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The Role of Industry in the Research of Agrochemicals (**)

1. Introduction

As long as mankind continues to cultivate and grow plants for food, feed and fibre, his crops will be threatened by insect pests, diseases and weeds. It follows that the future of pest control is hardly in doubt, but the specific direction it will take is being debated at great length. Much has been written about this subject.

I shall assume that this background is generally known and I shall also accept the validity of the premise that the judicious use of chemical agents will continue to be an essential part of future plant protection technology. However, the desire for integrated pest management actually represents a real goal of government policy-makers, scientists and users. This poses a technical challenge to the agrochemical industry to produce products with great efficacy against the target pests and freedom from adverse side effects. This paper presents some ideas and views on finding chemicals with such features. Since the principal crop protection problems of tropical countries arise from insect degradation, major emphasis was laid on this area of pest control.

2. Characteristics of Agrochemical Industry

Before discussing the technical factors that are likely to limit or to extend innovation in the agrochemical industry, the size, shape and trends of this industry will be briefly reviewed.

It is estimated (Wood Mackenzie, 1985) that the global end-user agrochemical

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market has grown from $ 850 m. in 1960 to $ 15.9 b. in 1985. During this period, herbicide sales grew by 16% to $ 7.1 b., insecticides by 12% to $ 5.0 b., fungicides by 9% to $ 2.8 b., plant growth regulators and others by 75% to $ 1 b. Little change in relative positions of the product groups is expected between now and 1990. The character of the market in which the agrochemical industry operates, and its opportunity for new product introduction, are indicated by its geographical and crop breakdown. About 73% of the herbicide usage occurs in the developed nations of Western Europe, USA and Japan. In contrast to the herbicide sector, the main areas for the use of insecticides are in the developing countries of the world. This is no wonder, because in tropical countries, cash crops are cultivated according to the economic principle designed to ensure the highest possible yields and quality. These crops include not only traditional tropical fruits, but also coffee, tea and cocoa; fibre plants and sugar cane; and various spices which have a limited but very profitable market. Crop protection is an indispensable activity here and could not be abandoned without ruining the general economy of these countries.

Virtually, all agents in practical use for crop protection have been developed by industry rather than by academic, governmental, or nonprofit organizations, and I believe that industry will continue to have a remarkable record in producing new and improved products. However, agrochemical innovation is experiencing troubled times. The complexity of technical problems and the expanding regulatory requirements combine to make it increasingly difficult to find profitable new products.

Commonly quoted figures are that some 8% of proceeds is spent annually in R & D within the industry. Perhaps the major change which has taken place in the R & D budget is that average expenditure for innovative research is threatening to fall consistently rather than occasionally. At the same time, all elements of the so-called defensive research (studies of residues, metabolism, toxicology and environmental impact) have correspondingly increased.

The strict requirements now necessary for registration and re-registration within the majority of developed countries and an ever-increasing number of developing countries, pose severe problems for the innovation and development of new agrochemicals. Now I am not using this paper to criticise the attitudes and demands of registration authorities. It is a fact that assurances of safety are welcomed and observed by responsible industry. But it must be realized that the development of a really new and marketable product takes at least seven years from discovery to commercialisation and costs over $ 10 m. This does not include the investment in new manufacturing facilities. One very unfortunate result of this high cost is that it has made it increasingly difficult and unprofitable for a manufacturer to develop a compound which is specifically intended to be effective only in a restricted and specialised market. Perhaps biochemical and toxicological sciences have advanced sufficiently to adapt requirements and testing procedures to the specific properties and uses of a chemical in a particular risk/benefit situation.

