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Insecticide Resistance Resulting from Sequential Selection of Houseflies in the Field by Organophosphorus Compounds*

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Although cross-resistance in houseflies to the organophosphates has eliminated numerous potentially useful compounds from field use, the " subgroup " specificity of this phenomenon has permitted housefly control to be carried out for nearly a quarter of a century by changing from one toxicant to another within this class of insecticides. A question of considerable importance in insect control is whether the development of resistance to one subgroup of organophosphates will be at the expense of resistance to a subgroup applied previously. The development over several years of resistance in a field population selected sequentially by a number of organophosphates was studied. It was observed that the resistance spectrum expanded progressively to include, finally, organophosphates originally thought to belong to more than one subgroup—namely, malathion (resistance greater than 100 times), fenchlorphos (114 times), diazinon (163 times), coumaphos (greater than 100 times), Ciodrin (greater than 100 times), fenthion (18 times) and naled (9.3 times). Resistance to each compound continued to rise to levels considerably higher than those achieved at the time when the field use of the compound ended. The possible coexistence of subgroup cross-resistance in a population is discussed in the light of these results.

The ability of the housefly (*Musca domestica* L.) to develop resistance to every insecticide used for its control is one of the outstanding examples of accelerated microevolution in insects. Strains resistant to chlorinated hydrocarbon, organophosphorus, and carbamate insecticides can now be found in all areas where intensive housefly control operations have been carried out with these materials.

It has been demonstrated that a biochemical resistance mechanism that is enhanced by selection from a given insecticide is not specific to that compound alone but also protects against several other related insecticides. The phenomenon is referred to as cross-resistance and is now defined as the type of protection against several compounds resulting from the discrete action of one and the same mechanism. It is noteworthy that biochemical cross-resistance does not extend to the entire range of compounds in a certain class (e.g., organochlorine, organophosphorus, carbamate, etc.) but is restricted to those that possess specific sites vulnerable to attack, i.e. *subgroup cross-resistance*. Thus, while DDT-dehydrochlorinase renders DDT and many of its analogues ineffective, its action can be blocked by *o*-chlorination, α-fluorination, or by certain alterations in the aliphatic portion of the molecule (Metcalf & Fukuto, 1968). Similarly, while malathion carboxylesterase protects also against the *n*-propyl and *n*-butyl analogues, its action can be abolished by replacing the carboethoxy group of malathion by carbomethoxy (Dauterman & Matsumura, 1962). It is also of interest that where resistance is apparently not due to a biochemical mechanism, it tends to encompass a broader spectrum of compounds. Such is the case with dieldrin resistance, which extends to all cyclodiene insecticides investigated (Busvine, 1964; Metcalf & Georghiou, 1962). Also, one or more pleiotropic genes in the third linkage group of the housefly (*kdr*, *organotin*, *r-DDT*) appear to confer low but significant levels of resistance to

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insecticides in disparate chemical groups (Georghiou, 1969).

Although cross-resistance has eliminated numerous insecticides from field use, the subgroup specificity has enabled housefly control to be conducted for nearly a quarter of a century with essentially two classes of chemicals—namely, chlorinated hydrocarbons and, more importantly, organophosphates.

For the past 20 years, housefly control in California has relied on empirical transition from one organophosphate to another, involving in approximate sequence malathion, fenchlorphos, diazinon, and currently, dimethoate, naled, dichlorvos and Gardona (2-chloro-1-(2,4,5-trichlorophenyl)vinyl dimethylphosphate). Although the presence of subgroup resistance is strongly indicated, its characteristics, especially under field conditions, have not been fully defined in the organophosphates, and even less so in the carbamates.

