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PUBLIC HEALTH SIGNIFICANCE OF INSECT RESISTANCE TO INSECTICIDES AND FUTURE ORIENTATION OF VECTOR CONTROL PROGRAMS (1)

Riassunto. — Fin dal 1897 è stata segnalata la resistenza degli insetti ai prodotti chimici. Da tale epoca in poi, tale fenomeno è stato constatato nei diversi insetti in numerose parti del mondo. Fino al 1941, i problemi sollevati da questa resistenza non sono quasi stati studiati se non negli insetti nocivi alle piante, ma a quell'epoca è stato constatato che certe mosche potevano essere selezionate per mezzo della loro resistenza alla fenotiazina.

Le zecche dell'Africa meridionale si sono mostrate refrattarie a soluzioni di arsenito di sodio e poi al Gammesano. Quando si è scoperto il DDT, non si è pensato abbastanza alla possibilità che gli insetti avrebbero di diventare rapidamente resistenti a questo prodotto il quale mostravasi così efficace. Ora, nel 1946 circa, la resistenza al DDT si è generalizzata nelle mosche comuni in Italia. Questa proprietà si è manifestata ben presto in quasi tutti i paesi del mondo, adesso che molte resistono a un certo numero di altri insetticidi a base di idrocarburi alogenati. Si è constatato recentemente, qui e là, casi di resistenza di alcune zanzare vettrici — culicinate e anofeli. Questo fatto potrebbe influire grandemente sul successo dei piani di sradicamento delle malattie stabiliti dall'Organizzazione Mondiale della Sanità. Inoltre la resistenza insetticida si è ora estesa a certi pidocchi, pulci, cimici e blatte. Attualmente informazioni provenienti da 33 paesi e regioni segnalano che 35

(*) This document is based on research performed in the Communicable Disease Center and throughout the world. In addition to furnishing data, Dr. A. L. Perry, Dr. R. W. Fay, and Mr. K. D. Quarterman, of the Technology Branch, CDC, made major contributions in assimilating information for various portions of the orderly compilation and presentation of the data.

specie di insetti vettori di malattie (fra l'altro della peste) resistono agli insetticidi moderni.

La resistenza può essere naturale o acquisita. La resistenza naturale è di carattere fisiologico, morfologico o ecologico; non risulta dalla selezione occasionata dagli insetticidi: essa esisteva già al momento della prima applicazione dei metodi di lotta contro gli insetti. La resistenza acquisita può provenire: 1) da meccanismi fisiologici che permettono all'organismo degli insetti di neutralizzare l'effetto tossico dell'insetticida; 2) da meccanismi fisiologici e morfologici che permettono all'insetto di eliminare in parte l'insetticida; e 3) da meccanismi inerenti al comportamento naturale o alla fisiologia dell'insetto che spingono alcune specie a sottrarsi ecologicamente alle applicazioni dell'insetticida prima che queste abbiano raggiunto la dose mortale.

Estremamente oscure rimangono la natura e le cause della resistenza delle mosche comuni ai nuovi insetticidi organici. Gli studi concernenti la fisiologia della mosca hanno dimostrato la capacità delle mosche resistenti a convertire il DDT in un prodotto relativamente privo di tossicità, il DDE. Sebbene questa teoria spieghi in una larga misura la resistenza degli insetti dal punto di vista fisiologico, pare comunque che altri fattori intervengano. Quando si espone all'azione del DDT mosche resistenti e mosche non resistenti, si constata che il ritmo della respirazione è molto meno elevato nelle prime che nelle seconde. Le mosche che resistono al DDT presentano un aumento dell'ossidasi citocromo. Dal fatto che il DDT inibisce quest'enzima respiratorio, si può dedurre che le mosche aventi un enzima particolarmente attivo siano maggiormente capaci di resistere al bloccaggio parziale di questo metabolismo. Le mosche resistenti sopportano meglio gli sbalzi di temperatura ed hanno un ciclo di vita più lungo; le esperienze sembrano dimostrare che il meccanismo collettore è ereditario, ma il suo modo di azione è estremamente vario e non è stato studiato in modo soddisfacente se non in casi isolati. Certi ceppi sperimentali di mosche comuni resistenti al DDT (qualunque sia del resto il loro grado di resistenza) di cui si sono allevati in laboratorio diverse generazioni successive al riparo del DDT, hanno perduto gradualmente la loro resistenza a questo prodotto. Non si conosce la natura del fattore che origina questo fenomeno. Quantunque si possieda un'importante documentazione sulla resistenza delle mosche comuni, non si sa gran chè sul meccanismo della resistenza al DDT in altri insetti vettori di malattie ed in particolare delle zanzare. Inoltre non si è ancora studiato sufficientemente l'effetto di prodotti altri che il DDT.

Esiste un rapporto diretto fra la resistenza e la sanità nel senso che l'utilizzazione delle formule attuali non permette di garantire nuovi progressi nella lotta contro le malattie trasmesse dai vettori. Infatti in certe date condizioni dopo essere riusciti a far sparire i vettori, non si potrezze mantenere il risultato così ottenuto. Tuttavia non è il caso di affrontare questo problema con troppo pessimismo. La resistenza tra i principali vettori di malattie è relativamente limitata e sembra che certe specie non raggiungano mai un grado di resistenza notevole. Disgraziatamente non si possono fare raccomandazioni specifiche rispetto ai metodi da seguire per chiarire questo problema. Per l'avvenire, converrebbe mettere in opera un ampio programma di sorveglianza avente per scopo di mettere in evidenza i primi segni di resistenza nelle specie attualmente non resistenti, di sviluppare ricerche basali sui nuovi insetticidi o nuove tecniche, di scegliere prodotti chimici per quanto sia possibile diversi per l'azione larvicida e per le polverizzazioni ad effetto rimanente, e di considerare i progressi costanti della bonifica come facente parte integrale di tutto il programma di distruzione degli insetti.

Résumé. — La résistance des insectes aux produits chimiques a été signalée dès 1897. Depuis cette époque, le phénomène a été constaté chez divers insectes en de nombreux points du monde. Jusqu'en 1941, les problèmes que pose cette résistance n'ont guère été étudiés que chez les insectes nuisibles aux plantes, mais à cette époque il a été établi que certaines mouches pouvaient être sélectionnées par leur résistance à la phénothiazine. Les tiques de l'Afrique méridionale se sont montrés réfractaires à des solutions d'arsénite de sodium, puis au gamméxane. Lors de la découverte du DDT, on n'a pas envisagé suffisamment que les insectes pouvaient assez rapidement devenir résistants à ce produit, qui se montrait si efficace. Or, vers 1946, la résistance au DDT s'est généralisée chez les mouches communes en Italie. Cette propriété s'est manifestée bientôt dans presque tous les pays du monde. Les mouches résistent maintenant à un certain nombre d'autres insecticides à base d'hydrocarbures halogénés. Plus récemment, on a constaté ici ou là, des cas de résistance chez quelques moustiques vecteurs — culicinés et anophèles. Ce fait pourrait influer grandement sur le succès des plans d'éradication des maladies établis par l'Organisation Mondiale de la Santé. En outre la résistance aux insecticides s'est maintenant étendue à certains poux, puces, punaises et cancrelats. Actuellement des informations venant de 33 pays ou régions signalent que 35 espèces

d'insectes vecteurs de maladies (notamment de la peste) résistent aux insecticides modernes.

