Alcohol withdrawal and abstinence. Naltrexone may be of use as an adjunct to psychotherapy in maintaining abstinence after alcohol withdrawal in patients with alcohol dependence (p.1626). Two systematic reviews[1,2] have concluded that oral naltrexone is safe and effective for the short-term treatment of alcohol dependence, although there is less evidence for long-term benefit. However, since the risk of relapse is particularly high early after alcohol withdrawal, treatment for at least 3 to 6 months has been recommended.[2,3] Compliance with oral naltrexone may be a problem,[1,2] and promising results[4,5] have been reported with a long-acting intramuscular injection given monthly.

Naltrexone appears to be more effective at reducing the amount of alcohol consumed than producing complete abstinence;[1] reports[6] from patients who continued to drink during therapy suggest that naltrexone may reduce the pleasure associated with drinking, possibly by blocking the effect of endorphins released as a result of alcohol consumption.

Although naltrexone does not appear to be hepatotoxic at the oral dosage of 50 mg daily used for alcohol dependence, caution is recommended in patients with liver disease;[3] careful monitoring is recommended if it is given with disulfiram since hepatotoxicity could potentially be increased.

Other opioid antagonists have also been studied. Preliminary results[7,8] suggest that nalmefene may also be effective, although there is insufficient evidence to recommend its use.[2]

1. Carmen B, *et al.* Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review. *Addiction* 2004; **99:** 811–28.
2. Srisurapanont M, Jarusuraisin N. Opioid antagonists for alcohol dependence. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 04/10/05).
3. Berg BJ, *et al.* A risk-benefit assessment of naltrexone in the treatment of alcohol dependence. *Drug Safety* 1996; **15:** 274–82.
4. Garbutt JC, *et al.* Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *JAMA* 2005; **293:** 1617–25. Correction. *ibid.*: 1978.
5. Swainston Harrison T, *et al.* Extended-release intramuscular naltrexone. *Drugs* 2006; **66:** 1741–51.
6. Volpicelli JR, *et al.* Effect of naltrexone on alcohol "high" in alcoholics. *Am J Psychiatry* 1995; **152:** 613–15.
7. Mason BJ, *et al.* A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCl for alcohol dependence. *Alcohol Clin Exp Res* 1994; **18:** 1162–7.
8. Mason BJ, *et al.* A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. *Arch Gen Psychiatry* 1999; **56:** 719–24.

Autism. Autistic disorders have been linked with abnormalities in the endogenous opioid system and there is some evidence[1] that naltrexone may be of benefit in children with autism, especially in those with self-injurious behaviour.

1. ElChaar GM, *et al.* Efficacy and safety of naltrexone use in pediatric patients with autistic disorder. *Ann Pharmacother* 2006; **40:** 1086–95.

Opioid dependence. ***MAINTENANCE.*** Naltrexone is a long-acting, non-addictive oral opioid antagonist. It can be effective in maintaining abstinence in opioid addicts after detoxification, but compliance with therapy is difficult to maintain because although it blocks the euphoriant effects of opioids it does not block the craving for narcotics. It is thus most effective in highly motivated addicts with good sociological and psychological support to discourage impulsive use of opioids. Subcutaneous formulations have also been used but have been associated with serious complications (see Rapid Detoxification, below).

For a discussion of the management of opioid dependence, see p.101.

References.

1. Gonzalez JP, Brogden RN. Naltrexone: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of opioid dependence. *Drugs* 1988; **35:** 192–213.
2. Minozzi S, *et al.* Oral naltrexone maintenance treatment for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 02/09/08).
3. NICE. Naltrexone for the management of opioid dependence: Technology Appraisal Guidance 115 (issued January 2007). Available at: http://guidance.nice.org.uk/TA115/guidance/pdf/English (accessed 02/05/07)
4. Lobmaier P, *et al.* Sustained-release naltrexone for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 21/07/08).

RAPID DETOXIFICATION. Naltrexone has been used in various regimens for rapid detoxification;[1,2] opioid withdrawal may be achieved in only a few days, although benefits for long-term outcome are not yet established. It has also been used for ultrarapid detoxification under anaesthesia, although a systematic review[3] concluded that the risks outweighed the benefits of using opioid antagonists in such procedures. A later study[4] also failed to support the use of such a regimen. After detoxification, patients may be given oral naltrexone for maintenance; subcutaneous formulations of naltrexone have also been used in an attempt to improve compliance, although serious complications, including deaths, have been reported[5-7] with their use.

1. O'Connor PG, Kosten TR. Rapid and ultrarapid opioid detoxification techniques. *JAMA* 1998; **279:** 229–34.
2. Gowing L, *et al.* Opioid antagonists with minimal sedation for opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 02/09/08).
3. Gowing L, *et al.* Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 02/09/08).
4. Collins ED, *et al.* Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial. *JAMA* 2005; **294:** 903–13.
5. Hamilton RJ, *et al.* Complications of ultrarapid opioid detoxification with subcutaneous naltrexone pellets. *Acad Emerg Med* 2002; **9:** 63–8.
6. Gibson AE, *et al.* Opioid overdose deaths can occur in patients with naltrexone implants. *Med J Aust* 2007; **186:** 152–3.
7. Lintzeris N, *et al.* Unplanned admissions to two Sydney public hospitals after naltrexone implants. *Med J Aust* 2008; **188:** 441–4.

Pruritus. For reference to the use of opioid antagonists, including naltrexone, in pruritus, see under Nalmefene, p.1453.

Preparations

USP 31: Naltrexone Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Revez; ***Austral.:*** Revia; ***Austria:*** Dependex; Ethylex; Nalone†; Naltrexin; Nemexin; Revia; ***Belg.:*** Nalorex; ***Braz.:*** Revia; ***Canad.:*** Revia; ***Chile:*** Nalerona; ***Cz.:*** Nemexin; Revia; ***Denm.:*** Revia; ***Fin.:*** Revia; ***Fr.:*** Nalorex; Revia; ***Ger.:*** Nemexin; ***Gr.:*** Nalorex; ***Hong Kong:*** Revia; ***Hung.:*** Antaxon; Nemexin; Revia; ***India:*** Nodict; ***Indon.:*** Nutrexon; Phaltrexia; ***Irl.:*** Nalorex; Revia; ***Israel:*** Revia†; ***Ital.:*** Antaxone; Nalorex; Narcoral; ***Malaysia:*** Trexan†; ***Mex.:*** Revia; ***Neth.:*** Nalorex; Revia; ***Norw.:*** Revia; ***NZ:*** Revia; ***Port.:*** Antaxone; Basinal; Destoxican; Nalorex; ***Rus.:*** Antaxone (Антаксон); ***S.Afr.:*** Revia†; ***Singapore:*** Trexan†; ***Spain:*** Antaxone; Celupan; Revia; ***Swed.:*** Revia; ***Switz.:*** Naltrexin; Nemexin; ***Thai.:*** Revia; ***UK:*** Nalorex; Opizone; ***USA:*** Depade†; Revia; Trexan; Vivitrol.

Obidoxime Chloride *(USAN, rINN)*

Cloruro de obidoxima; LüH6; Obidoxime, Chlorure d'; Obidoximi Chloridum. 1,1'-[Oxybis(methylene)]bis[4-(hydroxyimino)methyl]pyridinium dichloride.