A challenging question in applied insect control is whether subgroup resistances within a class are mutually exclusive, i.e., whether the development of resistance to one subgroup will be at the expense of resistance to a subgroup applied previously. An answer to this question must await further elucidation of the genetic and biochemical bases of resistance to organophosphorus compounds. In the meantime, valuable information may be obtained from an analysis of empirical data on the kinetics (development and stability or regression) of resistance to insecticides that have been employed in sequence. It is believed that as the history of insecticide usage over several years becomes known, and the patterns of change in susceptibility are carefully followed, a degree of perspective is gained that permits the detection of trends not usually apparent in specific short-term studies of resistance.

During the past 6 years, fly-control practices in California and the changes in susceptibility to insecticides resulting from these treatments have been closely observed (Georghiou, 1966, 1967; Georghiou & Bowen, 1966; Georghiou et al., 1967). In this article the sequential use of insecticides and the trends in resistance in one study area for which the data are reasonably adequate is described and the results are discussed.

MATERIALS AND METHODS

The study site

This study was carried out at a poultry ranch near Moorpark, California, in a semi-hilly area about 20 miles from the coast. The ranch was established in 1962 and expanded rapidly to its present size, accommodating some 2 million hens. The birds are kept in wire cages above ground, and the operation is almost entirely automated. Waste was originally disposed of twice a year but in recent years disposal has been more frequent. Fly production in the accumulated droppings is heavy, the main pest species, in order of importance, being *M. domestica* L., *Fannia canicularis* (L.) and *F. femoralis* Stein. Several other poultry ranches are located in the area, the closest being about 1 mile away, downhill. This proximity to other ranches may tend to reduce the discreteness of the fly population at the study site. However, there is indirect evidence that intermingling of fly populations between ranches in this area is minimal, probably because ample breeding medium, shade, and water is available on each ranch, and the ranches are separated by tracts of land with temperate to semi-arid environments. A special study of the geographical distribution of resistance in the area revealed that excepting " old " types of resistance involving DDT, dieldrin, and malathion, which were found to be evenly distributed, fly strains from each ranch presented a resistance pattern essentially characteristic of the history of insecticide use on that ranch (Georghiou, 1966).

Because of the strict enforcement of county ordinances concerning fly production, and of practical difficulties in the prompt disposal of poultry manure, fly-control practices on this and other ranches have been based almost entirely on the frequent, routine use of insecticides. From February to the end of October, general coverage sprays are applied weekly, or even more often, while sugar–insecticide bait is selectively distributed almost daily. In addition, aerosols are used daily in the packing house. The same schedule is followed during the winter months but at a lower intensity. The total number of general coverage sprays in a year exceeds 50, the choice of insecticides having been based on the performance of various compounds against *M. domestica*, which is the most resistant of the pest species (Georghiou, 1967), although populations of *F. canicularis* and *F. femoralis* tend to predominate in early spring.

The specific history of insecticide use on this ranch is as follows: during 1962, fenchlorphos sprays were applied regularly to the manure and other resting sites used by flies both inside and outside poultry houses. In addition, malathion was used occasionally in space sprays but was abandoned by the end of 1962 because of the development of resistance. The use of fenchlorphos was continued until mid-1964 when it was replaced by diazinon. The latter became ineffective by June 1965 and naled was substituted. This insecticide has been used regularly since then, except in early 1966, when fenchlorphos was briefly reintroduced into the programme. The use of naled was reduced in 1969, mainly because of mechanical difficulties, and Gardona was alternated with dichlorvos space sprays. From 1964, dichlorvos has been used frequently in dry sugar baits while pyrethrins–piperonyl butoxide aerosols have been used daily in the packing-house and cafeteria. In addition, carbaryl has been applied up to 6 times a year since 1963 to control the northern fowl mite, *Ornithonyssus sylviarum* (Canestrini & Fanzago). Generally, the same sequence of insecticides has been followed by the other poultry ranches in the Moorpark area. For several years prior to 1962, fly control was based on malathion and fenchlorphos, and before that, in the late 1940s and early 1950s, on DDT, lindane, and dieldrin.

