NEUROTOX '91
Molecular Basis of Drug & Pesticide Action

Papers presented at: Neurotox '91, an SCI Meeting held at The University of Southampton, UK, 7–11 April 1991.

NEUROTOX '91

Molecular Basis of Drug & Pesticide Action

Editor

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Preface

NEUROTOX '91 was the fourth meeting in a series which started in 1979. The '91 meeting, like its predecessors, was held under the patronage of the Society of Chemical Industry, and despite the unfortunate proximity of hostilities in the Arabian Gulf attracted a truly international mix of industrial and academic pesticide scientists.

This volume contains the text of invited papers read at the meeting and presents the dramatic developments which so excited those who attended. The potential of molecular neurobiology for gaining knowledge of target sites for neurotoxicants is now starting to be realised. These studies, in conjunction with developments in molecular imaging and modelling, provide new opportunities for chemists and biologists to gain insights into molecular interactions underlying intoxication. Molecular techniques have also enabled rapid advances on a second front, where the cloning of genes controlling pesticide resistance should have a profound impact on our understanding of this commercially important problem.

The understanding of molecular events will undoubtedly be vital in future developments in chemical control of pests; however, the value of understanding the way in which the nervous system controls behaviour and how behaviour can be modified by chemicals of bath synthetic and natural origins was highlighted. Natural products and their synthetic analogues have continued to provide new and interesting molecules which are already proving their worth as tools for the neuroscientist and may offer leads for commercial synthesis.

Lest we are carried away on a wave of enthusiasm by the exciting developments described in this book, a number of industrial colleagues point out in their papers the relatively small impact such research has had on the discovery of the existing commercial pesticides. This caveat must of course be considered seriously but the optimism and enthusiasm which pervaded NEUROTOX '91 leads me to anticipate that in future a balance between the pragmatism of industry and the speculative approach of academia offers the best chance of success for both. Conferences such as NEUROTOX have a role to play in fostering this relationship and it is my hope that this volume provides a valuable account of current developments in pesticide science and some of the challenges facing us.

I. R. Duce
Nottingham, UK
July 1991

Prologue

Presented at NEUROTOX '91, Southampton, April 1991
International Symposium on the Molecular Basis of Drug and Pesticide Action

Invertebrate Neuroscience and its Potential Contribution to Insect Control

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When we attended the first NEUROTOX Meeting in York 12 years ago, we were simply quiet consumers of lectures, posters and group discussions on insect neurobiology and pesticide action. We went back to our laboratory in Basle with expectations that at least some of the newest findings and academic recommendations provided at the meeting would prove beneficial for the work of industrial chemists and biologists alike. This was particularly true with regard to facilitating a more rational discovery of toxicants as expressed by Dr Graham-Bryce in his foreword to the Proceedings of the 1979 Symposium.

In contrast to York, however, NEUROTOX '91 in Southampton gives us a less comfortable feeling. Firstly, the former lab bench scientists have turned into managers who now realise that speaking to those who know better is more difficult than listening to them. Secondly, the fun of science, its progress, prospects and promises as being communicated among the participants of this meeting puts us at a clear disadvantage: they are all much more attractive than the well-known complaints of and constraints to the insect control business: (1) a stagnant world market, (2) the pressure on product prices, (3) the lack of hard currency in Third World countries, (4) cheap product imitations, (5) insecticide resistance and pest acceleration, (6) smaller and smaller innovation steps versus higher costs of R&D, and (7) the media-driven public belief that most plant protection chemicals can be replaced by 'soft' technologies including biological products, even though most of them are still unreliable, uneconomic and of a very limited practical value.

We are not neurobiologists ourselves, we have never inserted a microelectrode into an insect nerve or muscle, and our past experimental background is limited to using vertebrate and invertebrate enzymes as tools in comparative and analytic biochemistry, for screening purposes, in insecticide resistance monitoring programmes, mode of action studies and other practical applications of interest to industrial R&D. When we agreed to present our thoughts at this prestigious symposium on 'Invertebrate neuroscience and its potential contribution to insect control' we did not do it because we felt most qualified, but we accepted the challenge as managers who are often said to make quick decisions on problems they are unable to grasp themselves. We hope, however, that many years of experience in industry and many working relations with chemists, screening biologists, biochemists, field entomologists, production chemists and colleagues from marketing will partly compensate for our deficiencies in the area of neurobiology.