3. The Need for New Agrochemicals

Ideally, crop protection should prevent damaging effects from pests, diseases and weeds economically, safely and without harming the environment. Present methods, based mainly on agrochemicals and resistant crop varieties, effectively control many damaging organisms but have limitations. The continuing development of resistance to older compounds, the lack of good solutions to some existing problems, the elimination of older agrochemicals with an insufficient safety margin are well acknowledged reasons for discovering new products. As already pointed out, the slots into which new compounds will fit become fewer and the criteria with respect to performance and acceptability become more stringent. This does not mean, of course, that there are no opportunities left. There is a continuous search for different types of activity in both conventional and some allied areas. The evolution in agrochemical research, which has taken place over the last 15 years, has manifested itself in an intensive interdisciplinary effort which includes chemists, biologists, biochemists, toxicologists and other specialists. When such groups are well motivated to work together, the chances of success are increased. However, it is equally important that industry and academia collaborate. The universities have made and are making significant contributions to agrochemical science and I expect them to make further efforts to explore selected fields of plant and insect physiology and biochemistry. Scientists working in subtropical and tropical regions have increased in number and professional capability during the past two decades. They also must provide basic information on the peculiar features of subtropical and tropical crop ecosystems. This information is of fundamental importance to elaborate an approach to pertinent problems by more rational biochemical and chemical means.

4. Agrochemical Rationale and Design

Most of the agrochemicals in use today were discovered by *empirical synthesis and random screening*. Although this approach lacks intellectual finesse, it has produced compounds of very high biological activity and exemplary selectivity. Year after year, it is becoming obvious that owing to the huge number of compounds already synthesized and tested, the chances of discovering a marketable agrochemical by such an approach are very low. The most productive approaches are chemical modifications and biochemical design.

Chemical modifications probably form the greater part of present research projects. The basic structure which is to be modified can arise from the random screening, the technical literature, or it could be a bioactive natural product. In recent years great progress has been made in the development of mathematical methods to save chemists some of their work. By using these methods, a chemist can be more confident that a given series has been fully exploited and that all reasonably accessible substructures with potentially useful activity have been made. Paradoxically, progress has been less in the ability to discover new leads

than in the ability to process them. The search for new chemical leads, which originate from natural sources, is attracting increasing attention. As new synthetic models become more difficult to find, the structural diversity of bioactive natural products of botanical or microbial origin might fill the void.

Currently, there is high expectation in designing useful agrochemicals through knowledge gained from fundamental research into biological and biochemical processes of pests and plants. The aim of this approach, referred to as *biochemical design*, is to consider the pest as a biochemical machine containing essential enzymes and receptors for which it might be possible to predict specific inhibitors. Indeed, some critical target-sites and biochemical mechanisms in pests have been identified and used to develop sophisticated screening systems for the discovery of agents with new mechanisms of action. These are summarized in Figure 1.

5. Research Opportunities in Chemical Insect Control

In examining the research opportunities in chemical insect control, it is instructive to consider the time scale of disclosure of different classes of current

INSECTICIDES:

- **The GABA complex.**
- **Insect NEUROPEPTIDES and their physiological degradation.**
- **Neural CALCIUM sensitive phosphorylation systems.**

FUNGICIDES:

- **The binding sites of TUBULIN from resistant fungal strains.**
- **ERGOSTEROL biosynthesis.**
- **MELANIN biosynthesis.**

HERBICIDES:

- **ACETOHYDROXYACID synthase.**
- **GLUTAMINE synthetase.**

Fig. 1. - Major agrochemical targets explored to find new agrochemicals.

