12.4 Disorders of purine and pyrimidine metabolism

12.4 Disorders of purine and pyrimidine metabolism 2015

ESSENTIALS These disorders are due to abnormalities in the biosynthesis, inter- conversion, and degradation of the purines—adenine and guanine— and of the pyrimidines—cytosine, thymine, and uracil. All are heterocyclic bases which exist in tri-, di-, and monophosphorylated forms, and as either deoxyribosylated or ribosylated derivatives (de- oxyribose and ribose are pentose carbohydrates). The phosphor- ylated deoxyribosylated and ribosylated derivatives are termed ‘nucleotides’, and the purely ribosylated derivatives, which lack the phosphate group, are ‘nucleosides’. The purine nucleotides, their cyclic derivatives (cAMP and cGMP), and their more highly phosphorylated derivatives have functions in many aspects of intermediary metabolism. Purine compounds also function as signal transducers, neurotransmitters, vasodilators, and mediators of platelet aggregation. The polynucleotide deoxyribonucleic acid (DNA) contains equimolar amounts of adenosine monophosphate (adenylic acid, AMP), guanosine monophosphate (guanylic acid, GMP), thymidine monophosphate (thymidylic acid, TMP), and cytidine monophosphate (cytidylic acid, CMP). Uridine monophosphate (uridylic acid, UMP) re- places TMP in the polynucleotide ribonucleic acid (RNA). Disorders of purine metabolism The end point of purine metabolism in humans is uric acid. When uric acid levels become supersaturated in body fluids, uric acid and sodium urate monohydrate crystallize, causing gout. This re- sults from either overproduction or underexcretion of urate, or from a combination of these defects. Decreased net tubular urate secretion is most often due to genetic polymorphism in uric acid transporters and is the most common cause of primary (‘idiopathic’) gout. Gout may be secondary to a wide variety of renal disorders, ranging from simple reduction in glomerular filtration rate (chronic kidney disease) to specific defects, for example, the autosomal dom- inant tubulointerstitial kidney diseases caused by mutations in the genes encoding uromodulin (UMOD), hepatocyte nuclear factor-1b (HNF1B), renin (REN), and mucin-1 (MUC1). Gout is also a consequence of enzymatic defects that accel- erate de novo purine synthesis. X-linked hypoxanthine-guanine phosphoribosyltransferase deficiency results in a clinical spectrum extending from hyperuricaemia alone to hyperuricaemia with profound neurological and behavioural dysfunction (Lesch–Nyhan syndrome). Phosphoribosyl pyrophosphate synthetase superactivity presents with uric acid lithiasis or gouty arthritis in childhood or early adult life. Acute attacks of gout are treated with nonsteroidal anti- inflammatory

drugs, colchicine, or steroids. First-line treatment to prevent acute attacks or manage chronic tophaceous gout is with the xanthine oxidase inhibitor, allopurinol. Hypouricaemia may be caused by inherited disorders of uric acid biosynthesis (e.g. xanthine oxidase deficiency) or may be due to in- herited or acquired renal tubule transport defects. Other diseases of purine metabolism cause diverse abnormalities and are generally the result of single gene defects, for example, ad- enosine deaminase and purine nucleoside phosphorylase catalyse sequential steps in the metabolism of purine ribonucleosides and deoxyribonucleosides and are highly expressed in lymphoid cells; their deficiency causes lymphotoxic metabolites to accumulate and leads to lymphopenia and severe combined immunodeficiency. Disorders of pyrimidine metabolism The de novo synthesis of pyrimidine nucleotides involves a series of six reactions beginning with the formation of carbamyl phosphate and concluding with orotidine monophosphate, which then under- goes a series of interconversion and salvage reactions. The inherited disorders of pyrimidine metabolism (e.g. orotic aciduria), which have diverse presentations, are much less common and/or much less easily recognized than disorders of purine metabolism. Disorders of purine metabolism Purine metabolism Biosynthesis, interconversion, degradation, and salvage The purine nucleotides are built up in a stepwise manner (de novo synthesis) and undergo a series of interconversion and salvage re- actions and a final degradative process to yield uric acid, as shown in Fig. 12.4.1. The dietary intake of nucleoproteins contributes to uric acid formation. Ingested adenine and guanine nucleotides are degraded to free purine bases and, hence, to uric acid by enzymes 12.4 Disorders of purine and pyrimidine metabolism Anthony M. Marinaki, Lynette D. Fairbanks, and Richard W.E. Watts† † It is with great regret that we report that Richard W.E. Watts died on 11 February, 2018.

 in the intestinal fluids and in the mucosa of the small intestine, so that the products of their metabolism do not mix with the cor- responding endogenous metabolic pools except at the final uric acid stage. De novo synthesis contributes about 300 to 600 mg (1.8–3.6 mmol/ day) and dietary purines about 600 to 700 mg (3.6–4.2 mmol/day) to the dynamic urate metabolic pool of about 1200 mg (7.2 mmol) expressed as uric acid. Each day about two-thirds of the uric acid is excreted in the urine and about one-third is excreted via the gut where it is destroyed mainly by bacterial uricolysis. Renal handling of urate The urate anion is freely filterable at the renal glomerulus, only 5 to 10% being very loosely bound to the plasma proteins (α1–2- globulin fraction). The physiologically important pKa value of uric acid is 5.75, so that it exists mainly as the monovalent urate anion in plasma (pH 7.4) and assumes more of the free acid form when it passes into regions of the renal tubule, the contents of which are at lower pH values. The kidney handles urate by: • glomerular filtration (virtually no hindrance to passage through the glomerular filtration barrier) • proximal tubular reabsorption by urate anion exchangers, pre- dominantly URAT1, OAT4, and OAT10 in the endothelial brush border (99% of the filtered load) • reabsorption into the circulation at the basolateral membrane, predominantly by the fructose–urate transporter GLUT9 (SLC2A9) • urate excretion at the apical membrane by MRP4, NPT1, NPT4, and BCRP/ABCG2. The net renal clearance of uric acid is approximately 10% of the filtered load and is in the range of 6 to 11 ml/min per 1.73m2 (1.73 m2 = average body surface area of an adult). Genome-wide association studies have led to considerable ad- vances in the understanding of this complex process by identifying genes in uric acid transport and genetic variants predisposing to gout (Fig. 12.4.2). PRPS ADSL DNA dATP dADP dAMP AMP sAMP GAR ATP HCO3 H2O Aspartate ATP Glutamine ATP Fumarate Fumarate FGAR FGAM AIR CAIR SAICAR AICAR FAICAR IMP ADP ATP RNA Polyamine metabolism Adenine Deoxyadenosine Adenosine Deoxyinosine Inosine Deoxyguanosine

Guanosine GTP GDP GMP XMP dGMP dGDP dGTP DNA RNA 8-OH Adenine 2-8-OH Adenine Uric acid Xanthine Hypoxanthine Guanine ADSL NT APRT ADA PNP PNP HPRT NT ATIC XO XO Guanase Ribose-5-Phosphate +ATP Phospho-D-ribosyl -1- pyrophosphate + glutamine 5-Phosphoribosyl-1-amine + Glycine-ATP Fig. 12.4.1 Pathways of purine metabolism in humans. ADA, adenosine deaminase; ADSL, adenylosuccinate lyase; APRT adenine phosphoribosyltransferase; ATIC, AICAR transformylase/IMP cyclohydrolase; HPRT, hypoxanthine-guanine phosphoribosyltransferase; NT, 5′-nucleotidase; PNP, purine nucleoside phosphorylase; PRPS, phosphoribosylpyrophosphate synthetase; XO, xanthine oxidase. De novo synthesis intermediates: AICAR, 5-phosphoribosyl-5-amino-4-imidazolecarboxamide; AIR, 5-phosphoribosyl-aminoimidazole; CAIR, 5-phosphoribosyl-5-amino-4-imidazolecarboxylate; FAICAR, 5-phosphoribosyl-5-formamido-4-imidazolecarboxamide; FGAM, 5-phosphoribosyl-N-formylglycinamidine; FGAR, 5-phosphoribosyl-N-formylglycinamide; GAR, 5-phosphoribosyl-glycinamide; SAICAR, 5-phosphoribosyl-5-amino-4-imidazole-succinocarboxamide.

12.4 Disorders of purine and pyrimidine metabolism 2017 URAT1, encoded by the gene SLC22A12, was the first uric acid transporter to be identified and is involved in urate reabsorption in the proximal tubule. It is expressed apically in the brush border epithelium and is an anion exchanger stimulated by an outwardly directed chloride gradient. Lactate, pyrazinoate, and nicotinate are substrates for the antiporter activity of URAT1 thereby increasing urate reabsorption. The uricosuric agents benzbromarone, pro- benecid, and losartan are inhibitors. OAT4 (SLC22A11) and OAT10 (SLC22A13) are also expressed in epithelial cells of the proximal tu- bule apical membrane and play a role in the reabsorption of uric acid from the proximal tubule in exchange for dicarboxylates. The multidrug resistance protein MRP4 and the transporter ABCG2 contribute to uric acid efflux into the tubular lumen. ABCG2 is also expressed in the intestine and plays an important role in the extrarenal excretion of uric acid through the gut. An amino acid substitution p.Q141K in ABCG2 is associated with significantly increased plasma uric acid levels and an increased risk for gout in multiple ethnic backgrounds. The data suggests that at least 10% of gout cases in individuals of European descent are attributable to this variant. The p.Q141K variant is unexpectedly also associated with increased urinary uric acid output because of the decreased intestinal excretion associated with the variant. More recently, the ABCG2 p.Q141K variant has been associated with a poor response to allopurinol therapy, although the mechanism for this is unclear. The urate fructose–glucose transporter GLUT9 (SLC2A9) is a voltage-dependent uric acid transporter. Alternative splicing leads to two transcripts, GLUT9a encoded by 12 exons with 540 amino acids and GLUT9b, a shorter protein of 512 amino acids encoded by 13 exons. GLUT9b expression is restricted to liver and kidney, whereas GLUT9a has a broad tissue distribution including liver, kidney, intestine, leucocytes, and interestingly, chondrocytes. It is suggested that the functions of this urate anion transporter is to transport urate formed intracellularly by purine catabolism and so maintain intracellular urate concentrations below the solubility limit and prevent intracellular crystallization. In the kidney, GLUT9 may be the principal pathway of basolateral urate transport from the proximal tubule cell. Plasma urate concentration Reference range The currently quoted overall reference range for plasma uric acid in adults is 3.5 to 8.1 mg/dl (210–480 μmol/litre) for men and 2.5 to 6.5 mg/dl (150–390 μmol/litre) for women. The corresponding value for children is 1.0 to 4.0 mg/dl (60–240 μmol/litre), with the lowest values in infancy. It rises to adult values at puberty with values being lower in women than in men. Extrinsic factors, particularly diet, plumbism, the prevalence of a high ethanol intake in the com- munity, and the prevalence of diseases such as malaria and thalas- saemia, which lead indirectly to either

increased purine biosynthesis or decreased excretion (Table 12.4.1), affect the plasma urate distribution in different populations. The plasma urate concentration decreases during pregnancy, the reference range being 1.7 to 4.5 mg/dl (100–270 µmol/litre). Hyperuricaemia is a characteristic and often an early feature of pre-eclampsia, preceding proteinuria and hypertension, and is a Basolateral membrane Tubular cell GLUT9 Urate Urate Urate Urate Urate Urate URA11 OAT4 ABCG2 MRP4 NPT1 and NPT4 OAT10 OAT1 OAT3 Apical membrane (brush border) Approximately 90% of filtered uric acid is reabsorbed Circulation Approximately 10% of filtered uric acid is excreted Tubular lumen Fig. 12.4.2 Proximal tubule uric acid anion transport. OAT1 and OAT3 mediate urate uptake from the basolateral membrane. Secretion at the apical membrane into the tubule is via ABCG2, MRP4, NPT1, and NPT4. Tubular reabsorption is via URAT1, OAT4, and OAT10. GLUT9 promotes reabsorption of urate back into the circulation. Approximately 90% of urate filtered in the glomerulus is reabsorbed in the proximal tubule. This increases to approximately 95% in patients with hyperuricaemia due to uric acid underexcretion.