Perhaps some of you would have preferred to listen to an introductory lecture providing 'neuroscientific visions' instead of being bothered with the realities and contradictions of industrial R&D. Nevertheless, it is these realities and contradictions that we wish to discuss. Among them are:

—the undeniable economic importance and value of neuroactive insecticides versus their negative public image;
—the very small number of useful modes of neurotoxic action as compared to hopes and claims that additional and more selective neurotargets exist;
—the discrepancy between our continuing reliance on random *in vivo* screening and often heard promises that the rational *in vitro* design of insecticides is just around the corner.

We have tried to summarize our personal attitude towards and judgement of neuroscience and its value for R&D insect control in four theses. The first one reads as follows:

Thesis 1—Real or perceived safety problems associated with neuroactive insecticides force industry to divert more R&D resources to new and alternative pest control technologies.

Pesticides are no exception to the experience of mankind that beneficial inventions are often not free of risks. Since organophosphates and carbamates inhibit acetylcholinesterases of both invertebrates and mammals, their misuse can cause accidental intoxications in unprotected and uneducated users, especially in developing countries. Some of these and other neuroactive, but also non-neuroactive insecticides can also affect aquatic and terrestrial wildlife, or kill beneficial insects such as bees, parasites and predators. In spite of an increasingly broad industrial and regulatory risk assessment for the benefit of users, consumers and the environment (Table 1), and in spite of all the progress made in minimizing adverse effects through product enhancement or replacement, our mass media continue to generalize and to inflate the actual risks of plant protection chemicals in general, and neuroactive insecticides in particular. This is especially true in affluent countries where safe and well-studied chemical specialities are regarded more as consumer or environmental poisons than as valuable productivity tools for agriculture. Insufficient information about the benefits of agrochemical products coupled with public campaigns capitalizing on the 'fear of the unknown' can have quite dramatic

TABLE 1
Toxicological and Environmental Studies

Toxicology		*Environment*
Acute:	oral, dermal, inhalation	Physico–chemical parameters
Subacute:	dermal, (inhalation)	Hydrolysis
	4–weeks feeding	Photolysis
Subchronic:	3–months feeding	Leaching in soil (laboratory, field)
Chronic:	2–years feeding	Evaporation from water and soil
Special:	mutagenicity	Soil metabolism (aerobic, anaerobic)
	carcinogenicity	Plant metabolism
	2–gen. reproduction	Ecotoxicity (laboratory, field)
	neurotoxicity	Behaviour in the food chain
	teratogenicity	
	skin, eye irritation	
	allergy potential	
	animal metabolism	

effects as exemplified by a survey published in *Scientific American* in 1982 (Table 2). When college students, members of the league of women voters and business men in the US were asked to rank 30 types of activities or products with a known risk potential, pesticides were placed in positions 4, 9 and 15, respectively, as compared to their real place in rank 28.

The plant protection industry and its customers in agriculture have to accept the challenge that their own benefit/risk assessments often differ from those of the public, and that actions may be taken by Government bodies that would change the pest control picture and make chemical control less attractive. As a consequence, industry has already shifted considerable R&D, production and

TABLE 2
Risks in the USA[a]

1	Smoking	150 000
2	Alcohol	100 000
3	Motor vehicles	50 000
4	Handguns	17 000
5	Electric power	14 000
6	Motorcycles	3 000
7	Swimming	3 000
8	Surgery	2 800
9	X-rays	2 300
11	General aviation	1 300
14	Hunting	800
15	Home appliances	200
25	Vaccinations	10
28	**PESTICIDES**	**<10**
30	Spray cans	<10

[a] Reproduced from *Scientific American*.

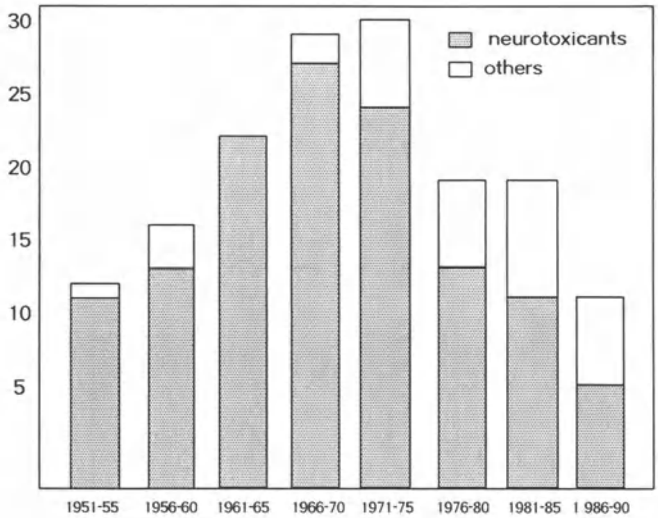

FIG. 1. Numbers and types of insecticides/acarides introduced between 1950 and 1990. Data from *Pesticide Manual, 1990.*

