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Some Observations on Insecticide Resistance

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SOME OBSERVATIONS ON INSECTICIDE RESISTANCE[1]

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ABSTRACT

A model for development of resistance to an insecticide in an insect population is presented. The rate of development of resistance increased with increases in the proportion of the breeding population exposed to the insecticide and with increases in the survival from exposure to the insecticide. Restricting application of insecticides to an "only if needed" basis and, within limits, dosages that assure minimal survival of the exposed insects are suggested as means of impeding resistance to insecticides. The huge gene pools represented by the large populations of pest species are assumed to maintain insecticide resistance as a continuing problem in crop protection.

Individual insects vary in their susceptibility to insecticides. This is most clearly seen in laboratory tests in which insects selected for uniformity are exposed to different dosages of an insecticide. That some insects survive dosages that kill their cohorts is expected in these tests and the log-probit curve is well established as descriptive of the relationship of dosage-mortality. This curve is an asymmetrical sigmoid with a short lower end, a rapidly ascending central portion, and prolonged upper end (Fig. 1). The important part of the curve for this discussion is the prolonged upper end that shows that a few individuals, even among the relatively small number of insects used in laboratory trials, can survive dosages that will kill the great bulk of their companions.

Field testing of insecticides is done under much more variable conditions than in the laboratory. The insects vary in size, vigor, sex, and even in stage; the exposure of the individuals is variable and some may escape exposure entirely; and the results are always subject to the specific circumstances (such as weather) at the time. Insecticide, dosage, type and time of application, formulation, and other details for practical control are selected on their expected reliability in reducing the numbers of insects. The recommended dosage would usually place it high on the log-probit curve if it were a laboratory test. If accepted, the insecticide may be widely used and enormous numbers of that insect will be exposed to that insecticide.

Insect populations are so huge that every possible combination of genes is bound to occur. These combinations probably include genotypes that confer some degree of immunity to insecticides, or any other control measure, that could be used against that insect. A smaller portion of the individuals with these genes will be killed by exposure to the insecticide than will those with the susceptible genetic make up. It is the percentage of the insects killed that is measured in most control studies even though it is the number that survive to cause damage that should be of concern. Even more importantly it is the survivors that will breed succeeding generations. The differential survival of resistant and susceptible individuals over time can result in a high enough frequency of resistant genes that the population can no longer be adequately controlled with the standard application of the insecticide.

The development of resistance through the selective reduction in frequency of the susceptible genes is simple in concept. The actual development of a resistant population in the field, however, is subject to a multitude of highly specific circumstances. One such

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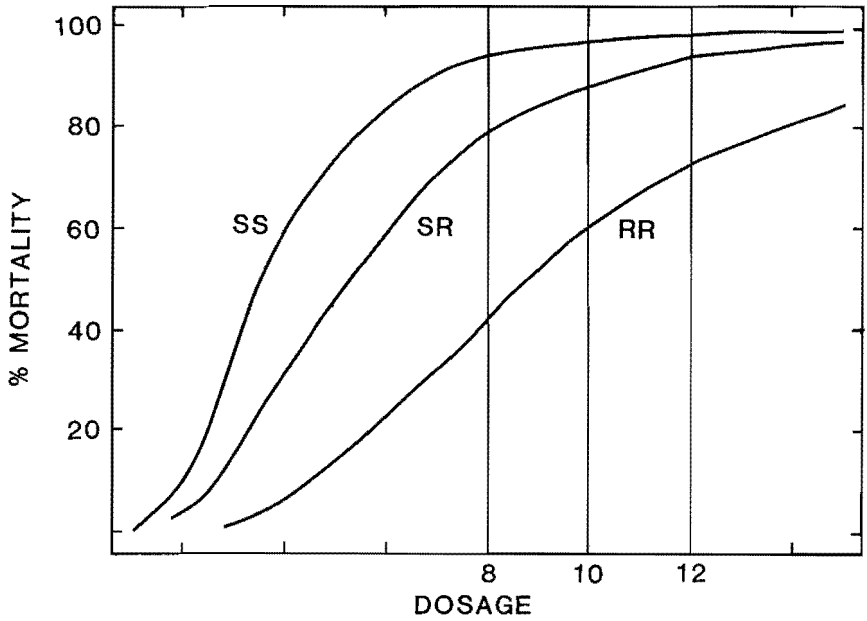

Fig. 1. Percent mortality on dosage of an insecticide for the homozygous susceptible (*SS*), hybrid, (*SR*), and homozygous resistant (*RR*) genotypes used in the example. The 8, 10, and 12-unit dosages used in the example are shown.

circumstance, for example, is the continuous, widespread use of a given insecticide that depends entirely on the individual choices of the applicators. With all the alternative materials available, one must wonder why resistant populations ever occur. Cross resistance, resistance to one insecticide conferring some degree of resistance to a second (usually, but not always, a related) insecticide, does occur and can facilitate development of resistance even when more than one insecticide is used. Resistance can, therefore, develop even when several insecticides are used given the proper circumstances, once again.

