Insecticide Resistance: Challenge to Pest Management and Basic Research

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The agricultural use of synthetic insecticides usually protects crops but imposes strong selection pressures that can result in the development of resistance. The most important resistance mechanisms are enhancement of the capacity to metabolically detoxify insecticides and alterations in target sites that prevent insecticides from binding to them. Insect control methods must incorporate strategies to minimize resistance development and preserve the utility of the insecticides. The most promising approach, integrated pest management, includes the use of chemical insecticides in combination with improved cultural and biologically based techniques.

BY 1980, 260 SPECIES OF AGRICULTURAL ARTHROPOD PESTS (*1*) had insecticide-resistant strains, compared to 68 for disease vectors (*2*). Yet most research efforts in the genetics and mechanisms of insecticide resistance have been devoted to public health pests such as houseflies and mosquitoes, largely because of the urgent problems they cause and their suitability for genetic and biochemical studies. Little is known about resistance mechanisms and their inheritance in agriculturally important insects. The available information about resistance mechanisms in disease vectors is not directly applicable to agricultural pests because of differences in the physiology and ecology of blood- and plant-feeding species and differences in control strategies.

We will review the basic factors in insecticide resistance and identify some of the existing information gaps. We will then discuss some of the proposed resistance management strategies, emphasizing the need for an inclusive approach to pest control that considers all components of the agroecosystem and integrates the use of chemicals with other available techniques. Integrated pest management (IPM) programs are the most promising attempts yet made to protect crops. Their success, biological and economic, can be improved by better understanding of resistance mechanisms in agricultural arthropod pests.

There are many excellent reviews (*3*) of insecticide resistance, but each addresses a specific aspect of the topic and there is a strong dichotomy between laboratory and field approaches. Comprehensive, multidisciplinary efforts have been attempted only recently (*4*).

Resistance Evolution and Mechanisms

Insecticide resistance is a dynamic, multidimensional phenomenon, dependent on biochemical, physiological, genetic, and ecological factors. All of these vary with species, population, and geographic location. Resistant strains develop through the survival and reproduction of individuals carrying a genome altered by one or more of many possible mechanisms that allow survival after exposure to an insecticide. The selective pressure exerted by the insecticide sharply increases the frequency of the genetic condition expressed as resistance within the exposed population.

Insects have developed resistance to all major classes (*5*) of insecticides and will develop resistance to future insecticides as long as present application techniques and use patterns prevail. This is not surprising when viewed in ecological and evolutionary perspectives. Herbivorous insects have coexisted with higher plants for 250 million years. Plants produce many allelochemicals, such as alkaloids, terpenes, and phenols, for defense against insects and pathogens (*6*). These chemicals are often appreciably toxic and have favored the evolution of counteradaptions in plant-feeding insects, including behavioral adaptations, modified physiological processes, and biochemical mechanisms. Insects often rely on a complex of general-purpose defensive enzymes to overcome the potential toxicity of the plants they eat.

In sharp contrast to the slow evolution of resistance to natural toxicants, resistance to synthetic insecticides has developed extremely rapidly, probably in part because the insects can use some of the same mechanisms that evolved in defense against plant allelochemicals or pathogens. Insecticides are used intensively in situations that otherwise favor rapid pest reproduction. The insecticide then becomes the only major selecting agent. A good example of this is the development of resistance to *Bacillus thuringiensis* in the Indian meal moth *Plodia interpunctella* (Hubner) living in treated grain bins (*7*).

Genetic factors. Resistance mechanisms arise through inheritable changes—mutations—in the genome of individual insects. Mutations may include substitutions in DNA base pairs, amplifications of preexisting genes that confer defense mechanisms, translocations, chromosome inversions, or other DNA rearrangements. Gene amplification may be important in resistance based on sequestration of toxins by binding to lipids or proteins or on a reduced rate of penetration through the integument. Base pair substitutions are more likely in target site resistance, where the target macromolecule is modified so that it no longer binds the insecticide. Both gene amplification and base pair substitutions may be important in resistance that is due to increased metabolic detoxification. The best support for the gene amplification hypothesis to date was found in the green peach aphid *Myzus persicae* (Sulzer) (*8*). In seven clones of the aphid, the content of a protein with esterase activity increased in a geometric series from one unit in an organophosphate-sensitive clone to 64 units in a highly resistant clone.

