REPORT ON

SCIENTIFIC WORKING GROUP MEETING ON MALARIA
NICOSIA, CYPRUS

27 - 29 November 1979
The views expressed in this Report do not necessarily reflect the official policy of the World Health Organization.
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I. INTRODUCTION

A Meeting of a Scientific Working Group (SWG) on Malaria, with the participation of members of the Regional Malaria Panel, was held in Cyprus from 27 to 29 November 1979. A list of participants and the Agenda are given in Annex I and II respectively.

The Meeting was opened by H. E. The Minister of Health for Cyprus, Dr A. Mikellides, who welcomed the participants and outlined the role Cyprus has played in the war against malaria in the Eastern Mediterranean.

Dr. A.H. Taba, the Regional Director of the Eastern Mediterranean Region of the World Health Organization thanked the Minister for the kindness and courtesy extended by the Government of Cyprus in hosting the meeting. Dr Taba then underlined the main objectives of the meeting, namely:

1. to formulate a coordinated regional research programme; and
2. to identify areas for collaborative efforts in the different fields of malaria epidemiology and control, with particular emphasis on training requirements.

In order to limit the size of the report, it will only contain the essential points which were raised in technical discussions. The Regional Director, however, wishes to thank all those Panel members who brought to the meeting, or sent by post, such a large volume of technical papers describing malaria projects in their own countries. This material will be inserted into the Inventory of Malaria Research which has already been established at EMRO, and some of it will form the basis of future publication.

The Agenda was adopted without amendments and the following officers were nominated:

Chairman, Dr A. Markides (Cyprus), Moderator, Dr H. El-Dabbagh (Saudi Arabia), Rapporteur, Dr A. R. Zahar (Egypt).

1 Inaugural speech by the Minister of Health, H. E. Dr A. Mikellides, (Annex III).
2 Opening Address of Dr A.H. Taba, Director, WHO Eastern Mediterranean Region, (Annex IV).
II ANALYSIS OF THE MALARIA SITUATION IN THE EASTERN MEDITERRANEAN REGION

About one-tenth of the population in the Region still lives in areas where there are no organized anti-malaria measures. To extend the programme to these areas and to maintain and improve upon the achievements already made, a number of difficulties have to be overcome, such as:

1. Increasing cost of anti-malaria programmes

A good example of the high scale of funds which are spent on controlling malaria is to be found in Iran, where the annual budget for this purpose is $50 million, of which $20 million is for insecticide alone (Propoxur).

However, there has been an increasing volume of financial assistance given to the less fortunate countries of the Region by their more affluent neighbours, and this, to a certain extent, together with financial assistance through other international and bilateral sources, may keep malaria control programmes running.

2. Reduced availability of specifically trained health manpower

Training is being promoted in the Region, but steps have to be taken to ensure that the staff so trained find it rewarding to remain in malaria services.

3. Resistance of malaria vectors to insecticides

A working paper was presented, outlining the present situation as regards the 17 vectors of malaria in this Region, 13 of which are resistant to insecticides, as represented in tabular form in Annexes V and VI.

4. Increased malarial potential

Since the beginning of national anti-malaria campaigns in the 1950s in the countries of the Eastern Mediterranean Region (EMR), there has been a vast expansion of water development schemes for irrigation. Population increase, with its greater demand for food, agricultural products, and energy have necessitated numerous irrigation and hydro-
electric projects, which have favoured the multiplication of malaria vectors and produced a dramatic increase in the prevalence of malaria.

Examples of man-made malaria, through development schemes, can be found in most countries of the Region, such as in the Gezira in the Sudan, the Indus basin in Pakistan, the Nangarhar and Hilmand Valley in Afghanistan, the Ghah Valley and Euphrates Dam in Syria, the Northern Jordan Valley, the Abyan cotton plantation project in Democratic Yemen, the Johar Sugar plantation project in Somalia, etc.

In contrast to the above, however, in El Hassa Oasis in Eastern Saudi Arabia, the establishment of a large irrigation and drainage project by the Ministry of Agriculture helped to reduce the extent of breeding places for the vectors, so that since 1977, in spite of withdrawal of any type of control measures in these areas, no indigenous case has been reported from this sector.

From the above, it is clear that there is an urgent need for active cooperation among the responsible agencies and professional cadres at national level. Irrigation engineers, sanitary engineers, sociologists, biologists, epidemiologists and public health administrators must be deeply involved at all stages of the planning, designing, execution and operation of these schemes.

There is also a great need for research in order to improve the technology used to manipulate the environment for larval control. Development of efficient and economical material for lining canals and ponds, precision syphons for water level management, or distribution boxes which would help in minimizing breeding of mosquitoes in irrigation systems, are some examples of new lines of research which are being tried. An irrigation system for rice growing which eliminates long-lasting water collections also should be studied.
Investigations to identify local larvivorous fish could be another contribution for vector control in anti-malaria campaigns.

Study and research into anti-malaria measures to be used to combat urban malaria should be given high priority.

The training of engineers in the health aspects of water resource development and management, and their encouragement to develop locally simple, effective and cheap machinery for maintenance operations, would enhance the possibility of obtaining the cooperation and the self-help of the local population.

It can be, therefore, concluded that training and research are key factors in the application of an integrated control methodology (multi-directional approach), so as to overcome such technical problems as insecticide resistance of vectors and increased malariogenic potential.

Having reviewed the malaria situation, and also having identified the major difficulties which are being faced, the WHO Regional policy is directed towards the achievement of the following objectives:

1. Promotion of realistic malaria control programmes adapted to various malaria situations and to the availability of resources;
2. Collaboration in planning the timely integration of malaria activities into the general health services;
3. Promotion of inter-sectoral (at country level), inter country (at Regional level) and international collaboration and cooperation;
4. Promotion of self-reliance and self-help; and
5. Support to research.
III THE ROLE OF THE MALARIA ACTION PROGRAMME IN GLOBAL ANTIMALARIA CAMPAIGN -
SOME SPECIFIC AREAS OF COOPERATION WITH WHO REGIONS

Resurgence of malaria has occurred in most countries of Asia, in Turkey and in a number of countries in Latin America. Following discussions at the fifty-ninth session of the Executive Board, the Director-General submitted a report on the status of the malaria programme to the Thirty-first World Health Assembly. A new malaria control strategy was proposed, having the following basic pre-conditions:

1. Expression of national will, through government decisions to undertake and support malaria control programmes on a long-term basis;
2. The malaria control/eradication programme should be an integral part of the country health programme; and
3. Community participation should be secured.

Community participation should include intersectoral cooperation between different government departments (health, agriculture, public works, overall planning, finance, educational) at the political decision-making level and, at the level of execution, the acceptance by the population of the measures applied, including their participation in measures of individual protection. Two basic principles have been advocated, i.e., flexibility and an epidemiological approach. The measures to be applied should be based on the objectives of the programme and on the manpower and financial resources available. On the other hand, the epidemiological approach and the measures to be used vary according to the various ecological and epidemiological conditions favouring malaria transmission.

There are four kinds of activities which countries with a programme aimed at reducing mortality, morbidity and prevalence should undertake at this stage, and these are:

1. Control of epidemics, and prevention of the spreading of malaria transmission;
2. Preparation of a long-term malaria control/eradication programme;

3. Training; and

4. Research.

In response to the request of the World Health Assembly, the Director General has established a Malaria Action Programme at the global level. This Programme, which is responsible for overall cooperation, collaboration and coordination of malaria programmes throughout the world has been defined as "a cooperative effort of Member States affected or threatened by malaria, the World Health Organization and international and bilateral agencies, to implement anti-malaria activities with the object of reducing the impact of the disease on the health and productivity of the population". The terms of reference of this Programme at the global level are shown in Annex VII.

Under the aegis of MAP, it is necessary to formulate, promote, implement, and coordinate a dynamic malaria control/eradication programme on a worldwide scale. To implement this programme the following steps should be taken:

1. Identification and analysis of technical, administrative and operational problems;

2. Preparation of a coordinated programme at regional level with well-defined aims and targets, using appropriate and clearly defined methods, assessing inputs required at each level (global, regional, country) and setting up a system for monitoring the programme; and

3. Formulation of projects at country level including the following provisions, as appropriate:

   (a) control and/or prevention of malaria epidemics;

   (b) consolidation of malaria control/eradication programmes, including elaboration of long-term malaria control plans;
(c) the provision of a training component as part of the regional training programme;
(d) applied field research, aimed at providing solutions to technical problems encountered locally;
(e) prevention of reintroduction of malaria in malaria-free areas; and
(f) implementation of new programmes.

The preparation of long-term programmes is basically the responsibility of the national service, but the expertise available in the Regional Office is at the disposal of the national authorities, if required. The development of the global programme is based on plans prepared at country and regional level. The Regional Offices organize meetings at the regional level at which the programme as a whole is discussed.

There are other aspects of collaboration and coordination which are carried out by the Malaria Action Programme, particularly with respect to bilateral and multilateral assistance to national malaria control or eradication programmes. While Regional Offices make every effort to secure assistance for programmes, MAP can also make a contribution to this effort. A good example of this was the assistance provided, in the form of a consortium, to the Sri Lanka Malaria Programme; a similar one is now being prepared for Bangladesh.

Among problems met by national malaria eradication or control programmes is the availability of insecticides meeting WHO specifications, and the availability of a sufficient quantity of anti-malaria drugs. The Division of Vector Biology and Control is responsible for specifications for insecticides, their chemical analysis and toxicological aspects in general, and is cooperating with Member States on these matters.
IV THE PLACE OF RESEARCH IN MALARIA CONTROL

All malaria programmes should be built on sound epidemiological principles, having recourse to a multi-directional methodology, and should have proper reporting and monitoring systems which will allow precise evaluation of results and timely decisions for change of method when necessary.

Research in malaria control should be directed to improve existing methods of control, to find new methods, to increase efficiency and to reduce costs.

The prerequisites are:

1. Knowledge of epidemiology: stratification of malaria endemicity according to topography, climate, vectors and vector ecology, and to man's habits and customs;
2. Coordination of the malaria control programme with curative and preventive health services, and through a malaria board with other concerned ministries;
3. The existence of a national malaria service staffed with some professional personnel representing the main disciplines of malariology, namely, epidemiology, parasitology, entomology, engineering and health education;
4. Close connection of the malaria service with research centres, medical colleges, international organizations, possibly through a malaria technical committee;
5. The existence of a sound reporting system and regular assessment of the progress in control activities; and
6. Training facilities for the development of competent staff and the inclusion of research methodology and principles of scientific research in the curricula.

In view of financial and manpower limitations, particularly in the research field, it is evident that only those problems the solution of which will give the best returns in cost-benefit/effectiveness are those which need purposeful action with the least delay.
Further on in this report, it will be seen that the Scientific Working Group identified those areas where they felt malaria field research was most urgent, and made recommendations as to how best and where these projects should be established.

V RECENT TRENDS AND PERSPECTIVES OF DEVELOPMENTS RELATED TO VECTOR BIOLOGY AND CONTROL

A valuable reference paper was submitted for consideration of the Scientific Working Group by Dr A. R. Zahar. This paper is attached to the Report in toto as Annex VIII.

The paper stimulated interesting technical discussions, the most relevant of which are included in Chapter VII.

VI RESEARCH AND DEVELOPMENT OF VECTOR CONTROL EQUIPMENT FOR ANTI MALARIA PROGRAMMES

Equipment is essential for application of various methods of vector control. Continuous efforts are being made to be sure that such equipment is low cost, simple and economical for operation, maintenance and repair.

WHO has had a long-lasting programme of research and development in respect of equipment, consisting of:

(a) laboratory and field testing, as well as advising and assisting manufacturers to improve their equipment to suit WHO's requirements; and
(b) development of specifications to monitor quality and performance of equipment supplied to programmes.

Recommendations for improvement (material, design, performance) are submitted to, and discussed with, manufacturers for introduction into their equipment.

Several makes of hand compression sprayers, mist-blowers, aerosol generation (hand-carried and vehicle-mounted), nozzles and nozzle-tips are presently under testing,
Some 55 laboratory and field testing projects were carried out during 1977/78 on pesticides application equipment and their parts and accessories. Specifications are drawn up by WHO normally in the form of an interim specification and later on, after a few years, as a final one.

Future trends and prospects

In 1975 it was estimated that some 43,500 compression sprayers were required for the seven years 1975-1981. The number of sprayers in operation in that year must have been well over 100,000.

With the revision of the WHO malaria strategy and inclusion in the malaria control programme, gradually a more diversified control strategy was adopted in programmes resulting in the increased application of other methods of chemical control (larviciding, cold and thermal fogging, ULV, etc.) as well as biological and environmental management methods. This change has focussed attention on types of equipment other than compression sprayers and a number of these machines have been gradually tested, improved and introduced into programmes.

Equipment which applies electrostatistically charged insecticide formulation is to be tested. This machine delivers droplets which adhere to walls more firmly, thus preventing wasteful "run-off" and rebound, and ensuring that an adequate dosage and residual lethal effect is obtained.

A device to measure the degree of abrasiveness of pesticide formulations is also under development, so as to monitor whether these formulations meet WHO specifications. This is expected to considerably reduce the long-standing and costly problem of nozzle replacement in anti-malaria programmes. It is to be noted that some formulations were found to cause up to 30% increase in the discharge after the passage of only one
thousand litres of malathion wdp. Bearing in mind the high cost of malathion, the over-
dosing and wastage of this insecticide represents a considerable amount of money.

With diversification of control methods, plans have now been made to test equipment
for environmental management work. This will include power equipment used for excavation,
filling and levelling and for maintenance of irrigation and drainage ditches. The
introduction of this kind of machinery should facilitate source reduction in anti-malaria
programmes.

VII STATUS OF MALARIA RESEARCH IN SOME COUNTRIES OF THE REGION AND PLANS FOR
THEIR DEVELOPMENT

WHO/EMRO has for some time been reviewing the research projects which have been
carried out over the last 10 years in the Region. Such sources of information as periodic
and special reports, answers to questionnaires, and observations and discussions made in
the countries themselves have provided the basis for the presentation of a report to the
Scientific Working Group on the above item. This report, though could not possibly include
all research projects (Iran alone has carried out some 40 researches/studies during the
last 10 years) served as basis for comprehensive and extensive discussions on the various
research areas of direct concern and interest to our Region.

A special record file is under preparations in the Regional Office which will include
the relevant aspects of all field research carried out during approximately, the last ten
years in countries of this Region.

It will be seen from the Recommendations (Chapter XII) that a wide range of technical
matters was tackled by the Scientific Working Group. As far as was possible, items were
classified under such headings as, epidemiology, epidemiological surveillance(including
sero-diagnostic surveys), the parasite, the vectors, insecticides (effectiveness, odour
and toxicity), larvicides, equipment, chemotherapy, biological control (larvivorous fish,
B. thurigiensis, etc,) community participation and environmental manipulation, but there
was unavoidable overlapping of the borders between these categories.