La résistance peut être naturelle ou acquise. La résistance naturelle est de caractère physiologique, morphologique ou oecologique; elle ne résulte pas d'une sélection occasionnée par les insecticides: elle existait déjà au moment où ont été appliquées les méthodes de lutte contre les insectes. La résistance acquise peut provenir 1) de mécanismes physiologiques permettant à l'organisme de l'insecte de neutraliser l'effet toxique de l'insecticide; 2) de mécanismes physiologiques et morphologiques permettant à l'insecte d'éliminer en partie l'insecticide et 3) de mécanismes inhérents au comportement naturel ou à la physiologie de l'insecte, qui poussent certaines espèces à se soustraire oecologiquement aux applications d'insecticide avant que celles-ci aient atteint la dose mortelle.

La nature et les causes de la résistance des mouches communes aux nouveaux insecticides organiques demeurent extrêmement obscures. Les études concernant la physiologie de la mouche ont montré l'aptitude des mouches résistantes à convertir le DDT en un produit relativement dépourvu de toxicité, le DDE. Bien que cette théorie explique dans une large mesure la résistance des insectes du point de vue physiologique, il semble néanmoins que d'autres facteurs interviennent. Lorsqu'on expose à l'action du DDT des mouches résistantes et des mouches non résistantes, on constate que le rythme de la respiration est beaucoup moins élevé chez les premières que chez les secondes. Les mouches qui résistent au DDT présentent une augmentation de l'oxidase cytochrome. Du fait que le DDT inhibe cet enzyme respiratoire, on peut s'attendre que les mouches ayant un enzyme particulièrement actif soient plus capables de resister au blocage partiel de ce métabolisme. Les mouches résistantes supportent mieux les écarts de température et ont un cycle de vie plus long. Les expériences sembleraient indiquer que le mécanisme protecteur est héréditaire, mais son mode d'action est extrêmement varié et n'a été étudié de façon satisfaisante que dans des cas isolés. Certaines souches expérimentales de mouches communes résistantes au DDT — quel que soit d'ailleurs leur degré de résistance —, dont on a élevé en laboratoire plusieurs générations successives à l'abri du DDT, ont perdu graduellement leur résistance à ce produit. On ne connaît pas la nature du facteur qui est à l'origine de ce phénomène. Bien que l'on possède une importante documentation sur la résistance des mouches communes, on ne sait pas grand-chose du mécanisme de la résistance au DDT chez d'autres insectes vecteurs de

maladies, en particulier chez le moustique. De même, on n'a pas encore étudié suffisamment l'effet des produits autres que le DDT.

Il existe un rapport direct entre la résistance et la santé, en ce sens que l'utilisation des formules actuelles ne permet pas de garantir de nouveaux progrès dans la lutte contre les maladies transmises par des vecteurs. En fait, dans certaines conditions données, après avoir réussi à faire disparaître les vecteurs, on ne pourrait pas maintenir le résultat ainsi obtenu. Cependant, il n'y a pas lieu d'envisager le problème avec trop de pessimisme. La résistance, parmi les principaux vecteurs de maladie, est relativement limitée et il semble que certaines espèces n'atteignent jamais un degré de résistance bien considérable. On ne peut malheureusement pas faire de recommandations spécifiques sur les méthodes à suivre pour élucider ce problème. Pour le moment, l'utilisation de diverses combinaisons des techniques disponibles offre le moyen le plus satisfaisant de s'attaquer au problème. Pour l'avenir, il conviendrait de mettre en œuvre un vaste programme de surveillance ayant pour objet de déceler les premiers signes de résistance chez les espèces actuellement non-résistantes, de développer les recherches de base sur de nouveaux insecticides ou de nouvelles techniques, de choisir des produits chimiques aussi différents que possible pour l'action larvicide et pour les pulvérisations à effet rémanent, et de considérer les progrès constants de l'assainissement comme devant faire partie intégrante de tout programme de destruction des insectes.

Summary. — Insect resistance to chemical products has been noted since 1897. Since that time, the phenomenon has been observed among various insects in many different parts of the world. Until 1941, the problems set by this resistance were scarcely studied except in insects that are harmful to plants, but at that date it was established that certain flies could be selected by their resistance to phenothiazine. The ticks of southern Africa have been shown to be refractory to solutions of sodium arsenite, and also to gamexane. After the discovery of DDT, it was not sufficiently foreseen that insects could become resistant quite quickly to this extremely useful product. But by 1946, resistance to DDT had become general among house flies in Italy. This characteristic has made itself evident in practically all the countries of the world. Flies are now resistant to a certain number of other insecticides with a halogen hydrocarbon base. More recently, cases of resistance have been observed here and there among several mosquito vectors — culicineae and anopheles. This fact may have a considerable influence on the success of the plans which have been set up by

the World Health Organization for the eradication of disease. Apart from this, resistance to insecticides has now extended to certain lice, fleas, bugs and cockroaches. At present, information coming from 33 countries or regions states that 35 species of insect vectors of disease (especially of plague) resist modern insecticides.

Resistance can be natural or acquired. Natural resistance has a physiological, morphological or ecological character; it does not result from a selection caused by insecticides; it already existed at the moment when active measures against the insects were applied. Acquired resistance can result (1) from physiological mechanisms which allow the insect organism to neutralize the toxic effect of the insecticide; (2) from physiological and morphological mechanisms which allow the insect to eliminate the insecticide in part; (3) from mechanisms inherent in the natural behaviour or the physiology of the insect, which lead certain species to escape ecologically from insecticide applications before these have reached the fatal dose.

The nature and causes of resistance by the domestic fly to the new organic insecticides remain extremely obscure Studies relating to the physiology of the fly have shown the ability of resistant flies to convert DDT into a product (DDE) relatively denuded of toxicity. Although this theory explains to a great extent the resistance of insects from the physiological point of view, it seems nevertheless that other factors intervene. When resistant and non-resistant flies are exposed to the action of DDT, it is observed that the rhythm of respiration is much less raised in the former than in the latter. Flies resistant to DDT show an increase in the oxydase cytochrome. From the fact that DDT inhibits this respiratory enzyme, one might expect that flies having a particularly active enzyme would be better able to resist a partial blockage of this metabolism. The resistant flies tolerate differences in temperature better and have a longer life cycle. The experiments would appear to indicate that the protective mechanism is hereditary, but its mode of action is extremely varied and has not been studied in a satisfactory fashion except in isolated cases. Some experimental stocks of house flies resistant to DDT — whatever their degree of resistance otherwise — of which several successive generations were raised, sheltered from DDT, gradually lost their resistance to this product. The nature of the factor causing this phenomenon is not known. Although considerable information is available on the resistance of the house fly not much is known about the mechanism of resistance to DDT on the part of other insect vectors of disease, particularly the mosquito.

Similarly, not enough work has yet been done on the effect of products other than DDT.

There is a direct correlation between resistance and health, in the sense that the use of present formulae does not give any guarantee of fresh progress in the campaign against vector- transmitted disease. In fact, in certain given conditions, the vectors were successfully made to disappear, but the result thus achieved could not be maintained. However, there is no need to view the problem with too much pessimism. Resistance, in relation to the principal vectors of disease, is relatively limited, and it appears that certain species never attain any considerable degree of resistance.

Unfortunately, it is not possible to make specific recommendations on the methods to be adopted in order to elucidate this problem. For the moment, the utilization of various combinations of available techniques offers the most satisfactory means of attacking this problem. For the future, it will be appropriate to inaugurate a vast programme of supervision, with the object of discovering the first signs of resistance among species that are now non-resistant, to develop basic research on the new insecticides or on new techniques, to choose chemical products as different as possible for larvicidal action and for long-term spraying, and to consider the constant progress of sanitary improvement as forming an integral part of any insect destruction programme.

