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A MODEL FOR THE ELIMINATION OF INSECTICIDE RESISTANCE USING HETEROZYGOUS DISADVANTAGE

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RECENT models have indicated the conditions under which the rate of evolution of insecticide resistance may be slowed (Curtis, Cook and Wood, 1978; Georghiou and Taylor, 1977; Curtis, 1981; Wood and Mani, 1981). Such models are derived from the general equations used in population genetics to describe the fate of genes under selection pressure. These models show that the rate of increase can be slowed in various ways, all of which amount to increasing the relative fitness of susceptible compared to resistant animals. It does not appear to have been realised that population genetics theory provides a mechanism whereby the spread of resistance could be reversed. This could arise if the heterozygotes in a population heterogenous for resistance were put at a fitness disadvantage compared with both homozygotes. The conditions under which this could occur and the implications for the control of resistance are discussed in this note.

When the fitness of a heterozygote is less than that of either homozygote, a single point exists where the gene frequencies are in equilibrium (Li, 1955). Li (1955) also showed that away from this equilibrium point selection would tend to move the gene frequencies towards fixation and that the direction of fixation would depend on whether the gene frequency was above or below the equilibrium point. If heterozygous disadvantage existed in a population polymorphic for insecticide resistance, then assuming resistance due to a mutation at a single locus, the equilibrium point in terms of the frequency of the susceptible gene (q) can be found by solving,

$$q = \frac{w_1 - w_2}{(w_1 - w_2) + (w_3 - w_2)} \qquad (1)$$

where w_1, w_2 and w_3 are the respective net relative fitnesses of the resistant homozygote (RR), the heterozygote (RS) and the susceptible homozygote (SS). If the frequency of the susceptible gene is above the equilibrium point it will increase in frequency, if it is below the equilibrium point the frequency of the susceptible gene will decrease. Thus given heterozygote disadvantage and an appropriate gene frequency it should be possible to reduce the frequency of resistance genes in a population.

It seems unlikely that heterozygous disadvantage would occur naturally in a population containing resistant individuals. However, under certain conditions of insecticide treatment, it should be possible to place the heterozygotes at a disadvantage compared with the homozygotes. The major requirement is that in an insecticide free environment the resistant

homozygote and the heterozygote have reproductive fitnesses which are less than that of the susceptible homozygote. With insecticide treatment this intrinsic fitness difference would still be present but would be countered by the fitness difference due to the insecticide. Many examples are known (Curtis *et al.*, 1978; Keiding, 1967; Georghiou, 1972; Inoue, 1980) where a reduction in the frequency of resistance follows the removal of insecticide treatment and it is generally assumed that this is the result of a fitness disadvantage of the resistant animals. Relative fitness values of between 0·8 and 0·5 for resistant compared with susceptible animals have been obtained from populations of mosquitoes (Curtis *et al.*, 1978), mites (Inoue, 1980), blowflies (White and White, 1981) and beetles (Müggleton, in preparation) living in the absence of insecticide.

If the requirement relating to fitness in the absence of insecticide is met, what strategies can be adopted to ensure that with insecticide treatment the heterozygotes are at a disadvantage? The simplest situation that can be considered is where the resistant gene is recessive and the fitnesses of the resistant homozygote and heterozygote are equal. In this case treating the population with a dose that does not kill the homozygous resistants but which kills anything less than 100% of the other two genotypes would put the heterozygotes at a disadvantage. The dose required would depend on the frequency of the susceptible gene and the fitness values. A more realistic situation is one where the fitness of both the resistant homozygote and the heterozygote are equal but the dose response of the heterozygotes is intermediate between the two homozygotes. In this case it would be necessary to use a dose large enough to kill all the heterozygotes and susceptibles but which did not kill the homozygous resistants, and to ensure that a random portion of the population was not treated. In other words an equal proportion of heterozygotes and susceptibles must survive. A slightly different approach needs to be adopted if both the fitness and the dose response of the heterozygotes are intermediate between the values for the two homozygotes. Using a dose sufficient to kill all the heterozygotes and susceptibles, it would be necessary to ensure that the proportion of animals left untreated was such that the net fitness of the heterozygotes after treatment was less than that of the resistant homozygotes.

