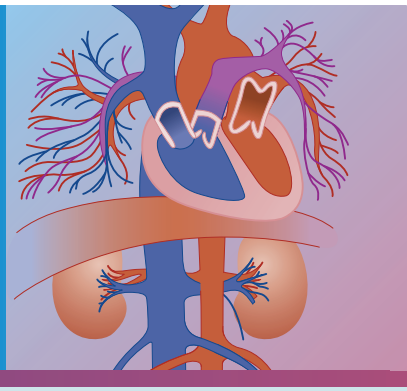
SECTION H
PESTICIDES



76 Organophosphates and Carbamates

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At a Glance...

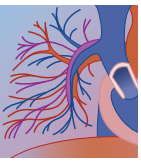
- Organophosphate and carbamate compounds produce toxic effects largely from inhibition of acetylcholinesterase.
- Manifestations of poisoning are variable but commonly include muscarinic signs (e.g., salivation, diaphoresis, abdominal cramps, vomiting, diarrhea, bronchorrhea, bradycardia, miosis, coma, seizures, apnea) and nicotinic signs (e.g., fasciculations, flaccid paralysis, tachycardia).
- The most common cause of death is respiratory failure associated with refractory hypotension.
- Treatment for poisoning from these agents includes health care provider self-protection and patient airway protection; administration of atropine, oximes, and benzodiazepines; and decontamination.
- Atropine is frequently underdosed in serious poisonings and should be titrated to clearing of pulmonary secretions and adequate oxygenation.
- Atropine should be administered rapidly and in escalating doses.
- Benzodiazepines may be cerebroprotective and should be used liberally in all severely ill patients.
- Oxime therapy should be used in all patients requiring atropine.
- Oxime therapy is recommended for all carbamate poisonings with the exception of carbaryl.
- Clinical findings suggestive of severe organophosphate poisoning warrant immediate treatment presumptively, before the results of lab testing are available.

RELEVANT HISTORY

Pesticides are the leading cause of fatality from acute poisoning worldwide.[1,2] In 1990, the World Health Organization (WHO) estimated that 3 million severe pesticide poisonings occur annually and are associated with up to 200,000 deaths.[3] To better characterize and track the epidemiology of these exposures, the WHO established the International Programme on Chemical Safety Poison Information Database Management (IPCS INTOX) Pesticide Project in 2002.[4] In the United States alone, the Environmental Protection Agency (EPA) estimates 10,000 to 20,000 physician-documented pesticide exposures annually among 3,380,000 agricultural workers. The EPA has instituted the Sentinel Event Notification System for Occupational Risk (SENSOR) Pesticides Program to monitor the incidence of these exposures.[5]

Pesticides are a diverse group of chemicals designed to kill and control various insects, animals, fungi, or plants. Insecticides, or chemicals designed to kill insects, are within the class of pesticides. Organophosphorus compounds, organophosphates (OPs), and carbamates, or other cholinesterase inhibitors, are the most commonly used insecticides worldwide and account for more human poisonings and death annually than any other pesticide class.[6] In 2004, there were 10,994 OP and carbamate exposures reported to U.S. poison centers; 70 (0.6%) resulted in major toxicity and 3 (0.3%) in death.[7] As potent eukaryotic toxins, OPs have been used broadly, serving as both military-based nerve agents and agricultural pesticides. Nerve agents have been in military arsenals since World War II. One of these agents, sarin, achieved international notoriety after its release by terrorists in Matsumoto and Tokyo in 1995[8] (see Chapter 105A).

OP and carbamate insecticides are a mixed group of chemicals. OPs are derived from phosphoric acid–containing compounds.[9] The OPs achieved great popularity after World War II because of their effectiveness and lack of environmental persistence. For the most part, they have an unstable chemical structure and disintegrate into harmless by-products within days under the influence of sunlight, oxygen, and reactive soil chemicals.[10] Except for the highly fat-soluble agents, OPs are less persistent in body tissues and the environment than dichlorodiphenyltrichloroethane (DDT) and other organochlorines. Because of their lack of persistence, OPs have replaced DDT as the insecticide agent of



choice. Carbamates are commonly used both as insecticides and medicinals for the treatment of human disease. Pyridostigmine and neostigmine are both used to treat myasthenia gravis, neostigmine has been effective for adynamic ileus, and physostigmine is most often used to treat the anticholinergic syndrome. Donepezil and memantine, central nervous system (CNS) reversible inhibitors of acetylcholinesterase, are used to treat the relative acetylcholine deficiency existing in Alzheimer's disease.

The first OP, tetraethyl pyrophosphate (TEPP), was synthesized in 1854, but the class was not actively used commercially until World War II when the Germans used TEPP as a substitute for the scarce botanic insecticide nicotine. The human toxicity of OPs was exploited by the Germans at the end of World War II with the development of the nerve agents tabun, sarin, and soman (GA, GB, and GD). The allies developed VX after the war (see Chapter 105A).

OP poisoning can occur in various settings. Occupational exposures occur during application in farm workers and pest control workers and during their manufacture, storage, and transport. Children are accidentally exposed to these agents through domestic use or inappropriate home storage. Intentional or unintentional misuse and suicide gestures and attempts account for the remainder of civilian cases. The toxicity of OPs varies greatly. The most highly toxic group is used primarily for agricultural and military purposes. Those with lower toxicity are available for use by households and commercially around populated areas. Table 76-1 lists some of the better-known commercial OPs, their uses, and their relative human toxicity. Table 76-2 lists some common commercial carbamates (in decreasing order of toxicity).

STRUCTURE

OPs are a heterogeneous group of compounds but share some common chemical properties. OPs contain a central phosphorus atom with a double bond to either oxygen (P=O) or sulfur (P=S), two organic side chains (R_1 and R_2), and an additional side chain that becomes the leaving group (X). The leaving group is specific to the individual OP and may be a cyanide, thiocyanate, halide, phosphate, phenoxy, thiophenoxy, or carboxylate group (Fig. 76-1). The R_1 and R_2 groups are aryl or alkyl groups and, in most of the common pesticides, are either two methyl or two ethyl ester groups that form the dimethyl (dimethoxy) or diethyl (diethoxy) OPs. Carbamates are similar but have nitrogen bound to oxygen or sulfur instead of a phosphoric acid residue (Fig. 76-2).