SECTION 12 Metabolic disorders 2018 diagnostically valuable parameter. It results from a reduced renal urate clearance and tends to be associated with hypocalciuria. Epidemiological studies show significant variations in plasma urate concentrations between different ethnic groups, for example, Maoris and Polynesians have higher values than Western Europeans and Americans. This illustrates the genetic, presumably polygenic, aspects in the control of serum uric acid. Other epidemiological studies em- phasize the importance of the environmental factors of purine, pro- tein, and alcohol intake. For example, Gresser and Zöllner showed that the cumulative frequency of plasma urate, expressed as uric acid, rose from approximately 6.2 mg/dl (370 µmol/litre) to about 9.0 mg/ dl (536 µmol/litre) between 1962 and 1971 in association with the im- proved nutritional state of the Bavarian population from the near star- vation conditions following the Second World War (Fig. 12.4.3). This effect was not apparent in the female population. Similarly, the plasma urate levels of immigrant communities with low values in their home- lands rise towards the values prevailing in the host country as they adopt the lifestyle and dietary habits of that country (e.g. Filipinos migrating to the United States of America). Migrants with genetically determined high urate levels become even more hyperuricaemic. The frequency distribution of plasma urate values based on asymptomatic populations is only approximately Gaussian, with an excess of higher values due to the inclusion of some asymptom- atic hyperuricaemic subjects. Although plasma is saturated with monosodium urate at a concentration of 7.0 mg/dl (420 µmol/litre), higher concentrations of urate can remain in a stable supersaturated solution in plasma without producing any symptoms. Ignoring the slight asymmetry of the frequency distribution and defining nor- mality as the mean value ±2 standard deviations about the mean, normal values of 7.0 mg/dl (420 µmol/litre) for men and 6.0 mg/dl (360 µmol/litre) for women have been widely adopted and this has led to considerable overtreatment of patients with quite innocuous plasma urate concentrations. Asymptomatic hyperuricaemia: to treat or not to treat? Routine biochemical screening frequently identifies patients with hyperuricaemia. The treatment of asymptomatic hyperuricaemia with urate-lowering therapies carries a significant risk of toxicity and in the absence of evidence for clear clinical benefit, recommenda- tions are that asymptomatic hyperuricaemia should not be treated. The evidence for a causal association between hyperuricaemia and hypertension, cardiovascular disease, metabolic syndrome, and an increased risk of renal failure is contradictory. If indeed causal, any association is likely to have a small effect of limited clinical significance compared to other comorbidities. A few studies have compared measures of renal function in patients with asymptom- atic hyperuricaemia treated with allopurinol to those in patients not treated for

hyperuricaemia, and although there is some evidence for an improvement in estimated GFR with treatment, these small studies have had a duration of a few months rather than years. There is also little evidence that asymptomatic hyperuricaemia increases the risk of gouty arthritis. However, although there is currently insufficient evidence to suggest that treatment of asymptomatic hyperuricaemia is beneficial, lifestyle advice on diet and exercise should be given to the patient and may be of benefit in lowering uric acid levels as well as improving other comorbidities. Gout (For further discussion see Chapter 19.10.) The incidence of gout has been estimated at about 0.2 to 0.35 per 1000. The incidence in- creases with age and is higher in men than in women, although the incidence in women rises with age. In men the first attack has usually occurred by 50 years of age and in women by 70 years of age. Table 12.4.1 Causes of hyperuricaemia and gout Increased uric acid synthesis Decreased renal clearance Increased uric acid production due to HPRT deficiency or PRPS synthase superactivity Genetic polymorphism in urate transporters URAT1, GLUT9,
and ABCG2 Dietary sources including fructose Chronic kidney disease Chronic haemolytic anaemia of
any cause Autosomal dominant tubulointerstitial kidney diseases Myeloproliferative disorders Hyperparathyroidism Malignancies Bartter’s syndrome Psoriasis Hypothyroidism Obesity Obesity Down’s syndrome Diabetes Glycogen storage diseases Lead poisoning Fructose intolerance Lactic acidosis Gaucher’s disease Drug administration (e.g. diuretics, pyrazinamide, and ethambutol) Cumulated frequency (%) 100 80 60 40 20 Serum uric acid (mg/dl) Men Cumulated frequency (%) 100 80 60 40 20 Serum uric acid (mg/dl) Women 1962 1989 1971 1962 1989 1971 12 0 2 4 6 8 10 12 0 2 4 6 8 10 Fig. 12.4.3 Differences in the cumulative frequencies in urate levels in female and male blood donors in Bavaria between 1962 and 1989. Urate deposition in man and its clinical consequences. Reproduced from Gresser U, Zöllner N (1991). Urate deposition in man and its clinical consequences. With kind permission of Springer Science + Business Media.

12.4 Disorders of purine and pyrimidine metabolism 2019 Gout is a classic example of a multifactorial disease in which there is an interplay of genetic and environmental factors. The overall ef- fects of this interplay are wide, extending from cases where there is a clear-cut family history with autosomal dominant inheritance (Fig. 12.4.4) to those where environmental factors may be major de- terminants, although often against a genetic background that may be either unifactorial or multifactorial. Gout per se does not shorten life, although some of its complications may do so in the absence of treatment. Gout is defined as the syndrome brought about by the crystalliza- tion of monosodium urate monohydrate in vivo from body fluids supersaturated with this salt. This results from either overproduc- tion or underexcretion of urate, or from a combination of these de- fects (Table 12.4.1). The underlying causes of hyperuricaemia and gout are as follows:
• Decreased net tubular urate secretion: this occurs in those cases of gout previously described as being idiopathic (or primary), and the hereditary predisposition is often compounded by environ- mental factors (e.g. high dietary purine and alcohol intake). • Identifiable enzymatic defects that accelerate de novo urate syn- thesis: X-linked hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency, if complete or virtually complete, causes Lesch–Nyhan syndrome. Lesser degrees of deficiency cause X- linked recessive hyperuricaemia, gout, and uric acid stones with minor neurological abnormalities in some cases. • Phosphoribosylpyrophosphate (PRPP) synthetase superactivity: this also presents as X-linked recessive hyperuricaemia, gout, and uric acid stones and, in some cases, neurological manifestations (e.g. deafness). Gout due to urate under-excretion is characterized by a reduced fractional excretion of urate defined as the ratio of urate clearance to

the GFR. In the presence of normal overall renal function, this can be measured on a timed urine sample with a simultaneous plasma sample. The equation simplifies to: Fractional clearance of urate = U [urate] × P [creatinine]/P [urate]
× U [creatinine] where U and P represent urate and plasma concentrations. The fractional clearance can be used to assess the role of renal tubular dysfunction in the production of hyperuricaemia provided that the overall renal function is normal. An elevated urinary urate to creatinine ratio is indicative of purine overproduction. Associations of hyperuricaemia and gout are shown in Box 12.4.1. Hyperuricaemia may be a marker of coincident cardiac disease. Elevated plasma uric acid concentrations are observed in patients with ischaemic cardiac disease, however there is no evidence that uric acid is directly toxic to the myocardium. Increased urate levels could arise from up-regulated vascular adenosine synthesis associ- ated with ischaemia and subsequent degradation of adenosine to uric acid. Plasma uric acid accounts for 60% of the free-radical scavenging activity in human plasma, for example, it interacts with peroxynitrile to form a stable nitric oxide donor, so promoting vasodilatation and reducing the potential for peroxynitrile-induced oxidative damage. Conversely, it could have an adverse effect on endothelial function by promoting leucocyte adhesion to the endothelium. Clinical features Acute gouty arthritis Acute gout is a sodium urate monohydrate-induced crystal in- flammation of joints, bursae, and tendon sheaths. Clinically the affected structures—classically the first metatarsophalangeal joint is the first joint affected—become acutely inflamed, exquisitely tender, warm to the touch, and the overlying skin becomes red, shiny, and itchy and may desquamate as the inflammation subsides spontaneously over the course of 5 to 15 days in the absence of treatment (Fig. 12.4.5). Inflammation is usually maximal within 24 h of onset and is accompanied by pyrexia and malaise. The American College of Rheumatology criteria for the clinical diagnosis of acute gout are shown in Box 12.4.2. The presence of 6 I II III IV V VI 3 2 1 7 3 2 1 1 2 1 2 3 4 5 4 5 6 4 5 6 6 7 8 9 8 9 2 1 * 3 * Fig. 12.4.4 Pedigree chart of a family showing autosomal dominant inheritance of gout complicated in some cases by renal failure (autosomal dominant tubulointerstitial kidney disease). ■, ●, male and female subjects, respectively, with hyperuricaemia and renal failure; ■, ●, male and female subjects not known to be affected; ■, ●, deceased male and female subjects; ↗, propositus; ↘, subjects whose rates of mononuclear cell de novo purine synthesis were measured and shown to be normal; *, babies who were examined clinically but not further investigated. Reproduced with permission from McDermott, et al. (1984). Clin Sci, 67, 249–58.
 Box 12.4.1 Associations of hyperuricaemia and gout The following abnormalities (features of the ‘metabolic syndrome’) are commonly associated with, but not causally related to, hyperuricaemia and gout: • Obesity • Dyslipidaemia (usually type 4) with raised very low-density lipopro- teins and normal cholesterol levels, and sometimes hypercholester- olaemia with elevated low-density lipoprotein cholesterol and low high-density lipoprotein cholesterol • Hypertension • Insulin resistance with hyperinsulinaemia and impaired glucose tolerance • Ischaemic heart disease Thus, these patients may display the features of the ‘metabolic syndrome X’.

