General Discussion—Session VIII

BARTHEL: I think that the group gathered here today includes the majority of those persons at present directly engaged in research on synthetic pyrethroids. It is interesting that the first publication on the chemistry of the pyrethrins and pyrethroids dates back to 1909 when Fugitani first reported his work, and that some men have thus devoted a large portion of their lives to this study.

What then is the future of these pyrethroids, and why has none of them become really significant in the pesticide industry? What changes can we expect in the future? May I refer to a paragraph that I wrote in 1963 for the Fifth Pesticide Congress in London: "The astonishingly low mammalian toxicity of these compounds, about 15 to 40 grams per kilogram of body weight against rats, has focused interest in their direction from a number of sources. It is expected that the increasing concern over insecticidal residues, particularly of chlorinated hydrocarbons, may bring about commercial exploitation." This commercial exploitation has not been forthcoming in the last 7 years, even though we have the amazingly effective 5-benzyl-3-furylmethyl chrysanthemate synthesized by Dr Michael Elliott. The toxicity of this compound for many insects compares very favourably with that of organophosphorus compounds having high toxicity for mammals. It has a relatively low toxicity for mammals, as have other synthetic chrysanthemates, it is readily metabolized, and it does not give rise to long-lasting residues.

In retrospect, one can see several factors that have defeated the synthetic pyrethroids. The work of Barthel and his colleagues that produced barthrin and dimethrin was carried out in a government laboratory and the compounds were patented in such a way as to make them available to all without licence. The cost of marketing a compound today is so tremendous that no company can undertake the necessary toxicological work without patent protection. These compounds, although highly effective and of low toxicity for mammals, were "killed" by the US public-use patent. Dr Elliott's compound is difficult to synthesize and commercial concerns may be reluctant to develop such a compound fully in view of the poor economic returns from other synthetic pyrethroids.

I think all this can be reversed, however. The cost of manufacture can be brought down and the toxicological work can be done; it can be done in a government laboratory if industry will not undertake it, because these compounds are of interest to the whole world. If there is interest in them as public health insecticides a simple request from someone in authority is all that would be necessary to get the work done. Once the compounds were being used in large quantities the cost of production should drop markedly. If a manufacturer did not have to bear the tremendous expense of the toxicological investigations he might be even more interested in putting the product on the market than if he had all the patent protection in the world, because he would be in a less hazardous marketing position: if the compound were to be banned to avoid contamination of the environment, he would not lose a million dollar investment.

What I wish to emphasize is that the synthetic pyrethroids have a very definite place in the fight against insects, but that they are denied this place not by their efficacy but rather by economics.

There is another way in which greater use of pyrethroids can be facilitated. While we have made tremendous strides in the introduction of new toxicants, we have done very little to improve formulations. Formulations could be developed that would release the insecticide slowly over a long period of time, yet we have done very little in this respect, except for the use of plastic strips with dichlorvos. Nature has shown us the way in this field. In the Mississippi Delta we collected pollen that had considerable residues of parathion 6–8 months after the last application of the insecticide. The residue amounted to several parts per million and could not have been much higher at any time or it would have caused high mortality among the bees. Apparently the waxes and oils in the pollen protected the parathion from natural degradation.

Certain algae were also found to concentrate parathion from water by a factor of 10 million and they then preserved this residue for 6–8 months. These algae also had a measurable wax content and apparently some of the parathion dissolved in it. Regardless of what actually took place we know that highly fugitive pesticides such as parathion can be made persistent.

I think we should try to discover whether pesti-

cides such as the pyrethroids can be formulated so that they will be protected from degradation and at the same time kill insects. I would not be surprised to find that in investigating such formulations it would be possible to increase the efficiency of the insecticide and thus lower the cost.

METABOLISM OF PYRETHROIDS

HOLMSTEDT: With reference to the studies conducted by Dr Yamamoto with labelled pyrethroids in rats, does he have any information about the metabolism of these substances in man? In drug work there is often a great difference between the rat and man.

YAMAMOTO: No, although the low toxicity of pyrethroids for mammals will make it possible to carry out such studies.

BARNES: Is it possible to explain the low toxicity of pyrethroids for mammals on the basis of the speed with which they are metabolized by the liver mixed-function oxidase system? It seems rather improbable that this could account for such large differences unless the rate of absorption from the gut is very slow. Is it possible that the same reaction that accounts for photodecomposition could take place in the mammal and not in the insect?