marketing efforts to new and 'softer' technologies, which include safer formulations, packaging and application systems, more selective chemicals with better fitness for integrated pest and resistance management, and various biological products. The impact of this development on the relative importance of neurotoxicants is evident (Fig. 1): ingredients introduced into the market during the 1960s were almost exclusively neuroactive, whereas the 1970s and 1980s have seen a growing proportion of products with other modes of action, but also a significant decrease of the total number of insecticides and acaricides introduced. The obvious trend to non-neurotoxicants which we expect to continue is probably a reflection of both the growing need for and acceptance of novel types of products capable of solving new problems, and the difficulty of identifying and utilizing additional neuroactive principles that provide new effects on insect nerves and sufficient biological activity at the same time.

The ongoing shift to 'soft' insecticides, however, sharply contrasts with the present situation in the market (Fig. 2). According to our own estimate these low toxicity non-neurotoxic insecticides (synthetic analogs of juvenilhormones, chitin biosynthesis inhibitors and a few others) have not even gained a 10% share of the world-wide insect control market. The large number of neuroactive insecticides, depicted as circles sized in proportion to sales (primarily organophosphates, carbamates, and pyrethroids) continue to dominate the market, although several of them are quite toxic. There is no doubt that they still provide the most effective, reliable and economic solutions to pest problems in agriculture, stored products, animal health and public hygiene, and we do not believe that quick and adequate replacements are at hand.

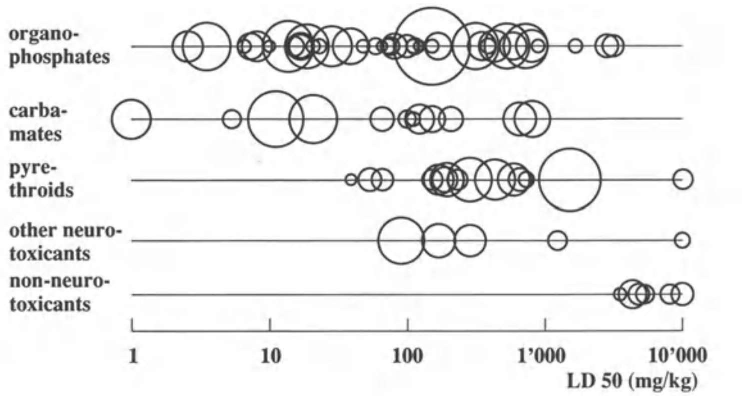

FIG. 2 Insecticides and their acute mammalian toxicities (circles: proportional to sales). Data from *Pesticide Manual, 1990* and CIBA-GEIGY Marketing.

According to published figures (Table 3) the total sales value of insecticides and acaricides will reach approximately 7 billion US$ by the year 1995. DDT and the cyclodienes will continue to lose market share, whereas the pyrethroids are still expected to grow. Organophosphates will grow slightly and remain by far the most important single group of insecticides. Carbamates will hold their position, whereas the remaining products—other neuroactive compounds as well as all non-neurotoxicants—are expected to almost double their sales volume between 1988 and 1995. Disregarding the GABA activated ion channels and a few other neurotargets of minor importance, we must conclude that only two modes of action represent the base for 80% of the insecticide market: the voltage dependent sodium channels and the acetylcholinesterases of the insect nervous system. Our reliance on these two targets appears to be tremendous; their protection from becoming ineffective through resistance is an absolute must.

