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.

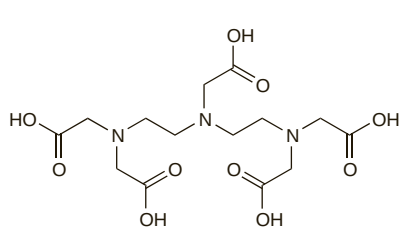
Proprietary Preparations (details are given in Part 3)
Arg.: Cuprimine; Cupripen; ***Austral.:*** D-Penamine; ***Austria:*** Artamin; ***Belg.:*** Kelatin†; ***Braz.:*** Cuprimine; ***Canad.:*** Cuprimine; Depen†; ***Cz.:*** Metalcaptase; Trolovol†; ***Denm.:*** Atamir; ***Fr.:*** Trolovol; ***Ger.:*** 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.

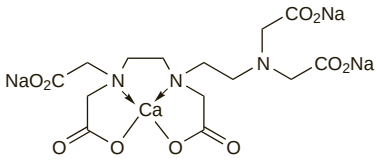
Calcium Trisodium Pentetate *(BAN, rINN)*

Ca-DTPA; Calcii Trinatrii Pentetas; Calcium Trisodium DTPA; NSC-34249; Pentetate Calcium Trisodium *(USAN)*; Pentétate de Calcium Trisodique; Pentetato calcio y trisodio; Trisodium Calcium Diethylenetriaminepentaacetate.

Кальция Тринатрия Пентетат

$C_{14}H_{18}CaN_3Na_3O_{10}$ = 497.4.

CAS — 12111-24-9.



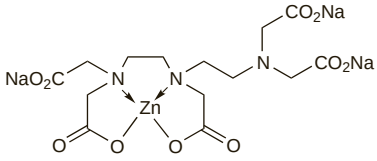
Zinc Trisodium Pentetate *(rINNM)*

Pentétate de Zinc Trisodique; Pentetate Zinc Trisodium; Pentetato zinc y trisodio; Trisodium Zinc Diethylenetriaminepentaacetate; Zinci Trinatrii Pentetas; Zn-DTPA (zinc pentetate or zinc trisodium pentetate).

Цинка Тринатрия Пентетат

$C_{14}H_{18}N_3Na_3O_{10}Zn$ = 522.7.

CAS — 65229-17-6 (zinc pentetate); 125833-02-5 (zinc trisodium pentetate).



Adverse Effects and Precautions

Adverse effects that have been reported with calcium or zinc trisodium pentetate include headache, nausea and diarrhoea, and injection-site reactions. Bronchospasm has occurred after inhalation. Pentetates chelate trace metals and supplements may be needed with long-term use. Serum-electrolytes should be monitored during use. Pentetates should be used with caution in patients with haemochromatosis since fatalities have been reported.

Uses and Administration

Pentetic acid and its salts are chelators with the general properties of the edetates (see Edetic Acid, p.1445). Calcium trisodium pentetate is used in the treatment of poisoning by heavy metals; both calcium trisodium pentetate and zinc trisodium pentetate are used for poisoning with radioactive metals such as plutonium, americium, and curium.

In heavy-metal poisoning, calcium trisodium pentetate has been given in a dose of 1 g daily by intravenous infusion for 3 to 5 days, with further treatment, if necessary, after an interval of 3 days.

For poisoning with plutonium and similar radioactive metals, either calcium trisodium pentetate or zinc trisodium pentetate may be used. Calcium trisodium pentetate is more effective within the first 24 hours and is preferred for the initial dose; however, zinc depletion may occur and if further chelation is required treatment should be continued with zinc trisodium pentetate if possible. The usual dose is 1 g of either calcium or zinc trisodium pentetate once daily, by slow intravenous injection over 3 to 4 minutes or by intravenous infusion. Treatment is usually continued for 5 days and then modified depending on the estimated radioactive body burden. For patients with poisoning by inhalation only, the calcium trisodium pentetate or zinc trisodium pentetate may be given by nebulisation.

