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REVIEW

New Concepts and Trends in Pesticide Chemistry

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This survey to identify new concepts and trends in pesticide chemistry was conducted as an activity of the American Chemical Society Division of Pesticide Chemistry Program Committee. Division members and others were queried about research opportunities, serious world pest problems, and pest control in the distant future (i.e., 21th century). In addition, recent symposia and reviews were consulted. The responses were organized into the following areas. (A) Research Opportunities: Insect Control, Weed Control, Disease Control, Surveillance of Pesticides, and Regulation of Plant Growth. (B) Most Serious Problems in World Pest Control: Persistence, Resistance Buildup, Chronic Toxicity, and Pesticide Availability. (C) Pest Control in the 21st Century: Pesticide Availability, Marketing, Registration, and Regulation of Pesticides, Integrated Pest Management, and the Practice of Pesticide Chemistry in the 21st Century.

In recent years, there has been increased participation in staff meetings, review panels, and scientific meetings by scientists who are concerned with identifying new concepts and trends in their field of activity. The motivations for these activities in the science of pesticide chemistry (and most others) include required accountability to supporting organizations, economic, environmental, regulatory, and various professional and scholarly considerations. From a personal standpoint, there is the belief that a scientist should dedicate his efforts to research that is of the greatest and most lasting value to society.

Stimulated by considerations such as these, and also by my relationships with the Division of Pesticide Chemistry (DPC), American Chemical Society (ACS), a survey was conducted as an activity of the DPC program committee to identify more systematically the new trends and concepts in pesticide chemistry. Questionnaires were sent to all members of the DPC. In addition, questionnaires were sent to approximately 100 biologists who were known to have effective research programs in various aspects of pest control chemistry.

The questions were as follows:

1. What do you perceive as the most important research opportunities in pest control (i.e., pesticide) chemistry? Why?
2. What chemical pest control research are you and/or your organization doing that you believe is promising and should receive emphasis?
3. Are you acquainted with new concepts that have not been widely utilized, but that you believe can be integrated into pest control strategies?
4. What do you perceive as the most serious

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problems in world pest control and how would their solutions be more amenable to new chemical pest control strategies?
5. Because of regulatory and environmental considerations, much analytical, toxicological, and metabolic research must be continued. What new trends and strategies are developing in these areas, and how do you believe they integrate with modern Pest Control Chemistry?
6. How do you visualize the discipline of Pest Control Chemistry as practice and prrofession in the 21st century?
7. Additional comments.

Attached to the questionnaire was a list of 36 strategies as examples of research areas that could be promising. It was hoped that these suggestions would sharpen the responses.

Initially, 52 individuals provided 205 suggestions, some of which were essentially duplications. These responses were sorted into categories related to research opportunities, serious problems in world pest control, and pest control in the 21st century. Within each of these categories, the suggestions were grouped into general strategies or problems. Subsequently, the survey results were supplemented by suggestions obtained from approximately 40 conversations with recognized leaders in the various subfields and by reviewing recent Division of Pesticide Chemistry meeting abstracts. Additionally, several books including some that had been generated by symposia were reviewed for additional suggestions.

It was recognized that the value of the report to the reader would be increased by the inclusion of as many literature citations as possible. By the nature of the objectives of this report, many of the citations are of recent meeting abstracts or personal communications; however, these should be sufficient to provide an entrance into the literature. An effort has been made to achieve a relatively equal emphasis for all areas of pest control chemistry, but it should be understood that because this report is of a survey rather than a review, some significant areas may not have been identified by the responders and therefore are not included.

A. RESEARCH OPPORTUNITIES

I. Insect Control

a. Sythesis of Insecticides

1. Insecticides: Design, Synthesis, and Utilization. The prognosis for these strategies has been competently reviewed by Menn (1980) in his paper "Contemporary Frontiers in Chemical Pesticide Research". Menn states that most known pesticides were discovered via empirical and analogue synthesis in combination with conventional screening and optimization by structure relationships. However, in recent years, a number of natural products with biological activity has been identified, but these have been sparingly exploited as synthetic models or as actual pesticides. With the emergence of the pyrethroids, rotenoids, and the insect antifeedants, rational design (*biorational synthesis*) of pesticide chemicals based on metabolic pathways, enzyme function, and mode of action of pesticides may be a goal whose time has come (Menn, 1980). Menn further states that innovative screening such as that needed to assess the activity of insect growth regulators and pheromones is a vital aid to biorational synthesis. Other examples claimed for the effectiveness of biorational synthesis in addition to those of Menn were presented in a 1979 ACS symposium "Biorational Approaches to New Pesticides and Growth Regulators" organized by Hollingworth (1979). Synthesis based on structure–activity relationships is not new. However, the capability for computer-based design of biologically active compounds is growing rapidly. Quantum chemical treatments are another facet of this approach.

2. Trends in Insecticides. The development of pyrethroid chemistry from structural assignment of natural pyrethrins to recent developments has transpired over the middle third of the 20th century and is steadily finding increased utilization. Much of the status of the synthetic pyrethroids is summarized in a book edited by Elliott (1977). Additional compounds and functions are continually being uncovered. Martel (1980) recently stated that the future of pyrethroid research would focus on economic considerations and efficacy, control of target, and new associations (of compounds with activity). Development of insecticides on noncholinesterase bases is being actively pursued from several aspects. A 1978 ACS symposium organized by Narahashi (1978) on the chemistry of neurohormones and neurotransmission and later published as a book (Narahashi, 1979) summarizes some of the current efforts.

The use of insecticides as a factor in pest management systems is another approach to the use of insecticides which is receiving increasing emphasis. A recently completed boll weevil management program in which phosphorous insecticides, diflubenzuron, and the boll weevil pheromones were used is an example of integrated pest management (Cross, 1980).

The use of dyes that are subsequently sensitized (activated) by photooxidation in insects is an approach being developed by Heitz and co-workers (Carpenter and Heitz, 1979). In a series of investigations they evaluated several dyes, used them successfully in pilot tests, and described three different toxic mechanisms.

3. Pesticide Delivery Systems. The formulation of pesticides will continue to provide challenges. Requirements for efficacy, economy, and safety will provide a focus for this research. The overall objective is to develop an innovative formulation technology that will maximize activity and minimize adverse effects. A book edited by Scher (1977), "Controlled Release Pesticides", contains 16 chapters addressing various aspects of formulation science including formulating materials and types of pesticides. An earlier book edited by Beroza (1976), "Pest Management with Insect Sex Attractants", secondarily provides information about formulation of pheromones where maintaining activity for extended periods is difficult. Butler and McDonough (1981) have established conditions under which the half-life of pheromone pesticides can be extended to 20–30 days with various elastomeric polymers. Specifically, their research is focusing on relationships between the half-life and cross-link density of different size molecules. The identification of superior carriers will continue to have high priority.

4. Reproduction, Development, and Growth Modifiers. Presently, regulators such as juvenile hormone (JH) mimics, anti-JH compounds, reproduction inhibitors, ecdysones, antiecdysones, precocenes, prostaglandins, diapause hormones, and the chitin inhibitors are examples of compounds that either have been synthesized or where synthesis is being attempted. Menn (1980) has reviewed many of these efforts. The synthesis of a number of classes of insect reproduction modifiers has been investigated by Borkovec (1976). They are presently focusing their efforts on the identification and/or synthesis of chitin synthesis inhibitors, juvenile hormone mimics, insect neurohormones, brain hormones, and other agents affecting insect maturation (Borkovec, 1976; DeMilo and Borkovec, 1980). Opportunities in this area for synthesis research will continue to follow biological descriptions of activities and identification of active agents. For insect pests of cotton, there are presently three benzoylphenylureas of sufficient promise for application to foliage. They are diflubenzuron and penfluron (Philips, Dupher B.V.) and trifluron (Bayer A.G.) (Bull et al., 1979). These compounds primarily disrupt the synthesis of chitin but also affect muscular function and larvae emerging from eggs of treated females. There is some species specificity, in that several beneficial insects are evidentally not harmed. The insect growth regulators also include a number of structurally diverse juvenile hormone analogues. The great interest manifested in insect growth regulators is due in part to the fact that they possess unique modes of action, often of great specificity, and are active at low concentrations.

5. Asymmetric Synthesis. Stereoisomers of pesticides often possess different toxicological, metabolic, attractant, or hormonal properties for insects. Differences in toxicity of stereoisomers have also been demonstrated for insects and mammals. The status of the stereochemical aspects of pesticide chemistry was summarized in a symposium organized by Siddall (1978). Two examples of the current interest in asymmetric synthesis are illustrated by studies reported by Sonnet and Heath (1980) on the white peach scale pheromone and by Mori et al. (1978) on the antipode of the boll weevil pheromone. Also, asymmetric synthesis of a number of forest insect pheromones has been accomplished during the past 10 years by Silverstein and coworkers (Brand et al., 1979). Opportunities in asymmetric synthesis will be derived from requirements for increased biological activity and specificity. Control of populations by confusion with stereoisomers may also continue to develop.

b. Biochemical and Toxicological Studies on Insecticides

1. Biochemical Mechanisms in Insects, Target Mode of Action, and Coincidental Effects. With the continued regulatory requirements including those of environmental impact, these factors will continue to receive attention as new insecticides, often with novel modes of action, are introduced. The emphasis will be on the development of new techniques and structure–activity investigations. A continuing source of information on current trends in this area is the journal *Pesticide Biochemistry and Physiology*. Effects of pest-specific compounds on metabolic pathways and cellular structures will also receive attention, the chitin synthesis inhibitors being an example.