TABLE 76-1 Examples of Organophosphate Insecticides

COMMON NAME	PRODUCT EXAMPLE	CHEMICAL NAME	ESTIMATED FATAL ORAL DOSE (g/70 kg)
Agricultural Insecticides (high toxicity)			
Tetraethyl pyrophosphate	Miller Kilmite 40	Tetraethyl pyrophosphate	0.05
Phorate	Thimet (American Cyanamid)	*0,0,*-Diethyl (*S*-ethylmercaptomethyl) dithiophosphate	
Parathion	Niagara Phoskil Dust	*0,0,*-Diethyl-*0*-*p*-nitrophenyl phosphorothioate	0.1
Phosdrin	Mevinphos (Shell)	Dimethyl-0-(1-methyl-2-carbomethoxy-vinyl) phosphate	0.15
Disulfoton	Disyston	Diethyl-*S*-2-ethyl-2-mercaptoethyl phosphorodithioate	0.2
Animal Insecticides (intermediate toxicity)			
Coumaphos	Co-Ral Animal Insecticide	Diethyl-*0*-(3-chloro-4-methyl-7-coumarinyl) phosphorothioate	
Chlorpyrifos (Dursban)	Rid-A-Bug (Kenco)	*0,0*-Diethyl-*0*-(3,5,6-trichloro-2-pyridyl) phosphorothioate	
Trichlorfon	Trichlorfon Pour On (Hess & Clark)	Dimethyl trichlorohydroxyethyl phosphonate	
Ronnel	Korlan Livestock Spray (Dow)	*0,0*-dimethyl-*0*-(2,4,5-trichlorophenyl) phosphorothioate	
Household Use or Golf Course/Community Spray (low toxicity)			
Diazinon	Security Fire Ant Killer (Woolfolk)	Diethyl-*0*-(2-isopropyl-4-methyl-6-pyrimidyl) phosphorothioate	25.0
Malathion	Ortho Malathion 50 Insect Spray	Dimethyl-*S*-(1,2-bis-carboethoxy) ethyl phosphorodithioate	60.0
Vapona (dichlorvos, DDVP)	Shell No-Pest Strip	*0,0*-Dimethyl-*0*-2,2-dichlorovinyl phosphate	
Acephate	Chevron Orthene	*0,S*-Dimethylacetylphosphoramidothioate	

TABLE 76-2 Carbamate Insecticides

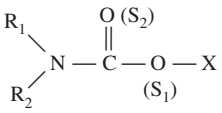
COMMERCIAL NAME	CHEMICAL
Temik	Aldicarb
Matacil	Aminocarb
Vydate	Oxamyl
Isolan	Isolan
Furadan	Carbofuran
Lannate	Methomyl
Zectran	Mexacarbate
Mesurol	Methiocarb
Dimetilan	Dimetilan
Baygon	Propoxur
Sevin	Carbaryl

From Coye MJ, Barnett PJ, Midtling JE, et al: Clinical confirmation of organophosphate poisoning by serial cholinesterase analyses. Arch Intern Med 1987;147:438.

Organophosphorus compound

R_1 and R_2 = alkyl or aryl groups
X = leaving group and may be linked via O or S
Y = O or S or absent

FIGURE 76-1 Organophosphorus compound.



Carbamate

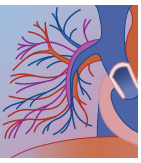
FIGURE 76-2 Carbamate.

PHARMACOKINETICS

Organophosphorus agents are a diverse group of agents with widely variable human toxicity. The toxicity is largely determined by the individual agent, formulation, dose, route of exposure, duration of contact, and health status of exposed individuals. Estimates of relative human toxicity are typically based on the acute oral LD_{50} measured in rats. The WHO updated its toxicity ratings in 2002 and classified agents as extremely hazardous (Ia) (liquid state: LD_{50} < 20 mg/kg); highly hazardous (Ib) (20–200 mg/kg); moderately hazardous (II) (200–2000 mg/kg); and slightly hazardous (III) (>2000 mg/kg).[11] Extremely and highly hazardous agents are designated as "Poison or Toxic" on commercial labels. The WHO classification is different from that promulgated by the EPA, which classifies OP compounds as high toxicity (rat LD_{50} < 50 mg/kg), intermediate or moderate toxicity (LD_{50}, 50–1000 mg/kg) and low toxicity (LD_{50} > 1000 mg/kg)[12] (see Table 76-1). Thus, lethal doses for human adults may vary from a few milligrams for the highly toxic agents (e.g., TEPP) to 50 g for the low-toxicity agents (e.g., malathion). Nerve agents are even more potent, with as little as 1 mg of sarin or soman being lethal to adult humans after inhalation of its vapors.[13] For nerve agents and other highly volatile or aerosolized OPs, toxicity is designated by a concentration time (Ct) variable that is a better measure of exposure by inhalation. For nerve agents, the lethal Ct_{50} ranges from 10 to 400 mg/min/m^3 (see Chapter 105A).[14]

Most OPs are effectively absorbed by all routes—dermal, respiratory, gastrointestinal, and conjunctival. The rapidity of onset and severity of effects may vary after exposure by different routes. The most common route of exposure is dermal, as occurs from most occupational and accidental poisonings. Most suicide attempts result from ingestion. Inhalation exposure may occur when agricultural pesticides (malathion and parathion) are dispersed as aerosols of solids in a liquid carrier or as a dust. Liquids may be mixed in a hydrocarbon vehicle for easy dispersal. The latter may facilitate absorption and add to the toxic effects (e.g., pulmonary toxicity). Aerosols can be absorbed through the skin, mucous membranes, and lungs, whereas liquids can be absorbed through the skin or ingested. Breaks in the skin may enhance absorption, and hot, humid environments or persistent skin contact can enhance toxicity. Gaseous, aerosolized, or dust forms of OPs have a rapid onset of action because they are taken immediately into the pulmonary circulation, leading to shortness of breath, bronchorrhea, bronchoconstriction, and rapid development of systemic signs and symptoms. Liquid and aerosolized forms can be absorbed through the skin; absorption depends on agent volatility, ambient temperature, and lipophilicity. These agents may show immediate local effects (local fasciculations and diaphoresis) or have delayed systemic effects. Ingested agents tend to have a rapid onset of action. Many OPs are highly lipophilic, which enhances their dermal absorption. High lipophilicity may also lead to agent sequestration in body fat stores and result in delayed and erratic toxicity that could occur for several days to weeks after initial exposure.