 of the 11 criteria has a 95% specificity in differentiating gout from pseudogout (calcium pyrophosphate gout) and an overall sensi- tivity of 85%. Although acute gouty arthritis is typically a monoarthritis, some patients have short, recurrent, mild attacks of discomfort and swelling of other affected joints. Some 10% of attacks affect more than one joint, and typical attacks may provoke migratory attacks in other joints. Multiple, simultaneous attacks are rare. Some attacks are triggered by trauma, intercurrent illness, surgery, alcohol, dietary ex-

cess, diuretics, and other medications (Box 12.4.3). An acute septic arthritis is the most important differential diagnosis of acute gouty arthritis. The joint fluid contains negatively birefringent sodium urate monohydrate (Fig. 12.4.6) as opposed to the positively birefringent crystals of calcium pyrophosphate in pseudogout and is diagnostic. Attacks of acute gouty arthritis usually occur when the plasma urate is rising or falling. The cells in the joint fluid are a mixture of mono- cytes, macrophages, and polymorphonuclear leucocytes. The spontaneous resolution of an attack of acute gouty arthritis depends on the differentiation of monocytes to macrophages that ef- ficiently phagocytose crystals. This conclusion is based on studies of the changing pattern of proinflammatory cytokines tumour necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) secreted by monocyte/macrophage cells at different degrees of differentiation and their ability to phagocytose monosodium urate crystals in vitro. The crystals are removed by mature phagocytes. It is proposed that this mechanism prevents the development of acute gouty arthritis in stable asymptomatic hyperuricaemic patients. TNFα, IL-1β, and IL-6 secretion promote E-selectin expression and secondary neutro- phil capture. Differentiation over 3 to 5 days leads to development of a noninflammatory phenotype with lack of proinflammatory cyto- kine secretion, lack of endothelial cell activation, and lack of sec- ondary neutrophil recruitment. Acquisition of the noninflammatory phenotype correlates with expression of macrophage antigens but not with dendritic cell marker or activation marker. Monocytes and macrophages are similarly phagocytic and control particle, zymosan-elicited secretion of all the cytokines in both cell types. Coincubation with monosodium urate suppressed zymosan- induced TNFα secretion from macrophages but not monocytes. In summary, differentiated macrophages provide the mechanism for removal of sodium monohydrate crystals. Fig. 12.4.5 Gout presenting in the metatarsophalangeal joint of the big toe. Note the slight redness of the skin overlying the joint (arrow). Image by James Heilman, MD ((CC BY-SA 3.0 (http://creativecommons.org/licenses/ by-sa/3.0)). Box 12.4.2 American College of Rheumatology criteria for the diagnosis of acute gouty arthritis • More than one attack of acute arthritis • Maximum inflammation developing within 1 day • Monoarthritis • Redness over the affected joint • The first metatarsophalangeal joint is painful and swollen • Unilateral first metatarsophalangeal joint involved • Unilateral tarsal joint attack • Tophus (proven or suspected) • Hyperuricaemia • Asymmetrical swelling of a joint on radiography • Subcortical cysts with an erosion on radiography • Joint fluid culture negative for microorganisms during an attack The patient must have at least six of the listed criteria or have either proven sodium urate monohydrate crystals in the joint fluid or a proven tophus. Reproduced with permission from Hochberg MC (2001). Gout. In: Silman AJ, Hochberg MC (eds) Epidemiology of the rheumatic diseases, 2nd edition, pp. 230–42. Oxford University Press. Box 12.4.3 Drugs and dietary supplements causing hyperuricaemia and gout • Thiazide diuretics (including bendroflumethiazide, chlortalidone, cyclopenthiazide, indapamide, metolazone, and xipamide) • Loop diuretics (including furosemide, bumetanide, and torasemide) • Pyrazinamide and ethambutol • Low-dose aspirin • Nicotinic acid Reproduced with permission from Gibson TJ (2013), Hypertension, its treat- ment, hyperuricaemia and gout. Curr Opin Rheumatol, 25, 217-22. Copyright © 2013 Lippincott Williams. Fig. 12.4.6 Negatively birefringent uric acid crystals in synovial fluid. Under polarized light, horizontal crystals appear as yellow. Reproduced from Dalbeth, N. Laboratory testing in gout diagnosis and management. In (Ed.), Gout (Oxford Rheumatology Library). Oxford, UK: with permission from Oxford University Press.

12.4 Disorders of purine and pyrimidine metabolism 2021 Chronic tophaceous gout Large deposits (tophi) containing monosodium urate monohydrate crystals produce firm nodules over affected

joints on the extensor surfaces of the fingers (Box 12.4.3, Fig. 12.4.7), hands, olecranon bursas (commonly bilateral), extensor surfaces of the forearm, Achilles tendon, the helix of the ear, and in the renal parenchyma. Tophi may discharge white chalky material, containing sodium urate monohydrate. They cause the bone erosions and joint destruction with secondary degenerative arthritis that is seen on radiographs. Tophus formation can be regarded as an attempted, but disordered, healing process in response to the presence of sodium urate monohy- drate crystals in tissues. Saturnine gout The link between alcohol consumption, lead poisoning, and gout should be considered in socioeconomic backgrounds where the il- licit brewing of alcohol is commonplace. Lead solder and piping in the equipment used for the illicit brewing and distillation of alcohol may be a source of lead contamination in the beverages produced. Lead toxicity and saturnine gout may also derive from occupational exposure, lead-based paints (particularly in childhood), ceramic glazes, additives to petrol, drinking water systems, and even nat- ural remedies. The association between lead and hyperuricaemia remains poorly understood but is most likely to be a consequence of chronic kidney disease. In addition to the symptoms of gouty arthritis, symptoms of lead poisoning are usually present. The condition occurs equally in both males and females, and often at a relatively young age of 40 to 60 years, even younger in those where there has been excessive child- hood exposure to lead. These symptoms and signs include protein- uria and chronic kidney disease, as well as anaemia characterized by red cell basophilic stippling due to the inhibition of pyrimidine-5′- nucleotidase. Burton’s lines, a bluish line on the gums, may be present. Lead excretion in urine is elevated, and serum lead levels are ele- vated in cases with current lead exposure. Treatment includes limi- tation of continued lead exposure, lead chelation therapies such as EDTA, dimercaprol, and succimer, as well as xanthine oxidase in- hibitors to lower blood urate levels. Gout due to autosomal dominant tubulointerstitial kidney disease Rare cases of familial gout, presenting in early adulthood or before, have been identified for a long time in families with a history of renal failure. It is now known that familial (juvenile) hyperuricaemic nephropathy is associated with at least four gene defects, and these disorders are more accurately known as the autosomal dominant tubulointerstitial kidney diseases (ADTKD). ADTKD-UMOD is due to defects in the gene encoding uromodulin (UMOD) and a specific syndrome ‘medullary cystic kidney disease: familial juvenile hyperuricaemic nephropathy’ (MCKD/FJHN) is now recognized. These patients show impaired urine concentrating ability, hyperuricaemia and hypouricosuria due to a reduced net tubular excretion of uric acid, cysts (specifically at the corticomedullary junction), interstitial fibrosis, and ultimately renal failure. These cases are associated with mutations in the gene directing the synthesis of the glycoprotein uromodulin, also known as Tamm–Horsfall protein, which occurs in the cells of the thick, as- cending segment of Henle’s loop, and in renal collecting tubule cells. Uromodulin excretion is diminished. Heterozygous missense gene mutations or small insertion/deletion events in the gene encoding uromodulin have been demonstrated, and it is proposed that these produce changes in the tertiary structure with conformational changes in the protein due to reduction in the intramolecular disul- phide bonding, which alters the folding pattern of the protein and glycosylation. Uromodulin is an 85-kDa glycoprotein which also has a role in preventing renal stone formation, the modulation of im- mune responses, and urothelial cytoprotection. Management Acute attack Full doses of any of the nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in terminating attacks of acute gout. Indomethacin is particularly favoured by some clinicians. Colchicine remains a very effective remedy. The American College of Rheumatology guidelines recommendation is that acute gout can be treated with a loading dose of 1.2 mg of colchicine followed by 0.6 mg 1 h later. This regimen can then be followed by prophylaxis dosing of 0.6 mg once or twice daily 12 h later, until the gout at- tack resolves. For countries where

0.5 mg tablets only are available, the advice is 1.0 mg colchicine as the loading dose, followed by 0.5 mg 1 h later, and then followed, as needed, after 12 h, by continued colchicine (up to 0.5 mg three times daily) until the acute attack re- solves. Lower total doses (1.5–1.8 mg) have comparable efficacy to higher doses in acute gout but appear to be without the unwanted gastrointestinal toxicity. High doses of colchicine can cause gastro- intestinal haemorrhage and favour the development of other severe side effects, including profuse diarrhoea, rashes, renal and hep- atic damage, and (more rarely) peripheral neuropathy, myopathy, and alopecia in the long term. Intravenous colchicine is no longer recommended. An attack of acute gout can be effectively terminated by the adrenocorticotropin analogue, tetracosactrin, by a single intra- venous dose of hydrocortisone, with a short course of oral prednis- olone (typically 30 mg daily), or (for some joints) by steroid injection into the affected joint. Rebound attacks of acute gout tend to occur unless the situation is covered by either colchicine or an NSAID. Fig. 12.4.7 Thiazide or loop diuretic treatment for hypertension are frequent causes of hyperuricaemia and gout. Tophus overlying a Heberden’s node in an elderly patient taking bendroflumethiazide for hypertension. Reproduced with permission from Gibson TJ (2013), Hypertension, its treatment, hyperuricaemia and gout. Curr Opin Rheumatol, 25, 217–22. Copyright © 2013 Lippincott Williams.

SECTION 12 Metabolic disorders 2022 Pharmacological doses of colchicine disrupt the microtubular function in inflammatory cells. This mode of action gives it the po- tential to do more widespread damage. Short intensive courses of colchicine should not be repeated at less than 3-day intervals, al- though lower doses (0.5–2 mg/day) can be used for longer periods, as in the treatment of familial Mediterranean fever. Rasburicase (dosage 20 mg/kg per day, treatment for more than 5 days is not recommended) is a recombinant urate oxidase derived from Saccharomyces cerevisiae. It catalyses the oxidation of urate to allantoin which is five times more soluble than uric acid at urinary pH values and is the purine metabolite excreted by nonprimate spe- cies. Acute hypersensitivity reactions have been reported in 5% of patients who do not have a history of allergy. It should not be used in pregnancy or in glucose-6-phosphate dehydrogenase deficiency. It can be used to terminate an attack of acute gouty arthritis, but this seems unnecessary with the availability of well-established methods. However, it may have a place in the treatment of acute uric acid neph- ropathy in tumour lysis syndrome and in patients who are allergic to allopurinol and the other drugs used to treat hyperuricaemia and gout. More recently, pegloticase a polyethylene glycol conju- gate of a recombinant porcine uricase which is less immunogenic than rasburicase and therefore more suited for longer-term therapy, has benefited patients with a severe gout disease burden and re- fractoriness to oral urate-lowering therapies, but has not been ap- proved for this purpose by the National Institute for Health and Care Excellence in the United Kingdom. The agent appears to have powerful hypouricaemic effects with debulking of tophi in severely affected patients resistant to other therapies. Infusion reactions are frequent, although frank anaphylaxis appears to be uncommon. Rapid breakdown of plasma urate by uricase has been associated with a high frequency of acute exacerbations of gout in the early weeks after its introduction. Moreover, since all putative treatments of hyperuricaemia based on the action of uricases have the potential to generate abundant hydrogen peroxide and other oxidants, their introduction for long-term use carries with it an appreciable risk of tissue injury (see contraindication for use of rasburicase, in ‘Acute uric acid nephropathy’). Although pegylated and other preparations of uricases from various sources demonstrate clear efficacy in vivo and remain attractive for therapeutic research, at the time of writing, this approach does not yet have an established place for the treat- ment of severe chronic gout. Interval treatment Asymptomatic