After many years of unfulfilled hopes and unkept promises we sense a growing reluctance on the part of industry to fund speculative neuroscience

TABLE 3
Neuroactive Insecticides and Their Economic Importance

Types of successful insecticides/acaricides	*Mio US$ world sales*[a]			*Interference with or inhibition of*
	1972	*1988*	*1995*	
Cyclodienes DDT	1 580	500	350	GABA activated ion channels
Pyrethroids	none	1 150	1 500	Voltage–sensitive sodium channels
Organophosphates	1 375	2 325	2 520	Acetylcholinesterase
Carbamates	885	1 400	1 400	Acetylcholinesterase
All others	175	700	1 330	

[a] Source: County NatWest Woodmac 1990.

projects aiming at the design and discovery of new insecticides. Firstly, requirements for safety evaluations of new products and re-registrations of existing ones absorb more and more funds to the disadvantage of innovative basic research and, secondly, the shrinking fraction of financial resources left is more and more directed to 'softer' technologies, such as growth regulators, pheromones, microbial products and other promising biological agents.

Our first thesis pointed to the conflict between reality and wishes, between rationality and emotion. It results from the existence of and the continuing need for successful neuroactive insecticides versus the public demand, to replace them by less risky products or methods, a demand that industry cannot afford to neglect. The second thesis, however, carries a more technical message. It reads as follows:

Thesis 2—Insecticides have to comply with the needs of the market and society. The multitude of positive product features required for safety, performance, selectivity, manufacturing, costs and patenting cannot be 'designed' by neuroscience.

Industry is expected to discover and develop 'ideal insecticides' designed to satisfy the needs of several 'user groups' in our society: farmers and workers in agriculture, employees of the plant protection industry, consumers of agricultural produce, environmentalists, legislators and others. Thus, the ideal insecticides should be

—highly researched but low-priced;
—superior to existing products but not more expensive;
—highly selective but big in market size;
—long-lived in the market but should not create resistance problems;
—broadly active on pests but inactive on non-target species;
—long-lasting on crops and in insect pests but not causing residues in crops and the environment;
—fast-acting on pests but preferably not as a neurotoxicant;
—mobile in plants but immobile in soil.

In order to cope with these contradictions and to 'optimize the compromise' between them, the entire product creation process for new insect control agents has become much more sophisticated and problem oriented than it has been in the past (Fig. 3), when markets were wide open to absorb all the many broad-spectrum insecticides discovered and developed by the plant protection industry. Today the insect control market is saturated and a rigid, insufficiently harmonized legislation, strong competition, increasing costs as well as high performance standards difficult to exceed determine the environment in which industrial R&D has to discover and develop products with acceptable modes of action, stabilities and physicochemical properties. Customers, society and industrial marketing request and expect R&D to solve new or still existing practical problems, such as multi-resistant diamond-back moths in South-East Asia, whiteflies and aphids in cotton, planthoppers in rice, scale insects in

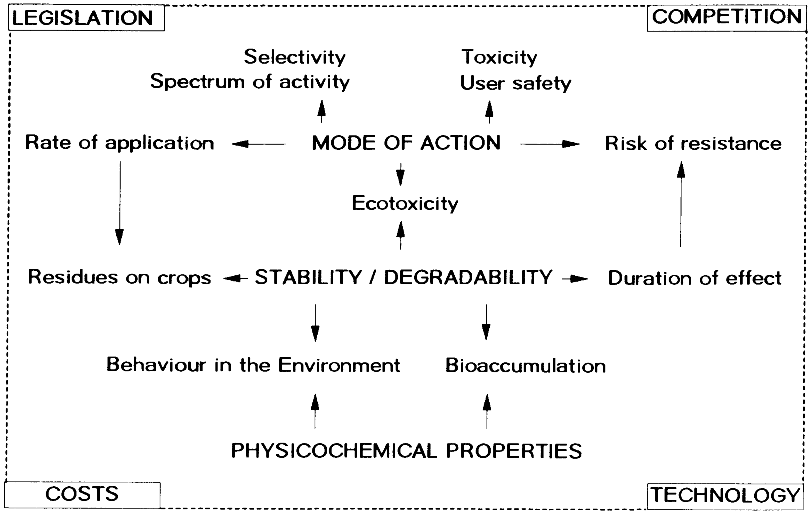

FIG. 3. R&D insect control—framework and topics.

citrus, spider mites and psyllids in deciduous fruits, or the corn rootworm in soils of the American corn belt. Only a more and more sophisticated random screening on live target species in the appropriate development stage can provide the right answers; in-vitro and in-situ test systems based on neurophysiological models prepared from locusts, cockroaches, houseflies, *Manduca* and others are inappropriate tools for identifying the best products for the envisaged market at the lowest cost in the shortest possible time. What we need are safer and more selective insecticides designed for markets and problems large and important enough to justify development, not inhibitors of enzymes or receptor ligands designed for or discovered in neurobiological model systems. Although 'biorational' in-vitro concepts are often perceived to be scientifically and intellectually more demanding than 'simple' random screening on target insects followed by chemical, physicochemical, biological, toxicological and economic optimization, industrial R&D must continue to rely on its traditional but highly successful 'try and see' approach.

