Toxicity may occur after inhalation, ingestion or skin contamination of organophosphorus (OP) compounds. Although dermal absorption tends to be slow, severe poisoning may still ensue if exposure is prolonged.

OP compounds act primarily by inhibiting acetylcholinesterase (AChE) activity in blood, brain and other tissues, thereby allowing acetylcholine to accumulate at autonomic and central synapses, autonomic post-ganglionic nerve endings and neuromuscular junctions. The rate of spontaneous reactivation of the inhibited AChE depends on the chemical structure of the particular OP. Most of the commonly used insecticides of this type have either two methyl (eg demeton-S-methyl, dichlorvos, dimethoate, malathion) or two ethyl (eg chlorpyrifos, diazinon, parathion) groups attached to the phosphorus atom so that dimethyl-phosphorylated AChE or diethyl-phosphorylated AChE respectively is generated. Spontaneous reactivation of dimethyl phosphorylated AChE proceeds quite rapidly and individuals poisoned with them improve even without oxime therapy. However, unless oximes are employed, there is no such expectation of rapid recovery for patients intoxicated with diethyl phosphoryl insecticides.

OP-induced delayed neuropathy results from phosphorylation of a nervous tissue esterase known as neuropathy target esterase (NTE), "aging" of which leads to axonal degeneration and demyelination of axon sheaths. Only certain OPs are capable of causing this syndrome.

The onset and severity of toxicity depends on the speed and degree of depression of AChE activity. The onset of signs of intoxication may be delayed and their duration prolonged because some OP compounds require biotransformation before becoming biologically active. Furthermore, prolonged occupational misuse of OP compounds may cause progressive depletion of AChE activity until toxic effects occur.

The duration and severity of intoxication depends on the route and magnitude of exposure and on the treatment given. Thus, the deliberate ingestion of an OP is likely to result in more severe intoxication than occupational exposure.

Acute toxicity

The first symptoms of poisoning are usually a feeling of exhaustion, weakness and mental confusion. These effects may be experienced during exposure, or up to 12 hours later, and could well be ignored by an individual using OP compounds occupationally. Vomiting, cramp-like abdominal pain, sweating and salivation may follow. Constriction of one or both pupils and a sensation of tightness in the chest during inspiration may also occur at an early stage but these signs are not reliable indices of the severity of systemic poisoning because they may be caused by local effects of spray mist in the eyes or bronchi.

As poisoning progresses muscular twitching begins in the eyelids, tongue, face and neck. The respiratory muscles become involved and generalised muscle weakness ensues. Convulsions may occur. Tachycardia is likely to be present (although some patients may have a bradycardia). Constriction of the pupil may be prominent and progressive. Later effects may include diarrhoea, tenesmus, incontinence, ataxia and mental confusion. Bronchial hypersecretion with bronchoconstriction and cyanosis may lead to respiratory depression and mental confusion, gradually advancing to coma and death from respiratory failure. Cardiac effects include A-V block, S-T changes, peaked T waves and QTc prolongation. Ventricular arrhythmias are a common cause of death and tachyarrhythmias may progress to ventricular fibrillation and/or asystole.

Glycosuria and hyperglycaemia are commonly seen in OP poisoning. Leucocytosis and low-grade fever are also frequently noted, even in the absence of infection. A low PaO_2 and metabolic acidosis will be seen in those severely poisoned and serum creatine kinase activity may be high.

The intermediate syndrome

Relapse after apparent resolution of cholinergic symptoms has been reported in patients who have ingested highly lipophilic organophosphorus compounds. Paralysis of limb muscles, neck flexors and cranial nerves develops some 24-96 hours after exposure and probably represents the nicotinic effects of acetylcholine. Optimum use of pralidoxime (see antidotes below) may prevent this "intermediate" syndrome.

Delayed neuropathy

Delayed, mixed, sensorimotor peripheral neuropathies can result from acute exposure to certain OPs. Symptoms appear one or two weeks after acute exposure and include paraesthesiae in the toes and feet, fatigue and cramp. Gait disturbances can develop and persist for several months and are occasionally permanent.

