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The Present Status of Insecticide Resistance

J. R. BUSVINE [1]

The author first considers the concepts of " behaviouristic resistance " and " vigour tolerance ". He concludes that neither phenomenon, if it exists at all, is likely to present a serious obstacle to major insect control schemes. On the other hand, physiological resistance is a real and important problem and the number of resistant species is growing at an alarming rate. However, since resistance is often localized and usually confined to one or a few insecticides, the full impact has not yet been felt. This situation is likely to change and resistance may eventually become sufficiently general to jeopardize the success of campaigns to eradicate malaria and other vector-borne diseases. The author discusses the various countermeasures that have been adopted on the recommendation of the WHO Expert Committee on Insecticides and adds some suggestions of his own for future research and for the application of insecticides in ways calculated to prevent or overcome resistance.

DIFFERENT TYPES OF RESISTANCE

Several forms of resistance have been described. The seventh report of the WHO Expert Committee on Insecticides (1957) included a definition of resistance that distinguished between physiological resistance and " behaviouristic resistance ". The use of the latter term was endorsed in the tenth report of the Committee (1960). Another term in common use is " vigour tolerance ".

Perhaps it might be useful to consider first whether the phenomena of " behaviouristic resistance " and " vigour tolerance " really exist as separate entities and, if so, to assess their importance.

Behaviouristic resistance

The term " behaviouristic resistance " dates back at least as far as 1952 (Hess, 1952). Despite some objection to the term (see Thomson, 1960) it has been accepted by WHO, as already mentioned. At one time, the concept was the subject of much confusion, mainly because normal mosquitos and flies may change their behaviour following contact with DDT; but this, of course, is not what is meant by behaviouristic resistance.

At present it is recognized that strains of insects with inherently different behaviour patterns *could* be selected by extensive use of insecticides. Attention has been concentrated on mosquitos because of the importance of malaria eradication. Two main types of change have been suggested: (1) hyperirritability following contact with DDT; (2) increased exophily or exophagy, or both.

(1) Some field evidence for the existence of hyperirritability was adduced by Trapido (1952) for *Anopheles albimanus* in Panama. Efforts have been made to confirm this by development of an irritability test method (WHO Expert Committee on Insecticides, 1960) which has been used by a number of experienced entomologists on *A. albimanus* and other insects. So far, there has been no clear evidence for the existence of this type of behaviouristic resistance in *A. albimanus* or other mosquitos.

It should be pointed out that the test kit mentioned measures only irritability. An increased phototaxis following contact with DDT might be equally rewarding to the mosquito, but would not be detected by this test.

(2) Changes towards increased exophily or exophagy can be observed only under natural conditions. Accordingly, they are much more difficult to verify, since they involve comparisons from one year to another or in different localities, which introduces a great many uncontrollable variables. Claims to have detected such changes have been made for *A. punctimacula* in Columbia (Ronnefeldt, 1957) and *A. gambiae* in Rhodesia (Thomson, 1960). However, the validity of these claims has not been established beyond all doubt.

Neither type of behaviouristic resistance seems to be a serious problem in insect control in general,

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or mosquito eradication in particular. This does not mean that DDT-irritability and exophagy are not important on their own account; it means that they are not readily altered by insecticide selection.

Vigour tolerance

The term " vigour tolerance " was coined by Hoskins & Gordon (1956) to describe a hypothetical condition of increased tolerance due to miscellaneous physiological improvements contributing to survival. The concept itself is earlier than this. Thus, Harrison (1950) observed: " It does not seem unlikely that during the selection for DDT resistance, a selection of flies which were generally ' stronger ' than normal may have taken place." A paper by Morrison (1950) has a section entitled " Instances of generally greater vigour and resistance to other chemicals and environmental hazards ". Coming to more recent times, a sophisticated interpretation was made by Spiller (1958) with his hypothesis of " multicomponent resistance ".

In my own opinion, this type of tolerance has never been adequately demonstrated; there certainly seems little evidence for its existence in the field. Indeed, such a development would seem incompatible with natural conditions of ecological competition. Presumably, all species are subject to continual selection for " vigour ", and it seems unlikely that one particular toxic hazard would alter an overall physiological balance reached after eons of time.