A hypothetical question can easily clarify our point of view: could neuroscience have contributed to the discovery of today's pyrethroids, or—to phrase it in a different way—what could neurobiology contribute to product optimization and development if pyrethrins were to be discovered now instead of 70 years ago? An answer to this question may well provide information where knowledge could have led to faster success in the past and where it could assist in making better decisions in the future.

The history of pyrethroids (Fig. 4) can be divided into three phases: (1) the discovery of useful insecticidal properties within the Pyrethrum plant some 170 years ago; (2) the elucidation of the underlying chemical structures about 100

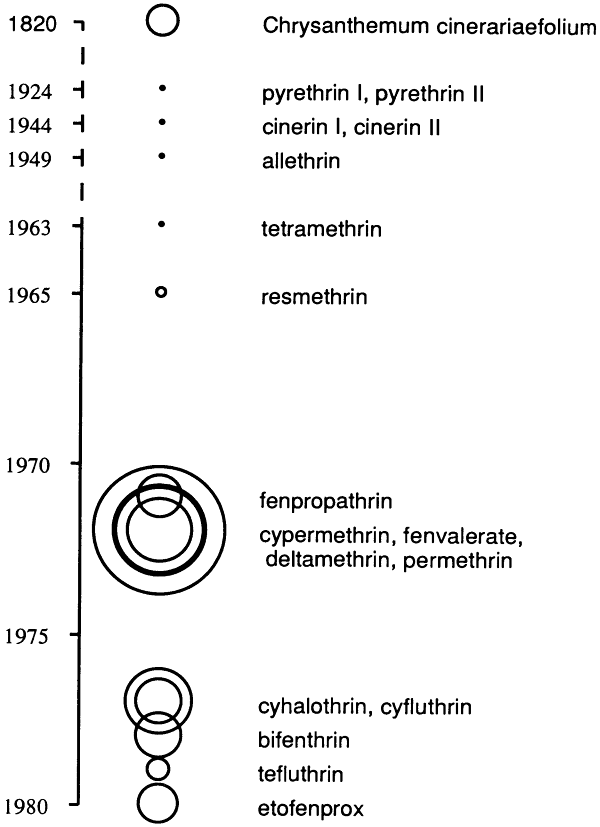

FIG. 4. The history of pyrethroids (circle area proportional to sales).

years later; and (3) the modification of these structures aiming at very respectable sales products that fulfill the needs of the market.

Let us look at the first phase: can neurophysiology help to find natural insecticides? Our answer is, 'No!' We would not like to spend limited R&D funds on such attempts, because tests on target insects are faster, cheaper and more relevant. Moreover, they provide a broader information base, since the whole range of potential targets can be tested at the same time on a live insect.

Also the second phase, structural elucidation of natural products, does not need neuroscience; perhaps an in-vitro bioassay could support in-vivo data. The third phase, however, lead optimization, appears to be an area for using neurobiological expertise. Has its application really happened, could it have happened and if not, can it happen in the future? We would be surprised if those chemists who engaged themselves in the stepwise optimization of pyrethroids that even led to pyrethroid ethers like ethofenprox would give any credit to neuroscience when writing their success stories. Primarily it was not the intrinsic activity that needed to be improved when moving from the pyrethrins to the pyrethroids, but the products' hydrolytic and oxidative stability. Therefore, we conclude that neurophysiology did not help synthesis chemists in the discovery and optimization process of pyrethroids, whose sales, however, have helped to finance a lot of basic neurophysiological research.

What about organophosphates and carbamates? Farmers do not necessarily prefer to use the most potent cholinesterase inhibitors. They want products that are both effective and safe, properties mainly based on differential metabolism. Also for another class of insecticides, the non-neurotoxic chitin synthesis inhibitors, intrinsic activity at the site of action was found to be of secondary importance. Here a compromise had to be achieved between stability in the insect gut and acceptable environmental degradation.

