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**EXPERT COMMITTEE ON  
MALARIA**

**Fifth Report**

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## EXPERT COMMITTEE ON MALARIA

### Fifth Session

*Istanbul, 7-12 September 1953*

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\* Was unable to attend.

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# EXPERT COMMITTEE ON MALARIA

## Fifth Report \*

### 1. INTRODUCTION

The Expert Committee on Malaria met in Istanbul from 7 to 12 September 1953.

This session was preceded by an informal meeting of the members of the WHO Expert Advisory Panel on Malaria attending the Fifth International Congresses of Tropical Medicine and Malaria (held in Istanbul from 28 August to 4 September). Twenty-eight members of the Panel and other malariologists participated in this meeting, which took place on 1 September and which was presided over by Professor G. Macdonald. The debate dealt mainly with the available experience on the interruption of residual-insecticide spraying campaigns.

In opening the session of the committee the Secretary summarized the activities undertaken by WHO in the field of malaria since the previous session. He emphasized the importance of the present one occurring at a time when many countries were carrying out long-term plans for nationwide malaria control, while others had interrupted their spraying campaigns following achievement of nationwide malaria control.

The documentation distributed to the members is listed in Annex 1 (see page 27).

The committee unanimously elected Dr. M. Vaucel as Chairman and Dr. M. K. Afridi as Vice-Chairman. Instead of appointing rapporteurs, the committee split into two groups, each entrusted with the drafting of parts of the present report.

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\* The Executive Board, at its thirteenth session, adopted the following resolution:  
The Executive Board

1. NOTES the fifth report of the Expert Committee on Malaria;
2. THANKS the members of the committee for their work;
3. REQUESTS the Director-General to give special attention to the recommendations of the committee, and to their implementation within budgetary limits; and
4. AUTHORIZES publication of the report.

(Resolution EB13.R5, *Off. Rec. Wld Hlth Org.* 52, 3)

The provisional agenda was adopted. The committee decided to discuss under item 10 of the agenda two proposals presented by members of the Panel as follows: (1) designation of strains of human malaria parasites; (2) terminology of repellent action of insecticides on mosquitos.

## 2. THE PRINCIPLES OF MALARIA CONTROL

The Second World Health Assembly resolved to work for the elimination of malaria from the world as a public-health problem. At the time, this aim seemed to many to be beyond the possibility of achievement, but a review of the present situation shows that very material progress towards it has been made. In the Regions of the Americas, Europe, Eastern Mediterranean, and South-East Asia advancement is continuous and widespread. The obstacle of principle which once existed in the African Region has been removed by the Kampala Conference.<sup>1</sup> Encouraging progress has now been made in the African Region as well as in the Western Pacific.

The inspiration and guidance for this action have largely come from WHO, and the committee feels that without them no comparable advancement could have been made. Local programmes have in some cases been initiated and carried out exclusively by individual governments, but many others have been facilitated by WHO or by other bodies acting internationally, such as the United Nations Children's Fund and various agencies of the USA Government. This assistance has been of great value and is welcomed, and it is gratifying to note that the Colombo Plan is now offering similar help.

The committee notes with pleasure that increasing activity in the field of malaria has occurred at the regional level of WHO, and that governments which originally carried out schemes with the guidance and help of WHO are tending to accept sole responsibility in continuing and enlarging them. The continuation and increase of this tendency will measure the true success of WHO's work.

It appears therefore that the original aim of WHO was not over-ambitious and that material progress towards it has been made. Stimulus and guidance are, however, still needed, and new problems calling for solution are constantly presenting themselves. The completion of control evidenced by the elimination of malaria presents problems of time and method of ending insecticidal applications and of the system of inspection needed to replace them. These are dealt with in a later section. Fears that some species of anopheles such as *Anopheles gambiae* and *A. minimus flavirostris*

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<sup>1</sup> See *Wld Hlth Org. techn. Rep. Ser.* 1951, 38.

might not be susceptible to attack by insecticides have died down under experimentation. It is now known definitely that members of the *Kerteszia* group are not controllable in this way in part of their range, and there is prima facie evidence that others, such as *A. sergenti*, may perhaps by their normal habit not come into contact with the insecticide in part of their range. Specific resistance to insecticides by anophelines has now been reported and is discussed more fully later, but so far such resistance has not seriously hampered control schemes. Another type of resistance evidenced by modification of behaviour to avoid contact with the insecticide is suspected in some places, although this, also, has not yet had serious effects. These happenings show the necessity for a continued imaginative and elastic programme of investigation and guidance.