Zusammenfassung. — Die Resistenz der Insekten gegen chemischen Produkten ist seit 1897 gemeldet worden. Seit dem wurde die Erscheinung bei verschiedenen Insekten in zahlreichen Weltteilen beobachtet. Bis 1941 wurden die Probleme, die diese Resistenz in Anbetracht nehmen, nur bei Insektenschädlinge der Pflanzenwelt studiert, aber zu jener Zeit wurde festgestellt dass gewisse Fliegen, wegen ihrer Resistenz gegen Phenothiazine, selektioniert werden konnten. Die Milben von Süd-Afrika haben sich für einigen Lösungen von Natriumarsenit und darnach für Gamexane nicht empfindlich bewiesen.

Als DDT entdeckt wurde, hat man nicht hinreichend in Anbetracht genommen, dass die Insekten sehr bald gegen diesem Produkt, der sich so wirksam zeigte, resistent werden konnten. Nun, gegen 1946, verbreitete sich die DDT-Resistenz in Italien auch bei Hausfliegen. Diese Eigenschaft äusserte sich sehr bald in fast allen Ländern. Die Fliegen widerstehen jetzt auch gegen eine Anzahl anderer Insektiziden, die aus Halogen-Kohlenwasserstoff bestehen. Ganz neulich hat man hie und da einige Resistenzfälle bei einigen blutsaugenden Mücken — *culicinae* und *anopheles* — beobachtet.

Diese Tatsache könnte sehr viel auf den Erfolg des Krankheits-Ausrottungsplans der Welt-Gesundheits-Organisation ausüben. Die Resistenz gegen Insektiziden hat sich jetzt ausserdem auf einigen Läuse, Flöhe, Wanzen und Blatten verbreitet. Zur Zeit wird es von 33 Ländern oder Gegenden gemeldet, dass 35 Arten von Insekten, welche die Krankheiten übertragen (die Pest insbesondere) gegen den heutigen Insektiziden widerstehen.

Die Resistenz kann entweder natürlich oder erworben sein. Das Wesen der natürlichen Resistenz kann entweder physiologisch, morphologisch oder oekologisch sein; sie wird nicht aus einer Selektion durch Insekticiden hervorgerufen; die Resistenz war nämlich schon vorhanden wann die Bekämpfungsmittel gegen Insekten angewandt wurden.

Die erworbene Resistenz kann entstammen: 1) aus physiologischen Mechanismen, die dem Organismus des Insekten die giftige Wirkung des Insektiziden zu neutralisieren ermöglichen; 2) aus den physiologischen und morphologischen Mechanismen, die dem Insekten das Insektizide zum Teil auszuscheiden ermöglichen; 3) aus zu dem natürlichen Verhalten oder zur Physiologie der Insekten gehörenden Mechanismen, die einige Arten dazuführen, sich bei der Anwendung von Insektiziden, vor Erreichung der tödlichen Dose, oekologisch zu entziehen.

Das Wesen und die Ursache der Resistenz der Hausfliegen gegen den neuen organischen Insektiziden sind äusserst unklar. Die Untersuchungen bezüglich der Physiologie der Fliegen haben die Fähigkeit der resistenten Fliegen gezeigt, DDT in einen Stoff zu verwandeln, der verhältnissmässig giftlos ist, nämlich DDE. Obwohl diese Theorie zum grossen Teil die Resistenz des Insekten von physiologischen Standpunkt aus erklärt, scheint es nicht desto weniger, dass, auch andere Faktoren dazu mitwirken. Wenn man die resistenten und nicht-resistenten Fliegen der DDT-Wirkung aussetzt, bemerkt man dass, bei den ersteren das Atmungsrythmus viel niedriger ist als bei den letzteren. Die DDT-resistenten Fliegen zeigen einen Ansteig von Cytochrome-Oxidase. Da DDT diese Atmungsenzymen aufhebt, kann man voraussehen dass, die Fliegen die mit einem besonderen, wirksamen Enzym versehen sind, mehr fähig sind der teilweisen Verhinderung dieses Stoffwechsels zu widerstehen. Die resistenten Fliegen ertragen die Temperaturunterschiede viel besser und zeigen ein längeres Lebenzyklus. Die Erfahrungen scheinen gezeigt zu haben dass der Schützmechanismus vererbt wird; seine Wirkungsweise ist aber äusserst verschieden, sie wurde jedoch nur in einigen Fällen in befriedigender Weise studiert. Einige experimentellen Abstammungen von

DDT-resistenten Hausfliegen — unbeachtet ihres Resistenzgrad — wovon im Laboratorium gebrütete, zahlreiche, aufeinanderfolgende Generationen, die mit DDT nicht in Beruhrung kamen, haben ihre Resistenz gegen dieses Produkt stufenweise verloren. Das Wesen des Faktoren, der diese Erscheinung zu Stande bringt, ist unbekannt. Obwohl man eine grosse Dokumentation über die Resistenz der Hausfliegen besitzt, ist der Mechanismus der Resistenz gegen DDT bei anderen Insekten die Krankheiten übertragen, insbesondere bei Mücken, sehr wenig bekannt. Ebenfalls hat man die Wirkung anderer Produkten, DDT ausgenommen, noch nicht hinreichend untersucht.

Zwischen Resistenz und Gesundheit gibt es ein direktes Verhältnis in dem die Anwendung der heutigen Formeln gestatten nicht neue Fortschritte bei der Bekämpfung gegen Krankheiten, die von Insektträger übertragen werden, zu versichern. In der Tat, unter besonderen Umständen, nach der gelungenen Vernichtung der Krankheitsträger, könnte man die so erhaltenen Ergebnisse nicht beihalten. Trotzdem, gibt es keinen Grund die Frage mit zuviel Pessimismus zu betrachten. Die Resistenz ist unter den hauptsächlichen Krankheitsträger ziemlich beschränkt und es scheint dass, einige Arten niemals ein sehr bedeutendes Resistenzgrad erreichen.

Leider kann man keine spezifischen Anweisungen über die zu verfolgenden Methoden empfehlen um diese Frage erklären zu können. Zur Zeit liefert die Anwendung der verschiedenen, technischen Mittel, die uns zur Verfügung stehen, den befriedingsten Weg das Problem anzugreifen.

In der Zukunft, wird es nötig sein, einen ausgebreiteten Überwachungs-plan einzuführen der bezwecken sollte die ersten Zeichen der Resistenz bei der jetzt nicht-resistenten Arten aufzuspüren; die gründlichen Forschungen der neuen Insektiziden oder der neuen Technik zu entwickeln; die chemischen Produkten so verschieden wie eben möglich für die larvicide Wirkung und für die Zerstäubung mit Residual-Wirkung auszuwählen; und endlich, die konstanten Fortschritte der Sanierung als ein wesentlicher Teil des ganzen Programms der Insekten-Vernichtung zu betrachten.

Insect resistance to chemicals is by no means a new phenomenon in the history of insecticides. As early as 1897, Dr. John B. Smith published an article in which he noted that, although certain species of insects in the Atlantic coast States readily succumbed to kerosene, the

same species in Colorado remained unaffected by it ([1]). Conversely, washes that controlled San Jose scale in California were highly ineffective when tried against this scale insect in the Atlantic coast States.

The first major economic problem arising from insect resistance to chemical control developed with various scale insects. In 1902, lime-sulfur sprays were effective against the San Jose scale, *Aspidiotus perniciosus* Comst. ([2]), but some failures were observed by 1908; and the magnitude of the problem increased until resistant strains were suspected ([3]). Data subsequently confirmed that the resistance was not due to environmental conditions or faulty application of the insecticide, but rather was characteristic of certain strains of the species.