After absorption, OPs are commonly metabolized by hepatic oxidation, hydrolysis, and conjugation with glutathione. Some agents may undergo glucuronidation and demethylation. Oxidation occurs through the cytochrome P-450 system and often leads to bioactivation, or production of a more reactive oxon metabolite. Serum enzymes such as paraoxonase 1 (PON1) contribute to endogenous hydrolysis of several OPs, lipids, and other prodrugs.[15] Most OPs are rapidly degraded and eliminated in the urine; some may be detectable more than 48 hours after exposure.[16] OPs that are metabolized to para-nitrophenol, however, can be detected by measuring this metabolite in the urine. There is a rough correlation between the excretion of para-nitrophenol and the occurrence of illness.[17] Because the effect of cholinesterase inhibition is cumulative, toxicity may be evident after complete elimination of the OP, particularly with the fat-soluble agents.



Although OP and carbamate insecticides are rapidly absorbed through dermal, respiratory, gastrointestinal (GI), and conjunctival routes, all OPs must be in the oxon formation (P=O) to inhibit acetylcholinesterase. Those agents that do not initially have the phosphorus bound to oxygen, such as the phosphorothioate (P=S), are metabolized by the hepatic cytochrome P-450 system into the activated oxon.[9] Parathion and malathion are examples of oxon activation; they must first be converted to paraoxon and malaoxon, respectively (by substitution of an oxygen for sulfur), to be physiologically active. Because of this activation step, the rapidity of symptom onset after OP exposure is partially dependent on the OP's initial state. Rate of activation and rate of enzyme inhibition may be equally important for toxicity. For example, in Sri Lanka, patients with dimethoate ingestions presented extremely ill but had acetylcholinesterase levels about one third to one fourth of normal, whereas patients similarly ill from chlorpyrifos and fenthion had almost no detectable cholinesterase levels. Most deaths from dimethoate occurred 24 to 36 hours after ingestion, at a time when their enzyme activity was continuing to decrease. All agents shared similar solvents, and the difference may reflect the low fat solubility of dimethoate, leading to a higher blood concentration.[18]

OPs that are already in the oxon form may cause symptoms earlier than those that need metabolic activation. However, some agents, such as parathion, are rapidly activated and can produce symptoms in less than 30 minutes.[19] Most OPs are readily lipid soluble, but certain agents (i.e., azinophos-ethyl, bromophos-ethyl, chlorpyrifos, coumaphos, diazinon, parathion, phosalone, sulfotep, and fenthion and chlorfenthion) are highly lipid soluble and tend to accumulate in adipose tissue.[15] Initial exposure may not lead to acute signs and symptoms of toxicity. After agent bioaccumulation and a time delay, the signs and symptoms of toxicity become evident.[9]

Carbamates have rapid onset but are less fat soluble. They may significantly inhibit acetylcholinesterase but undergo spontaneous hydrolysis with resumption of enzyme activity, usually within 24 hours. This is not an absolute, as some carbamates, such as carbosulfan, may have prolonged systemic effects.[20]

PHARMACOLOGY AND PATHOPHYSIOLOGY

OPs and carbamates produce toxicity by binding to and inhibiting the action of acetylcholinesterase at its serine active site. Acetylcholine accumulates at nerve terminals, initially stimulating, then paralyzing, cholinergic neurotransmission at both central and peripheral nicotinic and muscarinic receptors. Under normal physiologic conditions, acetylcholinesterase hydrolyzes acetylcholine into two primary inert fragments, acetic acid and choline, decreasing postsynaptic effect and neurotransmission and generating choline for reuptake and resynthesis. When acetylcholinesterase is inhibited, acetylcholine cannot be broken down and accumulates at the nerve or myoneural terminal, leading initially to postsynaptic excitation followed by inactivation of the synapse or myoneural junction.[21] Inactivation occurs from depolarizing blockade at postsynaptic receptors.

True acetylcholinesterase (E.C. 3.1.1.7) is important for physiologic neurotransmission and is found primarily in nervous tissue but is also expressed on the surface of red blood cells (erythrocyte or red blood cell cholinesterase). Pseudocholinesterase or butyrylcholinesterase is found in serum and the liver and is important in the metabolism of xenobiotics. Erythrocyte acetylcholinesterase activity closely mimics neuronal acetylcholinesterase and is a more accurate measure of its physiologic activity.[22-24] Because butyrylcholinesterase (EC 3.1.1.8) measurements are technically simpler to perform, this is the more readily available assay in hospitals and in the field.[25]

Acetylcholinesterase is a convoluted protein structure with a pit containing a serine binding site and a catalytic site. Initially, the electrophilic OP oxon forms a reversible Michaelis-Menten complex, binding to the serine enzymatic active site followed by rapid phosphorylation of the serine residue. Once this happens, the leaving group (X) on the OP is released. As this reaction occurs, the OP becomes covalently bound to the enzyme, sitting in the pit and changing the conformation of the enzyme, preventing the active site from binding acetylcholine, and subsequently inhibiting catalytic activity.[26] The organophosphorylated enzyme can then undergo two different reactions. The enzyme can become "aged" or irreversibly bound and inactivated by cleavage of one of the R groups. This dealkylation process leads to a monosubstituted phosphoric acid residue that remains firmly attached to the enzyme. The rate of aging depends on the specific OP agent. Alternatively, reactivation of the enzyme can occur when the bond between the serine and organophosphorus moiety hydrolyzes. Enzyme reactivation occurs spontaneously at an extremely slow rate for diethyl-containing organophosphates or may be markedly accelerated with the addition of a nucleophilic oxime. The rate of reactivation and irreversible inactivation by aging is highly dependent on the attached R groups. Smaller side groups allow for more rapid reactivation and aging, whereas the presence of branched side chains provides steric hindrance and greater bond stability, thereby delaying reactivation and aging.[27] For instance, dimethyl OPs have significantly faster rates of spontaneous reactivation and aging (half-lives of about 0.7 hours and about 3.7 hours, respectively) than diethyl OPs (half-lives of 31 hours and 33 hours, respectively). Although dimethyl phosphorylated OPs age more rapidly than diethyl OPs, they are relatively resistant to oxime therapy, particularly pralidoxime. Although there is more time to reactivate diethyl OPs, they require significantly more oxime to achieve this reactivation.[9,28] Regardless of these differences, however, once the enzyme has "aged," it is no longer susceptible to reactivation by endogenous hydrolysis or oxime therapy.[9,29]

Carbamates bind to the same binding site of acetylcholinesterase by carbamylation (C-O bond). The carbamate–acetylcholinesterase covalent bond is not as

strong as that produced by OPs (P-O or P-S bond). Because of this, spontaneous hydrolysis or decarbamylation occurs more readily, usually reactivating acetylcholinesterase within 24 hours. Some carbamates may take longer to spontaneously hydrolyze. For example, in Sri Lanka, carbofuran-poisoned patients required ventilatory support for up to 48 to 72 hours.[17] Carbamylated acetylcholinesterase does not undergo irreversible binding or "aging" and can be reactivated using oximes.[24,30,31]