Pentetates, labelled with metallic radionuclides, are used in nuclear medicine (see Indium-111, p.2054, and Technetium-99m, p.2056).

Thalassaemia. Iron overload in patients with thalassaemia (p.1045) is usually treated with desferrioxamine, but auditory toxicity can result. Calcium pentetic acid has been used as an alternative. A study[1] in 5 patients in whom desferrioxamine had to be withdrawn because of high-tone deafness found that the pentetate was as effective as desferrioxamine and hearing improved during treatment. Oral zinc supplements were necessary to maintain adequate plasma-zinc concentrations.

1. Wonke B, *et al.* Reversal of desferrioxamine induced auditory neurotoxicity during treatment with Ca-DTPA. *Arch Dis Child* 1989; **64:** 77–82.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Ditripentat; ***Ger.:*** Ditripentat-Heyl.

Potassium Polystyrene Sulfonate

Poliestirenosulfonato potásico; Potassium Polystyrene Sulphonate.

CAS — 9011-99-8.
ATC — V03AE01.
ATC Vet — QV03AE01.

Profile

Potassium polystyrene sulfonate, the potassium salt of sulfonated styrene polymer, is a cation-exchange resin that exchanges potassium ions for calcium ions and other cations and has been used in the management of hypercalciuria and renal calculi.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: *Ger.:* Ujostabil†.

Pralidoxime *(BAN, rINNM)*

Pralidoksiimi; Pralidoxim; Pralidoxima; Pralidoximum. 2-Hydroxyiminomethyl-1-methylpyridinium.

Пралидоксим

$C_7H_9N_2O$ = 137.2.

CAS — 6735-59-7; 495-94-3.
ATC — V03AB04.
ATC Vet — QV03AB04.

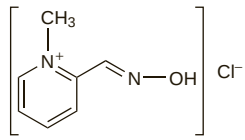
Pralidoxime Chloride *(BANM, USAN, rINNM)*

2-Formyl-1-methylpyridinium Chloride Oxime; 2-PAM; 2-PAM Chloride; 2-PAMCl; Pralidoxima, cloruro de; Pralidoxime, Chlorure de; Pralidoxim Chloridum; 2-Pyridine Aldoxime Methochloride.

Пралидоксима Хлорид

$C_7H_9ClN_2O$ = 172.6.

CAS — 51-15-0.
ATC — V03AB04.
ATC Vet — QV03AB04.



Pharmacopoeias. In *US.*
USP 31 (Pralidoxime Chloride). A white to pale yellow, odourless, crystalline powder. Freely soluble in water.

Pralidoxime Iodide *(BANM, USAN, rINN)*

Ioduro de pralidoxima; NSC-7760; 2-PAM Iodide; 2-PAMI; Pralidoxime, Iodure de; Pralidoxim Iodidum.

Пралидоксима Йодид

$C_7H_9IN_2O$ = 264.1.

CAS — 94-63-3.
ATC — V03AB04.
ATC Vet — QV03AB04.

Pharmacopoeias. In *Chin.*

Pralidoxime Mesilate *(BANM, rINNM)*

Mesilato de pralidoxima; 2-PAMM; Pralidoksiimimesilaatti; Pralidoksim Mezilat; Pralidoxime, Mésilate de; Pralidoxime Mesylate *(USAN)*; Pralidoxime Methanesulphonate; Pralidoxim Mesilas; Pralidoximmesilat; P2S.

Пралидоксима Мезилат

$C_7H_9N_2O,CH_3O_3S$ = 232.3.

CAS — 154-97-2.
ATC — V03AB04.
ATC Vet — QV03AB04.

Pralidoxime Metilsulfate *(BANM, rINNM)*

Pralidoxima, metilsulfato de; Pralidoxime Methylsulphate; Pralidoxime, Métilsulfate de; Pralidoxim Metilsulfas.

Пралидоксима Метилсульфат

$C_7H_9N_2O,CH_3SO_4$ = 248.3.

CAS — 1200-55-1.
ATC — V03AB04.
ATC Vet — QV03AB04.