hyperuricaemia should not be treated with urate- lowering drugs unless the patient experiences more than one acute attack of gout per year (Box 12.4.4). Allopurinol, a xanthine oxi- dase inhibitor, is effective in preventing acute gout by reducing the serum urate concentration to a value below the solubility of sodium urate monohydrate in plasma so that tophaceous deposits are mo- bilized and healing occurs. This applies to the tophi in bones as well as elsewhere. The drug should be introduced at a low level (e.g. 100– 200 mg daily) and increased under cover of either colchicine or an NSAID, which should be continued until the serum urate concen- tration has stabilized at a normal level. Allopurinol is then continued indefinitely. Initiating allopurinol without cover may cause attacks of acute gout as the serum urate concentration falls. Moderately severe gout may require as much as 300 to 600 mg allopurinol daily and occasionally as much as 700 to 900 mg/day given in divided doses. Between 10 and 20 mg/kg body weight per day is an appropriate dosage for children. The incidence of adverse reactions to allopurinol is low but they can be severe and occasionally fatal. Reactions include erythema multiforme progressing to Stevens–Johnson syndrome and toxic epidermal necrolysis (associated with the HLA B*5801 allele), ex- foliative dermatitis, vasculitis, interstitial nephritis, eosinophilia, hepatocellular damage, polyneuropathy, bone marrow suppres- sion, disturbances of vision and taste, as well as gastroenteropathy. Allopurinol potentiates the effect of coumarin anticoagulants (e.g. warfarin), azathioprine, and 6-mercaptopurine, and predisposes to an ampicillin or amoxicillin rash. At high dosage and in the presence of greatly increased purine synthesis, it may cause radiotranslucent xanthine and oxypurinol urinary stones. There is also an increased risk of toxicity with captopril (especially in the presence of renal failure) and with ciclosporin. Much of the overall toxicity of allopurinol is due to the metabolite oxypurinol, which has a much longer half-life in vivo than the parent compound. Special care is necessary in the presence of advanced chronic kidney disease and a dose of 100 to 150 mg is usually suffi- cient in this circumstance. Patients with hyperuricaemia due to renal failure rarely develop gout, possibly due to their immunoparesis. Treatment when allopurinol produces adverse reactions The specific xanthine oxidase inhibitor, febuxostat, has been ap- proved by the European Commission, the National Institute for Health and Care Excellence in the UK and by the Food and Drug Administration in the United States of America, for the treatment of chronic gout in which it rapidly decreases serum urate concen- trations. Febuxostat is appropriate for patients hypersensitive to or intolerant of allopurinol, those in whom allopurinol has failed to control symptomatic hyperuricaemia, and in patients with chronic kidney disease where uricosuric therapy is contraindicated. As with allopurinol, suitable prophylaxis against exacerbation of acute gout is indicated (e.g. with colchicine) when treatment with febuxostat is started. The drug is approved in European countries at 80 and 120 mg daily. In the United States of America, the label is for a daily dose of 40 mg, increasing to 80 mg after at least 2 weeks if the serum urate concentration remains elevated. Febuxostat at a dose of 40 mg/day is associated with a higher likelihood of achieving a target serum uric acid level of 6 mg/dl (0.36 mmol/L) than allopurinol given at Box 12.4.4 Hyperuricaemia detected on routine biochemical screening • Search for an identifiable cause (e.g. dietary factors, myeloproliferative disease, medications) • Check renal function • Imaging to detect the presence of uric acid urinary calculi • Measure uric acid excretion after eliminating dietary and medication factors • Treat if:

— more than one attack of acute gouty arthritis per year

— chronic joint damage attributed to gout

— tophi

— hyperuricaemic nephropathy

— uric acid urolithiasis.

12.4 Disorders of purine and pyrimidine metabolism 2023 the commonly used doses of 300 mg/day. Nevertheless, a meta- analysis dating from 2013 concluded that there was no evidence that febuxostat is superior to allopurinol for clinically relevant out- comes. Given the higher cost of febuxostat, the evidence suggests that febuxostat should not be routinely used as a first-line treat- ment for chronic gout. Since it is an inhibitor of xanthine oxidase, febuxostat, like allopurinol, has the potential for highly toxic drug interactions with azathioprine, 6-mercaptopurine, and theophylline and its derivatives. Patients for whom the treatment of hyperuricaemia and gout is essential and in whom therapy with xanthine oxidase inhibi- tors have been ineffective present a special problem, especially if they have impaired overall renal function. The uricosuric drugs sulphinpyrazone, probenecid, and benzbromarone, together with a sufficiently high fluid intake to provide a measured urine output of at least 3 litres/24 h and alkalization of the urine with sodium or potassium bicarbonate or sodium or potassium citrate, are an approach to this problem, but may be inappropriate in the overall clinical context, for example, in patients with cardiac or renal failure. Only sulphinpyrazone is readily available in the United Kingdom. Uricosuric drugs may be inefficient in the presence of renal failure and are contraindicated in the presence of uric acid urinary stones. The uricosuric agent benzbromarone is sometimes effective in pa- tients with renal failure when other uricosuric agents have lost their efficacy. The use of oxypurinol (at low dosage) has also been pro- posed. Protocols are also available for the desensitization of patients who have experienced adverse reactions to allopurinol and in whom the risk of uric acid stone formation, with the potential for further reduction of renal function, presents a problem. Other hyperuricaemic conditions Acute uric acid nephropathy This complicates the treatment of widespread malignant disease, particularly chemotherapy and/or radiotherapy of leukaemias and lymphomas. The nephropathy is of multifactorial origin and may form part of the acute tumour lysis syndrome with accompanying tubular necrosis. These patients are usually underhydrated, acid- otic, and have high rates of uric acid production from nucleoprotein degradation in the apoptotic tumours. Acute uric acid nephropathy has occasionally been reported after extremely severe muscular ex- ercise, after severe epileptic seizures, and in patients with gout due to grossly increased rates of de novo purine synthesis. The renal lesion is the intratubular precipitation of uric acid crys- tals. In addition, the renal pelvis and ureters may also be blocked by crystal aggregates and/or uric acid stones. Acute uric acid neph- ropathy can be avoided by giving allopurinol for several days be- fore starting the chemotherapy or radiotherapy. The condition presents as acute oliguric renal failure. Imaging techniques should be used to exclude the presence of bilateral ureteric obstruction by radiotranslucent uric acid stones. Treatment is by: • induction of an alkaline diuresis • haemodialysis, peritoneal dialysis, or haemofiltration • percutaneous nephrostomy and/or ureteric catheterization may be needed if there is an element of postrenal obstruction due to impacted aggregates of sodium urate crystals or uric acid stones • disruption or removal of impacted stones. Rasburicase has been licensed for use as a single-course therapy for hyperuricaemia in the acute paediatric and adult tumour lysis syndrome. The enzyme has a plasma half-life of 18 to 24 h and is markedly antigenic, therefore having little application as an off- label agent in severe tophaceous gout and certainly not sustainable for more than a few months. On

account of its capacity to induce oxidant injury and thus haemolysis in susceptible individuals, rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency. Ethanol-induced hyperuricaemia Ethanol is oxidized to acetaldehyde by the liver. This raises the ratio of reduced nicotinamide adenine dinucleotide to nicotina- mide adenine dinucleotide, which in turn promotes the reduc- tion of pyruvate to lactate in the hepatocytes. Lactate competes with urate in the renal tubular excretory mechanisms and thereby promotes urate retention. There is often an element of starva- tion ketoacidosis in chronic alcoholics, with acetoacetate and β-hydroxybutyrate also competing for the renal tubular excretory mechanisms which subserve urate tubular secretion. In addition, there is increased urate production associated with ethanol intake, first due to the high purine content of some alcoholic beverages (e.g. beer) and second because the metabolism of alcohol involves increased dephosphorylation and degradation of adenine nucleo- tides in the liver. Uric acid urolithiasis Pure uric acid stones account for 5% of all urinary stones in patients in the United Kingdom, but there is a much higher incidence else- where (e.g. in the Middle East). In Israel, about 40% of urinary cal- culi are composed of uric acid and 75% of patients with primary gout develop renal calculus disease. Overall, uric acid urolithiasis occurs in about 10% of patients with gout, more often in secondary gout than in primary gout, and sometimes associated with an im- paired ability to alkalinize the urine. Ileostomy predisposes to uric acid urolithiasis because of (1) chronic bicarbonate loss, which leads to a persistent acidification of the urine, and (2) a concentrated urine due to excessive water loss. Urinary uric acid concentrations close to or more than those at which spontaneous crystallization begins are frequent in these circumstances. The genetic causes of uric acid urolithiasis are rare: (1) HPRT deficiency, (2) PRPP superactivity, and (3) inherited renal hyporuricaemia (congenital failure of the renal tubular reabsorp- tion of urate). The urinary uric acid concentration is the main determinant of uric acid stone formation. The concentration depends on the state of hydration, the rate of de novo purine synthesis, the rate of metabolic turnover of purine compounds, the dietary intake of purines and alcohol, and the action of uricosuric drugs (e.g. sulphinpyrazone). Calcium oxalate stone formation is increased 30-fold in patients with gout, and hyperuricosuria is common in nongouty stone- formers. Uric acid microcrystals may act as epitaxial nucleation sites for calcium oxalate crystallization. It is also possible that colloidal uric acid adsorbs urinary glycosaminoglycan inhibitors of crystal- lization and crystal growth. Uric acid stone disease is treated by hydration to maintain a urine volume of at least 3 litres/24 h, alkalization of the urine, and allopur- inol if there is hyperuricosuria. The use of sodium and potassium

 salts for alkalization has to be carefully reviewed in the light of con- current diseases, particularly impaired renal and cardiac function. The standard imaging techniques (particularly ultrasonography) are required for the diagnosis of these radiotranslucent stones. Stones can be fragmented or removed by standard procedures. For further discussion of urinary stones, see Chapter 21.14. Hereditary renal hypouricaemia and uric acid stones The causes of hypouricaemia are summarized in Box 12.4.5. Renal hypouricaemia may be due to renal tubular damage by gen- etic diseases or by toxic damage (Box 12.4.5), and this may be as- sociated with other features of Fanconi’s syndrome. Reduced net tubular reabsorption of urate occurs as an isolated renal tubular reabsorption defect due to loss of function mutations in the genes directing the synthesis of the urate carriers. Type 1 is due to loss of function mutations in URAT1 (SLC22A12) and type 2 due to mutations in GLUT9 (SLC2A9). Inheritance is autosomal reces- sive. Hyperuricosuria is a feature and may amount to 1000 mg (5.9 mmol) per 24 h in homozygous patients, with a lesser degree of hyperuricosuria in heterozygotes. Uric acid urolithiasis occurs in