Chronic neuro-behavioural effects

Neuro-behavioural symptoms including depression, irritability, confusion, chronic tiredness, apathy, headache, dizziness and emotional lability have been associated occasionally with repeated symptomatic exposure to OP insecticides, particularly those contained in sheep dips. Such patients can be difficult to manage. An approach to their problems is outlined in Appendix 6.

In general, the more seriously poisoned the victim, the more important it is to get him to hospital as quickly as possible. In such circumstances first aid should not delay transfer but should be confined to measures required to maintain life (eg artificial respiration, cardiac resuscitation, control of convulsions) and ensure that transportation is as safe as possible. If the poison has been swallowed, oral activated charcoal (50-100 g for an adult) may be given if readily available and impairment of consciousness and convulsions are not present; its value is unproven. There is no role for gastric emptying as a first aid measure. If circumstances and time permit, thorough skin decontamination, if appropriate, should be carried out as described in Appendix 3. Similarly, eye exposure can be managed as described in Appendix 4.

All cases of OP poisoning should be dealt with as an emergency and the patient admitted to hospital as quickly as possible.

Supportive

The first priority if to stabilise the patient's clinical condition. A clear airway and adequate ventilation must be maintained. Bronchorrhoea requires prompt removal of secretions by suction and relief with intravenous atropine (see below). Supplemental oxygen should be given to maintain arterial PaO_2 > 10 kPa (75 mm Hg). If these measures fail the patient should be intubated and mechanical ventilation instituted.

Thorough skin decontamination should be carried out if appropriate (see Appendix 3). Gastric lavage should be considered in all potentially serious cases if ingestion has occurred less than one or two hours previously, although its value is unproven. Lavage should be performed with care and with an endotracheal tube in situ if consciousness is depressed, or if hydrocarbon solvents are present in the product ingested. Heart rate, blood pressure, ECG and arterial blood gases should be monitored routinely.

Patients with the intermediate syndrome require close observation to detect involvement of the respiratory muscles and the possible need for assisted ventilation.

Antidotes

Two specific antidotes exist for use in OP poisoning.

Atropine antagonises the effect of accumulated acetylcholine at muscarinic receptors. Atropine sulphate (2 mg intravenously for an adult or 0.02 mg/kg body weight for a child) should be given as soon as possible in moderately or severely poisoned patients. Repeated doses may have to be given over the first few hours and should be adjusted to control peripheral muscarinic signs, principally bronchospasm and bronchorrhoea. In severe cases, particularly when oximes are not administered, adults may require a total dose of atropine of 100 mg or more.

Oximes such as pralidoxime and obidoxime are able to reverse enzyme inhibition as long as the inhibited AChE remains in the "unaged" form. The oxime employed in the UK, pralidoxime mesylate, can be obtained from holding centres (see Appendix 5) and is given intravenously in a dose of 30 mg/kg body weight over 5-10 minutes. It should be administered as soon as possible in any severe or progressive case of intoxication. Repeat doses at four to six hour intervals or an intravenous infusion of 8 mg/kg body weight/hour in an adult may be necessary. Administration of pralidoxime should continue for as long as atropine is required.

It is commonly, but erroneously, believed that within one day of intoxication virtually all inhibited AChE will be in the "aged" form so that oxime therapy, if employed, would be useless. However, there are good reasons for believing that as soon as an effective concentration of oxime is achieved in the patient's tissues, the balance of "aging" and reactivation is altered in favour of the latter and that progress towards complete inhibition may be slowed markedly. Oximes may therefore be of benefit even when therapy is commenced or continued several days after intoxication has occurred. They are of particular value when diethyl phosphoryl insecticides are involved because of the very slow rate of spontaneous reactivation of AChE inhibited by these compounds.

Diazepam, in doses of 5-10 mg intravenously for an adult or 250 μg/kg body weight for a child, appears to have a beneficial, non-specific effect in addition to controlling tremors or convulsions.

Individuals who have marked depression of AChE will be more susceptible to the effects of further exposure to an OP compound and should not be allowed to return to work or come into contact with any OP compound until normal AChE activity has been restored.

Diagnosis of poisoning by OP compounds can be confirmed by demonstrating significantly reduced cholinesterase activity in red blood cells and plasma. A low plasma cholinesterase activity should always be confirmed by the measurement of red blood cell cholinesterase activity.