We do not hesitate to state that so far neuroscience has not been able to design new types of insecticides which would have had the potential to compete with existing products in the market. Obviously, the aim of industry to search for even more selective compounds targeted to pre-defined uses will even further minimize the chances for neurobiological success in product design and discovery.

Also our third thesis does not leave room for much optimism. It reads:

Thesis 3—The number of neurotargets providing acceptable and economic pest control opportunities is much smaller than anticipated by academic research.

Our colleague Dr Jack Benson has compiled about two dozen neuronal target sites for insecticides, that are either known to exist in invertebrates or have been proposed as hypothetical targets (Table 4)

—The first part refers to the potential of utilizing receptor ligand recognition sites. In the area of 'classic' neurotransmission, only the nicotinic acetylcholine and octopamine receptors as affected by nicotine, cartap and the new nitromethylenes on the one hand, and the formamidines on the other hand, are of practical importance. Commercial insecticides working on the muscarinic acetylcholine receptor site or acting as glutamate, serotonin, dopamine and histamine mimics are unknown, as are commercial insecticides based on neuropeptides.

—Only one commercial target has so far been identified among the receptor activated ion channel types: the GABA activated chloride channel appears to be the target of the aging cyclodiene insecticides. The non-receptor activated voltage dependent sodium channel, however, represents one of the most important targets for insecticides: it is affected by DDT and the pyrethroids. The natural product derivatives milbemycin and avermectin are said to work on the passive chloride channel, whereas the voltage dependent calcium and potassium channels as well as the metabolic sodium pump have never been shown to be targets for insecticides.

—There has to be at least one system for the removal of each transmitter

TABLE 4
Neuronal Targets and Insecticides

Receptor Ligand Recognition Sites

cholinergic (nicotinic)—nicotine, cartap, nitromethylenes
cholinergic (muscarinic)—none
GABAergic—see Cl channel
octopaminergic—formamidines
glutamatergic—none
serotonergic—none
dopaminergic—none
histaminergic—none
neuropeptides—none

Ion Channels

Cl channel—GABA—cyclodienes
Na—voltage—DDT, pyrethroids
Cl channel—passive—milbemycin, avermectin
Ca channels—voltage—none
K channels—voltage—none

Metabolic Ion Pumps

Na pump—Na exclusion—none

Transmitter Re-uptake and Breakdown

AChE—ACh—organophosphates, carbamates
MAO—monoamines—none

Transmitter Synthesis

Choline acetyl transferase—none
Glutamate and other decarboxylases—none
GABA transaminase—none
Neuropeptide post-translational processing—none

Second Messenger Systems

Cyclic AMP—e.g. octopamine—none
Cyclic GMP—e.g. eclosion hormone—none
Phosphotidylinositol—e.g. salivary glands—none

after it has served its purpose at the site of action, be it by metabolism or direct re-uptake. Two metabolic systems are well known in insects: acetylcholinesterase and monoamine oxidase. Inhibitors of cholinesterases, the organophosphates and carbamates, have become the most successful commercial insecticides, whereas monoamine oxidases have so far never shown potential as an insecticide target. The same is true for several transmitter synthesis and second messenger systems.

We cannot hide feelings of irritation and disappointment that 50 and 40 years after the introduction of DDT and the first organophosphates, respectively, insect control continues to rely on only two major neurotargets that really work: the voltage dependent sodium channels and acetylcholinesterases. Three targets are of minor economic importance: the nicotinic acetylcholine receptor which may become more attractive as the nitromethylene insecticides develop, the octopamine receptor and the GABA activated chloride channels. The remaining 20 targets listed, however, have so far failed to fulfill their promise for the insect control business.

In spite of the fact that at least five million chemicals have now been screened for insecticidal activity, only two major and three minor neurotargets of practical value have emerged. This unpleasant situation will have to be discussed and thoroughly analysed by those who know much more about the insect nervous system than we do; our own contribution can only be to ask a few strategic and philosophical questions:

—What are the chances of success for discovering novel types of chemical structures that interfere with sodium channels and acetylcholinesterases in insects? Do we really need such compounds? Would their development not even increase the risk of losing the two most valuable modes of action through target site related cross-resistance? What are the chances for new products designed to cope with modified sodium channels and acetylcholinesterases to assist in resistance management?