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The karyotypes of moths, butterflies, and beetles show many small, morphologically similar chromosomes, and there are usually few morphogenetic markers. Flies and mosquitoes, on the other hand, are suitable for chromosome mapping because they have many morphogenetic markers and, generally, large chromosomes. Radioisotopes, fluorescence probes, and immunologically activated chromophores (*9*) can be used to analyze genes, but have not been used to study resistance mechanisms in agricultural insect pests.

It would be difficult to detect whether field exposure to insecticides increases the frequency of spontaneous mutations, one of which could lead to resistance. Many insecticides are, however, genotoxic in laboratory experiments with a variety of organisms (*10*). Spontaneous mutation rates may also be increased by plant allelochemicals: linear furanocoumarins, pyrrolizidine alkaloids, and aflatoxins can alter DNA (*11*). Insects exposed to such allelochemicals on alternate host plants could introduce mutations to populations under selection pressure in agricultural fields.

In addition to mutations that spread through selection, some cases of resistance may have developed by selection of a few individuals that had a resistance mechanism all along, reflecting the genetic heterogeneity in a species. Such a rare spontaneous resistance mechanism could not impose any competitive disadvantages on its bearer in the absence of toxicants. This is the only case of truly preadaptive resistance.

The genetic basis for insecticide resistance represents local adaptation. There is no evidence that a newly acquired resistance mechanism has allowed an insect species to utilize a new food plant previously unavailable because of its toxic allelochemical content. Decreased sensitivity to toxic chemicals provides an opportunity for host-race (*12*) formation and may have occurred in nature with herbivorous insects encountering new toxic plant allelochemicals. This may be an integral part of the speciation process (*13*).

Laboratory- and field-selected resistance may develop in different ways. The genetic starting material in a laboratory colony is limited, and biological and environmental stress factors are minimized. This tends to promote development of resistance due to moderate contributions from several different mechanisms. In a field population, genetic diversity is considerable and environmental and biological stress factors may limit insect survival. Resistance in field populations may therefore more often be based on a single major mechanism. This is one of the many limitations in efforts to understand field resistance by laboratory experiments.

Physiological processes. Mechanisms of physiological resistance to toxic chemicals include diminished penetration, sequestration, and excretion. The rate of penetration depends on the physical characteristics of the molecule and on the properties of the insect integument, which vary considerably between species and life stages. Delayed penetration provides more time for detoxification of the incoming dose (*14*). This form of resistance can be counteracted by the addition of penetration adjuvants to the spray formulation.

Sequestration of synthetic insecticides may be a more common resistance mechanism than generally appreciated. The esterase responsible for resistance in the green peach aphid has high binding affinity but low catalytic reactivity and therefore functions as a storage protein for carbamates, organophosphates, and pyrethroids (*8*). Toxic plant allelochemicals are frequently sequestered (*15*). With increasing use of less acutely toxic insecticides, such as growth regulators and metabolic antifeedants, sequestration could become a more important resistance mechanism.

Accelerated excretion of unmetabolized material is not known to be an important resistance mechanism against synthetic insecticides. However, extremely rapid passage of food through the gut followed by excretion enables certain adapted insects to feed on tobacco plants containing high concentrations of the natural insecticide nicotine (*16*). Black swallowtail (*Papilio polyxenes* Fabr.) larvae adapted to feed on umbelliferous plants containing linear furanocoumarins excrete xanthotoxin nine times faster than do fall armyworm, *Spodoptera frugiperda* (J. E. Smith), larvae (*17*). Xanthotoxin is toxic to nonadapted species such as the fall armyworm but not to the black swallowtail, which also detoxifies the compound faster.