2. Metabolic Fate of Pesticides in the Environment Including Nontarget Organisms. Two recent books that were generated by symposia, "Pesticide and Xenobiotic Metabolism in Aquatic Organisms", edited by Khan et al. (1979), and "Xenobiotic Metabolism: In Vitro Methods", edited by Paulson et al. (1979), define much of the present knowledge in these research areas. They discuss the fate of pesticides and xenobiotic chemicals in aquatic organisms, biotransformation and elimination processes in aquatic organisms, xenobiotic metabolism in plants, animals, and insects, and a survey of the various methodologies currently being used to evaluate their significance. These investigations will continue to be required. Because of the magnitude of data required, considerable effort will be direct to developing faster and more sensitive methods, automated where feasible.

3. Toxicology of Pesticide Chemicals Including Carcinogenicity. Because pesticides must be evaluated for their toxicological effects, a number of questions must be addressed. Toxicological, biochemical, analytical, and regulatory aspects must be considered. Progress in this area (as in many others) requires multidisciplinary cooperation of toxicologists, physiologists, biochemists, and pesticide chemists. A recent special conference of the Division of Pesticide Chemistry, the proceedings of which have now been published (Bandal et al., 1981), attempt to summarize the status of knowledge, activities, and objectives in modern pesticide toxicology. They considered aspects such as pathology, long-term toxicity, genotoxicity, carcinogenic potential, reproduction and teratrogenic effects, epidemiology, pharmacokinetics and threshold, the methodology and statistics of analysis, risk–benefit analysis, animal data as a predictive tool, and the role of toxicology in developing pesticide regulations. Recently in a symposium organized by Chambers (1981), effects of chronic exposures to pesticides in animal systems were explored. Some of these were carcinogenicity, neurotoxicity, estrogenic actions and reproductive toxicity, and mutagenicity and teratogenicity. Future research can be expected to concentrate on the recognition and description of additional effects and, because of the vast scope of effects, improved methodology to evaluate them. Rapid screening procedures such as that achieved by the Ames test (i.e., enzymatic or immunochemical) will need to be further developed.

4. New Pesticides with Unconventional Modes of Action. These pesticides, in main, include the so called third and fourth generation insecticides that affect behavior, development, and reproduction and have been discussed earlier from other viewpoints. Their modes of action have been and are being elucidated by neurobiological procedures such as those summarized by the contributors to Narahashi's (1979) book. Their effects are in other ways subtle and/or delayed and less susceptible to the buildup of resistance in the insect. The biochemical mechanisms underlying the activity of these pesticides have only recently been the subject of investigations. The status on biochemical mechanisms of insect growth regulators was summarized by several of the participants in a Division of Pesticide Chemistry symposium organized by Cannizzaro and Siddall (1979).

5. Identification of Enzymes That Control Specific Processes. Pesticides, other xenobiotics, and even insect compounds can be used as bioassay tools to identify enzymes that control specific processes. Starratt and Steele (1979) isolated the neuropeptide proctolin from the cockroach and showed that it was inactivated by cockroach enzyme systems. The peptide was shown to have myogenic activity. This finding provides an approach to the design of enzymes resistant to analogues of proctolin.

6. Resistant Insect Strains Treated with Recombinant DNA. Evidently the application of recombinant DNA technology to insect control is just commencing. The manipulation of insects with recombinant DNA will likely receive increasing attention both in laboratory studies and for field control.

c. Natural Pest Control Agents

Several classes of these agents have already been discussed in sections a and b with regard to synthesis and biochemical studies. Natural pest control agents can be conveniently divided into two groups, those that modify insect behavior and those that modify insect growth, development, and reproduction. However, antifeedants may also be toxicants (antigrowth) and toxicants may also be antifeedants (behavioral); thus their designation is a function of the bioassay used.

1. Sex, Assembling, and Other Pheromones. The recent literature contains hundreds of citations attesting to the specificity, uniqueness, and efficacy of these compounds. Beroza's (1976) book on "Pesticide Management with Insect Sex Attractants" and Siddall's (1978) symposium on "Stereochemical Aspects of Pesticide Chemistry" are two examples of efforts to summarize the current status of the prospects for pheromone utilization. Two of the major drawbacks to utilization of pheromones are that marketing opportunities are limited and that the control achieved is usually less than complete. Pheromones may occasionally be suitable for control but may be most applicable in survey applications or as part of integrated pest management programs. Pheromones have repeatedly been used to demonstrate the presence of insects where scouting and other physical procedures are ineffective. It has been demonstrated that pheromones can be used both for attraction and for confusion. For confusion, either large quantities of the pheromone or isomers can be used. It has been further suggested that where several insects attack a crop, all of the pheromones may be formulated together. Where several components are required for an insect response, confusion may be achieved by altering the ratio or withholding one or more components.

2. Allelochemics. Food attractants, repellents, feeding stimulants, feeding deterrents, antifeedants, oviposition stimulants and deterrents, toxicants, and nutritional factors are examples of allelochemics. They are usually secondary plant constituents (nonnutritional chemicals affecting insect behavior and development). Allelochemics giving the host plant an adaptive advantage are called allomones, and factors giving the insect an adaptive advantage are called kairomones. Three recent books that discuss these agents and their activities are "Host Plant Resistance to Pests" (Hedin, 1977a), "Biochemical Interactions Between Plants and Insects" (Wallace and Mansell, 1976), and "Herbivores: Their Interaction with Secondary Plant Metabolites" (Rosenthal and Janzen, 1979).

For many years, the U.S. Department of Agriculture (USDA) has conducted a research program to identify attractants and repellents by bioassaying plant extracts and synthetic compounds, many related to plant compounds (Beroza, 1970). Attractants for the Mediterranean fruit fly, oriental fruit fly, and Japanese beetle were selected and widely used. However, in recent years, food attractants (kairomones) have found only infrequent applications. On the other hand, the antifeedant compounds have recently become the subject of renewed interest, and several have now been registered for commercial use. The work of Kubo and Nakanishi (1977) and Jacobson (1977) and the interests of several industrial companies have been instrumental in this new trend. The relative specificity and high activity of the antifeedants, along with several other attributes that will be discussed in the section on mechanisms, have promoted this interest.

3. Toxicants from Tropical and Desert Plants. The discussion of this subject has been separated from that of allelochemics to emphasize that novel compounds possessing high toxic activity and also often antifeedant action have been isolated from these plant sources. The work of Kubo and Nakanishi (1977) and Mabry et al. (1977) is illustrative of this area of interest. One of the apparent explanations for the large number of tropical and desert plants possessing highly toxic compounds is that they must coexist with higher insect (and often disease) infestations than plants grown in temperate climates. In evolutionary time, plants that are most able to coexist (in part because of their biosynthesis of toxicants) have been selected. An increase in the accessibility of these plant materials will depend largely on the activity of botanical and pharmaceutical collection programs.

4. Naturally Occurring Hormonal Agents from Insects and Plants. The juvenile, molting, brain, and diapause hormones, antihormones such as the precocenes, and the prostaglandins are examples. The book edited by Gilbert (1976) titled "The Juvenile Hormones" and that of Slama et al. (1974) titled "Insect Hormones and Bioanalogues" provide a general summary of the status of these classes of compounds. It is probable that additional hormonal and antihormonal agents with high activity and specificity will be isolated from plants or insects. Some will act in a direct manner while others may promote biosynthesis of a secondary compound(s) with toxicity or other activity toward the insect. The high activity and great specificity of these compounds make it probable that field applications can be carried out under optimal conditions, often as a part of pest management systems.

5. Microbial Agents for the Control of Insect Pests. Microbial agents traditionally have been visualized as contributing to biological control of pests. Some of these microbial agents can now be defined chemically. Huang and Bandal (1979) recently organized a symposium on microbial agents for control of insect pests. There were reports in this symposium on toxins that have been isolated from *Bacillus thuringiensis*, *Bacillus popilliae*, *Bacillus spaericus*, fungi, baculoviruses, and parasitic nematodes. Work is also progressing on fly control in animal production and antigens for nematodes and insects. Strobel and Myers (1980) have recently isolated a bacterium normally found on leaves of wheat, barley, and oats that can defeat the fungus responsible for Dutch elm disease. The bacteria is a pseudomonad that produces fungus-killing antibiotics. It is proposed that this approach may also be used with insects.

