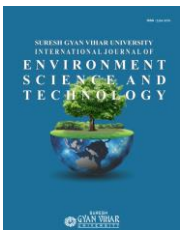

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Review article

Insecticide resistance, its origin & historical purview in reference to the mosquito vector

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Abstract

Resistance to insecticide in arthropods has been a subject of intensive and extensive investigation since their use in the control program at the close of the Second World War. Volumes of published work have piled up since then on the subject. In the present review article, only findings pertinent to insecticide resistance in local malaria vectors, its causes, and implications in disease control have been covered.

Introduction

Stephen Forbes immortal statements are pertinent as they were when made in 1915 that “the struggle between man and insects began long before the dawn of civilization, has continued without cessation to the present time and will continue, no doubt, as long as the human race endures. We commonly think of ourselves as the lords and conquerors of nature, but insects had thoroughly mastered the world and taken full possession of it long before man began to attempt. We cannot even protect our very persons from their annoying and pestiferous attacks, and since then the world began, we never yet exterminated- we probably shall never exterminate, so much as single insect species" (Rockstein, 1974).

These statements revealed the inherent power of resilience insects possess to overcome any attempt to exterminate them- a phenomenon well known to all of us as "resistance".

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Resistance has been defined as " the development of ability in a strain of insects to tolerate a dosage of toxicants which would prove lethal to the majority of individuals in a normal population of the same species. The term ‘behaviouristic resistance’ describes the development of the ability to avoid a dose that would prove lethal (WHO 1957).

The term behaviouristic resistance has been mainly employed in connection with mosquitoes. This phenomenon is not merely a change in the behavior of insects but a change due to selection following the use of insecticides (Busvine & Pal, 1958). Behaviouristic resistance covers diversified cases of changed response, many of which may occur without physiological resistance. These different responses could be phenotypic (irritability, repellence, and change in feeding behavior after DDT contact) or genotypic (exophilic/zoophily, WHO - 1980). Thus, there is a distinction between behaviouristic resistance and regular type of resistance indicated by the WHO standard tests, called "physiological resistance". A population is usually term "resistant" when it has been indicated by the control failure in the field and confirmed by the standard test method (Brown & Pal 1971).

The phenomenon of " resistance" is not of recent origin. The first case of arthropod resistance appeared in 1908 in the Clarkston valley of Washington, where "Sanjose scale insect" became resistant to lime sulfur (Babers & Pratt, 1951). However, the first instance of resistance to synthetic insecticide was detected in the natural population of the housefly, *Musca domestica* Lin. against DDT in Sweden in 1946 (Weisman, 1947) and *Culex molestus* in Italy (Brown & Pal, 1971). In *Anopheline* mosquitoes, DDT - resistance was discovered for the first time in 1951 in *Anopheles sacharovi* in Greece (Busvine, 1955), and dieldrin resistance in 1955, in *Anopheles gambiae* in northern Nigeria (Busvine, 1956).

Indian historical scenario of insecticide resistance in malaria vector

In India, the first report of resistance in mosquitoes to DDT was *Culex fatigans* (Pal *et al*., 1952). The first evidence of DDT - resistance among malaria vectors was discovered in *Anopheles stephensi* (larvae) during 1955 from Madras state (Rajgopalan, 1956). Subsequently, resistance in the adult stage was also detected from the same area (Bhombore *et al*., 1963). By 1967 DDT resistance was reported from 22 new locations/units of NMEP in five states, namely, Bihar, Karnataka, Madhya Pradesh, and Rajasthan (Brown & Pal 1971). During the period of 1977-1983, out of a total of 121 tests with 4.0% DDT in seven states, 109 showed less than 50% mortality (Bang, 1985). HCH

resistance in *Anopheles stephensi* was also reported for the first time from Tamil Nadu (Bhombore *et al*., 1964). Nine years after the first record of larval resistance to DDT, it appeared in five other states by 1983, including Rajasthan (Bang, 1985). The first instance of malathion resistance in the species was reported from Mandora, Haryana (Subbarao *et al*. 1984). *Anopheles culicifacies*- the principal malaria vector remained susceptible to DDT during the first 10-11 years of the general use of this insecticide (Sharma et al. 1957, Bhatia, et al. 1958 and Pal, 1958). The first report of DDT resistance in *Anopheles culicifacies* came in 1959 from the Panchmahals district of Gujarat (Rahman et al. 1959). This emerging DDT- resistance was confirmed by Luen & Shalaby (1962), who found LC_{50} of DDT to exceed 4.0% in the Panchmahals areas in 1961, with females frequently resting on fresh DDT deposits. Subsequently, DDT - resistance was also found in the district of Baroda, Broach, and Surat in Gujarat (Samnotra, 1961), Jalgaon, and Dhulia in Maharashtra (Shalaby, 1968), eastern Rajasthan and western U.P., and throughout Madya Pradesh (Krishnamurthy & Singh, 1962).

