4. Garrett JK, *et al.* Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. *J Allergy Clin Immunol* 2004; **113:** 115–19.
5. Rothenberg ME, *et al.* Mepolizumab HES Study Group. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med* 2008; **358:** 1215–28.

Mercaptopurine *(BAN, rINN)*

Mercaptopurina; Mercaptopurinum; Mercaptopurinum Monohydricum; Merkaptopuriini; Merkaptopürin; Merkaptopurin; Merkaptopurin monohydrát; Merkaptopurinas; Merkaptopurына; NSC-755; 6MP; Purinethiol; WR-2785. 6-Mercaptopurine monohydrate; Purine-6-thiol monohydrate; 1,7-Dihydro-6*H*-purine-6-thione monohydrate.

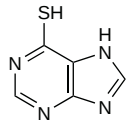
Меркаптопурин

$C_5H_4N_4S,H_2O$ = 170.2.

CAS — 50-44-2 (anhydrous mercaptopurine); 6112-76-1 (mercaptopurine monohydrate).

ATC — L01BB02.

ATC Vet — QL01BB02.



NOTE. In the UK, the CSM noted in October 2004 that confusion had arisen between mercaptopurine and mercaptamine (formerly cysteamine, p.2340) after the switch from prescribing by British Approved Name to prescribing by International Nonproprietary Name. Particular care should be taken to distinguish the two, since they are available in oral dosage forms of similar strength.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 6.2 (Mercaptopurine). A yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; dissolves in solutions of alkali hydroxides. Protect from light.

USP 31 (Mercaptopurine). A yellow, odourless or practically odourless, crystalline powder. Insoluble in water, in acetone, and in ether; soluble in hot alcohol and in dilute alkali solutions; slightly soluble in 2N sulfuric acid.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Bone-marrow depression with mercaptopurine, manifesting as leucopenia, thrombocytopenia, and anaemia, may be delayed; hypoplasia may occur. Mercaptopurine is less toxic to the gastrointestinal tract than the folic acid antagonists or fluorouracil but gastrointestinal disturbances may occur. Hepatotoxicity has been reported, with cholestatic jaundice and necrosis, sometimes fatal. Gastrointestinal and hepatic toxicity are reported to be more frequent in adults than in children, and are more likely at higher doses. Crystalluria with haematuria has been observed rarely as have skin disorders including hyperpigmentation. Fever may occur.

Mercaptopurine is potentially carcinogenic and mutagenic; an increased incidence of abortion has occurred in women given mercaptopurine during the first trimester of pregnancy.

Mercaptopurine should be used with care in patients with impaired hepatic or renal function. Hepatic function should be monitored periodically.

Effects on the blood. Measurement of the activity of thiopurine methyltransferase (TPMT) or the concentration of its substrate, tioguanine nucleotide, has been suggested as a way of predicting those individuals likely to have severe myelotoxicity with mercaptopurine and related drugs (see Azathioprine, p.1819). Patients with an inherited deficiency of the TPMT enzyme may be at increased risk of myelosuppression from mercaptopurine. US licensed product information suggests TPMT testing in patients with evidence of toxicity, and state that reductions in the dose of mercaptopurine may be necessary in those with TPMT deficiency, although optimal initial doses have not been established for these patients. The UK licensed information states that tests for TPMT deficiency have not been shown to identify all patients at risk of severe toxicity, and that close monitoring of blood counts should still be performed.

Effects on the pancreas. Pancreatitis occurred in 13 of 396 patients given mercaptopurine for inflammatory bowel disease.[1] Symptoms resolved on withdrawal but recurred in 7 who were re-challenged with mercaptopurine or azathioprine. Acute pancreatitis has also been reported in 2 children given mercaptopurine during maintenance chemotherapy for acute lymphoblastic leukaemia.[2] They had also suffered pancreatitis from asparaginase during earlier therapy, and the authors suggested that subclinical damage to the pancreas by asparaginase may have been exacerbated by mercaptopurine, but also noted that most patients who develop asparaginase-induced pancreatitis receive mercaptopurine without developing this complication.