6. Plant Growth Regulators and Natural Products as Inducers of Insect Resistance. Plant growth regulators have been shown to increase the biosynthesis of certain secondary plant constituents that in turn decrease plant attack by insects. α-Naphthaleneacetic acid, for example, elicits increased terpene biosynthesis in citrus, thus decreasing attack by fruit flies. In that several of the plant growth regulators are natural products, the approach of using both natural and synthetic plant growth regulators may continue to find applications in insect control. A synthetic plant growth regulator that has been found to elicit resistance in plants to insects is mepiquat chloride (PIX, BASF). The tannin content of cotton plants was reported to be increased by foliar application of PIX under specified conditions. The tannins have been implicated as resistance factors in cotton to *Heliothis* insects (Chan et al., 1978).

A general term for the compounds that are induced is "phytoalexin", a higher plant metabolite that is antibiotic to certain potential plant pathogens. The phytoalexins are biosynthesized in greater concentrations when the plant is subjected to stress. Therefore, the attacking agent (fungi, bacteria, or viruses in most work to date) elicits the initiation or increased synthesis of phytoalexins (antibiotic compounds). It has recently been shown that attack by insects and nematodes also can elicit the formation of phytoalexins. A number of chemical elicitors of phytoalexins have been identified (Keen and Bruegger, 1977), but none have warranted extensive application.

d. Pest Control Mechanisms

Many of the so-called novel pest control mechanisms (also identified as those being mediated by the third and fourth generation insecticides) have already been discussed in the earlier sections. They are included separately in recognition that they represent a body of effort and a perspective that is unique.

1. Neurochemical Targets. The focus of this research area is to identify pesticides that attack the insect neurotransmission system at a "novel point". Cholinesterases may be the prime target for certain insecticides such as the organophosphates and carbamates, but no specific enzyme system has been clearly established as the target for other insecticides. Ionic channels of the nerve membrane, the major site that triggers excitation, have been shown to be the target for pyrethroids and certain chlorinated hydrocarbons. The molecular nature of such insecticide–channel interactions has not been elucidated.

In pheromone perception by insects, two different antennal receptor cells have been found to be involved. These receptors are sufficiently flexible to perceive more than one compound and are sensitive to precise ratios of compounds. Receptor specificity is further demonstrated in the differential response to chiral forms of pheromones and in the responses from receptors on the antennae of males and females. Some future studies will be directed to understanding the messenger–receptor interactions that are involved in the mechanism of energy transfer. The role of the lipoproteins and sulfhydryl groups in energy transfer will be further explored. The symposium and subsequent book of Narahashi (1978, 1979) summarize much of the present knowledge about neurochemical targets.

2. Mechanisms of Agents Controlling Growth, Development, and Reproduction. The status of research in these areas has been summarized by Menn (1980), Hollingworth (1979), Borkovec (1976), and Cannizzaro and Siddall (1979) and previously discussed from other aspects in this report. The most active agents at present appear to be the diflubenzurons that inhibit chitin synthesis and the precocenes which prevent JH biosynthesis. Other classes have similar manifestations, though they are not as active. The juvenile hormones and their analogues, the ecdysones, and the diapause and brain hormones also are the subject of mechanistic studies. Law (1980) has identified the rate-controlling step in juvenile hormone biosynthesis and are examining which endogenous and exogenous factors act to modify the rate of this step. These approaches appear to hold promise for finding novel control agents. Quistad et al. (1981) have been able to inhibit the production of juvenile hormone with tetrahydro-4-(fluoromethyl)-4-hydroxy-2*H*-pyran-2-one, a cholesterol inhibitor. Kubo et al. (1981) has recently identified two previously known photoecdystones from *Ajarga remota* (Lab.), cytasterone and ecdysterone. These compounds act through ecdysis inhibition in successive molts until death is the result. Another mechanism which apparently involves insect hormones concerns the tobacco hornworm, the larva of which switches from excreting to storing uric acid as it prepares to enter the pupal stage, and juvenile hormone prevents storage during the larval stages (Buckner and Reinecke, 1981). The identification of a hormone mimic or other chemical to inactivate the switch could provide practical control.

Additional information about recent trends in insect hormones and related areas can be obtained from a book now in press, "Regulation of Insect Development and Behaviour", edited by Sehnal et al. (1981).

The antifeedant compounds, the subject of investigation by a number of workers, particularly Kubo and Nakanishi (1977) and Jacobson (1977), have been known for many years but now are finding renewed interest. Electrophysiological studies with the sugar receptors of insects by Kubo and Nakanishi show that the antifeedants act by irreversibly blocking the sense of taste. The antifeedants tested to date are specific for certain insects, active at very low concentrations, generally active against a few insects, and generally inactive against the Southern armyworm *Spodoptera eridonia*. These variable activities may serve as the basis both for structure–activity studies and mechanistic studies at the receptor level.

The use of antifeedants has an added advantage over that of toxicants in that the insect consumes little if any of the plant, thus limiting damage. Pest control materials which are specific for insects and which affect metabolic pathways or anatomical structures (including cellular) which are unique for insects may possess less toxicity for mammals and thus may be superior as pesticides. It has also been speculated that the highly specific lipolytic and proteolytic enzymes will be found to control specific processes in insects, as they do in mammals; thus they will be important targets for research.

3. Modifiers of Insect Behavior. The categories of insect behavior compounds mediating insect–insect and plant–insect interactions have precipitated several types of mechanistic studies. They include studies on the neurological level (Narahashi, 1978, 1979), studies on laboratory and field insect responses to insect or plant compounds [i.e., pheromone, attraction and feeding (kairomone) repellent and antifeedant (allomone), and oviposition], and studies on biosynthesis of the insect agents (Beroza, 1976; Brand et al., 1979; Hedin, 1977a; Wallace and Mansell, 1976). The last approach, in addition to the basic aspects, proposes that biosynthesis of the agent can be manipulated to either optimize or restrict its output (Hughes, 1974; Hedin, 1977b). An example of this is work by Hedin et al. (1982) in which boll weevil pheromone biosynthesis was optimized (increased 3×) by addition of JH III (1.0 ppm) to the diet. Presumably, the rationale for continued work on the mechanisms of modifiers of insect behavior will be to optimize the utilization of the respective agents or to restrict their presence and/or action.

4. Induced Autointoxication. The goal of this approach is to apply precursors that develop activity only in the target species. Although photosensitization is not always required to develop activity, this has been reported as occurring with several dyes in flies (Carpenter and Heitz, 1979) and with acetylenes and furanocoumarins (Berenbaum, 1978) that affect the insect melanins and are phototoxic. The advantage of this approach for practical application is that it may permit foliar application of compounds with low toxicity and perhaps high specificity for the target insect; continued studies of the mechanisms of activation can be expected to generate more efficient precursors.

5. Insect Resistance to Xenobiotic Agents. During the past 20 years, a high percentage of the research effort expended on pesticides has been to survey for developing resistance by insects and their mechanisms of detoxification. Typical of this effort was the symposium organized by Plapp (1973) which included reports on insect resistance to DDT, genetic studies affecting cross resistance, the biochemistry of insect resistance–nonmicrosomal mechanisms, induction of detoxifying enzyme systems, the resistance to JH analogues by hydrolysis and oxidation, and oxidative metabolism. Although research will continue to elucidate the mechanisms of developing resistance in insects to pesticides, much of the concentration will be on the development of agents with specific targets and on superior delivery systems.

6. Photoperiod Manipulation of Insect Diapause. Although this approach can be considered physical and, therefore, not precisely in the realm of pesticide chemistry, the mechanistic effect of photoperiod manipulation is to modify insect pigments or hormonal activity in a manner that is harmful to the insect. Hayes et al. (1979), by increasing the length of both light and dark periods of the European corn borer, prevented fall diapause and reduced the spring emergence of adults. The use of photoflash for insect control was suggested by several responders.

e. Plant Resistance to Insects

The development of resistant host plant varieties has several advantages compared with the traditional and other alternative approaches to pest control. There is no complicated technology for the grower to understand, and it is inexpensive, because any increased seed costs will be more than offset by decreased costs for pesticides and their applications. According to a recent economic survey, Headley (1979) forecast that resistant varieties will have a major role in pest control in 1992; chemical methods will continue to have a major role, but biological methods including pheromones will not have significant usage. Under some circumstances, resistance may be sufficiently great and unique to suffice alone. However, in most instances, resistant varieties will be used as a part of integrated pest management programs. There are several areas of investigation on chemical aspects of plant resistance to insects that are currently receiving attention and are considered promising.

