in combination with atropine, speedily reverses symptoms of poisoning and reactivates phosphorylated acetylcholinesterase. When residual Parathion is left in the body after the concentration of P-2-AM has fallen below effective levels symptoms and phosphorylation return and no reactivation or improvement occurs when the phosphorylated acetylcholinesterase is of the aged type.

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Physiological and Clinical Effects of Organophosphorus Compounds

by W S S Ladell MB MRCS LRCP (*Salisbury*)

The physiological effects of acute anticholinesterase poisoning are believed to be entirely due to the accumulation of acetylcholine (Holmes 1953). These effects are seen at three main sites: (*a*) At neuromuscular junctions where transient overstimulation of the muscles is followed by paralysis. (*b*) In the brain where synaptic transmission involving acetylcholine is interrupted. This is particularly important in the respiratory centre. (*c*) In the autonomic nervous system where ganglionic transmission is paralysed and cholinergic nerve endings are over-stimulated.

The effects at (*a*) and (*b*) are lethal as they lead to asphyxia; the autonomic effects are not lethal in themselves but are the source of most of the signs and symptoms, e.g. bronchoconstriction, salivation and sweating.

In sublethal poisoning both primary and secondary effects can be distinguished. The secondary effects are those associated with prolonged cerebral anoxia and may be seen in animals or men after recovery from severe poisoning. Sublethal poisoning, even without acute symptoms, may lead to delayed changes in the central nervous system with degeneration of myelinated nerve fibres in certain long nerves and spinal tracts and the later development in man and other susceptible species of the syndrome known as 'ginger paralysis', or 'organophosphorus neurotoxicity'. There is some evidence that this is not a direct anticholinesterase effect (Davies *et al.* 1960).

Animals given repeated small doses over a period of weeks may develop neurotoxicity as the small doses are cumulative. Other than this there is no recognizable chronic toxicity; true anticholinesterase effects are believed to be always acute. On the other hand with repeated small doses of anticholinesterase at frequent intervals the blood, and presumably the brain cholinesterase, falls lower and lower so that the dose of anticholinesterases required to precipitate acute poisoning becomes progressively less. With this type of poisoning inhibited cholinesterase is partly replaced and partly reactivated, and the agent itself is metabolized and excreted. Animal experiments show that as much as one-third of an LD50 of certain anticholinesterases may be absorbed daily without deleterious effects.

The signs and symptoms of acute poisoning in the early stages vary with the route of entry. With the respiratory route there is bronchoconstriction, felt as a tightness in the chest, salivation and rhinorrhœa; salivation is also seen in the late stages in animals when it becomes very marked. If the eyes are exposed to an anticholinesterase vapour or become contaminated with spray or aerosol there is acute miosis; very slight traces of an anticholinesterase will produce miosis locally in this way, e.g. in the case of Sarin, exposure to 0·33 mg/cu.m for 15 minutes. In systemic poisoning, however, miosis only occurs with gross intoxication and is almost an indication that a lethal dose has been absorbed. Skin contamination may result in local fasciculation and sweating, but these signs also do not appear in systemic poisoning until late. Gastro-intestinal cramps, with defæcation, occur early with oral administration, but otherwise are indicative of severe poisoning with the absorption of a substantial fraction of a lethal dose; convulsive emptying of the bladder is also a late sign. Cardiac slowing occurs and is especially marked with the intravenous route of administration.

True clinical convulsions are not invariably seen. In animals convulsions tend to be limited and may in part be anoxic in origin. A large animal given a lethal dose of anticholinesterase gradually becomes unsteady on its feet, then gently keels over, gives a few convulsive jerks and stops breathing; a few spasmodic efforts of breathing may take place before death and there is a copious flow of saliva. At this stage the pupils will be closely constricted, and urine and fæces may be passed. The course of death in untreated anticholinesterase poisoning in man has rarely been described; in insecticide accidents men have either been found dead or *in extremis* or else they