Pharmacopoeias. In *It.*

Adverse Effects

Use of pralidoxime may be associated with drowsiness, dizziness, disturbances of vision, nausea, tachycardia, headache, hyperventilation, and muscular weakness. Tachycardia, laryngospasm, and muscle rigidity have been attributed to giving pralidoxime intravenously at too rapid a rate. Large doses of pralidoxime may cause transient neuromuscular blockade.

Precautions

Pralidoxime should be used cautiously in patients with renal impairment; a reduction in dosage may be necessary. Caution is also required in giving pralidoxime to patients with myasthenia gravis as it may precipitate a myasthenic crisis. Pralidoxime should not be used to treat poisoning by carbamate pesticides.

When atropine and pralidoxime are given together, the signs of atropinisation may occur earlier than might be expected when atropine is used alone.

Pharmacokinetics

Pralidoxime is not bound to plasma proteins, does not readily pass into the CNS, and is rapidly excreted in the urine, partly unchanged and partly as a metabolite. The elimination half-life is about 1 to 3 hours.

◊ References.

1. Sidell FR, Groff WA. Intramuscular and intravenous administration of small doses of 2-pyridinium aldoxime methochloride to man. *J Pharm Sci* 1971; **60:** 1224–8.
2. Siddell FR, *et al.* Pralidoxime methanesulfonate: plasma levels and pharmacokinetics after oral administration to man. *J Pharm Sci* 1972; **61:** 1136–40.
3. Swartz RD, *et al.* Effects of heat and exercise on the elimination of pralidoxime in man. *Clin Pharmacol Ther* 1973; **14:** 83–9.
4. Schexnayder S, *et al.* The pharmacokinetics of continuous infusion pralidoxime in children with organophosphate poisoning. *J Toxicol Clin Toxicol* 1998; **36:** 549–55.

Uses and Administration

Pralidoxime is a cholinesterase reactivator. It is used as an adjunct to, but *not* as a substitute for, atropine in the treatment of poisoning by certain cholinesterase inhibitors. Its main indication is in poisoning due to organophosphorus insecticides or related compounds (see p.2047). These compounds phosphorylate and consequently inactivate cholinesterase, causing acetylcholine accumulation and muscle paralysis. Pralidoxime acts principally to reactivate cholinesterase, restoring the enzymatic destruction of acetylcholine at the neuromuscular junction and relieving muscle paralysis. However, concomitant use of atropine is required to counteract directly the adverse effects of acetylcholine accumulation, particularly at the respiratory centre. Pralidoxime is not equally antagonistic to all organophosphorus anticholinesterases as reactivation is dependent on the nature of the phosphoryl group and the rate at which inhibition becomes irreversible. It is not effective in the treatment of poisoning due to phosphorus, inorganic phosphates, or organophosphates without anticholinesterase activity. It has usually been contra-indicated in the treatment of poisoning by carbamate insecticides (including carbaryl poisoning) as it may increase toxicity (see p.2037). The use of pralidoxime has been suggested for the treatment of overdosage by anticholinesterase drugs, including those used to treat myasthenia gravis such as neostigmine; however, it is only slightly effective and its use is not generally recommended.

Pralidoxime is usually given as the chloride or mesilate but the iodide and metilsulfate salts have also been used. Doses are usually expressed in terms of the salts.

Pralidoxime may be given by slow intravenous injection over 5 to 10 minutes, by intravenous infusion over 15 to 30 minutes, or by subcutaneous or intramuscular injection; it has also been given orally.

In the treatment of **organophosphorus poisoning** pralidoxime should be given as soon as possible. After about 24 hours it becomes less effective since cholinesterase inactivation usually becomes irreversible after this time; however, patients with severe poisoning may occasionally respond up to 36 hours or longer after exposure, depending on the organophosphate involved. Injections of *atropine* should be given intravenously or intramuscularly and repeated as necessary until the patient shows signs of atropine toxicity; atropinisation should then be maintained for 48 hours or more. Large amounts of atropine may be required.