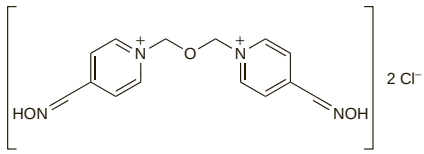
Обидоксима Хлорид

$C_{14}H_{16}Cl_2N_4O_3$ = 359.2.

CAS — 7683-36-5 (obidoxime); 114-90-9 (obidoxime chloride).

ATC — V03AB13.

ATC Vet — QV03AB13.



Profile

Obidoxime chloride is a cholinesterase reactivator with similar actions and uses to pralidoxime (p.1460). It is given with atropine in the treatment of organophosphorus poisoning in a usual initial dose of 250 mg (4 mg/kg) by slow intravenous injection. This may be followed by intravenous infusion of 750 mg over 24 hours, continued until the concentration of organophosphate is below critical levels; alternatively, repeated doses of 4 to 8 mg/kg may be given at intervals of 2 to 4 hours. It has also been given by intramuscular injection.

◊ References.

1. Thiermann H, *et al.* Cholinesterase status, pharmacokinetics and laboratory findings during obidoxime therapy in organophosphate poisoned patients. *Hum Exp Toxicol* 1997; **16:** 473–80.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Toxogonin; ***Chile:*** Toxogonin; ***Cz.:*** Toxogonin; ***Ger.:*** Toxogonin; ***Neth.:*** Toxogonin; ***S.Afr.:*** Toxogonin; ***Swed.:*** Toxogonin; ***Switz.:*** Toxogonine.

Penicillamine *(BAN, USAN, rINN)*

Penicilamin; Penicilamina; Penicilaminas; Penicillamin; Pénicillamine; D-Penicillamine; Penicillaminum; Penicylamina; Penisilamin; Penisillamiini. D-3,3-Dimethylcysteine; D-3-Mercaptovaline.

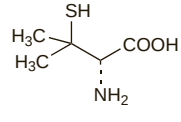
Пеницилламин

$C_5H_{11}NO_2S$ = 149.2.

CAS — 52-67-5 (penicillamine); 2219-30-9 (penicillamine hydrochloride).

ATC — M01CC01.

ATC Vet — QM01CC01.



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

Ph. Eur. 6.2 (Penicillamine). A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in alcohol. A 1% solution in water has a pH of 4.5 to 5.5.

USP 31 (Penicillamine). A white or practically white, crystalline powder having a slight characteristic odour. Freely soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 1% solution in water is between 4.5 and 5.5. Store in airtight containers.

Adverse Effects and Treatment

Adverse effects of penicillamine are frequent. Gastrointestinal disturbances including anorexia, nausea, and vomiting may occur; oral ulceration and stomatitis have been reported and impaired taste sensitivity is common.

Skin rashes occurring early in treatment are commonly allergic and may be associated with pruritus, urticaria, and fever; they are usually transient but temporary drug withdrawal and use of corticosteroids or antihistamines may be required. Lupus erythematosus and pemphigus have been reported. A Stevens-Johnson-like syndrome has been observed during penicillamine treatment. Prolonged use of high doses may affect skin collagen and elastin, resulting in increased skin friability, eruptions resembling elastosis perforans serpiginosa, and a late rash or acquired epidermolysis bullosa (penicillamine dermatopathy) that may necessitate dosage reduction or discontinuation.

Haematological adverse effects have included thrombocytopenia and, less frequently, leucopenia; these are usually reversible, but agranulocytosis and aplastic anaemia have occurred and fatalities have been reported. Haemolytic anaemia has also occurred.

Proteinuria occurs frequently and in some patients may progress to glomerulonephritis or nephrotic syndrome. Penicillamine-induced haematuria is rare but normally requires immediate discontinuation.

Other adverse effects associated with penicillamine include Goodpasture's syndrome, bronchiolitis and pneumonitis, myasthenia gravis, polymyositis (rarely with cardiac involvement), intrahepatic cholestasis, and pancreatitis.

Incidence of adverse effects. References describing the range and incidence of adverse effects associated with of D-penicillamine.[1-3] The L- or DL-forms are much more toxic.[4]

1. Kean WF, *et al.* Efficacy and toxicity of -penicillamine for rheumatoid disease in the elderly. *J Am Geriatr Soc* 1982; **30:** 94–100.
2. Steen VD, *et al.* The toxicity of -penicillamine in systemic sclerosis. *Ann Intern Med* 1986; **104:** 699–705.
3. Munro R, Capell HA. Penicillamine. *Br J Rheumatol* 1997; **36:** 104–9.
4. Kean WF, *et al.* Chirality in antirheumatic drugs. *Lancet* 1991; **338:** 1565–8.

Effects on the blood. Of the 18 deaths ascribed to penicillamine reported to the UK CSM between January 1964 and December 1977, 14 were apparently due to blood disorders, at least 7 of them being marrow aplasias. The myelotoxicity of penicillamine was reviewed in 10 patients with confirmed or suspected marrow depression during penicillamine treatment for rheumatoid arthritis or scleroderma; 6 died.[1]

An incidence of 12 to 27% has been reported for penicillamine-induced thrombocytopenia in patients with rheumatoid arthritis, possibly due to bone-marrow suppression and a reduced platelet-production rate.[2]

There have been isolated reports[3-5] of thrombotic thrombocytopenic purpura attributed to the use of penicillamine, with some fatalities.

1. Kay AGL. Myelotoxicity of D-penicillamine. *Ann Rheum Dis* 1979; **38:** 232–6.
2. Thomas D, *et al.* Thrombokinetics in patients with rheumatoid arthritis treated with D-penicillamine. *Ann Rheum Dis* 1984; **43:** 402–6.
3. Ahmed F, *et al.* Thrombohemolytic thrombocytopenic purpura during penicillamine therapy. *Arch Intern Med* 1978; **138:** 1292–3.
4. Speth PAJ, *et al.* Thrombotic thrombocytopenic purpura associated with D-penicillamine treatment in rheumatoid arthritis. *J Rheumatol* 1982; **9:** 812–13.
5. Trice JM, *et al.* Thrombotic thrombocytopenic purpura during penicillamine therapy in rheumatoid arthritis. *Arch Intern Med* 1983; **143:** 1487–8.

Effects on the breasts. Breast enlargement has been reported both in women[1-5] and in men[6] taking penicillamine and may be a rare adverse effect. In some patients breast enlargement was prolonged with poor resolution and others required surgery.

Danazol has been used successfully to treat penicillamine-induced breast gigantism.[2-4]

1. Thew DCN, Stewart IM. D penicillamine and breast enlargement. *Ann Rheum Dis* 1980; **39:** 200.
2. Taylor PJ, *et al.* Successful treatment of D-penicillamine-induced breast gigantism with danazol. *BMJ* 1981; **282:** 362–3.
3. Rooney PJ, Cleland J. Successful treatment of D-penicillamine-induced breast gigantism with danazol. *BMJ* 1981; **282:** 1627–8.
4. Craig HR. Penicillamine induced mammary hyperplasia: report of a case and review of the literature. *J Rheumatol* 1988; **15:** 1294–7.
5. Tchebiner JZ. Breast enlargement induced by D-penicillamine. *Ann Pharmacother* 2002; **36:** 444–5.
6. Reid DM, *et al.* Reversible gynaecomastia associated with D-penicillamine in a man with rheumatoid arthritis. *BMJ* 1982; **285:** 1083–4.