Acetylcholinesterase inhibition is not an equilibrium-dependent reaction and is most sensitive to the concentration of OP present at the enzyme interface. After a person is exposed to an OP, the formation of oxon peaks and then declines in the serum. However, even with a declining OP and oxon serum concentration, acetylcholinesterase inhibition continues to increase because this reaction proceeds by covalent binding. Physiologically, the exposed individual can continue to function normally until a minimum amount of functioning acetylcholinesterase is left unbound. Once this threshold has been reached, even removal of circulating OP will not enhance enzyme function. Enzyme catalysis then becomes entirely dependent on the restoration of a critical mass of uninhibited acetylcholinesterase. However, if the phosphorylated acetylcholinesterase can undergo a rapid endogenous reactivation such as with some dimethoxy OPs, then removal of the offending agent may contribute to recovery, but this is not true for dimethoate. The ability of a nucleophilic oxime to reactivate the enzyme depends then on the structure of the OP bound to acetylcholinesterase, the time that the reactivator is present at the site, and the concentration of the reactivator.[9,28]

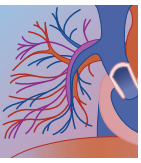
The actual process of reactivating the phosphorylated acetylcholinesterase with a nucleophilic oxime involves formation of an intermediate step. At some point, a transient complex forms consisting of the phosphorylated enzyme and oxime. Because formation of this complex undergoes saturation kinetics, further increases in oxime concentration does not enhance reactivation. After the oxime has pulled off the OP from the enzyme, the phosphorylated oxime complex becomes a strong inhibitor of acetylcholinesterase. In addition, oximes themselves can inhibit acetylcholinesterase. The net effect is that even during treatment of an OP-inhibited enzyme with an oxime, there may be a transient, but undocumented, increase in inhibited acetylcholinesterase and worsening of symptoms.[9] This has not been shown to occur with pralidoxime because the phosphorylated oxime formed is very unstable, transiently present, and likely without clinical effect. More likely, there is no net difference. If the oxime removes the organophosphate from acetylcholinesterase and forms an active phosphorylated oxime, it can still only react with one acetylcholinesterase molecule so the stoichiometry remains unchanged (personal communication, Peter Eyer, 2006). Obidoxime produces a much more stable phosphorylated oxime and could have clinical consequences. This, however, has not yet been documented in vivo in humans.[32]

Despite oxime treatment, poisoning with highly fat-soluble agents (e.g., fenthion) or large exposures to agents that require bioactivation or prolonged elimination (e.g., fenthion) may lead to recurrent or delayed clinical toxicity. This is because the newly regenerated enzyme becomes reinhibited as the OP leaches out of the fat tissue or is bioactivated over a longer period of time.

The signs and symptoms of OP intoxication result from the overabundance of acetylcholine. This leads to initial excitation followed by paralyzed neurotransmission at cholinergic synapses.[26] Cholinergic neurotransmission occurs throughout the CNS, at the parasympathetic nerve endings, at a few sympathetic nerve endings such as the sweat glands (muscarinic effects), and in the somatic nerves (e.g., neuromuscular junction) and ganglionic synapses of autonomic ganglia (nicotinic effects). The signs and symptoms of OP poisoning are an expression of acetylcholine excess at numerous different nerve terminals (Table 76-3) and can manifest predominantly as muscarinic or nicotinic effects, or as a combination of both. The effects of OPs on acetylcholinesterase affect m-receptors differently than n-receptors and may account for some of the clinical variation. The OP effect on cholinesterase affecting m-receptors appears to be long-lasting, whereas n-receptors rapidly desensitize. Acetylcholine overstimulation at the neuromuscular junction leads to depolarization inactivation of myocytes; repolarization and, thus, recontraction are inhibited. This leads to muscle paralysis. In addition, the cholinergic nervous system has significant interplay with other neurotransmitters (i.e., γ-aminobutyric acid [GABA]) and results in additional toxic effects. CNS effects result largely from m-receptor stimulation but also occur from activation of n-receptors and *N*-methyl-*d*-

TABLE 76-3 Clinical Effects of Organophosphate Poisoning (Acetylcholine Excess)

ANATOMIC SITE OF ACTION	SIGNS AND SYMPTOMS
Muscarinic Effects	
Sweat glands	Sweating
Pupils	Constricted pupils
Lacrimal glands	Lacrimation
Salivary glands	Excessive salivation
Bronchial tree	Wheezing
Gastrointestinal	Cramps, vomiting, diarrhea, tenesmus
Cardiovascular	Bradycardia, decrease in blood pressure
Ciliary body	Blurred vision
Bladder	Urinary incontinence
Nicotinic Effects	
Striated muscle	Fasciculations, cramps, weakness, twitching, paralysis, respiratory embarrassment, cyanosis, arrest
Sympathetic ganglia	Tachycardia, elevated blood pressure
Central Nervous System Effects	Anxiety, restlessness, ataxia, convulsions, insomnia, coma, absent reflexes, Cheyne-Stokes respirations, respiratory and circulatory depression



aspartate (NMDA) glutamate receptors and inhibition of central GABA neurotransmission.[19,33,34]

After the OP–acetylcholinesterase complex has undergone complete aging, enzyme resynthesis is the only means to restore acetylcholinesterase function. This may take weeks to months and necessitate prolonged pulmonary support for patients until sufficient enzyme resynthesis has occurred.[9]

TOXICOLOGY

Clinical Presentation

The onset and severity of clinical effects is variable and depends on the identity of the agent, its formulation, and the dose, duration, and route of exposure. Initial symptoms may range from mild to immediately life threatening. The most rapid onset of symptoms occurs with inhalation, and the slowest with dermal exposure. The onset of clinical effects may take up to 24 hours after skin exposure to highly lipophilic agents that require bioactivation. In contrast, systemic effects and respiratory arrest can occur within minutes of inhalation of an aerosol or vapor of nerve agents. After OP ingestion, clinical effects usually occur within 30 to 90 minutes. Although OP toxicity generally occurs within 4 to 12 hours, full-blown toxicity may not manifest for 24 hours.[35]