1. Present DH, *et al.* 6-Mercaptopurine in the management of inflammatory bowel disease: short- and long-term toxicity. *Ann Intern Med* 1989; **111:** 641–9.
2. Willert JR, *et al.* Recurrent mercaptopurine-induced acute pancreatitis: a rare complication of chemotherapy for acute lymphoblastic leukemia in children. *Med Pediatr Oncol* 2002; **38:** 73–4.

Handling and disposal. A method for the destruction of mercaptopurine or tioguanine in *wastes* by oxidation with potassium permanganate in sulfuric acid.[1] Residues produced by this method had no mutagenic activity. *Urine and faeces* produced for up to 48 hours and 5 days, respectively after a dose of mercaptopurine should be handled wearing protective clothing.[2]

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73*. Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Overdosage. Despite substantial overdose, no acute renal or hepatic toxicity occurred in 2 children. In one case, in which no specific detoxification measures were implemented, neutrophils reached a nadir on day 11 followed by a gradual recovery to normal by day 46. In the other case, gastric lavage was performed and activated charcoal was given; no evidence of neutropenia was seen. The authors recommended that management of acute accidental ingestion should include gastric lavage if the patient presents within 1 hour or if the amount ingested is large. Haemodialysis may be considered if the patient presents within 3 hours of ingestion. Liver function should be monitored. Severe myelosuppression may be managed with granulocyte colony-stimulating factor and a bone-marrow harvest may be of benefit if performed within several hours of the overdose.[1]

1. Chow LML, *et al.* Toxic ingestion of 6-mercaptopurine by young siblings of pediatric oncology patients. *J Pediatr* 2004; **144:** 669–71.

Porphyria. Mercaptopurine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

Mercaptopurine should be given with particular caution with other hepatotoxic drugs. Its effects are enhanced by allopurinol and the dose of mercaptopurine should be reduced to one-third to one-quarter of the usual dose when allopurinol is also given.

Allopurinol. Mercaptopurine plasma concentrations were markedly increased by allopurinol when mercaptopurine was given by mouth but not when it was given intravenously.[1] The results appear to indicate that allopurinol inhibits the first-pass metabolism of mercaptopurine.

1. Zimm S, *et al.* Inhibition of first-pass metabolism in cancer chemotherapy: interaction of 6-mercaptopurine and allopurinol. *Clin Pharmacol Ther* 1983; **34:** 810–17.

Anticoagulants. For reference to mercaptopurine diminishing the activity of *warfarin*, see p.1429.

Antineoplastics. For a suggestion that *doxorubicin* might enhance the hepatotoxicity of mercaptopurine, see under Daunorubicin Hydrochloride, p.709.

Giving mercaptopurine with low-dose oral *methotrexate* increased mean peak plasma concentrations of mercaptopurine by 26% compared with the same dose of mercaptopurine alone in a study in 14 patients with acute lymphoblastic leukaemia.[1] The effect was probably due to inhibition of the first-pass metabolism of mercaptopurine by methotrexate, which is a potent inhibitor of xanthine oxidase. In another study[2] of 10 children with acute lymphoblastic leukaemia, high-dose intravenous methotrexate (2 or 5 g/m^2) increased the peak plasma concentrations of mercaptopurine by 108 and 121% respectively. However, the clinical effect of this pharmacokinetic interaction is probably only minor because of the low, and highly variable, mercaptopurine bioavailability and the lack of correlation between mercaptopurine plasma concentrations and effect.[3] Mercaptopurine and methotrexate have been widely used in combination chemotherapy regimens for acute lymphoblastic leukaemia for their synergistic pharmacodynamic interaction.