There are no means of accurately predicting the development of resistance in a given field population to a given insecticide. There are some very general parameters that can be used to make models of the development of resistance, however, to illustrate their importance in resistance. The first of these is the genetics of resistance. Laboratory studies have shown that the inheritance of resistance is rarely simple. Simple escapes from actual exposure and the accumulation of resistant genes from the cross resistance from past applications plus the other special circumstances of all field applications make only gross studies of resistance in the field possible. Because of the uncertainties, a single pair of alleles, *S* for susceptible and *R* for resistant, are used to represent the phenotypic responses in the simple model. It is assumed that the alleles affect only resistance and do not otherwise affect the insect and that the individuals with different genotypes (*SS*, *RS*, and *RR*) will mate randomly. The segregation from random matings is expressed by the equation:

$(S + R)^2 = SS + 2RS + RR$

where S = susceptible and R = resistant genes.

An important point is that the initial frequency of the resistant gene must be low enough to obtain adequate initial control or the insecticide would be discarded in the original

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screening tests. The proportional numbers of the different genotypes (*SS*, *RS*, and *RR*) in the population is determined by the equation:

proportional number = $SS(1-F)^2 + RS2F(1-F) + RR\ F^2$

Where F = frequency of the resistant gene, *R*. For example if F = 0.1

Proportional number = $SS(1-0.1)^2 + RS\ 2 \times 0.1\ (1-0.1) + RR\ 0.1^2$

$= 0.81\ SS + 0.18\ RS + 0.01\ RR$

The model also assumes a differential survival of the insects that are exposed to the insecticide. Note survival, not mortality, is the parameter. The percent-control with a given frequency for the resistant gene, F, and with proportional survivals of A, B, and C for the *SS*, *RS*, and *RR* geneotypes, respectively, is determined by the equation:

% control = $100[1 - [A(1-F)^2 + 2BF(1-F) + CF^2]]$

Where 100 = adjustment for percentage and A, B, C, and F are as noted. For example, if A = 0.05, B = 0.2, C = 0.5, and F = 0.1:

% control = $100[1 - [0.05(1-0.1)^2 + [2 \times 0.2 \times 0.1(1-0.1)] + (0.5 \times 0.1^2)]]$

$= 100\ [1-[0.04505 + 0.036 + 0.005]]$

$= 91.85$

The differential removal of the *S* and *R* genes by the insecticide changes the frequency of the *R* gene. The new frequency of the *R* gene, F′, among the insects exposed is determined by the equation:

$F' = [BF(1-F) + CF^2] \div [A(1-F)^2 + 2BF(1-F) + CF^2]$

If the values for A, B, C and F used in the prior example are used:

$F' = (0.018 + 0.005) \div (0.045 + 0.036 + 0.005)$

$= 0.2822$

Substituting the changed value, F′, of the resistant gene for the original frequency of the gene, F, in the equation for percent control given earlier would result in a percent control of 85.34 of the next generation, a drop of 6.51%, if only the surviving insects exposed to the insecticide were to breed the next generation.

All individuals of a breeding population are rarely (if ever) exposed to an insecticide in the field. In one way or the other some individuals in the treatment area escape contact with the insecticide and some individuals of the breeding population move in from untreated areas. Insects restricted to intensively cultivated crops that are sprayed routinely with insecticides (such as some fruits and vegetables) will have a large proportion of their populations exposed. Insects of more extensively cultivated crops will usually be less exposed to insecticides. There are exceptions. The corn rootworms, *Diabrotica* spp., in field corn developed resistance to the chlorinated hydrocarbon insecticides and undoubtedly still have a large part of their total population exposed to soil insecticides. The proportion of the breeding population exposed to the insecticides will affect the frequency of the *S* and *R* genes in the subsequent generations as their frequencies in the unexposed portion will remain unchanged while the frequencies in the exposed portion will be altered. The equation for determining the new frequency of the resistant gene, F′, following the exposure of a proportion, P, of a breeding population is:

$$F' = \frac{F(1-P) + P[BF(1-F) + CF^2]}{(1-P) + P[A(1-F)^2 + 2BF(1-F) + CF^2]}$$

where A, B, C, and F′ are as noted earlier and P = proportion of the breeding population exposed to the insecticide. To continue with the example that was used previously with the proportion of breeding population set at 90% (P = 0.9) and A = 0.05, B = 0.2, C = 0.5, and F = 0.1:

$$F' = \frac{0.1\,(1-0.9) + 0.9[0.2 \times 0.1\,(1-0.1) + 0.5 \times 0.1^2]}{(1-0.9) + 0.9[0.05\,(1-0.1)^2 + [2 \times 0.2 \times 0.1\,(1-0.1)] + (0.5 \times 0.1^2)]}$$

$$= \frac{0.01 + 0.9\,[0.018 + 0.005]}{0.1 + 0.9\,[0.0405 + 0.036 + 0.005]}$$

$$= 0.1771$$

The percent control obtained by an insecticide application is determined by the frequency of the resistance gene and the differential kill of the genotypes. The frequency of the resistance gene, F, was held at 0.1 in all of the computations of the model. This is probably a very high frequency, but was used to reduce the calculations in the model. The selective survivals of the genotypes were adjusted to give at least 90% control in the initial exposure as a lesser control very probably would not be accepted for use. The proportions of each genotype surviving an exposure to different dosages of an insecticide were estimated by plotting hypothetical log-probit curves with equal slopes for each genotype and calculating the percent mortality of each genotype at standard (10 units), low (8 units), and high (12 units) dosages. The retransformed curves of percent mortality on dosage are shown in Figure 1. The proportional survival of each genotype at each dosage were:

	Dosage		
Genotype	Low	Standard	High
SS	0.060	0.023	0.009
SR	0.208	0.106	0.054
RR	0.575	0.403	0.274

The proportions of the breeding population exposed to the insecticide, P, were set at 0.7, 0.8, and 0.9 (70, 80, and 90%). These exposures may be unrealistically high for any insect, but they were selected as they make the point without unduly prolonging the calculations. A control of less than 75% was used as the level at which the population would be classed as resistant; I believe that this is a realistic level for suspecting that a problem exists.

The results of the model using the selected parameters are shown in Figure 2. The rate of development of resistance increased with each increment in the proportion of the breeding population exposed and with each increment in the proportion of survival of the exposed insects. The reason for the increased rate of resistance with increased exposure of the population is simply that increasing numbers of susceptible individuals were eliminated from the progenitors of the subsequent generation by exposure to the insecticide. The reason for the increased rate of resistance with increased survival is not so obvious. The first thought would be that an exposure that results in a high survival should slow down resistance by having a large proportion of the susceptibles survive to breed the next generation. Indeed, reduced dosages of insecticides that would give increased survivals have been recommended as a means of minimizing the risk of development of resistance. The differential reduction in gene frequency, however, has its greatest effect on the hybrids which have equal numbers of resistant and susceptible genes independent of the frequencies of these genes in the total population. This means that a resistant gene survives with every susceptible gene that survives in the hybrid population. An extreme example of the importance of the survival of the hybrids is shown in Figure 3 where F = 0.1, P = 0.5, and values of A, B, and C were selected for dominance of *S*, dominance of *R*, and no dominance:

	Survival Level		
Genotype	*S* Dominant	No Dominance	*R* Dominant
SS (A)	0.01	0.01	0.01
SR (B)	0.01	0.5	0.99
RR (C)	0.99	0.99	0.99

The model presented is genetically simplified as a single pair of alleles, *S* and *R*, that determine susceptibility to an insecticide is assumed. Considering the many uncertainties of field applications (reduced exposures, escapes, and the like), the model is probably very realistic in its gross effect and has some implications in explaining risks of developing