" Vigour tolerance " has achieved its rather glib usage through efforts to explain low levels of resistance to several insecticides. There is no doubt that this sometimes occurs; but it could well be due to a single cause (e.g., reduced cuticular penetration of lipophilic compounds). Such cases deserve investigation, particularly in regard to the suggestion that, when resistance develops to compound A, a low-level cross-tolerance to compound B may develop at the same time and enhance the chances of rapid emergence of true resistance to B, if that compound is used. The use of the terms " vigour tolerance " or " generalized resistance " can be stultifying in two ways. Appending a label to a certain type of cross-resistance gives a specious impression that the trouble has been diagnosed; and by implying that numerous contributing factors are involved, these terms suggest that research into the cause of the resistance is not feasible.

It is my view that the term " vigour tolerance " should be abandoned until a specific instance of generalized tolerance to diverse insecticides has been shown to be causally associated with genotypically enhanced vigour (i.e., a strain characterized by greater size, resistance to starvation, desiccation, etc.). Whether this view is justified or not, it seems true that there is little or no evidence of hindrance to major insect control schemes due to vigour tolerance.

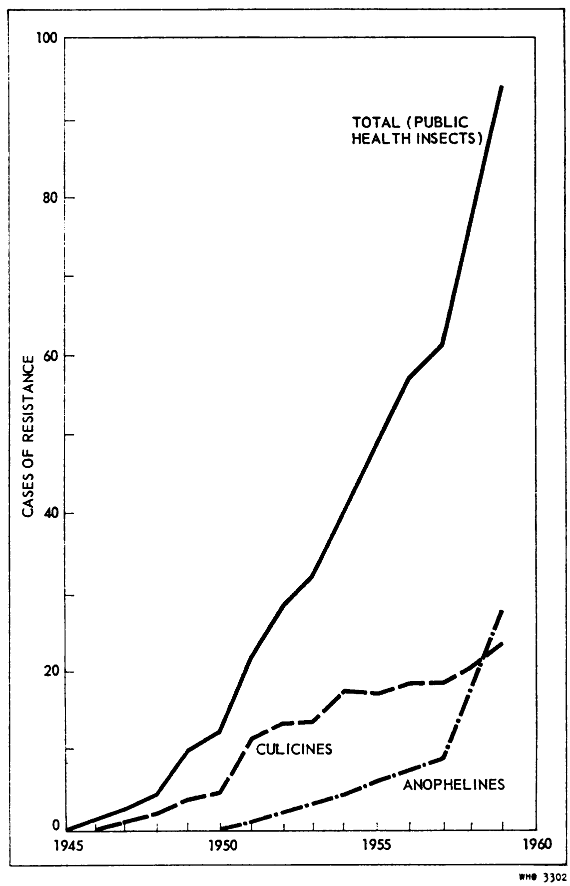
Growth and importance of physiological resistance

There is little need to discuss the reality of physiological resistance in the normally accepted sense; data accumulating from both the field and the laboratory are beginning to provide a fair picture of the extent and the nature of the trouble.

(1) *Aspects of the rate of growth of resistance.* The numbers of different species showing resistance continue to grow at an alarming rate (Figure 1). One or two aspects of this rate of growth invite comment.

FIG. 1

GRAPH SHOWING INCREASE IN REPORTS OF RESISTANT SPECIES



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(*a*) Resistance has been growing so fast that one is tempted to wonder how insecticides can still be effective. There are two main reasons. Firstly, many instances of resistance are quite localized: even in the more serious and widespread instances (e.g., dieldrin resistance in *Anopheles gambiae* or DDT resistance in *Aedes aegypti*), resistance does not occur throughout the full range of distribution of the species. A second and even more important reason is that only a limited number of species show resistance to both groups of chlorinated residual insecticides. Until this happens, there is no real difficulty in maintaining control.

