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THE HEALTH HAZARD ASSOCIATED WHITH THE USE OF INSECTICIDES FOR VECTOR CONTROL

Riassunto. — L'insetticida ideale sarebbe quello tossico solo per gli insetti, ma lo stato attuale delle nostre conoscenze non ci permette di dire come lo si potrà trovare. Scoperte dovute al caso sono sempre possibili. L'assenza di rischio di tossicità di un composto dipende evidentemente dall'ingegnosità dei chimici, la quale potrà esercitarsi sempre più efficacemente a misura che i biologi conosceranno meglio il meccanismo d'azione dei veleni. Sarà sempre temerario anticipare un giudizio sulla tossicità basandosi sulla struttura chimica di un corpo. Le prove su animali daranno indicazioni, ma non forniranno mai una risposta definitiva. Si potrà sempre trovare sorprese sgradevoli.

Il TDE apparentemente inoffensivo, distrugge nel cane la corteccia surrenale indispensabile alla vita; alcuni insetticidi organo-fosforati distruggono il sistema nervoso del pollame e dell'uomo. Sono forse questi casi eccezionali, ma un nuovo composto, da cui ci si aspetterebbe molto, acquisterebbe ingiustamente una cattiva fama se lo si introducesse e manipolasse senza precauzioni iniziali presumendo che sia inoffensivo unicamente per via del risultato di prove sull'animale. Bisogna sempre mostrarsi molto prudenti quando si espone l'uomo a nuovi prodotti chimici che si sanno tossici per certe forme viventi, a meno che sia imperiosamente necessario, per salvare delle vite, rischiare la vita di alcuni individui.

La lotta contro gli insetti i cui effetti sono meno distruttori di quelli della zanzara Anophele, richiede una maggior cura della salute degli uomini esposti al prodotto utilizzato a questo fine.

Gli insetticidi più tossici possono essere manipolati con sicurezza se ci si circonda delle necessarie precauzioni, ma ricorrendovi si rischia di aumentare il costo dei prodotti a tal punto da renderli inutilizzabili. Sembra che vi sia una grave lacuna negli studi dell'igiene dell'ambiente

per ciò che concerne l'applicazione degli insetticidi. Si è certo studiata l'efficacia degli spruzzamenti, ma non dal punto di vista del rischio che possono provocare le particelle trascinate dall'aria. Questa indicazione dovrebbe figurare fra le caratteristiche degli apparecchi. Più le gocce sono grandi e più cadono presto con la conseguenza che ci si protegge più efficacemente coprendosi il viso con un semplice velo. Bisognerebbe studiare l'importanza della contaminazione attraverso i vestiti e attraverso la pelle per mezzo di soluzioni colorate e prospettare le misure di precauzione semplici permettendo di eliminare questo rischio per quanto sia possibile. Fintanto che non si avranno conoscenze più precise su questa questione, sarà difficile preconizzare l'uso di prodotti che implicano notoriamente il rischio certo di intossicazione acuta, a meno che questo rischio sia controbilanciato da benefici incontestabili per la salute dell'uomo.

Résumé. — L'insecticide idéal est celui qui ne serait toxique que pour les insectes, mais l'état actuel de nos connaissances ne nous permet pas de dire comment on pourra le trouver. Des découvertes dues au hasard sont toujours possibles. L'absence de risque de toxicité d'un composé dépend évidemment de l'ingéniosité des chimistes qui pourra s'exercer de plus en plus efficacement à mesure que les biologistes connaîtront mieux le mode d'action des poisons. Il sera toujours téméraire de prédire une certaine toxicité d'après la structure chimique d'un corps. Les expériences sur les animaux donneront des indications mais ne fourniront jamais une réponse définitive. On peut toujours avoir des surprises désagréables. Le TDE, apparemment inoffensif, détruit chez le chien le cortex surrénal indispensable à la vie; certains insecticides organophosphorés détruisent le système nerveux des volailles et de l'homme. Ce sont là peut-être des cas exceptionnels, mais un nouveau composé dont on attendrait beaucoup risquerait d'acquérir à tort une fâcheuse réputation si on l'introduisait et le maniait sans précautions initiales en le présumant inoffensif uniquement d'après les épreuves sur les animaux. Il faut toujours se montrer très prudent en exposant l'homme à des nouveaux produits chimiques dont on sait qu'ils sont toxiques pour certaines formes vivantes, à moins qu'il ne soit impérieusement nécessaire, pour sauver des vies, de risquer la vie de quelques individus. La lutte contre les insectes dont les effets sont moins dévastateurs que ceux du moustique anophèle, demande un plus grand souci de la santé des hommes exposés au produit utilisé à cette fin.