Stimulation of the muscarinic parasympathetic system will cause miosis, bradycardia, hypotension, bronchoconstriction, hyperactivity of GI smooth muscle, and oversecretion of the exocrine glands (salivary, lacrimal, bronchial, and pancreatic). Stimulation of the autonomic ganglia (nicotinic effects) produces sympathomimetic effects that include tachycardia, hypertension, and mydriasis. Nicotinic effects at the neuromuscular junction lead to muscle weakness, fasciculations, and muscle paralysis. This is also known as type I paralysis.[18] (see Table 76-3). GI symptoms are the most common manifestations early after ingestion of OPs. Aerosol exposure typically presents with respiratory and ocular complaints, whereas dermal exposure may cause localized fasciculations and sweating. The wide and mixed spectrum of clinical effects that occur with significant exposures may lead to misdiagnosis. In one study, 16 of 20 transfer patients were incorrectly diagnosed as having other conditions.[36] The presence of excessive salivation, lacrimation, fasciculations, noncardiogenic rales or rhonchi, and muscle weakness during the initial phase of poisoning is suggestive of OP poisoning. Miosis, a typical muscarinic sign, is not always present because mydriasis may result from concomitant and overriding nicotinic stimulation. Senanayake and colleagues developed a nonvalidated scoring system for organophosphorus intoxications called the Peradeniya Organophosphorus Poisoning Scale (POP Scale).[37] This system ranks the severity of poisonings using five clinical signs (miosis, bradycardia, heart rate, level of consciousness, and respiratory rate). Each sign is graded on a scale from 0 to 2, with an additional point given for those that seize. Based on results from the initial study, severe intoxications (score of 8 to 11) have a higher mortality rate, greater need for ventilatory support, and higher dose of atropine in the first 24 hours.

CNS effects generally include anxiety, restlessness, agitation, slurred speech, ataxia, confusion, lethargy, stupor, coma, seizures, and centrally mediated respiratory depression.[38] In addition, chorea, psychosis, depression, and choreoathetosis have been described.[39] Muscle weakness and paralysis develop in severe exposures. The most common cause of death is primary respiratory failure with subsequent cardiac arrest.[40] Early respiratory failure is largely mediated by CNS respiratory center depression from increased, uncoordinated CNS muscarinic neuronal activity.[19,26] In animal studies, such early respiratory depression can be prevented by anticholinergic agents that cross the blood-brain barrier.[26] Peripheral nicotinic and muscarinic effects contribute to respiratory failure and include excessive oral and tracheobronchial secretions, laryngospasm, bronchoconstriction, and paralysis of the diaphragm and intercostal muscles. There may be additional noncholinergic-mediated effects.[34]

Other findings associated with acute OP intoxication include hyperamylasemia with or without clinical pancreatitis.[41] Electrocardiogram abnormalities have been reported and include conduction disturbances (e.g., atrioventricular block, ST-segment elevation, QTc prolongation) and arrhythmias (e.g., supraventricular and ventricular dysrhythmias, including torsades de pointes).[42,43]

Diagnosis

The diagnosis of acute OP poisoning is made clinically and based on history and suggestive physical findings. The diagnosis should be considered whenever a patient presents with the cholinergic toxidrome or muscarinic signs and symptoms such as miosis, increased airway secretions, lacrimation, bradycardia, and GI complaints. The added presence of nicotinic findings such as muscle fasciculations and weakness further suggests the diagnosis of OP poisoning. A history of exposure is helpful but not often available. The simultaneous presence of muscarinic and nicotinic findings on physical exam are characteristic of organophosphorus poisoning and often warrant empiric treatment with atropine and oxime therapy. Clinical findings suggestive of severe OP poisoning (i.e., mental status changes, coma, seizures, bronchorrhea, bronchoconstriction, fasciculations, autonomic instability, and paralysis) warrant immediate treatment presumptively. When multiple victims become comatose or seize within minutes of an inhalational exposure, a terrorist incident with nerve agents should be suspected and empiric antidotal treatment given provided that supportive physical findings are present[14] (see Chapter 105A). When the diagnosis of OP poisoning is not evident or when toxicity is mild or chronic, a depressed serum or red blood cell cholinesterase level may be obtained to assist diagnosis. Cholinesterase levels, however, are rarely available in a timely manner.

Thus, if OP poisoning is suspected, therapy should be initiated before confirmation by laboratory values.

Laboratory confirmation of poisoning is demonstrated by depressed erythrocyte or butyrylcholinesterase activity. Because non–hemoglobin normalized acetylcholinesterase levels are extremely variable between individuals, a mild intoxication may not be confirmed until serial levels document a steady increase in enzyme activity over time.[22,23] Erythrocyte acetylcholinesterase that is standardized to hemoglobin does not exhibit the same interindividual variability. As erythrocyte acetylcholinesterase is expressed on the erythrocyte membrane, in the absence of reactivation, restitution of normal, preintoxication enzyme activity levels are dependent on formation of new erythrocytes, a process that takes about 90 to 120 days and mimics neurologic function.[23,24] However, erythrocyte acetylcholinesterase regenerates more slowly than neuromuscular junction acetylcholinesterase. Butyrylcholinesterase is an acute-phase reactant and may normalize in 14 to 30 days. There is a genetic variant in about 3% of the population, causing baseline depression of butyrylcholinesterase activity level. Other conditions that may depress butyrylcholinesterase include parenchymal liver disease, secondary hepatic insufficiency from congestive heart failure, metastatic carcinoma, reduced levels of serum albumin, pregnancy, and several medications.[44,45]

The remainder of diagnostic studies are nonspecific and include elevated leukocyte count and hyperglycemia.[46] Occasionally, elevated levels of urinary p-nitrophenol may be found in cases of OP intoxication in which para-nitrophenol is the leaving group (e.g., parathion).[19,47]

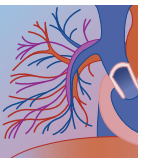
Management

Treatment of OP poisoning consists of aggressive supportive care and antidotal therapy.