about 25% of the homozygotes, most commonly in patients with combined hyperuricosuria and hypercalciuria. Treatment with allopurinol has, counter-intuitively, been used to prevent the recurrence of renal stones in patients who have experi- enced acute renal injury after exercise. The rationale is to decrease the generation of uric acid thereby decreasing the filtered uric acid load and lowering the risk of precipitation in the renal tubules. Reduced tubular urate reabsorption can occur in other inherited or acquired renal tubule transport defects (Box 12.4.5). Hypoxanthine-guanine phosphoribosyltransferase deficiency: Lesch–Nyhan syndrome and its variants Lesch–Nyhan syndrome results from mutations in the gene encoding HPRT, an enzyme which catalyses the salvage of hypo- xanthine and guanine to inosine monophosphate (IMP) and guano- sine monophosphate (GMP), respectively, as shown in Fig. 12.4.1. In affected male hemizygotes, the lack of HPRT results in increased levels of PRPP due to failure to salvage hypoxanthine or guanine. Elevated PRPP levels then act as a driver of de novo purine syn- thesis, resulting in purine overproduction. The clinical spectrum extends from hyperuricaemia alone to hyperuricaemia with pro- found neurological and behavioural dysfunction. The biochemistry and molecular genetics of this disorder have been studied exten- sively. Functional assays of HPRT on cultured fibroblasts or intact red cells, rather than erythrocyte lysates, give a better correlation between the degree of residual enzyme activity and clinical pheno- types. Mutation analysis is a valuable tool for genetic counselling, the identification of carriers, and prenatal diagnosis. Pathophysiology Both the de novo purine synthesis and the HPRT-catalysed purine salvage pathways are present in all parts of the normal brain. HPRT activity is absent or defective but the de novo synthesis pathway remains active in patients with the Lesch–Nyhan syndrome. The present view is that the neurological manifestations are brought about by a neurotransmitter imbalance, probably mainly in the basal ganglia. This imbalance is possibly due to a deficient supply of metabolic energy resulting from the nonsalvage of hypoxan- thine and guanine causing a deficiency of adenine nucleotides that provide energy for short bursts of neurotransmitter syn- thesis. However, the positron emission tomography evidence of dopamine receptor deficiency is the main concrete evidence for a neurotransmitter defect, either directly or indirectly because of guanosine triphosphate deficiency underlying the Lesch–Nyhan syndrome. There is increased excretion of the serotonin metabolite 5-hydroxyindoleacetic acid and decreased levels of homovanillic acid, a major metabolite of dopamine, in the cerebrospinal fluid. Deficiency of basal ganglia dopamine systems emerging during the first 2 months of life has been demonstrated in a mouse model of Lesch–Nyhan syndrome. Failure of pubertal development and testicular atrophy in HPRT deficiency are attributed to an inadequate supply of purine nucleo- tides to meet the increased metabolic energy requirement in the Box 12.4.5 Causes of hypouricaemia Inherited disorders of uric acid biosynthesis • Genetic defects in the molybdoflavoprotein enzymes:

— Xanthinuria type I (isolated xanthine oxidase deficiency)

— Xanthinuria type II (combined xanthine oxidase and aldehyde oxi- dase deficiencies)

— Molybdenum cofactor deficiency (xanthine oxidase, aldehyde oxi- dase, and sulphite oxidase deficiency) • Purine nucleoside phosphorylase deficiency Secondary reduction in uric acid biosynthesis • Allopurinol and oxypurinol medication • Hepatic failure • Acute intermittent porphyria Inherited renal hypouricaemia (isolated renal tubule reabsorption defect) • Loss of function mutations in urate transporters URAT1 (SLC22A12) and GLUT9 (SLC2A9) • Inherited causes of Fanconi’s syndrome and its variants (the syndrome of multiple renal tubule reabsorption

defects) Acquired causes of Fanconi’s syndrome and its variants • Metal poisoning (Cd, Zn, Cu, Pb, Hg, Ur) • Multiple myelomatosis • Nephrotic syndrome • Malignant disease (paraneoplastic syndrome) • Autoimmune disease (i.e. Sjögren’s syndrome) • Thermal burns • Primary hyperparathyroidism • Acute renal tubular necrosis • Renal transplant rejection Drugs • Drugs used either as uricosuric agents or to block other aspects of renal tubule excretion (sulphinpyrazone, probenecid, benzbromarone) • NSAIDs with uricosuric properties • Phenylbutazone • Azapropazone • Aspirin dosage greater than 4 g/day • Coumarin anticoagulants (e.g. warfarin) • Outdated tetracycline (5α-6-anhydro-4-epitetracycline) Nutritional deficiencies • Vitamins B12, C, and D • Kwashiorkor

12.4 Disorders of purine and pyrimidine metabolism 2025 testis at this time. A similar inability to meet energy requirements may underlie the neurological manifestations. A partial defect in adrenocortical 11β-hydroxylation of steroids is demonstrable in patients with the Lesch–Nyhan syndrome after ACTH stimulation and is thought to be linked with a failure to modulate mitochon- drial function for this hydroxylation due to a deficiency of purine nucleotides. Clinical features The clinical features of the most severely affected patients who are correctly referred to as having classic Lesch–Nyhan syndrome or as having ‘complete or virtually complete HPRT deficiency’ are sum- marized in Box 12.4.6. In some cases, the enzyme has altered kin- etics or is unstable but has 1 to 5% residual activity. Patients with partial enzyme defects of 0 to 5% HPRT activity in red cell lysates but more than 8% activity in the fibroblast assays have gout and renal complications but no neurological manifestations. The disease fre- quency is about 1 in 380 000 births. Infants affected by HPRT deficiency have a lower than average birth weight, indicating some degree of intrauterine growth retard- ation. The first clinical sign may be the presence of red grit (uric acid crystals with absorbed urinary pigments) on the nappy. Affected in- fants are hypotonic from birth, although this is frequently not re- marked on before poor head control becomes apparent at the age of about 3 months. Postnatal growth, which becomes more marked after the second year of life, is also subnormal (Fig. 12.4.8) as indicated by sequential measurement of body weight, accurate assessment of body length being impossible due to the dystonic posturing. The overall pattern of weight growth follows centile lines for the first 2 years of life and thereafter slows to about 1 kg/year, or about half normal; a pubertal growth spurt is not observed. Head growth and bone development are less affected than weight. The poor weight gain cannot be attrib- uted to either renal failure or malnutrition. Torsion dystonia, with its two components of abnormal pos- turing and episodic rigidity, is superimposed on the basic hypotonia that is present between the dystonic episodes. Severe dysarthria is associated with dyskinesia of the face, mouth, pharynx, and the larynx, which greatly limits communication and even the ability to point accurately, leading to great frustration. The self-injurious be- haviour and dyskinesia are eliminated or much reduced when the child is concentrating on a self-selected activity, such as watching an interesting television programme. Self-injury and dyskinesia are exacerbated by excitement, such as the arrival of a visitor, fear, frus- tration, and unsuccessful attempts at volitional motor activity. The children also appear to be aware of the value of this behaviour as an attention-seeking manoeuvre, and sometimes appear to use it in a manipulative manner. Although learning difficulties have been stressed as a feature of the Lesch–Nyhan syndrome, they are of inconstant severity and are neither marked nor specific. The apparent degree of intellectual dis- ability may be affected by the extensive disorder of expressive motor functions that exceeds the comprehension defect, by the lack of basic social and educational opportunities, and by the lack of intel- ligence tests for older children who have lacked these opportunities. However, for whatever combination of reasons,

there does appear to be a decline of intellect from the age of 8 to 10 years. Self-injurious behaviour usually begins at about 2 years of age. Its severity and the ingenuity with which the patients exploit new ways of self-injury exceed that encountered in any other clinical situation. It is not a constant feature and some patients never show it; in most its severity waxes and wanes. Self-injury can produce very severe damage, such as complete destruction of the lower lip or trau- matic amputation of a fingertip. The patients feel pain normally and are aware of their compulsion; they are afraid of it but are unable to control it. Nyhan and his colleagues consider it to be the clinical hallmark of complete HPRT deficiency, as opposed to those patients with some residual enzyme activity (which may or may not be meas- urable in erythrocyte lysates). The severe dystonic spasms with violent extension of the neck can produce damage to the cervical spinal cord and produce motor pyramidal tract signs in the legs. The phenotypes associated with appreciable residual HPRT activity vary from the neurological def- icit described for the complete Lesch–Nyhan syndrome but without self-mutilation (Lesch–Nyhan variant), to patients with only X- linked gout and/or urolithiasis and only very subtle, if any, neuro- logical features. Box 12.4.6 Clinical manifestations of the Lesch–Nyhan syndrome (complete or virtually complete absence of HPRT deficiency) • X-linked recessive inheritance • Failure of overall growth • Muscle hypotonia • Delayed motor development • Torsion dystonia • Aggressive behaviour • Dysarthria • Variable degree of intellectual deterioration in later childhood • Megaloblastic anaemia (in some cases only) • Hyperuricaemia and hyperuricaciduria with gout and tophus develop- ment after puberty and urolithiasis occasionally during the first decade of life • Failure of pubertal development and testicular atrophy at the age when puberty would be expected to occur 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 Age (years) 0 10 20 30 40 Weight (kg) Fig. 12.4.8 Patterns of growth in the weight of 13 boys with the Lesch– Nyhan syndrome: each patient is shown by a different symbol. The 50th and 3rd centiles are shown. With kind permission from Springer Science+Business Media: J Inherit Metab Dis, Lesch-Nyhan syndrome: Growth delay, testicular atrophy and a partial failure of the 11β-hydroxylation of steroids, 10, 3, 1987, 210–223, R. W. E. Watts. Copyright © 1987, SSIEM and MTP Press Limited.

 Investigation There are no structural or ultrastructural changes in the brain as judged by light and electron microscopy or on electroencephalog- raphy. Reductions in the size of the caudate nucleus, the putamen, and total cerebral volume have now been demonstrated by refined MRI. Dopamine transporter reduction and hence dopamine defi- ciency has been demonstrated by positron emission tomography. Imaging studies have supported the concept that HPRT defi- ciency constrains brain development with particular emphasis on the basal ganglia, and defective function of dopaminergic neurons is specifically involved. A more recent study of adult patients with classic Lesch–Nyhan syndrome showed larger reductions of white (26%) than grey (17%) matter volume relative to healthy controls. These reductions were less marked in patients classified as Lesch– Nyhan variant with reductions of white (14%) and grey (15%) matter volume. Both patient groups demonstrated reduced volume in medial inferior white matter regions. Compared with the variant group, classic Lesch–Nyhan syndrome patients showed larger re- ductions in inferior frontal white matter adjoining limbic and tem- poral regions and the motor cortex. These regions likely include such long association fibres as the superior longitudinal and un- cinate fasciculus. Patients with Lesch–Nyhan syndrome whose hyperuricaemia has been controlled and who have not had renal damage, often live be- yond their third decade, but may succumb to sudden death, usually due to respiratory problems. Management Control of hyperuricaemia Allopurinol should be administered to reduce the plasma urate and urine uric