Dieldrin- resistance appeared in *Anopheles culicifacies* in 1958, after only 2-3 rounds of dieldrin spraying in Thana district of east-while Bombay state (Patel *et al*.,1958). In Rajasthan, dieldrin - resistance was reported to have developed in Udaipur during 1960 after only two rounds of dieldrin spraying (Brown & Pal, 1971). A marked tolerance to dieldrin was found in the Krishna district (Hyderabad) and Andhra Pradesh, where there has been no dieldrin / HCH in the houses (Naidu et al. 1961). Subsequently, malathion resistance was reported in *culicifacies* soon after 6-9 rounds of malathion spray under NMEP during 1970-72 in Gujarat (Rajgopal, 1977). At the end of 1984, DDT- resistance in *Anopheles culicifacies* had spread over an area covering 262 million population, double resistance from 203 districts in 17 states (125 million population) and triple resistance to DDT, HCH, and malathion from 32 districts in 4 states with a population of 7 million (Bang, 1985).

Anopheles fluviatilis - a sub- mountainous hilly species, was a significant vector in the Uttar Pradesh terai-region, parts of Karnataka, Maharashtra, Andra Pradesh, and Orissa (Rao, 1982). It was also a vector of secondary importance, mainly in the southern region of Rajasthan (Bhatia, 1968). The species has remained susceptible to DDT and dieldrin in most of the countries, except stray cases of resistance to DDT & DLN reported from Karnataka, Maharashtra, Orrisa Tamilnadu (Bang, 1985). The high susceptibility of this species in other parts of the country has

made this very scarce in its previous predominant areas (Das, 1985).

In the two major vectors, viz. *Anopheles culicifacies* and *Anopheles stephensi* have been a progressive increase in the number of resistance cases and the degree of resistance and has emerged as a common phenomenon all over the country (Sharma, 1986).

Origin, nature & characterization of resistance

Resistance is an inherent characteristic dependent on genetic mechanisms. The factors making for resistance being already present in a shallow frequency in an average population before the insecticide is applied (Crow, 1957). The resistance mechanism responsible is inherited apparently by the normal Mendelian process of selection (Metcalf, 1955; Gordon & Hoskin,1956; Crow, 1957; Busvine & Pal, 1958). Milani (1956) confirmed through closer genetic studies on the inheritance of resistance that in insects, it is monofactorial in origin.

Four different kinds of resistance to insecticides used in public health have been identified due to their varying genetic characteristics, namely; **a)** DDT-resistance, **b)** to cyclodiene derivatives, **c)** to organophosphorus compounds & **d)** to carbamate and synthetic pyrethroid group of compounds (Brown & Pal, 1971 and WHO, 1976). Various studies have identified the genetic characteristics of 4 principle types of resistance. Brown & Pal (1971) reported DDT- resistance in 13 species of public health importance due to a single gene. DDT- resistance gene has been reported to be usually recessive and occasionally " intermediate" or incompletely dominant in mosquitoes. The degree of resistance in DDT is relatively low. Zulueta (1968) and Haridi (1972) defined the role of ancillary genes forming part of the background of DDT resistance in modifying the expression and influencing selection speed. Davidson & Zahar (1973), while describing the dynamics of DDT resistance in mosquitoes, stated that in its initial stage, its level might not be distinguishable from that of commonly known "tolerance". Furthermore, they reported the selection process to be slow and may take a long time, though the process may be accelerated due to enhanced selection pressure by the use of DDT in agriculture.

Dieldrin resistance

In anopheline mosquitoes, it is usually well pronounced, and the gene expression is mainly incompletely dominant. Once it appears, it grows rapidly from a very low gene frequency (Macdonald, 1959). Brown & Pal (1970) reported a single gene to be responsible in 16 insect species. La. Face (1952) & D' Alessandro et al. (1952)

indicated for the first time the genetic separateness of cyclodiene compounds (chlordane, dieldrin, etc.) from DDT resistance. Busvine (1954) later confirmed the above findings by means of back-crosses and selection studies.

Organophosphorus & carbamate resistance

It has always, without exception, been reported to be dominant in expression (Brown & Pal). In this type of resistance, a single gene was also demonstrated to be responsible for organophosphorus compounds in 5 species and carbamates in two species (Ibidem, 1971).

Pyrethroid resistance

In mosquitoes, selection for resistance to pyrethroid and DDT is governed by the same kdr gene; hence, DDT-resistant strains of mosquitoes manifest cross-resistance to pyrethroids (WHO, 1976 & 1980). It has been proposed that strains that possess 'kdr gene' have fewer target sites receptor for DDT and pyrethroid than normal, and thus they bind less insecticide and are affected to a lesser extent. The binding affinities of preparations from resistant and susceptible strains were the same, indicating that the major difference between strains was quantitative than qualitative. Such a quantitative decrease in target sites is consistent with a broad spectrum of resistance to pyrethroids, which is observed after selection by any number of this class of insecticides. There is evidence suggesting that pyrethroids exhibit two types of insecticidal action (although some display an intermediate type of action), and cross-resistance appears to extend reciprocally to both types. This broad - spectrum of resistance within the pyrethroids emphasizes the need for coordinated efforts to limit their excessive use and thus prevent the rapid development of resistance.