Within a few years, the red scale, *Aonidiella aurantii* (Mask.), and the black scale, *Saissetia oleae* (Bern.), showed increased resistance to hydrocyanic acid gas fumigation, ([4]) apparently due to a state of protective stupefaction produced by low initial concentration of HCN ([5-7]). Resistant insects were able to close their spiracles for longer periods of time than were the susceptible individuals ([8]) and tests after fumigation demonstrated more HCN in the non resistant insects. ([9]) Genetic studies indicated that the resistance was sex-linked, inherited through a single gene or through a group of closely linked genes on the X-chromosome ([10]), and that both nonresistant and resistant insects existed in resistant and nonresistant stock strains ([11]). Resistance levels were maintained over considerable periods of time without selection or change ([11-12]). The same resistance to HCN existed in the scale nymphs as in the adult insect ([13]). No differences in growth rates, in the permeability of the wax coverings of the insect ([11]), or in the reproductive ability or normal mortality at various temperatures were detected between resistant and susceptible strains of scales ([14]).

In the period from 1920 to 1940 resistant strains of the codling moth and of citrus thrips were reported from the field and confirmed in the laboratory. On apples sprayed with lead arsenate, larvae of strains of the codling moth from Colorado penetrated the apples to a greater degree than did those of Virginia strains ([15-16]). Increased penetration by resistant larvae was also evident in apples treated with cryolite, barium fluorsilicate, and rotenone ([17]). When arsenious oxide was fed to test larvae of the two strains ([18]) or sodium arsenite or lead arsenate was injected into the haemocoel ([19]), no differences in susceptibility were detected. This seems to be a case of behavioristic resistance.

Strains of the citrus thrips, *Scirtothrips citri* (Moult.), that showed promise for control by tartar emetic and sucrose mixtures in 1938 ([20]) had developed considerable resistance by 1941 ([21]).

Up to this time problems in resistance had been confined mainly to plant infesting insects, but in 1941 laboratory studies revealed that larvae of the primary screw worm fly, *Callitroga* (=*Cochlimyia*) *americana* C. and P., and of the greenbottle flies, *Phaenicia* (=*Lucilia*) *sericata* (Meig.) and *Lucilia cuprina* (Wied), could be selected for resistance to phenothiazine ([22]). After selection for eight generations, progeny of these strains showed markedly higher survival rates following exposure.

Certain field strains of the blue tick, *Boophilus decoloratus* (Koch), were found to be resistant to sodium arsenite dips in South Africa ([23]). Gammexane (1,2,3,4,5,6-hexachlorocyclohexane) dips were introduced in 1947 ([24]) and were effective until 1949 when resistance to this compound became evident ([25-27]). More recently *B. microplus* in Australia has been reported to be developing a tolerance for Gammexane ([83]).

Present Extent of Resistance.

DDT [2,2,bis-(*p*-chlorophenyl)-1,1,1-trichloroethane] first came into prominence in the late World War II years. Public health workers were intrigued with the almost boundless possibilities of this highly effective insecticide. Enthusiastic advocates hailed its advent and could visualize the solution to virtually all insect vector problems. DDT, however, carried the seeds of its own vulnerability, namely, that insects could become refractory to its lethal effectiveness.

DDT was first used extensively in the field — including Italy ([28]) — in 1944. Three years later the first intimation of DDT resistance was received from Professor Missiroli and Dr. Saccà of the Istituto Superiore di Sanità in Rome ([29-30]). By 1945-46 resistance had become widespread among house flies (*Musca domestica* L.) and a new subspecies, *M. domestica* var. *tiberina* was suggested for the resistant strains. Experiments in 1946 on two strains of Swedish flies revealed that one strain, which was able physiologically to withstand 100 to 200 times more DDT, also displayed variations in morphologic characteristics of the tarsi, which were believed to play a significant part in this difference in DDT sensitivity ([31]). In the United States, a DDT-resistant strain of house flies was secured in the laboratory by selection through space sprays in 1947 ([32]), and during the following year the first resistant field strain was reported from New York state ([33]). Numerous reports on DDT resistance in the house fly have appeared since that time from Canada ([70]) and Mexico ([44-71]), Central ([44]) and

South ([44, 71]) America, Europe, ([29, 30, 44, 67, 68, 69, 82]) and Australia ([44]). Information currently available gives no indication of DDT-resistant flies in Korea or Japan ([44]).

No resistance has been reported for *Musca vicina* Macq. in India, Ceylon, or Uganda ([34, 35, 55]), but the species has shown resistance to DDT in the Near East ([36]) and to BHC (Gammexane) in Egypt ([37]). *M. nebulo* has developed some DDT resistance under laboratory selection ([35]) but not so far in the field.

Numerous studies made with other halogenated hydrocarbon insecticides have revealed resistance in house flies to methoxychlor [2,2-bis (*p*-Metoxyphenyl)-1,1,1-trichloethane], TDE [1,1-bis-(*p*-Chlorophenyl)-2,2-dichloroethane], lindane (*Gamma*-1,2,3,4,5,6-hexachlorocyclohexane), chlordan (1,2,4,5,6,7,8,8-Octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindane), heptachlor (1,4,5,6,7,8,8-Heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene), dieldrin (1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7, 8,8a-octahydro-1,4,5,8-dimethanonaphthalene), toxaphene (chlorinated camphene), and Dilan [mixture of 2-Nitro-1,1-bis-(*p*-chlorophenyl)] propane (1 part) plus 2-Nitro-1,1-bis-(*p*-chlorophenyl) butane (2 parts), indicating that resistance to one insecticide leads to a more rapid development of resistance to a second related one.

Flesh flies, *Callitroga* spp., *Phaenicia* spp., and *Phormia* spp., have not been reported as becoming resistant under field control operations. In a laboratory study, *Phaenicia pallescens*, selected for dieldrin resistance through exposure to residual deposits, showed some increased resistance apparently coupled with reduced oviposition ([38]). Filter flies, *Psychoda alternata* Say, have been reported as DDT-resistant ([39]) and as chlordane-resistant ([40]).

At the time that house fly resistance to DDT was first evident in Italy, 1945-46, it was noted that certain strains of *Culex pipiens autogenicus* Roubaud were also less affected by this residual spray ([41]). By 1950 these strains had become resistant to combined residual deposits of DDT and chlordan ([42]). The adults of *C. pipiens* from Latina were resistant to DDT but the larvae remained quite susceptible ([43]). *C. molestus* (*C. pipiens autogenicus*) was reported as DDT-resistant in Greece ([44]). In the United States larvae of *C. pipiens* collected from heavily treated areas showed a significantly lower mortality when exposed to DDT than did larvae from untreated areas ([55]). In a laboratory strain, *C. fatigans* Wied. (*C. quinquefasciatus* Say) showed a greatly increased resistance to DDT and gammexane (BHC) ([45]). Field strains of this species were also suspected of DDT resistance in Venezuela ([44]). By 1951 *C. tarsalis* in the United States had developed

resistance to DDT as well as toxaphene, lindane, aldrin (1,2,3,4,10,10-Hexachloro-1,4,4a,5,8,8a-hexahydro-1,4,5,8-dimethanonaphthalene), and heptachlor applied as larvicides ([46]).

Among the other culicine mosquitoes in the United States, adults and larvae of the salt marsh species, *Aedes sollicitans* (Wlkr.) and *Ae. taeniorhynchus* (Wied.), developed not only DDT resistance but resistance to other halogenated hydrocarbons to a lesser degree ([47, 48]). *Ae. nigromaculis* was proved resistant to DDT larvicides in California during 1949, ([49]) and indications of DDT resistance were also reported for *Ae. dorsalis* ([50]).