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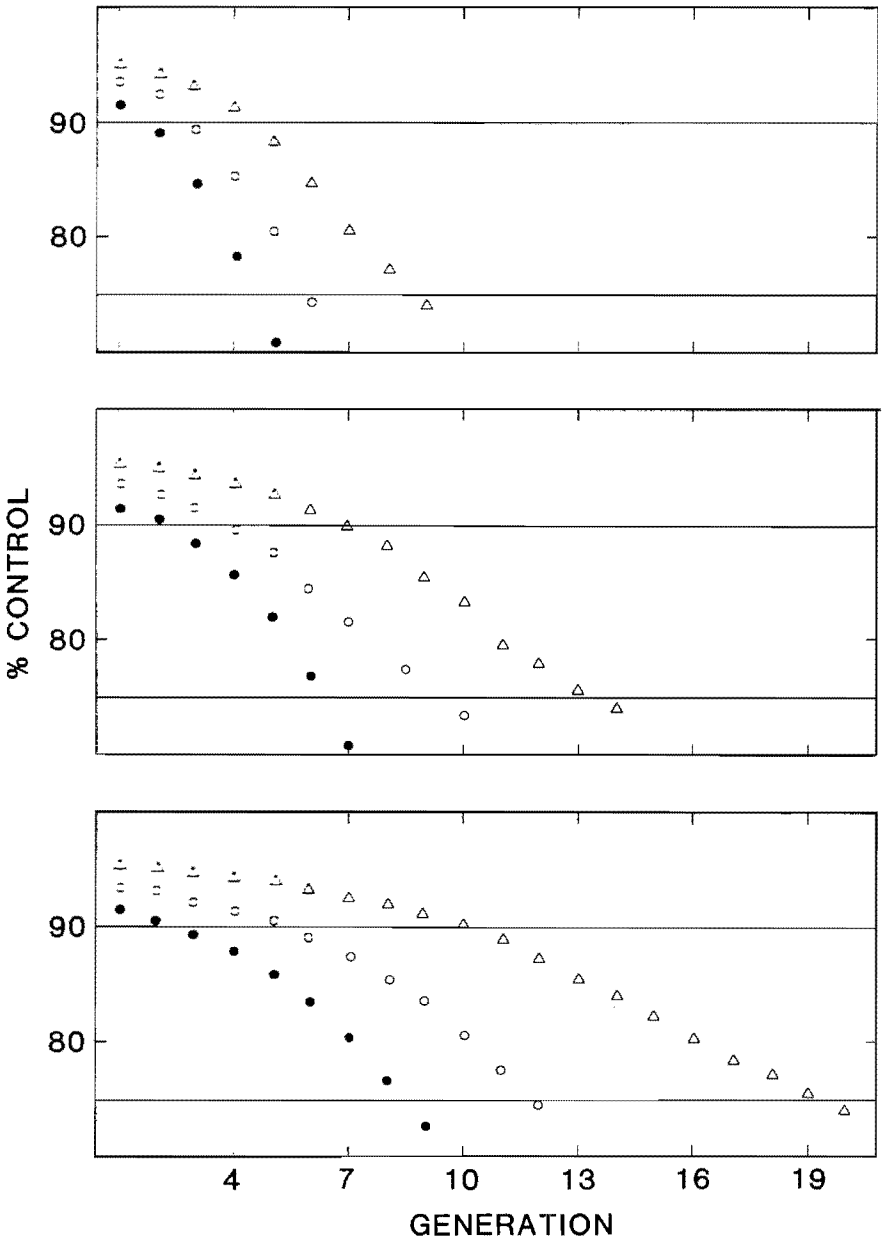

Fig. 2. Percent control of an insect obtained with successive exposures to an 8 (•), 10 (○), and 12 (△) unit doses of an insecticide when 90% (P = 0.9; upper graph), 80% (P = 0.8; center graph), and 70% (P = 0.7; lower graph) of the breeding population is exposed.

