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The Evolution of Insecticide Resistance: Have the Insects Won?

James Mallet

'It will probably never again be possible to achieve chemical control of insects on the scale achieved between 1945–1965' (R.J. Wood, 1981[1]).

While insecticides have greatly improved human health and agricultural production worldwide, their utility has been limited by the evolution of resistance in many major pests, including some that became pests only as a result of insecticide use. Insecticide resistance is both an interesting example of the adaptability of insect pests, and, in the design of resistance management programmes, a useful application of evolutionary biology. Pest susceptibility is a valuable natural resource that has been squandered; at the same time, it is becoming increasingly expensive to develop new insecticides. Pest control tactics should therefore take account of the possibility of resistance evolution. One of the best ways to retard resistance evolution is to use insecticides only when control by natural enemies fails to limit economic damage. This review summarizes the recent literature on insecticide resistance as an example of adaptation, and demonstrates how population genetics and ecology can be used to manage the resistance problem.

Unlike most evolutionary hypotheses, those involving resistance to man-made disturbance can be tested using historical data as well as experiments. The evolution of industrial melanism in moths and of heavy metal tolerance in plants are two examples of resistance that are widely cited in textbooks on evolution. It is especially important to understand the evolution of resistance in pests and diseases because this understanding can enable us to avoid or reverse the process. Evolutionary biology is usually a pure science, but it here has a valuable opportunity to provide material benefits.

Arthropods have been among the most troublesome pests to control chemically. The WHO programme to eradicate malaria worldwide failed in large part because the vectors, anopheline mosquitoes, became resistant to insecticides[2–4]. Modern cotton production depends on heavy insecticide use (in the USA about 20–50% of all insecticides purchased are used on cotton), and has in a number of regions ended in financial disaster as pest after pest became resistant[5–7]. Fears that the budworm *Heliothis virescens* would become resistant to pyrethroids, the last known group of insecticides that can effectively control this pest of cotton, has led in the USA to cooperation on resistance management by companies competing in the insecticide marketplace[8]. Such cooperation would have been unthinkable during the insecticide boom of the 1950s and 1960s.

The number of insect pests known to be resistant to pesticides has exploded in the latter part of this century (Fig. 1). At the same time, the introduction of new insecticides has slowed because regulatory measures to limit environmental damage have resulted in increased development costs. Resistance to the biological insecticide *Bacillus thuringiensis* has already been documented[9] and resistance to biologically engineered insecticidal crops could well develop soon after they are widely grown[10]. Some workers (e.g. Ref. 4) doubt whether chemically-based pest control will be useful at all in the future, especially since some mechanisms of resistance are effective against a variety of toxic chemicals.

The nature of resistance

Prior to the Second World War, insecticides were often inorganic (e.g. HCN, arsenicals, lime sulphur) and almost as dangerous to humans as to their competitors. The multiplicity of modes of action ('target sites') of such chemicals may have prevented the evolution of resistance: only 12 cases of insecticide resistance were reported before 1946 (Fig. 1)[11]. The newer lipophilic organic insecticides (especially organochlorines, organophosphates, carbamates and synthetic pyrethroids) were generally safer and could be more selective against insects because each affected only a single biochemical site. However, this target-site specificity may also have permitted rapid evolution of resistance[5].

Insects have exploited virtually every conceivable means of withstanding insecticides. Adaptations are known that increase behavioural avoidance, reduce cuticle permeability, speed conversion of insecticides to excretable polar compounds, or decrease sensitivity of the biochemical target (Box 1). Herbivorous insects, especially generalist herbivores, often develop resistance before their parasites or predators. This may be due to the inherently high activity of detoxifying enzymes in herbivores, which must normally handle plant secondary chemistry: such insects, rather than their enemies, are preadapted to evolve resistance because their existing detoxifying systems can be enhanced by selection[12] (there may also be ecological reasons why pests can adapt to pesticides better than their enemies – see below). It is therefore no surprise that many of the world's most devastating resistant arthropods (e.g. spider mites, scale insects, aphids, and leaf-feeding Lepidoptera) are artificial, 'secondary' pests that only become a problem after insecticides release them from control by natural enemies[4,7].

