus capable of binding to the active site of the XO enzyme just like hypoxanthine. However the enzyme does not recognise that allopurinol is not hypoxanthine, and the structural difference means XO cannot function properly. As a result XO is inhibited to varying degrees depending on the allopurinol dose - thereby lowering blood and urinary uric acid levels. The problem for gouty patients is that such inhibition leads to the accumulation of not only the benign and soluble hypoxanthine, but also the

even more *insoluble* xanthine which, as already mentioned, can itself cause severe kidney damage. As a result, xanthine nephropathy has been precipitated during aggressive therapy in patients with malignant disorders given too much allopurinol simultaneously to reduce the risk of uric acid nephropathy which results from the massive cell breakdown produced during chemotherapy!

PROBLEMS CAUSED BY ALLOPURINOL IN GENETIC DISORDERS OF PURINE METABOLISM

Our first booklet described Lesch-Nyhan disease (LND), which is associated with gross uric acid over-production due a deficiency of the salvage enzyme HPRT, resulting in the production and excretion of excess uric acid in the urine. Allopurinol is also used to control uric acid levels in LND. However, it must be used with extreme care to avoid the excess xanthine accumulation that can occur readily in such purine overproducers, in turn leading to kidney stones, or severe kidney disease. The same caution must apply to its use in FJHN, a disorder where kidney function is already compromised, as discussed in our earlier booklet (see Caring for Patients with FJHN).

Patients with pre-existing kidney disease and reduced kidney function are also a special case, and here too allopurinol must be *used with extreme care* and the dose reduced (to as little as 100mg on alternate days) depending on renal function. The reason for such caution is that the accumulation of oxipurinol (the active molecule to which allopurinol is converted by XO in patients with severe renal disease) can sometimes lead to severe bone marrow depression. This is because oxipurinol resembles hypoxanthine enough to interfere at high dosages with its incorporation into DNA, which is essential for the supply of new cells which are produced in huge quantities every day from the bone marrow.

HETEROGENEITY IN XANTHINURIA

Two types of defect (Types 1 and 2) have been revealed in patients given allopurinol, as discussed above. - Type 1 patients lack only XO. Type 2 patients have a double deficiency of both xanthine oxidase (XO) and aldehyde oxidase (AOX). Both types of patients have normal activity of sulphite oxidase (SO), the enzyme which is also deficient in patients with Molybdenum co-factor (MOCO) deficiency.

NEW URIC ACID LOWERING AGENTS WHICH INHIBIT XO

Stewart Cameron

In 1993 a new compound that turned out to be a potent inhibitor of XO, was synthesised in Japan. It was a member of a group of chemical substances know as thiazoles and surprisingly bore no resemblance to the normal substrate for XO, hypoxanthine (see Figure 6). Subsequently it has been developed as a hypouricaemic agent under the name of febuxostat, and has proved to be at least as effective as allopurinol in lowering uric acid concentrations, with a similar low incidence of side effects. Although, as expected, it leads to an accumulation of xanthine (and the innocuous hypoxanthine), it appears from animal work that febuxostat is less prone to lead to stone formation, which would be an advantage if true in humans. One advantage that febuxostat does have over allopurinol is that it can be given to those with kidney disease and reduced renal function in the same dose as to normal people, as its excretion depends little on the level of kidney function. It may well prove to be widely used in the future.

Summary

Inherited xanthine oxidase deficiency, or xanthinuria, was first reported by Dent and Philpott in 1954. Two types of xanthinuria (Types I and II) have been demonstrated since that time in xanthinuric patients given allopurinol as follows:

a) Classical xanthinuria type I, where XO activity alone is lacking,

b) Xanthinuria type II, where a similar enzyme, AOX, is deficient together with XO.

However, both types of xanthinuria have normal activity of SO, the enzyme missing, together with the above two enzymes, in patients inheriting molybdenum cofactor (MOCO) deficiency

Xanthinuria Types I and II are rare autosomal recessive disorders. The combined incidence has been reported to be 1/69,000. Affected individuals may develop kidney stones, acute, or chronic kidney failure, as well as muscle inflammation (myositis) due to deposition of xanthine in muscle tissue.