1. Costs of Defense and Yield. Plants that stand exposed to pests over long periods generally develop defense systems that require a relatively large quantity of the resistance agent(s), and these agents often bind dietary protein or otherwise interfere with digestion. Plants that are exposed to pests over a short period generally develop defense systems that involve the biosynthesis of a small amount of a highly toxic agent. Although the latter requires that the plant divert less energy from yield to defense, in evolutionary time the insect may be able to adapt to the plant and defeat the resistance. This concept about the costs of defense and yield is discussed in "Biochemical Interaction Between Plants and Insects" (Wallace and Mansell, 1976) and "Herbivores: their Interaction with Secondary plant Metabolites" (Rosenthal and Janzen, 1979).

2. Coevolution of Plants and Insects. Plants and insects coevolve, and the continuing adjustments of one to the other reflect the biosynthesis of defensive compounds by the plant and the development of detoxification or avoidance mechanisms by the insect. The dynamic nature of this relationship is illustrated by the ability of insects to induce detoxifying enzymes within 24 h when challenged by a toxic agent. Plant injury, in turn, can elicit the biosynthesis of additional quantities of resistance agents. The challenge to elucidate the roles of these agents and mechanisms in a myriad of plant–insect interactions is evident.

3. Identification and Role of Plant Resistance Compounds. Not all expressions of plant resistance are chemical, but of those that are, the so-called secondary plant compounds appear to be dominant. Among those shown to manifest resistance are various classes of phenolic compounds including flavonoids and aromatic acids, terpenoids including the sesquiterpene lactones and heliocides, and nitrogenous compounds including amino acids and amides, glucosinolates, cyanolipids, cyanogenic glucosides, alkaloids, proteinaceous compounds including protease inhibitors, phytohemagglutinins, and lectins, toxic seed lipids including unusual fatty acids, acetylenic and allenic lipids, fluorolipids and cyanolipids, the saponins, and the tannins and lignins (Hedin, 1977a; Wallace and Mansell, 1976; Rosenthal and Janzen, 1979). The roles of these compounds are difficult to elucidate for several reasons. Not all compounds toxic to one insect are toxic to another. In evolutionary time, some insects develop mechanisms by adaptation to detoxify compounds in plants on which they must feed whereas others do not. As a result, a compound toxic to one insect may be a feeding stimulant for a second. Also, several resistance mechanisms may be operative in the plant. To the extent that the biosynthesis of these compounds is an expression of genetic information, the elucidation of these compounds and their roles can provide a guide to selections by plant breeders. Additionally, as genetic studies become more sophisticated, the assignments of the role of individual genes in directing biosynthesis of resistance compounds will be expedited.

4. Multiple Factor Contributions. There is increasing evidence for multiple factor contributions to plant resistance. In laboratory feeding studies, it has been shown that growth of the tobacco budworm is retarded by a number of compounds isolated from the cotton plant including gossypol and related compounds, several flavonoids, catechin, the tannins, cyanidin, delphinidin, and their glucosides (Bell and Stipanovic, 1977; Chan et al., 1978; Hedin et al., 1980b). Field studies have now shown that varieties high in several components possess the greatest insect resistance (Hedin and Jenkins, 1981). Thus, there is the potential to breed for variety crosses high in several components, the biosynthesis of each of which may be controlled by separate genes. Improved gene splicing technology should eventually be applicable to these objectives. Multiple factor resistance should be less susceptible to adaptability by insects and may be less costly to the plant in terms of energy diverted to biosynthesis of defensive compounds.

5. Differential Sensory Perceptions of Plant Compounds by Insects. These perceptions are a function of the chemical composition of the plant and the chemical sensory (neurological) resources (including the brain) of the insect. The result of these interactions is a behavioral response. The understanding that not all insects respond identically to a stimulus brings diversity to these investigations. The current approaches to sensory perception studies are those of behavioral analysis and evaluation of neurotransmission, previously discussed with regard to the synthesis of novel insecticides.

6. Photosensitizers, Elicitors, and Primitive Immune Systems. These approaches have been discussed previously with regard to synthesis strategies, pest control agents, and pest control mechanisms but are also plant resistance strategies.

7. Phytochemical Disruption of Hormonal Processes in Insects. This approach has been discussed previously with regard to pest control agents and mechanisms. Plants biosynthesize many compounds that act at very low concentrations in insects as hormones or antihormones. Slama (1979) has summarized much of the current knowledge.

8. Location and Differentiation of Secondary Constituents within Plants. Secretory and storage organs, specialized cells, and specific plant parts often biosynthesize a single compound or a group of related compounds that may have resistance properties. The presence or absence of these organs, cells, or parts has often been demonstrated to be genetically controlled. A widely recognized example is the pigment (gossypol) gland in cotton, the chemistry and biological significance of which have been intensively investigated. Insects feed differently on plants according to their morphological, developmental, and behavioral characteristics. For instance, aphids feed on the phloem. Unless the concentration of the resistance compound is high in the phloem, the insect will feed successfully. Changes in the concentration of resistance compounds also vary seasonally and with maturity. In breeding for resistance, the location of the resistance compound in the plant must be considered.

f. Integrated Pest Management

Philosophically, the assumptions on which integrated pest management programs are based and the associated objectives are that (1) the use of insecticides and other agents that have a serious environmental impact should be restricted, (2) the population of insects attacking the crop can be decreased to a level causing a minimal economic loss, but conscious efforts to eliminate the insect should not be emphasized, (3) the profit from the crop, but not necessarily the yield, can be maximized, (4) beneficial insects and other biological elements should make the maximum feasible contribution, (5) procedures that could accelerate the buildup of insect resistance should be restricted, and (6) the use of multiple control procedures can defeat the insect's efforts to survive by adaptation. The proposed chemical contributions to an integrated pest management program have been discussed in detail previously. They are (1) insect behavior modifiers, (2) insect development modifiers, (3) insect reproduction modifiers, (4) breeding for plant resistance factors, (5) inducing plant resistance factors, (6) synthesis of superior pesticides, (7) development of improved formulations, (8) development of pesticides with novel modes of action, and (9) identification of natural product pesticides.

II. Weed Control

Weed control is defined as the selective application of stress agents that can be chemical (synthetic or natural), tillage, fertilizer, cultural practice, or other. It has been suggested and is generally recognized that control of weeds must follow the approach of integrated pest management. Some of the desired results are that the system (1) be energy efficient, (2) conserve soil, (3) be environmentally safe, (4) be inexpensive, (5) be effective, (6) be broad spectrum where desirable, and (7) kill every species except the crop (hardly ever achieved). Shaw has reviewed the status of weed research and proposed systems for future weed control in a series of publications (Shaw, 1974, 1976, 1979).

a. Trends in Herbicide Synthesis, Formulation, and Application

1. Categories of Herbicides and Their Use. Chemical weed control in the modern sense was not used extensively until after World War II. Herbicides have found acceptance because they reduce tillage, fertilizer, irrigation, harvest, and grain drying costs and reduce crop yield losses, transportation, storage costs, and the number of acres needed for crop production. Adler et al. (1977) has listed the various categories of herbicides in present use and their applicability. Shaw and Jansen (1972) have proposed chemical weed control strategies for the future. As a part of the proposed strategies, they have considered ecological aspects, advances in technology, the impact of control on crop production practices, problems, risks and benefits, and research, regulatory, and educational needs.

2. Herbicide Synergists. Kolattukudy (1968) found that dalapon reduces the cuticular layer of weeds to make them more susceptible to thiocarbamates. This mechanism is in effect synergistic. Presumably there are other synergistic mechanisms and compounds.

3. Herbicide Antidotes (Safeners). The compound 1,8-naphthalic anhydride has been identified as an antidote (or safener) for thiocarbamates on corn and for alachlor on sorghum, molinate on rice, and barban on oats. Other active herbicide antidotes include allyl- and propargylamides of oxalic acid and halogenated alkanoic acid amides (Hoffmann, 1977). Sites of uptake and action of herbicide antidotes and aspects of glutathione conjugation with the herbicides have been investigated. Research to elucidate the mechanisms of antidote action and to develop more effective compounds is in progress.

4. Controlled Release of Herbicide from Crop Seed. Dawson (1980) has shown that EPTC, a thiocarbamate, can be impregnated in alfalfa and *Phaseolus* seeds by soaking. EPTC is believed to move in soil as a vapor. The concentration is initially very high in and near the seed, but the seed is immune to the herbicide. The seedling that emerges is tolerant and the developing plant is somewhat susceptible, but by this stage, the herbicide has largely spread out in the soil or dissipated. It has been proposed that EPTC can also be formulated as seed-sized granules and sown together with the crop seed. The controlled release agents are often, in effect, safeners. The compound 1,8-naphthoic anhydride, in such commercial products as alachlor and metribuzin, is believed to retard leaching by physical adsorption or chelation. Foley and Wax (1981) found that starch xanthate retarded the release rate from granules when certain specially prepared herbicides were incorporated in the soil.