Unfortunately, however, both these mitigating factors have only temporary validity. There seems no reason why resistance should not gradually spread through the range of a species if the selective pressure is continued. Alternatively, if the type of insecticide is changed, a secondary resistance may develop, as is shown by the steadily growing number of species possessing double or treble resistance (see Table).

ARTHROPODS OF PUBLIC HEALTH IMPORTANCE FOR WHICH DOUBLE OR TREBLE RESISTANCE HAS BEEN REPORTED

	Year resistance first reported		
	DDT	BHC & dieldrin	organo-phosphorus compounds
Anopheles sacharovi	1951	1952	—
„ *sundaicus*	1954	1960	—
„ *stephensi*	1955	1959	—
„ *albimanus*	1958	1958	—
„ *pharoensis*	1959	1959	—
„ *quadrimaculatus*	1959	1953	—
„ *aconitus*	1959	1962	—
Aedes aegypti	1954	1959	—
„ *nigromaculis*	1949	1951	1958
„ *dorsalis*	1951	1951	—
„ *sollicitans*	1947	1951	—
„ *taeniorhynchus*	1949	1951	—
Culex fatigans	1952	1951	1959
„ *tarsalis*	1951	1951	1956
Musca domestica	1946	1949	1955
Chrysomyia putoria	—	1949	1954
Pediculus humanus	1951	1955	—
Cimex lectularius	1947	1956	—
„ *hemipterus*	1952	1956	—
Ctenocephalides felis	1952	1956	—
Dermacentor variabilis	1959	1959	—

(*b*) Generally speaking, rates of growth of resistance are well correlated with selective pressure, i.e., the intensity of insecticidal usage. In this connexion, it is interesting to compare the growth of resistance in anopheline and culicine mosquitos shown in Figure 1. The sharp rise in resistance among anophelines in recent years may perhaps be due to the attack on them connected with the world malaria eradication campaign.

In contrast to this, one could instance the relative infrequency of resistance in England shown in Figure 2. This must surely be due to the lack of systematic and intensive use of insecticides in a country where insects do not constitute a serious public health problem owing to the cool temperate climate.

(*c*) Surveying the growth of resistance up to 1960, Brown (1961) records 36 instances of resistance to DDT, 58 to the BHC-dieldrin group and 9 to organophosphorus compounds. The relative frequency of the three types of resistance partly reflects the usage of the insecticides concerned, but some other factor seems to be responsible for the remarkable speed of development of resistance to dieldrin and, perhaps, to the organophosphorus compounds. This is probably the mode of inheritance, which in nearly all cases investigated seems to depend on single gene pairs. As Macdonald (1959) has pointed out, when resistance is dominant (or semi-dominant) the heterozygotes may survive insecticide; whereas, if resistance is recessive, the insects derive no benefit until homozygous resistant forms appear. In the latter situation, resistance will be slow to develop from the early stages in which resistant genes are rare.

Recent genetical investigations have revealed remarkable consistency in the mode of inheritance of BHC/dieldrin resistance, which is semi-dominant in the following species: *Anopheles gambiae*, *A. albimanus*, *A. quadrimaculatus* and *Culex fatigans* (Davidson & Jackson, 1961); *Lucilia cuprina* (Shanahan, 1960); *Aedes aegypti* (Khan & Brown, 1961); *Musca domestica*, *Cimex lectularius* and *Pediculus humanus* (Guneidy & Busvine [1]). Similarly,

[1] Reported in unpublished WHO *Information Circular on Insecticide Resistance*, 1962, No. 35, p. 9.