Effects on the gastrointestinal tract. There have been isolated reports of acute colitis in patients taking penicillamine.[1,2] Ileal ulceration and stenosis in a patient with Wilson's disease was considered to be related to elastosis probably resulting from long-term penicillamine therapy.[3]

1. Hickling P, Fuller J. Penicillamine causing acute colitis. *BMJ* 1979; **2:** 367.
2. Grant GB. Penicillamine causing acute colitis. *BMJ* 1979; **2:** 555.
3. Wassef M, *et al.* Unusual digestive lesions in a patient with Wilson's disease treated with long-term penicillamine. *N Engl J Med* 1985; **313:** 49.

Effects on the heart. For reports of heart block, Stokes-Adams syndrome, and fatal myocarditis in patients taking penicillamine, see Polymyositis under Effects on the Muscles and the Neuromuscular System, below.

Effects on the kidneys. Proteinuria associated with penicillamine[1] has usually occurred within 4 to 18 months of starting therapy, although onset can be later. A greater incidence has been found in patients with rheumatoid arthritis and cystinuria than in those with Wilson's disease. The severity varies; proteinuria of nephrotic proportions usually develops rapidly but resolves on drug withdrawal. Minimal change, mesangioproliferative, and membranous nephropathy have all been associated with penicillamine; progressive glomerulonephritis has been observed in a few patients with features of Goodpasture's syndrome (see Effects on the Respiratory System, below).

Although there is some evidence of a relationship between nephropathy and penicillamine dose and its rate of increase,[1] a study of 33 rheumatoid arthritis patients with penicillamine-induced nephropathy found no correlation with the dose or duration of treatment.[2] Appreciable proteinuria could still be detected 12 months after stopping penicillamine in 40% of these patients, but subsequently resolved in those whose proteinuria was solely related to penicillamine.

Penicillamine was successfully reintroduced and continued for at least 13 months in 5 patients with rheumatoid arthritis who had developed proteinuria during the first course of therapy. Proteinuria did not recur.[3] Another study[4] in 8 patients with proteinuria but no oedema suggested that penicillamine could be safely continued; proteinuria resolved in 5 of the patients during continued therapy.

Corticosteroids have been used in patients developing rapidly progressive glomerulonephritis[5] but may be unnecessary and potentially hazardous in patients who develop nephrotic syndrome.[2]

1. Anonymous. Penicillamine nephropathy. *BMJ* 1981; **282:** 761–2.
2. Hall CL, *et al.* Natural course of penicillamine nephropathy: a long term study of 33 patients. *BMJ* 1988; **296:** 1083–6.
3. Hill H, *et al.* Resumption of treatment with penicillamine after proteinuria. *Ann Rheum Dis* 1979; **38:** 229–31.
4. DeSilva RN, Eastmond CJ. Management of proteinuria secondary to penicillamine therapy in rheumatoid arthritis. *Clin Rheumatol* 1992; **11:** 216–9.
5. Ntoso KA, *et al.* Penicillamine-induced rapidly progressive glomerulonephritis in patients with progressive systemic sclerosis: successful treatment of two patients and a review of the literature. *Am J Kidney Dis* 1986; **8:** 159–63.

Effects on the liver. Penicillamine has been associated with hepatotoxicity. A case report and review of the literature[1] described 9 patients, all of whom had liver function profiles consistent with intrahepatic cholestasis; 1 patient died of acute renal failure but the others improved rapidly after drug withdrawal. In a later report,[2] a 72-year-old man with rheumatoid arthritis developed jaundice about 4 weeks after starting penicillamine therapy. Liver biopsy indicated a slight degree of cholangitis with eosinophils in the portal tracts and severe predominantly intrahepatocellular cholestasis. Jaundice cleared within 3 weeks of stopping penicillamine and liver enzyme values approached normal after 6 weeks. However, in another case[3] cholestasis persisted despite withdrawal of penicillamine and the patient died of sepsis 14 months later. Monitoring of liver function and eosinophil counts in the early weeks of penicillamine therapy has been recommended.[1]

1. Seibold JR, *et al.* Cholestasis associated with D-penicillamine therapy: case report and review of the literature. *Arthritis Rheum* 1981; **24:** 554–6.
2. Devogelaer JP, *et al.* A case of cholestatic hepatitis associated with D-penicillamine therapy for rheumatoid arthritis. *Int J Clin Pharmacol Res* 1985; **5:** 35–8.
3. Jacobs JWG, *et al.* Fatal cholestatic hepatitis caused by -penicillamine. *Br J Rheumatol* 1994; **33:** 770–3.

Effects on the muscles and the neuromuscular system. Neuromyotonia,[1] and profound sensory and motor neuropathy that responded to pyridoxine supplementation,[2] have occurred in patients taking penicillamine. Low back pain with fever and rash has also been reported;[3] back pain and fever recurred on rechallenge. It was suggested that an allergic mechanism was involved.

1. Reeback J, *et al.* Penicillamine-induced neuromyotonia. *BMJ* 1979; **1:** 1464–5.
2. Pool KD, *et al.* Penicillamine-induced neuropathy in rheumatoid arthritis. *Ann Intern Med* 1981; **95:** 457–8.
3. Bannwarth B, *et al.* Low back pain associated with penicillamine. *BMJ* 1991; **303:** 525.

Myasthenia. Myasthenia gravis is a well recognised, though uncommon, complication of long-term penicillamine therapy, particularly in patients with rheumatoid arthritis or other auto-immune disorders.[1-5] Symptoms are similar to those seen with spontaneous myasthenia gravis and include ptosis and diplopia, and generalised weakness, occasionally affecting the respiratory muscles. The onset of symptoms usually occurs within 6 to 7 months but may be delayed for a number of years. Myasthenic symptoms usually resolve spontaneously once penicillamine is withdrawn, but some patients require anticholinesterase therapy. Acetylcholine receptor antibodies have been reported in 75% or more of affected patients.[2,3] Several reports have suggested a genetic tendency to penicillamine-induced myasthenia, and an association with HLA antigens DR1 and Bw35 has been found in some studies,[1,4] although others[5] have not replicated these findings.

1. Delamere JP, *et al.* Penicillamine-induced myasthenia in rheumatoid arthritis: its clinical and genetic features. *Ann Rheum Dis* 1983; **42:** 500–4.
2. Carter H, *et al.* La myasthénie au cours du traitement de la polyarthrite rhumatoïde par la D-pénicillamine. *Therapie* 1984; **39:** 689–95.
3. Katz LJ, *et al.* Ocular myasthenia gravis after D-penicillamine administration. *Br J Ophthalmol* 1989; **73:** 1015–18.
4. Garlepp MJ, *et al.* HLA antigens and acetylcholine receptor antibodies in penicillamine induced myasthenia gravis. *BMJ* 1983; **286:** 338–40.
5. Drosos AA, *et al.* D-penicillamine induced myasthenia gravis: clinical, serological and genetic findings. *Clin Exp Rheumatol* 1993; **11:** 387–91.