In general only scattered reports of resistance in anopheline mosquitoes have been forthcoming. Laboratory tests with a selected strain demonstrated that adults of *Anopheles quadrimaculatus* Say could develop some DDT resistance ([51]), and recent studies in the Tennessee Valley area of the United States have indicated some resistance of this species to DDT larvicides ([52]). Subsequent work by these investigators has revealed factors other than resistance, which could account for the differences observed. It is of practical significance that when both larvae and adults of insects are subjected to treatment with DDT and related compounds, resistance in the population is acquired at an accelerated pace. Larviciding alone, particularly in the case of mosquitoes, apparently produces a resistant population more rapidly than when only adulticides are used. To a large extent this is probably due to the fact that a much larger proportion of the population is usually exposed in larviciding operations.

Increased numbers of *A. albimanus* have been observed in DDT-treated houses in Panama and it is believed that resistance is developing ([53]). Increases in *A. albimanus*, *A. albitarsis*, and *A. pseudopunctipennis* populations have been observed in DDT-treated areas of Venezuela ([54]). *A. darlingi* presents a conflicting picture since in some regions it has been eradicated ([55]) while in others it persists despite DDT residual applications ([54, 55, 56, 57]). This paradoxical situation may arise from the anthropophilic and zoophilic tendencies of various strains of the species ([54]). *A. elutus* (*sacharovi*) in Greece shows increasingly larger numbers of adults in treated areas which are able to survive and lay fertile eggs ([58]). Reports indicate that *A. maculipennis* in Greece ([44]) and *A. superpictus* in Turkey ([55]) are developing resistance to DDT. Anophelines in Africa (*A. gambiae* and *A. melas* in Nigeria and *A. gambiae* in Uganda) have altered their typical behavior patterns; they apparently enter DDT-treated houses only to feed and rest on outside unsprayed surfaces ([78, 79, 80]).

Within the past two years the resistance pattern has expanded to include the human body louse *Pediculus humanis corporis*, the German cockroach *Blattella germanica* (L), the oriental roach *Blatta orientalis* L. ([77]), the common bed bug *Cimex lectularius* L., and various species of fleas. In Korea DDT resistance in the human body louse created a serious problem among prisoners of war ([59]). Studies revealed that head lice were still susceptible to DDT while body lice could be controlled for the time being by various halogenated hydrocarbons other than DDT and methoxychlor ([60]). Resistant body lice have also been reported from Egypt ([55]) and Japan ([85]). Resistance in the German cockroach has been developed for chlordan and lindane in certain sections of the United States ([55, 61, 62]), and DDT- and BHC-resistant strains have been selected in laboratory studies ([63]). DDT-resistant strains of the bed bug have been reported from Greece ([58]), Hawaii ([64]), the Belgian Congo ([65]), and the United States ([81]). Fleas resistant to DDT dust applications have been mentioned in reports from Greece (*Pulex irritans*) ([44]), the Near East (*P. irritans*) ([55]), the United States (*Ctenocephalides* spp.) ([84]), and South America (*P. arritans*, *Xenopsylla cheopis*, *Ceratophyllus loninensis*, *Polygenis* spp.) ([44, 74, 75]). Laboratory studies in the U.S. with the oriental rat flea, *X. cheopis*, demonstrated that DDT resistance may be developed in this species through sublethal exposures to dust applications ([66]). Experiments in Chile showed that the effect of DDT on *Triatoma infestans* decreased considerably within 3 to 4 months after which time its action was practically imperceptible ([76]).

To date, resistance to modern insecticides has been reported from 33 countries or regions among 35 species of insects of vectoral or pestiferous significance (Table 1). From this it is apparent that the occurrence of effective counteraction to public health insecticides is widespread, both geographically and entomologically.

Types and Mechanisms of resistance.

Natural resistance to certain insecticides and operational procedures may exist in certain species of insects and may be physiologic, morphologic, or ecologic in nature. Natural resistance does not arise as the result of population selection pressures from insecticides but rather is already present at the time the control measures are applied and leads to their failure. For example, DDT has not been effective against the Mexican bean beetle, *Epilachna varivestis* Mulsant, and certain other insects. A majority of the naturally resistant individual insects tested initially possessed a physiologic mechanism for detoxifying

DDT ([86]). Inherent morphologic differences between strains have been credited with determining the capabilities of certain insects to withstand exposure to insecticides ([31], [108]). Residual applications of DDT have not been equally successful in controlling all species of mosquitoes. The behavioristic and ecologic patterns of *A. minimus flavirostris* in the Philippines have been reported to interfere with their control by residual spray ([55]).

In contrast to these types of natural resistance there are the various forms of resistance induced in populations through intensive exposure to insecticides which, as they progress, produce a change in the composition of the population. Induced resistance may arise from the following types of mechanisms:

1. Physiologic mechanisms which permit detoxification of the insecticides within the insect.

2. Physiologic and morphologic mechanisms which permit the partial exclusion of the insecticides, such as the protective stupefaction shown by scale insects to HCN ([5, 7]), and the structural differences discussed for certain house fly strains ([31]).

3. Behavioristic or physiologic mechanisms which act to separate the species ecologically from the insecticide applications before lethal dosages have been obtained, e.g., the changes in resting habits of some strains of house flies ([40, 87]) and of *A. gambiae* ([78, 79, 80]).

The nature and causes of house fly resistance to the newer organic insecticides are still highly uncertain. Numerous differences between susceptible and resistant flies have been suggested, among which the simplest is greater general vigor in those individuals which survive exposure and hence in their progeny ([88]). The term vigor, however, has never been clearly defined.

Only a few investigators have as yet accepted the challenge of fundamental research on the complex problem of resistance from a biochemical viewpoint; but these, in probing deeper into the physiology of the house fly, have obtained significant results. The ability of resistant flies to convert absorbed DDT to the relatively nontoxic derivative DDE [2,2-bis-(*p*-clorophenyl)-1,1-dichloroethylene] has been demonstrated ([89, 90, 91, 92, 94, 95, 96]). A similar reaction occurred with the bromine analog of DDT ([93]).

In recent studies, significant correlations have been obtained between the degree of resistance or survival of house flies exposed to topical applications of DDT and the conversion of DDT to DDE ([97]). An

index for measuring the degree of DDT-resistance in various strains of flies was proposed. The index figure would correspond to the percentage conversion of absorbed DDT to DDE two hours after application of a measured dosage of approximately 5 to 10 micrograms of DDT per fly. Based on the strains tested, the following general classification has been recommended by PERRY et al. ([97]) as one measure of house fly resistance to DDT:

Resistance Index	Resistance Classification
0 - 10	None
11 - 20	Slight
21 - 35	Moderate
36 - 55	Medial
56 - 75	High
> 75	Extreme

The ultimate usefulness of this device will be determined only after it is known what proportion of resistance is by the conversion of DDT to DDE. In the meantime, from a practical viewpoint, it could be assumed that a strain having an index of 0 to 10 was a susceptible strain and could be controlled with DDT.

