Cholinesterase Inhibition by Organophosphorus Compounds and its Clinical Effects*

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The clinical manifestations of acute poisoning by organophosphorus compounds in man are in accord with, initially, the stimulation and, later, the blocking of cholinergic transmission due to acetylcholinesterase inhibition. The manifestations involve mainly the parasympathetic nerves, the neuromuscular junctions, and the central nerve synapses, and to a smaller degree the cholinergic sympathetic nerves. Miosis and muscle fasciculations are useful signs for diagnosis and for the control of therapy. Blood cholinesterase determination is the best diagnostic test. The cause of death is usually respiratory paralysis. Persistent manifestations have not been confirmed. Atropine and pralidoxime are effective for treatment and useful for diagnosis. Other oximes are promising but their clinical value has not been established. Poisoning by malathion is characterized by a prolonged course and by motor signs. Poisoning by organophosphorus compounds in man differs from animal experiments in several ways: in man, exposure may occur by several different routes, the manifestations are detected more easily, and therapy is given throughout the course of illness.

The introduction during the Second World War of new insecticides, particularly chlorinated hydrocarbons and organophosphorus compounds, marked a rapid technological advance. DDT is representative of chlorinated hydrocarbons, and it has been widely used in agriculture, forestry, vector control, and for other purposes, with little apparent toxic effect on humans and other vertebrates. On the other hand, organophosphorus insecticides have frequently caused poisoning in humans and other animals. Many of them are highly toxic; indeed, the organophosphorus compounds were initially developed as chemical warfare agents.

However, the potential and persistent hazards of DDT and other chlorinated hydrocarbon insecticides have become evident in recent years. These compounds are stable, and are found unchanged ubiquitously in soil, air, and water (including rain) in almost all areas of the earth (Crosby, 1969). They accumulate particularly in the adipose tissue of man and other animals. DDT has been found in penguins and seals in the Antarctic, where the compound has never been used. Moreover, the concentration of chlorinated hydrocarbons increases in each step of the food chain. The decline of populations of wild animals, birds, fish, and useful insects has been attributed to the use of these compounds.

Since they are at the highest end of the food chain, humans also accumulate chlorinated hydrocarbon insecticides. In the USA, the concentration of DDT and its metabolites is about 11 ppm in the adipose tissue of the general population (Durham, 1969), 4 ppm in penguins (Zavon et al., 1969), and 0.08–0.13 ppm in human milk (Durham, 1969). Although there is little evidence at present that DDT or other chlorinated hydrocarbons in human tissues is harmful, and although some studies have indicated that the concentration has been constant for years, there is concern that it may eventually become unbearable high as these stable compounds further accumulate on the earth. Chlorinated hydrocarbons are neurotoxic, and high concentrations in the nervous tissues may be attained when the adipose tissue is mobilized—for example, in disease or starvation states.
TOXICITY OF ORGANOPHOSPHORUS COMPOUNDS

The toxicity of organophosphorus compounds is mainly, if not entirely, due to their inhibition of cholinesterase. These compounds are absorbed into the human body through all possible routes, including the skin, lungs, gastrointestinal tract, and conjunctiva; they may also enter the body by injection, although this is of rare occurrence. Some of them are used medically for the treatment of glaucoma and (rarely) myasthenia gravis. The most toxic of the organophosphorus compounds are the chemical warfare agents, whose oral lethal dose for man is estimated to be in the milligram range or less.

Of the organophosphorus insecticides, parathion and malathion are the most widely used. Parathion ($O,O$-diethyl-$O$-$p$-nitrophenyl phosphorothioate) is one of the most toxic, and most organophosphorus-insecticide poisonings have been caused by this compound. In volunteers, an oral intake of 0.07 mg of parathion per kg of body-weight did not cause any manifestations (Eicken, 1954); 0.1 mg/kg produced uneasiness, warmth, tightness of the abdomen, and frequent urination, with a reduction in cholinesterase levels of 3% in plasma and 12% in whole blood in one subject and 5% in plasma in another subject (who showed no symptoms); and 0.4 mg/kg resulted in increased peristalsis, tightness of the chest, and a reduction in cholinesterase levels of 69% in plasma and 47% in whole blood (Takahashi, 1956). The last case appeared to be on the verge of developing manifest poisoning. The dermal application of 1 g or 2 g of parathion for 4 hours produced a 10–20% reduction in plasma cholinesterase but no symptoms (Ueda, 1957). Death has occurred following the ingestion of 900 mg, 120 mg, and 50 mg of parathion by adults and 2 mg by children (Hayes, 1963). The oral lethal dose of parathion is estimated to be 1.43 mg per kg of body-weight—that is, 100 mg for a man weighing 70 kg (DuBois, 1958).

Malathion (diethyl mercaptosuccinrate $S$-ester with $O,O$-dimethyl phosphorodithioate) is one of the least toxic organophosphorus insecticides. The ingestion of 16 mg of malathion daily for 47 days by volunteers did not cause symptoms or affect blood cholinesterase, while the ingestion of 24 mg daily for 56 days caused a 25% decrease in blood cholinesterase (Moeller & Rider, 1962). There were no symptoms and there was no decrease in blood cholinesterase following the dermal application of 1%, 5% or 10% malathion dust 5 times weekly for 8–16 weeks (Hayes et al., 1960), or following exposure to air containing 0.15 g, 0.6 g, or 2.4 g of malathion per 1000 ft$^2$ 84 times in 42 consecutive days (Golz, 1959). Death has occurred following the ingestion of about 5 g, 25 g, 35 g, 70 g, or 60–90 g, and severe poisoning following the ingestion of 15 g, 25 g (Namba, Greenfield & Grob, 1970), 35 g (Mathewson & Hardy, 1970), 30 g, or 35–50 g (Windsor, 1968). Poisoning probably caused by the dermal absorption of malathion has been described, although it seems exceptional in view of the low toxicity of the compound. The estimated oral lethal dose of malathion, 858 mg per kg of body-weight, is less than the lethal dose of DDT, 429 mg/kg (DuBois, 1958), or even aspirin, 400–500 mg/kg (Dreisbach, 1969). If malathion is administered with EPN† another organophosphorus insecticide, potentiation occurs in experimental animals, but in man there is an additive effect (Moeller & Rider, 1962).