In the countries which are economically underdeveloped, there is still a pressing need for a further reduction of costs to ensure that schemes are planned so that they will remain within the routine budgetary capacity of the country when outside assistance ends. This calls for experimentation in organization, training, and insecticidal practice which can be encouraged by WHO. Such experimentation should clearly include further studies on the most economic and at the same time most effective combinations of dosage and cycle of the insecticide—a subject elaborated below—and on the more strategic use of insecticides. There are good epidemiological grounds for believing that in some countries malaria is kept alive in limited residual foci from which it extends, annually or less frequently, to other areas. If this is so, localized treatment of such foci might have an effect over much larger areas and save much wastage. Investigation to determine this point seems fully justifiable. The employment of personnel should also be examined more critically than in the past. The early stages of malaria-control schemes undoubtedly demand the exclusive attention of full-time employees, but as these schemes progress it may be possible to enlarge the functions of the staff to include other public-health work. A development of this type must be undertaken with great care to avoid disruption of the malaria control, but pilot schemes could well experiment in this way.

A most important direct activity of WHO in securing progress has been through its demonstration teams. The committee considers that they have been of the greatest value in training, in the stimulation of interest, and in investigation, the lack of which might otherwise have greatly delayed control. A prominent example of this is the experimental demonstration that *A. minimus flavirostris*, once believed to be unsusceptible to control by insecticides, can be readily prevented from carrying malaria. The committee hopes that investigations of this character will constitute an even larger part of the teams' functions in future, and it welcomes the increase of their period of operation to at least three years.

WHO conferences at a regional level are likely to be valuable in securing appraisal, co-ordination, and stimulation of work. The international courses of malariology have been of much value, as has also been WHO's activity in helping to found malaria institutes and in granting fellowships. It is felt, however, that there is still a need to press for the full co-operation of Member Governments in the selection of the most suitable men to undergo training in courses sponsored by the Organization.

Despite the great success of the newer forms of insecticidal work, there remains room for the use of more traditional methods. In some areas, constructional or drainage work alone may be indicated, as in some of the places infested by *A. aquasalis* or by *A. melas*. In others, insecticidal work may be reinforced by other measures. The object, which is the permanent elimination of malaria, may be hastened by selective schemes of therapy. It is increasingly desirable that the changes in agriculture, animal husbandry, and social conditions, which have by themselves eliminated malaria from great territories in Europe and America, should be studied and encouraged elsewhere, because in some places ultimate freedom from the disease may largely depend on them.

The committee does not concur with the widely expressed opinion that the application of public-health techniques such as malaria control should be delayed for fear of increasing the population. It believes that the means to health should not be deliberately withheld and that any problems created by their provision should be countered by other methods. It recognizes, however, that malaria control and other health measures, although essential parts, do not alone constitute a balanced progress, since this must also include agricultural, social, and other forms of advancement. The committee considers this to be another reason for encouraging the co-ordination of malaria-control programmes with developments in other fields.

## 2.1 Malaria Control by Insecticides

### 2.1.1 *Quantitative needs of insecticides*

An analysis of present practice shows that the doses and cycles of insecticides used are very varied and that differences do not always—or even usually—correspond to known epidemiological conditions. Examination of the experimental basis on which dose and cycle are prescribed shows that our knowledge is generally fragmentary and inadequate for their proper prescription. For this reason, the committee's statements on the subject are made with the greatest caution and local experimentation remains desirable on any major scheme. A part of the difficulty has been removed by the work of the Expert Committee on Insecticides, which has

produced specifications of materials, formulations, and equipment,<sup>2</sup> but much of it remains.

Present evidence indicates that the toxicity to insects of residual insecticides, especially the non-volatile ones, depends not so much on dosage as on the physical form. The continued presence of the insecticide on treated surfaces in a form easily picked up and retained by insects settling on them is the main criterion of efficiency. Dosage is important in so far as it affects the persistence of the insecticide in this available form, and it will depend to a very large extent on the nature of the surface, especially the absorptive properties, to which the particular formulation is applied.

The physical form which the insecticide assumes after its application in solution or emulsion to non-absorbent surfaces depends largely on the types of solvents used in these formulations, and to some extent on the nature of the treated surface. In the case of water-dispersible powders the particle size of the insecticide can be standardized and specifications have been prepared by the Expert Committee on Insecticides.

The problem of the application of residual insecticides to absorbent surfaces, such as those of mud, so common in malarious countries, is far from solved and is discussed in section 2.1.2 (see page 9).