5. Foliar Application of Herbicides. The application of dichlofop [methyl 2-[4-(2,4-dichlorophenoxy)phenoxy]propionate] over the tops of soybeans eliminated johnson grass and other grasses. This capability may provide a savings in energy costs in comparison with the customary soil incorporation if it is assumed that the weeds have not already competed with the crops by the time of such postemergence treatment. Two other relatively new agents, sulfonylureas (DPX-4189, 5648), have been shown to be active at low rates (30–100 g/ha) as a foliar application. They have been found to possess good crop tolerances; they have varying activities for broadleaf weeds and grasses which can be changed by altering the substituent groups (Moreland, 1980a,b; Shaw, 1980).

b. Biochemical Studies on Herbicides

1. Modes of Herbicide Action. Modern herbicides have been classified with regard to interference with processes such as lipid synthesis, with membrane integrity, changes in photosynthetic and mitochondrial electron transport, oxidative phosphorylation, synthesis of pigments, RNA, DNA, and proteins, and binding of herbicides at the IAA and other growth regulator sites. They have also been classified with regard to modifications in structural organization, energy supply, and growth and reproduction (Corbett, 1974). Moreland (1977, 1980a,b, 1981) has proposed that more studies are needed to elucidate the action of the diverse groups of herbicides that interfere with the photochemistry of isolated chloroplasts. Research is also needed to identify the sequence of events that lead to lethality when the formation of ATP or NADPH, or both, is inhibited by herbicidal interference with the photochemical reactions of the chloroplasts. He further suggests that additional research is needed to determine the mechanisms of action of herbicides at the cellular and molecular level and other factors that lead to phytotoxicity. He suggests that a better understanding of plant membrane structure and function, the role of membrane turnover, and bioenergetic regulation will provide new insights. Finally, he suggests that studies (some in progress) be carried out to elucidate the active form of the herbicide, the primary trigger, and the secondary effects.

2. Regulation of Cold Hardiness. St. John (1976) and St. John and Christiansen (1976) have shown that regulation of cold hardiness has been achieved by alteration of the cell membrane lipid content. Various substituted pyridazinones have been used to alter the C18:2/C18:3 ratio. The C18:3 was decreased and the C18:2 was increased; thereby cold tolerance in cotton, wheat, barley, and rye was reduced. Investigations of other cell wall constituents such as polysaccharides and protein may lead to the recognition of other cold hardiness controlling compounds.

c. Mechanisms of Weed Control

1. Promotional of Early Weed Germination. The germination of weed seeds has been promoted with ethylene-producing agents such as Ethrel (ethephon, Union Carbide). Ammonium and potassium salts have also been applied to promote rapid germination of johnson grass and other grasses. This in effect converts dormant seeds to nondormant seeds so that they can then be killed with herbicides while seedlings, thus depleting the "bank" of weed seeds including those of perennial weeds that are found in soils. The identification of additional chemicals and the development of treatment systems could provide a new means for control of problem fields.

2. Breeding for Herbicide Tolerance in Crops. Hartwig et al. (1980) found that the soybean variety Tracey was one of the best adapted varieties for production on slowly drained clay soils. However, its use was limited because of its sensitivity to metribuzin, a preemergence herbicide that is effective for the control of several broadleaf weeds. Tracey M was selected from the Tracey population as metribuzin tolerant. This work suggests that selections can be made from varietal populations or by breeding that may have increased tolerance to herbicides and perhaps also to chemicals leached by weeds.

3. Herbicide–Plant Growth Regulator Interactions. The action of bentazon on beans and on Canada thistle has been enhanced by treatment with gibberellin in the greenhouse (Sterrett, 1980). Sterrett is also working to elucidate the mechanism of this enhancement.

d. Herbicides from Natural Products

1. Natural Products in Weeds That Regulate Plant Growth. Natural products that possess growth regulating activity can be broadly categorized into two groups: (1) growth substances such as auxins, gibberellins, cytokinins, abscisic acid, and ethylene and (2) the so-called secondary plant growth substances such as the phenols, aliphatic and aromatic carboxylic acids and their derivatives, steroids, alkaloids, terpenoids, amino acids, and lipids. Of these, some of the unsaturated lactones, terpenoids, steroids, and alkaloids tend to have limited species distribution, are produced in small quantities, but may possess some specific activity. Nearly all of the so-called secondary plant growth substances can be viewed as originating from the acetate and shikimic acid pathways. Mandava (1979) has listed these compounds and their activities in a recent review. Investigations of the role that these natural products play in the metabolism of the plants where they are produced and whether they control growth and developmental processes appear of interest. Also, the nature of the control mechanisms and their efficacy for herbicidal activity may warrant investigation.

2. Allelopathic Agents. Weeds (and other plants) secrete chemicals from the roots and tops that inhibit seed germination and growth of proximate plants. It has been hoped that one or more of these allelopathic (herbicidal) agents would be sufficiently active and otherwise suitable for commercial use, but none has been found to have this capability to date. Nevertheless, there is a continuing and considerable effort to identify allelopathic agents. Rice (1974) has summarized most of the chemical information about compounds that had been identified up to 1974. Other tests have been carried out in which the leachates from a given crop have been shown to suppress weeds in the succeeding crop, e.g., sunflower and oats (Leather and Florence, 1979).

III. Disease Control

Diseases in plants may be categorized as resulting from viruses, bacteria, nematodes, and fungi. This survey has focused mostly on fungal diseases, although some of the antibiotics, in particular, have antibacterial activity. With regard to nematodes, studies are proceeding on juvenile hormones, attractants, pheromones, etc. similar to those agents controlling insects. Work is also proceeding to synthesize more effective nematicides. At present, there are evidently no efficacious chemicals for viruses. Therefore, the need for a revolutionary breakthrough on the chemistry of viral infections is urgent.

a. Synthesis of Fungicides

1. Design, Synthesis, and Utilization of Fungicides. It has been stated that the modern organic fungicides have in effect biorationally evolved from the past use of sulfur, copper sulfate, and copper sulfate hydrated lime. Actually, the progression has become evident after the fact, so that Kohn (1980) has suggested that it may be more accurate to use the term "retrobiorational". In any event, the first organic fungicides were the dialkyldithiocarbamates. There are now about 40 registered fungicides (Horsfall, 1977). The major groups of fungicides are the dithiocarbamates, metalloorganics, benzimidazoles, oxathiins, surfactants (Cyprex), sulfenimides, and natural antibiotics. Kohn organized a symposium, later published (1977), that summarized the status of fungicide production and utilization up to 1976. Some of the current emphasis on synthesis of fungicides appears to follow what Menn (1980) has chosen to characterize as the "biorational" approach. Whether the development of these fungicides has depended on a "biorational" approach or is, alternatively, serendipitous, the discovery of biochemical information often leads to discovery of more effective pesticides. For example, on the basis that benomyl and thiophanate fungicides act through transformation to alkyl benzimidazolecarbamates and the knowledge that derivatives of BMC were potent anthelmintics, several phosphorylated thioureas were synthesized and also shown to be active anthelmintics. Chloroacetanilide compounds of the Lasso type (Ciba-Geigy) that were synthesized for herbicidal activity have also been found to possess fungicidal activity. Compounds that have been found to block sterol biosynthesis have been subsequently found to have activity against mildews and rusts.

The design of fungicides must take into consideration a number of constraints. Compounds such as the sulfenimides that are susceptible to nucleophilic attack should therefore possess a low hazard for mammals. Although selectivity has merits, in field situtations fungi are able to develop resistance to water-soluble single site and variably translocatable compounds, whereas multisite agents are less likely to elicit resistance in fungi. The sulfenimides are an example of the latter. A good fungicide should not be phytotoxic. The systemic fungicides have gained recognition as providing a practical form of immunity. However, fungi can develop resistance to them because of the massiveness of their attack, thus destroying nearly all susceptible fungi but in the process selecting for a strain of surviving fungi that is resistant. A successful system should be chemically relatively stable and not a highly reactive nucleophile or electrophile. Finally, new fungicides will need to satisfy regulatory requirements and market competition.

2. *Trends in Fungicides.* Although many metals have been investigated, only the dialkyl- and trialkyltins appear to have a great deal of promise (Van der Kerk, 1977). However, systematic studies of the physiological properties of the organo transition metals (the so-called sandwich compounds) such as ferrocene, dibenzenechromium, di(π-alkyl)nickel, and cyclobutadiene–metal complexes have been carried out. Among the sulfenimides, Captan, Phaltan, and Difolatan are relatively simple and thus provide a number of opportunities for synthetic modification. However, there does not seem to have been any recent work on sulfenimides. Because of their desirability, additional systemics of which Benomyl and Chloroneb are examples will be sought. However, they will probably be used in conjunction with other agents because of their susceptibility to resistance buildup. Several new chloroacetanilides have been introduced; they include triagimefon (Baycor), Nuarimol (Baytan), and Fenarimol (Elanco). Ciba-Geigy and Chevron have introduced "Lasso"-type compounds.