OCCURRENCE OF POISONING BY ORGANOPHOSPHORUS INSECTICIDES

Poisoning has frequently resulted from the agricultural use of organophosphorus pesticides, the compounds usually having been absorbed dermally or by inhalation during application or during subsequent work in the fields. A high incidence of poisoning was reported among pilots who engaged in the aerial application of these compounds, because even a mild symptom—e.g., blurred vision—resulted in aircraft accidents or because even a minor accident caused exposure of the pilot to concentrated prepara-

† Names against which this symbol appears are identified in the Glossary on pages 445-446.
tions of organophosphorus compounds (Reich & Berner, 1968). Industrial poisoning in plants synthesizing these compounds occurred during the early stages of their development, but it is now generally rare since the manufacturing processes are supervised by specialists. Accidents occur more frequently in the formulation plants where concentrated preparations of organophosphorus compounds are diluted with solvents, emulsifiers, dusts, or other vehicles. Formulation plants are more numerous than synthesizing plants, the processes involve steps that may result in greater exposures, and seasonal insecticide demands may necessitate the employment of unskilled temporary workers. Poisoning has occurred among industrial or scientific research workers, particularly with new compounds of unknown toxicity. Poisoning during vector control operations has been rare, since such operations are carried out under the supervision of experts and compounds of low toxicity are generally used. Poisoning of persons and animals not involved in spraying operations has been reported occasionally, but only when highly toxic compounds were involved. The spraying of a field with parathion led to the appearance of this pesticide in a neighbouring drinking-water well. In Utah, USA, 6,000 sheep died from exposure to organophosphorus warfare gas that drifted after aerial spraying during a military exercise (Boffey, 1968). Food that had been sprayed with organophosphorus insecticides immediately before harvest caused poisoning in only a few persons living in the neighbourhood, since hydrolysis of these compounds results in a rapid loss of toxicity. However, the contamination of flour or barley with concentrated parathion during shipment caused outbreaks of poisoning involving hundreds of cases in Colombia, India, Mexico, Singapore, and the United Arab Republic. Accidental poisoning has occurred more often in children than adults, particularly in farm communities. The cause has often been unknown. Children have absorbed organophosphorus insecticide dermally or orally while playing with a container or spray machine or while playing in an area to which the insecticides have been applied. Adults have ingested these insecticides by mistake for liquor, fruit juice, or remedies for toothache or cough, and have applied them externally for body lice, fleas, or skin diseases. Clothes contaminated by parathion during shipment have caused poisoning in the weavers. Most household insecticides and those used by professional exterminators for residential areas contain organophosphorus compounds, and their use has resulted in poisoning. Such compounds have been used for suicide to a considerable extent, in areas where the suicide rate is high and where the compounds are readily available, and the mortality rate has been high. The use of organophosphorus compounds for homicide has also been reported.

The numbers of cases of parathion poisoning in Japan in 1960–69 were as follows: poisoning resulting from application of the insecticide, 2,059 cases (110 deaths); accidental poisoning, 113 cases (56 deaths); and suicidal poisoning, 3,243 cases (3,040 deaths). In California, USA, there were 950 cases of poisoning by organophosphorus compounds during 1957–60 (789 agricultural, 91 industrial, and 70 from other causes). In Dade County, Fla., there were 90 cases in 1964–67, 24 of them occupational (1 death), 44 of them accidental (10 deaths), and 22 of them suicidal (16 deaths) (Reich et al., 1968). In Denmark 273 fatal poisonings by organophosphorus compounds were recorded from 1957 to 1962—6 accidental, 263 suicidal, and 4 homicidal (Frost & Poulsen, 1964).

Even malathion, a compound of low toxicity, has caused substantial numbers of poisonings. In Japan during 1957–69 there were 100 poisonings with 21 deaths resulting from occupational handling or accidents and 1,024 poisonings with 844 deaths resulting from suicidal or homicidal attempts. In British Guiana 3 deaths by accident and 43 deaths by suicide occurred during 1959–64 (Mootoo & Singh, 1966). In Denmark 3 of the 273 fatal organophosphorus-compound poisonings were cases of suicide with malathion (Frost & Poulsen, 1964).

Legislation and campaigns to promote the safe use of these compounds have effectively reduced the numbers of poisonings. In Japan during 1953 and 1954 there were 3,949 cases of parathion poisoning. Following legislation governing the application and handling of parathion and a nation-wide campaign on its proper use, the number of cases of poisoning was reduced to 2,194 in 1960–61, but it still accounted for 72% of all poisonings by pesticides. Further restriction of the use of parathion reduced the number of cases of poisoning to 753 in 1965–66—34% of the total number of poisonings by pesticides.

**PHYSIOLOGY OF POISONING BY ORGANOPHOSPHORUS COMPOUNDS**

Organophosphorus compounds are powerful inhibitors of carboxylic ester hydrolases, including
acetylcholinesterase (acetylcholine acetyl-hydrolase, 3.1.1.7), which is present in human erythrocytes, nerves, synapses, and skeletal muscle; and cholinesterase (acetylcholine acetyl-hydrolase, 3.1.1.8), present in human plasma (serum) and liver. These esterases are differentiated by (1) substrate specificity (acetylcholinesterase hydrolyses acetyl-β-methylcholine but very little benzoylcholine, propionylcholine, or butyrylcholine, while the opposite occurs with cholinesterase); (2) selective inhibition; and (3) substrate inhibition (acetylcholinesterase is inhibited by acetylcholine concentrations equal to or greater than 4 mm or higher and cholinesterase by concentrations greater than 100 mm). Organophosphorus insecticides generally inhibit both enzymes.

Non-synaptic acetylcholinesterase (AChE) is postulated to maintain excitability and to initiate and propagate action potentials in nerve and muscle by regulating passive and active transport of electrolytes. In patients with paroxysmal nocturnal haemoglobinuria, erythrocyte AChE activity is low, particularly in erythrocytes that are readily lysed upon the addition of complement (Kunstling & Rasse, 1969). However, no signs or symptoms are found in familial reduction of erythrocyte AChE (Johns, 1962). Cholinesterase (ChE) is considered to excite cardiac and smooth muscles locally, and to provide free choline in acetylcholine synthesis by hydrolysing butyrylcholine (Clitherow et al., 1963) or by dissociating conjugated choline (Funnel & Oliver, 1965). However, there was no clinical manifestation in two family members who had a complete lack of plasma ChE (Hodgkin et al., 1965). Plasma ChE is synthesized in the liver, and its activity is a sensitive indicator of liver function. The syndrome of genetically inherited qualitative change of plasma ChE produces hypersensitivity to succinylcholine, a cholinesterase inhibitor used as a muscle relaxant in anaesthesia, but patients with this syndrome do not have any other symptoms. Therefore, the effect of organophosphorus compounds is primarily, if not entirely, explained by the inhibition of AChE at the cholinergic synapses.