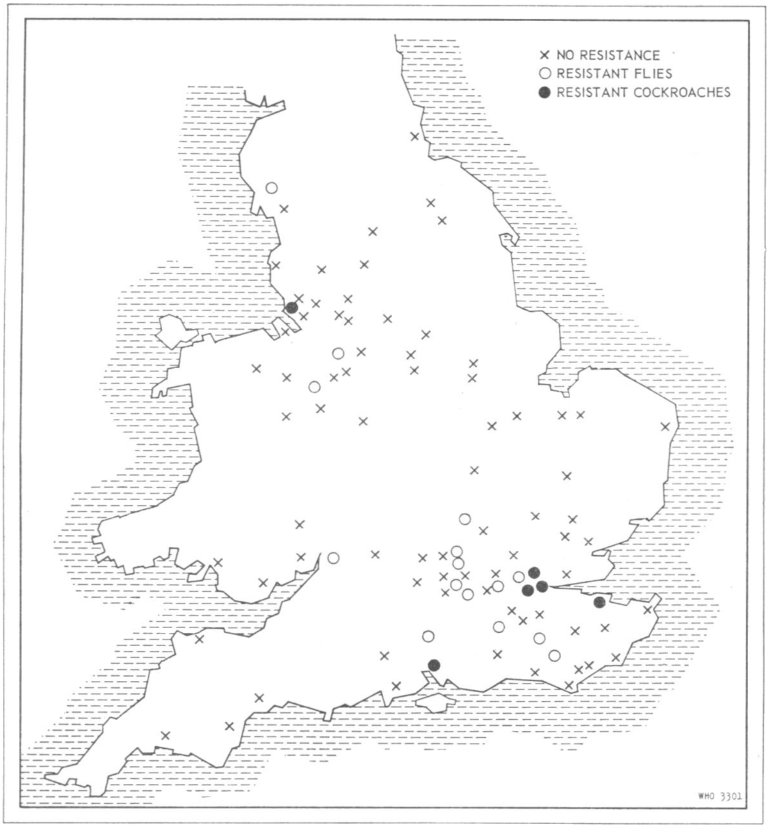


FIG. 2

OCCURRENCE OF RESISTANCE IN ENGLAND [a]

[a] Based on a questionnaire sent to public health authorities and pesticide firms (from Busvine, 1961)

inheritance of organophosphorus resistance has been shown to exhibit nearly complete dominance in *Musca domestica* (Nguy & Busvine, 1960), *Culex tarsalis* (Matsumara & Brown, 1961), *Chrysomyia putoria* (Busvine & Bell [1]) and *Tetranychus urticae* (Helle, 1962).

In contrast to this, DDT resistance is sometimes recessive, as in *Anopheles sundaicus*, *A. albimanus* and *A. stephensi* (Davidson & Jackson, 1961). In houseflies, the condition varies in different strains (Milani, 1962). In *Aedes aegypti*, there is partial dominance.

Generally speaking, then, the genetical studies partly explain the emergence of different types of resistance, especially as regards mosquitos.

(2) *Importance of resistance*. The most important question to be asked is: To what extent does resistance threaten the success of the malaria eradication campaign and other similar projects, such as those for the eradication of filariasis, typhus, relapsing fever and plague? Only a person fully aware of all aspects of the progress of these campaigns could attempt a reliable forecast. My own opinion, which is little better than a hopeful guess, is that the campaigns *can* succeed, though the threat is a very real one. Every effort, administrative as well as technical, will be needed to counteract the loss incurred when a group of insecticides becomes ineffective for a particular vector. Figure 3 gives an indication of the present state of resistance in major malaria vectors throughout the world.