Trends in the development of fungicides may be viewed from another perspective. They can be classified as (1) those that are fungitoxically active on the surface of the plant, (2) those that can penetrate the plant cuticle and are fungitoxic, and (3) those that are not fungitoxic but are pathogenic. When induced (stimulated) by the fungus, they elicit the formation of compounds that block vital fungal mechanisms. The di- and trialkyltins are examples of broad spectrum surface compounds. Fenarimol, Imazalil, and Triademfon are examples of tissue penetrating agents that block sterol biosynthesis in diseases such as apple scab and powdery mildew. In addition, one of them (Triademfon) also blocks gibberellin synthesis, thus controlling wheat stalk length and improving yields. These agents more specifically block ergosterol synthesis, the major sterol in fungi, whereas animals and higher plants generally synthesize other sterols. Examples of the group of compounds that are pathogenic but not fungitoxic are the dichlorocyclopropanecarboxylic acids that induce the plant to synthesize compounds that block spreading of the fungi. Examples of compounds with such activity are Tricyclazol and Probenazol which are reported to be effective in controlling rice blast. Siegel and Sisler (1977) have summarized much of this information in Volumes 1 and 2 of their book "Antifungal Compounds".

3. *Asymmetric Synthesis.* This area of work was not identified as promising with regard to fungicides. However, there may be significant and applicable differences of activity of isomers that may, for example, provide fungitoxicity but not phytotoxicity.

b. Biochemical and Toxicological Studies on Fungicides

1. *Biochemical Mechanisms in Fungi, Target Mode of Action, and Coincidental Effects.* As with insecticides, the continuing regulatory requirements will continue to receive attention as new fungicides are introduced. There has been pressure from the public sector for fungicides to be more selective, notwithstanding the resultant effect of increased susceptibility to resistance buildup of the fungus. The modes of action of the fungicides will continue to be investigated as a part of biorational synthesis efforts. For instance, the diorganotin compounds are antagonized by thiols whereas there is no single antagonist of triorganotin compounds that interferes on several levels with oxidative phosphorylation. The dialkyltin compounds inhibit the α-keto acid oxidases, by inference α-lipoic acid (Van der Kerk, 1977). Kohn (1977) has listed eight recorded biochemical mechanisms that have been invoked to explain manifestations of sulfenimide antifungal activity. They are (1) inhibition of glyceraldehyde dehydrogenase, (2) α-chymotrypsin inactivation, (3) oxidative phosphorylation uncouplers, (4) destructive membrane interactions, (5) destruction of mitochondrial systems, (6) inhibition of oxidation of $NADH_2$, (7) interaction with thiol enzymes, and (8) inhibition of chitin biosynthesis. These and other mechanisms can be used to develop bioassay screens to evaluate fungicides.

2. *Fate (Metabolism) of Fungicides in the Environment Including Nontarget Organisms.* See the section on insects.

3. *Toxicology of Fungicides Including Carcinogenicity.* See the section on insects.

4. *New Fungicides with Unconventional Modes of Action.* See section 1 above: the Lasso-type herbicides with antifungal activities, and sterol biosynthesis inhibitors that are active against previously difficult to control phycomyces and phytophthora root rots.

c. Natural Products with Fungicidal Action

During the past 30 years, enormous numbers of compounds have been synthesized and screened. The odds of finding new ones may be decreasing. Because of this, research groups are beginning to investigate plant and other extracts for fungicidal activity.

1. *Fungicides from Tropical Plants.* Plants from tropical regions of the world are subjected to severe disease pressures because of the heat and humidity. A number of highly active antifeedants for insects have been identified (Kubo and Nakanishi, 1977; Jacobson, 1977) which suggests that other types of biological activity such as antifungal activity may be found in these plants. The availability of plant material from the tropics has increased because of industrial and public sector groups securing them for examination of their pharmaceutical and anticancer properties.

2. *Compounds Affecting Fungal Development and Differentiation.* Fungi generally differentiate their living structures differently from their hosts. Some fungi have walls of chitin and reproduce through spores, whereas higher plants do not. Very few screens have been developed to exploit these differences, but the possibility of differences exists. A compound with fungal development activity that has been identified is griseofulvin which curls and twists the germ tubes so that they are unable to infect the host tissues. Another compound, blastin, prevents an appressorium of the rice pathogen from sending down an infection peg into the leaf. Polyoxin interferes with chitin synthesis. Horsfall (1977) has developed effective and rapid screens to select antisporulants and anticonidiophore compounds. In another vein, there is the need for work on soil organisms that attack the roots and stalks of plants and the development of compounds that would control these organisms.

3. *Antibiotics.* The successful use of antibiotics against bacterial diseases of humans has led to large-scale screening of antibiotics for plant disease control. They are produced commercially for use by microbiological processes. The antifungal antibiotics include cycloheximide, griseofulvin, blasticidin S, kasugamycin, polyoxin, ezomycin, and validamycin A. The antibacterial antibiotics

include streptomycin, cellocidin, chloramphenicol, and novobiocin. Misato (1977) has summarized the status of agricultural antibiotics. One of the problems with their use has been the buildup of resistance in the disease organism to the antibiotic. Now, new antibiotics of the crown ether types are being microbiologically produced, and they are reported to be less susceptible to the resistance buildup than earlier ones. In another area, Strobel and Myers (1980) have recently isolated a bacterium normally found on leaves of wheat, barley, and oats that can defeat the fungus responsible for Dutch elm disease. The bacterium is a pseudomonad that produces fungus-killing antibiotics. Alternatively, the bacteria could be directly used or the bacterial antibiotic could be microbiologically produced and used for control. The success with the Dutch elm disease fungus suggests that suitable screening programs may identify still other disease-killing agents.

d. Novel Pest Control Mechanisms

1. Recombinant DNA. It has been suggested that the so-called genetic engineering can be used to build in protective mechanisms against fungi in crop plants. If, for example, it would be possible to introduce genes of chrysanthemum that biosynthesize pyrethroids into crop plants such as corn, protection against insects and diseases could be achieved. It also has been proposed that genetic capability for biosynthesis of a disease (or other pest) agent might be introduced into a bacterial or other microorganism. Then the agent could be produced microbiologically, harvested, and used as a pesticide.

2. Cloning for Production of Resistant Crop Plants. Resistant crop plants are primarily selected by breeding techniques. It has been suggested that mutated cells could be cloned so that a plant with resistant capability would be produced that was an exact duplicate of the original mutant. It is also anticipated that screening of cells or isolated tissue for antifungal activity and subsequent cloning of the survivors would be more efficient than screening the whole plant.

3. Activation of Chemical Defense Systems against Disease in Plants. Plants may be protected against disease by using procedures that are essentially identical with those used to immunize animals. Plants treated with a variety of pathogens, virulent or avirulent, or high molecular weight products of infectious agents are protected against disease caused by subsequent infection by pathogens. These infectious agents elicit the accumulation of antibiotic chemicals (phytoalexins or stress metabolites) around the site of infection and rapidly attain concentrations that inhibit development of infectious agents. Phytoalexin production may also be elicited in plant tissues in the absence of living organisms by such agents as heavy metal ions, UV light, cyclic AMP, peptides, proteins, polysaccharides, and antibiotics (Keen and Bruegger, 1977). The phytoalexins are varied, chemically. They include compounds such as aromatic and nonaromatic phenols, flavonoids and their glycosides, gossypol, and terpenoids. This approach to disease control has been investigated by a number of workers including Keen and Bruegger (1977), Valent and Albersheim (1977), and Kuc and Caruso (1977). In that several of the plant growth regulators have been shown to increase the content of certain secondary plant constituents with plant resistance characteristics, hormonal-type elicitors may find field applications.

4. Breeding for Chemical Host Plant Resistance. In this approach to disease control, the resistance compound(s) may continually exist, or alternatively, the resistant plant may possess the inherited capacity to biosynthesize, on infection, larger amounts of the resistance compound(s) more quickly than susceptible plants. Bell and Stipanovic (1978) have found chemical resistance in cotton to several fungi, particularly verticillum wilt, and *Xanthomonas malvacearum*, a bacterium. The chemical basis for this resistance is the ability of the resistant cotton plant to biosynthesize larger amounts of gossypol, hemigossypol, and related compounds more quickly than the susceptible plant in response to injury. *Gossypium harbadense* has been shown to possess a greater capacity to methylate the gossypol terpenoids and to biosynthesize tannins (resistance compounds) than some other cotton varieties. However, in pecan, juglone, the resistance factor in varieties tolerant to *Fusicladium effusum*, does not appear to increase further on infection (Hedin et al., 1980a). In the public sector, chiefly, work to identify the chemical basis of resistance in crop plants to diseases and insects is in progress or has been completed on at least 20 economically important crops. This approach has a strong priority in the present environmental climate and according to economic surveys (Headley, 1979) is expected to continue. As with strategies proposed for insects that are integrated pest management oriented, the development of plants for maximum disease resistance rather than for maximum production may be more desirable. As an added dividend, fewer pesticides would be released into the environment in an effort to control the disease.