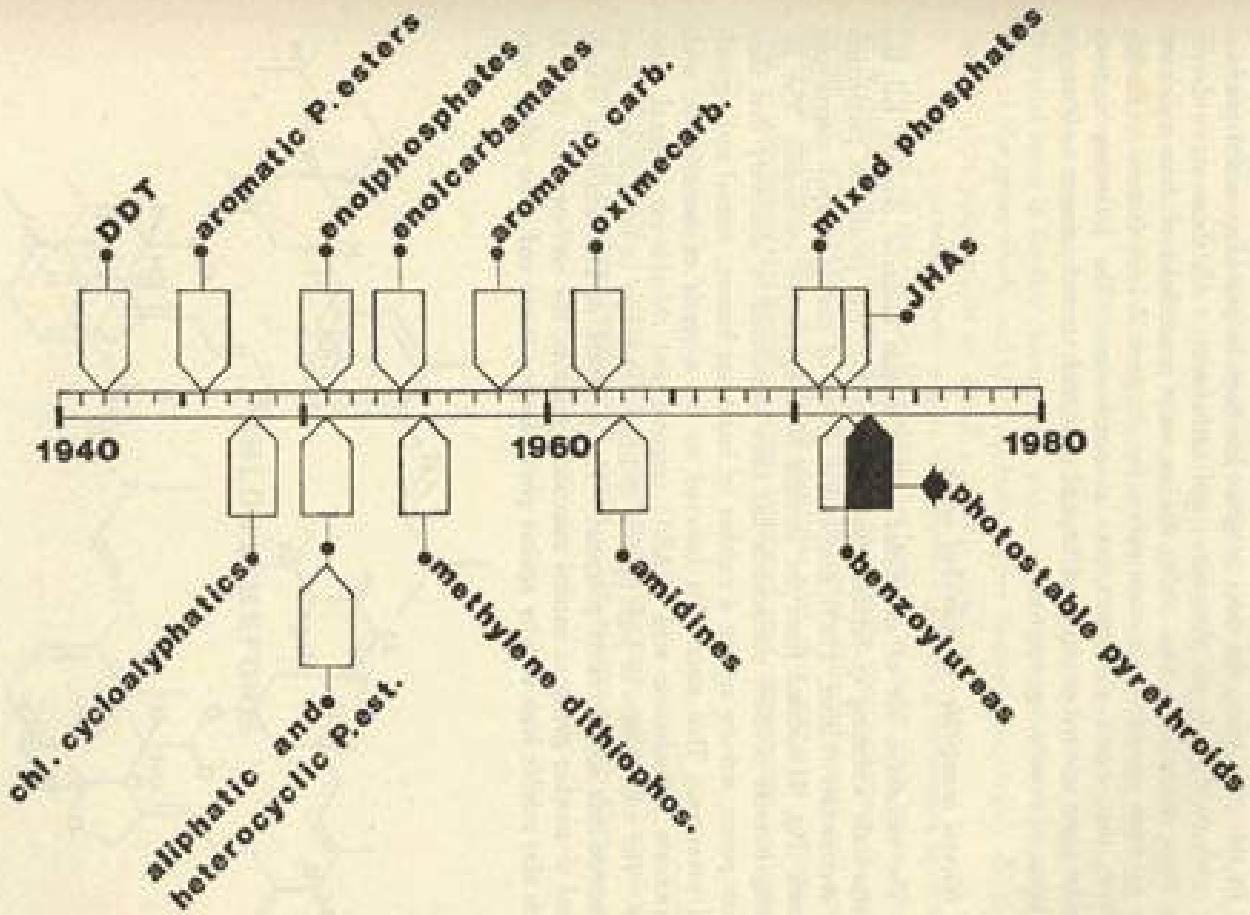


Fig. 2. - Time scale of disclosure of different classes of insecticides.

insecticides (Fig. 2). It took about 30 years of intensive fundamental research before sufficient general know-how had been built up to cause a break-through with the introduction of photostable pyrethroids.

In this time span, the most progress has been in providing useful products only with compounds of phosphorus and carbamates. All these act with the same toxic mechanisms, thus giving rise to many possibilities of cross-resistance. This situation represents the main reason for the general keen interest in finding products that attack the insect pest at novel sites. The following sections describe some selected examples of lines of industrial research, chosen to illustrate the range of present opportunities.

5.1 *Natural insecticides of microbial origin*

The successful use of antibiotics against human bacterial diseases has led to large-scale screening of fermentation products for crop protection properties. The *avermectins* (Fisher, 1985) comprise a group of closely related macrocyclic lactones (Fig. 3) isolated from the mycelia of *Streptomyces avermitilis*. The increasing interest of these compounds has been stimulated by discovery that they exhibit potent activity against a number of important human, animal and agricultural parasites. This activity is believed to be a result of interference with invertebrate aminobutiric acid (GABA) receptor and chloride-ion channel functions. The combination of high toxicity and high specificity to invertebrates gives the compounds an enormous potential. The structure of avermectins is closely related to another group of natural macrolide products, the *milbemycines* (Fig. 3) which also exhibit high activity against phytophagous mites and some other pests