Normal plasma cholinesterase activity varies widely making it difficult to interpret measurements in acutely and chronically intoxicated individuals. Those likely to be engaged repeatedly with handling OP compounds (eg pilots involved in aerial spraying, contract sprayers on the ground) should have their normal plasma and erythrocyte cholinesterase activities assessed before occupational exposure commences.

The direct measurement of OPs or their metabolites in body fluids has no place in the immediate diagnosis or early management of poisoning. In many cases, rapid hydrolysis prevents the detection of the parent compound although urinary metabolites may persist for several days. The measurement of metabolites may be most helpful as a measure of low level chronic exposure.

Pesticide incidents which occur during occupational use or accidentally involve the general public should be reported (see Appendix 7).

Glyphosate only causes systemic toxicity if ingested. Skin penetration of this herbicide is poor.

Glyphosate is an organophosphate which has no anticholinesterase activity. It inhibits an enzyme which is essential for the synthesis of aromatic amino acids in plants, but is not present in man. Animal studies suggest that glyphosate is less toxic than polyoxyethyleneamine, until recently the most usual surfactant in glyphosate formulations (including "Roundup"). It is believed that this surfactant was responsible for some of the features observed in cases of severe poisoning due to glyphosate-containing products. Although many, but not all, formulations now contain an alternative surfactant, older formulations are likely to be available domestically for some years to come and so may continue to be ingested deliberately or accidentally. The new surfactants are expected to be less toxic than polyoxyethyleneamine but there is inadequate human experience to verify this.

Gastrointestinal symptoms occur as a result of local irritation and corrosive injury. Hypotension, often the only cardiovascular manifestation in mild poisoning, may be due to dehydration from persistent vomiting, lack of fluid intake, diarrhoea and fluid loss into the wall of the gastrointestinal tract following corrosive damage and responds to intravascular volume replacement. Severe poisoning may be associated with myocardial depression and not respond to fluid replacement or inotropes. The pulmonary oedema observed in these cases is due to increased vascular permeability, possibly caused by a systemic effect of the surfactant in the formulation or aspiration of gastric contents during vomiting.

Local effects

The inhalation of spray mist may cause oral or nasal discomfort and swallowed mist may cause an unpleasant taste in the mouth, tingling and throat irritation. Diluted products are unlikely to cause skin irritation unless the skin is broken but prolonged exposure may produce temporary mild numbness. Splashes in the eye are irritating and superficial injury to the cornea is possible, particularly if irrigation is delayed or of inadequate duration. "Roundup" is not a skin sensitiser in guinea pigs or human volunteers.

Systemic toxicity

The minimum lethal dose reported is 40 millilitres and the maximum dose survived is 500 millilitres. In general, life-threatening symptoms are unlikely in healthy adults unless at least 85 millilitres of an undiluted, full strength commercial preparation (eg "Roundup") is ingested while a fatal outcome is likely if more than 150 millilitres has been consumed. However, these data relate to formulations containing the surfactant polyoxyethyleneamine and may need to be revised now that this has been replaced by other surfactants in many formulations (eg "Roundup").

Gastrointestinal effects predominate initially and are usually observed within one hour of ingestion. Oral and pharyngeal irritation (sometimes to the point of ulceration), vomiting, abdominal pain and dysphagia commonly occur; diarrhoea is less common. Haematemesis, melaena and paralytic ileus are recognised features but are uncommon, except in severe cases. In such patients endoscopy has shown erythema, oedema and erosions of the pharynx, oesophagus and stomach. Colitis has been found on colonoscopy. Mucosal damage and oedema throughout the gastrointestinal tract has been found in fatal cases.

Other systemic features usually develop within one hour of ingestion but the onset of hypotension may be delayed for up to 12 hours. It may appear suddenly and progress rapidly. Severe poisoning is characterised by hypotension, decreased cardiac output, oliguria, anuria and metabolic acidosis. Sinus tachycardia is observed in about 25% of cases and atrioventricular block may supervene. Pulmonary complications include cough, tachypnoea, cyanosis, pulmonary oedema and respiratory failure. Chest x-rays may show alveolar or interstitial infiltration which may progress to the characteristic changes of adult respiratory distress syndrome in severe cases. Confusion, coma and, rarely, seizures have also been reported in severe cases.