acid concentration in order to prevent gouty arth- ritis, urate nephropathy, and renal calculi. As HPRT deficiency leads to increased de novo purine synthesis and purine overpro- duction, allopurinol may lead to dramatically increased concentra- tions of xanthine in urine and consequent xanthine nephropathy. Allopurinol treatment should be titrated against plasma uric acid as well as urinary uric acid and xanthine concentrations. The pa- tient should also be kept well hydrated to minimize the risk of xanthine stone formation. Allopurinol treatment from birth does not prevent the behavioural phenotype. All therapeutic attempts at neuropharmacological manipulation have been unsuccessful. There are however anecdotal reports that intrathecal baclofen ameliorated the motor symptoms and also improved behaviours. Oral S-adenosylmethionine at doses of 20 to 25 mg/kg per day has been reported to dramatic reduce self-injurious and aggressive be- haviour, as well as a milder reduction of dystonia in five Malaysian patients. Behavioural manifestations Following on from the discussion of pathophysiology, some aspects of the Lesch–Nyhan phenotype may be related to dysfunction of the small central, but widely projecting, aminergic pathways involved in learning. It has been suggested that the self-injurious behaviour in the Lesch–Nyhan syndrome is due to an imbalance between the ac- tivities of catecholaminergic neurons and 5-hydroxytryptaminergic neurons, the former being largely concerned with learning by re- ward and the latter with learning by punishment. Patients with the Lesch–Nyhan syndrome are insensitive to punishing stimuli and do not learn when such stimuli are used to reinforce the desired behaviour, which in this case is to refrain from self-injury, and their ability to learn from rewarding stimuli is also impaired. Psychotherapeutic techniques that are effective in elim- inating self-injurious behaviour in other situations fail in patients with the Lesch–Nyhan syndrome. They could be modified by a pro- gramme of positive reinforcement of abstaining from self-injury and ‘time out’, but this has proved difficult to achieve in the long term. The reinforcement strategy was found to be unsuitable for use at home because it involved apparently ignoring the self-injury and only paying attention to the child in the absence of self-injurious behaviour, which was misinterpreted by friends and relations as un- kindness or indifference. Managing self-injurious behaviour therefore requires teaching good communication skills, relaxation techniques, consistent hand- ling from all those involved in care, as well as physical restraints and specially designed equipment. Dental extraction, physical restraints with splints and bandages, and strapping the patient into a specially designed padded wheelchair fitted with a firm padded head support to prevent cervical spine injury during violent opisthotonic spasms, are usually needed to limit the effects of compulsive self-mutilation. Children whose restraints have been temporarily released ask or indicate their wish for the bandages, straps, etc. to be replaced so that they are less able to damage themselves. Every effort should be made to exploit the intellect of these patients and to keep them in a stimulating environment. Clinical genetic aspects The Lesch–Nyhan syndrome and its variants are inherited in a sex-linked recessive manner. Clinical manifestations in the female carriers are rare, but subtle alterations in purine metabolism, with small increases in the rates of de novo purine synthesis and in- creased uric acid excretion and occasionally mild asymptomatic hyperuricaemia, have been reported. There are extremely rare re- ports of female Lesch–Nyhan cases which have been attributed to nonrandom inactivation of the X chromosome. Genomic analysis is preferred for the identification of carrier females. The demonstra- tion of mosaicism by HPRT+ and HPRT− hair roots due to random inactivation of the X chromosome is error prone and is not widely available. Similarly, autoradiographic techniques to demonstrate two cell populations (HPRT+ and HPRT−) in fibroblast cultures are rarely used. Prenatal diagnosis is possible using chorionic villus samples obtained during the ninth week of pregnancy; this permits elective termination of an affected fetus before the end of the first trimester of pregnancy. In vitro fertilization with enzymatic assay or

geno- typing on a cell removed at the four-cell stage to ensure that only unaffected embryos are implanted is possible. Other disorders of purine metabolism PRPP synthetase superactivity and PRPP synthetase deficiency The enzyme PRPP synthetase (PRPS) catalyses the production of PRPP, which is required for the first specific and rate-limiting re- action in the de novo pathway of purine synthesis, is encoded by the PRPS1 gene. It is subject to feedback inhibition by purine nu- cleotides. Mutations associated with diminished sensitivity to this

12.4 Disorders of purine and pyrimidine metabolism 2027 feedback inhibition, lead to increased PRPP production, which in turn acts as a driver for increased de novo purine synthesis, leading to hyperuricaemia, hyperuricosuria, and gout. The condition is in- herited in an X-linked recessive fashion. Affected males develop uric acid lithiasis or gouty arthritis in childhood or early adult life. Hyperuricaemia is often severe and in the range 0.5 to 1 mmol/litre, with uric acid excretion of 5 to 15 mmol/24 h. Heterozygous females are usually asymptomatic, al- though some degree of increased purine synthesis de novo and occa- sionally gout, may occur with nonrandom X-inactivation. In some families, the disorder presents in childhood with associ- ated neurological features such as motor retardation and learning difficulties, ataxia, deafness, hypotonia, disturbed speech, and the development of polyneuropathy, intracerebral calcifications, and dysmorphic facial features. Carrier females may have mild hyperuricaemia and some degree of hearing impairment. The con- stellation of associated disorders varies in different families. Carriers can be identified by mutation analysis and by studies in cultured skin fibroblasts. Amniocentesis, prenatal diagnosis, and preventive termination of pregnancy are not justified in this condi- tion, unless one of the unusually severe phenotypes is known to be segregating in the family. The hyperuricaemia, primary purine over- production, and uricosuria can be well controlled with allopurinol. Mutations in PRPS1 can also lead to PRPP synthetase defi- ciency of varying degree and a broad spectrum of phenotypes including syndromic and nonsyndromic hearing loss comprising Charcot–Marie–Tooth, X-linked recessive disease type 5 (CMTX5), nonsyndromic sensorineural deafness (DFN2), and Arts' syndrome. Hearing loss in affected males is bilateral and ranges from moderate to profound. Arts' syndrome is characterized by profound sensori- neural hearing impairment, early-onset hypotonia, delayed motor development, mild to moderate mental retardation, ataxia, and optic atrophy. Oral supplementation with S-adenosylmethionine (30 mg/ kg per day) has provided significant clinical benefit to two brothers diagnosed with Arts' syndrome. This suggests that other patients with PRPS synthetase deficiency, including mildly affected carrier females, may benefit from S-adenosylmethionine supplementation. Uric acid concentrations in patients with PRPS deficiency may be low or normal and levels cannot be used as a diagnostic marker. Adenine phosphoribosyltransferase deficiency and 2,8-dihydroxyadeninuria These patients lack adenine phosphoribosyltransferase activity; adenine accumulates behind the metabolic block and is oxi- dized by xanthine oxidase to the very insoluble compounds 2- hydroxyadenine and 2,8-dihydroxyadenine. These compounds are excreted in the urine along with adenine itself, where it forms radiotranslucent stones that are white or pale fawn in colour. These rough and friable calculi have, in the past, been widely misdiagnosed as uric acid stones because 2,8-dihydroxyadenine reacts as if it were uric acid in colorimetric assays. The use of enzymatic uric acid as- says has obviated this confusion. Adenine phosphoribosyltransferase deficiency has an autosomal recessive pattern of inheritance and is clinically silent in hetero- zygotes. There are two subtypes (I and II). Type I patients have no detectable enzyme activity, being homozygotes or compound het- erozygotes for null alleles. Type II patients have between 5 and 25% residual enzyme activity. Whereas type I patients are encountered in many racial groups, the type II subtype has so far only

been identi- fied in the Japanese population. This condition often presents in early life because of the extremely low solubility of 2,8-dihydroxyadenine in renal tubule fluid and urine. Severe obstructive uropathy and renal failure may occur in infancy. Treatment is by hydration and xanthine oxidase inhibition with allopurinol, and with standard measures to disrupt or remove the stones and to manage urinary infections and renal failure. Xanthinuria Xanthine stones occur in patients with xanthinuria due to deficiency of xanthine oxidase/reductase deficiency and occasionally, in those who are being treated with the xanthine oxidase inhibitor, allopur- inol. The latter is particularly likely in patients with accelerated de novo purine synthesis, as in patients with the Lesch–Nyhan syn- drome. Xanthinuria is inherited in an autosomal recessive manner, and hypoxanthine and xanthine accumulate behind the metabolic block. The plasma urate concentration and urine uric acid excretion are typically less than 0.06 mmol/litre (1.0 mg/dl) and 0.30 mmol/ 24 h (50 mg/24 h), respectively, when the patient is taking an un- restricted diet. It is a rare, perhaps under-recognized condition. Concentrations of urine oxypurines (hypoxanthine plus xanthine) are characteristically elevated. Normal subjects have plasma levels between 0.00 and 0.15 mmol/litre (0.00–0.25 mg/dl) and urine levels of 0.07 to 0.13 mmol/24 h (11–22 mg/24 h); patients with xanthinuria typically have plasma levels between 0.03 and 0.05 mmol/litre (0.00–0.90 mg/dl) and urine levels of 0.60 and 3.5 mmol/24 h (100–600 mg/24 h). Xanthine accounts for 60 to 90% of the total xanthine plus hypoxanthine excreted, presumably reflecting the more active meta- bolic turnover of hypoxanthine and its efficient salvage by hypo- xanthine phosphoribosyltransferase. Hypoxanthine and xanthine are mainly derived from adenine and guanine nucleotides, respect- ively (Fig. 12.4.1). Hypoxanthine has a relatively high solubility and causes no problems. At any age, about one-third of cases present with radiotranslucent xanthine stones. These stones are usually smooth, soft, and yellow- brown. Xanthinuric myopathy is a rare complication. Type 1 xanthinuria is due to an isolated defect in xanthine oxi- dase/reductase, while type 2 xanthinuria is due to a defect in mo- lybdenum sulphurase which catalyses the terminal step in the synthesis of the molybdopterin cofactor necessary for the activity of both aldehyde oxidase and xanthine oxidase. These patients present with xanthine stones and are detected by their inability to convert allopurinol to oxypurinol, a reaction normally catalysed by aldehyde oxidase. Xanthine stones also occur when there is a combined deficiency of the three molybdoflavoprotein enzymes, xanthine oxidase, sulphite oxidase, and aldehyde oxidase, because of defective molybdopterin cofactor synthesis. The clinical picture in these patients is overshadowed by the sulphite oxidase defi- ciency that produces severe brain damage and dislocation of the ocular lenses. Adenylosuccinase deficiency and ATIC deficiency Adenylosuccinase (adenylate succinate lyase (ADSL)) catalyses the eighth step on the 10-step de novo purine synthesis pathway and the second step in one of the purine nucleotide interconversion path- ways, the formation of ATP from inosine monophosphate.

 The patients present in infancy with severe psychomotor dis- abilities, autism, and axial hypotonia with normal tendon reflexes. Self-mutilation has been recorded in some cases and cerebellar hypoplasia is present on CT scans. The presence of succinyl adenosine and succinyl aminoimidazole carboxamide riboside in plasma, cerebrospinal fluid, and urine confirms the diagnosis. There is gross purine overproduction with high levels of purine ribosides in urine. Urine and plasma uric acid levels are normal. Partial enzyme deficiencies have been demonstrated in liver, kidney, muscle, lymphocytes, and fibro- blasts, with mutations identified in more than 70 patients. Clinical severity is variable and correlates with the ratio of succinyl ad- enosine to succinyl aminoimidazole carboxamide riboside in the cerebrospinal fluid.