1. Balis FM, *et al.* The effect of methotrexate on the bioavailability of oral 6-mercaptopurine. *Clin Pharmacol Ther* 1987; **41:** 384–7.
2. Innocenti F, *et al.* Clinical and experimental pharmacokinetic interaction between 6-mercaptopurine and methotrexate. *Cancer Chemother Pharmacol* 1996; **37:** 409–14.
3. Giverhaug T, *et al.* The interaction of 6-mercaptopurine (6-MP) and methotrexate (MTX). *Gen Pharmacol* 1999; **33:** 341–6.

Azathioprine. For a report of a fatality when a patient was prescribed mercaptopurine and azathioprine by separate practitioners, see Interactions, under Azathioprine, p.1819.

Gastrointestinal drugs. The enzyme thiopurine methyltransferase is inhibited *in vitro* by *sulfasalazine* and *mesalazine*, raising the possibility of an interaction in patients treated simultaneously with an aminosalicylate and a thiopurine such as mercaptopurine or azathioprine.[1] Myelotoxicity has been reported in a patient receiving mercaptopurine and *olsalazine*.[2] Similarly, severe pancytopenia has occurred in a 13-year-old boy when azathioprine was added to mesalazine therapy.[3] In a study[4] of 34 patients with Crohn's disease in which *balsalazide*, mesalazine, or sulfasalazine was added to established azathioprine or mercaptopurine therapy, mild leucopenia was common in patients given mesalazine or sulfasalazine, and whole blood concentrations of tioguanine nucleotide were found to be increased, probably due to thiopurine methyltransferase inhibition. These effects were not statistically significant in patients given balsalazide.

1. Szumlanski C, Weinshilboum RM. Sulfasalazine inhibition of thiopurine methyltransferase: possible mechanism for interaction with 6-mercaptopurine and azathioprine. *Br J Clin Pharmacol* 1995; **39:** 456–9.
2. Lewis LD, *et al.* Olsalazine and 6-mercaptopurine-related bone marrow suppression: a possible drug-drug interaction. *Clin Pharmacol Ther* 1997; **62:** 464–75.
3. Chouragui JP, *et al.* Azathioprine toxicity in a child with ulcerative colitis: interaction with mesalazine. *Gastroenterology* 1996; **110** (suppl): A883.
4. Lowry PW, *et al.* Leucopenia resulting from a drug interaction between azathioprine or 6-mercaptopurine and mesalamine, sulphasalazine, or balsalazide. *Gut* 2001; **49:** 656–64.

Pharmacokinetics

Mercaptopurine is variably and incompletely absorbed from the gastrointestinal tract; about 50% of an oral dose has been reported to be absorbed, but the absolute bioavailability is somewhat lower, probably due to gastrointestinal or first-pass metabolism, and is also subject to wide interindividual variation. Once absorbed it is widely distributed throughout body water and tissues. Plasma half-lives ranging from about 20 to 90 minutes have been reported after intravenous injection and the drug is not found in plasma after about 8 hours but this is of limited significance since mercaptopurine is activated intracellularly by conversion to nucleotide derivatives which persist for much longer. It is rapidly and extensively metabolised in the liver, by methylation and oxidation as well as by the formation of inorganic sulfates. Thiol methylation is catalysed by the enzyme thiopurine methyltransferase (TPMT). TPMT activity is highly variable in patients because of a genetic polymorphism in the TPMT gene. Patients with little or no detectable enzyme activity may accumulate excessive cellular concentrations of active tioguanine nucleotides, predisposing them to mercaptopurine toxicity. Considerable amounts of mercaptopurine are also oxidised to thiouric acid by the enzyme xanthine oxidase. Mercaptopurine is excreted in urine as metabolites and some unchanged drug; about half an oral dose has been recovered in 24 hours. A small proportion is excreted over several weeks.

Mercaptopurine crosses the blood-brain barrier to some extent and is found in the CSF, but only in subtherapeutic concentrations.