Les insecticides les plus toxiques peuvent être maniés avec sécurité

si l'on s'entoure des précautions voulues, mais en y recourant on risque d'augmenter le coût des produits au point de les rendre inutilisables.

Il semble y avoir une grave lacune, dans les études de l'hygiène du milieu, en ce qui concerne l'application des insecticides. On a certes étudié l'efficacité des pulvérisations, mais non pas au point de vue du risque que peuvent provoquer les particules entraînées par l'air. Cette indication devrait figurer dans les caractéristiques des appareils. Plus les gouttes sont grandes, plus elles tombent vite et plus on peut se protéger efficacement en se couvrant le visage d'un simple voile. Il faudrait étudier l'importance de la contamination par l'intermédiaire des vêtements et de la peau au moyen de solutions colorées et envisager des mesures de précaution simples permettant d'éliminer ce risque dans toute la mesure du possible. Tant qu'on n'aura pas de connaissances plus précises sur cette question, il sera difficile de préconiser l'emploi de produits qui impliquent notoirement un risque certain d'intoxication aigüe, à moins que ce risque ne soit contre-balancé par des bénéfices incontestables pour la santé de l'homme.

Summary. — The ideal insecticide would be poisonous only to insects but knowledge is not at a stage where its design can be foreseen. Chance discoveries are always possible. The hazard from the toxicity of the compound clearly depends on the chemist's ingenuity which may be applied more and more effectively as the biologist learns more about the ways in which poisons operate. It will always be hazardous to forecast toxicity from chemical structure. Animal tests will supply a guide but never the final answer. There is always the possibility of an unpleasant surprise. The apparently harmless material TDE destroys the vital adrenal cortex of dogs; some organo-phosphorus insecticides destroy nerve tracts in fowls and man. These are perhaps exceptional cases, but a new and promising compound might acquire an undeservedly bad name if it was first introduced and handled carelessly on the assumption, based only on animal tests, that it would prove harmless. The exposure of men to new chemicals known to be toxic to some forms of life should always be started cautiously unless the need for such use is so great to save life, that the lives of a few may be risked with more justification. The control of the insect pests less devastating in their effects than the anopheles mosquito demands greater care of the health of the men exposed during such control.

The most poisonous materials may be handled with safety if the proper precautions are used, but their use may so enhance the cost that the procedure becomes impracticable.

There seems to be a great lack of environmental hygiene studies in the application of pesticides. The efficacy of sprays has been studied but not in relation to the hazard from airborne particles they may produce. This should be included in specifications for apparatus. The larger the drops the sooner they fall and the more adequate is protection by a simple face shield. The extent of clothing and skin contamination should be studied by using dyed solutions, and simple precautionary measures devised to eliminate this as far as possible. Until more is known about this it will be difficult to recommend the use of materials known to carry a definite risk of acute poisoning unless these risks can be balanced by unquestionable benefit to human health.

Zusammenfassung. — Das ideale Insektizide sollte eigentlich der sein, der nur gegen Insekten giftig ist, aber unsere bisherige Kentnisse gestatten uns nicht zu sagen, wie man es finden kann. Zufällige Entdeckungen sind doch immer möglich.

Die Abwesenheit von toxischen Wagnisse einer Verbindung hängt offenbar von den sachsverständigen Chemiker, die sich mehr und mehr erfolgreich daran schrittweise widmen, je besser die Biologen gleichzeitig die Wirkungsweise der Giften kennen werden. Es wird immer zu gewagt sein, eine gewisse Giftigkeit nach der chemischen Struktur eines Körpers voraus zu sagen.

