ISRAEL JOURNAL OF ENTOMOLOGY VOLUME XI 1976

THE FUTURE OF INSECTICIDES - A PROBLEM OF HUMAN ENVIRONMENT*

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The civilised world is going at present through an anti-intellectual or rather an anti-scientific phase. It has accepted willingly and with pleasure the technological and social benefits of modern scientific research, but it has not been willing to accept that in fact we are going through a revolution which is bringing with it changes not less stringent than the first industrial revolution about 100 years ago. Moreover, the world is not willing to accept the fact that we are not always able to predict the changes that will occur in such a situation, in particular, whether these changes will be cumulative in nature.

This inevitable chain of cause and effect is made even more conspicuous by an amplifying mechanism which in itself has been generated by the revolution we are witnessing: the desire of the developing nations to reach the standard of living of the developed countries, and the ability of the Third World to obtain information on new ideas, processes and devices quickly and efficiently. This is of special significance with regard to the subject of our discussions, insect control, because the developing countries are situated in the tropical and sub-tropical zones in which the conditions for insect development are favourable and therefore the necessity for control is most urgent.

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* This paper was the Inaugural Lecture at the 2nd International IUPAC Congress of Pesticide Chemistry held in Tel-Aviv, 1971. It was published in 'Insecticides' (A.S. Tahori, Ed), 1972 and is reproduced by permission of the publishers : Gordon and Breach Science Publishers, New York, London, Paris.

The same uneasiness which is felt in the developing countries, exists in the developed countries themselves to the extent to which existing class differences or ethnic differences are accentuated by the progress of science and technology. It is this uneasiness which in my opinion is at the root of the anti-scientific sentiment with which we are confronted today: if not so much money had been spent on science and technology, the world would have been able to solve the human problems existing. I believe one has only to formulate this sentence in order to see how utterly unfounded it is. Surely it has not been a question of budget which has prevented our civilisation from dealing with the gap between the developed and the under-developed part of the world - in the national as well as in the international sense. I do not think this point is even arguable.

However, there is now a more serious argument which is used against science and scientists, namely that the ardor of discovery of the scientist and the greed of the industrialist are destroying the environment in which we are living, that the development of science and technology has disregarded the side-effects which are now threatening - so it is argued - the existence of humanity. We are told that the discoveries in the field of atomic energy have increased the radioactive background in the atmosphere and in our food, the antibiotics have led to the appearance of resistant bacteria against which we are helpless, the automobile industry and the industries of plastic materials and packaging are filling the countryside with wastage we do not know how to dispose of, and the insecticides have not so much controlled the insects as they have destroyed other forms of wild life and entered the foodchain of the human race. In fact, science and technology in our generation have upset criminally the natural ecological equilibrium.

This argumentation disregards one fundamental fact: there is no such thing as a defined environment, a natural ecological equilibrium, at least since the human race appeared on this planet. Everything it did, every invention it made, every step of its progress have changed the human environment. It has never been possible to predict what was going to happen, and in particular whether the changes in the long run would be for the better or not. It is impossible to assume that any change would be wholly good or wholly bad. It is the duty of the scientists and the planner to weigh the good and the bad against each other, to the extent to which he is capable of it. We have to recognise that this unfortunate limitation exists, and undoubtedly it puts on the scientist and the industrialist the heavy responsibility of updating constantly their knowledge on this point; but it would be foolish to draw the conclusion which has already been drawn from time to time - that the best we could do in order to preserve the environment, is to stop completely scientific inquiry and technological development, as it is foolish to think that - let me say - fifty years ago our environment was natural and pure and it has deteriorated through the unbridled efforts of the scientists in this generation.