have been picked up with early symptoms and been treated, when the clinical picture becomes distorted. There is no direct correlation between the cholinesterase depression in the blood and signs or symptoms; in general 85% or more of the red cell cholinesterase may be inhibited before there are any overt indications of poisoning. At a slightly lower degree of inhibition some men develop a general malaise and desire to stay quiet and rest, but this malaise can be overcome and men poisoned to this extent can still remain active and carry out normal routines. At about 90% depression gastro-intestinal symptoms may intervene. The relation between the dose required to give 50% cholinesterase inhibition in the blood and the LD50 varies with different agents and with different species. It may be as little as 1: 4 or as great as 1:16, but in no case does death occur until there is virtually complete inhibition of the blood cholinesterase and in general there is no cause for anxiety if the blood cholinesterase level does not fall to less than 25% of its normal value. Nevertheless spontaneous reactivation of the blood cholinesterase does occur and there are recorded cases of proved death by anticholinesterase poisoning, e.g. by Parathion, in which the cholinesterase level in the blood after death has been quite high; this suggests that brain cholinesterase may be reactivated more slowly than blood cholinesterase. There is also some suggestion, however, that with repeated minor exposures symptoms may occur at slightly higher cholinesterase levels (Holmes & Gaon 1956).

The cause of death in man is anoxia, but in warm climates there is an additional hazard as the heat regulating centre may also be put out of action and there may be alarming rises in the body temperature, to heat stroke levels. Artificial respiration may not therefore be enough to keep a casualty alive; he may die, or suffer irreparable damage, from hyperpyrexia.

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The Use of Organophosphorus Compounds in Veterinary Medicine

by S B Kendall PhD MRCVS (*Weybridge*)

At present the number of organophosphorus compounds in veterinary medicine is limited but there is every reason to believe that a wide range will become available. These compounds vary greatly in physical and biological properties, and especially in stability, solubility and mode of action *in vivo* (Spencer & O'Brien 1957). Some are contact poisons while others act systemically after absorption from gut, dermis or mucous membrane, in some cases after alteration in the body.

Available Organophosphorus Compounds

Among the compounds used in veterinary medicine are:

(1) *Neguvon* (Bayer 13/59; Dipterex Chlorophos)
0,0, dimethyl-l-hydroxy-2-trichlorethyl phosphonate

(2) *Ruelene:* (Dowco 132)
0-(4 tert. butyl 2 chlorophenyl)-0-methyl methylphosphoramidate

(3) *Asuntol:* (Bayer 21/199: Muscatox Coumaphos: Co-Ral)
0,0-diethyl 0-3 chloro-4-methyl umbelliferyl phosphorothioate

(4) *Delnav:* (Bercotox)
2 : 3-dioxane dithiol-S-bis (0,0-diethyl dithiophosphonate)

(5) *Diazinon:*
0,0 diethyl 0-(2-isopropyl-4-methyl-6-pyrimidyl) phosphorothioate

(6) *Etrolene:* (Dow ET-57, Ronnel, Trolene)
0,0 dimethyl 0-2, 4, 5-trichlorphenyl phosphorothioate

For convenience these substances are referred to below by their proprietary names.

Acaricides

Organophosphorus compounds have been used in several countries for the control of ticks but a small experiment carried out at Weybridge by my colleague Mr W N Beesley, has not confirmed the reports of the efficiency of Etrolene against sheep scab mite (*Psoroptes communis ovis*).

As acaricides, the organophosphorus compounds have the advantage of being stable in dip tanks and some have a long residual effect when on the hair or skin of cattle. Larvæ of boophilus were killed twenty-eight days after a spray application of Asuntol (Harbour 1960, personal communication). Neguvon, by contrast, although its effect on ticks may be more rapid, has little residual effect. Wood *et al.* (1960) showed that 0·1% Delnav gave five to six weeks protection against *Ixodes ricinus* (the only economically important tick in Britain). As the major period of activity of *I. ricinus* is for a few weeks only in March–May, a Delnav dip in late March or early May just before lambing should substantially protect against serious infestation.

Delnav has been successfully used in Australia, the U.S.A. and in East and South Africa for tick control, and in South Africa Delnav has been found effective against strains of boophilus resistant to Toxaphene and to chlorinated hydrocarbons.