Nachweise auf Tiere können wohl einige Andeutungen geben, doch werden sie niemals eine endgültige Antwort verschaffen: sie könnten immer einige unangenehmen Uberraschungen bereiten. TDE, der scheinbar unschädlich ist, zerstört beim Hunde die Kortex surrenalis, die für das Leben unentbehrlich ist; einige Organo-Phosphor Insektiziden zerstören das Nervensystem der Geflügel und der Menschen. Wahrscheinlich handelt es sich um Ausnahmsfällen, aber ein neues Präparat könnte mit Unrecht einen ganz falschen Ruhm erhalten, wenn man es ohne vorherige Fürsorge einführen und behandeln würde bei der Vermutung dass es unschädlich ist und zwar nur auf Grund der auf Tiere beobachteten Nachweisen.

Falls es nicht durchaus nötig ist, das Leben einiger Individuen zu riskieren um andere Menschen zu retten, muss man immer sehr vorsichtig sein wenn man Menschen zu neuen chemischen Produkten aussetzt, vowon man imvorderein kennt dass sie für lebenden Wesen giftig sind. Die Bekämpfung gegen Insekten, dessen Wirkungen weniger schädlich als die der Anophelen sind, erfordert viel grössere Sorge für die Gesundheit der Menschen die dem, zu diesem Zweck verwendeten Produkt, ausgesetzt sind.

Die giftigsten Insektiziden können mit Sicherheit behandelt werden

wenn man die nötigen Vorbeugung in Anbetracht nimmt; folgt man aber diese Massnahmen, dann riskiert man die Kostpreisen der Stoffen zu sehr zu erhöhen bis sie unkäuflich werden.

In Rahmen der hygienischen Forschungen gibt es scheinbar wegen der Verstreuung der Insektiziden eine grosse Lücke. Natürlich ist die Wirkung der Besträuung studiert worden, aber nicht vom Standpunkt aus der Wagnis die die Luftgetriebenen Teilchen hervorrufen können. Diese Anweisung sollte mit der Beschreibung der Eigenschaften der Geräte ausgeliefert werden. Um so grösser die Tropfen, um so schneller fallen sie hinunter und um so mehr kann man sich wirkungsvoll schützen indem man das Gesicht mit einem einfachen Schleier bedeckt. Man müsste die Bedeutung der Kontamination durch die Kleider und der Haut studieren, und zwar mittelst gefärbter Lösungen und anderer einfachen vorbeugenden Massnahmen damit die Wagnis soviel wie möglich abgeseitigt sei. Soweit man keine genauere Kenntnisse über diese Frage besitzt, wird es schwer sein, die Anwendung von Präparate vorauszusagen die bekanntlich ein bestimmtes, scharfes Intoxikations-Risiko darstellt, wenigstens wenn das Gleichgewicht dieses Wagnis nicht durch unbestreibaren Vorteilen für die Gesundheit der Menschen ausgeglichen wird.

The use of new materials or new uses for existing materials in insect control creates a demand for some information about the dangers to the health of those applying or coming into contact with the applied materials. It is a situation calling for a considered judgment on the merits of any particular case. There is always a need to keep in proper perspective the balance between the real benefits derived from the use of an insecticide and the risks run by those, other than the insects, who come into contact with them.

The risks may be real or hypothetical and it should be possible to control the real hazard and reduce the hypothetical ones by a proper application of information which may exist already or can be acquired.

This paper starts by defining and pointing out the information that is needed before the hazard can be assessed. It summarizes existing information and indicates where this is deficient. In some cases the defects can be remedied; in others they may be reduced but problably never completely eliminated.

Definition of hazard

The health hazard incurred by an individual working with an insecticide, or any other chemical, will be determined by:

(a) The exposure

(b) The toxicity of the material.

(a) The exposure will determine the « dose » absorbed, and the dose should always be considered as being made up of the amount and the time during which that amount was absorbed, e g., ct = concentration × time of exposure.

It would be generally accepted that any chemical is non-toxic if the dose administered is small enough but the size of the dose that can be safely ingested during continuous or intermittent exposure will depend very much on the toxic properties of the substance. These may be related to the persistence of the substance itself in the body or the persistence of the effects it produces.

The route of administration may also affect the size of a dose that may be safey given. Absorption through the lungs of vapour or particles may be the equivalent of an intravenous injection in that toxic material is rapidly carried to all the tissues of the body. To reach the alveoli of the lungs particles of unit density must be less than 5 microns and greater than 0.1 microns in diameter ([32]). Larger particles are trapped in the upper respiratory tract and eventually swallowed.