Therapeutic drug monitoring. For a discussion of therapeutic drug monitoring for mercaptopurine, see under Azathioprine, p.1819.

Uses and Administration

Mercaptopurine is an antineoplastic that acts as an antimetabolite. It is an analogue of the natural purines hypoxanthine and adenine. After the intracellular conversion of mercaptopurine to active nucleotides, including thioinosinic acid, it appears to exhibit a variety of actions including interfering with nucleic acid synthesis. It also has immunosuppressant properties. Its actions are specific for cells in S phase.

Mercaptopurine is used, usually with other agents, in the treatment of leukaemia. It induces remissions in acute lymphoblastic and myeloid leukaemias (p.651 and p.652, respectively) but other agents are generally preferred and mercaptopurine is chiefly employed in maintenance programmes, commonly with methotrexate. It may also be effective in chronic myeloid leukaemia (p.653). There is cross-resistance between mercaptopurine and tioguanine (p.779).

Mercaptopurine has been used for its immunosuppressant properties in the treatment of auto-immune disorders such as inflammatory bowel disease but has been largely replaced by azathioprine.

Mercaptopurine is given orally. The usual initial antineoplastic dose for children and adults is 2.5 mg/kg or 50 to 75 mg/m^2 daily but dosage varies according to individual response and tolerance. If there is no clinical improvement and no evidence of white-cell depression after 4 weeks, the dose may be cautiously increased up to 5 mg/kg daily. In maintenance schedules the dose may vary from 1.5 to 2.5 mg/kg daily. Blood counts should be taken at least once a week and if there is a steep fall in the white cell count or severe bone-marrow depression the drug should be withdrawn immediately. Therapy may be resumed carefully if the white cell count remains constant for 2 or 3 days or rises.

It has been used intravenously as mercaptopurine sodium. Thioinosine (mercaptopurine riboside) has also been used.

Administration. There is evidence[1] that the maintenance dosage of mercaptopurine should be tailored individually to achieve an appropriate systemic exposure in children with acute lymphoblastic leukaemia (although this would involve determining mercaptopurine pharmacokinetics in each child). Improvements in survival since 1980 may be associated with changes in the prescribing of mercaptopurine which have resulted in greater cumulative doses being given;[2] some children may have been undertreated in the past because of variations in the pharmacokinetics of mercaptopurine (particularly boys, who tolerate mercaptopurine better than girls,[3] but who have a poorer prognosis).[2] The concentration of tioguanine nucleotide metabolites in the erythrocytes has been shown to be directly related to the risk of relapse in children with acute lymphoblastic leukaemia.[4] Thiopurine methyltransferase (TPMT) activity (which results in methylation and inactivation of mercaptopurine rather than the formation of active nucleotides) may play a substantial role in this variation,[5] but titration of the dose of mercaptopurine until myelotoxicity occurs may prevent the problem:[2] despite gaps in therapy caused by more frequent drug withdrawal, it appears to result in greater accumulation of tioguanine nucleotides in the cells.[6]

1. Koren G, *et al.* Systemic exposure to mercaptopurine as a prognostic factor in acute lymphocytic leukemia in children. *N Engl J Med* 1990; **323:** 17–21.
2. Hale JP, Lilleyman JS. Importance of 6-mercaptopurine dose in lymphoblastic leukaemia. *Arch Dis Child* 1991; **66:** 462–6.
3. Lilleyman JS, *et al.* Childhood lymphoblastic leukaemia: sex difference in 6-mercaptopurine utilization. *Br J Cancer* 1984; **49:** 703–7.
4. Lilleyman JS, Lennard L. Mercaptopurine metabolism and risk of relapse in childhood lymphoblastic leukaemia. *Lancet* 1994; **343:** 1188–90.
5. Lennard L, *et al.* Genetic variation in response to 6-mercaptopurine for childhood acute lymphoblastic leukaemia. *Lancet* 1990; **336:** 225–9.
6. Lennard L, *et al.* Mercaptopurine in childhood leukaemia: the effects of dose escalation on thioguanine nucleotide metabolites. *Br J Clin Pharmacol* 1996; **42:** 525–7.