The main points discussed are summarized herebelow:

**Epidemiology and epidemiological surveillance**

Resistance of vectors to chlorinated compounds, followed by the first reports of malathion resistance in the Region, call for a better application of epidemiological criteria to guide in the selection of control strategies and techniques applicable in different situations.

There is now another period of grace (the first being the DDT era) before vectors became operationally resistant to the OP compounds. It should be used to introduce more permanent methods and, if possible, to phase out the use of insecticides.

Many field research trials on malaria have been conducted, but much work has been wasted because of poor presentation of the effect of measures on malaria transmission. Results of trials should be expressed as proper measurements of epidemiological indices.

Sero-diagnostic tests, such as the immunofluorescent antibody technique and the enzyme-linked immunosorbent assay, are being introduced into epidemiological assessment, together with the classical entomological and parasitological observations.

**The parasite**

Although *P. falciparum* is not yet resistant to chloroquine, the Scientific Working Group recognized the need to prepare a record through *in vitro* tests of *P. falciparum* chloroquine sensitivity levels throughout the Region. However, it is worthwhile to wait until the *micro in vitro* test is perfected for field use, before establishing a coordinated programme throughout the Region. In the meanwhile *in vivo* tests should be carried out.
regularly in all countries whenever reports of decreased response of *P. falciparum* to 4-amino-quinolines (and other drugs) are received.

As regards *P. vivax*, it would be as well to study the latency of *P. vivax* relapses, which cause spring transmission throughout the north of the Region.

The Vectors/Insecticides

It would be difficult to include all aspects of this discussion, but the most important interventions are herebelow summarized.

The Scientific Working Group learned that there have been instances of susceptibility tests to malathion being carried out with out-of-date papers. There are obvious dangers in this type of mistake, therefore a recommendation was made regarding the verification of reports of resistance of vectors to insecticides.

Although Iran is spending $20 million on Propoxur, they feel that this sum is still well-spent as 2, 3, or 4 rounds of malathion or DDT cost more than 1 round of Propoxur, which produces highly satisfactory results against *A. stephensi*. It is intended to study the cost-effectiveness of propoxur spraying, as compared to that of other insecticides.

In the meantime, a large-scale trial with Propoxur in Iran produced an 84% reduction in malaria prevalence. In one group of villages, Propoxur spraying was accompanied by surveillance activities and chemotherapy, but the effects were just as good in another group of villages where no such supplementary measures were applied.

Also in Iran, trials using Sumithion (OMS 43) against *A. stephensi* should this insecticide be effective for 2 months, but toxic effects are liable to occur in spraying. Trials with the carbamate bendiocarb (OMS 1394) produced a 3-month residual lethal effect against *A. stephensi*.
Although malaria control is costing in Iran approximately $3 per capita, it should be borne in mind that the morbidity, cost of treatment, absenteeism and disruption of socio-economic development imposed by malaria would probably result in a higher per capita cost, and would also endanger the two-thirds of the country already cleared of malaria.

In Syria, the acceptance of malathion water dispersible powder in several areas of the country has fallen to almost nil. There is a need to run a trial of malathion emulsifiable concentrate to assess the degree of impact of this formulation, which is now being utilized in problem areas of the country, on the malaria situation.

The correlation between residual effect and formulation of insecticide appears to be much influenced by the type of wall surfaces of Syrian houses. At one time, all houses in malarious areas of Syria were made of mud. Now, 90% of the houses are of cement.

Village scale trials with OP compounds and synthetic pyrethroids have been conducted in Syria. Further cost-effectiveness studies are required.

The small dosage and relative safety of the pyrethroids (PERMETHRIN), if efficacious, would represent an enormous economy over the organophosphorous and carbamates insecticides.

Members of the Scientific Working Group have requested up-to-date information from WHO on the newer insecticides which may be ready for malaria field research, including references to toxicity and safe use.

Equipment

The Scientific Working Group recognized the importance of continuing the overall collaborative effort in research aiming at the improvement of operational tools.

Chemotherapy

An important question was raised as to what anti-malaria drugs could be given to a pregnant woman without running the risk of inducing the abortion of her foetus.
A review of the effects of anti-malaria drugs on the termination or otherwise of pregnancy was given, as follows:

1. The enzyme-inhibitor drugs proguanil and pyremithamine, although having been demonstrated to produce teratogenic effect in rats, when administered in the dosages required in malaria control programmes would certainly not affect the natural course of human pregnancy.

2. The 4-amino-quinolilles (i.e., chloroquine, amodiaquine) have been suggested as possible teratogenic, by producing otosclerosis in the new-born, but in practical experience have never been shown to be remotely abortifacient. In fact, there is on record the case of one pregnant woman, treated in a Danish Hospital Ship in 1954, having twice ingested, by mistake, massive doses (in the order of 12 to 15 tablets of 100 mg base) of chloroquine without any effect in normal foetal development. Other participants to the meeting made observations which substantiated this finding from long experience in the field. Although large continuous dosage of chloroquine can cause retinitis, these doses, given for rheumatic arthritis and lupus erythematosus, are far in excess of those used in malaria programmes.

3. The situation, as far as the 8-amino-quinolines is concerned, is different from that of the 4-amino-quinolines because the former are oxidant drugs, which in general affect glutathione-status in erythrocytes. The haemoglobin may become fixed to the erythrocyte, resulting in haemolysis.

It is also pointed out that infants ingesting 8-amino-quinolines may be affected sometimes by liver damage, but usually by haemolysis.

8-amino-quinolines should certainly not be given in the presence of such blood dyscrasia as G6 P. deficiency.
4. Quinine

It has been known for many years that quinine is an abortifacient.

5. The Long-acting sulpha-drugs

Although there is no need as yet in this Region to have recourse to sulpha-drugs in combination with other anti-malarials such as pyremithamine, as is the case where P. falciparum resistance to chloroquine exists, it should be pointed out that Dapsone is the most toxic, and that sulphadoxine is the best synergist because of its long half-life.

Trials with Drugs in the Region

A long acting sulpha-drugs, sulphalene, in combination with pyremithamine, has been tried for mass prophylaxis in Afghanistan. Such a trial will be repeated, whenever possible and on a larger scale, to confirm that in vivax malarious areas appropriate utilization and distribution of anti-malarials may be more effective and less costly than residual spraying.

Biological control

The utilization of larvivorous fish such as gambusia affinis (Afghanistan, Iran) Aphanius dispar (Oman, Saudi Arabia) and Nothobranchius and Tilapia (Somalia) were discussed.

The utilization of herbivorous fish, such as Chinese grass carp (White Amur) which by eliminating the aquatic plants deprives the larvae of their shelters, was also considered.

The Scientific Working Group agreed that these predators could be of great advantage, if sufficiently effective, as they are self-perpetuating, cheap and do not pollute the environment. Thus far, their actual effect on malaria has not been accurately assessed.
Judgements can only be subjective when they are used as a supplementary measure. The establishment of a malaria field research trial of Tilapia in the arid north of Somalia will make possible an opportunity to get a more accurate assessment of value, as the fish are to be placed in man-made cisterns, which virtually constitute the only mosquito-breeding places in that malarious area.

This project is to be supported by WHO (TDR).

**Bacillus thuringiensis (sero-type 14)**

This bacillus, which lends itself to cultivation, very much as does the production of yeast in beer and wine manufacture, and with as much ease and simplicity, produces a crystalline protein, endotoxin, at the time of its sporulation. This endotoxin can be easily harvested to produce a powdered product inimical to mosquito larvae, which, having ingested it, succumb because of the fatal effects of the endotoxin on the mouth parts and gut.

The Scientific Working Group would like to see the final results of a WHO evaluation of the safe-use in the field of this bacterium. Egypt plans to test it.

**VIII THE UNDP/WORLD BANK/WHO/SPECIAL PROGRAMME FOR RESEARCH AND TRAINING IN TROPICAL DISEASE**

A memorandum of understanding, signed in 1978, established the administrative and technical structure of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

This global programme has two interdependent objectives of developing improved tools for control of tropical diseases, and strengthening the research capability of affected countries themselves. The diseases are the following:

- **Malaria**;
- **Schistosomiasis**;
- **Filariasis** (including onchocerciasis);
Trypanosomiasis (including Chagas disease); Leishmaniasis; and Leptosy.

The Governing bodies are the Joint Coordinating Board (JCB) constituted by donor and recipient agencies, and the Scientific and Technical Advisory Committee (STAC), comprising various scientists. The execution of the programme is followed-up by the standing committee, comprising the co-sponsors. The executing agency is WHO.

The programme operates through several Scientific Working Groups (SWG's), some are the Socio-Economic Research (SBR) and the Biological Control of Vectors (BCV) groups. Malaria has three SWGs, namely:

- on Chemotherapy (CHEMAL);
- on Immunology (IMMAL); and
- on Applied Field Research (FIELDMAL).

A separate branch of the programme is the Research Strengthening Group (RSG). All research is goal-oriented and any proposal should fill a gap in the general strategic plan which leads to a better control of disease. FIELDMAL has its own strategic plan, based on improved knowledge of epidemiological factors (parasite, vector and man), better use of tools and methods of malaria control including community participation, and development of planning and training methodologies. Important gaps and research areas are described in the report of the Second Meeting of the FIELDMAL SWG (Geneva, November 1979), which will be widely distributed in the near future. Each SWG has a Steering Committee (SC), which examines new research proposals and progress reports of ongoing research projects. The proposals recommended by the SC receive the support of the Special Programme (TDR). To this effect a contractual technical services agreement (CTS) is signed by the parties concerned, and this is renewed annually up to three years, subject to satisfactory progress and to availability of funds.
The Handbook for participants in Scientific Working Groups was distributed. It
contains, inter alia, a reproduction of the forms for project proposals. These were
examined, and some principles concerning the study design, ethical clearances, budget
estimates and equipment and supplies were discussed. The elaboration of a coordinated
Regional strategic plan and the improvement of study designs and presentations of
proposals would require the organization of a Regional Workshop, possibly in 1980.

It should be pointed out that the global annual budget of TDR available to FIELDMAL
projects is only $1.1 million, so that it may be necessary to supplement TDR grants by
funds from other national or international sources.

During the discussion, the SWG asked whether the proposal forms could be simplified; the
reply was that although smaller projects would require less documentation, there was
a definite need for the Steering Committee of FIELDMAL to receive all the information
which had been requested. The Special Programme was subject to strict audit, even in
the field if necessary.

The general impression gained by the SWG was the process of formulating proposals
to TDR was complicated. Many felt that the procedures involved could be reviewed during
the afore-mentioned Regional Workshop.

It should be pointed out that participants to this Workshop should include young
trained malaria field research personnel preparing to take over the execution of malaria
field research projects.

IX DEFINITION OF PRIORITY AREAS FOR RESEARCH IN THE REGION

The SWG agreed that it would be necessary to adhere to certain criteria when choosing
research projects. The basic criteria are:

a) The expected impact on malaria mortality and morbidity;

b) The attainment of lasting results;

c) Feasibility;
d) Achievement of success in as short a time as possible;

e) Cost-effectiveness;

f) Greatest benefit to socio-economic development; and

g) Adherence to national and Regional policy.

X RESEARCH PROPOSALS: POLICY AND SPECIFIC PROJECTS

Each member of the Advisory Panel gave a short description of malaria field research currently being conducted in his own country, from the discussion of which certain projects were selected for continuation or establishment, some urgently and immediately, and the remainder when the necessary requirements became available. The research projects chosen are reflected in the Recommendations.

XI TRAINING ASPECTS

THE PRESENT STATUS OF MALARIA TRAINED HEALTH MANPOWER, AND TRAINING FACILITIES IN THE REGION

A large number of national health personnel have been trained in malaria epidemiology and control during the last 20 years or so, but because malaria field work can be hard, unrewarding and uncompromising many of the malaria trained personnel have left the malaria control services. Governments find it difficult to meet even the minimal requirements of key personnel to keep programmes running smoothly.

One of the main problems is, therefore, that of retaining the trained personnel by offering better career prospects than hitherto has been the case. This, however, remains a strictly national problem, the solution of which will have to be found by the respective governments. EMRO supports the multi-purpose training and utilization of malaria personnel, which, inter alia, should lead to better career prospects for these health workers.
WHO, on the other hand, continues to promote training in malaria of all categories of health personnel. In addition to the international course for the Master's Degree in Epidemiology of Malaria and Other Parasitic Diseases, in Teheran, Iran, other inter-regional courses are being supported in Egypt, and recently in Iraq. The strengthening of national training centres and the supporting of local training remains a high priority within the regional policy, and requests forthcoming from governments, in this respect, receive immediate response.

The SWG considered in some detail the requirement of a Regional Malaria Training Programme.

One of the major difficulties is that there is no standard methodology (as there was in malaria eradication programmes) in non-time limited malaria control. Local ecology, epidemiology, and socio-economic conditions dictate strategy, and, therefore, training requirements. It follows that support to malaria training programmes is best given at national level, adapting curricula to take into account local requirements.

Availability of funds, educational facilities and equipment, quantity and quality of teaching staff, and the availability of an optimum number of suitably intelligent and motivated students are to be adequate.

Subjects taught should leave the student competent to solve all types of malaria problems.

Training in malaria should not be restricted to malaria personnel, but should also be offered, in varying degrees, to general health service personnel, general practitioner physicians, primary health care personnel, and, outside health altogether to agricultural workers and the general public.
For each training course, a set of educational objectives should be established, based on the expected tasks and responsibility of the category of personnel to be trained. Further, for the guidance of the teachers and the students, specific learning objectives (classroom objectives) should be defined, on the basis of which curricula and time allocation can be prepared.

Coordination of training activities at regional and even inter-regional level is essential to make mutually available the experience in neighbouring countries where common problems exist. Moreover, coordination would stimulate exchanges of teachers, teaching manuals, and could provide teacher training.

The SWG further felt that the regional malaria programmes would be facilitated by having an inventory of training facilities, which could be built up by exchanging, sharing and utilizing the combined experience of WHO and the Member States. This inventory has already been established in WHO/EMRO.

At the regional level, the following responsibilities should be discharged:

i) coordinating national training courses to avoid duplication and to secure quality and relevance;

ii) placement of trainees according to national needs and availability of courses;

iii) supporting national malaria activities by developing teaching materials and audiovisual aids, and by provision of consultative services in scientific and educational subjects;

iv) coordinating and supporting operational research in malaria and mosquito control;

v) promoting and supporting the training of malaria teachers;

vi) organizing educational activities at the regional level whenever necessary (refresher, specialized training, seminars, workshops, study tours, etc.);

vii) providing consultant services; and

viii) granting fellowships.
During the discussion, the shortage of malaria-trained personnel was referred to many times. The term "brain drain" was used by some members who had suffered the loss of key personnel, resulting in near paralysis of their malaria programmes.

There are only three countries with national entomologists and three international medical entomologists working in the whole Region. This situation is of serious concern. Many vector control programmes have been, are are being, carried out without epidemiological expertise, resulting in the wastage of valuable insecticides and sometimes even the mishandling of marginally safe insecticides. The execution and assessment of extremely demanding and highly technical research projects are being left to non-trained personnel, who cannot be expected to make the correct analyses and evaluation of results and take related decisions.