At the cholinergic synapses, acetylcholine is released from the nerve ending as the neurohumoral transmitter in response to the nerve impulse, and initiates excitation by reacting with the receptor (Fig. 1 and 2). Acetylcholine is then hydrolysed, as follows: (1) the acetylcholine is bound to AChE, the quaternary nitrogen to the anionic site and the carboxyl group to the esteratic site, forming a substrate–enzyme complex; (2) choline is split off, leaving acetylated AChE; and (3) the latter reacts with water, dissociating into acetic acid and active AChE. This reaction is completed rapidly and the synapse becomes ready for the next impulse. In cases of poisoning, AChE is bound with the organophosphorus compound, and its organic residue dissociates, leaving the phosphate group bound with

Fig. 1
Reactions of acetylcholinesterase

First row: acetylcholine hydrolysis by AChE. Second row: inhibition of AChE by organophosphorus compound (the dotted-line arrow indicates the practically negligible progress of this reaction). Third row: reactivation of phosphorylated AChE by pralidoxime.


Fig. 2
Transmission across cholinergic synapses


Modification of the toxicity of organophosphorus compound in vivo

Skin
Mucosa
Lung

Blood
Tissue (Liver)

Cholinergic synapses

Black circles: Molecules of the OP compound. Broad vertical lines: tissue as indicated. Horizontal lines: penetration of the OP compound into the tissues, the thickness of the line indicating the toxicity.

Fig. 3

Cholinesterase activity of erythrocytes and plasma in patients with mild, moderate, and severe parathion poisoning*

The activity is expressed as a percentage of the normal level, measured 3 months after poisoning.

the esteratic site of AChE (Fig. 1 and 2). Since the rate at which this phosphorylated AChE dissociates is so slow as to be practically negligible, organophosphorus compounds are said to be "irreversible" inhibitors. As the result of AChE inhibition, acetylcholine molecules accumulate at the synapse, initially causing excessive excitation and later leading to the blockage of synaptic transmission. The inhibition of AChE may be considered to be an extremely slow enzymatic hydrolysis of the organophosphorus-compound molecule.

The toxicity of these compounds in vivo does not always match their AChE-inhibiting activity in vitro, owing to differences in their metabolism in the body (Fig. 3). The rate at which they are absorbed and transported varies, depending on the nature of the compounds, the vehicle, and the characteristics of the ports of entry. A substantial proportion of the absorbed compound does not reach the cholinergic synapse because it is bound with non-synaptic cholinesterase or is detoxified in the liver or other sites. On the other hand, certain organophosphorus compounds are converted into more toxic derivatives in vivo. For example, parathion, which inhibits 50% of cholinesterase at a $2 \times 10^{-4}$ M concentration in vitro and whose intravenous LD$_{50}$ for the rat is 3 mg per kg of body weight, is converted in the liver into paraoxon, which inhibits 50% of cholinesterase at a $10^{-4}$ M concentration and whose LD$_{50}$ for the rat is 0.4 mg/kg (Heath, 1961); malathion is similarly converted into malafoxon, whose toxicity to the mouse is about 20 times that of malathion (Murphy et al., 1968). On the other hand, both malathion and malafoxon are detoxified in the liver by malathionase (Murphy, 1967).

Since synaptic AChE activity has been measured only experimentally (Namba & Grob, 1970), blood cholinesterase activity is used to assess the degree of inhibition of synaptic AChE. Signs and symptoms of poisoning by organophosphorus compounds occur when more than 50% of the plasma ChE or erythrocyte AChE is inhibited (Fig. 4), and therefore the threshold level of synaptic AChE inhibition is probably about 50%. The recovery of blood cholinesterase takes about 2 weeks in patients with mild poisoning. However, the recovery of synaptic AChE appears to be very rapid, since signs and symptoms disappear within 24 hours in patients with mild or moderately severe poisoning. Since inhibition by organophosphorus compounds is "irreversible," the recovery of cholinesterase is probably due to replacement and not reactivation. Since the recovery of
The cholinergic synapses, in which acetylcholine is the transmitter, include the synapses of the central nervous system, neuromuscular junctions, sensory nerve endings, ganglionic synapses of both sympathetic and parasympathetic nerves, postganglionic sympathetic nerve terminals that innervate the sweat glands and blood vessels, sympathetic nerve terminals (without ganglionic synapses) in the adrenal medulla, and all postganglionic parasympathetic nerve terminals (Fig. 6). Most of the postganglionic sympathetic nerve terminals are adrenergic, norepinephrine serving as the transmitter. The cholinergic and adrenergic manifestations are generally antagonistic. Most of the manifestations of poisoning by organophosphorus compounds are in agreement with excessive cholinergic action (Table 1). Exceptions—e.g., tachycardia and increased blood pressure—are explained by overwhelming cholinergic effects on the central nervous system, sympathetic ganglionic synapses, or adrenal medulla (Paul et al., 1954; Dirnhuber & Cullumbine, 1955; De Burgh-Daly & Wright, 1956; Hornykiewicz & Kobinger, 1956; Polet & De Schaepdryver, 1959).

**Fig. 5**  
Cholinesterase activity of blood and cholinergic synapses in repeated exposures to subtoxic doses of organophosphorus compounds*

* The arrows at the top of the figure indicate the days of exposure.

Tissue cholinesterase and detoxifying activity takes a long time, repeated exposures to organophosphorus compounds, even at levels below the toxic dose, decrease these protective mechanisms, resulting in increasingly greater exposure of synaptic AChE to the compounds and ultimately producing inhibition greater than the threshold level (Fig. 5).

**Fig. 6**  
Cholinergic synapses*

* The locations of the synapses are indicated by shading.

**SIGNS AND SYMPTOMS OF ACUTE POISONING**

The interval between exposure to organophosphorus insecticides and the onset of signs and symptoms varies from minutes to hours, but is usually less than 12 hours. Manifestations that occur more than 24 hours after the last exposure usually cannot be attributed directly to the insecticides.

The severity of poisoning is classified by clinical manifestations and the degree of inhibition of plasma ChE (Table 2; see also the Annex). The classification serves as a guide for prognosis and therapy. In mild poisoning, the manifestations are predominantly due to the stimulation of parasympathetic nerve endings. Manifestations resulting from the stimulation of other nerve endings appear in moderate or severe poisoning. Impulse generation at some sensory endings and their synapses in the central nervous system is cholinergic, but the sensory signs are not clearly identified.