Initial management of the OP- or carbamate-poisoned patient requires immediate attention to the airway. Cyanosis or other evidence of hypoxia, rales, excessive oral secretions, or bronchorrhea should be treated with oxygen and rapid atropinization. Although most texts state that the patient should be oxygenated before atropine administration, it may be impossible to oxygenate until secretions are controlled. In a large cohort of OP-poisoned patients, Eddleston successfully administered early atropine without evidence of enhanced cardiovascular toxicity.[48] Atropine should be dosed until the secretions have dried and evidence of pulmonary fluid has diminished. During rapid atropinization, respiratory paralysis or excessive secretions should be managed by controlling the airway with intubation, ventilation, and continuous suctioning. When rapid sequence intubation (RSI) is necessary to control the airway of an OP- or carbamate-poisoned patient, the use of a depolarizing paralytic (e.g., succinylcholine), although not contraindicated, is discouraged. In such cases, succinylcholine may result in prolonged paralysis because it is metabolized through butyrylcholinesterase.[49] In one patient poisoned with chlorpyrifos, the use of succinylcholine resulted in neuro-muscular paralysis that lasted 192 minutes.[49] There are no data on the effect of prolonged chemical paralysis with a nondepolarizing agent in the OP-poisoned patient.[50] Thus, the use of rocuronium or other rapidly acting nondepolarizing agents is preferable for RSI in these patients. Concomitant with atropinization, patients should be resuscitated with intravenous (IV) fluids. OP pesticides result in significant GI fluid losses and probably cause nitric oxide–induced vasodilation.[51] Rapid IV administration of 2 L or more of an isotonic solution may be necessary to return the patient to euvolemia. Vasopressors are indicated when hypotension is unresponsive to atropine and fluids. A direct-acting α-adrenergic agent (e.g., phenylephrine) is preferred because poisoned patients have a reduced systemic vascular resistance and relatively normal inotropic state.[38,43,52-54] Dopamine and norepinephrine may increase the heart rate, which could prove beneficial or detrimental, depending on the initial pulse. These pressor recommendations, however, are based on pharmacologic principles and not animal or clinical data.

Seizure activity should be rapidly controlled with an IV GABAergic agent such as diazepam, midazolam, or lorazepam. Aggressive use of benzodiazepines may improve survival and prevent cardiac and CNS injury in OP-poisoned patients with seizures.[34,55-62] Many dosing regimens have been suggested. Initial dosing recommendations include the use at least 10 mg IV diazepam or 5 to 10 mg intramuscular (IM) midazolam in adults (pediatric dosing, diazepam 0.1–0.2 mg/kg IV or midazolam, 0.1–0.3 mg/kg IM) and then titrate upward as needed. There is some evidence to suggest that OP-induced seizures involve NMDA-glutamate receptors in addition to GABA, suggesting that propofol may be a useful adjunct for continued seizure activity. Both central GABA and NMDA-glutamate receptor pathways are likely involved with seizure production and delayed CNS neuropathology associated with significant poisoning with these agents (personal communication, M. Eddleston and A. Dawson, 2004).[58-61,63,64]

After initial stabilization, patient decontamination becomes a priority. Patients with liquid contamination of skin and clothing may have ongoing percutaneous absorption of a pesticide. In addition, they may pose a skin contact risk to health care personnel. Interestingly, there have been almost no reports of clinically significant healthcare worker secondary contamination coming from the South Asian and Indian continents, where OP intoxicaation is extremetly common.[65,66] Thus, as soon as possible, the patient should be disrobed completely and the skin thoroughly washed with alkaline soap and water. This should not delay initial life-saving treatment and administration of antidotes. The removal of clothing eliminates 85% to 90% of a contamination hazard.[67] Although hypochlorite solutions deactivate OPs in vitro, their use on human tissues is discouraged and may lead to corneal burns and other toxicity.[68] A standard hypochlorite solution (5%) can be used to decontaminate equipment.[69-72] Alternatively, the U.S. Military has adopted dry agents for field decontamination.[68] In civilian use, agents such as soil, flour, or



talcum powder may be applied to the skin and then mechanically removed.[71]

One of the first priorities in OP and nerve agent treatment is health care provider self-protection and decontamination. Medical personnel participating in the decontamination process should have adequate personal protective equipment (PPE) and training. Ideally, the patient should have undergone initial decontamination at the scene by appropriate personnel trained in Hazardous Materials in Level A or Level B protection. At the Health Care Facility, medical staff should be dressed at the minimum in Level C PPE, including impermeable gowns and shoe covers; butyl, neoprene, or nitrile gloves; and facial splash protection[70,73] (see Chapter 103). Standard latex gloves are readily permeable to and do not protect from transdermal absorption of OP agents. Solutions or dry agents used for decontamination are considered hazardous materials, and arrangements for their disposal should be prearranged. Further discussion on appropriate PPE and training should be directed to the local Poison Control Center, Metropolitan Medical Response System, HazMat team, Hospital Disaster Plan, or State Department of Health.[72]

The utility of GI decontamination after ingestion of an organophosphorus ester pesticide is controversial. Because these agents are highly emetogenic, most patients have vomited before presentation. If a patient presents early (less than 30–60 minutes) after ingestion, empiric nasogastric aspiration of an ingested solution seems appropriate. There are, however, no published randomized controlled trials (RCTs) that have evaluated the efficacy of this modality. Some OP agents are known to bind activated charcoal. Thus, the administration of oral activated charcoal is usually recommended after oral OP pesticide exposure. As for gastric lavage and aspiration, the efficacy of activated charcoal for OP poisoning by ingestion has been not been adequately studied. Because many of the OP agents are dissolved in hydrocarbon solvents that can result in significant pneumonitis when aspirated, the potential benefits of gastric decontamination must be balanced against the risk for enhanced morbidity from aspiration for each patient treated.[50] Currently, there is an ongoing large RCT in Sri Lanka investigating these issues.[73,74] Gastrointestinal decontamination is rarely necessary after nerve agent exposure because these patients have been poisoned by inhalation or dermal contact (see Chapter 105A).

ANTIDOTAL THERAPY

The accepted mainstays of antidotal therapy in OP poisoning are adequate use of atropine to treat muscarinic symptoms and an oxime to regenerate the acetylcholinesterase.[9,28] Atropine, a competitive antagonist at muscarinic cholinergic receptors, inhibits the postsynaptic binding of acetylcholine. As a tertiary amine structure, atropine crosses the blood-brain barrier and works at both peripheral and central muscarinic sites. It has no effect at nicotinic cholinergic receptors. Although there have been no RCTs to demonstrate the efficacy of atropine for OP and carbamates poisoning, there are innumerable case reports that substantiate its efficacy and usefulness for this poisoning.[50] Atropine is indicated for muscarinic symptoms, primarily bronchorrhea and, sometimes, bradydysrhythmias and hypotension. The dosing of atropine is variable, and the dosing regimen used by Eddleston and colleagues is recommended. From their experience with OP poisonings in Sri Lanka, Eddleston and colleagues have shown that the administration of rapid, escalating doses of atropine ("rapid atropinization") followed by an atropine infusion is successful in controlling the airway and other muscarinic symptoms.[48,50] With this approach, patients with evidence of muscarinic excess are initially given 1 to 2 mg IV atropine, and doses are then doubled every 5 minutes as needed. This dosing regimen will rapidly yield a cumulative dose of 25 mg by 20 minutes and 75 mg by 25 minutes.[48] Patients with severe toxicity may require 75 to 100 mg atropine. The adequacy of atropine dosing is determined clinically by clearing secretions from the pulmonary tract as assessed by resolution of crepitus and rales, a heart rate greater than 80 beats/minute, dry skin, and a reasonable blood pressure (mean arterial pressure > 60 mm Hg or evidence of end-organ perfusion). Pupil dilation can be delayed up to 30 minutes and is not a useful sign initially, but the eventual aim is to have nonpinpoint pupils. However, in the Sri Lankan experience, patients with severe OP poisoning had mid to large but mildly reactive pupils after an adequate atropine dose had been administered (personal communication, M. Eddleston and A. Dawson, 2004).[48,50] After the patient has been stabilized, an atropine drip is established to maintain the patient at the appropriate level of atropinization, usually around 20% of the total loading dose per hour, and is titrated as needed. More than 5 mg/hr of atropine is rarely needed.[75] Glycopyrrolate has been suggested as an alternative to atropine. However, because it does not cross the blood-brain barrier, it should be reserved for patients with a purely peripheral muscarinic syndrome.[33,76-79] The use of inhaled atropine or ipratropium bromide has been recommended when pulmonary symptoms predominate to minimize systemic side effects produced by intravenous atropine administration.[33,34]