Fig. 1(a)–(c) shows the number of generations required for the frequency of susceptible homozygotes in a population to reach 99 per cent under conditions of heterozygous disadvantage. It is assumed that the population size is infinite and that the fitnesses of the resistant homozygote and the heterozygote are equal and less than that of the susceptible homozygote in the absence of insecticide. In an insecticide-free environment the number of generations taken to reach 99 per cent susceptibles can be found by counting the number of iterations required for the value of q^1 in the general equation for a change in gene frequency over one generation to reach 0·995. Thus,

$$q^1 = \frac{a_2pq + a_3q^2}{a_1p^2 + a_2 2pq + a_3q^2} \tag{2}$$

where p^2, $2pq$ and q^2 are the initial frequencies, and a_1, a_2 and a_3 are the intrinsic relative fitness values of RR, RS and SS. q^1 is the frequency of the susceptible gene after one generation of selection. To allow for the

effects of insecticide treatment we can modify equation (2) to,

$$q^1 = \frac{a_2 b_2 pq + a_3 b_3 q^2}{a_1 b_1 p^2 + a_2 b_2 2pq + a_3 b_3 q^2} \tag{3}$$

where b_1, b_2 and b_3 are the respective proportions of RR, RS and SS surviving insecticide treatment. Multiplying together the two components of fitness a and b will give a value equivalent to the net relative fitness value (w) in equation (1).

The examples shown in fig. 1(a)–(c) are for intrinsic relative fitness values of RR and RS ranging from 0·8 to 0·4 (the fitness of SS = 1·0) and for treatments killing 75 per cent, 50 per cent and 25 per cent of the heterozygotes and susceptibles. For each example the initial starting