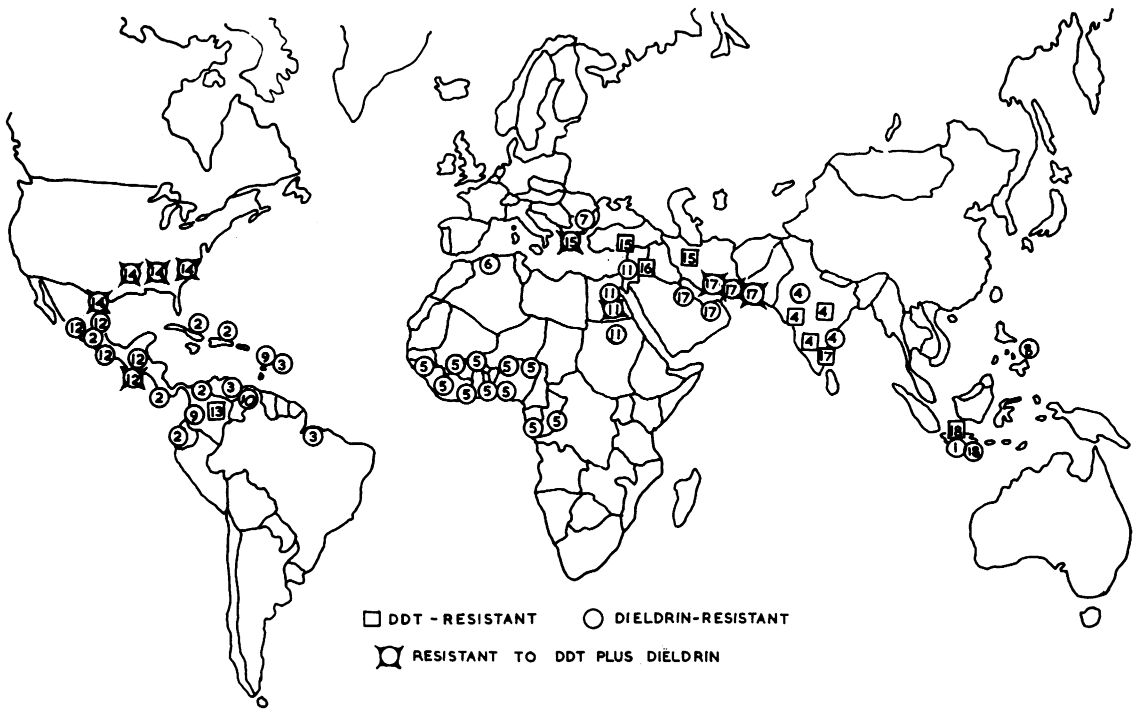
COUNTERMEASURES AGAINST RESISTANCE

The World Health Organization has been notably active in promoting countermeasures against resistance. The subject is fully discussed in the seventh, eighth and tenth reports of the WHO Expert Committee on Insecticides (1957, 1958, 1960) and forms

[1] Reported in unpublished WHO *Information Circular on Insecticide Resistance*, 1962, No. 35, p. 9.

FIG. 3

OCCURRENCE OF RESISTANCE IN ANOPHELINES (MAJOR VECTORS OF MALARIA ONLY) THROUGHOUT THE WORLD [a]



1. *Anopheles aconitus.* 2. *A. albimanus.* 3. *A. aquasalis.* 4. *A. culicifacies.* 5. *A. gambiae.* 6. *A. labranchiae.* 7. *A. maculipennis.* 8. *A. minimus flavirostris.* 9. *A. neomaculipalpus.* 10. *A. nunez-tovari.* 11. *A. pharoensis.* 12. *A. pseudopunctipennis.* 13. *A. punctimacula.* 14. *A. quadrimaculatus.* 15. *A. sacharovi.* 16. *A. sergenti.* 17. *A. stephensi.* 18. *A. sundaicus.*

[a] Based on data supplied by WHO.

most of the agenda for a forthcoming meeting. In the seventh report (1957), various activities were suggested, which have since led to the following useful results:

(1) *The collection and dissemination of information on the resistance problem*

In addition to the mimeographed WHO/Vector Control report series, WHO has put out a regular 2-monthly information circular, giving abstracts of research results (pre-publication as well as published data). The extent of the circulation and interchange of information can be judged from the widespread location of experts concerned (Figures 4, 5 & 6).

(2) *The promotion of needed research and the facilitation of procurement of personnel and funds*

In recent years, WHO has helped by directly providing funds to sponsor necessary research. In addition, it has given indirect help by drawing the attention of research workers to the interest and importance of the scientific problems involved.

(3) *The adoption of standard test methods for use in control problems*

The recommendation of standard test methods has been one of the most successful actions of the Expert Committee. For example, as a result of the wide adoption of standard methods of testing for resistance in adult and larval mosquitos, those planning the malaria eradication campaign have been able to rely on a detailed contemporary picture of prevalence of resistance among malaria vectors.