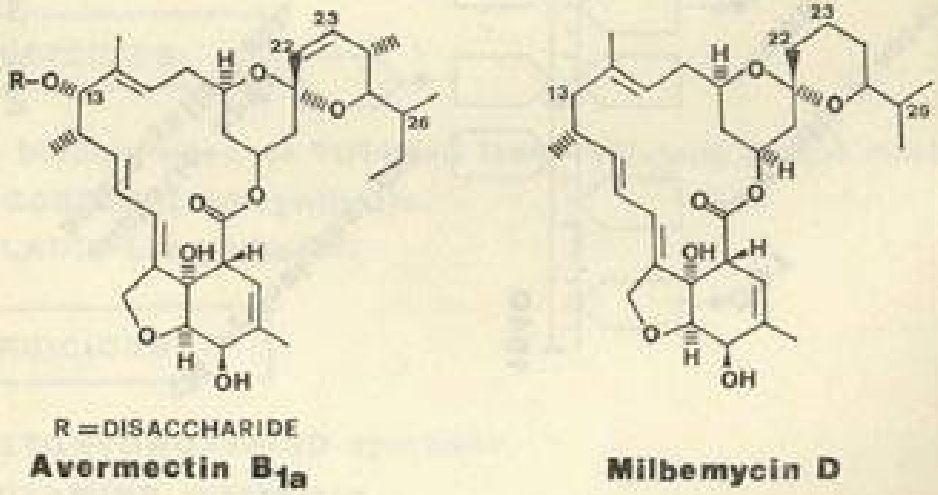


Fig. 3. - Structures of Avermectins B_{1a} and Milbemycin D.

(Mishima, 1983). Almost certainly milbemycines exert their action at the same receptor sites of avermectins. Discovery and exploitation of further such prototypes should be rewarding.

Other classes of microbial agents for insect control are bacterial insecticides. This is an area in which a substantial amount of academic and government research has been conducted for many years and to which industry has also made some significant contributions. Several products are already on the market and have been developed by traditional selection methods. Most are bacteria that attack a narrow range of insect pests, including the target one. The best known bacterial agent is *Bacillus thuringensis*, which is used for the control of caterpillars, such as the gypsy moth, and of mosquitoes. Other biopesticides already developed include virus preparations to attack a specific insect pest.

Work is currently under way to use genetic engineering techniques to increase the virulence of the insecticidal bacteria, as well as to make them more tolerant to environmental conditions and perhaps to broaden their spectrum of action. While few investigators believe that these improved microbial agents will replace chemical methods, there is a general consensus that they may play an important role as supplementary agents in many integrated pest management programmes.

5.2 *Insect behaviour modifiers*

Amidines (Fig. 4) are a group of compounds effective against a limited range of insects and acarines (Hollingworth, 1976). The subacute toxic effects underly-

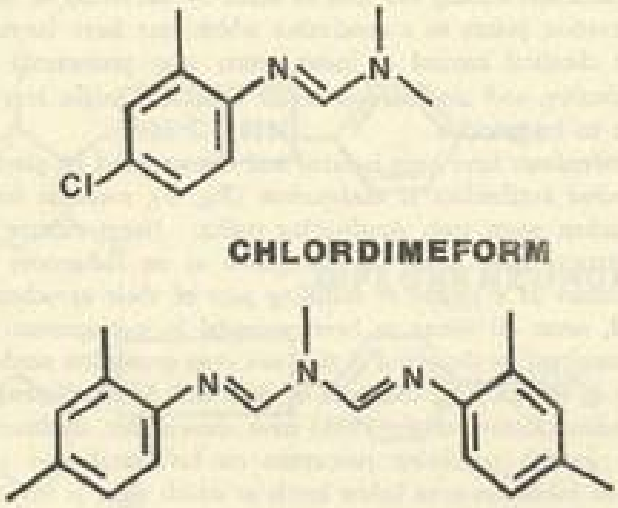
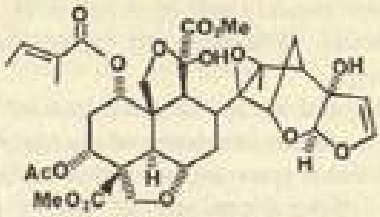
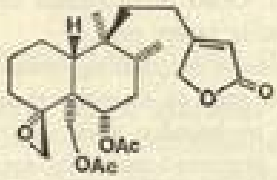


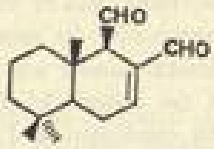
Fig. 4. - Structures of commercial amidines.



