PAPERS AND PROCEEDINGS OF THE 13th ANNUAL MEETING

OF THE AMERICAN MOSQUITO CONTROL ASSOCIATION HELD JOINTLY WITH THE FLORIDA ANTI-MOSQUITO ASSOCIATION MIAMI BEACH, FLORIDA, APRIL 28-MAY 2, 1957

PART I

A WORLD WIDE COOPERATIVE PROGRAM ON INSECT RESISTANCE TO INSECTICIDES

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The majority of persons concerned with public health today are no doubt aware of the existence of WHO, know it to be a specialized agency of the United Nations and realize that it has certain international responsibilities. However, it is unlikely that the aims and objectives of the Organization and the ways in which these are achieved are as widely understood. I propose therefore to outline and discuss one facet of its program, hoping that this will not only be of interest to those concerned with insect control, but that it will also provide some indication of how the solution to a problem common to all countries might be found through international collaboration.

WHO's fundamental goal is the attainment by all peoples of the highest possible level of health and one of its main functions is to act as a directing and co-ordinating authority in international health matters. Its membership now includes almost every country of the world and its interests extend into all branches of public health.

It is natural therefore that it should have a special interest in the control of diseases of man transmitted by insects and that work on this subject should always be given an important place in its programs. During the past ten years, emphasis has been placed on the development of large-scale vector-borne disease control projects and for the most part these have been remarkably successful.

For example, serious outbreaks of typhus fever are now rare; plague is being controlled where epidemics were once regular events; in some areas leishmaniasis and onchocerciasis have almost disappeared; hundreds of millions of people are being protected from malaria and the world-wide eradication of the disease is now considered to be technically possible.

These gains are of course due almost entirely to the high degree of efficiency of the residual insecticides. Since World War II their use in public health programs has increased steadily until the stage has been reached where almost complete reliance is being placed upon them for the control of the majority of vector-borne diseases. Insecticides-resistance has, as a result, particular significance and it is generally accepted that this phenomenon is the most important problem confronting public health authorities at the moment.

The situation is aggravated by the fact that impressive social and economic gains have resulted from the large-scale application of insecticides and further advance rests to a large extent on the ability of health authorities to maintain and extend

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their control over insect vectors of disease.

However, because of the emergence of resistance this has become severely diminished in many parts of the world and the welfare of millions of persons now depends on a solution to the problem.

Let us consider for a moment the present status of physiological resistance from a health viewpoint.

The number of proved cases has increased steadily since 1946, when resistance in house flies was reported from Sweden, and there is now evidence to show that at least ten species of insects are affected.

The house fly is now almost universally resistant to the chlorinated hydrocarbon insecticides. In addition, it has been reported that effective control of this insect can no longer be achieved with the organophosphorus compounds in Denmark and Florida in the U. S. A.

Physiological resistance has been proved to exist locally in at least five species of anophelines; namely, *A. sundiacus* in Indonesia and *A. stephensi* in Saudi Arabia, both to DDT; *A. gambiae* in Northern Nigeria and *A. quadrimaculatus* in Mississippi, U. S. A., to dieldrin; and *A. sacharovi* in Greece to both groups of insecticides.

WHO recently undertook a survey of the susceptibility of body lice to insecticides throughout the world. The results of this survey reveal that whereas susceptibility of lice to pyrethrins appears to be almost universal, significant resistance to DDT exists in many parts of the world and that there are several indications of resistance to BHC.

In *Aedes aegypti* two instances of resistance have been recorded. The first one is by the Director of the Pan-American Sanitary Bureau, who in his 1955 report states that "since the fourth cycle of DDT treatment in 1953 in Ciudad Trujillo, Dominican Republic, the *A. aegypti* index has been generally rising despite continuation of spraying cycles. It is concluded that this species has developed resistance to DDT." The second emanates from Trinidad, where concentrations of up to 1 p.p.m. of DDT gave no certainty of kill. Laboratory examination of larvae from the island showed a high degree of resistance. In addition, reports of resistance have been made in other areas of Latin America, but up to now these have not been published with the necessary supporting quantitative data.

Culex fatigans has been known for many years to possess a high degree of natural resistance to DDT which is often increased by exposure to residual insecticides. However, reports reveal that other species have become resistant to the chlorinated hydrocarbons, including *C. tarsalis* in California and *C. molestus* in Italy.

In addition, evidence of a conclusive character has been published showing that resistance exists in 12 species of insect vectors of minor or potential danger to man and that in 15 species resistance has been indicated but not proved.