There could not be a better example to demonstrate these points than the field of insecticides, because they are - directly or indirectly - related to two areas of importance to humanity, health and food production. It is equally true that the present level of malaria control would not be achievable without DDT (or in other words: that without the use of DDT one to two million people more would die of malaria every year), and that DDT has some side-effects, because its application entails (probably unavoidably) the contact with plants and animals other than insects which are either destroyed or pass the DDT into the food chain where it concentrates specifically in the lipids. The toxicity of DDT to animals other than insects has been known (it may not always have been emphasized sufficiently), but I doubt whether its fate and its cumulative effect could have been estimated without the data which have been collected in its prolonged use. We have to decide whether the benefits of DDT outweigh the damage or not, and this decision has to be reviewed and revised continuously. But I doubt the wisdom of a conclusion such as "let us stop using DDT altogether and wait until something better will be found". Because the implication that for this new means of insect control we will have collected experimental data for 15 or 20 years (as it is now sometimes suggested in the field of pharmaceutical drugs, e.g.) before we introduce it for practical use - this implication, I say, would effectively prevent all insect control. The balance of power between the insects and the human race is delicate indeed, and surely a prolonged interruption in our fight against insects would change the human environment to the worse not less than the present methods of insect control - though in a different and certainly undesirable direction.

Whilst I firmly believe that the prevalent approach to the problems of insect control is emotional and somewhat hysterical and does not simply reflect the known facts, I am convinced that we scientists will have to find new ways of insect control, and this for two reasons: firstly, even if it is true that most of the damage has been caused by misuse or over-use, this is a practically uncontrollable possibility: thus the entry of the pesticides into the food chain is unavoidable, even if it can be reduced in size. This surely is not a desirable phenomenon under any circumstances. Secondly and more importantly, the acquisition of resistance by the insects poses a problem which we try to solve by using other new types of compounds which are bound to have the same fate - and by using more and more toxic products.

In fact, research on alternative means of insect control is going on in many parts of the world, and I would like to devote part of my introductory lecture to a survey and characterization of these attempts.

What we should aim at, are means of insect control which are specific for insects and do not affect higher animals; if possible, they should be specific for one (or a small number of) insects species which we wish to eradicate. Essentially, this leads to two possible new routes. The one is to follow the principle which Paul Ehrlich formulated as the basis of chemotherapy: to find in the insect a biochemical pathway or a compound essential to the insect but which is not found in higher animals and - by a properly selected drug - to inhibit this pathway or interfere with the activity of this compound. Proper selection, then, means that the drug should be non-toxic to higher animals. If on the whole we accept as unlikely, that a method of control will be found that is specific for one single insect species, the other of the two possible routes would be a treatment of the insects which is carried out not in the field, but in the laboratory, but which affects the insects in the field.

I am referring here, of course, to the methods of sterilisation, either by ionising radiation or by chemosterilants. If one can sterilise the male insect without destroying its mating ability, then the release of a large number of sterile males will reduce proportionately the size of the insect population.

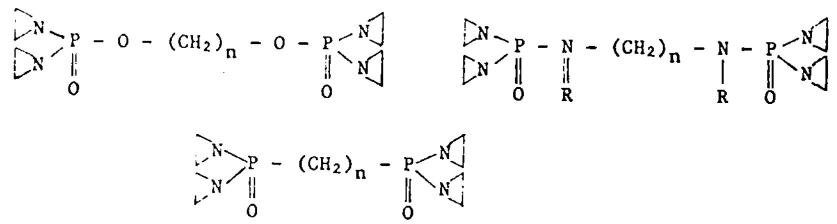
One speaks still mostly of the male sterilization technique, following Knipling's classical paper. There he calculated that if we have a natural population of 1 million virgin females in an area, the release of 2 million sterile males in each of four successive generations, will theoretically reduce the female population to zero. Later calculations, carried out here in Israel, have shown that the limitation to sterile males is not necessary. The use of both sterile sexes is sometimes even superior to the release of the sterile males alone.