Minor elevation of hepatic enzyme activity and hyperbilirubinaemia have been reported occasionally but though increased serum amylase activity has been noted, it arises from the salivary glands and not from the pancreas. A leucocytosis and fever may be observed even in the absence of infection. Blood glucose concentrations are commonly raised but seldom to a degree that would require treatment. These features resolve spontaneously in a few days.

In general, the more seriously poisoned the victim, the more important it is to get him to hospital as quickly as possible. In such circumstances first aid should not delay transfer but should be confined to measures required to maintain life (eg artificial respiration, cardiac resuscitation, control of convulsions) and ensure that transportation is as safe as possible. Wash out the mouth and give oral activated charcoal (50-100 g for an adult) if it is readily available and impairment of consciousness and convulsions are not present. There is no role for gastric emptying as a first aid measure. Application of a bland ointment may provide symptomatic relief if a rash develops. Drinking water and nasal irrigation may relieve irritation following inhalation of spray mist.

Any patient who has ingested glyphosate should be referred to hospital.

If spontaneous emesis has not occurred, the use of gastric lavage should be considered if the patient presents within 1-2 hours of ingestion, though its value is unproven. It has not yet been established that activated charcoal adsorbs glyphosate but there is evidence that charcoal binds polyoxyethyleneamine in vitro.

Hypotension should be treated initially with plasma expanders and CVP monitoring should be used to guide fluid replacement. If marked hypotension persists and the urine output is low, dopamine (2.5 μg/kg/min) should be given together with dobutamine (5-40 μg/kg/min). Significant metabolic acidosis should be corrected by a sodium bicarbonate infusion but dopamine and dobutamine must not be diluted in bicarbonate solutions. Dialysis is indicated for renal failure and intractable acidosis and, on theoretical grounds, might remove polyoxyethyleneamine. If pulmonary complications ensue, intubation and assisted ventilation may be necessary.

Glyphosate analysis is not readily available. Details of a high performance liquid chromatographic assay and another using cation exchange chromatography and a ninhydrin reaction detector are available from the major manufacturer, Monsanto.

Pesticide incidents which occur during occupational use or accidentally involve the general public should be reported (see Appendix 7).

Appendix 6

A SUGGESTED APPROACH TO THE PATIENT WITH CHRONIC SYMPTOMS WHICH ARE ALLEGED TO BE DUE TO PESTICIDE EXPOSURE

Not infrequently, patients complain that their chronic ill health is the result of exposure to environmental toxins, commonly pesticides, and hold this view with absolute conviction. The following protocol is one approach to dealing with them but clinical examination and extensive investigation usually fails to identify any pathological lesion.

1 Take the patient seriously.

2 Take a careful history paying particular attention to:
- the time relationship between symptoms and pesticide exposure
- the frequency and duration of pesticide exposure
- all the pesticides (and their solvents) to which the patient has been exposed
- other chemicals to which the patient may have been exposed during leisure activities

The patient should be asked to compile the list.

3 Carry out a thorough general and more detailed neurological examination.

4 The following investigations should be carried out as a basic screen:
- urine examination for albumin, glucose and blood
- a full blood count
- ESR or plasma viscosity
- renal function tests
- liver function tests
- thyroid function tests
- blood glucose
- serum B_{12} concentration
- chest x-ray
- Immunological profile

5 Measurement of plasma and red cell cholinesterase activity may be helpful if the patient has been exposed to organophosphate insecticides within the previous 24 hours and reassuring if found normal at a later stage.

6 A urine sample (as much as possible) may be helpful in identifying the presence of the metabolites of organophosphates if collected within 4-5 days of exposure.

7 More sophisticated investigations and assessment may be required:
- brain imaging (CT or MRI scanning)
- measurement of nerve conduction velocities
- a battery of neurobehavioural tests
- evaluation by a psychiatrist or clinical psychologist

It is possible that these could be arranged through your local consultant physician referral system. Alternatively, contact the National Poisons Information Service.