Excretory and other physiological resistance mechanisms can be assumed to evolve relatively slowly, since many finely tuned, integrated molecular interactions must be altered without losing function. Also, the high acute toxicity of modern synthetic insecticides may be difficult to overcome by modifications in complex and relatively slowly working physiological processes.

Biochemical mechanisms. Unlike physiological resistance factors, biochemical mechanisms require changes in single macromolecules only. The most intractable cases of insecticide resistance are usually associated with improved capacity to metabolically detoxify insecticides, modifications in target sites to decrease sensitivity, or both.

1) *Metabolic defenses.* Lipophilic insecticides are primarily detoxified by microsomal oxidases, in particular cytochrome P-450 (E.C.1.14.14.1), carboxylesterases (E.C.3.1.1.1 and E.C.3.1.1.2), and glutathione transferases (E.C.2.5.1.18). These enzymes, with exceptions such as conversion of DDT to DDE (Fig. 1), convert lipophilic foreign compounds to polar metabolites that can be excreted. The oxidase and esterase metabolites are frequently processed further by epoxide hydrolases (E.C.3.3.2.3), glutathione transferases, and other conjugating enzymes to the final, water-soluble, excretable products. The enzymes are functionally identical in insects and vertebrates, but qualitative and quantitative differences occur (*18*).

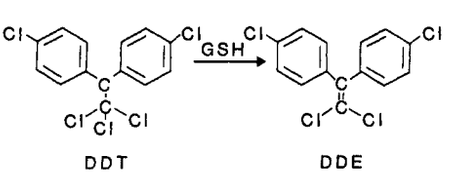

Fig. 1. Conversion of DDT to DDE.

The cytochrome P-450–dependent oxidases (polysubstrate monooxygenases), the carboxylesterases, the glutathione transferases, and the epoxide hydrolases share the requirement of a typically high degree of substrate lipophilicity. Each also occurs in multiple isoenzymic forms with different but broadly overlapping substrate preferences (*18*). All can be induced to higher activities by a wide variety of foreign lipophilic compounds, which may also be substrates (*19*). Induction is a temporary condition that persists only as long as the inducing chemical is present in the tissues in sufficient concentration. It results in the biosynthesis of more enzyme protein, either of the kind originally present or of different isoenzymic forms. In contrast, metabolic resistance results when individuals with permanently expressed high enzyme activities survive and reproduce in the presence of a selecting agent.

Cytochrome P-450 is implicated as a major factor in most cases of metabolic resistance to carbamates and also detoxifies organophosphates, pyrethroids, DDT, and other insecticides (*20*). Despite the large amount of information available about this enzyme, the mechanisms for regulating the activity in insects, certain aspects of the reaction mechanism, the inheritance of the activity, and the behavior of the enzyme in specialist insect herbivores and natural enemies are still unclear.

Although cytochrome P-450 appears to catalyze several different types of reactions, all are monooxygenations (Table 1). This may result from the general lack of specificity for the organic substrate

Table 1. Insecticide molecules attacked by cytochrome P-450.

Type of reaction	Examples	Toxicity of product
Expoxidation		
Aromatic	Carbaryl	Less
Alicyclic	Aldrin	Equal or more
Aliphatic	PyrethrinI	Less
Heterocyclic	Preocene I	More
Hydroxylation		
Aromatic	Carbaryl	Less
Alicyclic	Nicotine	Less
Aliphatic	DDT, diazinon, Pyrethrin I	Less
Heterocyclic	Piperonyl butoxide	*
N-dealkylation	Carbaryl monocrotophos	Less
O-dealkylation	Methoxychlor, tetrachlorvinphos	Less
Desulfuration	Parathion, diazinon	More
Phosphoester cleavage	Diazinon, parathion	Less

*A synergist.

combined with the existence of multiple forms with different substrate preferences. Consequently, an insecticide can be attacked in several different places depending on its molecular structure. In addition, many insecticides can be attacked by several different enzymes in an individual or a population, as in cases of multiple metabolic resistance, or in different strains or species (Fig. 2). Normally, an insecticide undergoes one major type of reaction in any one insect species or population.