The conversion of DDT to DDE *in vivo* appears to be controlled by an enzyme for it is totally inhibited when flies are killed by heat ([91]). This reaction is also interfered with by application of certain chemicals such as piperonyl cyclonene ([98, 93, 99]), and by certain structural analogs of DDT, e.g., DMC [1,1-bis-(*p*-chlorophenyl) methyl carbinol] ([100]). The latter studies have shown that DMC enhances the toxicity of DDT to resistant flies by reducing the ability of the insects to perform the conversion of DDT to DDE, and that mortality is then roughly proportional to the degree to which this conversion is suppressed. It is postulated that DMC replaces DDT as a substrate for the detoxifying enzyme, thus leaving the insecticide free to exert its lethal effect. Recently, an enzyme which can convert DDT to DDE *in vitro* has been isolated from resistant flies ([101]). Thus, the rapid dehydrochlorinating of DDT to DDE seems to have been partially explained. This same enzyme is either absent in a susceptible strain or has such a low order of activity that its presence has not been detected.

These studies present a more coherent and encouraging picture in explaining resistance from the physiologic viewpoint; yet this theory of detoxification of DDT, like many others, is not without its discrepancies. In some strains of resistant flies the measured rate of conversion to DDE often seems too slow ([102]), and resistant flies which survived exposure to DDT, in spite of having converted large amounts of DDT to

Table 1

REPORTED DISTRIBUTION OF INSECTICIDE RESISTANCE AMONG INSECTS OF MEDICAL IMPORTANCE
JULY 1953

	United States	Canada	Mexico	Puerto Rico	Trinidad	Panama	Costa Rica	British Guiana	Ecuador	Venezuela	Brazil	Peru	Argentina	Chile	Italy	Sardinia	Greece	Turkey	Sweden	Denmark	England	Egypt	Nigeria	Uganda	Belgian Congo	South Africa	Levantine States*	India	Ceylon	Australia	Korea	Japan	Hawaii
S																																	
ipiens	P [55]														P [41,42]		P [44]																
quefasciatus (fatigans)				p [44]						P [44]																		O [35]					
alis	P [46]																																
ollicitans	Pb [47,48]																																
iorhynchus	Pb [47,48]																																
alis	P [50]																																
omaculis	P [49]																																
es elutus (sacharovi)																	p [58]																
lipennis																	p [44]																
rpictus																		por b [55]															
iae																							B [78,79]	B [80]									
ingi								b [55]		b [54]	B [56]		B [44]																				
rimaculatus	Por B [51,52]																																
s																							B [78,79]										
manus				O [44]		Por B [53]	O [44]			b [54]																							
tarsis										b [54]																							
dopunctipennis			O [72,73]							b [54]																							
ES																																	
omestica	Pb [32,33]	P [70]	p [44,71]	p [44]	p [44]	p [44]				p [71]	p [44]	p [44]	P [44]		P [29,30]	Pb [44,82]	P [44]		P [31]	P [67]	P [68]						p [69]			P [44]	o [44]	o [44]	
icina																						P [37]		O [55]			PB [36]	O [44,55]	O [44,55]				
lo																												P [35]	O [40]				
omus pappatasii																	p [44]																
'a alternata	p [39,40]																																
rritans									P or B [74,75]			p [44]					p [44]										p [55]						
phalides spp.	p [84]																																
lla cheopis	P [66]								P or B [74,75]																								
hyllus lonimensis									P or B [74,75]																								
is spp.									P or B [74,75]																								
GIES																																	
ectularius	P [81]																p [58]								p [65]								p [64]
us h. corporis																						P [55]					p [55]				P [59]	P [65]	
a infestans														P [76]																			
la germanica	P [55,61 62,63]																																
orientalis															P [77]																		

banon, TransJordan, Palestine, Israel, and Cyprus.

ological Resistance; the ability through biochemical processes to withstand a toxicant after it has entered the body.
ioristic Resistance; the ability through protective habits of behavior to avoid injurious contact with a toxicant.
esistant.

ES	United States	Canada	Mexico	Puerto Rico	Trinidad	Panama	Costa Rica	British Guiana	Ecuador	Venezuela	Brazil	Peru	Argentina	Chile	Italy	Sardinia	Greece	Turkey	Sweden	Denmark	England	Egypt	Nigeria	Uganda	Belgian Congo	South Africa	Levantine Sta	India	Ceylon	Australia	Korea	Japan	Hawaii
pipiens	P 55														P 41.42		P 44																
nquefasciatus (fatigans)				p 44						P 44																		0 35					
salis	P 46																																
sollicitans	Pb 47.48																																
niorhynchus	Pb 47.48																																
salis	P 50																																
romaculis	P 49																																
les elutus (sacharovi)																	p 58																
ulipennis																	p 44																
erpictus																		por b 55															
biae																							B 78.79	B 80									
lingi								b 55		b 54	B 56		B 44																				
drimaculatus	Por B 51,52																																
as																							B 78.79										
imanus				0 44		Por B 53	0 44			b 54																							
itarsis										b 54																							
udopunctipennis			0 72.73							b 54																							
IES																																	
domestica	Pb 32.33	P 70	p 44.71	p 44	p 44	p 44				p 71	p 44	p 44	P 44		P 29.30	Pb 44.82	P 44		P 31	P 67	P 68						p 69			P 44	o 44	o 44	
vicina																						P 37		0 55			PB 36	0 44.55	0 44.55				
ulo																												P 35	0 40				
tomus pappatasii																	p 44																
da alternata	P 39.40																																
irritans									P or B 74.75			p 44					p 44										p 55						
ephalides spp.	P 84																																
ylla cheopis	P 66								P or B 74.75																								
phyllus lonmensis									P or B 74.75																								
nis spp.									P or B 74.75																								
EGIES																																	
lectularius	P 81																p 58								p 65							p 64	
lus h. corporis																						P 55					p 55				P 59	P 65	
ma infestans														P 76																			
lla germanica	P 55.61 62.63																																
orientalis															P 77																		

ebanon, TransJordan, Palestine, Israel, and Cyprus.

iologic Resistance; the ability through biochemical processes to withstand a toxicant after it has entered the body.
vioristic Resistance; the ability through protective habits of behavior to avoid injurious contact with a toxicant.
Resistant.
letters - Confirmed by experimentation.
se - Based on field observations only.

: work on *A. quadrimaculatus* in the United States (51, 52) has revealed factors other than resistance, which could account for the differences observed.
e of *A. gambiae* and *A. melas* in Nigeria (78, 79), and of *A. gambiae* in Uganda (80), the behavioristic pattern may be an inherent characteristic of the and not related to insecticides.

DDE, may still contain enough unchanged DDT within their bodies to kill several susceptible flies ([89, 91, 92, 93, 96]). What prevents this DDT from exerting its lethal effect? It is not the mere presence of DDE, for the pretreatment of susceptible flies with DDE has failed to confer resistance upon them ([102]). If the site of detoxification were at the site of action of DDT, or if DDT were detoxified before it reached the site of action, then the mere presence of DDT in tissues, especially the fatty ones, should be of no consequence. Contrary to expectations, however, the remaining unchanged DDT in the body of the resistant fly is not stored chiefly in the fat body but is well distributed in various tissues ([103]).

The rate of respiration in susceptible and DDT-resistant flies normally is equal; but when flies are exposed to DDT, this rate in susceptible strains increases markedly after delays of from a few minutes to four hours with high or low dosages, respectively ([99]). Under the same treatment resistant flies increase their rate of respiration much less than susceptible flies, and comparatively low maxima are obtained. When piperonyl cyclonene is added to the DDT to inhibit the detoxification process, the respiration curves of the resistant strain resemble those of the susceptible flies but reach lower maxima. Hence, it is concluded that the conversion of DDT to DDE, although of major importance in survival, is not the only factor in resistance.