The sterilisation-by-radiation technique has been employed in some cases and is being studied in others. There are a few instances in which, indeed, good success has been achieved with sterilization of both sexes, e.g. with the melon fly, ***Dacus cucurbitae***, and the navel orangeworm, ***Paramyelois transitella***. However, I believe the utility of the method has not been recognised sufficiently. Obviously, it is most reasonably employed in an area which geographically is protected against an inflow of a fresh insect population, but this is a problem of numbers and not of principle. It seems to me that the neglect of this point is responsible to some extent for the paucity of cases in which the male sterilisation technique has been used. An equally important deterring factor - which is to some extent linked to the first one - is the difficulty in rearing very large numbers of insects in the laboratory and - as far as considered necessary - in the separation of males and females. This requires a much deeper knowledge of the biochemistry and biology, e.g. of the spermatogenesis and oogenesis of the particular species, than we usually possess - not even taking into account the consequences of interaction in such an extremely dense population. If we know more, it might not be necessary to think of the sterilisation method only as an adjunct to the classical methods of chemical insect control, so as to destroy the survivors of these methods.

In any event it may be interesting to recall that in order to eradicate the screw-worm in Florida and the South-western part of the United States, an area of 85,000 square miles, it was necessary to release 3 1/4 billion sterile flies during 17 months.

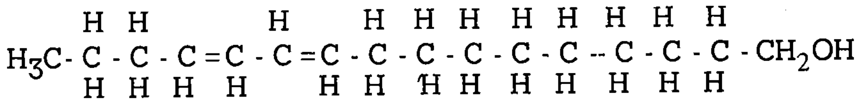
In principle, it can be assumed that the methods using ionizing radiation and the method employing chemosterilants, e.g. of the aziridinyl type, are identical in their mode of action: they both affect the DNA and cause dominant lethal mutations. At least for the chemosterilants it is rather obvious that the biochemical mechanism is the cross-linking of DNA chains. Regarding ionising radiation, we know that one of its targets are the pyrimidine bases of DNA which react with the primary radiation products, the hydrogen atom and the hydroxyl radical and are converted into free radicals. Thus, here too the conditions for cross-linking of DNA chains are given.

Amongst the chemosterilants, phosphorous aziridyl compounds have proven particularly useful. We have added in our laboratory to the Tepa type compounds some tetra-aziridides of the general formulae

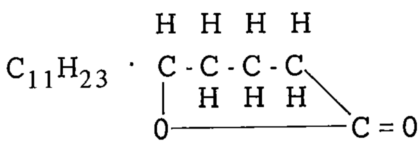


The outstanding positive feature of the sterilisation method is its species specificity; on the other hand, it is obvious that the decline in pest population is much slower than in the use of chemical pesticides.

In recent years, another species-specific potential method of control has been developed which rests on the use of the sex attractants. This method is in a sense also more selective than sterilisation because the sterilising agents often interfere undesirably with vital processes other than reproduction. The effectiveness of the method of the sex attractants measured in the quantities required, is enormous, or in other words, infinitesimally small quantities show a powerful action. Let me recall that according to Butenandt the sex attractant of the virgin female silkworm moth, hexadeca-***trans***-10-***cis***-12 -dien -1-ol (I) is active in quantities of $10^{-10}\mu g$. This

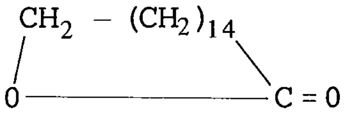
I 

compound, of which at ordinary temperature and pressure $1 cm^3$ of saturated air contains 192 individual molecules, is produced in quantities of 10^{14} individual molecules by a single female moth. This extremely high biological activitiy which almost makes us believe that the chemoreceptors of the insects are affected by individual molecules, often arouses the suspicion that a compound we isolate may not be the looked-for pheromone, but only contain it as a trace impurity, and indeed only if the synthesis leads to a product of equal activity as the natural one, can we really be sure. However, there is no doubt that we know the structure of some of these compounds and that they can be used practically to concentrate the insect population from a fairly large area and then to destroy it. If one looks at the formulae of at least some of these pheromones, one is struck by their simplicity; they are very conventional elaborations of normal biological structures, e.g. the straight chains of the fatty acids with 12, 14, 16 and 18 carbon atoms. We have in our laboratories been surprised to see that the pheromone of ***Vespa orientalis***

II 

is the lactone (II) of δ-hydroxyhexadecanoic acid, and even more that the assembling scent of ***Trogoderma granarium*** is a mixture of the methyl and ethyl esters of known fatty acids. By the way, it is interesting that the solitary bees ***(Halictus calceatus*** abd ***albipes)*** produce the lactone of ω-hydroxyhexadecanoic acid, the well-known dihydro-ambrettolide (III).