Absorption from the gut is probably the commonest route and may result from inhalation of large particles or by incidental contamination of the hands and thence food, cigarettes etc. Absorption is slower than by inhalation though a larger single dose may be received. The absorbed material passes first through the liver before being distributed to the other tissues. This may injure the liver or lead to destruction of the material or do both.

Absorption through the skin is quite common especially when substances are soluble in fats or are dissolved in fat solvents. Absorption is relatively slow, but the material might be held up in the skin and subcutaneous fat and released over long periods. When a material does not irritate the skin, it is easy for gross contamination to take place and persistent soaking of the clothes may be disregarded after accidental spills.

(b) Toxicity of the material: This is usually expressed in the simplest form as the lethal dose for laboratory animals, and this is

commonly expressed as the LD50 or dose that will kill 50 per cent of animals receiving it.

If the margin of safety is small, it is obvious that the toxicity of preparations should not vary widely. Reasonable constancy of composition and freedom from much more poisonous impurities should be insisted on in specifications.

The toxicity of a substance may be determined to some extent by the site of its action. Those acting on the heart or respiration or the vital centres in the brain are likely to be dramatic in their effects and rapidly fatal. Those injuring the central nervous system — brain and spinal cord — are liable to produce irremediable damage and lead to permanent crippling disabilities. Those which destroy the liver, lungs and kidneys may produce very considerable damage to these organs, before their effects are noticed, for the healthy animal may be deprived of over 50 per cent of these organs without suffering a fatal injury.

The speed with which a compound acts may be related to its chemical reactivity and probably to its stability. Delay in the onset of signs of poisoning may in some cases be accounted for by the fact that the chemical only becomes poisonous after it has been absorbed and altered by the metabolic processes of the body. The duration of toxic effects may be related to the persistence of the toxic material itself in the animal body or to the persistence of the effects it has produced. These may be chemical, as in the case of the inhibition of an enzyme and the reversal of this action, or structural, where tissue injury has been followed by scarring and fibrous tissue replacement, as in liver cirrhosis.

An attempt will now be made to consider insecticides suitable for vector control in the contexts just described. They will be considered in two groups.

1. The chlorinated hydrocarbon insecticides e.g. DDT, BHC, aldrin, dieldrin, chlordane.

2. The organo-phosphorus insecticides e.g. TEPP, parathion, malathon, diazinon.

1. *Chlorinated hydrocarbon group.*

In spite of the very large quantities of insecticides in this group that have been applied as fine sprays in or out of buildings, there seem to be little data on the sizes or concentrations of airborne particles to which those applying the materials have been exposed. Early experience

with DDT indicated that it could be applied safely under these conditions so that an urgent need for this kind of information never arose.

Men applying DDT in this way often had extensive skin contamination by a variety of solutions, suspensions or emulsion of DDT. No measurements have been made of the amount that could be recovered from the skins of these operators after they had finished work. No measurements have been made of the ability of such materials to penetrate human skin. There should be no great difficulty in getting some estimate of this by measuring the rate of disappearance of DDT from the skin. The absorption from different formulations could be studied.

It is apparent that from one aspect, namely exposure and dose, there is little information about this group of insecticides.

There is a considerable amount of information on their toxicity, but there are some very important gaps in this information. Given by mouth to rats in solutions in edible oil, the acute single lethal dose of methoxychlor and TDE exceeds 2g per kilo, that of chlordane, lindane, DDT and toxaphene is around 250 mg per kilo while that of aldrin and dieldrin around 50 mg per kilo. Thus there is a factor of about 40 in the difference between the least and the most toxic compound to rats. Where other species have been tested certain differences do appear, but only exceptionally are they striking. After a single dose by mouth signs of poisoning appear in about an hour and death after an average lethal dose usually takes place within 24 hours. With chlordane ([27]), and dieldrin ([23]) deaths delayed for several days do seem to occur more frequently than with DDT. If fractions of the lethal dose are given daily in oil it is not unusual for rats or rabbits to die before they have received an aggregate dose equal to the average single lethal dose. This might be due to poor absorption of the large single dose so that the effective dose was in fact much less than that administered. Or it may mean that the compound is rapidly destroyed and detoxified but that the effect produced before this is completed is only slowly reversed so that succeeding doses have a cumulative effect.