The characteristic central nervous system manifestation is disturbance of consciousness, which occurs in patients with severe poisoning and may appear without circulatory or respiratory disturbance. Mental signs such as anxiety, insomnia, excessive dreaming, and difficulty in concentration may occur as prodromal manifestations or after the disappearance of acute somatic manifestations.
Miosis and muscle fasciculations are valuable objective manifestations, and are found in about 50% of the patients. Muscle fasciculations occur in moderate or severe poisoning, particularly in the early stage, and disappear in later stages either because of improvement, with the disappearance of neuromuscular stimulation, or because of the advance of poisoning, with depolarizing neuromuscular block. Miosis occurs in patients with poisoning of any severity, generally lasts throughout the course of the illness, and is a good indicator of the effectiveness of treatment. However, miosis and muscle fasciculations may not be present even in severe poisoning. The most important manifestation and the usual cause of death is respiratory difficulty caused by weakness of the respiratory muscles, paralysis of the respiratory centre, bronchospasm, and increased bronchial secretion. Cardiac manifestations—including atrial fibrillation, conduction block, and ventricular fibrillation and flutter—may occur, but usually in the terminal stage. Recently there have been more reports of cardiac manifestations in poisoning by organophosphorus compounds because of prolonged courses resulting from improved respiratory care (Namba et al., 1970; Barckow et al., 1969; Harris et al., 1969; Heitmann & Felgenhauer, 1969; Singh et al., 1969). Tachycardia and increased blood pressure occur in the initial stage and bradycardia and decreased blood pressure in the later stages (Fig. 7).
Table 2

Signs and symptoms in patients with parathion poisoning

<table>
<thead>
<tr>
<th>Sign or symptom</th>
<th>Total no. of patients showing signs</th>
<th>No. of patients with the following plasma cholinesterase levels (% of normal) showing signs</th>
<th>0–10 %</th>
<th>11–20 %</th>
<th>21–50 %</th>
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<tbody>
<tr>
<td>weakness</td>
<td>77</td>
<td></td>
<td>27</td>
<td>25</td>
<td>25</td>
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<tr>
<td>nausea and vomiting</td>
<td>69</td>
<td></td>
<td>25</td>
<td>25</td>
<td>19</td>
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<tr>
<td>excessive sweating</td>
<td>62</td>
<td></td>
<td>23</td>
<td>17</td>
<td>22</td>
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<tr>
<td>headache</td>
<td>61</td>
<td></td>
<td>17</td>
<td>21</td>
<td>23</td>
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<td>51</td>
<td></td>
<td>24</td>
<td>15</td>
<td>12</td>
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<td>26</td>
<td>12</td>
<td>0</td>
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* In 77 patients who developed poisoning following the application of parathion or parathion-methyl

Patients with moderate or severe poisoning may have a low-grade fever, not related to infection, for about 1 week (Fig. 8). Hyperglycaemia and glycosuria are often present in severe poisoning (Fig. 9). Judging from the relatively mild hyperglycaemia accompanied by glycosuria, a lowered renal threshold for glucose excretion is also present. The absence of acetone bodies differentiates the condition from diabetic coma, except for coma in diabetes resulting from hyperosmolarity. Urobilinogen is present in the urine of about 50% of the patients on the first day. In moderate or severe poisoning there is leucocytosis, with a white-cell count of up to 20 000 per mm³ and with an increased number of neutrophils and a decrease in the proportion of lymphocytes and monocytes. In cases of severe poisoning, eosinophils are usually not found on the first day, unless there has been pre-existing eosinophilic leucocytosis (usually resulting from parasitic or allergic conditions).

Local exposure to organophosphorus insecticides produces comparatively severe local manifestations. Exposure of the eye causes severe miosis and lachrymation. Dermal exposure may cause copious sweating. Absorption from the respiratory tract may cause tightness of the chest initially and dyspnoea and bronchial secretions later. The ingestion of organophosphorus compounds is often followed by severe abdominal pain, diarrhoea, and vomiting. Fortunately, the vomiting reduces the amount of the compound that is absorbed.

The signs and symptoms and prognoses listed in the Annex are based on observations of poisonings that occurred following field spraying with parathion
and parathion-methyl. The situation is different in patients who have ingested (or injected) a large quantity of an organophosphorus compound; in such patients, the ingested compound in the gastrointestinal tract or other tissues is continuously released, and consequently the course of the poisoning is long, necessitating continuous treatment. The results of studies of extremely toxic organophosphorus compounds (the warfare gases) and of studies on experimental animals may not always be applicable to the poisoning of man by organophosphorus insecticides. For example, only a few minutes after the inhibition of AChE by warfare gases the enzyme can no longer be reactivated by pralidoxime, although it takes hours to reach this condition when AChE is inhibited by organophosphorus insecticides. Man is more sensitive to organophosphorus compounds than are experimental animals and shows signs and symptoms—particularly central nervous system manifestations—earlier than do the latter. Therefore, the quantity of absorbed organophosphorus compound necessary to produce a given effect may be relatively smaller in man.

Prognosis in relation to the severity of poisoning is indicated in the Annex. Untreated parathion poisoning leads to death within 24 hours of the onset of manifestations: if an untreated patient is alive after 24 hours, he will recover. Patients who are under treatment may die from 24 hours to 1 week after the onset of manifestations.

POISONING BY ORGANOPHOSPHORUS INSECTICIDES OF LOW TOXICITY

The organophosphorus compounds of low toxicity are expected to be used more widely as substitutes for chlorinated hydrocarbons. However, only limited information is available on compounds of this group other than malathion.

The toxicity of malathion is due mainly to cholinesterase inhibition following the conversion of the compound to malaoxon in the liver. Pure malathion has little cholinesterase-inhibiting action, but it may have an independent toxic activity, since it inhibits the growth and respiration of chicken embryo tissue in culture, whereas malaoxon at the same concentration does not (Wilson & Stinnett, 1969).

The time of onset of the signs and symptoms of malathion poisoning ranged from 5 minutes after ingestion to a gradual development over a period of 6 weeks when there were multiple exposures. Patients with malathion poisoning generally devel-
oped severe signs and symptoms, since 25 of 30 reported patients developed poisoning following the ingestion of a large dose of malathion with suicidal intent, or by accident (Namba et al., 1970; Windsor, 1968; Harris et al., 1969; Mathewson & Hardy, 1970). Of 30 patients, 27 (90%) became comatose, 8 (27%) had convulsions, and 7 (23%) died. Miosis was present in 27 patients (90%), but 3 patients did not show this condition. Muscle fasciculations were observed in 7 patients (24%) but not observed in 3 patients. There was paralysis of the extremities in 6 patients (20%), and loss of tendon reflexes occurred in 14 patients (47%). A long-lasting polyneuropathy was reported in 1 patient. Extensor plantar reflexes were observed in 5 patients. Signs of meningeal irritation occurred in 2 children. The course was protracted (up to 3 weeks) in 9 patients, who showed continuous or intermittent respiratory difficulty or unconsciousness, indicating continuous absorption of the compound from the gastrointestinal tract.