Although "rapid atropinization" is life saving, this method of atropine administration may occasionally overshoot and produce an anticholinergic delirium. In this situation, the atropine infusion should be halted and the patient closely observed until signs of cholinergic excess begin to reappear. At this point, the atropine can be restarted.[48] When this occurs, the patient may need sedation until the delirium recedes. Benzodiazepines appear to be the safest option in this situation.

Nerve agent intoxication does not appear to require similar atropine dosing (see Chapter 105A). Experience from the Matsumoto and Tokyo sarin incidents and declassified case reports suggest that 2 to 20 mg atropine appears to be adequate.[13,14,71,80,81] In the Tokyo sarin attacks, only 19% of poisoned patients required more than 2 mg of atropine.[7] Topical ocular homatropine or

atropine preparations may be effective for focal ocular cholinergic toxicity (e.g., eye pain, dim vision) produced by aerosol nerve agent exposures.[71]

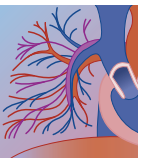
Oximes are used early after OP poisoning to regenerate active acetylcholinesterase. The use of oximes has become somewhat controversial after several Asian studies failed to demonstrate their efficacy for OP poisoning.[82-84,85] The conclusions of these studies, however, have been questioned because of flawed trial design and other reasons.[28,29] In Western countries, use of oxime therapy is fairly well accepted, and there are multiple animal studies and human case reports supporting its efficacy.[24,28,30,86-92] Pralidoxime (2-PAM chloride, Protopam) and obidoxime (Toxogonin) are the most commonly used agents, although P2S (pralidoxime mesylate), pralidoxime methiodide, TMB-4, HI-6 and HLö-7 (experimental use only) are used in other parts of the world. The H-series oximes (e.g., HI-6 and HLö-7) have greater efficacy against certain nerve agents (e.g., soman) and may be preferable for such poisoning. Multiple textbooks and the package insert for Protopam suggest that oxime therapy should be reserved for nicotinic signs and symptoms. There is no scientific basis for this because oximes will regenerate acetylcholinesterase at both muscarinic and nicotinic receptors. Many patients who were treated with only atropine may have had adequate endogenous hydrolysis of the phosphorylated acetylcholinesterase. Use of oxime therapy in carbamate poisoning is another area of uncertainty. On average, carbamylated acetylcholinesterase will spontaneously hydrolyze within 24 hours. Patients poisoned with carbamates, however, may become severely ill and require ventilatory support for greater than 24 hours, similar to an OP poisoning. There is good evidence to suggest that oximes are effective for treating these carbamate-poisoned patients and shortening intensive care unit time.[24,31,87,93-97] The exception to this may be carbaryl (Sevin), for which there is animal evidence to suggest that oxime use may worsen the cholinesterase block. There are no human data that demonstrate enhanced toxicity from oxime use in carbaryl-poisoned patients.[93,94,97] Currently, oxime therapy is recommended for all carbamate poisonings with the exception of carbaryl.

The apparent ineffectiveness of oximes for OP poisoning has several possible explanations. First, reactivation of acetylcholinesterase may be slowed and ineffective because of steric effects of certain OP compounds at the active site. Second, the rate of acetylcholinesterase inhibition may be greater than its rate of reactivation because of insufficient oxime dosing relative to the degree of OP exposure. Third, formation of phosphoryloximes during the reactivation process may paradoxically inhibit acetylcholinesterase to a greater extent and longer duration than would be present without oxime therapy. This is more significant with obidoxime than pralidoxime. Finally, oxime therapy may not be provided for a long enough time in instances in which OP metabolic activation or tissue redistribution occurs. Similarly, oxime therapy may not be initiated for patients who present late because of the belief that all the cholinesterases will have aged. Aging is a process, and it is believed that as the acetylcholine accumulates at the receptor, acetylcholinesterase competes with the OP for the binding site.[27]

Most oxime controversy relates to appropriate dosing. Most U.S. textbooks suggest a pralidoxime dose of 1 to 2 g IV or IM followed by 1 g every 6 to 12 hours. This dose has not been subjected to rigorous scrutiny and may lead to low serum oxime concentrations. A serum concentration of 4 mg/L has been suggested as the minimum oxime "therapeutic level" for OP poisoning; this value was derived from animal data.[98,99] A subsequent pharmacokinetic study by Medicis used a pralidoxime infusion in human volunteers to maintain this serum concentration.[100] Further study has suggested that 1 g pralidoxime every 6 to 8 hours or the infusion rate from the Medicis study are inadequate to treat significantly poisoned patients and that larger oxime doses are necessary.[32,98,101-103] There are a number of reasons for this, which include poor affinity of oximes for the phosphorylated enzyme complex, overwhelming inhibition by a large OP exposure, reinhibition of the enzyme by sustained or high levels of OP, OP persistence in a deep compartment such as seen with extremely fat-soluble agents (duration of treatment), and aging of the enzyme.[9,28] The WHO has recommended an initial dose of 30 mg/kg pralidoxime IV followed by an IV infusion of 8 mg/kg/hr. Alternatively, if a continuous infusion is not possible, 30 mg/kg pralidoxime should be administered IM or IV every 4 hours. Obidoxime is dosed at 4 mg/kg initially then 0.5 mg/kg/hr or 4 mg/kg initially then 2 mg/kg every 4 hours. Both agents may be administered IV or IM.[104] Based on computer kinetic modeling, Eyer and associates have determined that an ideal plasma concentration of 50 to 100 μmol/L for pralidoxime and 10 μmol/L for obidoxime should produce an acceptable half-life of reactivation of about 10 minutes.[19] These can be achieved with a pralidoxime dosing of 1 g IV followed by 0.5 g/hr or an obidoxime dosing of 250 mg initially followed by 750 mg over 24 hours.[27] Regardless, the ideal oxime dose has not yet been established and will probably depend on the OP agent, time since exposure, body load, pharmacogenetics, and other variables. The South Asian Clinical Toxicology Research Collaboration initiated a study in 2004 that compares the WHO pralidoxime regimen versus placebo in the treatment of OP poisoning in Sri Lanka (personal communication, M. Eddleston and A. Dawson, 2004). These data should help to clarify the optimal pralidoxime dosing strategy.