III



The organic chemist is naturally enchanted by the prospect that he might by judicious alteration of the active structure, arrive at even more potent compounds or at compounds which are much more easily accessible. Some such synthetic "lures" have been prepared, but on the whole even small modifications of the active structure cause a complete loss of activity. One might also think of the possibility to find antagonists to the natural pheromones which then would obviate the natural attraction of the sexes.

The possible use of pheromones in insect control has in fact brought us already into the second group of possibilities we mentioned, the utilisation of specific biological differences between the insects and other animals, although the analogy with chemotherapy may seem somewhat formal. However, the specific hormones of the insects present undoubtedly reasonable points of attack. The application of δ hexadecalactone to the worker wasps of the Oriental Hornet causes them to build queen cells at a time when there is no need for them, namely at the end of the season and in the absence of the queen.

This possibility is even more obvious for the insect hormones such as ecdysone and the juvenile hormone; their application can destroy the rhythm of the development of the insects, and one is tempted to assume that the synthesis of the juvenile hormone and the fact that there are now plentiful natural sources for the ecdysones (which appear to be much less accessible to a large-scale synthesis) may provide us with new powerful means of insect control. A particularly attractive idea in a similar direction has been suggested recently at the Beltsville Laboratory of the United States Department of Agriculture, namely the manipulation of the photoperiod of insect diapause. One has to combine two facts, that non-diapausing insects cannot survive vigorous weather conditions, and that the extension of the length of the day by artificial light prevents larvae from entering into diapause; promising experiments have been made with larvae of the European corn-borer *(Ostrinia nubilalis)* and of the codling moth *(Laspeyresia pomonella).*

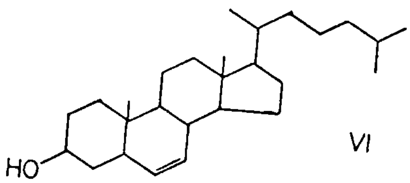
If we turn now to the more classical pathways of metabolism, trying to find some points of difference between the insects and other animals, we shall on the whole be disappointed. There are some - minor - deviations, but they hardly seem to offer a new, practical approach to pest control; perhaps antivitamines constitute such a possibility and have, indeed, been proposed from time to time. It might be useful to study the vitamin requirements of insect pests more extensively, escpecially as it is not impossible that compounds are required by the insects of which we do not know. I would only like you to remember carnitine

$$(CH_3)_3\overset{+}{N} \cdot CH_2 \cdot CH(OH) \cdot CH_2COO^-$$

that unusual insect amino-acid which is a factor required for the oxidative degradation of the higher fatty acids.

There is, however, one area in which the insects present an unexpected picture, a hiatus in the ladder of evolution. Insects are incapable of synthesizing sterols, but they require them for larval growth and pupation. This phenomenon has - naturally - aroused the interest of many research workers, and some picture is emerging from this work, although there are still details which remain obscure. It seems that the sterol required (for the formation of structural membrane units or for the elaboration of ecdysone or for other purposes) is cholesterol (IV) and that herbivorous insects are

IV



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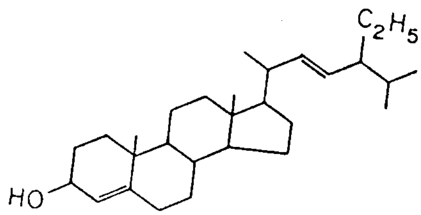

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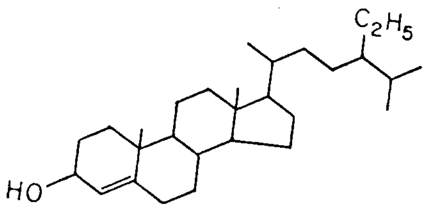
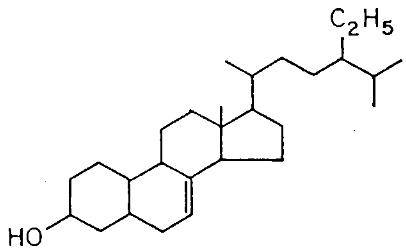