The cholinesterase activity of whole blood, erythrocytes, plasma, or serum was reduced to less than 20% of the normal value in 7 patients, but was 50% of the normal level in whole blood of 1 patient and 60% of normal in the serum of another patient. Some patients showed a progressive reduction, over a period of days, of both plasma ChE and erythrocyte AChE levels.

**DIAGNOSIS OF ACUTE POISONING BY ORGANOPHOSPHORUS COMPOUNDS**

Diagnosis depends on (1) history or evidence of exposure to organophosphorus compounds within the previous 24 hours, (2) signs and symptoms of poisoning (see the Annex), (3) inhibition of the cholinesterase activity of the blood or other tissues, and (4) the effectiveness of atropine and pralidoxime.

With most patients, a history or evidence of exposure to organophosphorus compounds within 24 hours before the onset of symptoms can be obtained. The patients may retain a characteristic garlic-like odour for several days. In gastric aspirate or urine and on the skin or clothing organophosphorus compounds can be identified by means of gas or thin-layer chromatography, or their presence can be demonstrated by the inhibition of cholinesterase activity *in vitro*. Metabolites of organophosphorus compounds—e.g., *p*-nitrophenol, a metabolite of parathion, parathion-methyl, Chlorthion,↑ dicapthion,↑ and EPN↑—may also be detected in urine (Fig. 10). However, a history of exposure and the detection of organophosphorus compounds or their metabolites do not always indicate that signs and symptoms are due to poisoning by such compounds. For example, cerebrovascular accidents may develop during the use of organophosphorus insecticides. Although *p*-nitrophenol was detected in the urine of 75 (83%) of 90 farm workers who had sprayed parathion in fields, none of them had any symptoms, and the *p*-nitrophenol concentration was not parallel with the degree of inhibition of serum ChE activity (Namba et al., 1971).

In poisoning by organophosphorus compounds the determination of erythrocyte AChE is theoretically preferable, but the determination of plasma ChE is advantageous in that it is simpler. Following the administration of pralidoxime, the erythrocyte AChE level indicates its effectiveness; plasma ChE indicates the prior presence of cholinesterase inhibition even after the recovery of erythrocyte AChE activity as a result of pralidoxime treatment (Namba & Hiraki, 1958) (Fig. 11). A finding of normal blood cholinesterase activity excludes systemic poisoning by organophosphorus compounds. In acute poisoning, manifestations generally occur only after more than 50% of the plasma ChE is inhibited, and the severity of manifestations parallels the degree of inhibition (Table 2). However, this correlation holds true only in the initial stage of acute poisoning, and inhibition of the activity remains even after the patient becomes symptom-free. Following severe
poisoning, recovery to the normal levels takes about 4 weeks for plasma ChE and about 5 weeks for erythrocyte AChE when pralidoxime is not administered (Fig. 4). Since plasma ChE is relatively stable, samples can be shipped to laboratories of other institutions. Plasma can be refrigerated for a week without appreciable loss of ChE activity.

The effect of pralidoxime and atropine may be of help in differential diagnosis. The intravenous injection of 1 g of pralidoxime generally results in some recovery from signs and symptoms, particularly in parathion poisoning. The failure of 1–2 mg of atropine administered parenterally to produce signs of atropinization (flushing, mydriasis, tachycardia, or dryness of the mouth and nose) indicates poisoning by organophosphorus compounds; conversely, the occurrence of these signs casts doubt on the diagnosis, or indicates that the poisoning is of mild degree.

**Treatment of Acute Poisoning by Organophosphorus Compounds**

Treatment consists of (1) the maintenance of respiration, (2) the administration of atropine and pralidoxime, (3) the removal of organophosphorus compounds, and (4) other supportive measures (see the Annex).

The therapeutic action of atropine in poisoning by organophosphorus compounds results from its bind-

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1 Pralidoxime also crosses the placenta (Edery et al., 1966).
1.0-2.0 g of pralidoxime, and the subsequent administration of atropine and additional pralidoxime as described above, is the easiest way to regulate doses. The injection of pralidoxime after the administration of a large dose of atropine may result in severe signs and symptoms of atropinization, although this condition rarely affects the prognosis.

The administration of cholinesterase from human plasma or erythrocytes or from animal sources is ineffective, since it does not affect the cholinesterase activity of synapses (Hiraki et al., 1956).

**Treatment with oximes**

Pralidoxime iodide, 2-formyl-1-methylpyridinium iodide oxime, was developed for the treatment of poisoning by organophosphorus compounds on the basis of the molecular reactions of AChE (Wilson & Ginsburg, 1955), and was the first compound to be effective in man (Namba & Hiraki, 1958). Pralidoxime is also used in the forms of the chloride and the methanesulfonate. Other oximes that have been used for treatment include obidoxime chloride, 1,1'-oxydimethylene)bis(4-formylpyridinium) dichloride dioxime, and trimedoxime bromide, 1,1'-trimethylenebis(4-formylpyridinium) dibromide dioxime (Fig. 12).

In addition to the reactivation of inhibited AChE, the actions of oximes may include prevention of the formation of phosphorylated AChE, which cannot be reactivated by these compounds; direct detoxification of organophosphorus compounds; and direct action on the synaptic receptor. High, lethal concentrations of acetylcholine were found in the brains of animals that had been given pralidoxime or obidoxime and thus saved from death from poisoning by organophosphorus compounds, indicating that reactivation is not the sole action of these oximes (Milošević, 1969, 1970). Dephosphorylation of the esteratic site by oximes, and therefore the reactivation of the enzyme, become difficult after several hours in cases of inhibition by parathion and other organophosphorus insecticides, and within minutes in cases of inhibition by sarin, a warfare gas. However, the reactivation of blood cholinesterase-

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**Table 3**

Signs and symptoms in patients with parathion poisoning before and 30 min after intravenous injection of 0.9-2.0 g of pralidoxime iodide

<table>
<thead>
<tr>
<th>Sign or symptom</th>
<th>Total no. of patients showing signs listed at left</th>
<th>No. of patients with the following plasma cholinesterase levels (% of normal) showing signs listed at left</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>nausea and vomiting</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>pallor</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>dizziness</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>headache</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>excessive salivation</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>paraesthesia</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>muscle fasciculations</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>dyspnoea</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>miosis</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>impairment of speech</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>cramps</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>bronchopharyngeal secretion</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>disturbance of consciousness</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Total no. of patients</td>
<td>25</td>
<td>8</td>
</tr>
</tbody>
</table>

---
ase and a reduction of signs and symptoms have been observed in clinical practice even 2 or 3 days after the onset of poisoning, probably because newly inhibited cholinesterase is constantly produced as a result of the continuing absorption of organophosphorus compounds from the gastrointestinal tract or other tissues.