Inflammatory bowel disease. Mercaptopurine has been reported to be of benefit in ulcerative colitis[1,2] and Crohn's disease,[3-5] although azathioprine has generally been preferred (see p.1820). The *BNF* considers that in resistant or frequently relapsing cases mercaptopurine 1 to 1.5 mg/kg given daily may be of use.

1. Adler DJ, Korelitz BI. The therapeutic efficacy of 6-mercaptopurine in refractory ulcerative colitis. *Am J Gastroenterol* 1990; **85:** 717–22.
2. George J, *et al.* The long-term outcome of ulcerative colitis treated with 6-mercaptopurine. *Am J Gastroenterol* 1996; **91:** 1711–14.
3. Present DH, *et al.* Treatment of Crohn's disease with 6-mercaptopurine: a long-term randomized, double-blind study. *N Engl J Med* 1980; **302:** 981–7.
4. Sandborn W, *et al.* Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1998 (accessed 16/05/08).
5. Markowitz J, *et al.* A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology* 2000; **119:** 895–902.

Polymyositis. Mercaptopurine has been tried in a few patients with polymyositis but has not been formally assessed.

Preparations

BP 2008: Mercaptopurine Oral Suspension; Mercaptopurine Tablets; ***USP 31:*** Mercaptopurine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Puri-Nethol; Varimer; ***Austral.:*** Puri-Nethol; ***Austria:*** Puri-Nethol; ***Belg.:*** Puri-Nethol; ***Braz.:*** Puri-Nethol; ***Canad.:*** Purinethol; ***Chile:*** Puri-Nethol; ***Cz.:*** Puri-Nethol; ***Fr.:*** Puri-Nethol; ***Ger.:*** Puri-Nethol; ***Gr.:*** Puri-Nethol; ***Hong Kong:*** Puri-Nethol; ***India:*** Puri-Nethol; ***Irl.:*** Puri-Nethol; ***Israel:*** Puri-Nethol; ***Ital.:*** Puri-Nethol; ***Mex.:*** Puri-Nethol; ***Neth.:*** Puri-Nethol; ***Norw.:*** Puri-Nethol; ***NZ:*** Puri-Nethol; ***Philipp.:*** Capmerin; Empurine; Puri-Nethol; ***Rus.:*** Puri-Nethol (Пури-нетол); ***S.Afr.:*** Puri-Nethol; ***Singapore:*** Puri-Nethol; ***Swed.:*** Puri-Nethol; ***Switz.:*** Puri-Nethol; ***Thai.:*** Empurine; Puri-Nethol; ***Turk.:*** Puri-Nethol; ***UK:*** Puri-Nethol; ***USA:*** Purinethol.

Methotrexate *(BAN, USAN, rINN)*

Amethopterin; 4-Amino-4-deoxy-10-methylpteroyl-L-glutamic Acid; 4-Amino-10-methylfolic Acid; CL-14377; α-Methopterin; Methotrexát; Méthotrexate; Methotrexatum; Metotreksaatti; Metotreksatas; Metotrexát; Metotrexat; Metotrexato; MTX; NSC-740; WR-19039. *N*-{4-[(2,4-Diamino-6-pteridinylmethyl)methylamino]benzoyl}-L-glutamic acid.

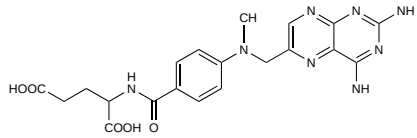
Метотрексат

$C_{20}H_{22}N_8O_5$ = 454.4.

CAS — 59-05-2.

ATC — L01BA01; L04AX03.

