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Problems in Countering Resistance [and Discussion]

R. M. Sawicki and D. Rudd-Jones

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PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Problems in countering resistance

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It has often been assumed that the discovery of new insecticides will keep pace with resistance. However, escalation in the cost of developing new pest control agents, and the ever-increasing number of insect pests with strains resistant to even the most recently introduced insecticides indicate the need for strategies to prolong the effectiveness of existing materials and prevent the obsolescence of newly introduced chemicals. The rational development of such strategies must be based on a sound knowledge of resistance at the level of both the individual insect and the population, and be placed in the context of general pest control. This will need major multidisciplinary research programmes with well defined targets, the full cooperation of the pesticide industry, government regulatory agencies, and legislature and a change in attitude and habits of the user. Some of the problems in achieving these objectives are discussed.

Introduction

Resistance is probably one of the most complex and intractable problems facing pest control. Its complexity stems from its variability, and its intractability from its virtual inevitability. Resistance is a manifestation of a most basic property of life: the capacity of organisms to evolve and adapt.

The relative abundance of new insecticides in the 1950s and 1960s circumvented the need to delay or prevent resistance because new chemicals were available to replace those to which pests had become resistant. It thus became assumed that the discovery of new insecticides would keep pace with resistance; the latter would thus be of no serious consequence to pest control or the pesticide industry.

Today the replacement policy is no longer as readily acceptable because it carries severe financial burdens. Fewer insecticides are introduced and development costs soar as does the number of insect species with strains resistant to one or more groups of insecticides. The risks are of course greatest in the most profitable sectors of the market such as cotton, where repeated applications of insecticides increase the possibility of rapid build-up of resistance. Hence pest control strategies that counteract, prevent or delay resistance are needed. Such strategies must treat both insecticides and the susceptible gene pool as irreplaceable resources to be preserved so as to maintain the effectiveness of existing, and prevent the premature obsolescence of new, insecticides.

Although strategies designed to delay, prevent or counteract resistance are very desirable, and were indeed among the major recommendations of the 7th Report of the Royal Commission on Environmental Pollution (Anon. 1979), their development and application is bound to be difficult and will require major changes in pest control research, and in the response of the chemical industry, government agencies and legislature as well as of users of insecticides.

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Requirements for research into resistance-countering strategies

Reliability and economic viability are the essential components of a successful resistance-countering strategy. The rational solution of resistance must be based on sound knowledge of this phenomenon at the levels of the individual insect and the population, and on the correct implementation of resistance-countering strategies in the context of general pest control. Research must be target-oriented to examine or resolve one or more well defined problems of resistance of a given species, and involve specialists covering the wide spectrum of relevant disciplines. So far, except in Japan, there have been few attempts to tackle resistance of even a single pest in this way, and our often inadequate knowledge of the subject stems from the largely *ad hoc* research into the many facets of resistance, which without coordination cannot generate sufficient information for resistance-countering strategies.

The fundamental difficulty is that resistance can only be studied once it has occurred because it is still impossible to predict if and when a species can become resistant to a given chemical, the level of this resistance, its nature, cross-resistance spectrum or economic importance. This unpredictability and the variability in the expression of resistance have led to doubts about the advisability and feasibility of taking action to counteract it especially when many new chemicals were available. Today, in spite of these difficulties, the problem of resistance must be tackled because of its very serious economic importance.

Resistance at the level of the individual insect

We probably understand best the genetic, biochemical and toxicological properties of resistance mechanisms of the individual insect, and in particular in Diptera because they, and especially the housefly, are the species most amenable for this type of research. In contrast, our knowledge of the nature of resistance in most of the agricultural pests, even of such economically important insects as *Heliothis virescens* (F.) or *Spodoptera littoralis* (Boisd.), is still far from satisfactory. Since knowledge of resistance at the level of individuals is the cornerstone on which strategies for countering resistance must be based, a better understanding of the mechanisms involved is essential, particularly in agricultural pests against which the bulk of insecticides is used. This knowledge is most likely to be gained from increased biochemical and physiological research into resistance, because the classical approach involving genetics and toxicology, which has yielded and is yielding much valuable information, is not possible for most of the species with resistant strains.