ELLIOTT: During 1969 I was involved at Berkeley in studies of the metabolism of pyrethrins I and II in the rat. These were preliminary studies designed to provide information where none was previously available. Therefore, the doses used were much greater than those that would be encountered in practice, to make it possible to isolate at least some products for spectroscopic identification; it did not seem practicable to attempt to synthesize possible metabolites of these esters when so many products seemed possible. Even with total doses of 1–3 g per rat, only 3 mg of some metabolites was obtained. However, now that we have some idea of the probable structures to be expected, the foundation has been laid for further work.

YAMAMOTO: Only a portion of pyrethrins I and II is excreted unchanged in the faeces; the rest is extensively metabolized. Therefore, metabolism seems to be a principal factor in low toxicity. Metabolism in insects principally involves modification of the acid moiety, whereas metabolism in mammals and photodegradation involve extensive modification of both acid and alcohol moieties.

HAYES: Do mammalian digestive enzymes metabolize these compounds?

YAMAMOTO: No direct answer is available. The methoxycarbonyl group of pyrethrin II may be hydrolysed, but all the metabolites of pyrethrin I, pyrethrin II, and allethrin that have been characterized from urine and faeces are esters—with the single exception that small amounts of chrysanthemum dicarboxylic acid are sometimes detected in urine. Therefore, hydrolysing enzymes have little if any effect.

METCALF: Do you have any information on the stability of synthetic pyrethroids incorporating tetramethylcyclopropanecarboxylic esters of various alcohols as compared with the stability of similar esters with chrysanthemic and pyrethric acids? If the former are more stable, would they not be more suitable for use in residual sprays even if they are somewhat more toxic to vertebrates?

ELLIOTT: In general, esters of tetramethylcyclopropanecarboxylic acids are more stable than those of chrysanthemic acid. However, the principal instability in these esters still remains in the alcoholic part of the molecule, either the cyclopentenolone or the furan ring.

DEVELOPMENT OF RESISTANCE TO PYRETHROIDS

HOLLINGWORTH: I wonder if anyone would discuss the potential for the development of resistance to pyrethroids by insects. If microsomal oxidases are responsible for degradation in houseflies, enhanced levels of this system already exist in resistant strains. Furthermore, in *kdr*-type resistance, in which " nerve insensitivity " is suggested as the basis for DDT-resistance, cross-resistance to pyre-

throids is seen. Does the existence of such genes in some current resistant populations suggest that resistance to pyrethroids may develop rapidly if their usage is widened?

ELLIOTT: In the insecticides department at Rothamsted Experimental Station, Andrew Farnham is studying the development of resistance by houseflies to the natural pyrethrins and to a number of synthetic pyrethroids; he has made considerable progress in separating the pure genetic strains for resistance to these compounds. As might have been predicted, the situation is complex; he has clarified and defined the problem and is now going on with a more detailed examination. An initial conclusion is that houseflies are less able to develop resistance to some of the synthetic pyrethroids than they are to the natural pyrethrins. However, when using the natural pyrethrins, it must be recognized that selection is being made with a mixture of six related esters. For the purposes of selection, pyrethrin I cannot be considered to exert the same action as pyrethrin II; neither can pyrethrin I and cinerin I be expected to undergo attack by detoxifying mechanisms in the same way. Any synergist, such as piperonyl butoxide, will complicate the situation. Consequently, interpretation is bound to be difficult and complex until results are available, as they will be, from selection with single compounds and pure optical isomers. Until then it is probably not profitable to speculate further on the mechanisms of the development of resistance.

OPPENOORTH: We have no personal experience of resistance to pyrethroids. From the literature it appears that both microsomal oxidation and *kdr*-type resistance contribute to resistance, and since the oxidation might be dealt with by synergists, the *kdr*-type is the more alarming. *Kdr* confers resistance to pyrethroids, DDT, and the compounds made by Mr Holan, which indicates that they indeed have something in common. Does Dr Elliott know whether this gene conveys resistance to many pyrethroids and, in particular, his synthetic compounds?