Test methods for mosquitos and human lice were the first to be provided. Since then, tests have been devised for bedbugs, fleas, sandflies, ticks, cone-nosed bugs, tsetse flies, houseflies, horseflies, stable-

FIG. 4
LOCATION OF EXPERTS CONCERNED IN THE INTERCHANGE OF INFORMATION ON RESISTANCE IN THE TROPICS

[a] Based on *Information Circular on Insecticide Resistance, Supplement A*, March 1961, Geneva, World Health Organization.

flies, and blackflies. These tests are in various stages of development, but a number should be finally adopted by the Committee in the very near future.

Another test method sponsored by the Committee has been for the detection of hyperirritability as a possible characteristic of behaviouristic resistance in mosquitos.

(4) *The procurement and testing of new insecticides*

It can be frankly stated that at present no practical way of overcoming resistance is known other than by changing to a different type of insecticide. Unfortunately, although there are dozens of different contact insecticides, there are only a few basic types that can be regarded as efficient:

(*a*) DDT and its analogues;

(*b*) gamma-BHC and the chlorinated cyclodiene compounds (dieldrin analogues and the chlorinated terpenes);

(*c*) organophosphorus compounds;

(*d*) carbamates;

(*e*) pyrethroids.

It is possible for resistance to develop to all of these types and it would be most valuable if another toxicologically distinct form of contact poison, suitable for residual spraying, could be found. Short of this, it may be possible to find effective members of classes (*c*) and (*d*) to which little resistance exists at present (type (*e*) is not suitable for residual use).

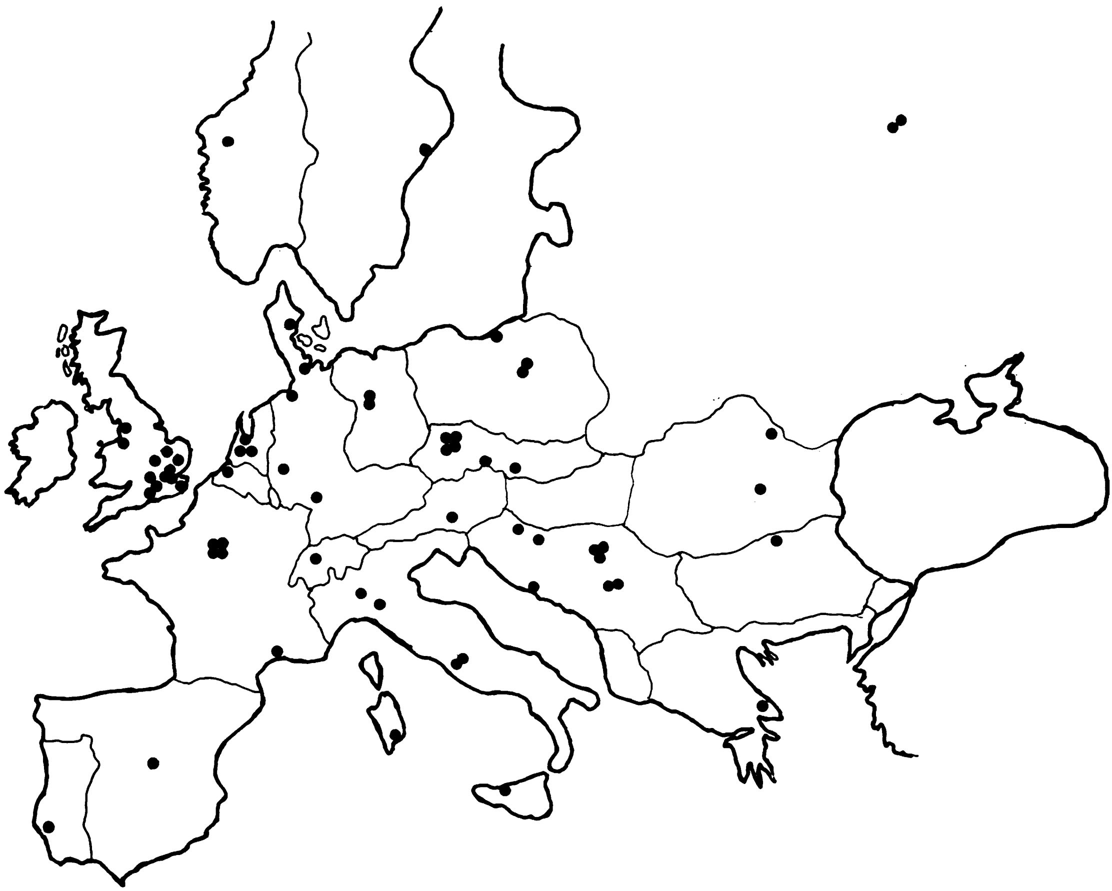
To assist the search for suitable new insecticides, WHO has sponsored a scheme involving collaboration between the chemical pesticide industry and various official laboratories. Possible new compounds are first screened at Riverside Citrus Laboratory (California), then examined for practical promise by panel-type tests at Orlando (Florida), Savannah (Georgia) and Porton (England). The mammalian toxicity of promising candidates is assessed at Carshalton (England) and suitable analytical tests are devised by the Tropical Products Institute (London). Preliminary field trials are carried out at Arusha (Tanganyika) and final trials are planned by the WHO testing unit in Nigeria.