It is urgently necessary to provide immediately at least one medical entomologist for each country. They need not be doctors, but could be graduates in science, agriculture or veterinary medicine.

Training of medical entomology is not satisfactory, being mostly given in the developed countries, and mainly combined with parasitology, which receives the lion's share of emphasis. Courses at MSc. level are not properly orientated to a country's relevant malaria control needs, and such courses become even more "unreal" at the Ph.D level.

This state of affairs must be remedied by organizing Master's, or, possibly, Ph.D., courses in Entomology, whose training objectives are orientated towards the needs of Member States.

The situation with respect to sanitary engineers is similar to that of medical entomologists.
The SWG reiterated the need for training malaria staff, health staff and others
afore-mentioned, not only in malaria but also in other vector-borne diseases of major
importance in their own countries.

Country participants requested that seminars and workshops should continue to be
held in order that they, and others who are destined to replace them, could keep abreast
of the new techniques and methods, and with recent advances in epidemiological knowledge
of malaria and its control.

The Handbook of Malaria Training (PA/66 185 1966) and various operational manuals
have proved very valuable to malaria eradication, but they now should be revised to
account for the more flexible approach required for malaria control. To this end, a
manuscript on malaria chemotherapy has already been prepared and will be shortly issued
as a second edition of the manual originally published in 1955. In view of the increased
use of anti-malaria drugs for therapeutic and chemoprophylactic purposes, and mass drug
administration, additional documents have been prepared dealing with the side-effects of
chloroquine, primaquine and pyrimethamine. A manuscript on the side-effects of long-
acting sulphonamides will be ready by the beginning of 1980.

With respect to training institutions, in the past, international training centres
played an important role in the training of malaria workers in eradication techniques.
However, in view of the experience gained over the years, it is now suggested that
regional training programmes should be developed as a cooperative effort of existing
national training institutions, with a permanent secretariat to coordinate the activities
of national training centres, to develop curricula for different types of courses and to
provide teaching material, teacher-training, and consultant-teachers (to this end, the
Permanent Coordinating Training Secretariat for malaria training programmes for Asia,
which is being established in Kuala Lumpur, Malaysia, could play an important role).
In addition to regular malaria training, most programmes will need greater specialization in new techniques. For this purpose, workshops, seminars and symposia need to be organized. MAP has so far organized workshops on serological techniques (Enzyme-linked immunosorbent assay-ELISA), seminars on epidemiology and, at the request of Regional Offices, seminars on field research, and courses to teach testing *P. falciparum* susceptibility to 4-amino-quinolines.

It is essential that a move be made towards preparing national teachers to train malaria workers and others, and there should be a two-way dialogue between the pedagogue and the consumer. Too many times in the past, there have been too many trained in one discipline, and not enough in another.

A much larger training programme would go some way towards satisfying the needs of the richer countries, eliminating the afflux towards some of them of much needed trained personnel in less economically fortunate countries.

Finally, it is the responsibility of the Ministry of Health to ensure that there are jobs waiting for the students after they are trained.
GENERAL RECOMMENDATIONS

1. RESISTANCE OF VECTORS:

Reports of resistance should be reconfirmed, and, whenever required, should be substantiated by epidemiological evidence that the insecticide in use is no longer having a significant impact on malaria transmission (through field studies and research) prior to deciding on changes of insecticides.

2. INTER-SECTORAL COOPERATION

While reiterating the corresponding operative paragraph of the Resolution WHA 31.45, the Scientific Working Group recommended increased inter-sectoral cooperation with particular reference to:

a) Water development schemes, in which a health component should be included in the planning stage, and should remain throughout construction and utilization, thus ensuring that the danger of promoting vector-borne diseases is minimized; and

b) The utilization of chemical pesticides in agriculture, which should be coordinated in order to reduce the pressure on mosquito populations, thus avoiding or delaying the development of insecticide resistance of vectors of human diseases, including malaria.

3. INTEGRATION

It is essential that basic health services should attain a degree of development which can permit integration of the malaria vertical structure. In certain cases, it may only be feasible, as an initial step, to transform the malaria service into a multi-purpose one.

Situations differ in each country, and the conversion of malaria into a multi-purpose service or its integration into the general health service should be the object of studies in each specific country. Such studies may call for field research projects.
4. INCENTIVES

In order to prevent the loss to the malaria services of trained manpower, governments are urged to offer career service status to each category of the malaria staff, and to revise their salary scales. Incentives should also include field allowances for all those who work in preventive medicine in arduous field conditions.

5. TRAINING

There is a need to update teaching in malaria so that it reflects the revised strategy on malaria control. Training in the epidemiology and control of other vector-borne disease should be associated with training in malaria.

5.1 The Scientific Working Group recognized the difficulty of obtaining medical officers for research and training in the field of malaria. However, experience has shown that science graduates in biology, agriculture or veterinary medicine, specializing in entomology and parasitology, can contribute considerably to research on malaria, and also to the technical management of malaria control eradication. Consequently, the SWG recommends that: one or two posts should be established within national malaria services for young science graduates with career prospects who, after undergoing appropriate training, would be responsible for research and training within the malaria control programmes. WHO may be called upon to assist Member States in the training of such personnel.

5.2 Short training courses in malaria and other vector-borne diseases of 3 - 4 months duration should be conducted at regional or country level, according to requirements, for various categories of health personnel.

5.3 Coordination of training activities undertaken by various countries of the Region is indispensable for ensuring high standards of training. The WHO Secretariat may provide such a coordinating role.
5.4 In view of the paucity of qualified national medical entomologists, efforts should be made to provide graduates of science, agricultural science or possible veterinary medicine with the opportunity to be trained in medical entomology. For this purpose, one or two national institutions should be selected in the Region for conducting post-graduate studies in medical entomology leading to the M.Sc. degree. Ph.D studies in medical entomology should also be encouraged.

Opportunities should also be offered to engineers to pursue post-graduate studies in environmental health.

Similarly, a new generation of malariologists are needed, with broader training in public health. Facilities for such training have already been provided in International Master of Public Health courses existing in the Region and elsewhere.

5.5 WHO is requested to review the Handbook on Malaria Training.\(^1\)

WHO is also requested to continue to revise all operational manuals that were originally intended for use by malaria eradication programmes.

6. **RESEARCH**

A component cell dedicated exclusively to research and training should be an integral part of every malaria control programme.

6.1 A Regional Workshop should be organized on research methodology so that research field projects may be carried out according to recognized scientific criteria. It has been proposed to have such a Workshop during the year 1980.

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\(^1\) PA/66 185
7. RECOMMENDATIONS ON SPECIFIC RESEARCH PROJECTS

7.1 Epidemiology, epidemiological surveillance including sero-diagnostic studies

7.1.1 Sero-epidemiological studies should be made to detect residual immune response in areas of advanced control or eradication (Syria, Jordan, Lebanon).

7.1.2 Sero-epidemiological studies are required in both nomadic and stable populations, using the immuno-fluorescent technique (Iran).

For the purpose of carrying out sero-epidemiological studies (including TSA and ELISA) in the field, the continuous in vitro cultivation of *P. falciparum* will be established in Iran.

7.1.3 Cost effectiveness studies should be made of active case detection and its comparison with other methods of surveillance (Jordan).

7.1.4 A surveillance mechanism should be developed enabling the monitoring of the possible introduction of non indigenous vectors (Cyprus, Egypt).

7.1.5 A search should take place for a practical methodology for the detection of symptom-less parasite carriers entering areas which have been freed from malaria.

7.2 The *Plasmodium*

7.2.1 With respect to testing of *P. falciparum* for resistance to chloroquine:

- the in-vivo testing should begin immediately; and
- the in-vitro testing should begin as soon as the micro test has been sufficiently perfected to be used in the field.

A Regional course to teach the technique of in vitro testing of *P. falciparum* sensitivity to chloroquine (Sudan) is required to enable the above field research.
7.3 The Vectors

7.3.1 Cytogenetic and possibly electrophoresis gene-enzyme studies should be made to discern the particular patterns of behaviour in the following anopheline vectors of malaria, in collaboration with the laboratory/laboratories especially equipped for this purpose:

7.3.1.1 *A. gambiae* complex (Sudan, Somalia, Saudi Arabia, Yemen and Democratic Yemen);
7.3.1.2 *A. pharoensis* (Egypt, Sudan);
7.3.1.3 *A. superpictus* (Iran, both desertic and mountainous);
7.3.1.4 *A. sacharovi* (Syria, Iraq, in comparison with the *A. sacharovi* population in Turkey);
7.3.1.5 *A. stephensi* (Iran, Saudi Arabia, Pakistan urban and Pakistan rural);
7.3.1.6 *A. culicifacies* (Pakistan, Yemen);

7.3.2 The effect of irrigation systems in rice cultivation on the bionomics of malaria vectors (Sudan, Egypt) should be determined.

7.4 Chemical Control

7.4.1 Studies are required to assess whether the alternate use of chemically unrelated insecticides may delay the spread of malathion resistance (Sudan).

7.4.2 Epidemiological assessment of the impact of malathion utilized in the emulsion concentrate formulation on malaria transmission should be made (Syria).

7.4.3 Trials should be begun to assess the epidemiological value of the application, during the winter, of ULV malathion by fogging operations (Syria, Iran).

7.4.4 Stage V/VI Field trials, as recommended by WHO, using the newer organo-phosphorous, carbamates and pyrethroides insecticides should commence (Iran, Sudan).
7.4.4.1 Cost effectiveness trials of permethrin emulsion concentrate on malaria transmission, as compared with malathion, should be initiated (Syria).

7.4.4.2 Epidemiological assessment of the cost effectiveness of propoxur in comparison with that of malathion should be carried out (Iran).

7.4.5 Assessment of the safe use of the insecticides mentioned in 7.4.4 should be established.

7.5 Equipment

7.5.1 Simple hand or power driven equipment which would be used for clearing and cleansing canals should be tested (Sudan).

7.5.2 Various types of ULV fogging equipment and electrophoretic sprayers, which have been recommended by WHO for use in malaria control programmes, should also undergo testing (Egypt, Iraq, Sudan).

In connection with field research related to the equipment, investigation of the possibility of establishing a WHO collaborating centre for testing tools and improving techniques for the application of insecticides was recommended.

7.6 Anti-malaria Drugs

Epidemiological assessment should be made of a cost effectiveness trial comparing the effect on malaria transmission of Metakelfin prophylaxis, pyrimethamine prophylaxis, and malathion spraying, used respectively in adjacent epidemiologically homogenous areas of vivax malaria. (Afghanistan).

7.7 Biological Control

7.7.1 The feasibility of utilizing local larvicidal fish in anti-malaria programmes should be researched, identified and studied (All countries).
7.7.2 The epidemiological impact and cost-effectiveness of larvivorous fish in controlling malaria transmission should be investigated, namely, among:

7.7.2.1 *Aphanius dispar* (Oman);
7.7.2.2 Chinese Grass carp (White Amur) - Non larvivorous, but effecting larvae habitat with its harbivorous habits (Sudan); and
7.7.2.3 *Nothobranchius* (Somalia).

7.7.3 Trials with mosquito pathogens, such as *B. sphaericus, B. thuringiensis* serotype 14 (Egypt) should be carried out.

7.7.4 Field trials of Insect Growth Regulators (IGR), using the methodology as recommended by WHO, are recommended (Egypt, Saudi Arabia).

7.8 Environmental Management (E.M.)

7.8.1 Studies to identify simple and inexpensive methods of E.M. using local manpower (Community participation), material and equipment should be made (all countries).

7.8.2 Cost/effectiveness studies of E.M. in arid and semi-arid areas are required (Iran)

N.B. The SWC also recognized the need to establish environmental management as an integral part of Municipality Sanitation, and, in order to recognize E.M. more efficiently, a WHO-sponsored environmental collaboration centre should be established.

7.9 Community Participation

Assessment of the epidemiological significance of personnel protection measures against malaria such as wide-mesh bed nets or of normal mesh impregnated with mosquito-repellants or with insecticides, the use of pyrethrum coils, and partialprofing of houses against the entry of vector mosquitoes was recommended (Iran, Sudan).
7.10 Comprehensive Health Services

Alternate methods of malaria control, through the establishment of a comprehensive health service in Iran, in an area where control of malaria by the vertical anti-malaria service has proved too expensive, were suggested for trial purposes.

7.11 Integrated Control

7.11.1 Studies on the methodology for detailed planning of integrated control in anti-malaria programmes were recommended (Sudan).

7.11.2 Trials on a comprehensive approach to the control of malaria and schistosomiasis have been planned (Sudan).
SCIENTIFIC WORKING GROUP MEETING
ON MALARIA

Nicosia, Cyprus, 27 to 29 November 1979

LIST OF THE MEMBERS OF THE PANEL
ATTENDING

CYPRUS

Dr A. Markides
Director Medical Services
Ministry of Health
Nicosia

EGYPT

Professor A.A. Soliman
Head of Malaria Research Unit
President Ain Shams University
Abbassiah
Cairo

Dr A.R. Zahar
Entomologist
Geneva

IRAN

Dr M. Motabar
Professor of Epidemiology
School of Public Health
University of Teheran
Teheran

Mr N. Eshghy
Director Kazeroun Research Station
Chief Biology Section
School of Public Health
University of Teheran
Teheran

Mr A.N. Hazrati
Deputy Director for
Malaria Eradication &
Schistosomiasis Control
Programmes
General Department of Malaria
Eradication & Communicable
Diseases Control
Ministry of Health and Welfare
Teheran
ANNEX I

page 2

IRAN (ct'd)

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School of Public Health
and Director
Institute of Public Health Research
University of Teheran
Teheran

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Specialist Physician
Endemic Diseases Institute
Ministry of Health
Baghdad

JORDAN

Dr M.R. Tawfiq
Director
Malaria Service
Ministry of Health
Amman

PAKISTAN

* Dr S.M. Mujtaba
Director
Directorate of Malaria Control
Rawalpindi

SAUDI ARABIA

Dr H. El Dabbagh
Director General Preventive Medicine
Ministry of Health
Riyad

SUDAN

Dr A. El-Gaddal
Technical Adviser and Director
International Affairs
Ministry of Health
Khartoum

SYRIA

Dr Z. Khawam
Director, MES
Ministry of Health
Damascus

OBSERVERS FROM THE HOST COUNTRY

Mr P. Eliades
District Medical Officer, Nicosia

Mr F. Neocleous
Health Inspector in-charge, Nicosia District

* Did not attend
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<td>Director, Malaria Action Programme</td>
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<td>Mr H.A. Rafatjah</td>
<td>Chief, Equipment, Planning and Operations, Vector Biology and Control Division</td>
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<td>Démetrio</td>
<td>Secretary</td>
<td>Regional Office for the Eastern Mediterranean, Alexandria</td>
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AGENDA

I Opening Session

II Election of Meeting Officers

III Adoption of the Agenda

IV Malaria Situation in the Region

4.1 Malaria situation analysis in the Region;

4.2 The malaria vectors in the Region: problems faced, ongoing studies, research requirements;

4.3 Man made malaria in the Region.

V The Malaria Action Programme

5.1 The role of the Malaria Action Programme in global anti-malaria campaigns - some specific areas of cooperation with WHO Regions.