Sampling, rearing and testing

During the first year of this study (1964), samples of 300–1000 larvae were collected at random from manure and adults were obtained from these larvae. In subsequent years (1965, 1966, 1968, and 1969), adults were collected directly from different parts of the ranch with a knapsack suction machine. All collections were made in late June or early July. Larvae were reared by standard techniques on CSMA[1] media at 80°F (27.2°C) and 60% relative humidity, as previously described by Georghiou et al. (1965). Adult females (F_1–F_4) were tested when 3 days old by the topical application of 1-μlitre droplets of insecticide solutions in acetone; 20 flies were used in each replicate test. At least 5 doses, repeated on 5 or more days, were used to establish dose–mortality regression lines (ld-p lines). The results of treatments were determined after holding the flies for 24 hours at 60°F (15.5°C) and 60% relative humidity, with 40% sucrose solution as food. The data were processed by probit analysis (Finney, 1952) on a programmed computer.

The insecticides used were technical grades of the highest obtainable purity and, in preparing solutions, were considered to contain 100% of active ingredient. Susceptibility levels are expressed in μg per gram of body weight. Female flies weighed an average of about 20 mg each. The degree of resistance is expressed as a resistance ratio at the LD_{95}, based on the level of susceptibility of the normal NAIDM[1] strain (Georghiou, 1967).

[1] CSMA, the Chemical Specialties Manufacturers' Association (USA), is the successor to NAIDM, the National Association of Insecticide and Disinfectant Manufacturers.

RESULTS AND DISCUSSION

The insecticides on which fly-control operations were based, or which had been used for this purpose in the past, i.e., malathion, diazinon, fenchlorphos, naled, and dichlorvos, were evaluated annually. Other materials introduced into the programme more recently, in particular, Gardona, were also included, together with compounds not licensed for use in poultry houses but used for fly control in other situations (dimethoate, fenthion).

Development and progression of resistance

Complete ld-p lines for malathion, diazinon, fenchlorphos, naled, dimethoate, and dichlorvos, obtained annually since 1964, are given in Fig. 1, 2, and 3. The calculated LD_{95} values and resistance ratios for all compounds tested are given in Table 1. The yearly changes in resistance ratio are plotted in Fig. 4, in conjunction with bar lines that indicate the approximate extent of insecticide usage in each year since 1962, this information being based on the frequency of application and degree of coverage with each insecticide.

The high resistance to malathion (Fig. 1), already present in the population in 1964 when this study was initiated, has persisted undiminished despite the

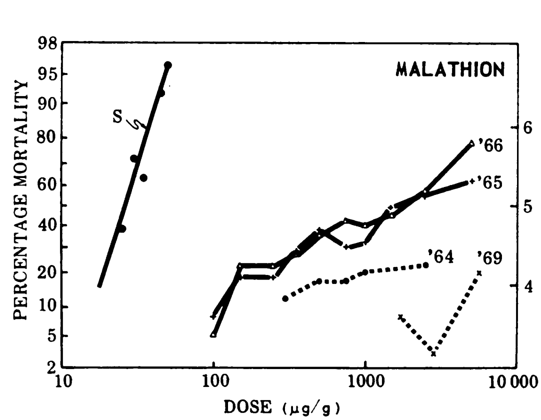

Fig. 1. Changes in susceptibility to malathion in the Moorpark strain of the housefly since 1964. (S = susceptible NAIDM strain).