The polar metabolites produced by cytochrome P-450 are sometimes more toxic (reactive) than the parent compounds (*18*). Carbon hydroxylations and *N*- and *O*-dealkylations result in detoxified products. Epoxidations often, and oxidative desulfurations of organothiophosphates always, produce more toxic metabolites. Highly reactive epoxide metabolites are detoxified by glutathione transferases or epoxide hydrolases (*21*).

Glutathione transferases are important in organophosphate detoxification (*22*) and provide the most important form of metabolic resistance to DDT through dehydrochlorination to DDE (*23*). Carboxylesterases are often a major factor in malathion and pyrethroid resistance (*24*).

2) *Target site insensitivity.* Compared to the number of cases in which metabolic resistance mechanisms have been implicated or documented, relatively few types of resistance are caused by a modified target site. The first case of resistance to modern, synthetic, organic insecticides occurred with DDT in houseflies (*25*) and was characterized as a target site resistance. It became known as "knockdown resistance" (KDR) and is associated with a recessive gene that also confers resistance to pyrethroids (*26*). These insecticides interfere with transmission of nerve impulses, the sodium channel being their primary target site.

The nature of the modification that confers resistance while allowing continued nerve signal transmission is unclear; it may include molecular modifications of the sodium channel itself, a large transmembrane protein molecule; changes in the number of channel molecules per unit of area; or changes in the phospholipid component of the adjacent membrane (*27*). It is possible, in some cases even likely, that different mutations result in resistance mechanisms with identical consequences, such as KDR.

The KDR mechanism has been demonstrated in one agriculturally important species only, the Egyptian armyworm *Spodoptera littoralis* (Boisduval), but is suspected to be more widespread (*28*).

A second major type of target site resistance is a modification in the synaptic acetylcholinesterase that renders it less sensitive by several orders of magnitude to inhibition by organophosphates and carbamates. The decreased affinity for insecticides in the enzymes from resistant insects indicates a change in the active site (*29*). This kind of resistance occurred first in a spider mite and has been observed in many other species, including a *Spodoptera* larva and a leafhopper. Acetylcholinesterase occurs in several different isoenzymic forms in ticks and houseflies and probably exists in multiple forms in other insects as well. A strain of the green rice leafhopper, *Nephotettix cincticeps* Uhler, has an acetylcholinesterase that is insensitive to *N*-methyl carbamates and dimethyl organophosphates but highly sensitive to inhibition by the corresponding propyl compounds (*29*).

3) *Combinations of resistance mechanisms.* According to a conservative estimate, at least 89 of 428 resistant species contained populations with multiple resistance by 1980 (*30*). Multiple resistance occurs when an insect population has more than one defense mechanism against a class of insecticides, for example, an insensitive target site combined with a metabolic resistance factor. Such populations are, in effect, also cross-resistant to other classes of insecticides to which they may never have been exposed, if those insecticides either have the same mode of action or are detoxified by the same enzyme as the selecting insecticide. Target site resistance to an organophosphate insecticide is often accompanied by cross-resistance to other organophosphates (*29*) and to carbamates (*31*). However, organophosphate target site resistance is not always accompanied by carbamate target site resistance, indicating that several different and probably genetically independent modifications exist. DDT resistance is correlated with resistance to pyrethroids (*26*) due to the KDR mechanism.

Resistance based on improved detoxification may result in cross-resistance to all other insecticides detoxified by the same enzyme. Carbaryl resistance due to increased oxidation may confer cross-resistance to many other insecticides with different modes of action but also detoxified by cytochrome P-450 (*18*).