Azadirachtin



Ajugarin 1



Polygodial

Fig. 5. - Potent insect antifeedants from plants.

ing the activity of these products have only recently been the subject of investigations (Hollingworth and Lund, 1983). Sub-lethal activity of amidines and related compounds can produce repellent-like behaviour in lepidopterous larvae, and the subsequent non-feeding can lead to death by starvation or desiccation.

This observation points to a conclusion which may have far-reaching implications for the chemical control of insect pests: crop protectants need not be lethal to be effective, and modifiers of insect behaviour might represent a practical alternative to insecticides.

Several *antifeedants* have been isolated and characterized by plants. The best known and studied antifeedant is *azadirachtin* (Fig. 5), available from processed seeds of the Indian neem tree, *Azadirachta indica*. Neem culture and the use of its crude extracts have often been proposed as an indigenous industry for developing countries as a means of fulfilling part of their agrochemical requirements. Indeed, neem oil seems to have potential in management of rice pests and viruses transmitted by them and it may suit crop protection needs of resource-limited farmers of rice-growing countries of Asia and Africa (Saxena, 1986).

Recent studies (Krauss *et al.*, 1986) have shown that azadirachtin has also systemic insect growth regulating properties on holometabolous insects, being capable of ecdysis inhibition even below levels at which there is feeding inhibition. All the biological effects of this product are much more subtle, delayed and less susceptible to the build-up of resistance in insects than those of the majority of natural antifeedants. Unfortunately, the structure of the product represents a formidable obstacle to further synthetic modifications.

In the recent past, most work on insect control by behaviour modification has centered on *sex pheromones* (Piccardi, 1980), whose chemical composition is now known for a large number of insect species. Nowadays, while we recognize that impressive results have already been achieved with pheromones in monitoring devices for pest management, we must also recognize that their application in the direct control of pests is still largely in the exploratory phase. Before these methods will have a noticeable impact on current pest control practice, a number of technical obstacles will still have to be overcome. In my opinion, there are actually only a few pest complexes and high-value, intensively managed crops that can justify or require insect control with pheromones, and even in these cases pheromone application should be integrated with other tools.

5.3 *Inhibitors of chitin*

Benzoylphenyl ureas (Fig. 6) were found (Verlop, 1976) to be a selective class of insecticides which indirectly cause the death of pests by virtue of their unique inhibitory action on chitin deposition. The compounds also show ovicidal and chemosterilant effects. Diflubenzuron was the first product of the class and was discovered in the course of a synthesis program aimed at searching for new urea herbicides. It has a very low level of acute toxicity to man, fish and wildlife, and, due to a combination of factors, it is relatively safe to most natural predators.

These outstanding properties made the product particularly well accepted in many integrated pest management programmes to protect orchards and forests.

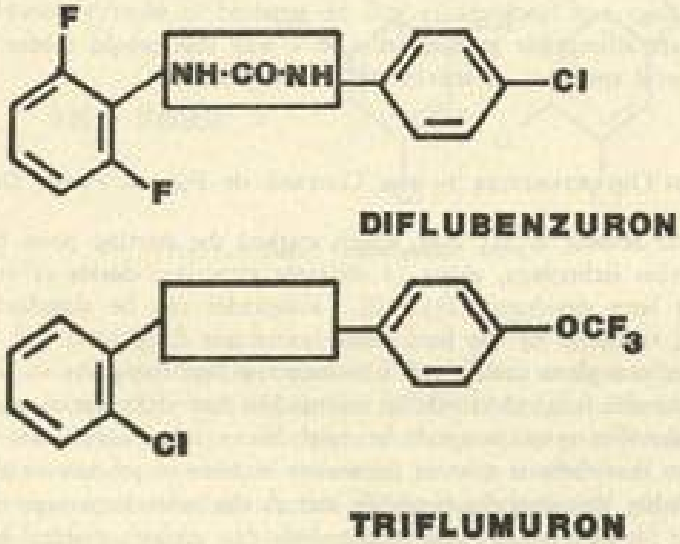


Fig. 6. - Structures of commercial benzoylphenyl ureas.