(5) *Liaison activities*

By arranging for experts to visit selected laboratories from time to time, WHO has helped to solve problems of technique and prevent duplication of research.

FIG. 5

LOCATION OF EXPERTS CONCERNED IN THE INTERCHANGE OF INFORMATION ON RESISTANCE IN EUROPE [a]



[a] Based on *Information Circular on Insecticide Resistance, Supplement A*, March 1961, Geneva, World Health Organization.

(6) *Meetings and conferences*

Seminars like the present one are a most helpful way of accelerating the interchange of information and views and clearing up misunderstandings. In particular, they can bring together field and laboratory workers to resolve their different points of view. Major seminars on vector control and resistance have been held in Delhi (March 1958), Panama (June 1958) and Brazzaville (November 1959). Apart from this, there have been smaller specialized meetings of heads of research laboratories.

Theoretically, workers in different countries can keep in touch with current knowledge through the published literature. However, the delays in publication as well as language difficulties retard this. Both barriers can be removed by liaison visits of individuals and by meetings as described above.

STATUS OF RESEARCH ON RESISTANCE

Research on resistance can be done at the following levels: (1) devising sound methods for detection and measurement; (2) investigation of cross-resistance patterns; (3) genetical investigations; (4) biochemical investigations. The two types of basic research (3) and (4) are discussed in other papers,[1] but I should like to point out here that

[1] See Agosin, page 69, Craig, page 89 and Milani, page 77 in this Supplement.

FIG. 6
LOCATION OF EXPERTS CONCERNED IN THE INTERCHANGE OF INFORMATION ON RESISTANCE IN NORTH AMERICA

Based on *Information Circular on Insecticide Resistance, Supplement A*, March 1961, Geneva, World Health Organization.

both need the groundwork provided by the simpler investigations (1) and (2). Thus, the genetical work cannot proceed without an accurate method of measuring resistance, while biochemical work is vitiated unless the type of resistance present is characterized by determining the resistance spectrum of the strain used.

A type of investigation which I think may prove valuable is the comparison of resistant strains of different species. From similarities or differences in their resistance spectra, modes of inheritance and, if possible, biochemical peculiarities, it should be possible to determine whether a particular type of resistance depends on the same mechanism in different species, or whether various insects find different solutions to the problem of overcoming the same insecticide. On existing information I hazard the following preliminary guesses: (1) DDT-resistance involves more than one mechanism (though perhaps dehydrohalogenation occurs in several species); (2) *gamma*-BHC/dieldrin resistance involves a remarkably uniform (though unknown) mechanism; (3) at least two types of organophosphorus resistance occur—one to malathion and one to diazinon, parathion and certain other compounds.