It is generally accepted that water-dispersible powders are the most efficient formulations for such surfaces, but even with these a marked loss in toxicity may occur and higher initial dosages or more frequent applications are required than on non-absorbent surfaces.

With volatile insecticides, such as BHC and aldrin, some degree of absorption seems to be advantageous in that it slows down the loss by volatilization, though kills are still maintained by their fumigant effects. Nevertheless, at the usual field dosages of 0.1 and 0.2 g of gamma-BHC per m<sup>2</sup>, decline in toxicity is still rapid and necessitates frequent re-application. The use of higher dosages of volatile insecticides on absorbent surfaces might well bring the effect of these compounds more in line with the long-lasting high efficiency of non-volatile ones, such as dieldrin, on non-absorbent surfaces.

The fumigant effect of volatile insecticides and the particulate effect of the non-volatile dieldrin, and to a lesser extent that of DDT, are great advantages in that they may offset deficiencies in spraying technique, especially lack of uniformity of application.

The marked irritant effect of DDT on mosquitos makes adequate dosage in readily available form imperative.

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<sup>2</sup> See World Health Organization (1953) *Insecticides. Manual of specifications for insecticides and for spraying and dusting apparatus*, Geneva.

Strictly subject to these qualifications, the following tentative observations are put forward :

(a) Field tests, experiment, and theory suggest that DDT alone may not be sufficiently lethal to control extreme conditions of transmission.

(b) DDT can, however, control malaria under most conditions, and meets the normal criterion of efficacy. A dose of 2.0 g per m<sup>2</sup> is likely to be effective on most types of surfaces, including many mud and soft-plaster walls, for about six months. On hard, non-absorbent walls it may be effective for 18 months or more.

(c) Smaller doses of DDT, such as 0.5 g per m<sup>2</sup>, are effective under many circumstances, and on many types of mud walls, for six to eight weeks, but the data on which to lay down a relationship between dose and period of efficacy are quite inadequate.

(d) A dose of 0.2 g of the gamma-isomer of BHC per m<sup>2</sup> on mud or other walls will often meet common requirements for three months, exceptionally severe ones for two months, and mild ones for about four months or perhaps longer.

(e) A dose of 0.1 g of the gamma-isomer of BHC per m<sup>2</sup> will sometimes meet common requirements for about six weeks and mild ones for a longer period, perhaps two to four months.

(f) Dieldrin applied at a dose of 0.6 g per m<sup>2</sup> on mud and gravel walls seems to meet exceptionally severe requirements for about 12 months, common requirements for about 18 months, and mild requirements for possibly two years. The possibility of mechanical removal, or obscurement by smoke deposits, during these long periods must, however, be borne in mind. The relationship between wall-surfaces and dieldrin persistence is as yet inadequately studied ; laboratory indications are that it may be less persistent on some types of mud wall.

(g) Field data on the action of smaller doses of dieldrin are not available. Doses such as 0.25 g per m<sup>2</sup> might well have a valuable effect, and deserve careful study.

The committee therefore considers that :

(1) Insecticide powders, and especially DDT water-dispersible powders, should not be brought into routine use unless they comply with the specifications laid down by the Expert Committee on Insecticides.

(2) Fundamental research on the physical and chemical properties of insecticides, their interaction with wall-surfaces, and their mode of action on insects should continue to receive vigorous support in the immediate as well as the remote interests of public health.

(3) Investigations on the total mortality inflicted by insecticides on mosquitos entering treated shelters, at serial intervals after application of

different doses, should be encouraged in close association with major control schemes and under the conditions of those schemes.

(4) Entomological studies need support, and a further change of emphasis related to the problems of control by insecticides is desirable. Increased attention might well be paid to sheltering habits, to the distinction of strains of mosquitos differing in their sheltering and feeding habits, and to the methods of measuring the age and average length of life of mosquitos. A new and possibly valuable technique for differentiation of strains is referred to in section 4.2 (see page 19), and a note on measurement of the average length of life appears in Annex 2 (see page 29).

(5) Surveys as a preliminary to control should preferably include examination of peak vector densities and normal feeding habits (including the anthropophilic index), analysis of mosquito sheltering habits and the most favourable temperature at which transmission occurs, and field tests of the efficacy of insecticides, as advised in (3) above, for each of the common types of wall-surface locally encountered.

(6) To facilitate precipitin testing of mosquito blood-meals, WHO might take steps to make available suitable sera.

(7) Reports on programmes of control by residual insecticides should include data on the subjects listed in (5) above, and also state clearly the insecticide and formulation used, the dose applied, the interval between applications, and the common types of wall-surface treated.