ATC Vet — QL01BA01; QL04AX03.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 6.2 (Methotrexate). A yellow or orange, hygroscopic, crystalline powder. It contains not more than 13% of water. Practically insoluble in water, in alcohol, and in dichloromethane; dissolves in dilute solutions of mineral acids and of alkali hydroxides and carbonates. Store in airtight containers. Protect from light.

USP 31 (Methotrexate). It is a mixture of 4-amino-10-methylfolic acid and closely related substances; it contains not less than 98% and not more than 102% of $C_{20}H_{22}N_8O_5$, calculated on the anhydrous basis. A yellow or orange-brown crystalline powder. It contains not more than 12% of water. Practically insoluble in water, in alcohol, in chloroform, and in ether; freely soluble in dilute solutions of alkali hydroxides and carbonates; slightly soluble in 6N hydrochloric acid. Store in airtight containers. Protect from light.

Methotrexate Sodium *(BANM, rINNM)*

Méthotrexate de Sodium; Methotrexate Disodium; Metotreksat Sodyum; Metotrexate sodium; Natrii Methotrexatum.

Натрий Метотрексат

$C_{20}H_{20}N_8Na_2O_5$ = 498.4.

CAS — 7413-34-5 (methotrexate disodium); 15475-56-6 (methotrexate sodium, xNa).

ATC — L01BA01; L04AX03.

ATC Vet — QL01BA01; QL04AX03.

Incompatibility. Methotrexate sodium has been reported to be incompatible with cytarabine, fluorouracil, and prednisolone sodium phosphate;[1] however, another study suggests it is compatible with fluorouracil.[2] Furthermore a mixture of methotrexate sodium with cytarabine and hydrocortisone sodium succinate in various infusion fluids has been reported to be visually compatible for at least 8 hours at 25°, although precipitation did occur on storage for several days.[3]

1. McRae MP, King JC. Compatibility of antineoplastic, antibiotic and corticosteroid drugs in intravenous admixtures. *Am J Hosp Pharm* 1976; **33:** 1010–13.
2. Vincké BJ, *et al.* Extended stability of 5-fluorouracil and methotrexate solutions in PVC containers. *Int J Pharmaceutics* 1989; **54:** 181–9.
3. Cheung Y-W, *et al.* Stability of cytarabine, methotrexate sodium, and hydrocortisone sodium succinate admixtures. *Am J Hosp Pharm* 1984; **41:** 1802–6.

Stability to light. Methotrexate undergoes photodegradation when stored in the light in diluted solutions, although undiluted commercial preparations are reported to show negligible photodegradation.[1] The bicarbonate ion catalyses this reaction and such admixtures should be avoided if possible, although they may be stable in light for 12 hours. Storage of solutions diluted in sodium chloride 0.9% injection in PVC bags was reported to protect against photodegradation although the length of the study was only 4 hours.[2] Photodegradation can take place under normal lighting, but is more rapid in direct sunlight, with about 11% drug loss from a 1 mg/mL solution after 7 hours; storage under normal lighting resulted in little change in drug concentration over 24 hours with a decrease of up to 12% by 48 hours.[3] Loss was greatest from unprotected polybutadiene tubing, with almost 80% drug loss in 48 hours.

1. Chatterji DC, Gallelli JF. Thermal and photolytic decomposition of methotrexate in aqueous solutions. *J Pharm Sci* 1978; **67:** 526–31.
2. Dyvik O, *et al.* Methotrexate in infusion solutions—a stability test for the hospital pharmacy. *J Clin Hosp Pharm* 1986; **11:** 343–8.
3. McElnay JC, *et al.* Stability of methotrexate and vinblastine in burette administration sets. *Int J Pharmaceutics* 1988; **47:** 239–47.

Adverse Effects

For general discussions see Antineoplastics, p.635.