However, up to 50% of subjects inheriting XO deficiency may remain asymptomatic throughout life, providing they do not live in hot climates.

The human gene for XO maps to chromosome 2p22-p23, that for MOCO to chromosome18q12.2

The most effective treatment, when renal function is normal, is a high fluid intake!

INSTRUCTIONS FOR A LOW PURINE/CAFFEINE FREE DIET

The instructions below apply to the collection of samples for purine investigations, but it may be helpful to parents to know which foods are rich in purines and thus should be avoided when preparing meals.

For purine studies it is advisable to try to eat a diet identical with your normal diet in terms of butter, fats, bread potatoes and other vegetables etc, but avoid the meat, fish and other food and drink outlined below with a high purine content in Section 1, and substitute a low purine equivalent from section 2 and 3.

1. Food and beverages not allowed

1.1   OFFAL - sweetbreads, heart, liver, kidney, and pate.

1.2   SEAFOOD - Sardines, sprats, herring, bloaters, fish roe, trout or salmon. Lobster, crab, prawns, oysters, cockles, mussels etc.

1.3.   VEGETABLES - Asparagus, avocado pears, peas, spinach, mushrooms, broad beans, cauliflower.

1.4   Soya products, pulses and legumes.

1.5   Alcoholic beverages (beer) and yeast extracts. Meat or vegetable extracts (Marmite, Vegemite, Bovril etc).

1.6   Tea, coffee (other than decaffeinated); cocoa products such as Ovaltine, chocolate or chocolate biscuits, chocolate puddings; and Coca-Cola, Pepsi-Cola, or Lucozade.

(NB 1.6 only refers to diet when samples are being collected for the laboratory. These foods and beverages all contain methylated xanthines, which make analysis difficult in the laboratory)

2. Foods and beverages allowed

2.1   Milk, cheese, eggs, butter, margarine, cream, ice cream

2.2   Bread, flour, cakes, scones, biscuits, cereals.

2.3   Sugar, jam, marmalade, honey and sweets.

2.4   Lettuce and tomato (e.g.: salads).

2.5   Fresh, cooked or tinned fruits, nuts.

2.6   Puddings (milk etc), except those containing chocolate/cocoa.

2.7   Decaffeinated coffee or tea.

2.8   Fruit juices, soft drinks EXCEPT Coca-Cola etc.

3. Foods allowed in moderation (one meal per day)

3.1   Beef, lamb or mutton, port, bacon, ham, poultry, sausages, tongue, and meat soups.

3.2   Small helpings of vegetables (except those in 1) carrots, potatoes, leeks, cabbage, brussel sprouts, runner and French beans, marrow, courgettes.

3.3   Fish (except those in 1)

SUGGESTIONS FOR FURTHER READING

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- these articles in turn contain details of a large number of other papers, and chapters in books, on the subject of kidney stones.

CONTACT ADDRESSES FOR FURTHER HELP

Information and support:

Mrs Joan Martin, Patient support group, PUMPA, Southlands, Keymer Road, Burgess Hill, West Sussex RH15 OAN tel: 01444 248 581.

The Purine Metabolic Patients Association (PUMPA), Purine Research Laboratory, 5th Floor Thomas Guy House, Guy's Hospital, London Bridge SE1 9RT or www.pumpa.org

Dr Lynette Fairbanks, Dr Tony Marinaki, or Dr. Anne Simmonds, Purine Research Laboratory, 5th Floor Thomas Guy House, Guy's Hospital, London Bridge SE1 9RT tel: O2O7 188 1276, fax: O2O7 188 128O. E-mail: lynette.fairbanks□kcl.ac.uk

Information and support (including financial grants, or grants in kind to patients with kidney diseases and their families):

NKRF: National Kidney Research Fund, King's Chambers, Priestgate, Peterborough PE1 1FG. www.nkrf.org.uk.

Helpline: O845 3OO 1499 or text to O7786 2OO 5O5, or helpline□nkr.org.uk

BKPA: British Kidney Patients association. President: Elizabeth Ward. Address: Bordon Hants GU35 9JZ. Tel: O142O 472O21 Fax: O132O 475831

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