VI Research Aspects

6.1 The place of research in malaria control: analysis of various research areas to improve control methodologies and techniques;

6.2 Recent trends and perspectives of development in research related to vector biology and control;

6.3 Field trials related to operational equipment: a global review;

6.4 Status of malaria research in some countries of the Region and plans for their development;

6.5 The Special Programme for Research and Training in Tropical Diseases;
6.6 Definition of priority areas for research in the Region; (Scientific Working Group discussions)

6.7 Research proposals: policy and specific projects. - ditto -

VII Training Aspects

7.1 Training programme on malaria;

7.2 Training of medical entomologists with special emphasis on malaria control/eradication needs;

7.3 Present status of malaria trained health manpower and training facilities;

7.4 Training of malarialogists and research workers: policy and specific programmes. (Scientific Working Group discussions)

VIII Summary report and recommendations.

IX Closing Session.
ADDRESS

by H.E. The Minister Of Health, Dr Andreas Mikellides,

to the opening ceremony of the Scientific Working Group
Meeting on Malaria organized by the World Health Organization
in collaboration with the Ministry of Health at the Philoxenia
Hotel on the 27th November, 1979 at 9:30 a.m.

Mr Regional Director, Distinguished participants,

On behalf of the Cyprus Government, I welcome you all to our beautiful island and
wish you a very pleasant stay and fruitful time.

I take this opportunity to express our pleasure and thanks to the organizers for
their decision to select Cyprus as the venue of this meeting.

Cyprus, being at the crossroads of three continents, offers itself as the ideal and
most convenient country for holding regional, and even international, meetings and this
has increasingly been the case over the last few years. In this context, we are aspiring
to see our country becoming not only a centre for cultural activities, but also as a bridge
of peace and a forum of understanding and friendship among the countries in the Region and
the world at large.

The subject matter of this meeting is malaria, which continues to constitute a very
serious health hazard for many countries in the world.

As we all know, malaria has been, for many centuries, a real scourge, that has
ravaged whole civilizations, and undermined the vitality of many nations, with the result
that socio-economic development in the countries concerned was jeopardized.

Hippocrates, the father of medicine, who is considered to have been the first
malariologist, set out a crude epidemiology, and rudimentary preventive measures, against
malaria. He pointed out, for example, that stagnant waters were a source of the malady,
and that they must be drained in order to prevent morbid manifestations (like protruding
bellies and enlarged spleens).
The introduction of quinine from South America in the early 17th Century was a significant step in the treatment of malaria.

The discovery, on the other hand, by Sir Roland Ross that the anopheles mosquito was the vector of the disease resulted in the implementation of certain measures aiming at the eradication of the mosquitoes, such as the oiling of surface of stagnant waters, and by protecting peoples homes with nets. These measures, though effective to some extent, could not solve the problem until the discovery of D.D.T. which changed the whole strategy of the anti-malaria campaign. Subsequently, other effective substances have been discovered which do not have the disadvantages of D.D.T.

The World Health Organization has placed particular emphasis on the eradication of malaria by adopting a very ambitious programme, in which large amounts of money are invested.

Out of 143 areas where malaria was endemic, 36 countries have been freed, and continue to be free, from malaria. The remaining countries still face a malaria problem. I need not elaborate on the practical, and other problems or the costs of the anti-malaria campaign for the countries concerned, as these are well known.

Insofar as the Eastern Mediterranean Region is concerned, only three countries are now free from malaria, one of them being Cyprus, which has been free since 1950, following an intensive campaign which started in 1946.

The maintenance service, which was instituted in 1950, the year during which the eradication of malaria from Cyprus was achieved, had to be strengthened since 1974, in view of the increased risk of its reimportation, as a result of the Turkish invasion and occupation of 40% of the Island's territory; this is because malaria is endemic in Turkey.

The Cyprus Health Services have acquired considerable experience in the various aspects of anti-malaria work and we shall only be too glad to share such experience with other countries.
I wish to conclude this short address by welcoming you again to our island and wishing you every possible success in your deliberations. I am sure that this meeting will contribute significantly towards the success of the anti-malaria measures in the various countries of the Region for the common benefit of our peoples which, no doubt, will have a beneficial effect to the whole world.

Before leaving the rostrum I would like to express great pleasure for having with us Dr A.H. Taba, the WHO Regional Director, whose interest and concern in the development of Health Services in the Region is acknowledged and appreciated by all. Whilst in Cyprus, he may wish to see some of our services and the way we in Cyprus translate into action WHO resolutions and how we utilize technical and other assistance.
OPENING ADDRESS OF DR A.H. TABA
DIRECTOR
WHO EASTERN MEDITERRANEAN REGION
FOR THE SCIENTIFIC WORKING GROUP MEETING ON MALARIA
Nicosia, Cyprus, 27 - 29 November 1979

It gives me great pleasure to welcome you in quality of members of the Regional Advisory Panel on Malaria to this Scientific Working Group Meeting.

I am most grateful to H.E. the Minister of Public Health of Cyprus for hosting this meeting and for all the facilities provided to us.

The Regional Advisory Panel on Malaria has been formed as result of our practice to promote an active participation of distinguished scientists from our Region in WHO collaborative programme activities. On this particular occasion you are invited, after a brief review of the malaria situation in the Region and of our regional programme, to:

1. Formulate a coordinated regional research programme
2. Identify areas for collaborative efforts in the different fields of malaria epidemiology and control, with particular emphasis on training requirements.

We have already benefitted on several occasions in the past in our Region, from your competent expertise and collaboration in conceiving and operating the regional anti-malaria programme. However, I am sure you will agree, through the mechanism of a Regional Advisory Panel, your contribution may be more fruitful since it will be possible to reciprocate experiences and knowledge on all aspects of our anti-malaria programme.
Although the initial expectation of malaria eradication from all countries of the Region has not yet come about, I can say with confidence that malaria is being well controlled in the majority of the countries where measures against this disease are being applied. Some of our former administrative, operational and technical difficulties have been resolved, yet others remain. I believe we can look back at how some of our problems were resolved and based on this experience, deal with those remaining. For example one can remember the burden which was forced upon national health services and national malaria programmes when many of our vectors became successively resistant to the chlorinated hydrocarbon insecticides. The question then was, "Can the poorer countries afford organophosphorous insecticides as substitute, lasting half as long and costing twice as much?". It was this and other similar questions which stimulated a far greater measure of collaboration between member countries and between countries and WHO in the financing of anti-malaria programmes than had hitherto been the usual practice. Through technical cooperation solutions have been sought in relation to aspects of the programme requiring a coordinated effort such as anti-malaria activities in border areas of countries sharing same problems, training of malaria workers and strengthening of epidemiological surveillance.

There are, however, many problems yet to be solved and your assistance as scientists of this Region will be valuable towards finding solution to persisting difficulties.

In this first meeting, I shall be pleased if you, after having evaluated the Regional malaria situation as it stands today, will pinpoint those administrative, operational and technical problems which are interfering with the progress of our anti-malaria programme. Subsequently you may decide which of these problems you feel are suitable for field research.

Research is already under way in the Region on several fields such as methodologies and techniques of biological control, application of new formulations of insecticides, slow release of larvicides, methodology of drug administration and testing of new or modified operational equipment. Further studies are certainly required to devise and evaluate measures of environmental management.
to reduce potential breeding places and man/vector contact. For biological control more studies are needed to assess the efficacy of local or imported larvivorous fish. Moreover, it is essential, whatever may be the type of research envisaged, that research projects are not carried out in isolation (and, possibly duplicated) by countries of the Region, without an interchange of information and expertise developed.

I, therefore, would like to request you to look into the aspects of a coordinated regional malaria research programme the results of which would not only benefit the country where the study is carried out, but many of the other countries afflicted with the same or similar problems.

Training of national scientists is being promoted in the Region as testified by our support to various national institutions undertaking training on malaria of post-graduate and undergraduate students. You may wish to consider how WHO can strengthen such activities possibly through greater cooperation amongst concerned countries.

Finally, I would like to say how pleased I am to see you all again. I am sure your meeting will lead to constructive recommendations and I wish you an enjoyable stay in Cyprus.
**ANNEX V**

**Vectors of malaria in WHO Countries and the relative importance of each**

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*+ = Species reported from the country; vectorial role not determined

(1) = Eradicated or non-existing at present

1 = Is or has been a primary vector

2 = Secondary

3 = Tertiary or of a minor vectorial role
### ANNEX VI

**Status of Malaria Vector Resistance to Insecticides in EMRO Countries, 1979**

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<th>A. <em>gambians</em> (ara-&lt;br&gt; &lt;i&gt;bianensis&lt;/i&gt;)</th>
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+ = Species present, no tests carried out
0 = " susceptible to all insecticides
1 = " resistant to DDT
2 = " Dieldrin/BHC
3 = " Malathion
4 = Species resistant to Penitrothion
5 = " Temephos(Atate)
- = No information available
( ) = Resistance suspected
ANNEX VII

TERMS OF REFERENCE OF THE MALARIA ACTION PROGRAMME

In close collaboration with the Regional Offices and relevant Division at global level, the Malaria Action Programme shall:

1. Plan the world-wide strategy of malaria control/eradication, formulating the tactical variants, thus guiding the global programme;

2. Promote epidemiological studies, establish technical standards for operational procedures and evaluation of malaria programmes;

3. Coordinate the global assessment of malaria control/eradication programme and take an active part in the periodical assessment of individual programmes jointly with nationals and Regional Offices;

4. Stimulate, plan, coordinate and assist operational research on malaria control/eradication;

5. Stimulate to the extent possible and coordinate basic research in malaria with particular relation to technical problems met with in malaria control/eradication programmes;

6. Collect, collate and disseminate information on the progress of malaria control/eradication programmes;

7. Cooperate with Member States and Regional Offices in the control of malaria epidemics and promote international assistance in emergencies;

8. Arrange for and assist in the training of personnel at different professional levels and in the development and dissemination of relevant training materials;

9. Evaluate the needs in insecticides, antimalarial drugs and advise on their production, formulations and availability;

10. Promote international cooperation for the mobilization of extra-budgetary resources for specific needs in malaria control/eradication, based on evaluated long-term requirements;

11. Maintain and develop coordination of the global programme with bilateral and internal agencies and with non-governmental organizations;

12. Prepare all relevant reports on malaria at global level as required.
Recent Trends and Perspectives of Development in Research Related to Vector Biology and Control

by

A. R. Zahar
WHO Consultant Entomologist
Introduction

I. VECTOR STUDIES

1. Vector bionomics

1.1 In field research on the epidemiology and control of malaria

1.2 In anti-malaria programmes

1.3 In special vector population studies

1.4 In solving specific problems

1.4.1 Age determination

1.4.2 Host attraction

1.4.3 Sampling

1.4.4 Detection of sporozoite infection in mosquitoes

2. Vector cytogenetics

II. VECTOR CONTROL

1. Chemical control

1.1 New insecticides

1.1.1 Organophosphorus and carbamate insecticides

1.1.2 Pyrethroids

1.1.3 Insect growth regulators

1.1.4 Larvicides

1.2 Insecticide application

1.2.1 Space application

1.2.2 Other application methods

1.2.2.1 Impregnation of bed-nets with repellents on insecticides

1.2.2.2 Mosquito coils

Cont'd
II. VECTOR CONTROL (Cont'd)

1.3 Insecticide resistance
   1.3.1 Discriminating dosages 22
   1.3.2 The effect of holding temperature in susceptibility testing 23
   1.3.3 Studies on vector resistance to insecticides 24
   1.3.4 Resistance counter-measures 26

2. Biological control 27

3. Genetic control 29

4. Environmental control 30

5. Integrated control 31

III. CONCLUSIONS 31
RECENT TRENDS AND PERSPECTIVES OF
DEVELOPMENT IN RESEARCH RELATED TO
VECTOR BIOLOGY AND CONTROL (1)

Introduction:

The global malaria eradication programme largely depended on residual insecticide house spraying for the attack on vector population. Many technical and administrative problems hampered the progress of several programmes.

Since the adoption of malaria control strategy by the Twenty-second World Health Assembly resolution in 1969 with malaria eradication being the ultimate goal, important developments have occurred. Although progress towards malaria eradication in some programmes continued to be seen, setbacks occurred in many other programmes due to a complex of technical, financial and administrative factors culminating in a sharp increase in malaria transmission reaching the level of epidemics in certain countries. This situation received serious consideration in subsequent World Health Assembly and Executive Board meetings, the last of which resulted in the WHA resolution (WHA31.45), calling for developing an effective malaria control strategy.

As is quite well-known, among the important factors that contributed to the deterioration of the malaria situation is vector resistance to insecticides which has been aggravated by the increasing massive application of pesticides in agriculture. The limited resources of the countries affected by vector resistance hampered the timely replacement of insecticides. The appearance of multiple resistance in some malaria vectors blunted the action of newer insecticides, and the dim prospect for developing new, effective and safe insecticides for public health added more complications. The world move towards the prevention of pesticide hazards to the environment created an impetus in the last decade for reorientation of research towards developing alternative methods of vector control. At the same time, research efforts have been intensified on vector resistance, developing and testing new series of safe compounds with low persistence, as well as chemicals which have biocidal

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(1) Prepared by A.H. Zahar, entomologist, for the first meeting of the Regional Advisory Panel on Malaria, WHO Regional Office for the Eastern Mediterranean Region, Alexandria, Egypt
In retrospect, the paper highlights the findings of vector studies and control in recent years. Without going into details of the theoretical aspects, the achievements of various researches which have practical relevance for pursuance on local vectors in malaria endemic areas in the Eastern Mediterranean Region are reviewed and a comprehensive list of references is given for detailed reading.