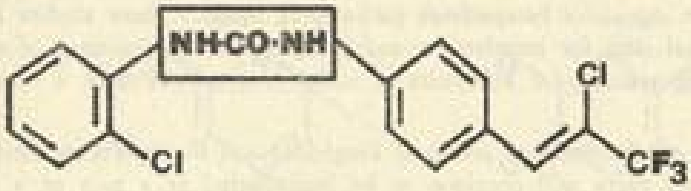
However, it did not obtain substantial market shares in the largest crop sectors. I believe that this failure is due mainly to the advent of photostable pyrethroids which overshadowed the product, and to a relatively slow-killing action as compared with that of other insecticides. In spite of these drawbacks, the search for new benzoyl ureas is still under way and second generation products (Fig. 7) have been announced (Piccardi, 1986). There are reasons to believe that, with the increased incidence of resistant problems to pyrethroids, products of this type will play a more significant role in crop protection.

5.4 *Insect growth regulants and antihormones*

Design of insecticides that interfere with the endocrine processes that control metamorphosis and reproduction in insects is to a large extent an unconquered frontier. For all the effort that has been put into search for juvenile hormone analogues (JHAs) (Fig. 8), commercial success has not followed. The main drawbacks to the widespread use of JHAs are strictly related to the nature of their physiological effects. Limitations to their application can, in fact, be anticipated if the insect's destructive stage is the larval one. This happens to be so in the case of the great majority of agricultural pests, so that the use of JHAs has been restricted mainly to Diptera that are harmful to public and animal health. Rather than applying mimics of juvenile hormone, it would be theoretically preferable to inhibit the production of the hormone in insects. From a common bedding plant, *Ageratum houstonianum*, Bowers (1976) isolated compounds (Fig. 9) that caused precocious metamorphosis in a few hemipteran species, thus providing a model for intensive follow-up synthesis in several industrial and academic laboratories. Little success has been achieved so far. The general impression is that if control agents of this type are to be made, then more basic research into insect physiology and biochemistry will be required to identify possible sites of action that are susceptible to disruption in a way that would confer a broader and more useful spectrum of activity on the compounds.

6. Research Opportunities in the Control of Fungal Plant Diseases

Since the Second World War, which marked the starting point for present plant protection technology, about 13 different structural classes of organic fungicides have been developed (Fig. 10). Fungicides can be classified as those that are not taken up by the host plant (protectant fungicides) and those that can penetrate the plant cuticle and translocate within the plant to the sites of infection (systemic fungicides). It is remarkable that after the successful introduction of the first systemic agent, benomyl, many other compounds have been developed, so that there is now an impressive number of products with systemic activity. Within the systemic fungicide sector, the most important commercialisations have been from the group of chemicals that act as ergosterol biosynthesis inhibitors (Schwinn, 1983) in fungal organisms. In contrast to other biologically



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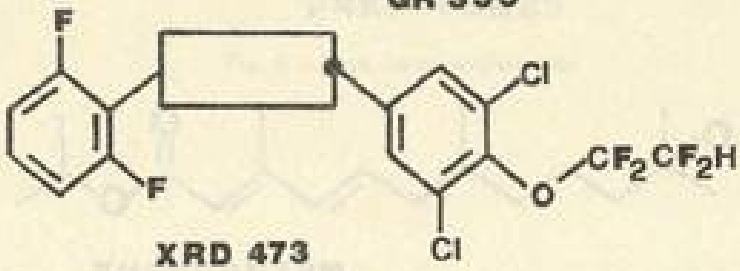

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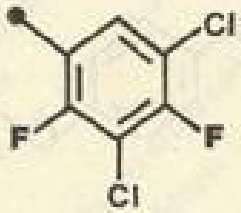