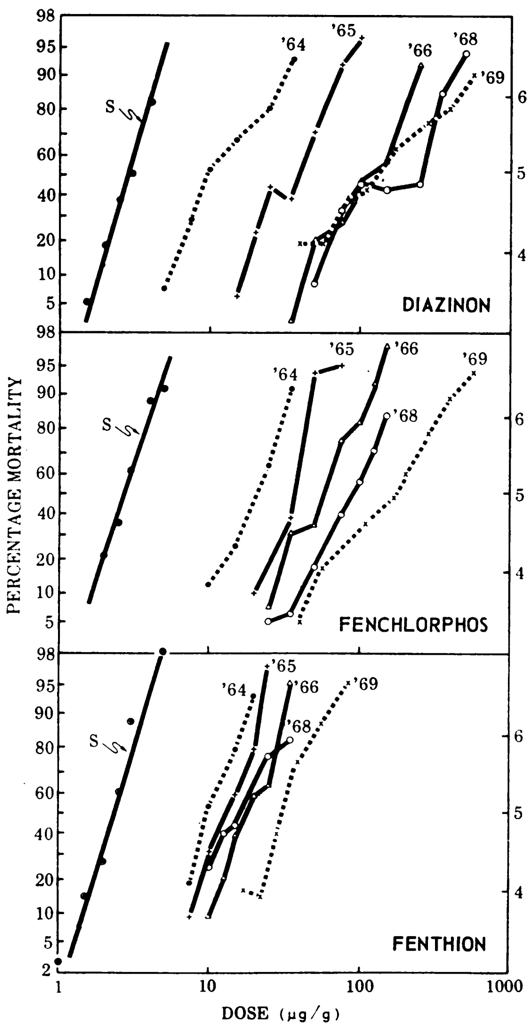

Fig. 2. Changes in susceptibility to diazinon, fenchlorphos and fenthion in the Moorpark strain of the housefly since 1964. (S= susceptible NAIDM strain).

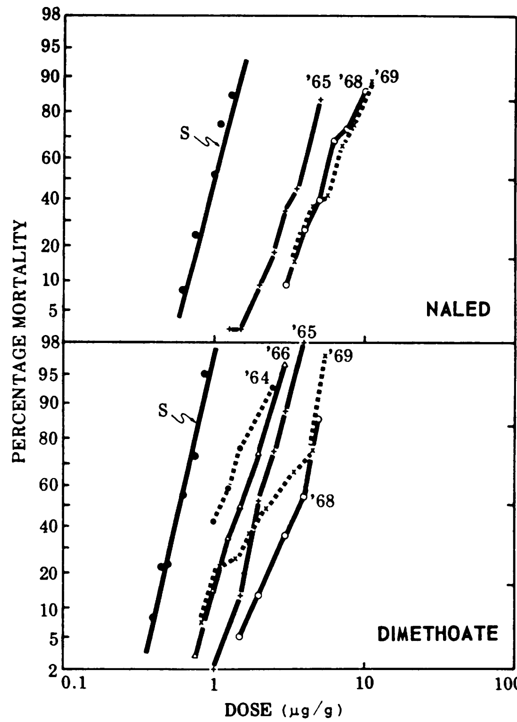

Fig. 3. Changes in susceptibility to naled and dimethoate in the Moorpark strain of the housefly since 1964. (S= susceptible NAIDM strain).

discontinuation of malathion treatments. A small decline in 1965 and 1966 was reversed by 1969, when the population was more resistant than in any of the previous years.

Resistance to fenchlorphos and diazinon (Fig. 2) was relatively low in 1964 (8.1 times and 7 times, respectively) but it rose steadily and sharply, thereby precluding their further effective use for fly control. More remarkable has been the fact that resistance to both these insecticides continued to rise after their use ended. Thus, resistance to fenchlorphos rose from 8.1 times in 1964 (end of use) to 114 times in 1969, and resistance to diazinon from 17.3 times in 1965 (end of use) to 163 times in 1969 (Fig. 4). The increase in resistance to fenchlorphos in 1965 is thought to be the consequence of diazinon pressure on fenchlorphos-resistant genotypes. The further subsequent increase of resistance to fenchlorphos and diazinon may be due in part to the preferential survival of fenchlorphos- and diazinon-resistant genotypes under selection pressure by naled. However, preferential survival could account only for the maintenance of an already acquired level of resistance. In the present case, further enhancement of the maximum tolerable doses occurred, as shown by the continued shift of ld-p lines toward higher doses. This situation is especially apparent with fenchlorphos (Fig. 2) and is discussed below.