ELLIOTT: I believe that Andrew Farnham has found that *kdr*-type resistance mechanisms are involved with both natural pyrethrins and synthetic pyrethroids.

BIOLOGICAL ACTIVITY OF PYRETHROIDS AND DDT

NARAHASHI: I would strongly suggest that more pharmacological studies be carried out on the toxicity of pyrethroids for mammals. The factors that might be responsible for the selective toxicity of pyrethroids are as follows: (1) mammals may have specific degrading mechanisms that are lacking in insects; (2) owing to their higher body temperature mammals may be able to detoxify pyrethroids more quickly than insects; (3) owing to their larger body size, mammals may be able to detoxify pyrethroids before they can reach the site of action; (4) insects may have special target sites for pyrethroids that are lacking in mammals; and (5) the negative temperature correlation of nerve-blocking action of pyrethroids, which we reported, may contribute to the strong insecticidal action. If factor (5) were important, its study might open new ways of approaching the design of effective insecticides with low toxicity for mammals.

BARNES: The action of DDT has been described by Dr Narahashi as " holding open the sodium gate ". Does allethrin have exactly the same effect as DDT and, if so, is there any similarity in the molecular shapes of the two insecticides?

NARAHASHI: Despite the superficial similarity between DDT and pyrethroids in their actions on the nerve, I have strong reservations as to whether their mechanisms of action are similar at the membrane or molecular levels. Both pyrethroids and DDT can certainly produce repetitive excitation in the nerve, yet DDT never causes a conduction block, which can be observed with relatively high concentrations of pyrethroids. The effective concentrations of DDT and pyrethroids are also different. I feel that more data are necessary before we can draw conclusions on this problem.

HEILBRONN: Is anything known of the metal-ion-binding capacity (especially for Ca^{++}) of these compounds?

NARAHASHI: I do not not know whether pyrethroids bind with Ca^{++} *in vitro*. However, it is possible that pyrethroids exert effects on ionic permeability by disturbing the binding of Ca^{++} with the membrane phospholipid. Alternatively, pyrethroids may be bound with the protein components of the membrane.

HOLAN: There is a relationship between pyrethroids and DDT. We synthesized a DDT analogue,

1,1-bis(*p*-chlorophenyl)-2,2-dimethyl cyclopropane, that contains the cyclopropane moiety of pyrethrins. Neurophysiological impulse measurement at a salt receptor of the housefly shows that there is a relationship between the *initial* neurophysiological responses in houseflies to pyrethroids and those to the DDT analogue.

MAIN: Is any information available on the toxicity of pyrethrins for mammals by routes of administration other than the oral route?

ELLIOTT: Chevalier (*Bull. Sci. pharmacol. (Paris)*, 1930, **37**, 154) found the natural pyrethrins to be highly toxic to mammals when injected intravenously; an i.v. dose of 2 mg/kg caused symptoms in a dog and 6-8 mg/kg was lethal (cf. Winteringham, F. P. W. (1962) *J. roy. Soc. Arts*, **110**, 719).

ALDRIDGE: I have been fascinated by the scintillating steric chemistry that has been discussed here, but I am bothered by the statement by Dr Elliott that pyrethrins are highly toxic to mammals when injected. The synthesis of new pyrethrin analogues may produce compounds of higher toxicity for mammals. If the reason why pyrethrins are so nontoxic by the oral or dermal routes of administration were known, it might be possible to incorporate the necessary features in new molecules.

BARNES: The low oral toxicity of the pyrethrins may be accounted for by their inability to build up sufficiently high blood levels. DDT is highly toxic if given intravenously. On the general point of toxicity for mammals, we should not assume that we need pay less attention to the derivatives of natural products than to other types of insecticides.

HAYES: Commercial pyrethrins and dimethrin cause the same liver changes in rats as are produced by DDT. The effects are additive or moderately synergistic.

ALDRIDGE: The low oral toxicity of DDT in comparison with its intravenous toxicity is probably the result of low absorption and distribution into inaccessible areas. If there were any possibility that the nontoxicity of pyrethrins were the result of the molecule being degraded, then the degree of degradation might vary for each of the different structures now being synthesized.

HOBBIGER: If the low toxicity of orally administered pyrethroids in mammals is the result of their hydrolysis in the stomach, they might be highly toxic to persons suffering from achlorhydria.