Applied in suitable solvents all these insecticides are absorbed through the intact skin of laboratory animals. The claim that aldrin and dieldrin are more toxic applied to the skin than when given by mouth may apply to rabbits ([35]) but certanly does not apply to rats ([44]).

There is nothing known about the mode of action of these compounds. Except for methoxychlor and TDE, all produce convulsions in laboratory animals and there is evidence of increased electrical activity of the brain ([14, 39]).Nevertheless a careful examination of the action

of DDT ([11]) on cats and other work on BHC ([25]) has suggested that the action may be peripheral, and that the central nervous system is upset by the abnormal responses reaching it from the periphery.

The convulsion produced by any of these compounds can be prevented by barbiturates. A claim has been made that aldrin acts as an inhibitor of cholinesterase ([21]). Though some of the pharmacological responses produced by aldrin in animals might suggest this, we have found no evidence of any depression of the cholinesterase activity on the brain or spinal cord of rats killed by aldrin ([44]).

On the liver large toxic doses of all but methoxychlor produce necrosis and fatty degeneration, but the animals die from the nervous effects, and not from the effects of liver damage.

Much has been said about the effects of small repeated doses of DDT on the liver of experimental animals ([33, 36]). There seems little doubt that there are histological differences between the livers of normal rats and those on diets containing DDT at 50 ppm. These are cytological differences between a small proportion of the cells of the whole organ. Enlargement of the liver is commonly seen in rats or dogs fed these insecticides but this is sometimes a simple hypertrophy which is the response of a healthy organ not that of a diseased organ. At higher doses more obvious fatty changes can be seen in the liver. In an experiment with aldrin we were impressed by the fact that marked damage of this kind could persist for a year in the liver of male rats without producing any of the signs of permanent injury of the organ e.g. fibrosis and scarring. These microscopical changes may therefore represent disturbances in function due to the presence of the insecticide or its metabolites rather than cell or tissue destruction.

Changes in the kidney of dogs have been described after toxaphene ([31]) and BHC ([15]) but renal function has not been assessed in animals receiving these compounds. The significance of the lesions has been disputed ([45]).

The molecule of DDT bears some similarity to that of stilboestrol and large doses have been said to produce oestrogenic effects in fowls which are on the whole less susceptible to DDT than mammals ([12]). It is also reported that DDT is stored in the lipoid of the ovary at concentrations greater than in the fat elsewhere ([48]). Disturbances in fertility have been reported in rats given diets containing DDT in otherwise non-toxic levels and the effect was carried through to the second generation ([18]). Aldrin has been reported as having an effect on the oestrus cycle of rats ([6]). The evidence that any of these compounds interferes

with reproduction in animals is not substantial, but the possible implications suggest a need for more work in this field.

Except for DDT little is known about the metabolism of these insecticides probably because of difficulties in estimating either the original compound or its possible metabolites.

DDT is fairly rapidly metabolised and a considerable part excreted, but it is also readily stored unchanged in the fat. What evidence there is suggests that few of the other compounds are stored as readily. This may be because they are so rapidly metabolised that time is not given for them to be carried away to fat deposits. Possibly they are stored partly or wholly as metabolites. The former seems to be the case with DDT ([43]) and the latter with heptachlor ([16]). A specific method of estimating aldrin exists and when added to tissue *in vitro* we have been able to recover aldrin. However, when aldrin was given to rats only traces may be detected outside the alimentary canal — even in animals dying in convulsions ([44]). No aldrin accumulated in the liver or fat of rats on a diet containing 50 ppm for 1 year ([44]). An insecticidal substance has been reported in the fat of animals receiving aldrin and the meat of sheep killed the dogs to which it was given ([29]).

Metabolism is probably carried out in the liver and in the case of methoxychlor this seems to be a detoxification. If this compound is given to rats that have had their liver damaged by carbon tetrachloride it will produce signs of poisoning typical of DDT, which are not seen in normal rats given methoxychlor ([34]). Our observations on aldrin suggest that it is a metabolite that is toxic. Toxaphene behaves like methoxychlor and TDE though it is much more toxic to dogs ([49]).

The level of insecticide in the diet necessary to produce obvious effects is about 600-800 ppm in the case of DDT and BHC, 300 ppm for chlordane, and 50-75 ppm for aldrin and dieldrin.

Though apparently innocuous to rats, TDE produces necrosis of the adrenal cortex in dogs ([41, 42]). This is an example of the unexpected that is not unusual in toxicity work.