Polymyositis. Penicillamine therapy has been associated rarely with polymyositis and dermatomyositis.[1-5] Cardiac complications may occur: at least 2 deaths have resulted from myocarditis,[1] and complete heart block[1,3,6] and severe Stokes-Adams attacks[3] have been reported. It is possible that some patients may have a genetically determined susceptibility to this complication.[4]

1. Doyle DR, *et al.* Fatal polymyositis in D-penicillamine-treated rheumatoid arthritis. *Ann Intern Med* 1983; **98:** 327–30.
2. Renier JC, *et al.* Polymyosite induite par la D-pénicillamine. *Therapie* 1984; **39:** 697–703.
3. Christensen PD, Sørensen KE. Penicillamine-induced polymyositis with complete heart block. *Eur Heart J* 1989; **10:** 1041–4.
4. Carroll GJ, *et al.* Penicillamine induced polymyositis and dermatomyositis. *J Rheumatol* 1987; **14:** 995–1001.
5. Aydintug AO, *et al.* Polymyositis complicating -penicillamine treatment. *Postgrad Med J* 1991; **67:** 1018–20.
6. Wright GD, *et al.* D-penicillamine induced polymyositis causing complete heart block. *Clin Rheumatol* 1994; **13:** 80–2.

Effects on the respiratory system. Pulmonary haemorrhage associated with progressive renal failure has been reported[1,2] with penicillamine and has generally been classified as Goodpasture's syndrome, although patients usually lack anti-glomerular basement membrane antibodies; an immune-complex mechanism has also been suggested.[1] There have been rare reports of obliterative bronchiolitis in patients with rheumatoid arthritis treated with penicillamine.[3-6]

Upper respiratory tract disorders have also been reported. A 76-year-old patient taking penicillamine developed rhinitis, bilateral blepharitis, and pemphigus foliaceus;[7] the rhinitis and blepharitis resolved when penicillamine was withdrawn. In addition, 2 patients with lower respiratory symptoms also developed persistent sinusitis,[6] which required surgery.

1. Turner-Warwick M. Adverse reactions affecting the lung: possible association with D-penicillamine. *J Rheumatol* 1981; **8** (suppl 7): 166–8.
2. Derk CT, Jimenez SA. Goodpasture-like syndrome induced by D-penicillamine in a patient with systemic sclerosis: report and review of the literature. *J Rheumatol* 2003; **30:** 1616–20.
3. Lyle WH. D-Penicillamine and fatal obliterative bronchiolitis. *BMJ* 1977; **1:** 105.
4. Epler GR, *et al.* Bronchiolitis and bronchitis in connective tissue disease: a possible relationship to the use of penicillamine. *JAMA* 1979; **242:** 528–32.
5. Murphy KC, *et al.* Obliterative bronchiolitis in two rheumatoid arthritis patients treated with penicillamine. *Arthritis Rheum* 1981; **24:** 557–60.
6. Wolfe F, *et al.* Upper and lower airway disease in penicillamine treated patients with rheumatoid arthritis. *J Rheumatol* 1983; **10:** 406–10.
7. Presley AP. Penicillamine induced rhinitis. *BMJ* 1988; **296:** 1332.

Effects on the skin. Penicillamine-induced skin lesions have been reviewed.[1] Reactions include those resulting from interference with collagen and elastin (see below); those associated with auto-immune mechanisms such as pemphigus, pemphigoid, lupus erythematosus, and dermatomyositis; and those classified as acute sensitivity reactions including macular or papular eruptions and urticaria. The effects on collagen and elastin tend to occur only after prolonged use of high doses, as in patients with Wilson's disease or cystinuria, whereas patients with diseases characterised by altered immune systems, such as rheumatoid arthritis, are more prone to develop the antibody-related adverse skin reactions. Acute hypersensitivity reactions tend to occur early in treatment, usually within the first 7 to 10 days, and appear not to be dose-related. Lichenoid reactions, stomatitis, nail changes, and adverse effects on hair have also occurred.

1. Levy RS, *et al.* Penicillamine: review and cutaneous manifestations. *J Am Acad Dermatol* 1983; **8:** 548–58.

Interference with collagen and elastin. Long-term, high-dose treatment with penicillamine can interfere with elastin and collagen production giving rise to increased skin friability, haemorrhagic lesions, miliary papules, and excessive wrinkling and laxity of the skin.[1] Penicillamine dermatopathy, characterised by wrinkling and purpura over bony prominences, has been described.[2] In addition, lesions resembling pseudoxanthoma elasticum have been reported.[3,4] Abnormal elastic tissue has also been reported in patients taking low doses of penicillamine (less than 1 g daily), not only in the skin but also in joint capsules,[5] and elastosis perforans serpiginosa has been reported[6,7] in 2 patients. In all these cases, histological findings generally show damage to elastic fibres giving them a typical appearance described as 'lumpy-bumpy' or 'bramble-bush'.

For reports of cutis laxa in neonates, see Pregnancy under Precautions, below.

1. Levy RS, *et al.* Penicillamine: review and cutaneous manifestations. *J Am Acad Dermatol* 1983; **8:** 548–58.
2. Sternlieb I, Scheinberg IH. Penicillamine therapy for hepatolenticular degeneration. *JAMA* 1964; **189:** 748–54.
3. Thomas RHM, *et al.* Pseudoxanthoma elasticum-like skin changes induced by penicillamine. *J R Soc Med* 1984; **77:** 794–8.
4. Bentley-Phillips B. Pseudoxanthoma elasticum-like skin changes induced by penicillamine. *J R Soc Med* 1985; **78:** 787.
5. Dalziel KL, *et al.* Elastic fibre damage induced by low-dose D-penicillamine. *Br J Dermatol* 1990; **123:** 305–12.
6. Sahn EE, *et al.* D-Penicillamine-induced elastosis perforans serpiginosa in a child with juvenile rheumatoid arthritis. *J Am Acad Dermatol* 1989; **20:** 979–88.
7. Hill VA, *et al.* Penicillamine-induced elastosis perforans serpiginosa and cutis laxa in Wilson's disease. *Br J Dermatol* 2000; **142:** 560–1.

Lichen planus. There have been rare reports of lichen planus in patients with primary biliary cirrhosis taking penicillamine,[1,2] although the role of penicillamine has been questioned. Oral lichen planus associated with penicillamine has also been reported[3] in patients with rheumatoid arthritis.

1. Powell FC, Rogers RS. Primary biliary cirrhosis, penicillamine, and lichen planus. *Lancet* 1981; **ii:** 525.
2. Powell FC, *et al.* Lichen planus, primary biliary cirrhosis and penicillamine. *Br J Dermatol* 1982; **107:** 616.
3. Blasberg B, *et al.* Lichenoid lesions of the oral mucosa in rheumatoid arthritis patients treated with penicillamine. *J Rheumatol* 1984; **11:** 348–51.

Pemphigus. Bullous skin disorders are established adverse effects of penicillamine and appear to have an auto-immune basis.[1] Pemphigus-spectrum disorders have been most commonly reported, including pemphigus vulgaris, pemphigus foliaceus, herpetiform pemphigus, pemphigus erythematosus, benign mucous membrane pemphigoid, cicatricial pemphigoid, and combined pemphigus and pemphigoid features.