Since resistance is normally accompanied by changes at the biochemical and physiological levels it should be possible to exploit such changes to restore effective control. This approach of research has been successfully followed by Japanese workers to counteract resistance in several species of leafhoppers and planthoppers attacking rice in south eastern Asia. They first investigated the causes of resistance (Ozaki & Kasai 1970; Hama & Iwata 1971, 1972, 1973; Nagata 1979; Ozaki 1980). They then demonstrated that *N*-propylcarbamates, which strongly inhibit the *N*-methylcarbamate insensitive acetylcholinesterase (AChE) (Hama & Iwata 1971), are able to restore the effectiveness of the *N*-methyl analogues widely used to control the green rice leaf hopper, *Nephottetix cincticeps* Uhler, and have explained the reasons for this effectiveness (Yamamoto 1979). They have also overcome resistance to many organophosphorus (OP) insecticides in this species by applying simultaneously the systemic organophosphorus fungicide,

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Kitazin P (*O,O*-diisopropyl-*S*-benzylphosphorothiolate), which controls rice blast and inhibits the esterases involved in OP resistance (Miyata *et al.* 1979). They have thus suppressed for the first time on a field scale both multiple and multiplicate resistance in the same pest species. This approach has limitations, of course, since suitable synergists or inhibitors cannot be readily available for a number of resistance mechanisms; nevertheless this achievement demonstrates that the very careful study of the resistance mechanisms, usually ignored in pests of agricultural importance, can lead to control even where at first sight this seemed impossible.

Resistance at the level of the population

However, the most urgent questions arise at the population level because the response of the whole population determines the economics of pest control with pesticides. Indeed, in a narrow sense, resistance can be defined as the stage beyond which control with a given pesticide is no longer economic. It is therefore in the interest of all concerned to know which control strategy is least or most likely to reach this stage, and when. Regrettably this is where our knowledge of resistance is weakest. This was recently highlighted at a workshop on 'Strategies for conserving susceptibility to insecticides' (Wood 1981), during which the following aspects were considered important: '(1) the correct choice of chemical, formulation, dosage and mode of application (to avoid the survival of the resistant heterozygotes in the early stages of selection); (2) the developmental stages exposed (to avoid density-dependent regulation and to reduce selection pressure); (3) the extent of escape and immigration (to conserve the optimum proportion of susceptible insects); (4) the order in which insecticides are applied (to avoid unnecessary cross-resistance); (5) the use of insecticides in agriculture (to avoid unnecessary selection . . . "of insects of health and veterinary importance"); (6) the integration of insecticide usage with biological and genetical methods and with environmental management (to reduce selection pressure and conserve susceptible insects). Although general agreement was reached on the importance of these matters in the evolution of resistance, '. . . it proved more difficult to agree on the practical action to be taken in each respect.'

This is not only through lack of adequate knowledge of the biological and operational parameters affecting resistance (Georghiou & Taylor 1977), but also because suitable bioassays are not available for measuring resistance accurately either in single insects or populations. Although standard bioassays are still the only means for confirming when control failure results from resistance, they are wholly inadequate to detect its presence at the very early stages when R individuals are very rare.

Since most strategies for countering resistance are likely to rely on maintaining resistant genes at very low frequencies, far below the detection rate of bioassays, monitoring should ideally be with biochemical techniques aimed at detecting resistance mechanism(s) in single insects. The potential of such techniques was recently demonstrated while monitoring for resistance in *Myzus persicae* Sulzer in the United Kingdom. After the identification of the enzyme responsible for resistance (Devonshire 1977), R individuals were readily identified biochemically, and could even be classified into the appropriate resistant variant group, a task impossible by bioassay (Sawicki *et al.* 1978, 1980). Analogous resistant enzymes have been detected in other species (Ozaki & Koika 1965; Ozaki & Kasai 1970; Yasutomi 1970; Georghiou & Pasteur 1978), and the identification of an AChE with decreased insecticide sensitivity has been successfully automated (Voss 1980). If the automation of monitoring of other resistance enzymes is feasible,

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remotely controlled monitoring for resistance becomes practicable, and greatly advances the feasibility of control strategies to maintain resistance below the level at which it becomes economically significant.

Simulations of control strategies

Available mathematical models based on computer simulations designed to improve the predictive capability of strategies for countering resistance (Comins 1977; Muir 1977; Curtis *et al.* 1978; Taylor & Georghiou 1979), which have highlighted some of the important parameters, are still insufficiently realistic to be applicable to specific practical situations, and on the whole, with some notable exceptions (Curtis & Rawlings 1980), very little is done to test such simulations under practical conditions to improve their reliability, especially in the agricultural sector.

We are at present investigating many aspects of resistance to photostable and unstable pyrethroids in the housefly (*Musca domestica* L.) on animal farms near Harpenden, to determine how the stability of insecticides affects rate of resistance build-up. This multidisciplinary approach, which includes biochemistry, genetics, ecology, population dynamics and insect toxicology, aims not only at producing more reliable mathematical models of the development of resistance, but also at establishing if in alternative circumstances the advice given by Keiding (1978) against the use of photostable pyrethroids in residual sprays for fly control on animal farms is applicable. Keiding considers the persistent pyrethroids more likely to exert much stronger selection pressures than the non-persistent analogues, and to result in more rapid development of strong pyrethroid resistance in houseflies.