Pralidoxime chloride (molecular weight, 173), iodide (molecular weight, 264), and methanesulfonate (molecular weight, 232) are approximately equally effective at equimolar doses (Namba et al., 1959d), but the chloride is preferable since it is more soluble and produces fewer side-effects than the other compounds.

The intravenous LD₅₀ of chloride oximes for mice are as follows (mg per kg of body-weight): pralidoxime, 93.6 (542 μmoles) (Namba et al., 1959d); obidoxime, 70.0 (195 μmoles) (Erdmann & Engelhard, 1964); and trimedoxime, 57.0 (158 μmoles) (O'Leary et al., 1961). At high concentration these oximes have cholinesterase-inhibiting activity in vitro, but neither plasma ChE nor erythrocyte AChE was inhibited in man following the intravenous injection of therapeutic doses of pralidoxime iodide, and the inhibition of blood cholinesterase was not more than 20% following the intravenous injection of lethal doses of pralidoxime iodide in rabbits (Namba et al., 1958a). Obidoxime appears to have a greater cholinesterase-inhibiting activity than pralidoxime (Zech et al., 1967).

When volunteers were given intravenous injec-
tions of 15–20 mg of pralidoxime iodide or methanesulfonate per kg of body weight, they experienced dizziness, blurred vision, diplopia, tachycardia, head-
ache, impaired accommodation, or nausea lasting for several minutes (Jager & Stagg, 1958; Sundwall, 1960). In another study no ill effects occurred follow-
ing the intramuscular or intravenous administra-
tion of 15–20 mg of pralidoxime chloride per kg of body weight (Calesnick et al., 1967). The more frequent side-effects that have been reported may be due to contamination of the drugs with aldehyde compounds. Following the ingestion of 1–10 g of pralidoxime iodide, some volunteers experienced tension and fatigue in the jaw, a bitter taste, and rhinitis, beginning 30 minutes after intake and lasting about 2 hours (Namba et al., 1958a). The bitter taste was also experienced with the chloride (Lipson et al., 1969). Pralidoxime chloride produced no side-effects when given orally in a single dose of up to 7 g (Calesnick et al., 1967; Sidell et al., 1969), or a daily dose of 0.25–4 g given for 3 weeks to 6 months, a total of up to 400 g (Calesnick et al., 1967; DeRoeth et al., 1965; Lipson et al., 1969), but the administration of a single dose of 8 g or more, or of doses of 2–5 g every 4 hours for 48 hours, produced anorexia, malaise, nausea, vomiting, or diarrhoea (Sidell et al., 1969). One person developed maculopapular rash (Lipson et al., 1969). In the author's experience pralidoxime iodide caused no side-effects when administered, to treat poisoning by organophosphorus compounds, in intravenous doses as large as 40.5 g over a 7-day period, 26 g of this total being given during the first 54 hours (Namba et al., 1959b). In one patient with malathion poisoning, the administration of pralidoxime was followed by respiratory difficulty and cyanosis, but these were attributed to the withdrawal of atropine (Richards, 1964).
The intravenous injection of obidoxime in dogs was followed by vomiting at doses of 20–50 mg per kg of body-weight and by generalized weakness at doses of 50–70 mg/kg (Erdmann & Clarmann, 1963). In 22 volunteers 1 or 2 intramuscular injections of 250 mg of obidoxime caused pain at the site of injection and transitory feelings of cold, heat, or tension in the nasopharynx, face, or head (Erdmann et al., 1965; Boelcke et al., 1970a). Both pralidoxime and obidoxime are rapidly excreted in the urine.

The intravenous injection of 15 mg and 20 mg of trimedoxime per kg of body-weight in 2 normal individuals caused marked hypotension, and, in one of them, tachycardia (Wills, 1959).

The effectiveness of oximes for the treatment of poisoning by organophosphorus compounds in man was first demonstrated in 1956 by Namba & Hiraki (1958), who used pralidoxime to treat patients with parathion poisoning. It was fortunate that these first patients had parathion poisoning and showed remarkable recovery after treatment with pralidoxime, a result that stimulated further work on oximes, since later studies showed that pralidoxime is most effective against poisoning with parathion and parathion-methyl (Namba et al., 1971). Four patients with EPN poisoning and a child who ingested diazinon have also been treated successfully with pralidoxime (Namba et al., 1959a, 1959b, 1959c). Pralidoxime was also reported to be effective for the treatment of poisoning with TEPP (2 patients); dicrotophos, carbophenothenion, dichlorvos, and dimethoate (1 patient each), and, to a lesser degree, mevinphos (9 patients). The effect was not clearly demonstrated in 1 case of phosphamidon poisoning, 1 case of azinphos-methyl poisoning, 2 cases of demeton-methyl poisoning, 13 cases of malathion poisoning (Namba et al., 1970, 1971), and 1 case of monocrotophos poisoning (Simson et al., 1969). However, these patients may have been given an insufficient amount of pralidoxime, late in the course of poisoning. Pralidoxime has also been shown to be effective in man against poisoning by non-insecticide organophosphorus compounds, including diisopropyl phosphorofluoridate and ec-thiopate¹ (used in the treatment of glaucoma), and by quaternary ammonium anticholinesterase compounds, neostigmine, pyridostigmine, and ambenonium (used in the treatment of myasthenia gravis).

The effectiveness of pralidoxime and trimedoxime in experimental animals suffering from poisoning by different organophosphorus compounds has been summarized by Durham & Hayes (1962) and Ellin & Wills (1964). However, the effect of chemotherapy in man may be different from that in animals, since animal experiments usually involve a single administration of both the organophosphorus compound and the therapeutic agent, while in man the organophosphorus compound may be absorbed by different routes and drugs are administered continuously throughout the course of illness.