1. Bialy-Golan A, Brenner S. Penicillamine-induced bullous dermatoses. *J Am Acad Dermatol* 1996; **35:** 732–42.

Psoriasiform eruptions. Two patients with rheumatoid arthritis developed psoriasiform eruptions during penicillamine treatment.[1] In 1 patient the eruption resolved when penicillamine was stopped but worsened when treatment was restarted.

1. Forgie JC, Highet AS. Psoriasiform eruptions associated with penicillamine. *BMJ* 1987; **294:** 1101.

Scleroderma. Penicillamine has been used in the treatment of scleroderma and systemic sclerosis (see under Uses, below). However, scleroderma, with evidence of pulmonary involvement, developed in a 14-year-old boy with Wilson's disease who had been treated with penicillamine for 11 years[1] and the suitability of penicillamine for this indication has therefore been questioned.

1. Miyagawa S, *et al.* Systemic sclerosis-like lesions during long-term penicillamine therapy for Wilson's disease. *Br J Dermatol* 1987; **116:** 95–100.

Toxic epidermal necrolysis. A 56-year-old woman developed agranulocytosis and toxic epidermal necrolysis 7 weeks after starting therapy with penicillamine 250 mg daily for primary biliary cirrhosis.[1] Severe toxic epidermal necrolysis has

also been reported[2] in a woman taking penicillamine for Wilson's disease.

1. Ward K, Weir DG. Life threatening agranulocytosis and toxic epidermal necrolysis during low dose penicillamine therapy. *Ir J Med Sci* 1981; **150:** 252–3.
2. Chan HL. Observations on drug-induced toxic epidermal necrolysis in Singapore. *J Am Acad Dermatol* 1984; **10:** 973–8.

Genetic factors. There is evidence that some patients may have a genetically determined increased susceptibility to the adverse effects of penicillamine. Several studies have suggested that rheumatoid arthritis patients with a poor capacity for producing sulfoxides may be more susceptible to the toxic effects of penicillamine.[1,2] Patients with primary biliary cirrhosis also appear to have poor sulfoxidation capacity,[3] and this may contribute to their high incidence of adverse reactions to penicillamine, although no association between penicillamine toxicity and sulfoxidation status was found in a study of 20 such patients.[4]

Several studies have also suggested that certain histocompatibility antigens may increase susceptibility to penicillamine toxicity. An increased incidence of adverse reactions was noted[2] in patients with HLA-DR3, while other studies have shown associations between proteinuria and HLA antigens B8 and DR3,[5,6] myasthenia gravis and Bw35 and DR1,[7] thrombocytopenia and HLA antigens DR4,[5,6] A1,[5] and C4BQO,[5] and polymyositis or dermatomyositis and HLA antigens B18, B35, and DR4.[8] However, not all studies have reported the same associations, and the clinical usefulness of sulfoxidation testing or HLA-typing is not established.[6,9]

1. Panayi GS, *et al.* Deficient sulphoxidation status and D-penicillamine toxicity. *Lancet* 1983; **i:** 414.
2. Emery P, *et al.* D-Penicillamine induced toxicity in rheumatoid arthritis: the role of sulphoxidation status and HLA-DR3. *J Rheumatol* 1984; **11:** 626–32.
3. Olomu A, *et al.* Poor sulphoxidation in primary biliary cirrhosis. *Lancet* 1985; **i:** 1504.
4. Mitchison HC, *et al.* D-penicillamine-induced toxicity in primary biliary cirrhosis (PBC): the role of sulphoxidation status. *Gut* 1986; **27:** A622.
5. Stockman A, *et al.* Genetic markers in rheumatoid arthritis: relationship to toxicity from D-penicillamine. *J Rheumatol* 1986; **13:** 269–73.
6. Moens HJB, *et al.* Longterm followup of treatment with D-penicillamine for rheumatoid arthritis: effectivity and toxicity in relation to HLA antigens. *J Rheumatol* 1987; **14:** 1115–19.
7. Garlepp MJ, *et al.* HLA antigens and acetylcholine receptor antibodies in penicillamine induced myasthenia gravis. *BMJ* 1983; **286:** 338–40.
8. Carroll GJ, *et al.* Penicillamine induced polymyositis and dermatomyositis. *J Rheumatol* 1987; **14:** 995–1001.
9. Hall CL. Penicillamine nephropathy. *BMJ* 1988; **297:** 137.

Systemic lupus erythematosus. A syndrome resembling lupus erythematosus developed in 6 women with long-standing severe rheumatoid arthritis while being treated with penicillamine;[1] this represented a frequency of penicillamine-induced lupus erythematosus of about 2%. All 6 had developed previous cutaneous reactions to gold therapy. A case of bullous systemic lupus erythematosus associated with penicillamine has also been reported.[2]

1. Chalmers A, *et al.* Systemic lupus erythematosus during penicillamine therapy for rheumatoid arthritis. *Ann Intern Med* 1982; **97:** 659–63.
2. Condon C, *et al.* Penicillamine-induced type II bullous systemic lupus erythematosus. *Br J Dermatol* 1997; **136:** 474–5.

Precautions

Penicillamine is contra-indicated in patients with lupus erythematosus or a history of penicillamine-induced agranulocytosis, aplastic anaemia, or severe thrombocytopenia. It should be used with care in patients with mild renal impairment and is contra-indicated in patients with moderate or severe renal impairment.

Penicillamine should not be given with other drugs capable of causing similar serious haematological or renal adverse effects, for example gold salts, chloroquine or hydroxychloroquine, or immunosuppressive drugs. Penicillamine is a degradation product of penicillin and patients who are allergic to penicillin may show cross-sensitivity to penicillamine although this appears to be rare.

Patients need to be carefully monitored for adverse effects. In particular full blood counts and urinalysis should be carried out; one recommendation is to perform blood counts weekly or fortnightly, and urinalysis weekly, for the first 2 months of treatment and after any change in dosage, and monthly thereafter. Treatment should be withdrawn if there is a fall in white cell or platelet count, or if progressive or serious proteinuria or haematuria occur. Liver function tests at 6-monthly intervals have also been recommended and renal function should be monitored.

Pyridoxine 25 mg daily may be given to patients on long-term therapy, especially if they are on a restricted diet, since penicillamine increases the requirement for this vitamin.

A reduced dose of penicillamine has been suggested for patients undergoing surgery (see Anaesthesia and Surgery, below).

Anaesthesia and surgery. Penicillamine may delay wound healing due to its effects on collagen and elastin and it has been suggested that the dose should be reduced to 250 mg daily for 6 weeks before surgery and during the postoperative period until healing has taken place.

The effects of penicillamine on muscle function should also be considered in patients requiring anaesthesia; a 57-year-old woman[1] with penicillamine-induced myasthenia developed prolonged postoperative apnoea, necessitating artificial ventilation.

1. Fried MJ, Protheroe DT. D-Penicillamine induced myasthenia gravis: its relevance for the anaesthetist. *Br J Anaesth* 1986; **58:** 1191–3.