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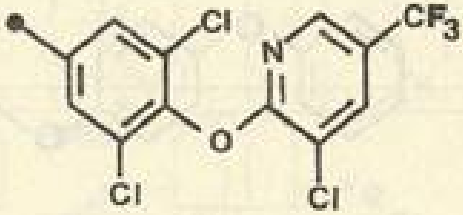


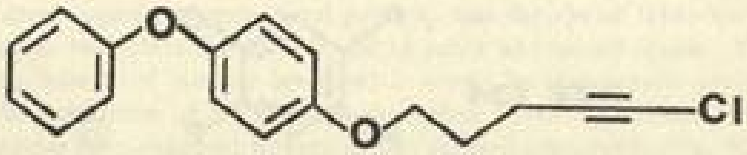
Fig. 7. - Novel benzoylphenyl ureas.

active organic molecules, their spectrum of action covers an unusually wide group of organisms, comprising plant and human pathogenic fungi and bacteria, and the morphogenesis of green plants. Their chemical versatility and low risk of losing efficacy due to the development of resistance, seem to render them still attractive for future improvements. Indeed, the chemical and biological potential of this class has not yet been fully explored, particularly in the field of plant growth regulation. Inhibitors of sterol biosynthesis have greatly facilitated fundamental

studies on the ergosterol biosynthesis pathway in fungi. These studies revealed many additional sites for interference and initiated the development of sophisticated screening systems for inhibitors of sterol biosynthesis with a new action mechanism.

Research on the mode of action of fungicides and the resistance mechanisms acquired against them will continue to be investigated as a part of a rational effort to identify new target sites within the fungal cell and to provide a guideline for the correct and sustained use of established products. There are many exam-

METHOPRENE



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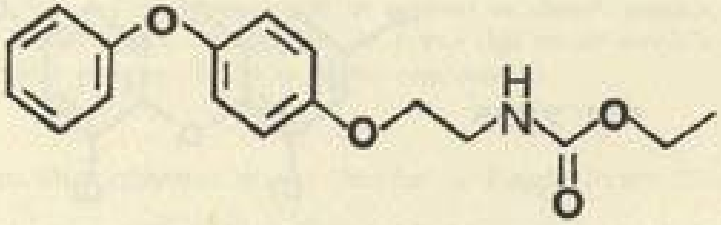

FENOXYCARB

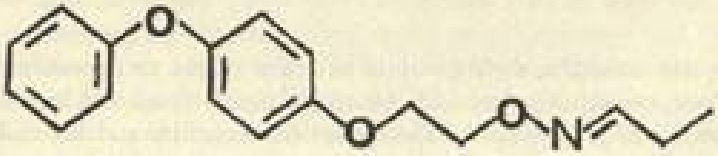

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Fig. 8. - Representative juvenile hormone analogues.

PRECOCENES

Fig. 9. - Plant insect antihormones.