There is every indication that the problem is outgrowing our ability to deal with it. Resistance to the chlorinated hydrocarbon insecticides has been known to exist for at least 10 years, but in that time we have not developed measures to prevent it. At the advent of DDT man's knowledge of biology was insufficient to permit him to grapple adequately with the problems that have resulted from its widespread use, and the use of similar chemicals; furthermore, insufficient scientific progress has been made since then. For example, our knowledge is imperfect now, as it was then, regarding the exact mode of action of the chlorinated hydrocarbon insecticides, and after almost a decade of experience we are still unable to describe with accuracy the causes of resistance.

It is reasonable to expect that having been presented with a means of vector control unparalleled in efficiency, man would have made every effort to retain its effectiveness by ensuring that an amount of research commensurate with its value and the extent of its use would be carried out. However, it does not appear that this has occurred.

During 1955 and 1956 WHO undertook a world-wide study to ascertain the extent of research being carried out on insect resistance and the potentialities for expanding research on this subject. One hundred twenty-four laboratories in 49 countries known or believed to be engaged in resistance research were approached. These were distributed as follows:

	Countries	Laboratories
Africa: South of the Sahara	11	20
America: North	3	33
America: Central and South	14	20
East Mediterranean	4	9
Europe	7	17
South-East Asia	1	2
Western Pacific	9	23

For the purposes of the study "research on resistance" was divided into two main groups. The first related to laboratory experimentation and the second to the field work. The former embraced biochemistry, genetics, physiology, morphology, biology and insecticide evaluation, while in the latter were included evaluation of insecticides, behavior, detection and biology.

It was found that in 47, or 38 percent, of the laboratories no research of any type on resistance was being performed. Fourteen of these (out of a total of 20) were in Africa; 14 (out of 20) in Central and South America; 2 (out of 9) in the East Mediterranean region; 3 (out of 17) in Europe; and 14 (out of 23) in the Western Pacific.

Sixty-six (53 percent) were engaged in laboratory research, although 15 were concerned with the evaluation of insecticides only.

This means that throughout the world no more than 51 laboratories are working on problems fundamental to the solution of resistance. Their location is interesting:

Two are in Africa: one in East Africa and one in West Africa.

North America has 27: 3 in Canada, 24 in the United States.

Two are situated in South America: one in Venezuela, one in Brazil.

Two are in the East Mediterranean region.

Europe has 11: one in Denmark, two in Germany, two in Italy, two in the Netherlands, one in Switzerland and three in the United Kingdom.

Western Pacific has 7: two in Australia, three in Japan, one in New Zealand and one in Malaya.

Thus the bulk of fundamental research on resistance is being performed in the U. S. A., Western Europe and Japan. Almost no work is being done in regions where insect-borne diseases are particularly important.

Only 41, or 32 percent, of the 124 laboratories were found to be performing field research. Twenty-one of these were concerned exclusively with the detection of resistance and 7 were working solely on the evaluation of insecticides. Five laboratories exclusive of these 28 were carrying out work on both subjects. This leaves only 8 institutions with what might be defined as a balanced program of field research on resistance. Of these, one was in Africa, three in North America, one in South America, one in the East Mediterranean, one in Europe and one in South East Asia.

The deficiency in field research on resistance is thus self evident. Services of this type should be an essential and integral part of every large-scale operating program, particularly as far as ecological and behavioral studies are concerned. Concentrated efforts on these lines could play a vital role in developing better and more economical programs and in delaying the onset of resistance where this is known to be potentially a problem.

A number of additional factors emerged from the study, affecting the quality and the quantity of research, which are not apparent from the statistics quoted above.

Much of the work being done, both in the laboratory and the field, is on a part-time basis. This is mainly due to inadequacy of funds and shortages in well-trained scientific and technical staff as related to the variety and breadth of problems requiring attention. The almost universal lack of money is reflected in a need for suitable equipment and physical necessities, such as rooms with temperature and humidity controls. In many countries research has only recently been started and

some time must still elapse before the first results will appear.

The importance of a better exchange of information between workers in the same and allied fields is stressed by scientists in almost every part of the world, particularly those in remote areas. This is related not only to published material but also to data which might not necessarily reach the technical press. There is also a widely-held belief that if some system could be evolved whereby advance information on articles awaiting publication could be made generally known, overlapping and waste would be avoided.

Many persons are of the opinion that publication channels as they exist today are inadequate for a rapid dissemination of scientific data, periods of up to 18 months often elapsing between the termination of a research project and the publication of the results.