Pregnancy. Penicillamine teratogenicity has been reviewed.[1] Evidence of the embryotoxicity of maternal penicillamine exposure in *animal* studies had been confirmed in humans by 5 reports of cutis laxa in neonates of mothers who had taken penicillamine during pregnancy; 3 further reports of intra-uterine brain injury were less characteristic. Nevertheless most pregnancy outcomes were normal. No birth defects had been reported when penicillamine was discontinued in early pregnancy. It is generally recommended that women receiving penicillamine for Wilson's disease should continue throughout pregnancy since the benefits outweigh the risks. However, in other conditions, particularly where there are safer alternatives, discontinuation of penicillamine is advised.

1. Rosa FW. Teratogen update: penicillamine. *Teratology* 1986; **33:** 127–31.

Interactions

Penicillamine forms chelates with metal ions and oral absorption may be reduced if it is given with iron or other metals, antacids, or food. Penicillamine should be taken on an empty stomach and it has been recommended that there should be an interval of at least 2 hours between taking penicillamine and iron supplements. Additive toxicity may occur if penicillamine is given with drugs that have adverse renal or haematological effects (see Precautions, above).

Antacids or food. In a single-dose study in 6 healthy subjects, penicillamine given orally immediately after food or a dose of an antacid mixture (aluminium hydroxide, magnesium hydroxide, and simeticone), resulted in plasma concentrations of penicillamine that were 52% and 66%, respectively, of those obtained in a fasting state. Results suggested that the reduction in plasma-penicillamine concentrations was associated with decreased absorption.[1] Another study[2] showed that the reduction of penicillamine plasma concentrations produced by aluminium- and magnesium-containing antacids did not occur with sodium bicarbonate, and thus the interaction was probably a result of chelation rather than a pH effect.

1. Osman MA, *et al.* Reduction in oral penicillamine absorption by food, antacid, and ferrous sulphate. *Clin Pharmacol Ther* 1983; **33:** 465–70.
2. Ifan A, Welling PG. Pharmacokinetics of oral 500 mg penicillamine: effect of antacids on absorption. *Biopharm Drug Dispos* 1986; **7:** 401–5.

Diazepam. For a report of exacerbation of intravenous diazepam-induced phlebitis by oral penicillamine, see under Diazepam, p.991.

Gold. There have been conflicting reports on the effect of previous gold therapy on the subsequent development of penicillamine toxicity in patients with rheumatoid arthritis.

Some studies[1,2] have suggested that adverse effects with penicillamine may be more common in patients who have previously reacted adversely to gold, but others[3,4] have found no correlation. One study[5] found that although the overall incidence of adverse effects with penicillamine appeared unaffected by prior gold therapy, bone-marrow depression and rashes were more common in those previously treated with gold. It has been suggested[2] that the interaction occurs due to mobilisation of gold from the tissues by penicillamine, and an interval of at least 6 months between gold and penicillamine in patients with prior gold toxicity was recommended. However, another report[6] found that the interval between gold and penicillamine had no influence on the development of toxicity and suggested that there might be a common genetic susceptibility in certain patients. A patient who had experienced myasthenia with penicillamine had a recurrence with gold therapy,[7] but another study[4] found no evidence that the adverse effects of gold were increased in those with prior penicillamine toxicity.

1. Hill H. Penicillamine and previous treatment with gold. *BMJ* 1978; **2:** 961.
2. Dodd MJ, *et al.* Adverse reactions to D-penicillamine after gold toxicity. *BMJ* 1980; **280:** 1498–1500.
3. Multi-centre Trial Group. Absence of toxic or therapeutic interaction between penicillamine and previously administered gold in a trial of penicillamine in rheumatoid disease. *Postgrad Med J* 1974; **50** (suppl 2): 77–8.
4. Steven MM, *et al.* Does the order of second-line treatment in rheumatoid arthritis matter? *BMJ* 1982; **284:** 79–81.
5. Webley M, Coomes EN. Is penicillamine therapy in rheumatoid arthritis influenced by previous treatment with gold? *BMJ* 1978; **2:** 91.
6. Smith PJ, *et al.* Influence of previous gold toxicity on subsequent development of penicillamine toxicity. *BMJ* 1982; **285:** 595–6.
7. Moore AP, *et al.* Penicillamine induced myasthenia reactivated by gold. *BMJ* 1984; **288:** 192–3.

Insulin. Unexplained hypoglycaemia in 2 patients with type 1 diabetes occurred 6 to 8 weeks after penicillamine treatment for rheumatoid arthritis was started.[1] Both patients required a reduction in their insulin dose. A possible immunological mechanism has been proposed.[1,2]

1. Elling P, Elling H. Penicillamine, captopril, and hypoglycemia. *Ann Intern Med* 1985; **103:** 644–5.
2. Becker RC, Martin RG. Penicillamine-induced insulin antibodies. *Ann Intern Med* 1986; **104:** 127–8.

Iron. Plasma-penicillamine concentrations were reduced to 35% when penicillamine was given after a dose of ferrous sulfate in healthy subjects.[1] Patients stabilised on penicillamine while on oral iron therapy were considered unlikely to respond fully to penicillamine and would be exposed to a large increase in penicillamine absorption with possible adverse reactions if the iron was stopped.[2]

1. Osman MA, *et al.* Reduction in oral penicillamine absorption by food, antacid, and ferrous sulfate. *Clin Pharmacol Ther* 1983; **33:** 465–70.
2. Harkness JAL, Blake DR. Penicillamine nephropathy and iron. *Lancet* 1982; **ii:** 1368–9.

Probenecid. Probenecid may reduce the beneficial effects of penicillamine in cystinuria, and it has been suggested[1] that hyperuricaemic cystinuric patients should not be given both drugs.

1. Yu T-F, *et al.* Studies on the metabolism of D-penicillamine and its interaction with probenecid in cystinuria and rheumatoid arthritis. *J Rheumatol* 1984; **11:** 467–70.

Pharmacokinetics

Penicillamine is rapidly but variably absorbed from the gastrointestinal tract and reaches peak concentrations in the blood within 1 to 3 hours. It is reported to be more than 80% bound to plasma proteins. It undergoes some metabolism in the liver, to *S*-methyl penicillamine, and is excreted primarily in the urine, mainly as disulfides, along with some *S*-methyl penicillamine and unchanged drug; a small amount may be excreted in the faeces. Elimination is biphasic with an initial elimination half-life of about 1 to 3 hours followed by a slower phase, suggesting gradual release from tissues.

◊ Reviews.

1. Netter P, *et al.* Clinical pharmacokinetics of D-penicillamine. *Clin Pharmacokinet* 1987; **13:** 317–33.

Uses and Administration

Penicillamine is a chelator that aids the elimination from the body of certain heavy-metal ions, including copper, lead, and mercury, by forming stable soluble complexes with them that are readily excreted by the kidney. It is used in the treatment of Wilson's disease (to promote the excretion of copper), in heavy-metal poisoning such as lead poisoning, in cystinuria (to reduce urinary concentrations of cystine), in severe active rheumatoid arthritis, and in chronic active hepatitis.

Penicillamine is given orally and should be taken on an empty stomach. A low initial dose increased gradually to the minimum optimal maintenance dosage may reduce the incidence of adverse effects as well as provide closer control of the condition being treated.