This apparently simple problem has proved unexpectedly complex to solve because of lack of initial knowledge of the biology, population dynamics and resistance of houseflies in the United Kingdom, the very complex qualitative and quantitative genetics of resistance to pyrethroids in this species, lack of information on the pyrethroid-resistance mechanisms, and the unexpected presence of autosome sex-determinants, found in Italian housefly populations (Rubini *et al.* 1972) and increasingly in Japanese insecticide-resistant houseflies (Hiroyoshi 1980), whose influence on rate of build-up of resistance had never even been considered previously.

Our work illustrates some of the many difficulties likely to be encountered in this type of study, emphasizes the need for a multidisciplinary approach, and demonstrates the futility of mathematical simulations without adequate information of the conditions in the field. It also emphasizes the general lack of precise knowledge of population dynamics of most of the important insect pests and the need for reliable techniques to determine precisely biological factors affecting selection, such as mobility of individual insects without which the accurate modelling of the gene flow is virtually impossible.

Insecticidal mixtures and rotations

Although control strategies based on fundamental research will probably provide the most reliable solutions, alternative procedures to extend the useful life of insecticides are now being investigated, and much has been done in this field, particularly in Japan. These alternative procedures include the use of synergists, referred to earlier, mixtures of established insecticides and fungicides (Ku 1979) and insecticide rotation (Georghiou 1980; Ozaki 1981). Research into

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these last two aspects has given interesting and encouraging results in the laboratory and in limited field trials particularly against rice leafhoppers (Ozaki 1981). These approaches rely on either the mutual suppression and prevention or delay of resistance to one chemical by the other or on the greatly decreased chance of the selection of resistance mechanism(s) common to all the materials used.

Although these resistance-preventing strategies are potentially very valuable, they must entail extensive evaluation since the effect of insecticidal mixtures is usually unpredictable, and differences in mode of action do not guarantee lack of a common resistance mechanism because cross-resistance often reflects only the substrate specificity of the enzyme responsible, for resistance. Furthermore, such mixtures must undergo extensive trials against different populations of the species tested because populations with widely differing histories of control and biotype do not always respond to selection with a given material in the same way: e.g., cultures of the sugarcane borer, *Diatrea saccharalis* (F.), from Louisiana have remained susceptible to azinphos-methyl and monocrotophos for 20 years, whereas populations from a different biotype in the Rio Grande Valley of Texas, while remaining susceptible to azinphos-methyl, have become resistant to monocrotophos (Reagan *et al.* 1979).

Exploitation of negative correlation can eliminate, theoretically at least, the dominant resistant genotype in heterogeneous populations and some interesting examples of negative cross-resistance between OPs and pyrethroids have recently been reported (Chapman & Peerman 1979; Ozaki 1980). Here more work is needed both to exploit and understand the reasons for the negative cross-resistance.

Consequences of the restricted use of insecticides on the pesticide industry

Unfortunately, all strategies based solely on chemical control can suffer premature breakdown through the unexpected development of resistance because in all these strategies insects are challenged with insecticides, and this can lead to resistance. Thus sole reliance on chemicals for pest control is not the correct answer to prevent resistance.

Common sense suggests that the most obvious way of slowing down a build-up of resistance is to use insecticides only when required, relying wherever possible on other forms of control such as integrated pest management (i.p.m.) to prevent crop damage. Unfortunately, such methods are not always as cheap or simple to achieve as control with insecticides alone.

Coupled with the advisability of using less insecticides is the undesirability of introducing new chemicals where prolonged use (sometimes exceeding 20 years) of the older materials has consistently given satisfactory control with no outbreak of detectable resistance in the pest, as in the sugarcane borer in Louisiana (Reagan *et al.* 1973), or has resulted instead in resistance in beneficial arthropods, as in some of the top fruit predator systems (Croft & Morse 1979).

The decreased application of existing insecticides, coupled with restrictions in introducing new material, raises serious problems for the pesticide industry, which largely depends for profits on volume sales of existing materials, and expensive screening programmes for their replacement. Because of the very high costs of production, research and registration, it is increasingly in industry's interest to preserve the useful life of existing materials by limiting their use. This long term policy is, however, hard to reconcile with the short-term loss of income resulting from decreased volume sales. It is also difficult to visualize how industry can

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recoup costs of development of new materials in a fairly static market without introducing new products wherever possible even though this may spell disaster to i.p.ms., which rely on the *status quo* of well established control methods for their success.

A number of possible solutions to this conflict have been suggested, including the extension of the patent rights, and the more active participation of industry in pest control through sale of control know-how as well as of the control chemicals themselves (Graham-Bryce 1976; Lewis 1977).