I. VECTOR STUDIES

1. Vector bionomics

Studies on vector bionomics and their perspectives are presented according to their scope and the contribution they have made:

1.1 In field research on the epidemiology and control of malaria

Vector bionomics formed an integral component in field studies on the epidemiology of malaria and in the assessment of intervention measures in two important projects: the Garki project, Nigeria, 1969 - 1975, and the Kisumu project, Kenya, 1972 - 1976. The former project aimed at developing a quantitative approach for studying the dynamics of transmission of the predominant malaria infection *P. falciparum*, and assessing the impact of Propoxur residual house spraying alone or combined with chemotherapy as a possible malaria control measure in the dry savanna belt of West Africa, Pull and Gramiccia (1976)

The latter project aimed at testing fenitrothion as a candidate insecticide for the control of malaria, also with *P. falciparum* predominant under the ecological condition of the trial area in East Africa, Fontaine et al (1978)

In both projects, *Anopheles gambiae* (*Species A*), *Anopheles arabiensis* (*Species B*) and *Anopheles funestus* were the main malaria vectors for which comprehensive baseline data were longitudinally obtained from representative localities, followed by data of observations made during and post-intervention periods, with parallel studies in untreated comparison areas. Thus, a wealth of information was accumulated from longitudinal sampling of vector populations found in daytime resting biotopes, biting man indoors and outdoors, and while making exodus from indoor sites. Added to this, other epidemiologically important parameters
were estimated: namely, the sporozoite rates, age structure (in the first project) and host preference represented by the human blood index, which had to be limited to base-line studies and to the post intervention period when adequate samples could be obtained. All this knowledge led to better understanding of the dynamics of the natural vector populations and their implications in malaria transmission under various seasonal climatic changes. With this background, the impact of insecticidal attack could be more reliably assessed. However, difficulties were encountered in determining the degree of exophily of members of the A. gambiae complex by direct evidence, particularly in the Garki project where there was indirect evidence of such behaviour indicated from other entomological observations. The sampling devices used did not seem to have been efficient in sampling the exophilic fraction of the population. In the Garki project, during the period of 18 months of base-line observations, the total number of females of A. gambiae s.l. collected by iron drums placed in and around 3 indicator villages was 199, of which 165 were obtained from one village (Molineaux et al., Entomology base-line report - unpublished report to WHO, May 1974). In the Kisumu project, the mean monthly density of females of A. gambiae s.l. per pit shelter was 1.1 (Clarke et al. - unpublished report to WHO, 1977). Since the impact of propoxur spraying on P. falciparum prevalence in various observation villages in Garki was not uniform, a retrospective analysis of the entomological variables was made by Molineaux et al. (1976) in an attempt to explain such differences. The authors examined the relationship of night biting collections on man (NBC) and house-resting density estimated by pyrethrum spray-capture (SPC) for A. gambiae s.l., A. funestus and Anopheles pharoensis in Garki area. Computation involved the pre-spraying NBC/SPC ratio and its relation with the residual NBC (observed/expected) for each observation village. The variation between the residual NBC of A. gambiae s.l. in villages was significantly positively correlated with pre-spraying density ratio. The variation was stable during the period of 2 years, and therefore it was inferred that it could have been due to differences in the degree of exophily of A. gambiae populations among villages. Some supporting preliminary evidence was provided from cytogenetic investigation. Applying the same method of analysis in Kisumu area, it was found that fenitrothion had a greater impact on A. gambiae s.l. populations than propoxur in Garki area. There was also a tentative cytogenetic and other indications that A. gambiae s.l. populations are largely endophilic in the Kisumu.
As a quantitative measure of the interaction of the entomological factors in malaria transmission, the vectorial capacity index was used in a mathematical model to calculate the expected parasite rate which was compared with the observed rate in Garki area, Molineaux (1977)\(^4\). In Kisumu, the entomological inoculation rate was utilized together with the parasitological inoculation rate derived from a follow-up study of a cohort of infants, Pull and Crab (1974)\(^5\).

In addition to the studies in the above projects, there has been also a wealth of data accumulated from the repeated studies on vector bionomics, namely, *A. gambiae s.l* and *A. funestus*, in the course of field testing of insecticides by WHO VBC Unit ACRU I, Kaduna, Nigeria, the respective documentation of which has been disseminated in WHO/VBC series.

1.2 In antimalaria programmes:

As far as the Eastern Mediterranean and adjacent Regions are concerned, there is some published information compiling the knowledge on vector bionomics that has been gathered during the years of malaria control operations. In the European Region, Postiglione, Talbani and Ramsdale (1973)\(^6\) reviewed the taxonomic problems, the spatial and seasonal distribution, larval habitat, adult behaviour and response to insecticides of vectors of malaria in Turkey. Zahar (1974)\(^7\) reviewed the ecology of malaria vectors in countries having malaria control or eradication programmes in the Eastern Mediterranean Region. Kouznetsov (1976)\(^8\) compiled data on the malaria situation and the distribution of anophelines in the Yemen Republic. Recent knowledge on vector bionomics gathered either from routine observations or incidental investigations seems to remain confined to projects' files or reviewed in unpublished assignment reports by WHO advisers or consultants.

1.3 In special vector population studies:

The following examples are given to show the importance of studying vector population dynamics to the planning of control measures. Breeland (1974)\(^9\) summarized the ecological studies conducted on *Anopheles albimanus* in El Salvador during 1967 - 1972. From a longitudinal series of adult and larval captures, the influence of rainfall, inundation, river flushing and closing and opening estuaries on the seasonal pattern of *A. albimanus* could be determined. The importance of this in planning the conventional imagocidal or antilarval operations
was shown. Also the knowledge gained could serve as a guide for planning the
geneic control trial implemented in this country using release of sterile males.

The data obtained from this trial was utilized by Weidhaas et al (1974)\textsuperscript{10} in refining the knowledge on the dynamics of \textit{A. albimanus} population. Thus, the absolute density of this species in the release area could be calculated. Also the rate of growth of the population, the competitiveness of the sterile males and the survival and fecundity of female populations could be determined. From some actual observations and certain assumptions, a model was constructed to predict the proportion of infective females of \textit{A. albimanus} at different levels of density, varying feeding intervals and survival rates. However, the model indicated the parameters for which good estimates would be needed. With such estimates, it will be possible to simulate the effect of a single or combined control measures on vector density and vectorial efficiency.

1.4 In solving specific problems:

1.4.1 Age determination:

Experience has shown that determination of the physiological age of vector population by the dilatation technique of Polovodova, Detinova (1961)\textsuperscript{11} cannot be performed on a routine basis and should be reserved to special investigation by skilled entomologists. On the other hand, the determination of the parous rate by the tracheal system of the ovaries developed by Detinova (loc cit) has been subject to controversy, although it is generally agreed that sampling should be as frequent as possible to minimize the variability of the results. The need for developing new age-grouping techniques became obvious. Initial trials were made by Schlein and Cratz (1973)\textsuperscript{12} applying the technique of counting the daily growth layers in the thoracic phragma on certain anophelines. Later, Schlein (1975)\textsuperscript{13} refined the technique and applied it on field collected samples of several malaria vectors. In most of the samples, age determination could be made up to 10 layers, each representing a calendar day. In a few specimens, the age could be determined up to 14 days, but, beyond that period, the growth of the phragma ceases or the growth lines become difficult to discern. Further, Spencer (1976)\textsuperscript{14} developed a method to differentiate between young and old parous female mosquitoes by observing the shape and distribution of the granulation
of the follicular debris in the intact ovaries. The method was developed on Anopheles farauti No. 1, the vector of malaria in Papua New Guinea.

Since then, both methods have been awaiting application in the field to assess their reproducibility and practicability from an operational standpoint.

Related to age determination is the estimation of the duration of the gonotrophic cycle which had been tackled by direct observations in the past, or by indirect evidence derived from the fed: gravid ratio of house-resting females of endophilic species or assumptions are simply made. Recently, Carnevale, Molinier and Mouchet (1977)\(^1\) developed a method for estimating the duration of the second phase of the gonotrophic cycle i.e. to maturity of the eggs. Freshly fed females of Anopheles nili from man-biting catches were confined in a cage placed at the edge of a forest. Periodical dissection was made on batches from these mosquitoes until the maturation of the eggs was reached. A mathematical relationship was found between the length of the follicles and the height of the yolk they contain for each developmental stage of the ovary. Such relationship can be utilized for determining the lapse of time needed for maturation of the ovary in wild caught populations provided that more experiments are conducted under varied climatic conditions. Further, Carnevale, Bosseno and Zoulani (1978)\(^2\) repeated these observations on A. nili and carried out studies on the other phases of the gonotrophic cycle involving mark/release/recapture experiments. It was found that the majority of females of A. nili seek a host for a blood meal after 8-14 hours from ovipositing, mature their ovaries in 35-40 hours and seek a breeding place for ovipositing 24 hours after the maturation of the ovaries.

The epidemiological significance of the length of the gonotrophic cycle and its implication in calculation of the probability of daily survival of vector populations is well-known. Therefore, such experimental work to be applied on various vectors indifferent climatic conditions should be encouraged.

1.4.2 Host attraction:

The orientation of flying mosquitoes to a host from a distance has received some attention in the past. Renewed interest on this subject since the early 1970s has been shown. Using a special trapping device in a series of experiments,
Gillies and Wilkes (1972) showed that *Anopheles melas* was attracted to a calf at greater distance than to the equivalent carbon dioxide source. Mosquitoes in their flight wander, first, until they are able to detect and orient themselves to the host odour plume until they reach their target. This orientation must be in response to certain chemical stimuli from the host as yet to be discovered. An investigation in this direction may lead to new sampling devices and control methods.

Another facet which has received some attention in the past is the differential vector biting in relation to the age/sex of the human host. Interest was renewed in this aspect in recent years. Carnevale et al (1976) conducted a series of man-biting catches in Brazzaville area where *A. gambiae s.s* (Species A) is the main malaria vector. Men and women nearly received equal bites, but the number of bites per night increased as the age of the host increased. Infants received half bites less than children and 2.5 times less than adolescents and three times less than adults. The parous rate of *A. gambiae* populations recorded in these observations was 77% and the sporozoite rate was 5.3%.

The epidemiological significance of these findings is obvious and awaits further elaboration for their inclusion in the present mathematical model. More similar observations on other vectors would be highly desirable.

Related to host attraction is the question of multiple feeding, i.e., vector feeding in the same night on more than one human host after an interrupted blood meal. Boreham and Lenahan (1975), utilized the techniques of identification of ABO blood group substances in mosquito bloodmeals and further developed a method for identification of haptoglobin types also in mosquito bloodmeals. The factors influencing multiple feeding were investigated by Boreham, Lenahan and Ohyeka (1978), under laboratory conditions involving several *Aedes* mosquitoes and anopheline vectors of malaria. Field application of the haptoglobin technique was hampered by ahaptoglobinaemia occurring in about 31% of the human population in West Africa, (Boreham et al - in press). The techniques are currently being utilized to determine the attraction of *A. gambiae s.s* to certain age/sex of the human population, (Boreham - personal communication 1977).
The normal precipitin testing could be useful as a research tool for determining the changes in vector human blood index under different ecological conditions. However, the WHO centralized service has been largely utilized as a routine activity by most of the malaria control programmes, the timely interpretation and the utilization of the data of which remains difficult or wanting, with a few exceptions.

1.4.3 Sampling:

The available sampling techniques for malaria vectors have undergone a long period of experience in the antimalaria programmes. In general, they have given satisfactory results whenever manpower and other facilities as well as adequate supervision are available, such as in field research projects. When such conditions are not adequately met, the findings are often considered redundant. Moreover, nearly all the available sampling techniques become insensitive when vector population densities are extremely low, as usually observed after the application of antivector measures. A few observations have been made in recent years using the available sampling methods. In incidental research in the malaria control programme, Pakistan, Akiyama (1974) found that increasing the number of door-traps from 1 to 4 per room increased the yield of Anopheles culicifacies and Anopheles stephensi. Inlet traps gave a very limited yield. Bailly-Choumara (1973) made a comparative study of several capture methods in Morocco, namely hand-capture indoors, Malaise trap, man-bait capture, bed-net traps, CDC light traps with normal and with ultra-violet lights and an illuminated cloth screen from which mosquitoes were collected by an aspirator. In addition to culicine species collected, several anopheline species were recorded, viz. Anopheles labranchiae, Anopheles algeriensis, Anopheles hispaniola, Anopheles ziemanni, Anopheles sergentii, Anopheles multicolor and Anopheles d’thali. The CDC light trap placed indoors was the most productive of all methods. Next to it was the man-bait capture which is irreplaceable for determining the degree of man-vector contact, but baited-net yield was much inferior. The illuminated screen gave the poorest yield and should be discounted.

In Tanzania, Garrett-Jones and Magayuka (1975) used a combination of CDC or Monks Wood Light (MW) traps and a man-bait protected by a bed-net in houses for selective trapping of A. gambiae s.s and A. funestus, i.e., trapping of unfed female mosquitoes. While both CDC and MW light traps were efficient in trapping
of *A. funestus*, Mw trap gave a better yield of *A. gambiense*. In combination with exit window traps Mw trap gave 1.86 times greater yield than that of CDC trap. The method was useful in determining the short term fluctuation in the parous rate.

Little has been done for studying the larval population of the main vectors and for improving larval sampling methods. Various techniques, however, have been utilized for a long time in research, but are not suitable for operational use. For this, various types of dippers have been utilized in malaria control programmes, but it is often difficult to quantitatively interpret their data. Since the work of Service (1971)\(^1\) on the life-tables of *A. gambiense* larval population, there has been no progress in this field, although good advances have been made in studies of culicine larval populations. Service suggested that it may be possible that a few estimates of the absolute population size can lead to a meaningful index (number of larvae per dip). Zahar (1975)\(^2\) reviewed the available types of larval dippers and proposed sampling procedures for evaluating antilarval operations. However, the wide variation in the types of breeding places and their surface areas, coupled with the clumped distribution of larvae necessitates a more profound study to select and standardize the larval sampling techniques and procedures.

### 1.4.4 Detection of sporozoite infection in mosquitos

An improved method for detection of sporozoite infection in mosquitos has recently been developed by Gabaldon and Ulloa (1978)\(^3\) in Venezuela using wild caught *Aedes squamipennis*, which was found to be the natural vector of avian malaria. Each mosquito was dissected, separating the head, thorax and abdomen. Each was placed in a drop of saline on the same slide and broken up with needles. Smears were made, dried, fixed with methanol and stained with Giemsa stain. In infected mosquitos, sporozoites were seen isolated or appear clustered in accumulations. With this method it was found that an auxiliary microscopist can master the technique in less than 3 hours. Another advantage is that the preparations are permanent and confirmation of findings of sporozoite can be made at a later date. It is worth trying this technique on malaria vectors as incidental research for assessing its advantages over the conventional technique.
2. Vector cytogenetic

The developments in cytogenetic studies of malaria vectors was reviewed by White, Coluzzi and Zahar (1975)\(^24\). Cytogenetic has been an important tool in separating members of the sibling species such as the \textit{A. gambiae} complex and \textit{A. nuneztovari} and the closely related species. In addition, investigations on inversion polymorphism are revealing important intraspecific biological divergences among carriers of certain chromosome arrangement. Coluzzi (1978)\(^25\) summarized the findings of his long-term investigation on inversion polymorphism in \textit{A. gambiae s.s} and \textit{A. arabiensis} in West Africa. The frequency of certain inversions exhibit important changes in different geographical zones. \textit{A. gambiae s.s} is widespread throughout the rain forest and Guinea savanna and extends its distribution into the dry Sudan savanna and even some parts of Sahel. \textit{A. arabiensis} prevails in the Sahel and most parts of the Sudan Savanna but becomes rare in the Guinea Savanna, being apparently absent in many localities in the rainy season. This species has not been so far recorded from the Rain Forest in West Africa. Both species show chromosomal variations due to paracentric inversions correlated with climatic conditions and vegetation zones. The forest \textit{A. gambiae s.s} is generally monomorphic for the standard 2R-2L arrangement while various inverted arrangements are frequently observed in savanna areas.