There is an almost complete absence of histories of occupational poisoning by these compounds. A single fatal accident to a girl who spilt a chlordane concentrate over herself during manufacture indicates that a hazard exists ([23]). There is no authentic report of intoxication during the application of these materials. Nevertheless there have been accidents following the deliberate or accidental misuse of the compounds which suggest man is more susceptible to their action than the usual laboratory animals.

BHC given to treat oxyuriasis has produced convulsions in doses equivalent to a few mgms per kilo ([22]). DDT consumed in pastry where it had been added instead of baking powder produced acute gastro-intestinal disturbances ([38]). Larger doses produced limb weakness and disturbances of sensation in addition to these changes ([19]). A report from a rural area of Greece strongly suggested that BHC wrongly used in the homes for killing bedbugs led to an « epidemic » of poisoning with a few fatalities ([51]). Aldrin taken for suicidal purposes had a prolonged action lasting several days ([46]). The deliberate ingestion of DDT and BHC by human volunteers led to vague symptoms often with an associated diarrhoea at doses well below those upsetting laboratory animals ([30, 50]).

Gastro-intestinal disturbances seem to be prominent after swallowing these compounds and nervous effects are only seen after much larger doses or prolonged exposure, as in the Greek cases.

Despite the many experimental studies on this group of insecticides no clear picture has yet emerged of their point of attack in the body or of their fate within the body. It is, therefore, not possible to suggest biochemical or other clinical tests to apply to people who have been exposed to and may have absorbed these compounds.

2. *The Organo-phosphorus Insecticides.*

A number of these have been widely used in agriculture and their extreme effectiveness as insecticides leads to a consideration of their use for killing those insects that are or have become insensitive to the chlorinated hydrocarbon group. A number of accidents in the factories and fields has led to the development of a cautious attitude to their use in new fields and this applies also to any proposed use for the control of domestic pests.

Considering the hazard as before to be a combination of exposure and toxicity there is a little information on the exposure to some of these compounds. The air near orchard sprayers using parathion was found to contain 2-15 µg/litre by Canadian workers ([28]). In America the figures in orchards during spraying averaged only 0.09 µg/litre ([23]). In both cases the aerial concentration round mixing points where the concentrated dusts were handled was much higher. This had been observed in earlier work with lead arsenate ([40]). A few recent studies suggest that it is possible to prepare powders that can be handled without the production of so much dust ([23]). All these figures are for outdoor

work. Parathion has been used in Germany inside buildings without injury either to the operators or to those sleeping in the rooms the night after they had been sprayed. No figures for the aerial concentration are available but the particle size is said to have been in excess of 40 microns. No respirators were worn ([47]).

Those organo-phosphorus compounds that have been tested will readily penetrate the skin of animals and probably that of man. Data on the speed and amounts absorbed in this way are not available. It has been shown in animals that if parathion is prepared in a solvent that does not itself penetrate the skin but presumably retains the parathion, much less penetration of animal skin takes place ([17, 24]).

The little information available suggests that exposure by inhalation is probably slight during the application of sprays in the open but greater during mixing of concentrates. Some accidents have occurred to mixers but it seems more likely that most accidents have been the result of carelessness and a failure to apply simple precautions. On the other hand nothing is known about the dangers of using these materials in closed spaces, where vapour hazards might arise at high environmental temperatures.

The toxicity of the organo-phosphorus compounds used as insecticides varies greatly. The single oral dose of TEPP or paraoxon is 1 mg/kilo, parathion 10 mg/kilo, potosan 20 mg/kilo, malathon 400 mg/kilo. Signs of poisoning are similar and they come on rapidly. If the dose is just not lethal they disappear usually within 12 hours.

Those animal species tested have a similar susceptibility to these compounds. Sex differences to some have been observed in rats but not in other species.

There is general agreement that these compounds kill by interfering with respiration. This is a combination of constriction of the airways, interference with myoneural conduction in the respiratory muscles and a disturbance of the respiratory centre in the brain ([26]). The part played by each factor differs in the animal species and may differ from compound to compound. Atropine will counteract the action on the airways and to some extent the effect on the respiratory centre but does not modify the action on myoneural conduction.