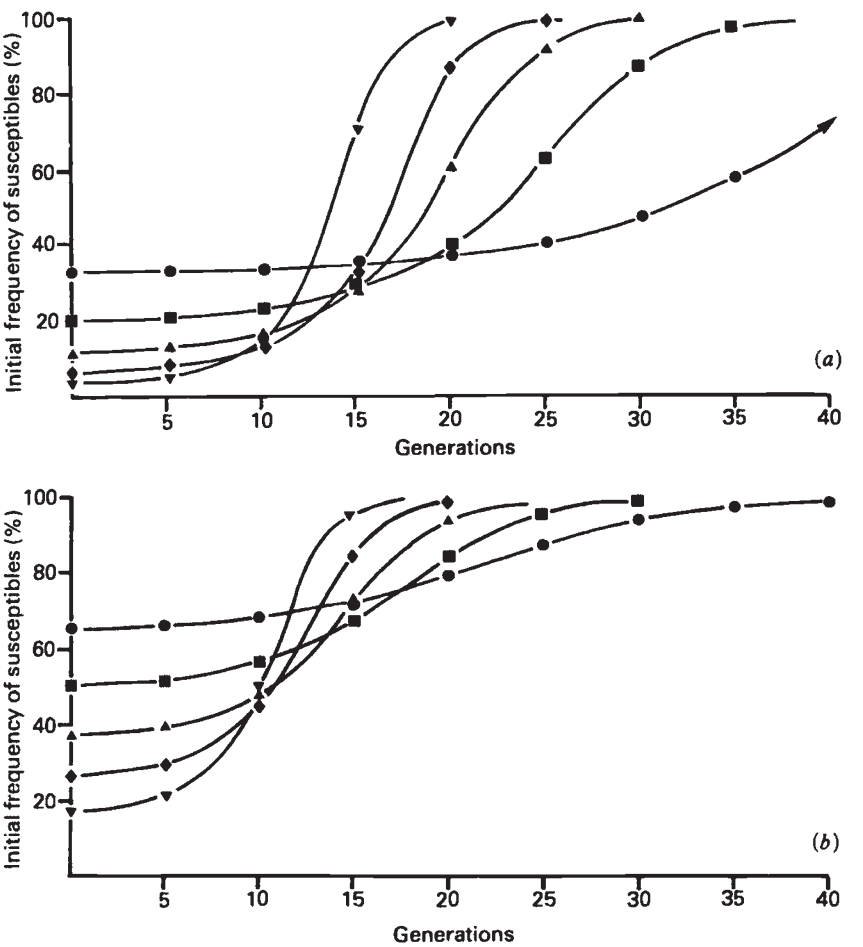

FIG. 1.—The change in the frequency of susceptibles in an infinite population, containing homozygous resistant and heterozygous individuals whose intrinsic relative fitness values ($a_{1/2}$) range from 0·4 to 0·8 in the absence of insecticide, which is subjected to treatments which kill (a) 25 per cent (b) 50 per cent and (c) 75 per cent of both the susceptibles and the heterozygotes. ▼$a_{1/2}$ = 0·4, ◆$a_{1/2}$ = 0·5, ▲$a_{1/2}$ = 0·6, ■$a_{1/2}$ = 0·7, ●$a_{1/2}$ = 0·8.

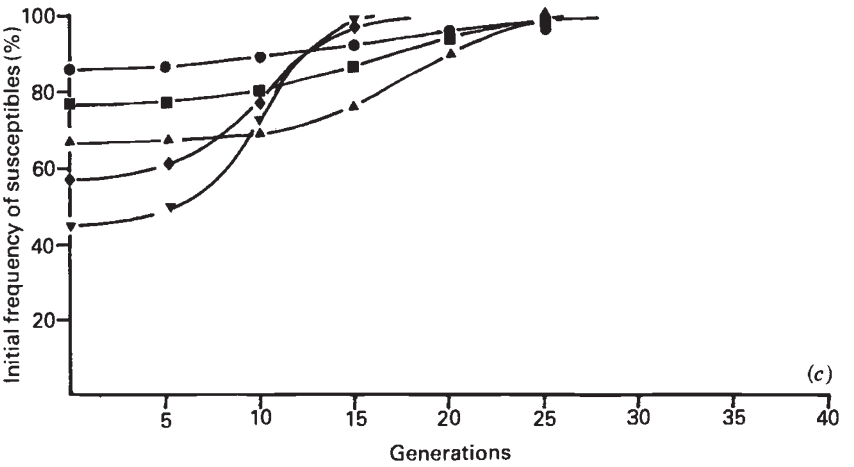

FIG. 1—continued

frequency of the susceptibles was taken as being the nearest whole number above the equilibrium frequency. It is to be seen that the rate at which the frequency of resistant animals decreases depends on the relative fitness of the resistant homozygotes and the heterozygotes in the absence of insecticide, and on the proportion of heterozygotes and susceptibles killed by the insecticide. At any given frequency of susceptibles the lower the fitness values and the lower the proportion of animals killed then the faster the resistants are eliminated from the population.

The model of insecticide treatment described here has certain similarities with that described by Wood and Mani (1981) in that it requires that the dose of insecticide applied should be sufficient to make the resistance effectively recessive and that as large a proportion of the population as possible is allowed to escape treatment. It differs from their model in that it allows for insecticide being applied to resistant and susceptible genotypes whose reproductive fitnesses are inherently dissimilar. As a result the model of insecticide treatment described here suggests that the spread of resistance can be reversed rather than merely slowed and that the loss of resistance can be promoted even when high frequencies of resistance have been obtained. Thus the conclusions of this model are very different from those of other models, including that of Wood and Mani (1981). A remarkable feature of a model based on heterozygous disadvantage is that elimination of resistance is achieved by the use of the insecticide to which resistance was developed. Thus the use of insecticide can be continued and a measure of control of the pest population maintained. The method may be relatively easy to adopt for field use as it requires that insecticide treatment should be inefficient. It perhaps differs only from much current insecticide treatment in that it requires the use of doses large enough to kill animals heterozygous for the resistant gene rather than the smaller doses needed to kill the susceptibles. Whilst the model does not allow for complete eradication of the pest population, it would be useful either when complete control is not required or when dealing with an existing resistant population that cannot otherwise be controlled.

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