It is important to be aware of the treatment distinction between diethyl and dimethyl phosphoryl OPs. Dimethyl-poisoned patients have a shorter window of opportunity for oxime treatment and necessitate higher doses. This discrepancy may be partially responsible for the variable results reported in the literature. Treatment of nerve agent poisoning follows similar precepts but uses a different dosing strategy. Because the G nerve agents age extremely rapidly, treatment must be started immediately (see Chapter 105A).

Adverse reactions from oxime therapy include hypertension, transient increases in neuromuscular block, and projectile vomiting after bolus administration of pral-



idoxime (personal communication, M. Eddleston and A. Dawson, 2004).[29,100,104] There are no good data on the effects of pralidoxime in the first trimester of pregnancy.[106,107] Pralidoxime is categorized by the U.S. Food and Drug Administration as a pregnancy category C medication. Thus, it should only be used with initial careful consideration of the relative risks and benefits to the mother and child.[108,109]

INTERMEDIATE SYNDROME

In 1987, Senanayake described a syndrome of proximal muscle weakness, weak neck flexors, and respiratory failure, which he designated as the intermediate syndrome (IMS) or type II paralysis.[110,111] The IMS has onset within 24 to 72 hours after the acute cholinergic crisis and can last several days to weeks.[112-116] Many authors have debated the existence of IMS versus continued neuromuscular junction (NMJ) acetylcholinesterase depression in the face of inadequate oxime therapy.[117-119] The syndrome has been characterized by absent muscarinic symptoms but continued severe acetylcholinesterase inhibition as measured by cholinesterase activity, and there is no therapy other than supportive care.[112,120-122] Electromyograms—Nerve Conduction Velocity Studies done during IMS have shown decrement pattern in neuromuscular transmission with repetitive stimulation at low rates consistent with presynaptic and postsynaptic impairment at the NMJ and desensitization.[123,124] At this time, there is no consensus on etiology; the pralidoxime study in Sri Lanka may provide some insight on this problem. Treatment of IMS is primarily supportive. Some recommend the administration of additional oxime, but few data support this recommendation.

DELAYED POLYNEUROPATHY (ORGANOPHOSPHATE-INDUCED DELAYED NEUROPATHY OR POLYNEUROPATHY)

Several classes of OPs (phosphates, phosphoramidates, and phosphonates) inhibit both acetylcholinesterase and neuropathy target esterase (NTE).[125,126] NTE is found on the Schwann cells lining the axons and, when aged, causes loss of the myelin sheath with a "dying back" axonopathy that is unresponsive to atropine and pralidoxime.[125,127-129] This leads to a symmetric demyelinating process with the patient complaining about cramping pain, paresthesias, and distal limb weakness. Patients notice the onset of weakness and paresthesias about 3 to 6 weeks after initial illness, with subsequent progression over weeks to months.[130,131] A lymphocyte NTE assay has been developed to assist diagnosis; depression of lymphocyte NTE correlates with development of organophosphate-induced delayed neuropathy (OPIDN).[132-138] There is no known treatment for OPIDN. Resolution may occur over 6 months to a year for those with mild symptoms, whereas those with severe OPIDN usually have persistent deficits.[125,130-136]

CHRONIC NEUROPSYCHIATRIC SEQUELAE

A number of other neurologic sequelae that have been associated with OP intoxication. Acutely, patients may develop severe encephalopathy.[139] Long-term effects have included short-term memory loss, fatigue, confusion, depression, psychosis, parkinsonism, and other extrapyramidal findings.[139-144] Some of these findings may resolve over time.

NEW TREATMENT DEVELOPMENTS

One of the difficulties in treating OP-poisoned patients is determining when to stop oxime therapy. Eyer and associates have started to assay whole blood for the ability of oximes to reactivate red blood cell cholinesterase before and during treatment. Ongoing acetylcholinesterase inhibition, recrudescent poisoning, and response to therapy could be recognized and diagnosed from a decrease in the ability to reactivate red blood cell cholinesterase in patient whole blood.[19] The increasing importance of pharmacogenomics is also being investigated. Depending on the paraxon concentration, studies in liver microsomal studies have shown that paraoxon has variable effects on the cytochrome P-450 enzymes (e.g., CYP1A2, 2B6, and 3A4). During parathion desulfuration, an electrophilic sulfur is released, which inactivates the cytochromes, leading to significant effects on other metabolic processes and detoxification of xenobiotics.[19]

Research on the use of hydrolases to treat OP toxicity has led to the potential for use of bacterial phosphotriesterases to cleave OPs.[145-147] The discovery of polymorphism in the *PON1* genetic coding suggests that there is a variable sensitivity to toxicity of OPs.[14,148] This may help to explain why some people exhibit a higher degree of toxicity when exposed to the same agents.

Other promising novel therapies for OP pesticide poisoning are being researched. There has been at least 10 years of work on the Hagedorn agents HI-6 and HLö-7. These two agents and others continue to show promise as the preferred oximes for nerve agent toxicity (see Chapter 105A).[28,86,89,90,149-152] Alkalinization with sodium bicarbonate has increased survival in animal models and may be useful in humans.[153,154] A recent Cochrane review of alkalinization for the treatment of OP intoxication suggested that it may be useful clinically, but there is insufficient evidence for routine use.[152] A promising new line of investigation is the use of OP hydrolases to break down OPs before they can covalently bind to acetylcholinesterase. Data from in vitro and animal models have demonstrated that the combined use of bacterial OP hydrolases and oxime therapy has been successful in preventing reinhibition of acetylcholinesterase.[155-157] Finally, human butyrylcholinesterase has been used to increase survival in soman-poisoned rats.[158,159]

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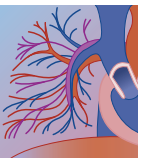

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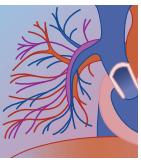

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