Microecological variations in inversion frequencies have been recorded. In the Garki area of the Sudan Savanna, carriers of certain inversions did not show random distribution in the indoor/outdoor environment. Habitat choice seems to be correlated with climatic conditions. Chromosomal types behaving as less endophilic are those more adapted to humid climates; thus, they are more adapted to avoid higher nocturnal saturation deficit of the indoor environment. From a practical point of view, intraspecific variation in house resting behaviour is expected to produce differences in vectorial capacity and in response to residual house spraying. Thus, the general assumption that all fractions of vector populations have identical probability of contact with the sprayed surfaces can no longer be valid for \textit{A. gambiae} and \textit{A. arabiensis} and this explains the poor impact of residual house spraying in previous malaria control trials conducted in the dry savanna areas.
II VECTOR CONTROL

1. Chemical control:

Chemical control of vectors has constituted, and will probably continue for some time to be the main measure in malaria control. It is necessary, therefore, to review the developments in insecticides and vector resistance studies.

1.1 New insecticides:

VBC (1979) summarized the situation regarding the development of new insecticides, their toxicity and potential use. Additional notes are given below.

The position of the WHO programme for evaluating and testing new insecticides as at 1975-1977 was reviewed by VBC (1977). It was shown that the number of compounds available for testing has considerably been decreasing since 1971. However, a new series of compounds such as synthetic pyrethroids and insect growth regulators (IRG) have been made available for testing. Reviews were made for new imidacloprids in stage V village scale trials by Stiles and Jurjevskis (1977), larvicides in stage IV-V trials, by Jurjevskis and Stiles (1978), pyrethroids toxicological aspects of insecticides used for residual house-spraying by VBC (1978) and IRG by Moreau and Stiles (1979).

The highlights that can be substantiated from various studies are as follows:

1.1.1 Organophosphorus (OP) and carbamate insecticides:

Malathion and propoxur have been in operational use in residual house-spraying for several years. With the necessary safety measures, no cases of malathion intoxication had been reported until the episode in Pakistan in 1976. Collaborative research organized by VBC has disclosed the problem of formulations and more precise specifications were established by the Expert Committee on Vector Biology and Control (1978). Safety measures have been re-emphasized in VBC circulars and in the document of (1978).

In the dry savanna of Gurki area, propoxur alone, or combined with drugs distribution, failed to interrupt *P. falciparum* transmission for more than a few months, Pull and Gramiccia (1976). However, prediction made through the
The mathematical model showed that if the intervention measures were continued, the prevalence of *P. falciparum* would have further been reduced in some of the villages treated with propoxur but not in villages receiving drugs. Obviously, such reduction would be at a high cost and is not feasible to maintain on a long-term basis. The above authors outlined the trend of future research and its aims, as substantiated from the experience of the Garki project, as follows:

(a) to select through the model simulations and using the relevant parameters, those methods of malaria control that would produce the best acceptable reduction in mortality and morbidity under various epidemiological and socio-economic conditions;

(b) to apply these methods in selected typical ecological situations;

(c) to evaluate the contribution made by the model simulation to the selection of control strategies; and

(d) to prepare guidelines for a feasible policy for malaria control in Africa and possibly in problem areas in other parts of the world.

The fenitrothion stage VI – VII trial showed that residual house-spraying with this insecticide produced marked reduction in malaria transmission, predominantly due to *P. falciparum*, under the ecological situation prevailing in Kisumu area in East Africa. The reduction in the risk of contracting malaria was estimated to be 90%, Fontaine et al 1978. Also here, it was indicated that if residual house spraying with this insecticide were continued for a longer period, further reduction in malaria prevalence could be anticipated, but complete interruption of malaria transmission would need supplementary mass drug administration during the wet season. The high cost of the insecticide would be prohibitive to apply in malaria programmes at the same scale of dosage and cycles as adopted in the trial. The YBC document (1979) cited the price of fenitrothion as computed a few years earlier as being 17 times higher than that of DDT. Thus, a study of the epidemiological situation may lead to reduction in dosage or frequency application, hence reduction in cost. Toxicological studies made in the trial showed that fenitrothion is safe when the recommended safety measures are observed.
Chlorophoxim (OMS - 1197) is an OP compound tested in stage V trials by the VBC unit in the Guinea savanna area of Kaduna, Nigeria, against A. gambiae s.l and A. funestus in three rounds each at 2 gm/sq m. It was highly effective for 3 months after each application and gave nearly similar impact on both vectors as that of fenitrothion. It was found to be safe for residual house spraying, with the usual precautionary measures undertaken.

Primiphos-methyl (OMS - 1424) is also an OP compound tested in Kaduna in three rounds at the same dosage as in the above. It gave satisfactory control for 3 months after each round and it showed the same level of safety as with the above compound.

Landrin (OMS 597) is a carbamate compound also tested in Kaduna in rounds during 1973 - 1974, gave consistent impact on vectors during the 12-week period after its application in each round and was nearly as equal in effectiveness as fenitrothion. It is safe as long as the necessary precautionary measures are strictly followed.

1.1.2 Pyrethroids:

Among the synthetic pyrethroids that were tested in Stage V village scale trials are decamethrin (OMS - 1998) and permethrin (OMS - 1821). The results of their evaluation were reported by Rishikesh et al (1978). Residual house spraying was made by 2.5% suspension prepared from 25% water dispersible powder of each of the two compounds, applied at a dosage of 0.05 g/m² and 0.5 g/m² respectively. Although both compounds gave a satisfactory reduction in vector indoor resting density, considerable exodus in exit window traps with high survival of fed and gravid female vectors was recorded. This confirmed the irritability of the two compared reported from stage IV trial in Bobo Dioulasso by Cooseman and Sales (1977). Permethrin exhibited higher irritability than decamethrin. Furthermore, a very high density biting man was recorded indoors in stage V trial and this was attributed to the possible infiltration of A. gambiae and A. funestus from the unsprayed surrounding area. Decamethrin proved superior to permethrin in its persistence on mud walls and caused a higher mortality among mosquitoes from the sprayed huts. Thus, decamethrin may show better impact on a larger scale trial for reducing the infiltration of mosquitoes. Both compounds proved to be safe for indoor residual spraying, at least on a village scale trial.
In the course of field trials in artificial ponds for assessing several synthetic pyrethroids against mosquito larvae, Mulla, Navab-Gojrati and Darwazeh (1978) determined the compounds tested on some non-target organisms. All pyrethroids were toxic to mayfly naiaids; although recovery was observed 2–3 weeks after the application of some compounds.

Dragonfly larvae and diving beetle larvae were not greatly affected, nor were chironomid larvae which were sifted out of mud at the bottom of the ponds. (For resistance to pyrethroids see II, 1.3.3).

1.1.3 IGR:

From Moreau and Stiles (1979) IRG compounds which can be considered for stage IV but scale trials are hydromethane (OMS 1696), methoprene, "Altosid" (1697), diflubenzuron (OMS 1803 and 1804), and the compounds OMS 1828, 1840 to 1843. In fact, "Altosid" (OMS 1697) and "Demilin" (OMS 1804) were recently subject to a small scale field trial in Indonesia respectively by Nelson et al (1976) and Self et al (1976) as well as "Demilin" in Bobo Dioulasso by Sales and Hervy (1977). The test mosquito was Culex pipiens fatigans in Indonesia, and C.p. fatigans and Aedes aegypti in Bobo Dioulasso. Thus, trials with anophele vectors of malaria are highly desirable.

The environmental and toxicological aspects of IRGs were reviewed by Wright (1976). The environmental aspects, such as those related to metabolism in soils, plants, insects, and animals, strongly suggest that these chemicals undergo rapid degradation and change to innocuous metabolites. The toxicological properties determined for registration of the juvenoid methoprene reflected no significant effect on any species tested. Toxicological experiments in swine, sheep, cattle, dogs, hamsters, rats, rabbits and guinea pigs revealed no clinical signs of toxicity. Moreover, teratological studies in swine, sheep, hamsters, rats and guinea pigs revealed no observable effects on these animals at the level of dosages administered.

The effect of methoprene, applied as specific for control of mosquito breeding on natural populations of aquatic organisms in marsh habitats, was studied by Bravard et al (1977) in Louisiana. Six aerial applications of methoprene (28 gm a.i./ha/application) over an 18 month period significantly reduced the populations of 14 aquatic organisms, but none of the affected organisms was eliminated.
The control of predator species caused corresponding increases in certain prey populations. Repopulation of the affected organisms in the treated area would occur from adjacent untreated marsh as was shown by the recovery of the aquatic organism population following a drought which occurred during the observation period. Georgiou (1978) showed that cross-resistance and induced resistance to methoprene were demonstrated in house-flies, mosquitoes and several other insect species.

1.1.4 Larvicides:

In the document of Jurjevskis and Stiles (1978) a bibliography was given covering the documents and publications on field trials with larvicides mainly OP compounds applied as emulsions, floating and sinking granules, water dispersible powders, oil sprays, ULV and, in one instance, as resin strips. Most of the test insects were Cx. fatigans, Ae. aegypti and other culicines. The early trials with Abate against A. gambiae are listed. Some trials were conducted with IRG, as shown above.

Interest has been revived in recent years in developing organic films to control mosquito immature stages by reducing water surface tension. Garret and White (1977) reviewed conventional mosquito control by the use of larvicides of petroleum oils incorporating surface-active spreading agents and the prospect of their replacement by insoluble organic monomolecular film forming chemicals. The physicochemical properties of such chemicals have been outlined. The most effective and persistent agents are those spontaneously spreading surface active liquids which can reduce the surface tension of the water to below 29 dynes/cm. One of the advantages of such agents is the very small volume of the liquid to be applied on the surface of the water which was estimated from laboratory experiments to be 0.04 ml/m². This dosage is at least 70 fold less than that of a petroleum oil mixed with a good surface active agent estimated to be 2.8 ml/m². One of the limitations is the difficulty in achieving total coverage with these liquids in large volumes of water under windy conditions. However, most of the breeding of mosquitoes occurs in small pools, irrigation canals or in swamps having vegetation which would protect the surface film.

The results of laboratory and semi-field experimental testing of 4 monomolecular surface films were given in detail by White and Garrett (1977). At a dosage of 0.04 ml/m², two of the four compounds produced 100% mortality in 4th instar larvae of Anopheles quadrimaculatus 24 hours after application in both laboratory and field tests, but none of the compounds was effective against Aedes
larvae. In artificial field pools frogs, toads, gerrids, nymphal stages of Odonata and Ephemeroptera as well as several species of aquatic Coleoptera, existed. Only species intimately associated with the airwater interface were affected, such as gerrids, but these again became active 24 hours after treatment. Further, White, Garrett and Monk (1978) tested 3 monomolecular surface films, applied at a rate of 0.04 m/m² in the laboratory and found 2 compounds achieved more than 96% control of 4th instar larval of A. quadrimaculatus.

Other experimental work is that of Reiter and McMullen (1978), who tested in the laboratory, pure egg lecithin against the immature stages of A. gambiae, A. stephensi, A. farauti, A. albimanus, A. quadrimaculatus, Aedes aegypti, A. rusticus and C.p. fatigans. The authors established the critical film pressures for each species, above which surfacing of larvae and pupae was inhibited. Anopheine larvae were prevented from surfacing and died in water of low oxygen content, but culicine larvae survived. The pupae of all species except C.p. fatigans were killed. Further, Reiter (1978) carried out laboratory experiments to investigate the action of lecithin monolayer on the respiratory structure of mosquito larvae and pupae. In the presence of this monolayer, a stable soap-like bubble type is formed, which prevents the insect from surfacing. Subsequently wetting the hydrophobic areas takes place. The power of floating of pupae is lost through flooding of the ventral air space.

The experience of Picher and Aspok (1978) was different from those field experiments cited above, as they found lecithin applied in the breeding places of Aedes spp to be exceptionally effective in waters free of vegetation and visible objects such as leaves and branches. Whenever the water surface showed interruptions, a closed film could not develop to the extent that larvae and pupae could easily come up for respiration. The authors indicated that their results suggest that the available preparations of lecithin is not appropriate for control of mosquitoes. This should not mean abandoning this safe and useful method, but more investigations should be made to find an appropriate preparation. A granulated form of the substance was undergoing testing.

Some field trials were carried out by members of Southampton University, under the leadership of Professor A.I. McMullen, the publication of which is awaited. The monolayer film approach needs extensive field research to assess its practicability and cost/effectiveness against the main malaria vectors,
under different ecological conditions.

1.2 Insecticide application:

It is not intended here to deal with the conventional methods of application of insecticides, such as compression sprayers, since this type of equipment has been in operational use in antimalaria programmes for many years, and several improvements have already been made. Reference is only made to other methods of application of insecticides, that may have a place in antimalaria programmes and are in need of development or field trials.

1.2.1 Space application:

Residual house spraying, applied with compression pumps, has not given an opportunity for introducing space application of insecticides in antimalaria programmes. There is a vast amount of literature on controlling culicine mosquitoes, including vectors of dengue haemorrhagic fever and Japanese encephalitis using ground or aerial space application with different insecticides. There is also a variety of machines either vehicle mounted or portable, for ground dispersal of insecticides. There is also a continuous development in these devices, mainly for agricultural use, but modifications are being introduced to suit their use in public health. Hadaway (1978) discussed the need for improving the formulations of the existing compounds to ensure better delivery and increased biological activity of the insecticide. He indicated that considerable advances have already been made, with the introduction of machinery based on rotary atomisers and ULV spray techniques.

Research in this field should continue to be encouraged. The more recent development in electrostatic spray technology should also be investigated with a view to improving the direction of spray droplets to targets. Rafatjah (1975) described the available methods of applying insecticides as thermal and cold fog, or mist, as well as the ULV technique. These methods would need field testing against malaria vectors, as it can be utilized as emergency measures of vector control in case of epidemics, for urban malaria control or in organized agriculture schemes in an integrated malaria control operation.

Reference is made to some trials with space spraying carried out in a few
malaria control programmes. In Turkey, a small scale trial was conducted to assess the effectiveness of different insecticides applied as aerosol by LECO HD vehicle mounted machines and as thermal fog by Swing SN 11 generators (Parker, VBC and Muir, MPD unpublished duty trip report to WHO). Caged *A. saccharovi* females were placed at sites in a linear array at 20 metre intervals for 100 m distance downwind of the track of application of the insecticide. Mortality counts were taken 24 hours after exposure together with counts of mortality in untreated control cages. Actellic 50% (pirimiphos methyl) applied at a rate of 31 g a.i./ha was the most effective ULV application. Neopybuthrin S 500 Q 52% (52% pyrethrins + synergist) applied at 65 g a.i./ha was the most effective thermal fog application. In cattle sheds respectively Actellifog 10% and Neopybuthrin S 500 Q were tested as thermal fog. The Swingfog generator was adjusted to give an output of 0.1 second application for each cubic metre of volume of the cattle sheds (60 m³ total volume which required 6 seconds of application). A high kill was observed with each product, both in caged *A. saccharovi* and its normal resting population in the cattle sheds. More trials are needed to determine the cost/effectiveness of these promising compounds and devices applied on a larger scale.