Animals that have absorbed these compounds all suffer a reduction of the cholinesterase of their tissues and it is assumed that death results from an accumulation of acetylcholine, the effects of which can only be counteracted by atropine at certain points.

The lives of animals and in a few cases those of man ([5, 24]) have been

saved by artificial respiration which need only be continued for a relatively short period before natural breathing starts.

These compounds inhibit cholinesterase because they are attacked by the enzyme as if they were its natural substrate but only one product of hydrolysis can then separate from the enzyme. The cholinesterase becomes « phosphorylated » by the attachment of the phosphate group of the inhibitors ([2]). This complex does slowly reverse at a speed determined by the nature of the alkyl groups attached to the phosphorus. With one particular cholinesterase 50 per cent of reversal takes place in an hour or two at 37° where methyoxy groups are attached, after 2-3 days where there are ethoxy groups and not appreciably where they are isopropoxy groups ([4]). Those compounds containing a P=O bond e.g. paraoxon may be very active inhibitors of cholinesterase but where there is a P=S e.g. parathion the compound itself is a poor inhibitor but is changed in the body to P=O and then acts as an inhibitor ([3]). Those compounds that are direct inhibitors if they are very poisonous are also very unstable so that they act rapidly but for short periods. The length of time their effects persist will depend upon the structure of the phosphate group i.e. the alkyl groups attached which control the rate of reversal of the inhibited cholinesterase.

The P=S compounds are much more stable so that they can persist in the tissues before they gradually become oxidised and turned into inhibitors. This means their effects may be delayed in onset as has happened in some cases of parathion poisoning in man where symptoms have appeared after work. On the other hand if the effects on cholinesterase are also rapidly reversed by many methoxy groups attached to the phosphorus group, it may be difficult to build up an effective concentration of inhibitor in the body. This may explain why malathon is so relatively non-toxic to mammals ([20]). At present little is known about the effect of the acidic group attached to the phosphorus. Where this is simple e.g. fluorine, the compound is toxic and unstable. Some of the less toxic compounds have a more complex group. The behaviour of any given compound as an inhibitor seems to be determined to some extent by the resemblance it bears to the natural substrate of the cholinesterase it attacks. This is why some compounds attack pseudo-cholinesterase in preference to true cholinesterase ([1]). However, the cholinesterases of different species and tissues vary to some extent in their substrate patterns, so that inhibitory activity or reversal of inhibition with any compound must be worked out separately for any particular cholinesterase preparation.

All this suggests that it should not be difficult by the application of the published data on the behaviour of these inhibitors to design componds likely to have a more specific effect on insects and less hazardous to man. It will be necessary to know more about the metabolism of the insect, and cholinesterase preparations from man rather than animals should be used. Fortunately these enzymes are available in good concentrations in normal human blood.

This fact also makes it possible to estimate with considerable ease and confidence the absorption of these compounds in quantities below that producing symptoms ([7]). Much work has been done on blood cholinesterase estimations in man so that given a reasonable competence accurate assessment of exposure can be made ([13]). This should make it much easier to control the safe handling of these materials by regular operators. They can be removed from work if they show evidence of exposure.

It has also been possible to estimate the products of hydrolysis of the inhibitor in the urine of people exposed to parathion because there is a sensitive method for estimating p-nitrophenol ([37]). Similar tests might be done on other compounds if the products of hydrolysis are likely to be excreted unchanged or in a readily detectable form.

The long term administration of these compounds to animals has not led to the appearance of any unusual chronic toxic effects ([8]). It is surprising how healthy rats may appear even when their blood and tissue cholinesterase levels have remained depressed to 10 per cent of their usual activity for months on end ([44]).

There is, however, one serious complication that may follow acute poisoning by some organo-phosphorus compounds, namely demyelination of certain nerve tracts in the spinal cord with the production of permanent paralysis ([9, 10]). It has not proved possible to forecast from chemical structure those compounds that will produce these effects, but the fowl seems to share with man a sensitivity to this type of reaction and acute tests on the bird should be done with any new compound. Chronic feeding ([44]) tests do not produce paralysis in birds.

In conclusion it can be said that a greater insight into the action of the organo-phosphorus insecticides on mammals makes it possible to control the hazards of their use. Their toxicity may be reduced by an intelligent approach to the design of new compounds and it is possible to detect their ingestion by men before enough has been taken in to produce symptoms.

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