All these facts were considered by an expert committee of WHO convened in July 1956 to advise the Director-General on the problem of resistance. This group concluded that "considering the magnitude and importance of operational programs for the control of insect vectors of disease, the proportion of funds devoted to research on the resistance problem is entirely inadequate and out of line with sound economic practice." As far as existing research is concerned, the lack of liaison and the inadequate exchange of information between workers could only give rise to "duplication of effort, increased costs and lowered efficiency."

On the basis of these findings the committee made a proposal with far-reaching implications. It recommended that a greatly accelerated effort be made on resistance research based upon world-wide scientific collaboration, with WHO assuming leadership for the co-ordination and stimulation of work on all aspects of the problem.

It is appreciated that "co-ordination" gives rise to different concepts in different individuals. To some it is synonymous with regimentation—a condition to be firmly resisted. To others it conjures up visions of something akin to organized plagiarism. Yet in modern public health it is far removed from either. Instead, it can and does mean a voluntary collaborative effort by scientists and field workers throughout the world to solve a problem common to mankind as a whole. There is little doubt that resistance justifies an approach of this nature. It appears unlikely, in the light of existing knowledge, that any one discovery will provide a complete solution to the problem. It is more probable that by piecing together the results of work performed by workers in different parts of the world a pattern will emerge from which it will be possible to draw certain conclusions.

But how is this to be achieved? How can the pieces be brought together and put into proper perspective?

The Director-General of WHO, who has referred to modern medical science as a "synthesis of all the disciplines that have as their ultimate aim the health of man," has written in his Report for 1956 of the role WHO might play in attaining this objective. He considers the "task of promoting the free exchange of information among research workers in the many branches of public health" to be a fundamental responsibility of the Organization. As far as international co-ordination of research is concerned, he states: "This aspect of the programs undertaken by WHO is related to one basic function of the Organization, which is to pool all available scientific and technical knowledge, constantly to appraise it, and to study its applicability to the solution of public health problems."

In line with this policy and with the authority of its governing bodies, WHO has initiated a program with the following general objectives:

1. *The collection and dissemination of information.* The Organization is acting as a depository for information on resistance from all sources and is distributing it to workers throughout the world. This service is still in its infancy and at present is related almost completely to

published material. However, there is an increasing amount of advance information becoming available and an extension of this is being encouraged. Up to now six information circulars have been distributed to research workers and contact has been made with almost 300 scientists in different parts of the world. As this two-way flow of information increases in volume, it is believed that all involved in the resistance problem will benefit.

2. *The stimulation of new research.* WHO's financial resources are too meagre to permit it to do anything but stimulate existing research institutes to do work in practical fields of international importance. The final decision for the allocation of funds for research must of necessity continue to rest with the national administrations or other authorities controlling the finances of laboratories. However, the Organization can and does provide small grants to laboratories with adequate leadership to assist in the procurement of equipment and in engaging technical personnel. It has been found that this type of support often has a catalytic effect on a total research program far in excess of the amount of money involved and at very much less cost than the value to the country concerned.

Financial support of an amount that will make an impression of substance to the research problem will continue to emanate from national governments, industrial bodies, universities, and, in particular, from the fund-granting foundations and agencies. WHO, through its contacts in different parts of the world, is in a favorable position to advise these bodies on the subjects in which the investment of funds might provide the greatest benefit.

3. *The co-ordination of existing research.* The Organization, through its staff and consultants, is building up a liaison system between laboratories designed to bring workers with common interests into personal relationship, with the aim of avoiding duplication and overlapping of effort.

4. *The procurement and training of professional and technical staff.* The fellowships program of WHO is being used to train both professional and technical staff. Governments may request assistance for key professional personnel to obtain advanced training. In addition, assistance is being given to national training programs for technical and auxiliary staff.

It is also planned that WHO should sponsor training seminars or symposia to which scientists actually working on research projects would be invited.

The exchange of scientific workers between different countries is another procedure which in specific circumstances is meeting an important need.

5. *The development of standard tests for determining resistance.* Accurate information on the pre-operational level of susceptibility of insect populations is an essential prerequisite to any program in which chemical control is contemplated. This permits an early definition of potentially dangerous areas to be made and provides a basis for comparison when the first signs of resistance appear. In addition, it is important that routine tests be performed throughout the course of a program to ascertain at an early stage any change in the susceptibility level.