In Malaysia, 5% malathion in diesel oil supplemented by 0.5% reslin (22.5% pyrethrins + synergist), in a 1:1 mixture was applied as a mist by knapsack mist blowers mounted on vehicles, Kirla and Hoek (1978)⁴⁸. The application was made around and under the raised floor houses as well as in the surrounding bushes, as possible outdoor vector resting sites. The main vectors of malaria in the trial area were *A. maculatus* and *A. campestris*. The discharge rate ranged between 280-370 ml/minute. The entomological evaluation depended on counting the 24-hour mortality in laboratory-bred *A. maculatus* confined in cages placed inside and under houses and in the surrounding bushes. 100% mortality was recorded in caged mosquitoes placed at different sites. No other entomological assessment was made. The application was meant as a main supplementary measure to DDT house spraying to combat the increasing malaria transmission in two foci considered as a problem area. Other measures were improved Abate larviciding, case detection and radical treatment.

1.2.2 Other application methods:

Reference should be made to some trials with certain methods of vector
control that may play a role in a self-help by the community in an integrated malaria control programme.

1.2.2.1 Impregnation of bed-nets with repellents or insecticides

Interest has been renewed in utilizing the standard bed nets or wide-mesh netting impregnated with repellents or insecticides. Grothaus et al (1972) impregnated wide-mesh bed nets (mesh width 0.635 cm) with 8 repellents at a rate of 0.5 gm/gm net weight but 3 of the repellents were applied at a rate of 0.25 gm/gm net weight. The bed-nets were used by volunteers in the field who caught the mosquitoes that attempted to feed on them. Several species of Aedes, Psorophora, Culex and Anopheles constituted the mosquito fauna in the study area. Observations were continued for 3 years. After each night observation, the bed-nets were hung in a store at room temperature. During winter months, they were packed separately in plastic bags at room temperature (19.5 - 25°C) until the following spring. The total protection (average percentage effectiveness) was established by comparing mosquitoes collected from an inside control with each repellent net combination. The average total effectiveness of "deet" (N, N-Diethyl-m-toluamide) used as a standard repellent was 98% but its efficacy fell below 90% after 30 days. One of the repellents (O-Ethoxbenzolpy) piperidine remained effective for 359 days after impregnation. Another repellent O-Ethoxy-N, N-diethylbenzamide remained effective for 787 days after impregnation. Further Grothaus et al (1974) evaluated 3 new repellents namely: O-ethoxy-N, N-diethylbenzamide; O-ethoxy-N, N-dipropylbenzamide; and 2-(p-methoxybenzyl)oxy N, N-dipropylacetamide. Protection times ranged from 83 to 236 days. Considering availability and toxicity, 2-(p-methoxybenzyl)oxy N, N-dipropylacetamide appears to hold promise as a repellent for wide-mesh netting. The authors indicated that wide-mesh netting is economical, easy to utilize and provides good ventilation when used for covering windows and doors or as bed-nets or protective shirts.

Zaugg (1978) impregnated wide-mesh netting similar to those used by the above authors at a rate of 0.5 gm/"deet" gm netting. Using CDC miniature light traps within treated and untreated nets showed that deet-treated wide-mesh netting was effective against mosquitoes, Culicoides spp. and phlebotomines during the rainy season in the Panama Canal Zone for about 64 days. Thus this treatment proved that it gave an effective, though temporary, protection under humid conditions.
Another approach for utilizing bed-nets is their impregnation with insecticides, Brun and Sales (1976)\textsuperscript{52}. Four insecticides were selected after laboratory experiments were made, namely: chloropyriphos-methyl (OMS-1155), pirimiphos-methyl (OMS-1424), chlorophoxim (OMS-1197) and fenitrothion as reference insecticide. The bed-nets were impregnated at a rate of 0.2 g/m\textsuperscript{2} using insecticide solution. They were placed in experimental huts (2 bed-nets in each) under which children slept. Dead mosquitoes were collected in the morning and those found alive were held for 24 hours mortality observations. Untreated control bed-nets were likewise operated. The species involved were \textit{A. gambiae}, \textit{A. funestus} and \textit{A. nili}. Only chlorophoxim showed satisfactory results as the mortality it produced exceeded 85\% for over 2 months on cotton bed-nets. More trials are needed for assessing the cost/effectiveness of this method versus the conventional residual house spraying.

1.2.2.2 Mosquito coils

Mosquito coils have been commercially produced and used by the public in many countries for protection against mosquito nuisance. Hudson and Esozed (1971)\textsuperscript{53} assessed the effectiveness of coils containing pyrethrin or DDT in experimental verandah trap huts with human baits in Tanzania. The smoke generated from 0.04 - 0.3\% pyrethrin coils deterred 24-84\% of \textit{A. gambiae} s.l and 71-93\% of \textit{Mansonia uniformis} from entering treated huts and that generated from 7.3-13\% DDT coils deterred 91\% of \textit{A. gambiae} and 92\% of \textit{M. uniformis}. Hudson (1974)\textsuperscript{54} combined evaluation of mosquito coils in tents placed in woodland in Canada against \textit{Aedes} spp. Both 0.3\% pyrethroids coils and 0.35\% allethrin coils caused more than 93\% reduction in mosquitoes entering human-baited tents.

The above results indicate the effectiveness of mosquito coils in deterring mosquitoes from entering individual huts or tents, but what is needed is to assess these devices on limited village scale trial. The possible divergence of the deterred mosquito to animals should be adequately assessed. Integration with other methods of vector control should also be investigated.
1.3 Insecticide resistance

1.3.1 Discriminating dosages

Subsequent to the development of WHO Standard procedures for determining the susceptibility of adult mosquitoes to organophosphorus (OP) and carbamate insecticides, and similarly for larval testing with OP compounds, a lot of tests were carried out, but difficulty arose regarding the interpretation of data in the absence of discriminating dosages, except perhaps for propoxur and Anopheles albimanus, Georghiou (1972)\textsuperscript{55}.

Investigation carried out at the Ross Institute of Tropical Hygiene, London, using 14 anopheline species including populations susceptible and resistant to DDT and dieldrin enabled establishing tentative discriminating dosages for testing with OP and carbamate insecticides, Davidson and Zahar (1973)\textsuperscript{56}. Further checking of abnormal reactions of certain species to the discriminating dosages of some insecticides was made and the investigation was extended to establish the discriminating dosages for larval testing. The detailed results were given by Davidson (1975)\textsuperscript{57} and the tentative discriminating dosages for anopheline adult and larval testing with organochlorine, OP and carbamate insecticides are summarized in WHO Tech. Rep. Ser. No. 585 (1976)\textsuperscript{58}. Stress has been laid on the need for testing the validity of the tentative discriminating dosages on field populations because these were derived from laboratory testing of male and female adult anophelines aged less than one day old and the fourth instar larvae. Under field conditions, there are many factors which cause variability of results of susceptibility tests not least of which are the non-homogenous physiological state of wild populations and the variations of climatic conditions. Thus, it is difficult to establish the exact discriminating dosages for each vector under conditions simulating nature. Using the tentative discriminating dosages as a guide a further refinement can be made by experienced entomologists for determining the LC\textsubscript{95} or LT\textsubscript{95} or more usefully LC100 or LT100 from the log-probit regression line derived from testing a fairly large sample of mosquitos as was adopted by Rosen (1967)\textsuperscript{59} for testing Culex pipiens fatigans with organochlorine and OP compounds and Haman and Sales (1970)\textsuperscript{60} for testing A. gambiae, C.p. fatigans and Aedes aegypti with OP and carbamate compounds. Having noted seasonal variations in C.p. fatigans susceptibility, the first author showed the minimum and maximum LC values. It is also extremely
important to designate the dosage which would ensure not only killing the normally susceptible individuals but also those exhibiting the extreme range of susceptibility.

Once the discriminating dosage has been reliably established for a local vector, the appearance of survivors of this dosage consistently would warrant verification tests as was recommended by Davidson and Zahar (loc cit). However, raising and testing offspring of survivors may not be feasible with limited facilities under field conditions. Thus despatch of material of the suspected cases of resistance to specialized laboratories should be sought.

1.3.2 The effect of holding temperature in susceptibility testing

Earlier studies indicated that DDT is almost always more toxic at lower temperatures and less toxic at higher temperatures, but the reverse was observed with the few OP compounds available at that time as was reviewed by Busvine (1971)\(^6^1\). *A. sacharovi*, which is the main vector of malaria notably in Syria and northern Iraq, has posed a great problem to the antimalaria programme in Turkey in the Çukurova plain area due to its resistance to organochlorine and OP compounds. Malathion replaced DDT and there was some concern about the susceptibility of this species to malathion, particularly with the extensive use of OP pesticides in agriculture.

In 1976, testing with 5\% malathion for one hour in the spring gave lower mortality than in summer (Ramsdale - unpublished report to WHO). An investigation was carried out by Davidson at the Ross Institute (1977)\(^6^2\) on the effect of temperature using different vector species and strains exposed to the discriminating dosages of several OP compounds at two temperature levels: 20\(^\circ\)C and 27\(^\circ\)C. In nearly all tests, mortalities were less at lower temperatures. Further, the population of *A. sacharovi* in Çukurova plain was tested in the field with several insecticides during August/September at temperatures of 31\(^\circ\)-33.5\(^\circ\)C and R.H. 50-60\%. The tests in general indicated that the population was largely susceptible to malathion. When tests were carried out at two temperatures: 21\(^\circ\)-27\(^\circ\)C and 31\(^\circ\).33.5\(^\circ\)C, survival was higher in the lower temperature range. Thus establishment of new discriminating dosages for temperature other than the usual range of 25\(^\circ\)-27\(^\circ\)C is indicated, Herath (1977)\(^6^3\).
1.3.3 Studies on vector resistance to insecticides

Cross resistance studies would help in identifying the compounds that are likely to be effective as replacement insecticides against a vector population exhibiting resistance to an insecticide or a group of insecticides. Genetic studies together with biochemical investigations would help in understanding the mechanisms causing resistance. These may eventually guide the development of effective insecticide for dealing with a specific resistance. The Expert Committee on Insecticide Resistance in its report (1976)\textsuperscript{58} drew attention to the fact that such studies, particularly through biochemical techniques, have been carried out on a few insect species, notably the housefly and called for the extension of these studies to important vectors of diseases. The whole subject has been thoroughly discussed by Oppenoorth (1975)\textsuperscript{64} and the recent findings of investigations carried out on the mechanism of resistance in certain malaria vectors has been reviewed by VBC (1979)\textsuperscript{65}. The present review will concentrate on the cross resistance patterns so far determined.

Research on OP and carbamate resistance in A. albimanus from Central America has been initiated and elaborated mainly by the Department of Entomology, University of California, Riverside, USA, Ariaratnam and Georgiou (1971)\textsuperscript{66}, Georgiou (1972)\textsuperscript{55}, Georgiou et al (1974)\textsuperscript{67} and Ariaratnam and Georgiou (1974)\textsuperscript{68}. Genetic and cross resistance studies indicated that carbamate resistance in A. albimanus from El Salvador under laboratory selection with propoxur remained fairly stable after the relaxation of selection pressure for 12 generations. Studies on the genetics of carbamate resistance in this strain showed that this resistance is monofactorial but influenced by modifying genes. Selection pressure resulted from the use of pesticides in agriculture for several years created an accumulation of ancillary genes that favoured the stabilization of this resistance. Further, it was shown that the strain was not resistant to some pyrethroids viz. hioresmethrin, bioallathrin, but a low level of resistance was recorded with cismethrin.

At the Ross Institute, London, studies have been pursued on insecticide resistance in A. sacharovi from Turkey, A. culicifacies from India, A. stephensi from Iran and A. arabiensis from Sudan, Davidson and Herath (1977)\textsuperscript{62,63}, (1979)\textsuperscript{69}. 

**A. sacharovi**: as mentioned earlier, the highly DDT/DT resistant *A. sacharovi* was largely susceptible to malathion, but the small survival of the discriminating dosage needs investigation. Regarding the other OP compounds tested, also some survival was recorded, the largest of which was with 1% fenitrothion for one hour. Some survival also appeared with 0.1% propoxur, but significant survival was observed with 5% carbaryl for one hour. It was surprising to find significant survival with one hour exposure to 0.2% permethrin and 0.001% decamethrin, as these insecticides were reported not to have been used in agriculture. This survival may have been associated with DDT resistance in this species.

**A. culicifacies**: The DDT/DT resistant *A. culicifacies* developed resistance to malathion as well. From survivors of 5% for one hour in the field in India, egg batches were obtained and a colony was established in 1976. This population showed complete survival on the above-mentioned dosage of malathion. When compared with susceptible populations from Sri Lanka and Pakistan, this population exhibited resistance to malaoxon, chlorophoxim, diazinon, totofenphos, fenitrothion, pirimiphos-methyl and chlorothion. This pattern of broad spectrum of resistance may indicate the involvement of other detoxication mechanisms other than those known to operate in malathion and malaoxon. In this series of tests, the species showed complete susceptibility to propoxur.

Mode of inheritance studies showed that malathion resistance depends on a single gene and it is incompletely dominant. The results of backcrosses to the susceptible parent and testing with malathion and fenitrothion discriminating dosages suggest that either a single gene is responsible for malathion and fenitrothion resistance or the factors of the two are closely linked.

**A. stephensi**: The DDT/DT resistant *A. stephensi* was first reported to be resistant to malathion in Iran by Manouchehri, Zaini and Djanbakhsh (1976). A colony was established in London which initially showed 98.5% mortality with one hour exposure to malathion. Selection with malathion stepped up the level of resistance, the mortality with above-mentioned exposure was not more than 12.5%. The laboratory selected population was exposed to malaoxon, fenitrothion, chlorophoxim, phoxin, pirimiphos-methyl, phenthoate, propoxur, carbaryl, permethrin and decamethrin. It was observed that with fenitrothion there was a twofold increase in the level of resistance as compared...
with the unselected population. A certain degree of tolerance to chlorophoxim, phoxim, pirimiphos-methyl and phenthoate was observed. Further, the survivors of fenitrothion exposure were used to establishing lines selected with this insecticide in order to determine its reaction to other OP compounds in comparison to the malathion selected and unselected populations with the following results:

- the malathion selected population which exhibited an 8-fold increase in malathion resistance showed no increase in the fenitrothion resistant individuals
- the lines selected with fenitrothion exhibited simultaneous increased tolerance to other OP compounds including malathion.