Certain compounds not used for fly control on this ranch were also found to have progressively lost some of their potency, apparently as a result of intensive selection pressure by these organophosphates. Thus, Ciodrin (α-methylbenzyl 3-hydroxy-

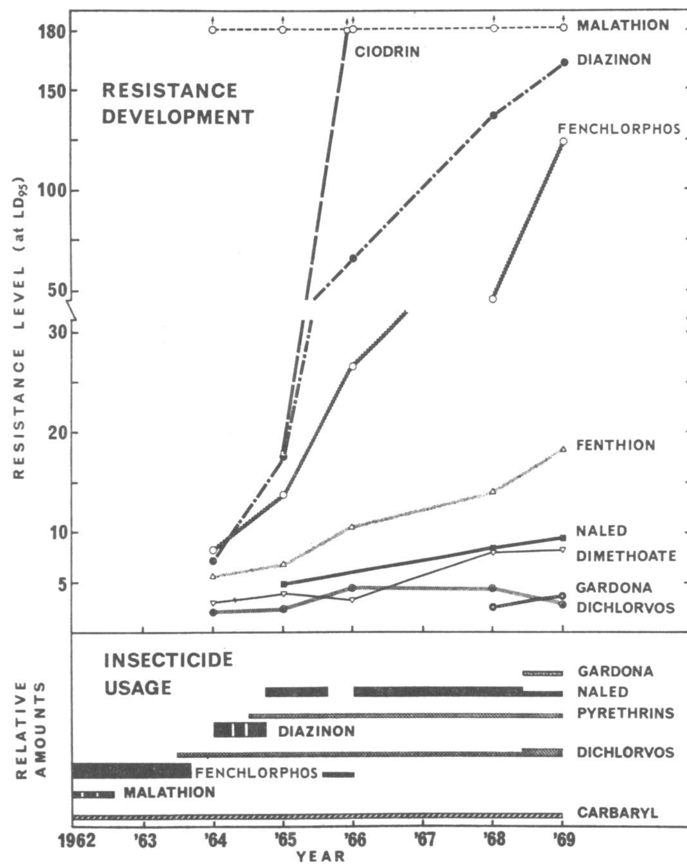

Fig. 4. Changes in resistance ratios in houseflies since 1964, and usage of various insecticides since 1962 at the Moorpark poultry ranch.

crotonate dimethylphosphate), which was only partly effective in 1965 (LD_{95} = 88.5 μg/g), was almost totally ineffective in 1966 by the testing method employed. Similarly, a steady rise in resistance towards fenthion occurred (18.1 times; Fig. 2) and to a lesser extent towards dimethoate (8.2 times; Fig. 3) although neither of these compounds has been used for fly control on or in the vicinity of the ranch.

Resistance to naled increased very gradually from a level of 4.7 times in 1965, when the compound was first introduced on to the ranch, to 9.3 times in 1969 (Fig. 3 and 4). Resistance to dichlorvos has been less pronounced, remaining low (2–4 times) despite its frequent use since 1964. Likewise, pyrethrins in combination with piperonyl butoxide showed no loss of toxicity to the resistant strain.