—Why have the cyclodienes remained the only GABAergic insecticides, and the formamidines the only ones that interfere with the octopamine receptor? Why have all conventional and biorational attempts failed to identify new chemistry with dieldrin- and chlordimeform-like activity? Are the octopamine and the nicotinic acetylcholine receptors promising targets to improve insect–insect selectivities, and if yes, why?

—What do we do with the apparently existing, but unutilized hypothetical invertebrate neurotargets? Do we continue to speculate that the day will come when at least a few of them will represent more than exciting subjects for academic research? How realistic are these hopes, how feasible are these targets as a base for safer, more selective, and economic commercial products? If these hypothetical targets would really work for test compounds applied orally or by contact, would we not have identified them in our large-scale industrial screening operations coupled to subsequent mode of action studies? And, last but not least, should a cost and priority minded manager in industrial R&D allow vague speculations to draw scarce R&D funds from more realistic projects that also wait to be implemented?

Real and perceived safety problems, the growing need to give the market what it requests, and the apparently very small number of useful targets limit the opportunities of neuroscience to contribute to the design, discovery and

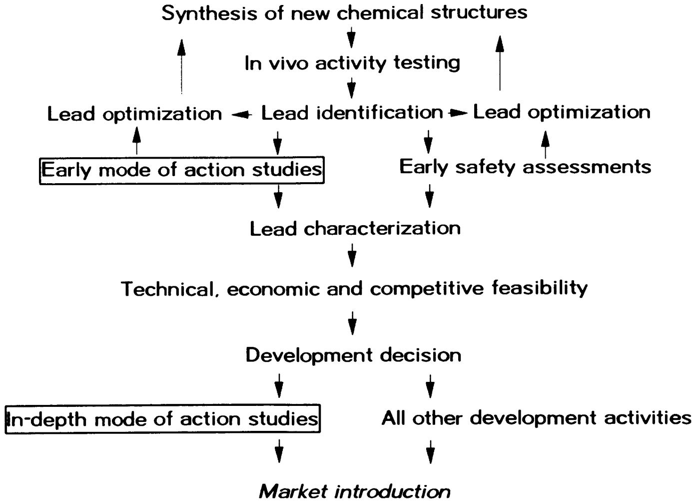

FIG. 5. R&D insect control—contribution of neuroscience.

development of better and safer insecticides that are wanted by everybody. In fact, we may claim that so far neuroscience has obtained more benefits from insecticides than the insect control business has from neuroscience.

We hope that the provocative statements made while presenting the first three theses can provide a base for some in-depth discussions. Thesis 4, however, carries a more optimistic and conciliatory message:

Thesis 4—Assessing and explaining the modes of action, resistance and selectivity of toxic and behaviour modifying chemicals represents the main value of invertebrate neuroscience.

Neurophysiology and biochemistry start to play their main role as soon as a new active ingredient with proven in-vivo insecticidal activity has been identified (Fig. 5). We are convinced that early—though admittedly superficial—mode of action studies done in parallel to chemical and biological optimization can tell us something about a new lead's value and assist in making better decisions faster. With progressing product development, however, in-depth mode of action studies become an essential part of the whole information package required to satisfy both regulatory authorities as well as the high quality standards of research-minded companies who want to know how their products act on the physiological, biochemical or molecular level in target and non-target organisms. It is primarily in this area where neuroscience will continue to produce its most valuable achievements, and where industry is prepared to cooperate with academic research.

Again, the group of pyrethroids can be used as a good example for the progress made in the mode of action area: Today we know, that

—pyrethroids act on axonal sodium channels, a finding confirmed by single channel recordings;
—only a small number of channels have to be affected to produce the well-known high potency of these insecticides;
—temperature-dependent toxicities can be explained at the neuronal level;
—and cross-resistance against DDT and pyrethroids have a common site.

All this is important and useful information for which neuroscientists in both academic and industrial laboratories deserve a lot of credit, although many questions are still unanswered: for the pyrethroids, we lack an explanation for the differences between type I and type II compounds at the molecular level, and for anticholinesterases and compounds acting on the acetylcholine receptor a closer insight into the relative importance of synapses located at different sites within the nervous system, and of isozymes would be welcome. We also need to know more about the lethal modes of action of those insecticides that do not directly interfere with the insect's nervous system, such as respiration inhibitors. What is their effect on the proper functioning of the nervous system as compared to other insect tissues.