Thus, it appears that there is a mechanism which generally increases the tolerance to all OP compounds and is independent from the mechanism specific for malathion and its analogs. As there has been evidence from genetic studies that only a single gene is responsible for malathion resistance, it is possible that there is a very close linkage between the two factors. As a working hypothesis, malathion pressure alone may lead to the eventual selection of multiresistant populations. The frequency of the gene of the general OP resistance mechanism would determine the speed of building up of the resistance. When the specific malathion resistant mechanism becomes well established, rapid selection for a more general defence mechanism can occur through the application of malathion or fenitrothion or any other OP compounds in the field.

A. arabiensis: A colony of the DDT/DB resistant A. arabiensis was established in London in 1977 from the offspring of survivors of 5% malathion for one hour in tests carried out in the Gezira area, Sudan, under malathion resistance in this species. Laboratory studies carried out by Mustafa Akood (1978) showed that 5 hours exposure to 5% malathion did not give more than 79.9% mortality and the offspring of the survivors to this exposure gave much lower mortalities on one and two hours exposure to 5% malathion respectively confirming the presence of resistance to malathion in this species in this area of Sudan. On the other hand, there has been no sign of cross resistance to fenitrothion. Further selection in field populations particularly with the pressure created by the extensive application of agricultural pesticides in the Gezira will not only step up the level of malathion resistance, but will influence its spread throughout the area.
The above citations illustrate the recent trend in research on insecticide resistance in malaria vectors which stemmed from the appearance of OP and carbamate resistance, as well as organochlorine resistance, aggravating the situation for vector control in antimalaria programmes. More light will be shed with the progress of studies on the characterization of the various mechanisms of resistance through blocking the pathways of enzymes involved by the appropriate synergists.

1.3.4 Resistance counter-measures

At present there is no easy way for overcoming the problem of insecticide multiple resistance. The possibility of reducing the selection pressure or retardation of resistance by judicious use of insecticides or use of mixtures or rotation of insecticides, is discussed in the Report of the Expert Committee on Insecticide Resistance of Vectors and Reservoirs to Pesticides (1976)\(^{58}\), VBC document on resistance (1976)\(^{71}\) and VBV recent working paper to the Expert Committee on Malaria (1979)\(^{65}\).

Judicious use of insecticides in malaria control is unlikely to prevent or even to retard the appearance of insecticide resistance because of the selection pressure created by the extensive use of chemically related pesticides in agriculture, Hamon (1978)\(^{72}\). As shown above cross-resistance studies have been a useful guide for selecting an alternative insecticide. Nevertheless, the potentiality of such an insecticide is substantiated from laboratory experiments which cannot reflect its operational life under field usage. This will depend on the amount of selection for resistance of agricultural pesticides. It has been postulated that possibly malathion pressure alone may lead to the eventual selection for OP multiresistant mechanism. Banning malathion in agricultural pest control is unlikely to prevent OP generalized resistance since other OP compounds will act as selecting agents. To ban all OP compounds in agriculture field is impracticable as it cannot be accepted because of the risk entailed for the cash-crops and the drive for more food. The only hope is the judicious use of pesticides in agriculture by an efficient pest management programme which would maximize crop protection with a limited group of pesticides, regulated in time and space.

Replacing an insecticide with an alternative is an important decision which cannot be based on the results of susceptibility tests. Even if these show indications of resistance, the decision must be based on
epidemiological/entomological field observations to determine the operational implications of vector resistance to the insecticide currently used, Expert Committee on Insecticide Resistance of Vectors and Reservoirs to Pesticides (1976).

Recently theoretical approaches have been developed for dilution or retardation of insecticide resistance through migration of susceptible individuals from untreated areas. Muir (1975 and 1977) advocated application of more than one insecticide in a strip or grid system leaving "buffer" unheated zones in between. Some form of protection by measures other than the insecticidal method would be applied in these "buffer" zones. Wood & Cook (1978) introduced some modifications to the method adopted by Muir (1975) for estimating the selection pressure of an insecticide. Comins (1977) developed a model incorporating migration of susceptible population from untreated areas so that the large variations in time required for the insects to develop resistance, can be better elucidated. He established a critical migration rate above which resistance is greatly retarded. The model also suggests that the density dependent factor is important in determining the optimal insecticide kill rate and that a larger kill rate will probably delay the onset of resistance.

All these theoretical approaches await demonstration of their feasibility and practicability under various epidemiological situations. Ross Institute/MRC has started an investigation in Sri Lanka for trying the grid system mentioned above with the release of insecticide susceptible males to prevent or dilute vector resistance. The results of initial studies will be given in the forthcoming Progress Report of Ross Institute (Dr Davidson - personal communication, 1979).

2. Biological control

Since the early era of malaria control, larvivorous fish were an important tool for control of mosquito breeding. With the advent of residual insecticides, interest in utilizing fish waned, except in a few countries where fish was utilized as a supplementary vector control measure. Motabar (1978) reviewed the knowledge on Gambusia affinis and outlined the procedures for its culturing, transportation and for the seeding of breeding places. Motabar also enumerated the advantages and limitations
of Gambusia. In recent years there has been some attempt to revive the use of Gambusia where it exists. In Turkey, the malaria control programme made a large scale distribution of *Gambusia affinis* holbrooki in Adana plains. Onori and Muir (Report on a visit to Turkey to assist the Malaria Programme: 1 May - 9 June 1978 - unpublished) observed that Gambusia co-existed with high densities of *A. sacharovi* larvae particularly in drains overgrown with aquatic vegetation which provide a favourable medium for the larvae. The effectiveness of Gambusia was found to be limited to areas of relatively open waters. In Sudan, following preliminary field studies in Gezira irrigated area, a plan was prepared for a large-scale trial of Gambusia as a supplementary measure. The implementation of the plan is awaited. In India, Menon & Rajagopalan (1978) carried out a large scale trial to control mosquito breeding in 3402 wells and subsequently in 3438 wells using *Gambusia affinis* and *Aplocheilus blochii*. Mosquitoes involved were *A. stephensi* and *C.p. fatigans*. One month after the introduction of the fish the percentage of positive wells fell from 32.8 to 0.47 for *A. stephensi* and from 11.9 to 2.1 for *C.p. fatigans*. In some wells control could not be achieved due to fish mortality. In wells where *G. affinis* did not survive, *A. blochii* was introduced because of its higher tolerance to salinity and high pH.

The annual fish *Notopterygion guentheri* has recently received attention through laboratory studies on its biology, such as in the series of papers by Markofsky and Pertmutten (1972), Markofsky (1973) and (1976), Markofsky and Matias (1977) and several other papers being published. It is understood that field trials are being planned for evaluation of the annual fish in Somalia and Turkey.

A WHO scheme for screening and evaluating the efficacy, safety and environmental impact of biological agents for control of disease vectors was established in 1975. Arata (1979) reviewed the present situation of various candidate agents.

Some information has been provided on certain promising pathogens by Dr J. Hamon, Director of VBC Division. Investigations on *Bacillus sphaericus* (strain 1593) conclusively showed that this strain is innocuous to mammals under routine exposure. Investigations on the toxin(s) of two strains (1593 & 5511-1) of *B. sphaericus* showed that they had different stability when exposed to heat, sonication, freezing, pressure and storage. The 1593 strain was more promising than the other. Laboratory and field studies carried out the
experimental formulation of *B. sphaericus* in USA confirmed the environmental safety of the strain 1593 and its effectiveness against mosquito larvae.

*B. thuringiensis* is another promising entomopathogen. Studies are underway for determining its safety to mammals. This agent showed promising results against *Culicidae* and *Simuliidae* and only affects some non-target organisms closely related to mosquitoes. Good results have been obtained with *B.t. israeliensis* (serotype 14) against mosquito and Simulium larvae although more improvement of formulations is needed. Investigations on endotoxin(s) of serotype 14 have so far indicated that the characteristics and mode of action of these endotoxin(s) are similar to those of the other serotypes of *B. thuringiensis* which are used extensively in agricultural post control. A standard spore-crystal powder of *B.t. israeliensis* has been produced as reference material for bioassay testing.

3. Genetic Control

Davidson (1978)\(^8^4\) reviewed all the possible methods of genetic control of culicines and anophelines. Pal (1979)\(^8^5\) summarized the position of research on genetic control of malaria vectors and outlined their potential use.

The largest genetic control trial of malaria vectors was that made by the release of chemosterilized males of *A. albimanus* in El Salvador, Breeland *et al* (1974)\(^8^6\), Dame *et al* (1974)\(^8^7\), Lofgren *et al* (1974)\(^8^8\), Weidhaas *et al* (1974)\(^8^9\) and Weidhaas *et al* (1974)\(^9^0\). The experiment gave promising results but the problem which remained was the sexing of pupae. In this experiment a total of 4,357,600 sterilized males of *A. albimanus* was released over 5 months. Because the method of sexing of the pupae by size was 86% efficient, 683,400 females were estimated to have been released as well. The repercussions of releasing potential vectors are obvious. Recently Seawright *et al* (1978)\(^9^0\) succeeded in developing a genetic method for separation of females of *A. albimanus* by inducing translocation which links the gene for propoxur resistance to the Y-chromosome. By back-crossing the translocation males to propoxur susceptible females, the male progeny will be resistant to propoxur while the females are susceptible. These can be eliminated by exposure to a suitable dosage of propoxur at the larval or the adult stage. By this method, 600,000 sterile males can be produced per day instead of 150,000 in the previous trials.
When the final success of the genetic control method is eventually demonstrated, it will represent an important tool as an alternative to insecticide. In the meantime, it may be worth conducting trials of genetic control in well isolated and circumscribed areas as in malarious oases.

4. **Environmental control**

The pre-DDT era saw the efforts made to control malaria vectors through the control of their breeding. In addition to the use of some larvicides such as oil and Paris-green and environmental management played an important role. Drainage, control of water level, and shore-line management, flushing, removal of vegetation, land reclamation of swampy areas, etc., were efficiently and successfully employed to prevent mosquito breeding and examples are well documented in the literature. The whole subject of environmental management was recently reviewed in the Seminar on the Prevention and Control of Vector-Borne Diseases in Water Resources Development Projects (1978). Rafatjah (1979) has further elaborated the role of engineering methods in a comprehensive approach for control of vector-borne diseases.

Under environmental control comes also the methods used for prevention of man/vector contact by house-proofing. As it is well known, the cost of elaborated types of house-proofing becomes prohibitive when one thinks of the housing situation in several areas in most of developing countries. Recently Kolstrup (in preparation) succeeded in modification of the rural houses on the coast of Tanzania. This was done by installing ceilings, doors and screening of window using locally available material. By this simple devices, *A. gambiae s.l.* the main vector of malaria and bancroftian filariasis and *C.p. fatigans* the vector of the latter infection could be prevented from entering sleeping rooms. The method was found to be acceptable by local inhabitants and needed simple organization and little of foreign currency.

More of such attempts are needed with the full participation of the rural community.
5. Integrated control

The term integrated control has repeatedly come up in the literature for the last 10 years or so, although in the pre-DDT era a combination of water management, biological control, larviciding and pyrethrum knock-down sprays constituted the tools of vector control. In this connection it is sufficient to make the following quotations. Mulhern (1978) stated: "it is now popular to promote integrated control", and it is implied that this is a newly discovered approach! Yet if you refer to Table 1, it may be considered as a check list of commonly applied mosquito control measures in use throughout most of the long history of successful mosquito control, and then you will become fully aware that within operational mosquito control the term "integrated control" is merely a new name for a very old and familiar balanced programme, one that combines in optimum fashion biological control, physical control and chemical control.

In his presentation to the Kenyan Academy, Hamon (1978) stated: "The intelligent use of scientific discoveries and the development of an appropriate technology constitutes some of the keys to the effective control of vectors and vector-borne diseases at a cost that endemic countries could afford. However, producing a tool is not enough. It must be applied after adjusting it to the local ecological, epidemiological and socio-economic conditions and one must remember that many useful, safe and reasonably cheap tools are not used, or not used properly.

III. CONCLUSIONS

In each of the foregoing sections, the achievements of various researches on malaria vectors and their control and the need for further studies have been outlined. With the exception of a few vectors well studied under certain ecological conditions our knowledge of vector biometrics is far from being complete. Even knowledge on those vectors which had been fairly well studied in the past needs updating. This is
in view of the important environmental changes that have occurred in the last 20 years as necessitated by socioeconomic developments in most of the developing countries involving expansion of agriculture for cash or food crops, creation of dams or reservoirs, etc. Arid areas are becoming more favourable for vector adaptation prolonging their seasonal abundance and deforested areas have influenced changes in vector behaviour. Associated with these, are the changes in human ecology and animal husbandry. Where such changes have occurred studies on vector bionomics should be intensified by the anti-malaria programme concerned.

Some specific aspects need special research efforts. For example, host preference studies should not be regarded as a dogmatic routine activity of precipitin testing but as a well planned investigation with clearly drawn objectives in selected situations. This will, however, await investigation for solving sampling problems particularly with respect to the outside resting populations. Knowledge on vector dispersal is fragmentary and it has often been extrapolated from a few old experiments conducted under certain ecologies. Sound knowledge on vector dispersal is indispensable for determining the extent of a control programme, if no generalized country-wide control is envisaged. Such knowledge will also benefit planning of genetic control. Knowledge of survival of adult vector populations is limited for certain species and areas. Factors influencing adult vector natural mortality are only known in general terms which do not help the full understanding of population dynamics. On the other hand, the study of the larval populations and vector output is nearly remaining as an untouched field while such knowledge is fundamental for developing effective larval control methods.

If one regards vector control as integral part of malaria control, it is obvious that this will not depend on a single measure but on a combination of methods. Thus malaria vector control will have to adopt the strategy of the old era but perhaps with much better tools awaiting the will and self determination for judicious implementation.
The malaria eradication strategy had foreseen the aggravated problem of vector resistance to insecticides, hence it advocated a time-limited attack on the vector with subsequent dependence on surveillance to clean the reservoir of infective cases. There is no disagreement today that the future long-term reliance on insecticides is dim, resistance-wise and cost-wise. Therefore, the use of insecticides in malaria vector control will have to be on a limited time basis, the aim of which is to reduce the malaria endemcity with the simultaneous support of chemotherapeutic measures. Non-chemical vector control measures whether by environmental or biological methods or both would need time to develop. Thus they should be introduced from the very start in a malaria control programme. As these become operational for long-term control, with the full support of passive surveillance, insecticidal application can be reduced or discontinued. Accordingly, insecticides can be reserved for emergency situations, hence they will become effectively used, cost-saving and environmental preservation will be achieved. This approach cannot materialize unless rigorous applied field research on vector control methods and their cost effectiveness is implemented in antimalaria programmes, soonest and without hesitation. Supporting laboratory research in a sine qua non, and, for both field and laboratory research, national expertise should be fully developed and utilized.

Needless to say that research on vector bionomics and control cannot go on in seclusion from the other epidemiological studies. Thus the key answer for well integrated findings is that the whole responsibility for investigation is to be shouldered by national multidisciplinary teams. Unfortunately, there is a paucity of national medical entomologist in many developing countries are lacking. Unless a new generation of appropriate university graduates are adequately trained in medical entomology, there is no hope for these tasks to be accomplished.
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