Levels of resistance and significance of slopes of ld-p lines

Since the early studies of resistance, it has been recognized that the slope (*b*) of ld-p lines reflects the degree of variability in response of a population to a given toxicant (Hoskins & Craig, 1962; Hoskins & Gordon, 1956). Assuming resistance to be monofactorial and the levels of response of susceptible (S), heterozygous (SR), and resistant (R) phenotypes to be clearly defined, it would be expected that *b* would decline with progressive selection as a result of the appearance of SR and R phenotypes in the population. Assuming further that selection of R for homozygosity is possible, it may be expected that *b* will eventually rise, reaching maximum values when S and SR phenotypes have been eliminated. This concept has been used with

Table 1. Development of resistance to various insecticides in a field population of houseflies under intensive insecticide pressure

Insecticide	LD_{95} of susceptible (NAIDM) strain (μg/g)	Moorpark strain									
		1964		1965		1966		1968		1969	
		LD_{95}	RR[a]	LD_{95}	RR[a]	LD_{95}	RR[a]	LD_{95}	RR[a]	LD_{95}	RR[a]
Malathion	49.0	>5 000	>100	>5 000	>100	>5 000	>100	>5 000	>100	>5 000	>100
Diazinon	5.5	38.5	7.0	95	17.3	365	66.4	750	136.4	896	162.9
Fenchlorphos	5.5	44.5	8.1	75	13.6	145	26.4	253	46	627	114
Fenthion	4.0	21.5	5.4	26.5	6.6	41	10.3	55.5	13.9	72.2	18.1
Naled	1.5	—	—	7.0	4.7	—	—	12.5	8.3	14.0	9.3
Dimethoate	0.95	2.6	2.7	3.4	3.6	2.9	3.1	7.5	7.9	7.8	8.2
Dichlorvos	3.8	7.0	1.8	8.0	2.1	16.0	4.2	16.0	4.2	10.1	2.7
Gardona	7.0	—	—	—	—	—	—	16.0	2.3	24.6	3.5
Ciodrin	5.0	—	—	88.5	17.7	910	>100	—	—	—	—
Coumaphos	5.5	—	—	>500	>100	—	—	—	—	—	—

[a] RR = resistance ratios = LD_{95} for Moorpark strain/LD_{95} for susceptible strain.

varying degrees of success in attempts to define the frequency of $++$, $R+$, and RR genotypes, especially in connexion with studies on the inheritance of resistance (see reviews by Georghiou, 1965, 1969).

Although this approach is applicable to laboratory studies of single genetic factors, evidence from field studies of resistance to organophosphates in houseflies reveals a more complex situation. The results presented here (Fig. 1–3) and elsewhere (Georghiou, 1966; Georghiou & Bowen, 1966; Keiding, 1963, 1965, 1967) indicate that two different types of response curve may be present. In the first, typified by malathion, coumaphos, trichlorfon, and possibly Ciodrin, as well as by DDT and the cyclodienes, the *RR* genotype is distinguished from the susceptible genotype by several-fold resistance, so that as selection progresses the ld-p line assumes extremely flat slopes. This condition may reflect high detoxification rates or physical limitations in rates of arrival of the toxicant at the site of action, or both. In any case, the strain eventually appears " immune " to the toxicant, by the testing method employed. Since the insect's defences are capable of dealing with the toxicant at the maximum rate of penetration consistent with application at economic and practicable dosage levels, the slope of the ld-p line is not reinstated.

In the second type, exemplified by diazinon, fenchlorphos, and many other organophosphates, as well as by certain carbamates (Isolan, dimetilan), there is a gradual migration of the ld-p line as a whole towards higher doses, accompanied by only a slight reduction in slope. The maximum doses tolerated by *RR* individuals continue to increase, indicating that secondary factors for resistance assume a progressively more important role, and possibly that the titre of detoxifying enzymes is increased. Subsequent selection by other organophosphates may increase the maximum level of resistance still further. However, penetration limitations do not impart full " immunity " since complete mortality can still be obtained.

An attempt was made to test whether a linear correlation exists between the resistance ratios and slopes of ld-p lines from the data in Fig. 2 and 3, e.g., whether the ld-p lines became flatter as the resistance increased. Although a correlation between increasing resistance and decreasing slope was evident in all data (Table 2), significant linearity was obtained only with fenchlorphos.