In addition to the house fly, *M. domestica*, several insects of agricultural importance, such as the Mexican bean beetle, *E. varivestis*, the differential grasshopper, *Melanoplus differentialis* (Thomas), and the red-banded leaf roller, *Argyrotaenia velutinana* (Walker), which exhibit natural resistance to DDT, have been shown to convert DDT to DDE ([86]). However, the mechanism of resistance to DDT cannot be said to be the same in all insect species which have exhibited resistance to this powerful insecticide. *Trogoderma* larvae, for example, which have natural resistance to DDT do not convert the latter to DDE ([104]).

A somewhat different line of approach has been taken by Sacktor ([105, 106]) who showed 1) that adults of a DDT-resistant strain of flies had 50 percent more cytochrome oxidase activity than a susceptible strain, and 2) that pupae of the resistant strain had less cytochrome oxidase activity than those of the susceptible strain but performed a higher percentage of their respiration via a cyanide insensitive system, possibly flavin. Since DDT inhibits the respiratory enzyme cytochrome oxidase ([107]), one could see that resistant flies which possess more of the enzyme would be in a better position to withstand a partial blocking of this vital metabolic pathway. Since the conversion of

DDT to DDE *in vitro* suggests that oxidation-reduction reactions might play an important role in this change, the detoxification mechanism might well be interwoven with a biologic oxidation-reduction system of which cytochrome oxidase is a part ([102]). This possible relationship is now under investigation (*).

While it has been claimed that structural differences, such as thickness and pigmentation of the tarsi, pulvilli, and articular membranes of the tarsal joints, exist between susceptible and resistant flies ([31, 108]), other studies failed to show any noticeable morphologic differences among strains of varying susceptibility to DDT ([109]). It might be expected that a slower rate of absorption through thickened integument would protect such flies. While it has been determined by laboratory tests ([110]) that a slow rate of absorption contributes to apparent resistance in flies, it has not yet been established whether a thickened integument is involved. However, these factors do not seem to provide an answer as to the mechanism of resistance, especially since resistance is independent of the route of administration ([111, 94, 82]). Greater tolerance in resistant flies for high and low extremes in temperature ([31]), or an increase in the duration of the life cycle of DDT-resistant strains of flies ([112]), may contribute to some extent to the overall mechanism of resistance but evidently cannot be solely responsible for imparting resistance to the fly.

Numerous observations have been made regarding the behavioristic responses of some insects to insecticide-treated surfaces, for example, the tendency of resistant flies to rest more on untreated horizontal surfaces than on treated walls ([113, 87, 40]). Similarly, some flies have adopted the stable fly habit of sitting still on one spot for extended periods of time ([114]). Resistance due to changes in resting habits of *M. vicina* has been reported ([36]). Behavioristic resistance has also been shown in several species of malaria mosquitoes ([78, 79, 80, 115, 116, 53]) and in certain agricultural insects ([117]).

Evidence would seem to indicate the genetic inheritance of protective mechanisms, but the method of action is exceedingly varied and has been satisfactorily analyzed only in isolated cases. Resistance to HCN fumigation by red scale has been shown to be inherited as a simple sex-linked factor ([10, 11]). A single, incompletely dominant autosomal gene was found responsible for susceptibility and resistance to knock-

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(*) Cooperative studies on this problem are being carried out at the Entomology Branch of the Army Chemical Center, Maryland, and at the Technical Development Laboratories, CDC, Savannah, Georgia.

down and DDT in house flies ([118]). In studies with reciprocal crosses of resistant with susceptible strains of the house fly, autosomal multiple gene inheritance was thought responsible ([40]). The general complexity in the inheritance of resistance to DDT is illustrated in reciprocal crosses of various DDT-resistant strains of house flies which indicate considerable variation in the genetic composition of these strains ([119]). Studies on the transmission of DDT resistance in the German cockroach indicated that the inheritance mechanism was complex and involved both chromosomal and cytoplasmic factors; the chromosomal factors were considered as both autosomal and sex-linked ([120]).

Field strains of DDT-resistant house flies, regardless of level of resistance, which have been reared in the laboratory for successive generations in the absence of DDT have shown a gradual reversion to susceptibility ([68, 71, 72, 88, 121, 122, 123]). This reversion suggests the existence of a factor which selects against resistant flies in an unexposed population. The nature of this factor remains unknown. A similar trend has occurred with lindane-resistant flies when they were not exposed to any insecticide ([123]). Little evidence of any significant degree of reversion has been observed in the field ([44]). This difference in field and laboratory experiences may be due to sublethal insecticide residues maintained through the widespread agricultural and household use of DDT and the persistence of DDT residuals over a number of years. The latter is further borne out by the fact that a strain of flies resistant to BHC, which is more volatile and shorter lasting than DDT, apparently reverted partially ([44]).

Although a substantial amount of information is available on house fly resistance, little is known about the mechanism of resistance to DDT in other insect vectors of disease, especially mosquitoes. Thorough study of the biochemical reaction in the insects is needed to support observations of acquired behavioristic patterns.

So far, this discussion of insect resistance to insectides has been limited largely to DDT since to date the majority of investigations on this subject have been concentrated on this compound with too little attention being given to the others. Studies using susceptible house flies and *Aedes* mosquito larvae as test insects for bioassay ([124]) showed that resistant flies of the Orlando strain could metabolize 5.9 micrograms of chlordan and 4.0 micrograms of toxaphane per fly of either insecticide. Workers at the Technical Development Laboratories of the Communicable Disease Center in Savannah, Georgia, have demonstrated by chemical and colorimetric methods of analysis, as well as by microbioassay techniques, that certain strains of resistant flies are able to

metabolize heptachlor, chlordan, lindane, and diledrin. Identification of degradation products of these insecticides is now in progress.

The task of establishing the mechanism of resistance to an insecticide is by no means a simple one. It is often complicated by the multiplicity of factors involved. Nevertheless, a good deal of progress has been made with regard to the mechanism of resistance to DDT.

Significance and Future Outlook of Resistance.

What is the significance of insect resistance to insecticides and what can be done about it?

The immediate problem is the widespread resistance among house flies to a majority of the chlorinated hydrocarbon insecticides. This relates directly to health in that further reduction of enteric diseases and infant mortality through fly control, in areas where resistance occurs, cannot be assured by the use of present-day residual formulations. The success of residual spray in fly control has been a major factor in the popularity of vector control programs and their endorsement by the public. Even though most of the new materials are still effective against malaria vectors public support will not be as enthusiastic as before fly resistance occurred. Alleviation of this complication would give a great impetus to the further development of vector control programs throughout the world. A more recent problem of importance is the development of resistance to DDT by body lice. The fact that thus far lindane formulations can be substituted against DDT-resistant lice renders this a less pressing difficulty at the moment, but it is one that must remain under close scrutiny.

The potential importance of the resistance problem is a matter for speculation. There have been reports from widely scattered areas of resistance of mosquitoes, including several « malaria vectors ». The significance of this will depend upon the degree of resistance which may subsequently be acquired by these insects and upon its geographical extent. Naturally, one wonders if the reporting of resistance, either suspected or confirmed, of malaria vectors from such widely distributed countries as Greece, Turkey, Panama, Venezuela, the United States, and Africa, is an ominous warning of future trouble. What would happen to the incidence of malaria if vectors should become resistant in once highly paludic areas that have recently been essentially freed from the disease by the use of residual insecticides? Can countries which have not yet received the benefits of insecticides look forward to only

temporary reductions in the occurrence of vertor-borne diseases? It has been estimated that 5 million deaths and 100 million illnesses have been prevented since 1942 by the use of DDT for controlling arthropod vectors of disease ([125]). Any circumstance which would hinder the continuation of such lifesaving procedures would be of paramount significance.