The effective dose of obidoxime and trimedoxime is smaller, and their therapeutic index greater, than those of pralidoxime when used to treat poisoning by organophosphorus compounds in experimental animals (Erdmann & Engelhard, 1964). Obidoxime was effective in experimental animals with poisoning by parathion, paraoxon, diisopropyl phosphorofluoridate (Bisa et al., 1964; Erdmann & Engelhard, 1964), sarin, tabun, soman (Heilbronn & Tolagen, 1965), mevinphos, oxymethon-methyl, or malathion, but was not effective in poisoning by dimethoate or formothion (Zech et al., 1967). The advantages of obidoxime over pralidoxime are said to be its stronger and more rapid reactivation of cholinesterase in animal experiments, the feasibility of intramuscular injection of a sufficient therapeutic dose in a small volume (1 ml of 25% solution) (Erdmann et al., 1965), and the ease with which it penetrates the blood–brain barrier (Erdmann & Clarmann, 1963; Erdmann, 1965; Falb & Erdmann, 1969).

Twenty-two patients suffering from poisoning by organophosphorus compounds have been given obidoxime in amounts ranging from a single dose of 250 mg to multiple doses totalling 3.25 g over a 22-hour period (Erdmann & Clarmann, 1963; Staudacher, 1963; Wohlenberg et al., 1965; Clarmann & Geldmacher–v. Mallinckrodt, 1966; Stoeckel & Meinecke, 1966; Himml & Sterz, 1968; Klemm et al., 1968; Barckow et al., 1969; Heitmann & Felgenhauer, 1969; Prinz, 1969; Wender & Owsiannowski, 1969; Knolle, 1970; Boelcke et al., 1970b).

Of these patients, 10 showed some indications of therapeutic response, either in signs and symptoms or in blood cholinesterase; 6 of the 10 patients had attempted suicide by ingesting parathion, 1 patient had been poisoned by an injection of paraoxon and 1 by an injection of fenthion, 1 patient had ingested an unknown organophosphorus compound, and 1 patient had been exposed to demeton and other insecticides during spraying in the garden. In two

¹ International nonproprietary name for S-(2-diethylaminoethyl)-O,O-diethylphosphorothioate methiodide.
patients the whole-blood cholinesterase returned to normal from levels of zero and 18% of the normal value, respectively; erythrocyte AChE in 1 patient recovered from less than 10% to 40% of the normal level and in another patient from zero to 80%; and serum ChE in 1 patient recovered from 1% to 40% of the normal level. Of the 10 patients, 2 ultimately died of parathion poisoning, but showed temporary improvement of manifestations. Atropine in doses from 1 mg to 332 mg was given to 9 patients, 1 patient received 0.5 g of pralidoxime iodide, and another patient received 1.5 g of pralidoxime iodide and 3 g of pralidoxime methanesulfonate. In 1 patient exchange transfusions of 3–4 litres had a dramatic effect. Therefore, the improvement in manifestations or the recovery of cholinesterase activity in these patients may not necessarily have been caused by obidoxime. At most only 3 of these patients received unequivocal benefit from the administration of obidoxime. Twelve patients poisoned by parathion, dimethoate, triamiphos, parathion, demeton, mephos, or PFU-267 received no therapeutic benefit from obidoxime. In at least 4 patients the administration of obidoxime did not affect the blood cholinesterase activity. Obidoxime is believed to cross the blood–brain barrier more easily than pralidoxime, but prompt disappearance of the central nervous system manifestations of poisoning by organophosphorus compounds has not been described. Of the patients noted above, 7 developed cholestasis, generally 1 week after the administration of obidoxime, accompanied by jaundice and elevated serum bilirubin, transaminases, and lactate dehydrogenase, although studies in experimental animals and in volunteers indicated that cholestasis was caused not by obidoxime but by the organophosphorus compound (Boelcke & Erdmann, 1969; Boelcke & Gaaz, 1970; Boelcke et al., 1970a). From these results, obidoxime does not appear at present to be superior to pralidoxime for the treatment of poisoning by organophosphorus insecticides in man. Obidoxime may be superior to pralidoxime for treating poisoning with non-insecticide organophosphorus compounds, including diisopropyl phosphorofluoridate, sarin, and tabun. The recommended dose of obidoxime is 3–6 mg per kg of body-weight, limited to 1 or 2 doses; it should be given only following the administration of, and in combination with, atropine (Erdmann, 1968).

Trimedoxime has not been used widely and only one report has described beneficial effects in patients with trichlorfon poisoning (Titova & Badjugin, 1970).

Opinions vary on the usefulness of oximes in the treatment of poisoning with organophosphorus compounds, probably as a result of the experience of different workers. Thus, investigators who have treated parathion poisoning in farm workers would find that pralidoxime has dramatic life-saving effects. Individuals who handle only experimental animals might not encounter the dramatic recovery of consciousness that occurs in man. Others who study poisoning by nerve gases would be disappointed with pralidoxime, and might consider it useless or only an adjunct to atropine, and might prefer obidoxime, trimedoxime, or 2,3-butanedioxone monooxime (DAM). Oximes are like other drugs in that they are not equally effective in all stages of poisoning, nor are they equally effective in the treatment of poisoning by different organophosphorus compounds. There is no doubt that pralidoxime is more effective than atropine in the early stage of poisoning with parathion or parathion-methyl, and it may be that certain oximes would be ideal for treating poisoning by certain organophosphorus compounds. This aspect has not yet been fully explored clinically.

The possible usefulness of oximes for preventing poisoning by organophosphorus compounds was studied by administering pralidoxime orally to workers who handled such compounds. The results showed an increase in the urinary excretion of metabolites (Namba et al., 1958b) or the prevention, to a slight degree, of a decrease in erythrocyte AChE activity (Quinby, 1968). However, since the preventive use of oximes requires oral intake every 3–4 hours in order to maintain an effective blood concentration, and possibly creates overconfidence in the workers, it does not seem to have practical value at present.

**PERSISTENT MANIFESTATIONS OF POISONING**

Poisoning by organophosphorus insecticides is an acute process, but there have been occasional reports of persistent manifestations.