It may be expected that compounds in the first category, referred to earlier, will have a shorter duration of practical usefulness, especially for use on populations that are already resistant to other mem-

Table 2. Analysis for correlation between degree of resistance and slopes of ld-p lines in various years [a]

Year	Diazinon		Fenchlorphos		Fenthion		Naled	
	x [b]	y [b]	x [b]	y [b]	x [b]	y [b]	x [b]	y [b]
1964	7.0	3.1	8.1	4.7	5.4	5.2		
1965	17.3	3.7	13.6	5.0	6.6	5.3	4.7	5.7
1966	66.4	3.2	26.4	3.9	10.3	4.8		
1968	136.4	2.3	46.1	3.5	13.9	3.7	8.3	4.7
1969	162.9	2.0	114.0	2.6	18.1	4.6	9.3	4.3
r (correlation coefficient between x and y)	—0.753		—0.962		—0.732		—0.999	
Statistical significance of the correlation [c]	NS		S		NS		NS	

[a] Data in Fig. 2 and 3.
[b] x = resistance ratio, y = slope (b) of ld-p lines, before log transformation.
[c] NS = not significant at the 5 % probability level; S = significant at the 1 % probability level.

bers of this category. Those in the second group would tend to retain their effectiveness over a longer period. Classification of new compounds into one or other category could be accomplished by tests on strains resistant to other insecticides (preferably related to the test compound), or by selection of field-caught flies for a small number of generations, or by both methods.

Effects of sequential selection

In field situations, such as the one under study, in which a number of organophosphates have been used sequentially, it is of interest to determine the changes occurring in pre-existing resistance as new compounds are introduced into the programme. Earlier work on laboratory strains indicated that organophosphorus-degrading enzymes are capable of attacking only a limited series of structurally related insecticides, and it was therefore inferred that changes in substrate specificity arise at the expense of activity towards former substrates (March, 1960). On the basis of this assumption, it was correctly reasoned that an organophosphorus-resistant strain may be incapable of resisting all organophosphorus insecticides at the same time. This situation may conceivably occur where a single defence mechanism is involved in resistance. Recent findings on the role of mixed-function oxidase systems, penetration of toxicant, and other mechanisms in resistance have shown that a variety of defensive resources is available to the insect against any one group of compounds. For this reason, the distinction of subgroup-specific cross-resistance tends to disappear in field strains, which possess a variety of defence mechanisms. Furthermore, the role of further insecticidal selection in expanding the range of specificity of these mechanisms remains unknown.

In the population under study (Moorpark strain), the spectrum of organophosphorus resistance continued to expand as new compounds were used in control operations, eventually reaching high levels of resistance towards malathion (greater than 100 times), fenchlorphos (114 times) and diazinon (163 times), as well as towards compounds not used in the programme—namely, coumaphos (greater than 100 times), Ciodrin (greater than 100 times) and fenthion (18 times). More important, resistance to compounds used previously continued to rise to levels considerably higher than those reached at the time the use of each compound ended. Diazinon selection pressure has been reported to yield a broad range of organophosphorus resistance in laboratory (Forgash & Hansens, 1959, 1967) and field populations (Hansens et al., 1967) of the housefly. In Denmark, Keiding (1967) observed that high diazinon resistance persisted on farms 11 years after diazinon was withdrawn and that, with certain annual fluctuations, the same was true of malathion (Keiding, 1969).

The coexistence of high resistance to malathion, diazinon, fenchlorphos, Ciodrin, and coumaphos in the Moorpark population, although disquieting, cannot be regarded as definitive evidence of unlimited ability of the housefly to develop an ever-expanding spectrum of resistance to organophosphorus compounds; neither can this possibility be disproved at present. It is perhaps significant that only relatively low levels of resistance to naled (9.3 times) have developed despite 4 years' intensive use of this material. Likewise, the low level of resistance to dichlorvos may be interpreted as reflecting such limitations. It should be noted, however, that naled pressure, and possibly dichlorvos pressure, are most likely to have been responsible for the continued rise in resistance to diazinon and fenchlorphos.