The bifunctional enzyme 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase (ATIC) cata- lyses the last two reactions of de novo purine synthesis. A deficiency of ATIC leads to the accumulation of the dephosphorylated sub- strate of ATIC, aminoimidazol carboxamide riboside, as well as the accumulation of succinylaminoimidazole carboxamide riboside and succinyladenosine in body fluids. Both deficiencies are inherited as autosomal recessive conditions. For ADSL deficiency, the growth retardation has been improved by adenine (10 mg/kg) and allopurinol. The latter promotes purine conservation by blocking hypoxanthine oxidation to xanthine and uric acid, and prevents the oxidation of administered adenine to 2,8-dihydroxyadenine. There is currently no effective treatment for either enzyme deficiency. Oral S-adenosylmethionine has been suggested as a purine replacement therapy in ADSL deficiency, but showed no clinical benefit in a patient treated for 9 months. Myoadenylate deaminase deficiency Myoadenylate deaminase is the muscle-specific isoenzyme of ad- enylate deaminase which catalyses the deamination of adenosine monophosphate nucleotide (AMP) to inosine monophosphate (IMP) during muscle contraction. This reaction is necessary for normal muscle function. Myoadenylate deaminase deficiency may be congenital, due to a mutation in the gene directing the syn- thesis of the protein, or associated with a wide range of muscle diseases including the muscular dystrophies, polymyositis, and dermatomyositis. Patients with congenital myoadenylate deaminase deficiency pre- sent at any age including early childhood with a syndrome of muscle weakness and muscle cramps during and after exertion. There is some decrease in muscle mass, some hypotonia, and a little muscle weak- ness. There may be a modest rise in plasma creatine phosphokinase levels and nonspecific electromyographic changes. The lack of am- monia and IMP occurs normally in the venous outflow from the af- fected muscles during exercise, and the enzyme deficiency can be demonstrated histochemically. The pattern of inheritance is auto- somal recessive, not all of the homozygotes have clinical symptoms, and the heterozygous carriers are clinically silent. The nonsense variant c.34C>T, (p.Q34X) in exon 2 is polymorphic in Caucasian populations. Exon 2 is alternatively spliced and transcripts lacking the c.34C>T, (p.Q34X) variant encode a functionally active protein. The acquired disorder may be due to the coincidental disease arising in a patient whose inherited myoadenylate deaminase deficiency would otherwise be silent. Myoglobinuria following strenuous exercise has been reported in a few cases and hence the risk of rhabdomyolysis has led some authors to recommend the avoidance of vigorous exercise. Such ad- vice is only appropriate if exertion-related myoglobinuria has oc- curred or been suspected. Oral ribose (2–60 g/day, or taking a dose before vigorous exercise) has been reported to produce symptomatic improvement. Inborn errors of purine metabolism and immunodeficiency Adenosine deaminase and purine nucleoside phosphorylase catalyse sequential steps in the metabolism of purine ribonucleosides and deoxyribonucleosides. These enzymes are highly expressed in the lymphoid cells and their deficiency, which causes the lymphotoxic substrates 2′-deoxyadenosine or 2′-deoxyguanosine to accumulate, leads to lymphopenia and immunodeficiency. Most patients with adenosine deaminase deficiency lack both cell-mediated (T-cell) and humoral-mediated (B-cell) immunity resulting in severe combined immunodeficiency disease. Although purine nucleoside phosphorylase deficiency causes defective T- cell-mediated immunity, these patients may possess either normal, hyperactive, or reduced humoral immunity. Most patients with these enzyme deficiencies present in infancy or early childhood, with se- vere infections caused by pathogens or opportunistic organisms. Adenosine deaminase deficiency About 85% of patients with adenosine deaminase deficiency present as infants with severe combined immunodeficiency disease. Among all severe combined immunodeficiency disease patients, adenosine deaminase deficiency accounts for 10 to 15% of

cases. Although ad- enosine deaminase deficiency classically presents in infancy (early onset), a minority of patients have a clinically less severe variant with delayed onset presenting with severe combined deficiency between the ages of 1 and 10 years. Very rarely, patients may presents in the second to fourth decade. The prevalence of adenosine deaminase deficiency has been estimated at between less than 1 in 106 and 1 in 2 × 105 live births. Adenosine deaminase deficiency is inherited in an auto- somal recessive fashion. The diagnosis is made by meas- uring adenosine deaminase activity in erythrocytes and the presence of deoxyadenosine nucleotides in red cell nucleotide pro- files. Heterozygote detection and prenatal diagnosis are best done by genetic characterization. In addition to immunoparesis, clinical feature include growth failure, absent tonsils and lymph nodes, and absence of a thymus shadow on radiography. Characteristic skeletal abnormalities in- clude anterior rib cupping, scapular spurring, and are present at diagnosis in about half of individuals. Sensorineural deafness and other neurological symptoms have been reported, but may be sec- ondary to infections, autoimmunity, or transplantation. The prognosis in untreated severe adenosine deaminase defi- ciency is very poor with death due to multiple recurrent infections during the first year of life. Adenosine and 2′-deoxyadenosine, derived from the breakdown of DNA due to cell death, accumulate proximal to the metabolic block; 2′-deoxyadenosine is the primary lymphotoxic precursor in adeno- sine deaminase deficiency and elevated levels are present in urine. Erythrocytes contain markedly raised levels of deoxyadenosine triphosphate and reduced activity of S-adenosylhomocysteine

 hydrolase due to inactivation by 2′-deoxyadenosine. Erythrocyte ATP is reduced. The level of deoxyadenosine triphosphate in erythrocytes correlates with clinical expression and with the level of residual adenosine deaminase activity. There are several mechanisms by which adenosine deaminase deficiency can impair immune function. Accumulation of deoxyadenosine triphosphate can induce apoptosis in lymphoid cells. This may be related to deoxyadenosine triphosphate-induced inhibition of ribonucleotide reductase blocking DNA replication in dividing cells and to deoxyadenosine triphosphate-induced DNA strand breaks in nondividing lymphocytes. Deoxyadenosine triphosphate also activates the protease (caspase 9) involved in apoptosis. S-adenosylhomocysteine hydrolase blocks S-adenosylmethionine-mediated transmethylation reactions. The for- mation of deoxyadenosine triphosphate from 2′-deoxyadenosine activates inosine monophosphate dephosphorylation thereby leading to depletion of cellular ATP. It has also been suggested that lymphocyte function may be impaired by aberrant signal trans- duction mediated by deoxyadenosine acting through G-protein-associated receptors or from an altered costimulatory function of T-cell-associated adenosine deaminase complexing protein CD26/ dipeptidyl peptidase IV. Treatment is based on enzyme replacement. Enzyme replace- ment therapy with pegylated bovine adenosine deaminase provides a source of the enzyme to remove the toxic metabolites in the short term until the patient can be transplanted. Allogeneic haemato- poietic stem cell transplant is done if a fully HLA-matched sibling or family donor is available. Transplants from unrelated or haplo- identical donors have been less successful. Haematopoietic stem cell gene therapy to insert a functional adenosine deaminase copy into the genetic material of the patient has recently become available and has shown curative potential. Measurement of deoxyadenosine triphosphate levels in red cells is useful for monitoring therapy. Purine nucleoside phosphorylase deficiency Purine nucleoside phosphorylase deficiency occurs less frequently than adenosine deaminase deficiency. In addition to the clinical results of immunoparesis, more than 50% of these patients have neurological abnormalities including disorders of muscle tone, de- layed motor and intellectual development, ataxias, tremors, spastic

tetraparesis, and behavioural difficulties. Autoimmune haemolytic anaemia and megaloblastic bone marrow changes have been occa- sional associations. There appears to be a particular susceptibility to virus infection such as varicella, vaccinia, and cytomegalovirus. The tonsils and the thymus are small or absent and the lymph nodes are deficient in the thymus-dependent areas. Circulating lymphocyte counts are usually very low with a low percentage of T lymphocytes and de- pressed or absent responsiveness to mitogen-induced transform- ation. Serum immunoglobulin levels and antibody responses to pneumococcal polysaccharide and keyhole limpet haemocyanin are typically increased in these children with purine nucleoside phosphorylase deficiency, and the occasional finding of mono- clonal IgM paraprotein strongly suggests that B-cell hyperactivity and changes in antibody production are secondary to T-cell dysregulation. Purine nucleoside phosphorylase deficiency is associated with the accumulation and excretion of 2′-deoxyguanosine and deoxyinosine as well as guanosine and inosine. Paradoxically there is massive purine overproduction and excretion. Plasma uric acid may be low, but not in all patients. Erythrocyte concentrations of deoxyguanosine triphosphate are markedly raised in purine nucleoside phosphorylase-deficient cells. T cells but not B cells appear to be particularly susceptible to 2′-deoxyguanosine toxicity, probably as a result of accumula tion of deoxyguanosine triphosphate, inhibition of ribonucleotide reductase, impairment of DNA synthesis, and eventually cell death. There are few reports of successful bone marrow or stem trans- plantation in purine nucleoside phosphorylase-deficient patients, possibly reflecting an avoidance of high-risk procedures in children with a later-onset presentation than seen in adenosine deaminase deficiency. There is, however, increasing evidence that early inter- vention may be beneficial and may also prevent further neurological deterioration. Other conditions Adenosine kinase deficiency has been reported in patients from three families presenting with severe developmental delay and liver dysfunction. Biochemical finding suggested a block in the methio- nine cycle, with plasma methionine, S-adenosylmethionine, and S-adenosylhomocysteine all elevated. A defect in deoxyguanosine kinase is associated with mitochon- drial DNA depletion with a predominantly hepatocerebral pheno- type. Liver transplantation may be beneficial in patients in whom neurological disease is absent or mild. Mutations in inosine monophosphate dehydrogenase type 1 (IMPDH1), which together with IMPDH2 catalyse the first step in the conversion of inosine monophosphate to guanosine monophosphate, are associated with autosomal dominant retinitis pigmentosa (RP10 form). Inactivating mutations in the gene NT5C2 encoding cyto- solic purine 5’-nucleotidase (cytosolic nucleotidase II), AMPD2 encoding adenosine monophosphate deaminase-2, and ENTPD1 (ectonucleoside triphosphate diphosphohydrolase 1) are associ- ated with hereditary spastic paraplegias, neurodegenerative motor neuron diseases characterized by progressive age-dependent loss of corticospinal motor tract function. Disorders of pyrimidine metabolism The pathways of pyrimidine biosynthesis interconversion and deg- radation are shown in Fig. 12.4.9. The de novo synthesis of pyr- imidine nucleotides involves a series of six reactions beginning with the formation of carbamyl phosphate and concluding with orotidine monophosphate, which then undergoes a series of inter- conversion and salvage reactions. The first three steps in the de novo synthesis pathway are encoded in a gene directing the synthesis of the multifunctional protein that encompasses carbamyl phosphate synthetase, aspartate transaminase, and dihydro-orotase. The fourth step is catalysed by dihydro-orotate dehydrogenase which is encoded in a single gene. The fifth and sixth steps are catalysed by the gene directing the synthesis of the bifunctional protein encoding orotate phosphoribosyltransferase and orotidine 5′-monophosphate de- carboxylase, which reside in separate regions of the protein uridine