PREVENTING OR OVERCOMING RESISTANCE

Prevention of resistance

Unfortunately, there is no known way of deriving the benefits of the new insecticides without some risk of provoking resistance. The following points, however, deserve some consideration.

(1) Insecticides should not be used regularly on a large scale unless there is some vital object to be attained, such as the elimination of an insect-borne disease. On some occasions the extensive use of pesticides against agricultural pests may induce resistance in other insects, such as mosquitos. The balancing of the benefits from improved crop production against loss of a method of mosquito control, however, appertains more to politics or ethics than to science.

(2) From time to time various people have suggested using mixtures of two different types of insecticide to prevent the emergence of resistance, a method that has proved useful in preventing resistance to antibiotics in bacteria. However, the problem is much more complicated where insects are concerned and the calculations of Crow (1952) suggest that mixtures would merely provoke double resistance. Again, laboratory experiments with houseflies exposed to certain insecticides and mixtures did not seem promising (US Department of Agriculture, 1957).

Two facts, however, suggest that the possibilities of mixtures should be reconsidered. Firstly, Crow's calculations were based on the assumption of polygenic inheritance of resistance, whereas it is now known that most important forms of resistance depend on single gene pairs. Secondly, it is not certain that laboratory experiments with houseflies provide any indication of what happens with other species in the field.

The use of two insecticides, either as a mixture or alternately, would certainly be valuable if compounds could be found whose toxic actions were negatively correlated. However, despite some early hopes, the method has not proved promising owing to the lack of suitable combinations of poisons (Ascher, 1962).

Overcoming resistance

There appear to be several possible ways of overcoming resistance.

(1) The addition to the insecticide of an appropriate synergist to counteract a particular resistance mechanism. So far, such synergists have not been discovered.

(2) Research on alternative insecticides, as in the scheme sponsored by WHO.

(3) Development of alternative methods of control. One interesting possibility is the use of chemosterilants and oviposition inhibitors.

RÉSUMÉ

L'auteur analyse la notion de « résistance de comportement » selon laquelle une sélection de souches à irritabilité très marquée, ou de souches exophiles, s'opérerait parmi les moustiques; il arrive à conclure que le phénomène ainsi décrit peut être mis en doute et, en tout cas, joue un rôle secondaire. Par ailleurs, la notion de « résistance constitutionnelle » semble devoir être abandonnée. En revanche, la résistance physiologique soulève un problème de toute première importance: les espèces résistantes voient s'accroître leur nombre selon un rythme inquiétant.

Les conséquences de cet état de choses ne se sont pas encore pleinement fait sentir parce que le phénomène de résistance est à l'ordinaire localisé; en général, il se limite aussi à un seul insecticide ou à un très petit nombre d'entre eux. Ces raisons expliquent qu'il a jusqu'alors été possible d'atteindre les résultats escomptés par la mise en œuvre d'insecticides qui avaient conservé une efficacité pleine et entière. Cependant le pronostic demeure réservé, et il semble même exister de bonnes raisons de redouter que la résistance ne se généralise au point de compromettre le résultat des campagnes visant à l'éradication du paludisme et d'autres affections transmises par des vecteurs.

Après avoir discuté les dispositions prises en conformité avec les recommandations du Comité d'experts des insecticides (1956), l'auteur émet quelques suggestions à titre personnel. Certaines d'entre elles concernent l'organisation de la recherche dans ce domaine, insistant notamment sur l'intérêt que présente une comparaison systématique entre espèces résistantes pour la découverte et l'étude des mécanismes en cause. L'apparition de la résistance pourrait être prévenue en évitant de recourir à l'emploi massif d'insecticides sans nécessité absolue. Dans le même but, il y aurait lieu d'étudier à nouveau, à la lumière des acquisitions scientifiques récentes, les possibilités offertes par les mélanges d'insecticides.

Trois thèmes de recherches sont évoqués qui ont trait à: l'adjonction à l'insecticide d'un produit synergique qui neutraliserait les mécanismes de résistance; la découverte d'insecticides de remplacement; et la mise au point de méthodes de lutte telles que l'application de produits stérilisants ou inhibiteurs de la ponte.

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