In order to further improve the safe use of neuroactive insecticides, we also plead for more research efforts in comparative neurobiology and biochemistry. Knowledge in these areas will lead to a better understanding of pre-existing and acquired insensitivities towards present and future insect control agents; to a better understanding of the neurological mechanisms causing selectivities between larger and smaller taxonomic units or among insect growth stages, and the mechanisms leading to resistance. The modified acetylcholinesterases of several insect species are very good examples for a practical application of neuroscience: these enzymes have become effective biochemical monitoring tools for organophosphate and carbamate resistance in pest populations.

In order to obtain a broader view of the neurobiological 'wants' of industry, we have asked a few fellow researchers of our own department to list areas where they feel neuroscience should and can contribute. Here are their main answers:

—Without underestimating the technical difficulties, more insect species of economic importance should be included in basic and applied neuroscience.
—Once a chemical lead has been identified in vivo, neurophysiological or biochemical test systems can predict, confirm or exclude a particular mode of action. This is valuable information. Depending on the type of knowledge gained, chemists may or may not profit, when optimizing new structures for biological efficacy and safety.
—Although the chances for discovering competitive neuroactive insecticides with novel modes of action appear to be small, much research will have to be done by industry and academia as soon as such products move to the market.

—Differential metabolism of insecticides is a well-established base for selectivities among representatives of different taxonomic units. What, however, is the role of the nervous system of different species in providing selectivities?

—Insecticide resistance is a great challenge for industry, agriculture and society. Research that does not just describe findings, but assists in early detection, prevention or successful management of the problem, will find the support of industrial companies.

—Natural or synthetic chemicals that modify insect behaviour, are becoming part of the R&D project portfolios of probably all major pesticide companies. The development, refinement and use of efficient and meaningful screening systems measuring behavioural responses in target insects are prerequisites for success.

—Where public concern against neuroactive insecticides appears to be unfairly exaggerated or unjustified, both academic and industrial neuroscientists must speak up in order to defend some of our most valuable, though admittedly not perfect, agrochemical specialities, for which we do not yet have satisfactory alternatives. The forum for getting better public acceptance, however, will not be scientific journals and conferences, but the media and some of our educational institutions. Should we not share the objectives, the methods and the results of a fascinating research area with its impressive progress but also its obvious shortcomings with those who worry more about the risks of neuroactive insecticides than they appreciate their benefits?

Obituary

CHARLES POTTER, 1907–1989

Charles Potter exerted a strong influence in inaugurating this series of conferences on Insect Neurobiology and Pesticide Action; the concept of this unique forum for communication between scientists concerned with improved pest control but from diverse disciplines was quite typical of the breadth and depth of his vision combined with his flair for perception of opportune, appropriate actions. His long, active career spanning some six decades was distinguished by a series of imaginative decisions which profoundly benefitted the progress of research on crop protection and on pesticides and their action. Yet Potter's contributions have never perhaps been adequately recognized, for he was an *éminence grise* deriving fulfilment from knowledge of the advances made under his influence rather than from the immediate approbation of the scientific establishment whose ill-judged decisions he was at intervals motivated to contest.

Potter's first research (1929–1938) at Imperial College, London greatly advanced knowledge of the control of stored products pests and enunciated for the first time the principle of using active residual films of contact insecticides, specifically, in this instance, pyrethrum in white oil. This technique, applied throughout World War II to protect stored foodstuffs from insect infestation, established a precedent for the effective use of DDT in films, when that insecticide became readily available at the end of the war. During 1944 and 1945 Potter, now entomologist at Rothamsted Experimental Station, made some of the first trials of the control of UK plant pests with DDT. He was appointed Head of the Insecticides and Fungicides Department in 1947, at a time when the introduction of organophosphorus and organochlorine insecticides, combined with the need for improved crop protection, had greatly stimulated new research on insecticides. With characteristic foresight, and drawing on his personal experience with pyrethrum, Potter chose to concentrate on the relationship between insecticidal activity and the structure of pyrethroids rather than on the more fashionable organochlorine and organophosphorus compounds. This was an outstandingly important decision, because in the early 1970s the need for new insecticides, not unduly persistent and with improved activity, became urgent; Rothamsted was then able, before any other academic or industrial research group, to provide, via patents