**Polyneuropathy**

Polyneuropathy may be a persistent manifestation of organophosphorus insecticides, since some non-insecticide organophosphorus compounds cause this condition. For example, tri-o-tolyl phosphate caused an outbreak of "Ginger Jake" paralysis in the USA in 1930 and 1931 and one of polyneuropathy in Morocco in 1959 in which thousands of people were poisoned by food contaminated with this compound. The use of mipafox as an insecticide was
abandoned after neuropathy occurred among workers in a pilot plant. In animal experiments persistent neuropathy has been caused by triaryl phosphates, S,S,S-tributyl phosphorotrithioite, diisopropyl phosphorofluoridate, and mipafox, none of which is used as an insecticide, and by the insecticide Dursban,† while Chlorthion,† demeton, diazinon, dichlorvos, parathion, paraoxon, and trichlorfon did not produce paralysis (Namba et al., 1971). The development of neuropathy is not related to the inhibition of cholinesterase, and is not prevented by the administration of pralidoxime or atropine. A possible cause may be the inhibition of other as yet unidentified esterases.

The present author has not found neuropathy among patients with acute poisoning by organophosphorus insecticides. One patient with peripheral neuropathy was exposed to non-insecticide organophosphorus compounds and their intermediates, which were synthesized in a research laboratory (Namba et al., 1971). No neuropathy was found during a 5-year follow-up of 398 workers who were exposed to organophosphorus insecticides, 108 of whom had had acute poisoning (Kovarik & Sercle, 1966). In the literature there are reports of only 7 patients who developed neuropathy that might have been caused by these insecticides: 3 patients had been exposed to trichlorfon, 2 to parathion, 1 to parathion, EPN,† and other insecticides, and 1 to malathion (Namba et al., 1971; Humperdinck, 1951; Šutov & Varanhiva, 1969).

CNS manifestations

Persistent central nervous system manifestations were first reported to include impaired memory, depression, impaired mental concentration, schizophrenic reaction, and instability, lasting for 6-12 months in 16 subjects who had been exposed to organophosphorus insecticides for 18 months to 10 years (Gershon & Shaw, 1961). However, an epidemiological study showed that admissions to mental institutions in areas where organophosphorus insecticides were widely used were no greater than in areas where they were little used (Stoller et al., 1965). There have been many reports of mental or behavioural changes, but most of these symptoms are transitory or are caused by non-insecticide organophosphorus compounds (Namba et al., 1971).

Liver function

There have been isolated reports of patients with increased serum bilirubin or abnormal liver function, and with histological abnormalities of liver structure with oedema or mild degeneration of parenchymal cells, hyperaemia, fat infiltration, or lymphoid-cell infiltration in liver obtained post-mortem or by biopsy. One month after 70 persons had suffered acute parathion poisoning, jaundice occurred in 4.3% of the patients, liver enlargement in 14.3%, increased urinary urobilinogen in 30%, and a positive serum Takata reaction in 17.1% (Maruyama, 1954). Of 12 patients with acute poisoning by parathion or other organophosphorus insecticides, 8 showed abnormal results of liver function tests (Lutterotti, 1961). However, our patients with acute poisoning showed normal results of liver function tests throughout the period of observation, except for increased urinary urobilinogen limited to the first day of acute poisoning, and persistent liver enlargement in one patient (Namba et al., 1971). A similar finding was reported in 15 patients who had been exposed 5 or more times to organophosphorus compounds during a 2-year period (Kauulla & Holmes, 1961).

Other effects

Other possible persistent effects of organophosphorus insecticides included changes in coagulation factors, effects on the fetus, dermatitis, stomatitis, bronchial asthma, and impotence (Namba et al., 1971). The number of reported patients is small, and no relationship between cause and effect has been established.

REFERENCES

Bisa, K., et al. (1964) Arzneimittel-Forsch., 14, 85-88
Boelcke, G., et al. (1970a) Dtsch. med. Wschr., 95, 1175-1178
Boffey, P. M. (1968) Science, 162, 1460-1464
Latent poisoning: no clinical manifestations

**Diagnosis:** depends on the estimation of serum cholinesterase activity, which is inhibited but is more than 50% of normal.

**Treatment:** unnecessary, but the patient should be observed for at least 6 hours, since poisoning may progress.

**Prognosis:** good.

Moderate poisoning: the patient cannot walk

**Diagnosis:** the patient shows generalized weakness, difficulty in talking, muscular fasciculations, miosis, and the signs listed under *Mild poisoning* above. The serum cholinesterase activity is 10–20% of the normal value.

**Treatment:** pralidoxime 1 g intravenously; atropine sulfate 1 mg subcutaneously.

**Prognosis:** good.

Mild poisoning: the patient can walk

**Diagnosis:** the patient shows fatigue, headache, dizziness, numbness of the extremities, nausea and vomiting, excessive sweating and salivation, tightness in the chest, abdominal cramps, diarrhoea. The serum cholinesterase activity is 20–50% of the normal value.

**Treatment:** pralidoxime 1 g intravenously; atropine sulfate 1–2 mg intravenously every 20–30 minutes until the signs of atropinization appear (dryness in mouth and nose, flush, and mydriasis).

**Prognosis:** recovery if treatment is given; without treatment, the condition may advance to severe poisoning.

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* Reproduced, in modified form, from Namba et al. (1971) by permission of the publisher. Compiled principally from experience with cases of poisoning by parathion and parathion-methyl. The dosages listed are for adults.
Severe poisoning: the patient is unconscious

Diagnosis: the patient shows marked miosis and loss of pupillary reflex to light, muscular fasciculations, cramp, flaccid paralysis, moist rales in the lungs, respiratory difficulty, secretions from the mouth and nose, cyanosis. The serum cholinesterase activity is less than 10% of the normal value.

Treatment: pralidoxime 1 g intravenously. If there is no improvement, an additional intravenous injection of 1 g. If these injections are not followed by improvement, intravenous infusion of pralidoxime at rates up to 0.5 g per hour. Atropine sulfate 5 mg intravenously every 20–30 minutes until the signs of atropinization appear.

Prognosis: Fatal if not treated.

Other therapeutic measures

(1) Maintenance of respiration by securing open airway by means of oropharyngobronchial suction and endotracheal tube; assistance of respiration by means of respirator, if necessary, using oxygen.

(2) Removal of organophosphorus compound (removal of clothing, washing of the skin and conjunctivae, gastric lavage).

(3) Other supportive measures, including:
   (a) intravenous fluids,
   (b) antibiotics if pulmonary infection is present,
   (c) diphenylhydantoin and other anticonvulsants if convulsions are not relieved by atropine and pralidoxime.

DISCUSSION

BOOTH: Can you consistently correlate or measure accurately either synaptic or nonsynaptic cholinesterase inhibition in man with the symptoms of poisoning? Or is a combination of the two types of inhibition perhaps involved?

NAMBA: It is not practicable to measure synaptic cholinesterase. In fatal cases in man, in which blood cholinesterase activity was almost zero, a marked decrease of cholinesterase activity was detected in the brain.