Resistance to organophosphates due to increased carboxylesterase activity may produce cross-resistance to synthetic pyrethroids also detoxified by a carboxylesterase in many insects (*24*). On the other

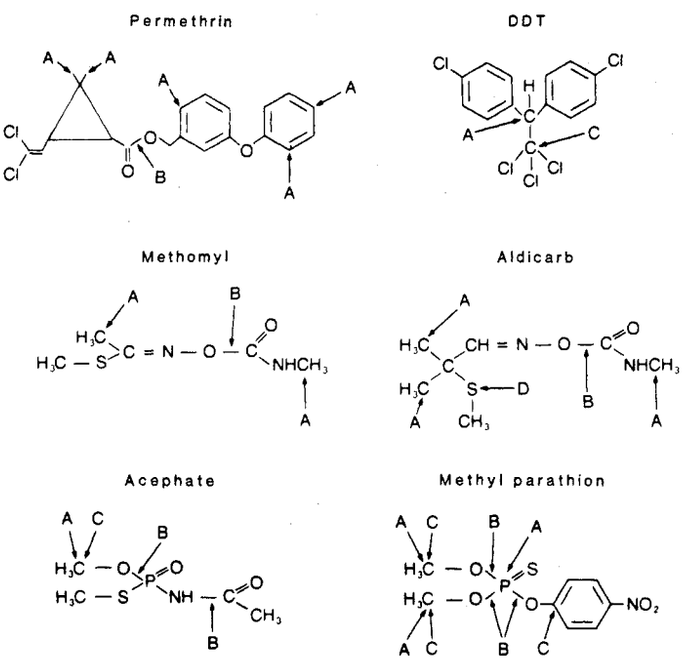

Fig. 2. Examples of insecticides that can be attacked by cytochrome P-450 (A), esterase (B), glutathione transferase (C), and flavin-adenine dinucleotide monooxygenase (D). FAD-monooxygenase (E.C.1.14.13.8) (*18*) has not been studied in insects.

hand, high cytochrome P-450 activity may lead to increased sensitivity (negative cross-resistance) to organothiophosphates such as parathion, which undergo metabolic activation by cytochrome P-450–catalyzed oxidation (*18*).

An insect population with target site and metabolic resistance, that is, multiple resistance, is extremely difficult to control with available insecticides. Integration of alternative control methods with judicious use of insecticides acting on different targets or detoxified by different enzymes can probably delay multiple resistance development.

Avoidance of pest insect populations with multiple resistance is one of the most urgent and compelling reasons for the development and implementation of IPM programs. The successful use of these techniques, however, requires thorough familiarity with all aspects of individual crop ecosystems, including the biochemistry of pests and natural enemies.

Behavior. Behavioral resistance mechanisms depend on the ability to learn or on genetic modifications in peripheral signal receptors or in central signal-processing systems. Behavioral adaptations are of major importance in insect avoidance of toxic components of their food plants in nature, but seem relatively unimportant compared to biochemical adaptations against synthetic insecticides. Scant attention has been given to insect behavior in agroecosystems, possibly because behavioral adaptations could also favor crop protection. If so, our insecticide use has still affected species and it would be useful to know about it. Several of the synthetic insecticides, such as chlordimeform, methomyl, and some of the synthetic pyrethroids, have antifeedant effects at low concentrations. For instance, fall armyworm larvae avoid feeding on leaves treated with carbaryl (*32*). However, this behavioral adaptation is an evolutionary dead end, since, without access to untreated plants or plant parts, the insect will starve and die without reproducing. Instead, we may expect adaptive behavioral changes in the adults such as in relative oviposition preferences for crop and weed species. This idea has not been investigated, even though a high degree of ovipositional variability between individuals of polyphagous species is known.

Resistance Management

Documentation of resistance. A critical prerequisite to resistance management is anticipation of resistance before control actually fails. On the basis of knowledge at hand, we can, to some extent, predict the occurrence of resistance by certain use patterns of present insecticides. However, since our knowledge is incomplete, predictions are vague and often incorrect. The major problem is the lack of a technique for detecting very low (less than 1 percent) frequencies of resistance genes present in a population before there is a failure of control, which occurs when the resistance gene frequency is about 10 percent.