In the treatment of **Wilson's disease**, a dose of 1.5 to 2 g daily in divided doses may be given initially. The optimal dosage to achieve a negative copper balance should be determined initially by regular analysis of 24-hour urinary copper excretion and subsequently by monitoring free copper in the serum. A maintenance dose of 0.75 to 1 g daily may be adequate once control is achieved and should be continued indefinitely; UK licensed product information recommends that a maintenance dose of 2 g daily should not be continued for more than a year. In children, a suggested dose is up to 20 mg/kg daily (minimum 500 mg daily) in divided doses. A dose of 20 mg/kg daily is suggested for the elderly.

In the management of **lead poisoning**, penicillamine may be given in doses of 1 to 1.5 g daily in divided doses until urinary lead is stabilised at less than 500 micrograms/day. Children and the elderly may be given 20 mg/kg daily in divided doses.

In **cystinuria**, doses of penicillamine are adjusted according to cystine concentrations in the urine. For the *treatment* of cystinuria and cystine calculi, the dose is usually in the range of 1 to 4 g daily in divided doses; a suggested dose for children is 30 mg/kg daily in divided doses. For the *prevention* of cystine calculi, lower doses of 0.5 to 1 g at bedtime may be given. An adequate fluid intake is essential to maintain urine flow when penicillamine is used for cystinuria.

In the treatment of **severe active rheumatoid arthritis**, an initial dose of penicillamine 125 to 250 mg daily is increased gradually by the same amount at intervals of 4 to 12 weeks. Remission is usually achieved with maintenance doses of 500 to 750 mg daily in divided doses, but up to 1.5 g daily may be required. Improvement may not occur for several months; US licensed product information suggests that penicillamine should be discontinued if there is no response after treatment for 3 to 4 months with 1 to 1.5 g daily; in the UK, a trial for 12 months is suggested. After remission has been sustained for 6 months an attempt may be made gradually to reduce the dose by 125 to 250 mg daily every 3 months but relapse may occur. Lower doses may be required in the elderly who may be more susceptible to developing adverse effects. Initial doses of 125 mg daily are recommended, gradually increased to a maximum of 1 g daily if necessary. In children the maintenance dose is 15 to 20 mg/kg daily; a suggested initial dose is 2.5 to 5 mg/kg daily increased gradually at 4-week intervals.

In the management of **chronic active hepatitis**, penicillamine may be given after liver function tests have indicated that the disease has been controlled by corticosteroids. The initial dose is 500 mg daily in divided doses, increased gradually over 3 months to 1.25 g daily, while at the same time reducing the corticosteroid dose.

Acetylpenicillamine has been used in mercury poisoning.

Chronic active hepatitis. Penicillamine has been tried in chronic active hepatitis (p.1501) as an alternative to prolonged corticosteroid maintenance therapy once control of the disease is achieved. The dose of penicillamine is increased over several months to a suitable maintenance dose and, at the same time, the corticosteroid dose is decreased.

Cystinuria. Cystinuria is an inherited disorder of renal amino-acid excretion in which there is excessive excretion of cystine (cysteine disulfide), along with ornithine, lysine, and arginine. The low solubility of cystine leads to the formation of cystine stones in the kidney, resulting in pain, haematuria, renal obstruction, and infection. Treatment is primarily aimed at reducing the urinary concentration of cystine to below its solubility limit of 300 to 400 mg/litre at neutral pH. Patients with cystinuria excrete 400 to 1200 mg cystine daily and should be advised to drink at least 3 litres of water daily, including at night, to maintain a dilute urine. Cystine is more soluble in alkaline urine and urinary alkalinisers such as sodium bicarbonate, sodium citrate, or potassium citrate may be used; however, high doses are required and calcium stone formation may be promoted. Penicillamine may also be used, particularly in patients where these measures are ineffective or not tolerated; it complexes with cysteine to form a more soluble mixed disulfide, therefore reducing cystine excretion, preventing cystine stone formation, and promoting the gradual dissolution of existing stones. Adverse effects are common and tiopronin, which has a similar action, may be used as an alternative. Surgical removal may be necessary for established stones but lithotripsy is not very effective.

Lead poisoning. Penicillamine may be used to treat asymptomatic lead intoxication and to achieve desirable tissue-lead concentrations in patients with symptomatic lead poisoning once they have received treatment with sodium calcium edetate and dimercaprol (see p.2332).

Primary biliary cirrhosis. Copper accumulation in the liver has been noted in patients with primary biliary cirrhosis (see under Ursodeoxycholic Acid,p.2408) and therapy with penicillamine to reduce liver-copper concentrations has been studied. Despite good preliminary results, most studies have found it to be ineffective and any benefit appears to be offset by the high incidence of adverse effects.[1,2]

1. James OFW. -Penicillamine for primary biliary cirrhosis. *Gut* 1985; **26:** 109–13.
2. Gong Y, *et al.* D-penicillamine for primary biliary cirrhosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 04/04/06).

Retinopathy of prematurity. Penicillamine has been investigated for the prophylaxis of retinopathy of prematurity (p.1994) in infants considered to be at risk, and a systematic review of 2 such studies considered that there was evidence for a reduced incidence of acute retinopathy.[1] Further studies were considered justified, with careful attention to possible adverse effects.

1. Phelps DL, *et al.* D-Penicillamine for preventing retinopathy of prematurity in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 04/10/05).

Rheumatoid arthritis. Penicillamine is one of a diverse group of disease-modifying antirheumatic drugs that have been used in rheumatoid arthritis (p.11) in an attempt to suppress the rate of cartilage erosion or alter the course of the disease. However, early enthusiasm for penicillamine has been tempered by a high incidence of adverse effects.[1] During long-term therapy as many as 50% of patients taking penicillamine have been reported to stop treatment because of adverse effects.[2] Low doses of penicillamine to reduce the incidence of adverse effects have been tried and while doses as low as 125 mg daily have been claimed to be effective in some patients, a 36-week multicentre double-blind study[3] involving 225 patients concluded that a dose of penicillamine 500 mg daily was only slightly more effective than placebo. A dose of 125 mg daily was not significantly different from either the 500-mg dose or placebo. However, a 5-year open study[4] comparing penicillamine in doses up to 500 mg daily with hydroxychloroquine, sodium aurothiomalate, or auranofin found penicillamine to be as effective as the other drugs and well tolerated, with 53% of the patients randomised to penicillamine still receiving it at 5 years, as opposed to about 30 to 35% of those randomised to other drugs.

1. Suarez-Almazor ME, *et al.* Penicillamine for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 04/10/05).
2. Moens HJB, *et al.* Longterm followup of treatment with -penicillamine for rheumatoid arthritis: effectivity and toxicity in relation to HLA antigens. *J Rheumatol* 1987; **14:** 1115–19.
3. Williams HJ, *et al.* Low-dose -penicillamine therapy in rheumatoid arthritis: a controlled, double-blind clinical trial. *Arthritis Rheum* 1983; **26:** 581–92.
4. Jessop JD, *et al.* A long-term five-year randomized controlled trial of hydroxychloroquine, sodium aurothiomalate, auranofin and penicillamine in the treatment of patients with rheumatoid arthritis. *Br J Rheumatol* 1998; **37:** 992–1002.

Scleroderma. Penicillamine affects the cross-linking of collagen,[1] and observational studies[2,3] have suggested that it may be of benefit in scleroderma (p.1817), and perhaps in some visceral manifestations of systemic sclerosis. A randomised study[4] comparing a conventional dose of penicillamine (up to 1 g daily) with a very low dose (125 mg on alternate days) found no difference in outcome, but there were more adverse effects with the higher dose. Although the lower dose was not expected to be effective, the skin score improved significantly in both groups; however, there was insufficient evidence to attribute this to use of penicillamine, and its role in scleroderma remains to be established.