The most common dose-related toxic effects of methotrexate are on the bone marrow and gastrointestinal tract. Bone-marrow depression can occur abruptly, and leucopenia, thrombocytopenia, and anaemia may all occur. The nadir of the platelet and white-blood cell counts is usually around 5 to 10 days after a bolus dose, with recovery between about 14 to 28 days, but some sources suggest that leucocytes may exhibit an early fall and rise, followed by a second nadir and recovery, within this period. Ulceration of the mouth and gastrointestinal disturbances are also early signs of toxicity: stomatitis and diarrhoea during treatment indicate that it may need to be interrupted, otherwise haemorrhagic enteritis, intestinal perforation, and death may follow.

Methotrexate is associated with liver damage, both acute (notably after high doses) and, more seriously, chronic (generally after long-term use). Hepatic fibrosis and cirrhosis may develop without obvious signs of hepatotoxicity, and have led to eventual death.

Other adverse effects include renal failure and tubular necrosis after high doses, pulmonary reactions including life-threatening interstitial lung disease, skin reactions (sometimes severe), alopecia, and ocular irritation. Neurotoxicity may be seen: leukoencephalopathy, paresis, demyelination are associated particularly with intrathecal use and are more likely when cranial irradiation is also given. Intrathecal use may also produce arachnoiditis, an acute syndrome of headache, nuchal rigidity, back pain, and fever. Other rarer reactions may include megaloblastic anaemia, osteoporosis, precipitation of diabetes, arthralgias, necrosis of soft tissue and bone, and anaphylaxis.

Methotrexate may cause defective oogenesis and spermatogenesis, and fertility may be impaired (this may be reversible). Like other folate inhibitors it is teratogenic, and it has been associated with fetal deaths. Lymphomas (generally reversible on withdrawal of treatment) have occasionally been reported with methotrexate therapy, although the association has been questioned (see Carcinogenicity, below).

Carcinogenicity. There are reports of lymphomas associated with low-dose methotrexate therapy for rheumatic disorders,[1-4] which in some cases have been associated with concomitant Epstein-Barr virus infection.[2] Transitional cell bladder cancer has also been associated with such therapy.[5] However, a retrospective analysis involving 16 263 patients with rheumatoid arthritis found no evidence of a relationship between the use of methotrexate as an antirheumatic and the development of haematological malignancy.[6] Nonetheless, the spontaneous remission of lymphoma after withdrawal of methotrexate in some patients seems to support an association[7] A later prospective study[8] of all new cases of lymphoma, detected over 3 years in patients treated with methotrexate for rheumatoid arthritis, also found a higher incidence of Hodgkin's disease compared with the general population. The carcinogenic risk with antimetabolites such as methotrexate has generally been considered less than with alkylating agents (p.635).

1. Zimmer-Galler I, Lie JT. Choroidal infiltrates as the initial manifestation of lymphoma in rheumatoid arthritis after treatment with low-dose methotrexate. *Mayo Clin Proc* 1994; **69:** 258–61.
2. Kamel OW, *et al.* Brief report: reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. *N Engl J Med* 1993; **328:** 1317–21.
3. Viraben R, *et al.* Reversible cutaneous lymphoma occurring during methotrexate therapy. *Br J Dermatol* 1996; **135:** 116–18.
4. Ebeo CT, *et al.* Methotrexate-induced pulmonary lymphoma. *Chest* 2003; **123:** 2150–3.
5. Millard RJ, McCredie S. Bladder cancer in patients on low-dose methotrexate and corticosteroids. *Lancet* 1994; **343:** 1222–3.
6. Moder KG, *et al.* Hematologic malignancies and the use of methotrexate in rheumatoid arthritis: a retrospective study. *Am J Med* 1995; **99:** 276–81.
7. Georgescu L, Paget SA. Lymphoma in patients with rheumatoid arthritis: what is the evidence of a link with methotrexate? *Drug Safety* 1999; **20:** 475–87.
8. Mariette X, *et al.* Lymphomas in rheumatoid arthritis patients treated with methotrexate: a 3-year prospective study in France. *Blood* 2002; **99:** 3909–15.