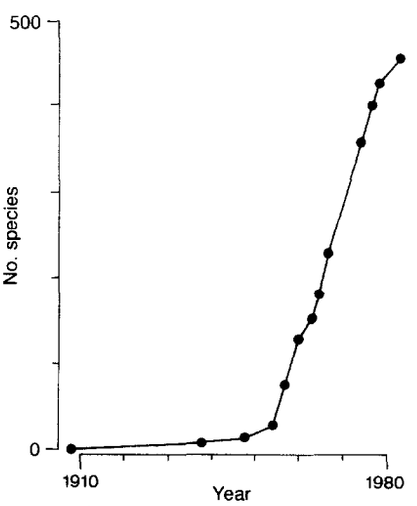

Fig. 1. The cumulative number of species known to be resistant to one or more insecticides. *After Georghiou*[11].

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Mosquitoes, which are also prone to resistance, may have similar detoxification mechanisms to cope with organic chemicals leached from plant material in the stagnant water of their larval habitats.

Neodarwinian theory predicts that novel traits will evolve fastest when many loci, each of which has a small effect, determine the phenotype. In contrast to these expectations, mechanisms based on relatively few or single genes (Fig. 2) account for most resistance in the field[13]. It seems likely that selection for field resistance can be so intense that only very rare extreme variants can survive, and these will be at single loci. In contrast, laboratory selection, which is necessarily weaker, may cause polygenic resistance[14] because many genes will have alleles with weakly resistant effects[13]. A similar argument has been advanced for the existence of major genes in the evolution of mimicry: a major jump is necessary to give a crude resemblance to a model species, and only thereafter can polygenic modifiers perfect the mimicry[15]. However, single-gene insecticide resistance could also be due to the very specific modes of action of modern insecticides, which permit target-site alteration as a viable means of resistance (Box 1).

The initial rarity of resistance alleles suggests that such alleles are selected against in the absence of pesticides[16]. However, experimental evidence for fitness deficits is weak[13]: laboratory studies all too often compare the fitnesses of resistant and susceptible laboratory strains, with little attempt to control genetic background, and field studies are plagued by the possibility that reductions in resistance frequency after selection is relaxed are due to undetected immigration of susceptibles (e.g. Ref. 17). In some cases, modifiers seem to have arisen that can reduce the negative side-effects of resistance genes[18,19].

Theory of resistance evolution

Insecticide resistance is characterized by rapid evolution under strong selection. In contrast, many analytical single-locus and quantitative genetic models obtain results by means of weak-selection approximations, and will therefore be hard to apply to the evolution of resistance[20]. An additional difficulty is that selection for insecticide resistance has its own quirks, as we shall see below. For these reasons, standard population genetic models have been of little use, and custom-made models, often based on simulation, have been developed[21,22].

A recessive allele for resistance would increase to fixation in a single generation if the mortality of susceptibles under insecticidal treatment were 100%. Since this never happens in the field, it is necessary to assume that there is a reservoir of untreated insects[23], i.e. that there is a less than 100% mortality of treated susceptibles. Provided that a reservoir exists, a rare mutation at a single locus will increase much more rapidly if dominant than if recessive to wild type. This well-known population-genetic result has the added twist that the 'effective' dominance of a resistance allele (Fig. 2) is reduced with increasing dose[23].

A reservoir can be due to two factors. Firstly, it is impossible to cover sprayed surfaces evenly with insecticide. For example, there may be several orders of magnitude difference between toxicant concentrations on canopy and understory leaves of cotton. Secondly, a reservoir population may exist outside the treated area, but partially mix with the treated population by means of dispersal. Resistance will never increase much above pre-treatment levels if the untreated reservoir is infinitely large, and much less resistance will evolve in the treated area than it would in the absence of migration. However, there will be a migration rate below which resistance levels increase rapidly, because the treated population then evolves virtually independently of the reservoir[24,25]. More realistically, the reservoir will be finite and resistance will eventually fix throughout the range (though this can be balanced by selection against the resistant form in the reservoir) because of emigration by resistants into the reservoir. Nonetheless, immigration from a finite reservoir will still considerably delay the increase in resistance[24].