The Busvine/Nash method has for a number of years been a means of providing such data on adult mosquitoes. Some of the data obtained with it have recently been assembled and published. In collaboration with the Expert Advisory Panel on Insecticides of WHO, a standard test method has been developed based upon this technique, and it is at present under trial in different parts of the world. This will provide an accurate and simple means of assessing susceptibility levels that will not only be comparable with earlier figures obtained with the Busvine/Nash method, but which permit comparison between resistance levels of the same species in different areas of the world.

Development of a standard test method for mosquito larvae is also well advanced

and this method will shortly be put into general use. The importance of this, particularly in respect to *Aëdes aegypti,* cannot be over-emphasized and it is hoped that it will be instrumental in bringing about clarity in areas where there is none at present.

Reference has already been made to the survey carried out between 1953 and 1956 on the susceptibility of lice. In this survey, a test method was used which was proposed originally by the U. S. Department of Agriculture laboratories in Orlando, Florida, to the Associate Committee on Insect and Rodent Control of the U. S. Forces. Although this technique is known to be prone to certain variables, its use as an accurate screening medium has been proved. It has recently been revised and is being adopted as an integral part of typhus control programs all over the world.

Test methods for determining the susceptibility of other insects of medical importance, such as flies and fleas, are also under study and will, it is anticipated, become available shortly.

6. *The procurement and testing of new insecticides.* It is important that new insecticides (or their formulations) be evaluated and put through field trials as soon as possible, so that their use on a wide scale is not delayed.

Work on the sorption of insecticides by mud walls is an example of this. In certain parts of the world, particularly Africa and Mexico, this phenomenon is a major problem, with the insecticide deposits on sprayed mud surfaces becoming ineffective in a matter of days. Collaborative work on formulations with anti-sorptive properties has made good progress and the Organization is at present sponsoring field trials with one of them in both Africa and Latin America.

7. *The sponsoring of meetings of scientists engaged in resistance research.* A meeting of the Expert Committee on Insecticides of WHO was held in 1956 and another is planned for this year. In July a group will be convened to study ways and means of bringing about effective coordination between individual national laboratories and between the laboratory and the field. Through these experts advice is obtained on all aspects of the resistance problem, together with an assurance that whatever form the Organization's program takes, it will be on realistic and scientific lines.

It is appreciated that a program of this type has many limitations. WHO does not play an executive role at the national level and can do no more than advise, coordinate and stimulate action. If the problem of resistance is to be solved, true international collaboration is essential: national governments to support more work, fund-granting agencies to provide the means to expand research where finances are limited. Above all, unrestrained collaboration between the scientific workers themselves is vital to the success of any scheme, whether proposed by WHO or any other body.

Bibliography

ANON. 1956. Report on laboratories performing research associated with the resistance of insects to insecticides. WHO/Insecticides/54, 1956, unpublished document.

BUSVINE, J. R. 1956. A survey of measurements of the susceptibility of different mosquitoes to insecticides. Bull. World Health Organization 15, 787–791.

GILKES, C. D., KELLETT, F. R. S. and GILLETTE, H. P. S. 1956. Yellow fever in Trinidad and the development of resistance in *Aëdes aegypti* Linn. to DDT formulations. W. Indian med. J. 5, 73–89.

GJULLIN, C. M. and ISAAK, L. W. 1957. Present status of mosquito resistance to insecticides in the San Joaquin valley in California. Proc. Calif. Mosq. Contr. Ass. (in press) 1957.

KEIDING, J. 1956. Resistance to organo-phosphorus insecticides of the house fly. Science, 123, 1173–1174.

LINDQUIST, A. W. 1957. Effectiveness of organo-phosphorus insecticides against house flies and mosquitoes. Bull. World Health Organization, 16, 33–39.

MOSNA, E. 1947. Su una caratteristica biologica del *Culex pipiens* autogenicus di Latina. Riv. di Parassitol. 8, 125–126.

PAN-AMERICAN SANITARY BUREAU. 1955. Annual Report of the Director, pp. 31.

WIESMANN, R. 1947. Untersuchung über das physiologische Verhalten von *Musca domestica* L.

verschiedener Provenienzen. Schweiz. Entom. Gesellsch. Mitt. 20, 484–504.

WORLD HEALTH ORGANIZATION. 1957. The work of WHO 1956. Annual report of the Director-General to the World Health Assembly and to United Nations. Official records of the World Health Organization No. 75, pp. 233.

WORLD HEALTH ORGANIZATION. EXPERT COMMITTEE ON INSECTICIDES. 1956. Seventh Report. WHO/Insecticides/53, unpublished document.

WRIGHT, J. W. and BROWN, A. W. A. 1957. Survey of possible insecticide resistance in body lice. Bull. World Health Organization, 16, 9–31.