A failure of control is, however, not always due to resistance. Other factors, including inadequate application techniques, weathering of the insecticide, target pest resurgence, and secondary pest outbreaks can also explain a control failure. Field monitoring of insect populations to evaluate their relative densities and susceptibility is, therefore, important. Both pre- and posttreatment population density data are necessary in determining the efficacy of insecticide applications.

Field monitoring complemented with laboratory tests may provide clues to the degree and kind of observed resistance. Theoretically, tests on insect cultures collected from individual fields provide more useful information than tests on populations resulting from mixed samples from different fields (*33*). This is because insects collected from individual fields may represent reproductively isolated populations with unique exposure histories. However, our understanding of genetic diversity in herbivorous insects vis-à-vis biochemistry and physiology is virtually nonexistent. There are no data to assess the extent of within-field versus between-field variability.

Bioassay mortality data compared to corresponding data from a suitable reference strain (a field population that can be controlled by the recommended dose) provide a "resistance ratio" that indicates development of resistance. Several factors make comparisons between field and laboratory data difficult. The materials used to formulate an insecticide for application can influence its toxicity (*34*), or weather-related factors such as ambient temperature can affect insecticide field performance. Also, laboratory testing methods rarely simulate natural conditions, usually bypass the role of the crop plant in toxicity, and do not take insect behavior into consideration.

Available strategies. Factors that influence the rate of resistance development in agricultural pest insects are broadly described as genetic, biological, and control-related factors (*35*). Genetic manipulation of agriculturally important insects is theoretically possible but not yet practically feasible. Genetic and biological factors such as inheritance mechanisms, behavior, reproduction, ecology, and population dynamics are intrinsic characteristics of a given species. However, insect biology can be manipulated to some extent. For example, pheromone lures may be used to attract susceptible insects to dilute a resistant gene pool (*36*). If only males respond to the long-range mating pheromone, the most common behavior among insects, this attraction scheme would not necessarily increase the population density.

Control-related factors, those directly related to insecticide use, are readily available strategies to minimize the insecticide selection pressure, the most important single factor in delaying resistance (*35*). The judicious selection and accurate application of chemical insecticides and their integration with other control methods consistent with basic IPM philosophy hold the most promise for effective resistance management.

Mixtures. The use of selected insecticide mixtures should retard resistance development because it should be more difficult for an insect to develop several adaptations simultaneously. This approach delays resistance in laboratory experiments and has been at least temporarily successful in a few field cases, particularly with certain organophosphate combinations (*37*).

Chemical mixtures closely simulate the chemical control of insects by plants, which usually contain mixtures of several allelochemicals to which a few specialized insects adapt but which minimize damage by nonadapted insects. Crop plants are genetically improved for yield and product quality, often at the expense of their defensive allelochemicals. These can be recruited as components of the insecticidal mixture. For example, the tobacco budworm *Heliothis virescens* (F) is more effectively controlled by fenvalerate on cotton varieties with a high tannin content than on low-tannin varieties (*38*). This is ascribed to a synergistic interaction between the tannin and the insecticide. Similarly, gossypol appears to improve the efficacy of monocrotophos and phosfolan in controlling the Egyptian armyworm (*39*).

Many plant allelochemicals are inducers or inhibitors of insecticide-detoxifying enzymes in insects (*19*). Several crop plants, including corn, cotton, and soybeans, contain such compounds and can thus modify the toxicity of insecticides used in these crops (*40*).

Mixtures, however, should be used with great caution. We do not understand how insects adapt to natural mixtures of plant allelochemicals or how long the process requires. Mixtures may be particularly effective in delaying the appearance of target site resistance but could cause reliance on metabolic or physiological defense mechanisms. In most cases in which natural insect-plant associations have

been investigated, metabolic, physiological, or behavioral mechanisms explain the resistance of the insect to the toxic plant chemical. The rarity of target site resistance to allelochemicals among natural insect-plant associations could reflect our limited ability to detect them or a real paucity of cases. Again, the examples from natural insect-plant associations may carry a warning that long-term use of mixtures could produce a few highly adapted insect species with versatile and effective defenses against most conceivable chemical treatments.