Box 1. Mechanisms of insecticide resistance

Behavioural resistance: The evolution of behaviour to detect and avoid insecticide seems a likely means of resistance, especially since some insecticides, such as pyrethroids, can act as irritants or repellants. Only a few clear examples are known[1,26], but behavioural resistance may have escaped detection due to the difficulty of behavioural bioassays.

Reduced penetration: Differences in transport across the cuticle have been demonstrated in houseflies and Lepidoptera[27,28]; in the housefly a single gene *pen* has a major effect.

Metabolic resistance: involves non-specific enzymes that normally detoxify foreign lipophilic chemicals. Examples are monooxygenases (mixed-function oxidases, microsomal oxidases, or cytochrome P-450 dependent oxidases), hydrolases (including esterases), and transferases[1,12]. Many of these enzymes are known to be inducible, and this induction on its own can provide temporary tolerance to pesticides. Inherited resistance often involves oxidases[29–37]. Resistant aphids and mosquitoes can have manifold amplifications of esterase genes[38,39]; in the aphid *Myzus persicae* this resistance is due to the increased amount of esterase protein acting as an insecticide sink as well as a catalytic enzyme, rather than to an increase in catalysis per molecule[39]. Usually the exact genetic mechanism of metabolic resistance is not known, although regulatory rather than structural changes are suspected in many cases[34]. 'DDT-dehydrochlorinase', regulated by the *Den* gene of houseflies, is an example of a glutathione S-transferase[12].

Target-site resistance: DDT and pyrethroids act by potentiating the voltage-sensitive Na^+ channels in nerve cells, leading to repeated nerve firing. The *kdr* ('knockdown resistance') gene of houseflies reduces the sensitivity of the sodium channels to both types of insecticide. Either a reduced number of Na^+ channels or, more probably, a change in the structure of the channel or an accessory protein is involved[40]. The organophosphates and carbamates mainly act by blocking acetylcholinesterase, which leads to repeated nerve firing due to an overabundance of the neurotransmitter acetylcholine. In mosquitoes, resistant acetylcholinesterases often form the basis for target-site resistance to these insecticides[1,27]. Cyclodiene insecticides (e.g. dieldrin), lindane and ivermectins appear to act on the Cl^- channel gated by the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Cross-resistance between lindane and cyclodienes probably involves insensitivity of the Cl^- channel proteins[40].

Multiple mechanisms of resistance: Some species seem to have developed resistance to any given compound in a variety of ways. For example, behavioural, penetration and metabolic resistance, as well as target-site insensitivity to pyrethroids, have all been reported in *Heliothis virescens*[27,28,41].

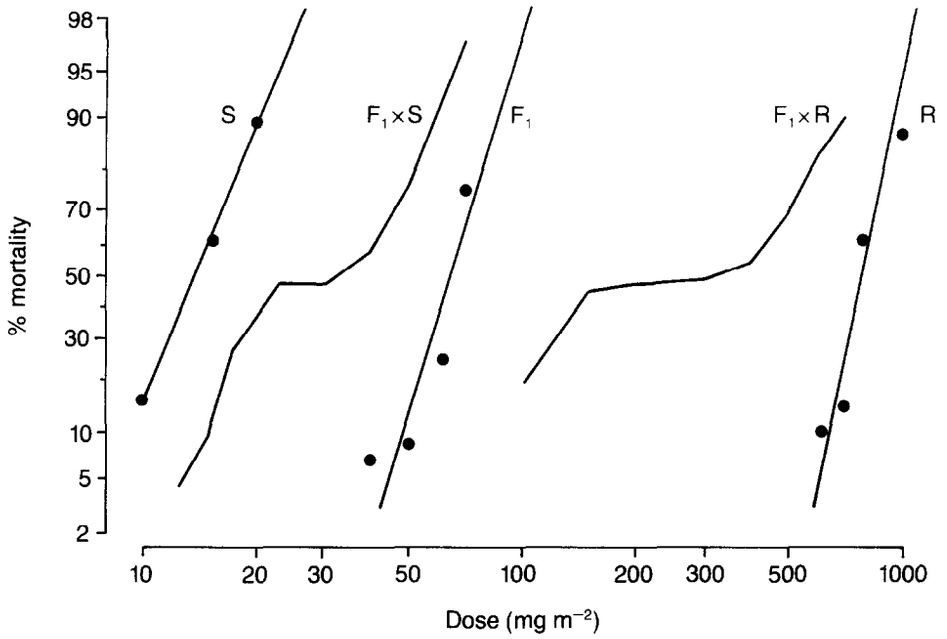

Fig. 2. Inheritance and effective dominance of resistance.