 monophosphate synthetase (UMPS). The pyrimidines are degraded to β-alanine and β-aminoisobutyrate. The inherited disorders of pyrimidine metabolism are much less common and/or possibly much less easily recognized than disorders of purine metabolism. Dihydro-orotate dehydrogenase deficiency
(Miller's syndrome) Dihydro-orotate dehydrogenase is located on the inner membrane of mitochondria and catalyses the conversion of dihydro-orotate to orotate, the fourth step in the de novo synthesis of pyrimidines. A deficiency of dihydro-orotate dehydrogenase causes Miller's syndrome or postaxial acrofacial dysostosis syndrome which is charac- terized by micrognathia, orofacial clefts, malar hypoplasia, aplasia of the medial lower lid eyelashes, coloboma of the lower eyelid, and cup-shaped ears, combined with postaxial limb deformities. Miller's syndrome was the first Mendelian disorder whose genetic basis was identified by whole-exome sequencing. Dihydro-orotate levels are not reported to be elevated in urine. Hereditary orotic aciduria Orotic aciduria is due to point mutations in the gene UMPS directing the synthesis of the bifunctional protein UMP synthase which cata- lyses the last two steps on the pyrimidine biosynthetic pathway. There is massive overproduction of orotic acid due to loss of feed- back inhibition of carbamyl phosphate synthase, which is the first and rate-limiting step on the metabolic pathway. Orotic aciduria presents during infancy with severe megaloblastic hypochromatic anaemia, orotic acid crystalluria, and occasionally, radiotranslucent orotic acid urinary stones. Cardiac malformations, mild intellectual impairment, and strabismus have been reported. Orotic aciduria is inherited as an autosomal recessive defect. Patients heterozygous for a UMPS mutation may have mildly elevated orotic acid in urine and this may explain some cases of benign hereditary orotic aciduria found on screening. Enzyme assays on erythrocyte lysates may show low levels of orotate phosphoribosyltransferase or orotidine 5′-monophosphate decarboxylase activity, or both, depending on the location and nature of the underlying genetic defect. Administration of uridine (100– 150 mg/kg per day), which is converted to uridine monophosphate (Fig. 12.4.9), produces a prompt haematological response in those patients with a megaloblastic anaemia. Treatment needs to be started as soon as the diagnosis is made during infancy in order to minimize the possibility of persistent neurological deficits. Orotic aciduria has been found in urea cycle defects, lysinuric protein intolerance, purine nucleoside phosphorylase deficiency, normal pregnancy, and during allopurinol administration. Pyrimidine 5′-nucleotidase deficiency (uridine 5'- monophosphate hydrolase) This autosomal recessive disorder leads to a life-long nonspherocytic mild to moderate chronic haemolytic anaemia. Uridine tri- phosphate and cytidine triphosphate accumulate in the red cells which show basophilic stippling and reticulocytosis. There is hepatosplenomegaly. The enzyme is assayed in erythrocytes and activities between 0 and 30% of normal have been reported. Developmental delay and learning difficulties have been reported in some patients. Treatment is supportive. Transfusions are rarely required and splenectomy is not indicated. Lead poisoning can also be associated with acquired erythrocyte pyrimidine 5′-nucleotidase deficiency. Deficiency of dihydropyrimidine dehydrogenase This autosomal recessive disorder presents with a variable pheno- type ranging from microcephaly, hypertonia, epilepsy, learning dif- ficulties, and autism, to mild behavioural abnormalities, even within the same family. Some cases have only been diagnosed during adult life when they have developed life-threatening or fatal toxicity - following cancer chemotherapy with 5-fluorouracil. Uracil and thy- mine are elevated in the urine of completely deficient patients, but not in carriers. Absent enzyme activities have been demonstrated in leucocytes, liver, and fibroblasts. There is no effective treatment for this condition and the prognosis for life is very variable. Partial dihydropyrimidine dehydrogenase deficiency due to a heterozygous variant genotype occurs in approximately 6% of Caucasian popu- lations, is

asymptomatic but is associated with severe toxicity to fluoropyrimidine-based chemotherapy. Deficiency of dihydropyrimidinase Dihydropyrimidinase catalyses the second step of the pyrimidine degradation pathway. Patients present with neurological and gastrointestinal abnormalities and markedly elevated levels of 5,6- dihydrouracil and 5,6-dihydrothymine in body fluids. There is con- siderable phenotypic variation, even within families. Patients with dihydropyrimidinase deficiency are also at risk of severe toxicity to fluoropyrimidine chemotherapy. Fig. 12.4.9 Pathways of pyrimidine metabolism in humans. 5′-NT, pyrimidine 5′-nucleotidase; CPSH, carbamyl phosphate synthetase II; DHPD, dihydropyrimidine dehydrogenase; NP, pyrimidine nucleoside phosphorylase; ODC, orotidine decarboxylase (OPRT

- ODC form uridine monophosphate synthase); OPRT, orotate phosphoribosyltransferase; TK, thymidine kinase; UK, uridine kinase; UPRT, uracil phosphoribosyltransferase.

12.4 Disorders of purine and pyrimidine metabolism 2031 ß-Ureidopropionase deficiency Ureidopropionase catalyses the conversion of N-carbamyl-ß- alanine and N-carbamyl-ß-aminoisobutyric acid to ß-alanine and ß-aminoisobutyric acid, ammonia, and CO2. Patients present mainly with neurological abnormalities (intellectual dis- abilities, seizures, abnormal tonus regulation, microcephaly). N-carbamyl-ß-alanine and N-carbamyl-ß-aminoisobutyric acid are markedly elevated in urine and blood. As with the other de- fects of pyrimidine degradation, phenotypic variability of ß- ureidopropionase deficiency was demonstrated in one family in which the index patient was clinically affected whereas the same genotype did not lead to overt symptoms in the mother of the patient. Thymidine phosphorylase deficiency Thymidine phosphorylase catalyses the conversion of thy- midine and deoxyuridine to thymine and uracil respectively. A deficiency of the enzyme results in the accumulation of both thymidine and deoxyuridine in blood and urine and results in the mitochondrial depletion syndrome mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). The intra- cellular accumulation of these nucleosides leads to imbalances of mitochondrial deoxynucleotide pools impairing mitochon- drial DNA replication and leading to depletion of mitochondrial DNA. MNGIE is a multisystemic autosomal recessive disorder with onset typically before the age of 30 years, with most pa- tients presenting as children, some within 5 months of birth. Symptoms include ptosis, progressive external ophthalmoplegia, gastrointestinal dysmotility, cachexia, peripheral neuropathy, and leukoencephalopathy. Allogeneic haematopoietic stem cell transplantation is reported to restore enzyme function and improve clinical manifestations in the long term. Thymidine kinase 2 deficiency Mutations in TK2 encoding thymidine kinase 2, which catalyses the phosphorylation of deoxypyrimidine nucleosides in the mito- chondrial matrix, are mainly associated with the myopathic form of mitochondrial depletion syndromes. The phenotypic spectrum ranges from infantile myopathy with motor regression and early death to milder forms of myopathy with prolonged survival, my- opathy with liver involvement, or chronic progressive external ophthalmoplegia in adults. FURTHER READING Cameron JS, Simmonds HA (2005). Hereditary hyperuricaemia and renal disease. Semin Nephrol, 25, 9–18. Dalvi SR, Pillinger MH (2013). Saturnine gout, redux: a review. Am J Med, 126, 450.e1–8. de Brouwer AP, et al. (2010). PRPS1 mutations: four distinct syn- dromes and potential treatment. J Hum Genet, 86, 506–18. Eckardt KU, et al. (2015). Autosomal dominant tubulointerstitial kidney disease: diagnosis, classification, and management—a KDIGO consensus report. Kidney Int, 88, 676–83. Fam AG (2001). Difficult gout and new approaches for control of hyperuricaemia in the allopurinol-allergic patient. Curr Rheumatol Rep, 3, 29–35. Ferraro PM, et al. (2015). A London experience 1995-2012: demographic, dietary and biochemical characteristics of a large adult co- hort of patients with renal

stone disease. QJM, 108, 561–8. Frampton JE (2015). Febuxostat: a review of its use in the treatment of hyperuricaemia in patients with gout. Drugs, 75, 427–38. Harkness, et al. (1988). Lesch-Nyhan syndrome and its pathogen- esis: purine concentrations in plasma and urine with metabolite profiles in CSF. J Inherit Metab Dis, 11, 239–52. Hart TC, et al. (2002). Mutations of the UMOD gene are respon- sible for medullary cystic kidney disease 2 and familial juvenile hyperuricaemic nephropathy. J Med Genet, 39, 882–92. Johnson RJ, et al. (2013). Uric acid and chronic kidney disease: which is chasing which? Nephrol Dial Transplant, 28, 2221–8. Khanna D, et al. (2012). 2012 American College of Rheumatology guide- lines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken), 64, 1431–46. Khanna D, et al. (2012). 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflam- matory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken), 64, 1447–61. Merriman TR (2015). An update on the genetic architecture of hyperuricemia and gout. Arthritis Res Ther, 17, 98. Mount DB (2013). The kidney in hyperuricemia and gout. Curr Opin Nephrol Hypertens, 22, 216–23. Rampoldi L, et al. (2003). Allelism of MCKD, FJHN, and GCKD caused by impairment of uromodulin export dynamics. Hum Mol Genet, 12, 3369–84. Rannou F, et al. (2015). Diagnostic algorithm for glycogenoses and myoadenylate deaminase deficiency based on exercise testing parameters: a prospective study. PLoS One, 10, e0132972. Scriver CA, et al. (eds) (2001). The metabolic and molecular basis of inherited disease, 8th edition. McGraw–Hill, New York. Sperling O (2006). Hereditary renal hypouricaemia. Mol Genet Metab, 89, 14–18. Torres RJ, Puig JG (2007). Hypoxanthine-guanine phosopho ribosyltransferase (HPRT) deficiency: Lesch-Nyhan syndrome. Orphanet J Rare Dis, 2, 48. van Kuilenburg AB, et al. (2010). Dihydropyrimidinase defi- ciency: phenotype, genotype and structural consequences in 17 pa- tients. Biochim Biophys Acta, 1802, 639–48. Van Kullenburg AB, et al. (2004). Beta-ureidopropionase deficiency: an inborn error of pyrimidine degradation associated with neuro- logical abnormalities. Hum Mol Genet, 13, 2793–801. Watts RWE, et al. (1987). Lesch-Nyhan syndrome; growth delay, tes- ticular atrophy and a partial failure of 11β-hydroxylation of steroids. J Inherit Metab Dis, 10, 210–23. Woodward OM (2015). ABCG2: the molecular mechanisms of urate secretion and gout. Am J Physiol Renal Physiol, 309, 485–8. Zanella A, et al. (2006). Hereditary pyrimidine 5′-nucleotidase defi- ciency from genetics to clinical manifestations. Br J Haematol, 133, 113–23. Zhang W, et al. (2006). EULAR evidence based recommendations for gout. Part II: Management Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis, 65, 1312–24.

Revision #1
Created 2026-01-22 16:37:36 UTC by Omar Ayman
Updated 2026-01-22 16:37:37 UTC by Omar Ayman