IV. Surveillance of Pesticides

a. Environmental Distribution of Pesticides

1. Detection of Pesticides, Metabolites, and Degradation Products. Because of regulatory and environmental considerations, much analytical and metabolic research must continue. Two recent books, previously discussed, by Khan et al. (1979) on "Pesticide and Xenobiotic Metabolism in Aquatic Organisms" and by Paulson et al. (1979) on "Xenobiotic Metabolism: In Vitro Methods" summarize the state of the art techniques in the field. Khan et al. (1979) states that if a choice must be made between determining the precise toxicity of all chemicals entering the environment and knowing which chemicals are formed and where and how long they persist, the latter may be more pertinent. A knowledge of the toxicokinetic properties of chemicals and their metabolic pathways in aquatic (and other) organisms will lead to surveillance programs reflecting the state of contamination of the environment.

2. Problem Metabolites. Two current classes of interest are the nitrosamines and the dioxins. The nitrosamines were recently surveyed in a session organized by Leng (1978). They were detected in agricultural and home-use products, in soil, in plants, and in commercial herbicides. The chemistry of chlorinated dibenzodioxins and dibenzofuran was the topic of a symposium organized by Plimmer (1979). Both of these issues have received wide attention and are examples of issues which will continue to arise. They present fine opportunities for the application of valid analytical chemical procedures.

3. Disposal of Pesticides. With recent wide public recognition that pesticides have not been safely disposed of, destroyed, or otherwise secured, new regulatory requirements have been established to meet this need. The disposal of pesticides is now often contracted out to companies with specific expertise. Procedures for disposal or destruction of pesticides have recently been developed. They include photochemical conversions, catalytic hydrodechlorination, microwave plasma detoxification, reprocessing, chemical treatment, incineration, and bioconversion. Kennedy (1978) has recently edited a book "Disposal and Decontamination of Pesticides" that summarizes many of the new approaches.

4. Risk Analysis. In a recent symposium organized by Enos and Green (1979), the role of risk analysis (assessment) in regulatory decisions, in extrapolation from animal studies, and its relation to epidemiology were evaluated. The efficacy of risk models based on data obtained from the physicochemical properties of the compounds in the environment was also evaluated. Since risk analysis is an objective building block upon which pesticide regulatory decisions are made, the analytical, metabolic, and toxicological studies on which risk assessment is based will obviously continue to be required.

b. Analysis of Pesticides

1. Development of New Methodology. In a recent ACS symposium organized by Harvey et al. (1979), recent advances in pesticide analytical chemistry were surveyed. The topics discussed included HPLC, chromatography, fluorometry, high-performance TLC, polymeric adsorption of volatiles, chemical derivatization, direct measurement from air and aqueous media, analysis of picogram quantities, liquid scintillation, FT-IR, radioimmunoassays, NMR, and MS including negative-ion MS. The trend in development of new methodology is toward the combination of sequential steps and the total automation of cleanup, final separation, and analysis. Where possible, multiple analysis on each sample is performed.

2. Total Method Analysis. As suggested in the previous section, routinized, automated, composite, analytical characterizations of pesticides and other industrial pollutants are now being developed with the availability of modern instrumentation. This systematized approach encompasses automated cleanup, separation chromatography, and multiple detection by procedures such as MS, FT-IR, radioisotope, electron capture, phosphorous, and sulfur detectors. Bowman's (1979) book "Carcinogens and Related Substances: Analytical Chemistry for Toxicological Research" supplies a perspective for this emerging work.

3. Immunological Assays. During the last several years, private citizens residing near the site of pesticide treatment of crops have complained of various symptoms that appear to be allergies. It has been speculated that these people may have been sensitized to pesticides, various industrial chemicals, or the dispensing solvents. If it is judged desirable to test large numbers of people for sensitivity to pesticides or classes of pesticides, simple, rapid, economical, and specific tests will need to be performed in very large numbers. It is now possible to attach a pesticide to the serum protein of humans, thus forming an antigen. The antigen can then be injected into a rabbit to develop an antibody titer. The rabbit antibody can in turn be used to test for pesticides present in human blood or other media. In the actual test which could be performed in large numbers on plastic plates with shallow wells, the test sample would be added to rabbit antibody and then mixed with a chromophore to produce a colored precipitate. This is a developing technology under investigation by a number of workers including Hammock and Mumma (1979), Banks at South Carolina, Street at Utah State, and Koch at Mississippi State.

V. Regulation of Plant Growth

Compounds used to regulate crop plant growth, promote or delay maturity of plant or fruit, and aid in harvesting by defoliation are not precisely pesticides. However, some of these compounds have also been found to possess various pesticidal activities that have been described in previous sections. When and where plant growth regulators are used to control weeds or insects they, of course, are to be recognized as pesticides. In fact, as selective plant growth regulators, they are the primary weed control agents.

It is not within the scope of this survey to evaluate their applications in crop plant production. However, two sources of information about their utility for these purposes are a book "Plant Growth Substances" by Mandava (1979) and a Division of Pesticide Chemistry—Plant Regulator Working Group Symposium on plant growth regulators (Holm et al., 1975).

B. MOST SERIOUS PROBLEMS IN WORLD PEST CONTROL

I. Hazards of Pesticides

a. Persistence

Studies have shown that the chlorinated hydrocarbon pesticides (and several industrial chemicals) have been found in areas as remote as the North and South Poles. Their presence in air, soil, water, and living tissues has been amply documented. Their retention in the ecosystem and their several deleterious effects on living organisms have been recognized. The additional consequences of the use of these pesticides over the past 30 years may be recognized. Large-scale detoxification efforts may be required in specific instances.

b. Lack of Specificity

Some commercial pesticides have a broad spectrum of action. While this provides advantages, there are possible concomitant dangers. They include killing or otherwise affecting nontarget organisms including beneficial insects, microorganisms, birds, wildlife, and other animals. However, it should be recognized that both wide spectrum and highly selective pesticides pose problems if there is an accident during production, transportation, or application.

c. Buildup of Insect Resistance

The reliance on too few pesticides hastens the natural selection of resistant strains of insects. This problem is aggravated by the costs manufacturers incur for production, registration, and marketing of new pesticides. If these pesticides are "too specific", they cannot be sold in sufficient volume to provide a profit.

Another grave problem associated with the buildup of insect resistance is that with time, larger and larger quantities of the pesticide must be applied with its associated dangers. Eventually, it becomes counterproductive to continue application of the pesticide which otherwise may have continued to provide useful control. The need to reduce the rate of resistance buildup by concentrating on alternate strategies such as biological control, attractants, and growth development agents and by initiating integrated pest management systems is again apparent. It was also stated that an understanding of the underlying biochemical and physiological processes of pesticide resistance buildup was necessary.

d. Chronic Toxicity

Some pesticides that have a low acute toxicity (LD_{50}) are likely candidates for carcinogenic activity in mammals. This relationship may occur more frequently with insecticides than with herbicides and fungicides. When it occurs, these pesticides may also cause the emergence or resistant strains by natural selection. Some of the implications associated with chronic toxicity were discussed in the section on toxicology of pesticide chemicals including carcinogenicity.

II. Distribution of Pesticides

a. Availability in Emerging Countries

Modern pest control agents and the knowledge and technology for their use are not always available in the developing countries. The losses in agricultural production because of these limitations are very large. Associated with this limited availability of pesticides in the emerging nations are the needs for additional education of the government administrators, pest control specialists, and the growers in these countries. Another problem is the lack of capital available for purchasing the pesticides and application equipment.

b. Production and Marketing of Unconventional Pesticides

While most of the public sector research effort in entomology is concentrated on the so-called "third and fourth generation" pesticides including attractants and hormonal agents, there has been only a limited production of these agents for commercial use. The reason for this limited use is that the specificity of the agents precludes broad spectrum application and thus limits opportunities for profits. Registration costs are appreciable, and a relatively complicated technology is involved in the application, often discouraging their use by growers. Until their efficacy can be demonstrated in more field situations, and until the ease of utilization can be improved, the market for these new pesticides will continue to be limited even though their increased use is of urgent priority.

c. Inadequate Market for Pesticides of Minor Crops

The U.S. government has initiated the IR-4 program to partially fund collection of information necessary for the registration of existing pesticides for minor uses in crops where there is an insufficient commercial incentive for the manufacturer. This aid is of value to growers of specialty crops who thereby can provide consumers with a greater diversity of food and plant products.

III. The World's Most Damaging Pests

a. Insects

Pink bollworm, mosquito complex, Heliothis complex, tsetse fly, Indian meal moth, granary weevil, rice weevil, locusts, Scolytids, and boll weevil. Also fleas, ticks, gypsy moth, termites, fruit fly, and housefly.

b. Weeds

Nut sedges, Bermuda grass, barnyard grass, jungle rice, goose grass, johnson grass, cogongrass, water hyacinth, common purslane, lamb's quarters, crabgrass, and field bindweed (Holm et al., 1977).

c. Plant Diseases

Wheat rust, rice blast, smuts of sorghum, Dutch elm disease plus phloem necrosis, fusiform rust on pine, *Fusarium* species on grains, root knot nematodes, golden nematode of potato, and soybean cyst nematode.