The percentage mortality of susceptible (S) and resistant (R) strains of the mosquito *Aedes aegypti* and their hybrids is plotted on a probability scale against the log dose of permethrin, a pyrethroid insecticide. These transformations linearize cumulative normal dosage–mortality curves. F_1 hybrids between S and R strains give intermediate mortality. Backcrosses ($F_1 \times S$, $F_1 \times R$), give curvilinear dosage–mortality lines representing a 50:50 mix of F_1-like and R (or S)-like types, each with its own normally distributed cumulative mortality curve. Polygenic inheritance would instead give a straight line in the backcrosses (i.e. a cumulative normal distribution), with a shallower slope (greater variance) than in S, R and F_1: thus the figure is good evidence for a single gene, or several tightly linked genes with major effects on resistance.

The figure also shows how an alteration of dose can change the effective dominance as well as the selection pressure on a locus under insecticidal selection. Spraying at a dose of 30 mg m^{-2} eliminates chiefly homozygous susceptible genotypes, whereas spraying at a higher dose, 300 mg m^{-2}, eliminates heterozygotes for resistance also. At the former dose, resistance is effectively dominant; at the latter, resistance is effectively recessive[23].

After C.A. Malcolm, in Ref. 1.

Another factor affecting resistance evolution is density-dependent population regulation. Suppose the pest population is only weakly regulated by predators and parasites. The population will then return only asymptotically to equilibrium levels after insecticidal treatment (the density dependence is said to be undercompensating). In this case, susceptible immigrants form a large fraction of the population, which will hinder the evolution of resistance more than if the treated population were to rebound exactly to the equilibrium size (perfect compensation, giving 'soft' selection, as assumed in many population genetic models).

Conversely, if the population tends to overshoot its equilibrium size (overcompensation), immigration will be less effective than under perfect compensation, and resistance will evolve more readily[24]. The strength of density dependence is roughly proportional to *r*, the intrinsic rate of increase in the population. Spraying with a contact insecticide tends to reduce numbers, both of pests and of their natural enemies. This will increase *r* for the surviving pests because of the relaxation of natural control, and so make overcompensation more likely, leading to rapid evolution of pest resistance. Meanwhile, the remaining natural enemies initially have difficulties finding their prey: this reduces their *r*, causes a greater tendency to undercompensation, and leads to a slowing of resistance evolution in natural enemies.

Population dynamics, as well as detoxification mechanisms (see above), will thus help to explain why pests often become resistant before their natural enemies[25,26]. Broad-spectrum insecticides seem almost designed to allow efficient evolution of resistance by herbivorous pests.

Insecticide resistance management

Can this knowledge suggest methods for slowing or preventing the evolution of resistance? There are disagreements about almost every method that has been proposed. One obvious strategy is to use very little insecticide, so that few susceptibles are killed[16]. The difficulty with this strategy is that good control often requires a high dose. An apparently contradictory alternative strategy is to use a high enough dose so that resistance is effectively recessive[23] (Fig. 2). This method would work well if the susceptibilities of each resistant genotype were known before resistance became common, which unfortunately is never the case. However, since alleles conferring resistance will become scarcer as well as more effectively recessive (see Fig. 2) when a higher dose is used, the best we can do is to avoid insecticides until they are absolutely necessary, and then use them at a relatively high dose, while permitting reservoirs of susceptibles to exist.