The early successes with DDT led many health authorities to believe that the panacea for all insect control problems had been found. This attitude was somewhat unrealistic since prior to the advent of DDT insects had developed resistance to a wide variety of insecticides. There was no assurance, therefore, that a similar condition would not be manifested with DDT and the possibility should have been anticipated. Events have demonstrated that DDT is not unique in this respect and now the other extreme is sometimes heard, that resistance to insecticides by all insect vectors is inevitable. One should not, in our opinion, view the problem too pessimistically. A careful examination of the records shows that resistance among the more important disease vectors is still relatively limited. In this document, we list 35 species of insects of public health importance which have been reported to be resistant. Among these, 26 species have been confirmed as resistant on the basis of experimentation and only 19 of these are proved disease vectors of importance. In view of the thousands of tons of DDT and related insecticides which have been used during the past several years, this record of resistance, while disappointing, should not be considered catastrophic. Some species, such as *A. darlingi*, have been eradicated from certain areas without the appearance of resistance, whereas in others they have exhibited the ability to sustain themselves in spite of control operations. A « middle-of-the-road » attitude toward the resistance problem seems to be indicated for the present. While some species are already highly resistant and others seem to be developing resistance in varying degrees, it also appears that some species may never develop a significant degree of resistance

Recommendations for the elucidation of this problem unfortunately cannot be specific. Currently, the utilization of various combinations of the available techniques affords the most satisfactory attack. Among insects of public health importance, resistance to insecticides has been acquired to a higher degree and on a wider scale by house flies than by any other species. We can both profit by and take some encouragement from the knowledge and experience gained from this circumstance. To date, the other species which have developed resistance have generally followed the same course as the house fly except at a more gradual rate.

When house flies first demonstrated their resistance to DDT, other residual-type insecticides were, for a time, successfully substituted for that compound. Most of the culicine mosquitoes which became resistant to DDT were, likewise, effectively controlled for varying periods of time by other chlorinated hydrocarbon insecticides. The human body louse in Korea which is resistant to DDT is susceptible to lindane. Assuming that this same pattern would be followed by other disease vectors which might become DDT-resistant, it is reasonable to believe that substitute residual insecticides which are already available would be successful at least temporarily. Since resistance in these other vectors has developed much less rapidly than it has in house flies, it is reasonable to expect that these DDT-substitutes would have a correspondingly longer period of effectiveness before resistance to them appears.

The following suggestions are made in regard to future vector control programs:

1. An attitude of careful watchfulness must be maintained to detect the first indication of resistance among presently susceptible species. A widespread surveillance program should be initiated to determine the susceptibility status of vectors to DDT or other residual insecticides for the information and consideration of program planners in initiating and revising vector control programs. Some simple field testing apparatus and procedure, such as the one recently developed at the Technical Development Laboratories of Communicable Disease Center ([126]), should be used regularly and extensively for this purpose.

2. Fundamental research on new insecticides or techniques should be expanded. Those responsible for financing control programs must be made to realize, if serious setbacks in the progress of disease control are to be avoided, that research is an integral part of such programs. Studies of the bionomics of resistant and susceptible strains of insects may provide clues to methods for overcoming the resistance problem in some species. Basic research on insect physiology and morphology is needed to elucidate the mechanism of resistance and to devise approaches for nullifying the detoxification process, if this is the basis of resistance. Practical laboratory and field studies should go forward simultaneously. Applied research on new chemicals, improved formulations, and new techniques may offer the most promise for immediate effectiveness in current control programs which must be kept in operation.

3. Past experience has shown that house flies and some mosquitoes develop a higher degree of resistance in less time when both immature and adult stages are exposed to the insecticides ([112, 127]).

Resistance of culicine mosquitoes to DDT in Florida and California first appeared and reached its highest degree in areas where both larviciding and adulticiding operations were conducted. The only reports of resistance for the principal malaria vector in the United States, *A. quadrimaculatus*, have been confined to localities where both adults and larvae were exposed to applications of DDT over a period of several years. It would appear desirable, therefore, to restrict malaria control operations to the use of residual sprays in homes and outbuildings, and to avoid the use of larvicides wherever possible. When it is necessary to larvicide, chemicals should be selected which are as different as possible from those being used as residual spray.

4. House flies resistant to DDT usually develop resistance rather rapidly to other chlorinated hydrocarbon insecticides. To date, a satisfactory substitute material has not been found. Certain new materials, such as the organic phosphorus compounds, do show some promise and should be explored further. Most of these formulations are too toxic to permit their use as over-all residual spray. However, in recent months a few compounds have appeared which compare favorably with DDT in so far as toxicity to man is concerned. These have not proved to have the long residual action of DDT, but research in this field is still relatively new, and it can be hoped that compounds of this type having a long residual action and a low order of toxicity for man might be developed. Two of these, malathon (0.0-dimethyl dithiophosphate of diethyl mercaptosuccinate) and NPD (tetra-n-propyldiothionopyrophosfate) have proved to be effective larvicides against some resistant mosquito species in the United States at dosage of approximately 0.4 lb. per acre ([128]). If resistance to chlorinated hydrocarbon residuals should make their continued use ineffective, larviciding with organic phosphorus compounds could be substituted for residual spraying for control of mosquito vectors in many situations. Where larviciding and residual spraying are carried on simultaneously, it would seem desirable to substitute such organic phosphorus compounds for chlorinated hydrocarbon insecticides in the larviciding operation, with a view to delaying the development of resistance to the latter.

As mentioned previously, the organic phosphorus compounds of low mammalian toxicity which have been developed to date have a relatively short residual effectiveness. Further investigations, however, may show that, in emergency situations, these materials could be used and more frequent applications employed.

New techniques may also make possible the use of some of the more toxic organic phosphorus compounds. Parathion (0,0-Diethyl-0-*p*-nitro-

phenyl thiophosphate)-impregnated cotton twine festooned from the ceilings and rafters of barns in the vicinity of Savannah, Georgia, has given excellent control of highly resistant house flies for several months without replacement of the treated cords ([129]). This technique needs further development but appears to offer one solution to the vexing problem of resistant house fly control in many situations.

The use of organic phosphorus compounds in fly baits exposed by several methods has shown promising results against resistant house flies in several localities in the southern United States ([130, 191, 132]).

Other new approaches or new modifications of old-established techniques for the use of organic phosphorus compounds and other new groups of insecticides can be expected to result from an expansion of applied research on vector control.

5. The use of repellents in disease vector control is still largely an unexplored field. Repellents were used extensively and effectively by the U. S. Armed Forces during World War II, both by individual applications to his person by each soldier and by impregnation of uniforms. Some interesting results have been reported from the use of repellents for fly control around animal pens ([133]). Adequate research in this field may result in new approaches to the control of vector-borne diseases. The possible application of repellents to dwelling surfaces, either indoors or outdoors or both, broadens the field of materials which could be used as compared to those with which skin contact is required.

6. One of the more important developments resulting from the resistance problem in house flies has been the realization of the importance of good sanitation practices. Aside from the value of such practices in the control of flies, good environmental sanitation has an over-all health value far beyond that inherent in the use of insecticide programs. In fact, where feasible, this is the preferred method of vermin control, irrespective of the resistance problem.

If resistance of disease-vectoring mosquitoes should develop to the point where available residual insecticides are ineffective, attention will have to be redirected to environmental practices which would reduce the breeding potential, where this is feasible.

New chemicals are being developed daily: new facts concerning the bionomics and physiology of disease vectors are being revealed. We believe that the capable army of scientists at work in this field will find solutions to our problems. Until something new and better is devised, however, we must make more effective use of the anti-vector procedures available to us at the present time.

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