C. PEST CONTROL IN THE 21ST CENTURY

I. Chemicals

a. Market Availability

It has been speculated that fewer pesticides will be available as the requirements for safety and efficacy become greater. Efforts will be concentrated on improving delivery and on pest management systems for the optimum effect with the least amount of chemicals in the most timely manner. This could have serious consequences for crop production efficiency.

b. Unconventional Pesticides

Economic and market surveys indicate that the new so-called third and fourth generation pesticides including the attractants will not gain a large share of the market until after 1990 (Headley, 1979). There will be increasing uses of pesticides with novel and specific mechanisms of action such as those affecting development, behavior, and reproduction. Toxins and antifeedants will also find increasing usage.

c. Expenditures for Crop and Animal Protection

It is predicted that it may be necessary to apply larger quantities of pesticides or, alternatively, to increase the proportion of the total crop investment expended for pest control to ensure higher yields. There will be an increasing emphasis on maximizing yields to feed the increasing world population. This is in conflict with the integrated pest management concept of maximizing profit but not necessarily yields.

II. Governmental Aspects

a. Registration and Regulation of Pesticides

Although it seems likely that the public will continue to demand additional and more stringent controls, it has been suggested that the increasing sophistication of pesticide chemistry and toxicology will eventually reduce the level of controversy by providing assessments of risks that can be received with greater confidence (Bowman, 1979; Harvey et al., 1979; Bandal et al., 1981). There is need to reduce dependence on the adversarial relationships in regulatory divisions. This may lead to less, or at least less controversial, regulations and return a greater degree of freedom and responsibility to the individual scientist or technologist who, because of broader and improved training, may be permitted a greater degree of discretion. Others visualized an increase in the number of governmental and private sector advisors who have expertise in specialized fields.

b. The Chemist and Society

The widely circulated Global 2000 Report recently summarized in *Chemical and Engineering News* concluded that the capacity of the environment to provide goods and services can no longer be taken for granted. The two major reasons cited were that (1) the demand for environmental goods and services is outstripping the capacity of the environment to provide them as both population and per capita consumption expand and (2) in many areas the ecological systems that provide the goods and services are being undermined, extinguished, and poisoned (Barney, 1980). The impact of pesticides is implicated as one factor that is contributing to this outlook. While the conclusions of this report are controversial, the need for pesticide chemists to pursue activities in the areas of these perceived trends is obvious.

Leng (1980) recently organized a symposium on "Responsibility of the Chemist to Society". The objectives of this symposium were to build models for improved relationships of scientists with the public, which are in fact their clients and supporters. There was general agreement that scientists must make a greater effort to explain the results, implications, and merit of scientific work to the users of research, the funders, and the general public. Greater candor and simplicity were urged. There was a reaffirmation of the recognition that scientists must not only be concerned with but also should be careful stewards of the world's resources and the public welfare. As the public becomes more sophisticated, it is hoped that the intellectual level of communication will be raised so that ideas can be conveyed with less chance for misunderstanding.

III. Industrial Trends

a. Crop Selection

Manufacturers of pesticides will orient their products toward a crop or a few crops to improve pesticide efficacy and profit while limiting the costs of complying with regulation requirements. Unless there is a compensation for this trend, many specialty crops may not be grown because the needed pesticides will be unavailable. An increased production of carbohydrate and fuel crops can be expected to help meet both food and fuel needs. There may also be an increase in the production of fiber crops for associated reasons. There will be a continuing trend to the use of pest control methods having low energy demand. This suggests that the control of weeds by herbicides will continue to increase and conventional tillage will decrease.

b. Food Production Systems

New food production and preservation technologies will be developed with a worldwide emphasis. There will be a trend toward standardization of production, protection, and preservation procedures compatible with energy-conserving methods to meet (or satisfy) harvesting, processing, marketing, and regulatory requirements. Inputs into food production systems will be computer controlled, interfaced between remote sensing devices and field applicators.

IV. Scientific Approaches

a. Trends in Integrated Pest Management

There will be a greater integration of insecticide, herbicide, and fungicide strategies. There will be more modeling to provide improved information about pesticide treatment schedules and procedures. Larger numbers of professionals will be associated with pest control. There will be a continued and greater emphasis on the use of resistant crop varieties or induced resistance. There will be improved studies of the population dynamics, biology, and ecology of pests.

b. Training of Pest Control Chemists

Pest control chemistry will be a major aspect of pest control science. Broad generalists will be required for problem solving. They must have competence in analytical, organic, and biological chemistry plus physiology, pharmacology, toxicology, and regulatory affairs. The orientation of instructional programs will be toward biochemical and genetic aspects. Chemists will be better trained mathematically and statistically and have a vastly improved capability for working with computers.

c. The Practice of Pesticide Chemistry

Pesticide chemists in the 21st century will have access to increasingly sophisticated instrumentation. Automated total method analysis will accept samples and, by computer programming, provide statistically processed results of multiple analyses. There will be an increasing use of robot technology for routine and processable laboratory work such as reactions and separations. Robots will replace technicians for many duties. Integrated programmable reactors will permit reactions to be performed under any set of conditions and with automated sequencing. Improved knowledge about genetic engineering will provide the technology for introducing lethal genes into pests and protective genes into crop plants and animals. The synthesis of pesticides will be stereochemically oriented and will be achieved for the most part biosynthetically by incorporating genetic information into microbial or related synthesizers. Pesticides will be employed at the submicrogram level to control specific processes such as behavior, development, and reproduction. The pesticides will be very target specific and have limited or no carcinogenic or other toxicological activity. In summary, the improved technology that can be expected in the 21st century will provide the pesticide chemist with an improved capability to provide meaningful answers to world problems of hunger and suffering.

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ARTICLES

Fruit Residue Data and Worker Reentry Research for Chlorthiophos Applied to California Citrus Trees

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Chlorthiophos [*O*-[2,5-dichloro-4-(methylthio)phenyl] *O*,*O*-diethyl phosphorothioate] was applied to California citrus trees. Residue methodology for the analysis of chlorthiophos, its sulfoxide, its sulfone, its oxon, its oxon sulfoxide, and its oxon sulfone on and in citrus fruit, on foliage, and in soil dust is presented. Residue dissipation curves obtained for these three substrates are given. Dermal dose–cholinesterase response curves for the six compounds are given for rats. These data are used to calculate safe residue levels on foliage. On the basis of the dislodgeable foliar residue data, a 70-day reentry interval is proposed.

Chlorthiophos [Celathion; *O*-[2,5-dichloro-4-(methylthio)phenyl] *O*,*O*-diethyl phosphorothioate], on the basis of preliminary results, appeared to be a potentially useful insecticide for the control of the California red scale, *Aonidiella aurantii* (Mask.), which is one of the major citrus pests in California. Consequently, a study was initiated to obtain residue data for chlorthiophos and any of its five cholinesterase (ChE)-inhibiting oxidation products which may be present after application of chlorthiophos to citrus trees. Figure 1 shows the chemical structures of these compounds. Fruit, dislodgeable foliar, and soil dust residues were obtained to assist in the setting of a fruit tolerance for consumer protection and of a safe reentry interval for protection of agricultural workers who may engage in prolonged and extensive contact with the treated foliage. the oral LD_{50} values for mouse, rat, and rabbit are 140, 13, and 20 mg/kg, respectively, and the dermal LD_{50} values for rat and rabbit are 58 and 48 mg/kg, respectively (Muacevič, 1976). Due to the high acute toxicity of chlorthiophos, dermal dose–ChE response data were generated for chlorthiophos and each of its five oxidation products. These data were used to calculate safe residue levels on foliage and, in conjunction with the dislodgeable residue data generated in this study, to calculate safe reentry intervals.

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EXPERIMENTAL SECTION

Treatment and Sampling. Mature orange trees were located on the University of California Citrus Research Center, Riverside, CA. Celathion 40WP formulation was supplied by EM Industries, Inc., Elmsford, NY, which represents Celamerk GMBH and Co. KG, Ingelheim, Germany.

Each plot consisted of four rows of six trees each. Three replicate plots were treated for each of two treatment rates. Applications were made by using an oscillating boom spray rig on Aug 8, 1980, at rates of 4.8 and 9.5 lb of AI (1900 gal)$^{-1}$ acre^{-1} [5.3 and 10.6 kg of AI (178 hL)$^{-1}$ ha^{-1}]. Samples were collected from the eight trees in the center of each plot. At each sampling, 1 fruit was removed from each quadrant from each of 8 trees to yield a 32-fruit sample. At each sampling, 5 leaf disks were collected from each of 8 trees as described by Gunther et al. (1973) to give a 40 leaf disk sample representing 5 disks per octant. At

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