Selection for resistance to a given chemical can also be reduced by using a rotation of different chemicals. Selection against resistance between treatments of the same insecticide, together with immigration of susceptibles, can reduce the frequency of resistant insects to an acceptable level. But resistance is probably more advantageous under insecticidal treatment than it is disadvantageous in the absence of treatment, so a rotation will have to include many different chemicals to work as a stable strategy[16]. Usually, resistance evolves in the long run. Since a naive strategy – of using insecticides in turn until resistance evolves to each – gives almost the same total control period as a planned rotation[23], rotations can hardly even be defined as management. However, in some cases rotations may be the only practical way of limiting resistance to a single favoured compound[23,27].

A mixture of insecticides, on the other hand, can delay the evolution of resistance by several orders of magnitude compared with a rotation[23,28]. Mixtures work because insects that receive a lethal dose of one insecticide are simultaneously dosed with the other insecticide as well. Only extremely rare individual pests, which have resistance mechanisms against both chemicals, will survive. With a reservoir of untreated insects or immigration, random mating and recombination tend to break up the doubly resistant genotypes, leading to very

slow evolution of resistance[23]. However, dominance, high initial frequency of at least one of the resistance genes, unequal persistence of the pesticides, together with low levels of immigration, can lead to slight advantages of rotations over mixtures[27,29]. Mixtures are a somewhat risky strategy with a very high potential pay-off, so it is worth researching each case to find out whether a mixture would be advantageous.

It might seem that spraying two insecticides in a mosaic would have the same advantages as a mixture. However, this is not so, because each individual insect does not receive a dose of each chemical and resistance evolves more rapidly than with a mixture[23,27] (G. Mani, unpublished).

Surprisingly, rotations rather than mixtures of insecticides are a key component of nearly all resistance management programmes. For example, pyrethroids are one of the last groups of chemicals effective against resistant budworms and bollworms (*Heliothis* and *Helicoverpa*) in cotton, and rotations of pyrethroids and moderately effective organophosphates are recommended in pyrethroid resistance management programmes worldwide[6]. A mixture is normally at least twice as expensive as a rotation if each compound is used at full concentration. Because farmers do not relish more than doubling their current costs even if the potential long-term benefit is high, rotations are usually more acceptable.

Have the insects won?

This problem of the acceptability of mixtures shows how one of the most intractable components of a resistance management programme are human beings. Different people value the resource of susceptibility genes in different ways. Consider a crop such as cotton: pesticide companies and salesmen aim to maximize profits in the short and medium term; farmers are sometimes interested in the longer term, but are averse to risk in the short term and can usually switch crops if insect control fails; local and central government organizations may be interested in continued cropping in the long term.

Perhaps the most successful example of resistance management has been in cotton-growing regions in Australia[30,31], where farmers experienced crop failures due to pyrethroid resistance in the bollworm *Helicoverpa armigera*. The farmers asked for a programme to be instituted, and a difficult agreement was reached between government researchers, farmers and the agrochemical industry. A voluntary rotation-based strategy has been implemented since 1983: pyrethroid use is restricted to a short period (Stage II; see Fig. 3) in the middle of the cotton growing season, whereas endosulfan is restricted to the early to mid season (Stages I and II). Neither endosulfan nor pyrethroids may be used in Stage III; other insecticides may be used at any time. However, even under this programme the frequency of pyrethroid resistance appears to be rising from year to year (Fig. 3). In the USA, a similar programme for *Heliothis virescens* has achieved a much lower level of compliance among farmers and pest control consultants, who claim that early and late season alternatives to pyrethroids are both less effective and more expensive. Many entomologists predict that US cotton crops will fail due to pyrethroid-resistant *H. virescens* within the next few years.

A related human problem is faced by advocates of 'integrated pest management' (IPM), so called