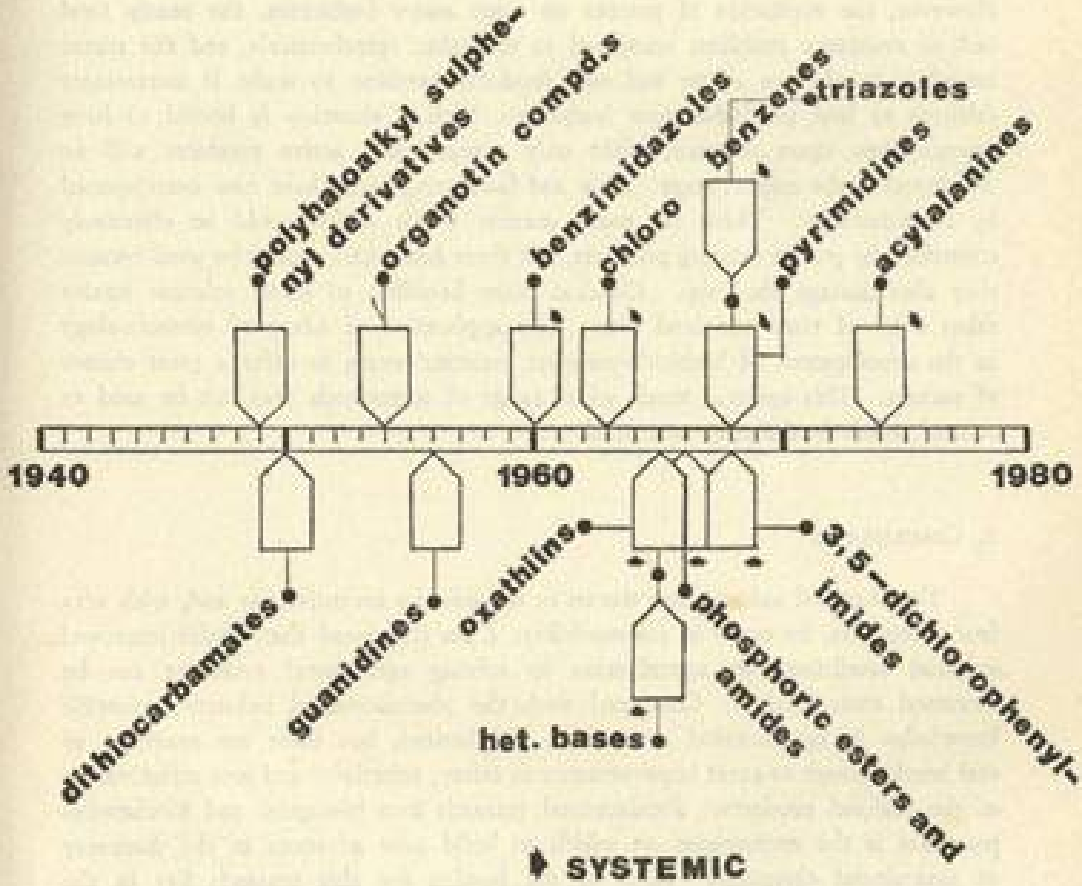

Fig. 10. - Time scale of disclosure of different classes of organic fungicides.

ples of the utility of this research approach, such as the practical use of some systemic products, in combination, or in formulation, with synergistic chemicals.

The search for new fungicides may be viewed from another perspective. Novel approaches could be directed towards the activation of phytoalexin synthesis or other natural defence mechanisms of the plant by the use of the so-called elicitors of host resistance (Bailey, 1986). However, prospects seem to be limited for the discovery of such alternative chemicals. At present, the origin and the chemical composition of the signal(s) involved in these systemic defence mechanisms are largely unknown. Their further investigation should be rewarding. If chemically accessible, such signal substances may provide a new method of plant disease control in the future.

7. Research Opportunities in Weed Control

In economic terms, the total value of herbicides now sold is impressive. However, the expiration of patents on some major herbicides, the nearly total lack of resistance problems compared to the other agrochemicals, and the recent introduction of very active and safe products combine to make it increasingly difficult to find profitable new herbicides. Such a situation is bound to have repercussions upon research, since only exceptionally active products will be developed to the market stage. New and fascinating vistas have now been opened by biotechnology. There are many current weeds which could be effectively controlled by potent existing products, but these herbicides cannot be used because they also damage the crop. Classical plant breeding to select tolerant strains takes a lot of time and land area. The application of advanced biotechnology in the development of herbicide-resistant varieties seems to offer a great chance of success. This opens a much wider range of compounds that can be used to control weeds in the crop concerned.

8. Conclusions

The chemical industry has shown in the past its inventiveness and, with very few exceptions, its sense of responsibility; I am convinced that, under improved external conditions, its contribution to solving agricultural problems can be increased even further. Compared with the pharmaceutical industry, scientific knowledge in agrochemical research is still limited, but there are examples of real breakthrough to great improvements in safety, selectivity and cost effectiveness of the realized products. Fundamental research into biological and biochemical processes is the cornerstone on which to build new advances in the discovery of agricultural chemicals. Most of the burden for this research lies in the universities and research institutes.

In tropical countries, especially the developing ones, insect pests and plant diseases determine whether or not the efforts of farmers are economically worthwhile and often are responsible for the entire loss of a harvest. In these countries, accelerated growth in food production requires solutions that make the benefits the greatest while reducing the costs and risks to the minimum. Chemistry's role in helping to solve these problems must be viewed in this light.

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