Cross-resistance

When insect populations are exposed to selective pressure with one insecticide (the selector), they may develop resistance to other insecticides. This phenomenon is called cross-resistance (WHO, 1976). In some of these cases, cross-resistance is found between insecticides with a closely related chemical structure; in others, chemical relation is less. As a rule, cross-resistance is explained by a common resistance (defense) mechanism, but there may be other possibilities. The problem is complicated by more than one resistance mechanism to a single insecticide, unspecific and specific resistance factors.

Multiple resistance

By exposure to two or more insecticides, either at the same time or one after the other, an insect population may develop

resistance to several insecticides, namely the selector, called multiple resistance.

Vigour tolerance

The term was introduced by Hoskin & Gordon (1956) to label cases of enhanced insecticide tolerance resulting from extra vigour of the strain rather than from any specific defense mechanism. It could be due to factors such as increased weight or improved biochemical conditions and as being inducible as a strain characterized by any selective pressure to be found in extremes of environmental conditions.

Dynamics of resistance & conducive factors

Principal factors on which the development of insecticide resistance in insect populations depends are classified into three main groups **a)** genetic, **b)** operational, and **c)** biological and ecological. The more important factors were identified as the presence and frequency of resistant genes and their nature of manifestation, selection pressure, type of insecticide application, previous exposure, and isolation of the insect populations (WHO, 1980).

Biochemical basis of resistance

Physiological and biochemical aspects of arthropod resistance to insecticides have been reviewed from the time of emergence of the problem by Brown (1958), Metcalf (1955), Hoskins and Gordon (1956), Crow (1957), Pant (1958) and Pal (1958). Metcalf (1955) was first to point out that " modern toxicological theory almost exclusively relates the mode of action of poisons to specific interferences with biochemical systems, largely enzyme in nature. It is most probable that secrets of insecticide resistance are to be found within the realm of biochemistry and enzymology.

So far, at least five resistance mechanisms have been detected (Davidson, 1989):

a). an increase in general esterase activity is responsible for broad-spectrum organophosphate and sometimes carbamates resistance in *An. albimanus* (Guetamala), *Ae. aegypti* (Thailand), *Ae. albopictus* (Sri Lanka), *Cx. Molestus* (Japan), *Cx. pipiens pallens* (Japan), *Cx. pipiens pipiens* (France), *Cx. quinquefasciatus* (Burma, Tanzania, USA, Japan, Keneya, Liberia, Sri Lanka), *Cx. geledus*, *Cx. fuscocephala*, *Cx. vishnui*, *Cx. tritaeniorhynchus* (Sri Lanka, all 4 being vectors of Japanese encephalitis), *Cx. tarsalis* (the vector of equine encephalitis in the USA), *S. soubrense* and *S. sanctipauli* (West Africa).

b). a change in carboxylesterase responsible for resistance to those organophosphates with a carboxyl grouping in the molecule, e.g. malathion and phenthoate but not to most other

organophosphates, in *An. arabiensis*, *Cx. P. pallens* (China), *Cx. tritaeniorhynchus* (Japan) and *Cx. tarsalis* (USA).

c). the presence of an acetyl cholinesterase insensitive to most organophosphates and carbamates, in *An. albimanus* (Elsalvador), *An. atraparus* (Spain), *An. nigerrimus* (Sri Lanka), *An. sacharovi* (Turkey), *Cx. P. pipiens* (France, Italy) and *Cx. tritaeniorhynchus* (Japan).

d). a change in multi-function oxidases responsible for resistance to DDT, organophosphates, carbamates and pyrethroids, in *An. subpictus* (to organophosphates in Sri Lanka) and *Cx. quinquesfasciatus* (to DDT, Pyrethroids and propoxur in the USA).

e). a change in dehydrochlorinase or glutathione - S- transferase responsible for DDT resistance in *An. gambiae s.s.* (Tanzania), *An. sacharovi* (Saudi-Arabia).

Detection & measurement of insecticide resistance

The standard susceptibility test method for mosquito vectors was designed and developed by WHO in 1957 to detect resistance and monitor its spread, as per the recommendations of the insecticide expert committee (Wright, 1958). The WHO-mosquito test kit adopted the screened plastic tube exposure chambers developed by Fay (1953) and oil-impregnation of insecticide test papers technique (@ 3.6 mg/sq.cm of oil solution) of Busvine & Nash (1954).

Formerly, the use of serial concentrations and calculation of LC_{50} & LC_{95} for the detection of resistance was made. The population was considered susceptible to exposure to 4% DDT for 1 hour, where up to 10% survival was recorded, 'intermediate' where survivals varied between 11 and 50%, and resistant where these exceeded 50%.

Davidson & Zahar (1973) advocated using a single discriminating dosage based on concentrations of insecticides that normally kill all the susceptible individuals for the early detection of a low level of resistance. They recommended a more stringent classification to encourage the earlier identification of resistance.

Implications of vector resistance

Vector resistance to the same insecticide may have a different epidemiological impact. Davidson & Zahar (1973) provided guidelines for evaluating the operational impact of vector resistance on disease control.

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