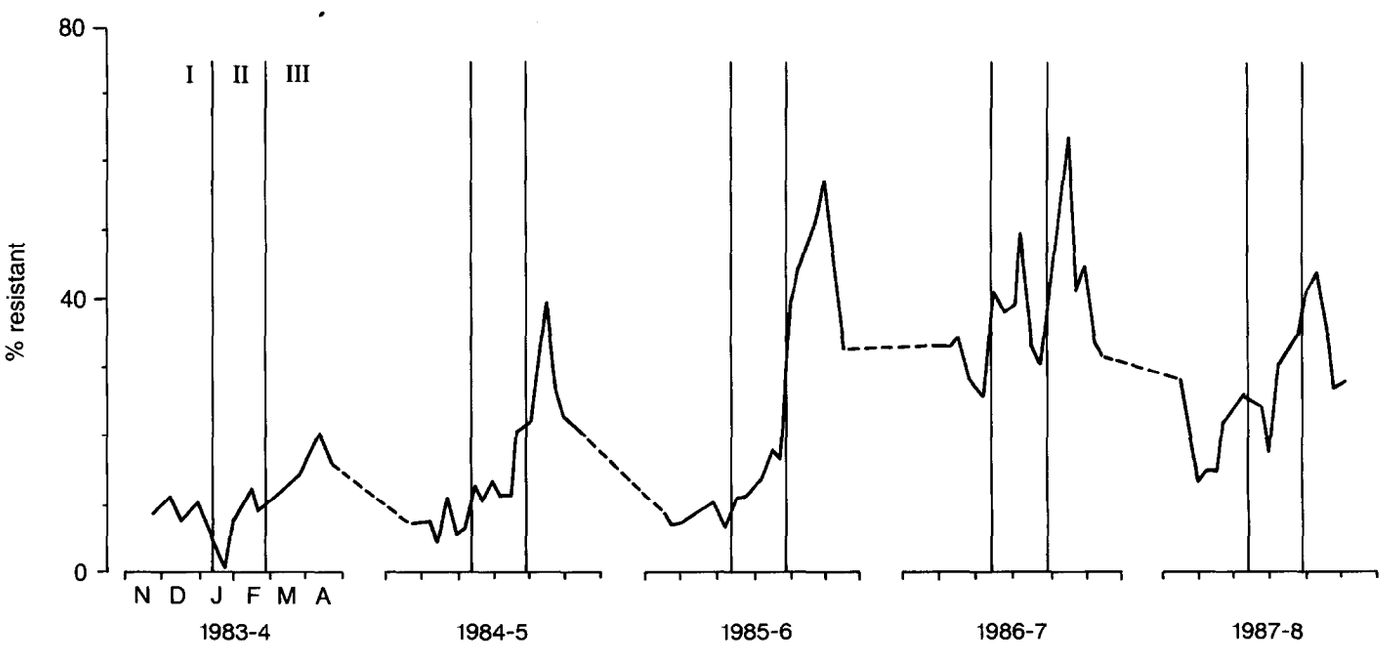

Fig. 3. Frequency of resistant *Helicoverpa armigera* (proportion that survive a dose of the pyrethroid fenvalerate that kills 99% of susceptibles) over five growing seasons in the Namoi–Gwydir cotton-growing region of New South Wales, Australia. In 1983 a programme was introduced to slow resistance to pyrethroids. Pyrethroid use was limited to a six-week period (Stage II) in January and February. Within each year, it can be seen that the frequency of resistance increases immediately after the pyrethroid applications. The frequency of resistance decreases every winter because of immigration and/or selection against the resistant moths. *After Forrester*[31].

because pesticides are integrated as far as possible with biological and cultural means of control[3,4,11]. IPM is complicated because it requires much more research and development, as well as scouting for pests, than a simple schedule of sprays. However, successful IPM can be enormously beneficial in the short term by reducing pesticide costs. An important added long-term advantage of IPM is that insecticidal selection is applied to pests only when other means of control fail. If appropriate methods for the control of primary pests (such as the boll weevil, *Anthonomus grandis*, in cotton) could be developed and used, the secondary pests, which as we have seen are often the most prone to resistance, could come largely under the control of their natural enemies[32]. We need a much better understanding of pest population biology and gene flow, as well as resistance mechanisms, if we are to plan effective IPM and resistance management strategies. Pesticide companies are unlikely to finance such research since it may reduce their own cash flow: this is a good example of an applied research area where non-industrial funds are needed, even though there is increasing political pressure for universities and public sector research institutes to obtain funding from industry.

The insects have won for the moment in tropical malaria control, and they seem to be winning in cotton, among a number of other crops. Pest susceptibility is a valuable natural resource that has been overexploited. Better management of this susceptibility resource will require a better knowledge of the ecology and population genetics of insects, as well as the political will to make resistance management strategies work.

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