Low levels of resistance to dimethoate (8.2 times) and a somewhat higher resistance to fenthion (18 times) are found in the Moorpark population although these compounds have not been used on the ranch or in its vicinity. Dimethoate continues to be employed effectively against houseflies in dairies in California (Georghiou et al., 1967) and elsewhere (Hansens et al., 1967; Keiding, 1969). But on at least one farm in Denmark, the emergence of high resistance to dimethoate has required a complete reliance on pyrethrum–piperonyl butoxide space sprays (Keiding, 1969).

Keiding & Yasutomi (1969), on the basis of field observations, considered that a positive correlation exists between dimethoate, fenthion, and trichlorfon resistance, but that the correlation between resistance to dimethoate and diazinon or fenitrothion is unclear.

The progressive expansion of the spectrum of resistance and the concurrent increase in levels of resistance toward compounds no longer in use raise serious questions concerning expectations for regression of resistance towards organophosphates as long as the population is under pressure by a compound belonging to this group. The multiplicity of defence mechanisms now known to be available to the housefly, such as phosphatases, carboxylesterases, mixed-function oxidases, and reduced penetration, alone or in combination, appears to endow field populations of the insect with the ability to resist simultaneously a far greater variety of organophosphates than had formerly been expected.

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RÉSUMÉ

RÉSISTANCE AUX INSECTICIDES CHEZ LA MOUCHE DOMESTIQUE APRÈS SÉLECTION CONTINUE PAR DES ORGANOPHOSPHORÉS SUR LE TERRAIN

De 1964 à 1969, on a étudié le développement de la résistance et de la résistance croisée aux insecticides dans une population de mouches domestiques placée dans des conditions naturelles et soumise à une sélection continue par des organophosphorés. On se proposait essentiellement de rechercher sur le terrain la résistance croisée à un sous-groupe d'insecticides et de voir si le phénomène se développe aux dépens de la tolérance à un sous-groupe de produits déjà utilisés. La population de mouches étudiée a subi une sélection continue par le malathion, le fenchlorvos, le diazinon et le naled associé au dichlorvos. L'emploi de chacun de ces composés a été interrompu dès qu'il s'est avéré commercialement non rentable.

La résistance élevée au malathion (>100 fois) notée en 1964 au début de l'étude a persisté, inchangée, jusqu'en 1969. La résistance au fenchlorvos et au diazinon, relativement modérée en 1964 (respectivement 8,1 fois et 7 fois), s'est progressivement et fortement accrue et ces insecticides ont été écartés (le fenchlorvos en 1964 et le diazinon en 1965). En dépit de l'arrêt de leur utilisation, la résistance à leur égard a continué à augmenter pour atteindre en 1969 les valeurs de 114 fois (fenchlorvos) et de 163 fois (diazinon). La résistance au naled est passée de 4,7 fois en 1965 à 9,3 fois en 1969, tandis que la résistance au dichlorvos se maintenait à un niveau faible (1,8 fois en 1964; 2,7 fois en 1969). On a relevé, à divers moments de l'étude, des taux élevés de résistance à certains composés non utilisés dans la lutte contre les mouches domestiques, comme le coumaphos (>100 fois), le Ciodrin (>100 fois), le fenthion (18,1 fois) et le diméthoate (8,2 fois).

On a donc assisté à une extension progressive du spectre de la résistance et à l'augmentation croissante de la tolérance à l'égard de composés dont l'emploi avait été suspendu. Il semble dans ces conditions qu'on ne puisse espérer une régression de la résistance aux organophosphorés aussi longtemps qu'une population de mouches subit la pression sélective d'un insecticide de ce groupe. La multiplicité des mécanismes de défense dont dispose l'insecte semble lui conférer une aptitude à résister simultanément à une variété d'organophosphorés beaucoup plus grande qu'on ne le supposait.

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