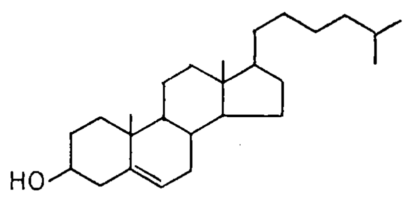
capable of transforming the phytosterols, such as sitosterol (V) and stigmasterol (VI), into cholesterol by eliminating specifically the supernumerary carbon atoms of the side-chain - in a kind of reversal of their biosynthetic introduction. Insects which are incapable of this degradation, e.g. *Dermestes maculatus*, must have cholesterol, although a large part of it can - so it seems - be replaced by β-sitosterol. There is only one case, that of the Mexican cactus fly (*Drosophila pachea*) by which none of the "natural" sterols is utilised but only the Δ^7-stigmastenol (VII) occurring in that Mexican cactus, *Lophocereus schottii.*

VII.



Much of the lack of clarity that exists in this area is due to the fact that the insects live in symbiosis with microorganisms which may play an important role in this steroid biochemistry, and to a less well recognised second fact that it is very difficult to have sterols completely free from traces of others; it would be most important in my opinion to repeat many of the experiments in this field with total-synthetic sterols. There are many interesting observations which might be discussed usefully, e.g. that 22-and 27-norcholesterol (VIII, IX) can be utilized by some insects, but this is not the

VIII.



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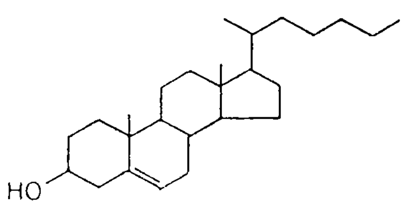

place to do so. Suffice it to state that there is an absolute requirement for an extraneous sterol in all insect larvae, and this surely is a fact which could be utilised as the starting point for insect control. One could think of steroidal antimetabolites in the chemotherapeutical sense; one could think of devising substances which prevent the assimilation of the required sterol from the food. It has indeed been observed that such simple compounds as cholesteryl chloride, cholestanol or cholestanone are antimetabolites of cholesterol, largely of competitive type. On the other hand, we have recently observed that a compound such as campesteryl fluoride, in the presence of small quantities of campesterol, does not prevent the development and pupation of the larvae of ***Dermestes maculatus.***

I believe that more reserach in this direction might lead to theoretically and technically important results; I would like to mention that we found Vitamin D to be highly toxic to insects. That the inhibition of uptake of sterols from the food is also a practical possibility follows I believe, from the observation that certain antibiotics such as filipin have insecticidal properties; these compounds form complexes with sterols and thus most probably destroy their biological availability.

I have tried to outline some areas the study of which may lead to new practical approaches to insect control, approaches which are less open to the objections raised to the present chemical methods. Those approaches seem particularly interesting, which will not entail the development of acquired resistance. However, it must be realised that none of these new methods, if they prove to be successful, will eliminate the use of chemical insecticides in the near future. A serious unemotional examination of the situation will prove that we cannot be without chemical insecticides in order to protect food production and public health, in order to help humanity in its constant fight against insects. A victory of the insects, as I said before, would change the human environment much more than any use, even any misuse, of chemicals.

In any event, as with all other problems of this type, pollution, waste disposal and the like, it is only the scientist who can find an answer. It is thus not by stopping research, but by encouraging it that we can progress. In fact, there are solutions to all environmental problems; but they all have one factor in common, they will increase the cost and therefore the price of the services we receive. I am convinced that this point has been realised by the authorities concerned, but has been disregarded because they will have to decide who is going to bear these additional costs - the manufacturer or the consumer, individually or as tax-payer. If we realise this, then the way is open for the scientist to offer a solution of the problems and to accelarate the progress which is characteristic of our generation and which cannot be stopped.