Insecticide synergists. Classical insecticide synergists inhibit enzymes involved in insecticide detoxification (*41*) and do not include materials that enhance penetration. A synergist is usually nontoxic in vivo at the rate used but can increase the toxicity of an insecticide up to several hundred times, particularly in resistant populations. Cytochrome P-450 inhibitors synergize all classes of insecticides to some extent and have widely differing molecular structures (*42*). Carboxylesterase inhibitors are usually organophosphates and may be toxic to susceptible insects. The synergistic action of organophosphates is probably the major factor in their successful use in insecticide mixtures.

The search for effective synergists has become more focused because of increased understanding of insect physiology and biochemistry. Synergists have been used analytically to delineate the relative importance of penetration, detoxification, and target site insensitivity in resistance (*43*) and to quantify the potential toxicity of a compound by removing interfering metabolic processes (*44*). By comparing the relative degree of synergism toward a group of structurally related insecticides, the site of enzymatic attack may be revealed (*45*).

Since the first demonstration of insecticide synergists, their effective application against agricultural pests has offered tremendous promise but achieved little utility. This is partly because their range of activity can be narrow. They are also less effective against the general population than against metabolically resistant strains. The extra cost is another major obstacle to their agricultural use. Devising compatible formulations and their resubmittal for registration as novel materials are additional hurdles in the development of synergists for agricultural use.

It has been suggested that synergists may be used to delay resistance devlopment in addition to their use in overcoming established cases (*46*). Exposing susceptible populations to an insecticide-synergist mixture could remove the selective advantage of metabolic adaptations. Insects with alleles for metabolic resistance would die in equal proportion to susceptible ones if the appropriate enzyme were blocked. The best chances for success would be with insecticides that are detoxified by one enzyme only. However, it will be difficult to choose a synergist to delay resistance, since different field populations of the same species show highly variable responses to a given synergist (*47*). The existence of multiple isoenzymic forms could be responsible for this variability.

The role of synergists in resistance management can also be indirect. The toxicity to beneficial insects would not be increased in cases where enhanced insecticidal activity is limited to a few related species or where pest and natural enemies rely on different detoxification mechanisms (*48*). In these cases the target species can be controlled with reduced insecticide rates in combination with a synergist without greatly affecting natural enemies. This would reduce the dose of insecticide needed and thus the selection pressure. Such an approach is compatible with IPM.

Dose and pattern of application. Application of the correct dose, whether of a single compound or a mixture, is a major factor in controlling insects and managing resistance. Susceptible populations should be controlled with the lowest possible dose to conserve the susceptible gene pool (*35*). However, exposing a population with incipient resistance to a low insecticide dose leads to rapid fixation of resistance. A low dose then allows survival and reproduction of resistant heterozygotes, the main source for the spread of the resistance allele, but kills susceptible homozygotes. A computer simulation with data from a field experiment involving fluorescence-marked mosquitoes demonstrated that a low or decaying dose of lindane allows sufficient survival of resistant heterozygotes to accelerate resistance development two to ten times (*49*). This creates a dilemma as a direct consequence of our inability to detect resistance until after it has developed to a significant extent (about 10 percent of the population).

Areas in dispersal regions left completely insecticide-free, so-called refugia, where susceptible individuals survive and reproduce, can delay resistance (*35, 49*). Thus, application of biochemically unrelated insecticides to adjacent fields could theoretically minimize resistance to each insecticide.

Timing and sequence of insecticide use. To preserve the usefulness of the insecticide and the susceptible gene pool, spray applications should be made only when economically determined threshold infestation levels are present. The threshold varies widely depending on crop, crop growth stage, major insect pests, and geographic locality (*35*) and can be determined only by constant monitoring of population densities.