It is inappropriate here to suggest how such difficulties can be resolved, but resolved they must be if the pesticide industry is to continue making a profit through providing chemicals for pest control. It is also obvious that successful countering of resistance cannot be achieved by the public sector without the active participation and cooperation of the pesticide industry.

Importance of regulatory legislature and of proper advice to users

It is probable, however, that so long as the cost of introducing new insecticides remains bearable, industry will prefer strategems bringing short-term profits to strategies whose profitability is long-term. Thus where for a particular treatment there is a choice between two approved analogues, one likely to result in fast, the other in slow build-up of resistance, the decision to sell either material is based on purely commercial considerations. In those circumstances, warnings about dangers associated with the use of the fast resistance-producing material are of no avail because commercial considerations are paramount, and convincing evidence about its unsuitability becomes available too late to prevent resistance becoming widespread.

In Denmark, however, the use of such materials can now be prohibited. The new Danish Act on Chemical Compounds and Products, effective from 1 October 1980 (Anon. 1980), empowers the Danish Ministry of Environment to require experimental data on cross-resistance and the potential for developing resistance before registration. Moreover, the Ministry and its advisers can monitor the occurrence or development of resistance in the population, and withdraw registration if the formulation and/or other insecticides become ineffective through resistance.

Advice must, however, be concentrated on the user to achieve the most dramatic decrease and delay of resistance because it is the user who through ignorance, bad advice, good faith or greed is ultimately responsible for premature resistance through either excessive or unnecessary use of insecticides; there is much to do in this area. Last but not least, there is conflict between economic thresholds that enable a proportion of the pest to survive and the complete absence of insects in food expected by the customer and sometimes required by law. This disparity between good agricultural practice and customer protection or appeal needs resolving since one delays while the other accelerates build-up of resistance.

Conclusions

Some of the many obstacles to development of resistance-counteracting strategies are formidable, but most can be surmounted. The Japanese have demonstrated an example of how this can be done. They instituted in 1976 a 5 year programme to counteract resistance in the two major pests: the green rice leafhopper and the citrus red mite *Panonychus citri* (McGregor). This programme, which has achieved considerable success, is funded by the Japan Plant

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Protection Association (Takahashi 1979) and coordinates at a national level research done by the universities, the national research institutes and prefectorial experimental stations.

Similar programmes are required to counteract resistance in other key pests, particularly in the warmer regions where resistance is more prevalent. This will be difficult, lengthy and expensive, but in the long run well worth while since resistance to insecticides will remain a problem as long as insecticides are used for insect control.

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Discussion

D. Rudd-Jones (*Glasshouse Crops Research Institute, Littlehampton, U.K.*). I wish to ask Dr Sawicki if the rate of development of resistance or insensitivity to insecticides is increasing, and if one can generalize about this phenomenon.

Dr Sawicki said that azinphos-methyl has remained effective against the stem borer of sugar cane for 20 years, yet clearly resistance has appeared more rapidly with other compounds used against other pests. Although the situation in fungicides may not be strictly comparable, it is notable that with broad spectrum compounds like the copper fungicides, resistance has never I think been reported, and with the organomercurial seed dressings, only one or possibly two instances of resistance have occurred after 50–60 years of use. By contrast, resistance to some of the systemic fungicides appeared within 5 years of their first commercial introduction.

Perhaps 10, certainly 20, years ago, no one would have thought of applying insecticides to control aphids on cereals, either because they did not cause serious losses or because they were too expensive to control. Today, as Dr Lewis has described, control of cereal aphids has become a normal practice. If, as Dr Braunholtz and Dr Menn have indicated, there are fewer new compounds being discovered and their development is vastly more expensive, then is there not a risk that we shall arrive at a 'doomsday' where an important pest on a major crop can no longer be controlled chemically? When this happens, shall we not then have to resort to the outmoded methods of reducing pest populations, such as crop rotation?

R. M. Sawicki. We do not know if the rate of development of resistance to insecticides is increasing because the worldwide detection and reporting of resistance is inadequate. Available

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data probably reflect not only an increase in the number of species of insects with resistant strains as a result of more widespread and prolonged use of insecticides, but also a greater awareness of resistance by the farmers and their attribution of control failure to resistance.

The causes of lack of resistance to insecticides and fungicides are not necessarily analogous, since there is no insecticide acting in the same broad manner as copper against fungi. There are many insecticides besides azinphos-methyl to which insects have not yet developed resistance; why they have not done so is unknown.

A few pests, such as tetranichid mites, *Boophilus microplus*, the housefly and some Noctuidae, have so far developed strains resistant to most of the materials used for their control. It is against such pests that strategies to delay build-up of resistance will be of greatest use.

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