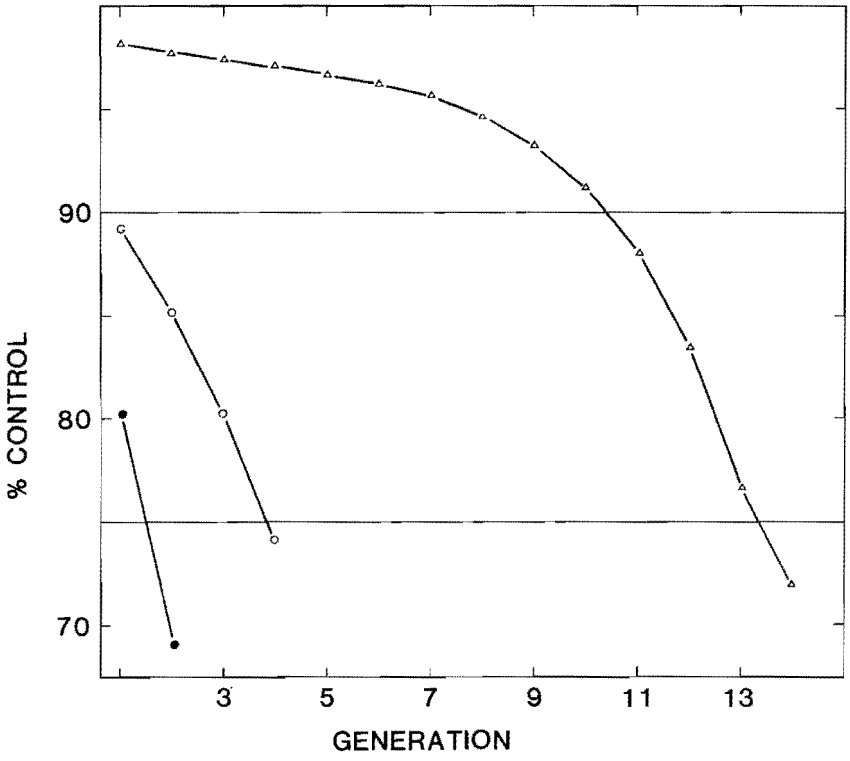

Fig. 3. Percent mortality of an insect obtained with successive exposures to an insecticide when the gene for resistance is dominant (•), the susceptible gene is dominant (△), and neither gene is dominant (○).

resistance, The most unrealistic parts of the model are its assumptions that growers will all treat the same year after year and that they will not make adjustments as the controls begin to drop. A point not in the model is that increasing dosage, as is often done, when resistance is suspected is of marginal value as (see Figure 1) the dosage recommended is nearly always near the upper end of the log-probit mortality curve. The increased dosage will result in a lengthened residue of the insecticide. This could be beneficial (an improved control because of the prolongation of residual efficacy, for example) or deliterious (excessive residue on the crop or an unwarranted exposure of a second generation of the insect to the residue, for examples) depending on the circumstances. Insecticides degrade on the logarithm of time. This means that the time of low dosages that allows high survival (or causes low mortality, if you prefer) is disproportionally prolonged. Insecticides with short residues, at least relative to the generation time of the insect, should, therefore, present a lessened risk of resistance. Increasing dosage to suppress the effects of resistance could, given the proper circumstances, actually increase the rate of development of resistance by prolonging the residue. The model definitely shows that sufficient dosage should be used to reduce survival of the hybrids. There must be a balance of the

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need for an effective dosage with the need for minimal residue. The mathematics of the differing curves for dosage-mortality and for degradation on time may be an absolute limit on achieving a satisfactory balance. Each case would be highly specific.

The original frequency of the resistant gene was held at a constant figure in the model both as a convenience and because increased survival with increased frequency of the resistant gene was assumed. The model was based on changing the frequencies of the genes, and we can assume that this has been ongoing since insecticides were first used. The result is that the frequencies of resistant genes have been steadily increasing in insect pests, slowly in some and faster in others, over the years. Remember, too, that all organisms in the treated field will be exposed to the insecticide. The gene frequencies of the non-target species will be changed right along with those of the targeted pest species. Means of exposing only the target pests to the insecticides would help reduce the changes in the other species. The closest that we have to selective applications at present is the use of attractant baits. The physiological pathways of the different insecticides vary, but the appearance of cross-resistance (that is, resistance to one compound accelerating resistance to a second compound) clearly shows that there are points in common. We can fully expect, therefore, an intensification of the problems with resistance over time. We may be able to slow down its development but, considering the variability and huge numbers of the insect pests, resistance will always remain a concern. Note that I attribute resistance to selection among existing genes and see no need of postulating mutants as the source of resistance.

The reduction in the proportion of the breeding population exposed to an insecticide appears to be an immediately feasible means of reducing the risk of resistance. One means of reducing exposure to a single insecticide is by using several different types of insecticides in rotation. This assumes, of course, that several types of insecticides are practical and that resistance to them is not influenced by the same genes. The rotation would arithmetically impede the development of resistance by the number of compounds used. The effectiveness of the rotation, however, depends on a number of circumstances and would be highly specific. The most practical means of reducing exposure is by reducing the applications to those that are actually needed. In its simplest form, checking fields for the pest and applying an insecticide only if it reaches a threatening level, rather than applying a blind preventative (or "insurance") application, is all that is required. This is not all that easy as it requires that an efficient means of checking for the insect and reliable indices of its threat must be developed, and that growers must be convinced that the system is reliable and that it is in their interest to accept the practice. This "only if needed" approach is sound economically and is steadily being more widely accepted. At its most complex, this reduction of exposure would be the full program of crop protection, an "integrated pest management" (but IPM is variously defined) type of program, that would minimize the risk of damaging infestations and, thus, reduce the need to use an insecticide. Our knowledge is limited even for the simple case, especially so in the area of reliably predicting eventual losses based on early samples of insect numbers. Usable information is rapidly becoming available, and research (and, to some extent, practice) directed at avoiding insect problems is well established. I am certain that more satisfactory means of avoiding losses to insects will be implemented in the near future. I am equally certain that the huge gene pools of the insects will keep even the best designed programs dynamic.