Traditionally, spray applications are directed at the most damaging life stage. However, other life stages may offer more susceptible targets and reduce resistance development. Resistance to azinphosmethyl has not yet developed in the cotton boll weevil, *Anthonomus grandis* Boheman, despite 25 years of intensive exposure. Only adult boll weevils are sprayed; the larvae are inaccessible but cause the damage. Adult boll weevils have weak metabolic defenses compared to the larvae (*50*). Ovicides could be used in cases where oviposition sites are accessible to treatment. The eggs of most pest insects have no detoxification abilities, which leaves them vulnerable to ovicides.

The sequence of insecticide use can be organized so that resistance and cross-resistance are avoided or delayed, although the possibilities are limited. Sequences in which unrelated insecticides are used successively or alternately provide refugia in time that may allow reversal of resistance by shifting selection pressure from one mechanism to a different one.

New insecticides. The goal of crop protection is to protect the crop from intolerable damage, not to kill as many insects as possible. A susceptible gene pool is a natural resource that allows economical and convenient control of insects by chemical insecticides, themselves a resource that is renewable only with difficulty. About 40 years of intensive effort have produced only four major kinds of insecticides—chlorinated hydrocarbons (1942), organophosphates (1944), carbamates (1956), and photostable pyrethroids (1978)—representing three different modes of action.

In the past, new insecticides were available to replace those to which resistance had developed. Today that is not the case. The insecticides should thus be managed to ensure their continued usefulness. Recommendations for doing this have been made by concerned scientists and agencies but have not been generally followed. Large-scale experimentation is needed to establish the validity of current theories of resistance management, most of which are based on isolated successes in specific crop systems and on laboratory experiments.

Antifeedants clearly have a potential as components of IPM programs and may be widely used in the future. The insect nervous system, of which peripheral receptors are a direct extension, has proven adaptable to both synthetic and natural toxicants when these are applied massively and therefore can act as selecting agents. Molecular adaptations allowing insects to feed on antifeedant-treated plants will probably develop. Resistance management will

then depend on thorough knowledge of insect behavior, biology, and neurophysiology.

A new insecticide need not be more toxic than current products; it should have a novel mode of action, rapidly kill insects or stop their feeding, and have reasonably short residual stability to enable use with precision. Field use of an insecticide should include considerations of its tendency to function as a resistance-selecting agent in the intended target species. Information about metabolism in the pest insects or about mode of action is usually lacking, and its development deserves high priority. The chemical discovery process can more strongly and purposefully emphasize biorational design. More robust in vivo and in vitro screens to detect new types of toxicity can be devised. The mode of action and metabolism of candidate insecticides should be investigated early in the development process.

Conclusions

Agricultural insecticide resistance provides many opportunities for multidisciplinary basic research. The accelerated evolution of insecticide resistance, with known selection pressures and definable adaptive mechanisms, can be used to design models for exploring the basic genetics and biology of host-race and species formation. Studies of the basic biology of insect-plant interactions in nature and in crop agroecosystems can produce ideas for improved use of chemicals and how they can best be integrated with nonchemical methods. Also, improved agricultural use of insecticides can minimize exposure of nontarget species, which can be particularly important in alleviating selection for resistance in public health species.

Insecticide resistance is a formidable practical problem for growers, and consequently our best efforts have focused on testing alternative chemical treatments in the hope of finding expedient solutions. This has been done largely at the expense of studying the insects and their interactions with the environment.

Many of our current ideas for managing resistance are incompletely conceived for lack of basic information, are untried on any economically significant scale, and represent the wisdom of hindsight. Resistance is still often considered a minor problem compared to the public health hazards and environmental destruction also associated with insecticide use. A better understanding of resistance and its effective management is likely to reduce the overall risks imposed by exaggerated insecticide use and to enhance the already substantial benefits of crop protection chemicals.

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