For a report of sclerodermatous lesions in a patient taking penicillamine for Wilson's disease, see Scleroderma, under Effects on the Skin, above.

1. Herbert CM, *et al.* Biosynthesis and maturation of skin collagen in scleroderma, and effect of D-penicillamine. *Lancet* 1974; **i:** 187–92.
2. Steen VD, *et al.* -Penicillamine therapy in progressive systemic sclerosis (scleroderma): a retrospective analysis. *Ann Intern Med* 1982; **97:** 652–9.
3. Derk CT, *et al.* A retrospective randomly selected cohort study of D-penicillamine treatment in rapidly progressive diffuse cutaneous systemic sclerosis of recent onset. *Br J Dermatol* 2008; **158:** 1063–8.
4. Clements PJ, *et al.* High-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis: analysis of a two-year, double-blind, randomized, controlled clinical trial. *Arthritis Rheum* 1999; **42:** 1194–1203.

Wilson's disease. Wilson's disease, or hepatolenticular degeneration, is a rare autosomal disorder of copper accumulation.[1-5] Excretion of excess copper, which normally occurs via the bile, is impaired and total body copper progressively increases. The excess copper accumulates in the liver, brain, and other organs including the kidneys and corneas, and eventually causes tissue damage.

Effective treatment of Wilson's disease involves the use of copper-reducing drugs to establish a negative copper balance. This prevents deposition of more copper and also mobilises excess copper that has already been deposited making it available for excretion. Once negative copper balance has been achieved, maintenance treatment must be continued lifelong. Dietary restriction of copper is not generally considered to be an important part of the treatment of Wilson's disease, although patients may be advised to avoid copper-rich foods, such as liver and shellfish, during the first year of treatment and to restrict their consumption thereafter. Symptomatic recovery from copper overload occurs slowly, but is usually complete if treatment is started early enough, and a normal life expectancy can be achieved. However, once irreversible organ damage such as liver cirrhosis has occurred, treatment can only prevent further deterioration; those presenting with end-stage liver disease do not benefit from copper-reducing therapy, and liver transplantation is necessary (although successful medical treatment has been reported in children). The drugs used to reduce copper concentrations in the treatment of Wilson's disease are penicillamine, trientine, and zinc. Ammonium tetrathiomolybdate, an investigational drug, may also be used.

Penicillamine reduces copper concentrations in several ways. Its main action is to chelate circulating copper, which is then excreted in the urine. In addition, penicillamine reduces the affinity of copper for proteins and polypeptides, allowing removal of copper from tissues. It also induces hepatic synthesis of metallothionein, a protein that combines with copper to form a non-toxic product. *Trientine* is a less potent copper chelator than penicillamine; it competes for copper bound to serum albumin and increases copper excretion. *Zinc* induces synthesis of metallothionein in the intestine so that absorption of copper from the gastrointestinal tract is blocked. It is usually given as the acetate as this form is less irritating to the stomach than the sulfate. *Ammonium tetrathiomolybdate* forms a complex with protein and copper. When it is given with food it blocks the intestinal absorption of copper, and when taken between meals it combines with albumin- and caeruloplasmin-bound copper.

CHOICE OF DRUG. Penicillamine is generally regarded as the drug of choice for the initial management of Wilson's disease as it produces a rapid reduction in copper levels. However, it may initially exacerbate neurological symptoms (possibly due to transiently increased brain and blood copper concentrations) and some practitioners therefore suggest starting with zinc; zinc is less suitable in those requiring rapid reduction of copper levels as it has a slow onset of action. Trientine, which may also exacerbate neurological symptoms, is principally used in patients intolerant of penicillamine. Ammonium tetrathiomolybdate is under investigation for the initial reduction of copper levels; it may be particularly suitable for patients with neurological symptoms.

Once a negative copper balance is achieved, maintenance therapy must be continued for life. Penicillamine, trientine, and zinc are all used for maintenance treatment. Patients taking penicillamine are also given pyridoxine to prevent deficiency (see Precautions, above). The adverse effects of penicillamine may be a problem during long-term use and zinc, which has low toxicity, is often preferred. Zinc is also used in patients in the asymptomatic stage of the disease.

1. Brewer GJ. Recognition, diagnosis, and management of Wilson's disease. *Proc Soc Exp Biol Med* 2000; **223:** 39–46.
2. Roberts EA, Schilsky ML. A practice guideline on Wilson disease. *Hepatology* 2003; **37:** 1475–92.
3. El-Youssef M. Wilson disease. *Mayo Clin Proc* 2003; **78:** 1126–36.
4. Merle U, *et al.* Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study. *Gut* 2007; **56:** 115–20.
5. Ala A, *et al.* Wilson's disease. *Lancet* 2007; **369:** 397–408.

Preparations

BP 2008: Penicillamine Tablets;
USP 31: Penicillamine Capsules; Penicillamine Tablets.

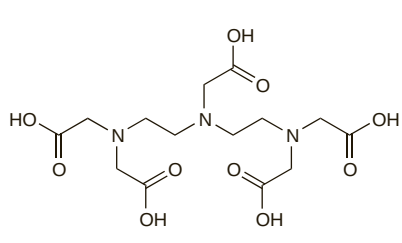
Proprietary Preparations (details are given in Part 3)
Arg.: Cuprimine; Cupripen; ***Austral.:*** D-Penamine; ***Austria:*** Artamin; ***Belg.:*** Kelatin†; ***Braz.:*** Cuprimine; ***Canad.:*** Cuprimine; Depen†; ***Cz.:*** Metalcaptase; Trolovol†; ***Denm.:*** Atamir; ***Fr.:*** Trolovol; ***Ger.:*** Metalcaptase; Trisorcin†; ***Gr.:*** Cupripen†; ***Hong Kong:*** Cuprimine†; ***Hung.:*** Byanodine†; ***India:*** Cilamin; ***Irl.:*** Distamine; ***Israel:*** Cuprimine†; ***Ital.:*** Pemine; ***Jpn:*** Metalcaptase; ***Malaysia:*** Artamin; ***Mex.:*** Adalken; Sufortan; ***Neth.:*** Gerodyl; ***Norw.:*** Cuprimine†; ***NZ:*** D-Penamine; Distamine†; ***Pol.:*** Cuprenil; ***Port.:*** Kelatine; Trolovol; ***S.Afr.:*** Metalcaptase; ***Spain:*** Cupripen; ***Switz.:*** Mercaptyl; ***Thai.:*** Cuprimine; ***UK:*** Distamine; ***USA:*** Cuprimine; Depen.

Pentetic Acid *(BAN, USAN, rINN)*

Acide Pentétique; Ácido pentético; Acidum Penteticum; DTPA; ZK-43649. Diethylenetriamine-*NNN′N″N″*-penta-acetic acid.

Пентетовая Кислота

$C_{14}H_{23}N_3O_{10}$ = 393.3.
CAS — 67-43-6.



Pharmacopoeias. In *US*.
USP 31 (Pentetic Acid). A white odourless or almost odourless powder.