(8) The present confusion in the literature caused by the wide use of a mixture of metric and other measures might well be brought to an end. Routine reporting in grams of active product per square metre is suggested.

#### 2.1.2 *Malaria control in areas where houses have mud walls*

It is well known that physical or chemical reactions, or both, between insecticides and mud walls may detract from the value of the insecticide. However, since most of the work now commented on is done in areas where mud walls are usual, the remarks on dosage already made refer in the main to such surfaces, and there is ample evidence that as a general rule control is not prevented by such a circumstance, though its costs are thereby increased. The proper analysis of this interaction with a view to its full understanding and possible prevention is much to be desired.

Considerable initial work has been done on two main lines, one concerned with the phenomenon of adsorption<sup>3</sup> and the other with the decomposition of insecticide by compounds of iron in the wall.<sup>4</sup> Despite this, the

<sup>3</sup> Hadaway, A. B. & Barlow, F. (1952) *Trans. roy. Soc. trop. Med. Hyg.* **46**, 236

<sup>4</sup> Bordas, E., Downs, W. G. & Navarro, L. (1953) *Bull. Wld Hlth Org.* **9**, 39

results do not yet provide a sufficient knowledge for understanding, forecasting of effects, or prevention of loss. The interest already shown by WHO is welcomed and its extension urged. Until this work is further advanced the local field trials of efficacy referred to in 2.1.1 (3) above will remain necessary on all major schemes.

It must also be recognized that in such houses the processes of repair and replastering are frequent, and may remove the insecticide in a notable proportion of houses within a few months of application. The rapid erection of many new houses, often as a result of malaria control, may augment this effect; and for these reasons the optimum period between application in such areas is relatively shorter than in places where hard-walled permanent houses are usual.

### 2.1.3 *Development of resistance to insecticides by anophelines*

In its fourth report the committee commented that no examples of acquired resistance had yet been described but that the phenomenon might well occur.<sup>5</sup> It therefore indicated the need for special research in which insect physiologists and organic toxicant chemists should collaborate in an attempt to determine some of the basic mechanisms involved. Since that time the occurrence of acquired physiological resistance has been reported in two areas, in a part of USA, where *A. quadrimaculatus* has developed some resistance to DDT following prolonged larvicidal practice with this chemical, and in Greece, where *A. sacharovi* has developed resistance after imagocidal work occasionally combined with larvicides.

In neither of these cases does there appear to have been a specific measurement of the resistance by laboratory techniques comparable to those used in the case of houseflies, and in neither case has the resistance been sufficient to prevent continued control. On the other hand, the committee has received reports concerning many large areas stating that there has been no apparent development of resistance in malaria vectors, despite the continued use of residual insecticide for periods of up to eight and nine years. It has also noted that laboratory efforts to produce resistance in anophelines have been very much less successful than in the case of the housefly.

It is very desirable that accurate measures of the susceptibility of anophelines to insecticides should be made before, and periodically during, major control schemes. The committee notes the development and successful use of a suitable technique, which is described in Annex 3 (see page 30). It strongly advises its general use, and its encouragement by the support by WHO of reference laboratories undertaking such tests as a routine. The

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<sup>5</sup> *Wld Hlth Org. techn. Rep. Ser.* 1951, **39**, 14 (section 3.1)

reporting of such tests should be standardized and preferably refer to corrected mortalities taking into account the mortality among controls.

In addition to this specific physiological resistance, a change in behaviour of anophelines resulting in partial evasion of contact with insecticide has been observed in *A. albimanus* in Panama, and postulated, but not, so far as the committee is aware, substantiated, elsewhere. Again, this has not been sufficient to present a serious impediment to control.

The committee does not feel that fear of producing resistance or changed behaviour should in any case deter governments from undertaking control on established principles. It does, however, consider that the subject merits serious study, taking various forms. It should include the combined studies by insect physiologists and organic chemists previously recommended, and examination of the strain composition of anopheline species and of the genetic characteristics of mosquitos.

The committee was glad to receive several reports from members of the Expert Advisory Panel on behaviour characteristics of mosquitos in direct or indirect relation to imagocidal control, and wishes to encourage such work. It does not support general classification of anophelines according to these characteristics because it believes that mosquitos are flexible in their behaviour, which may often vary from time to time or from place to place in accordance with climatic or other changes. It hopes, however, that such studies will continue and increase, as description of behaviour in known circumstances is of great value even when the behaviour is not a set characteristic of a species.

#### 2.1.4 *Interruption of residual-insecticide spraying*

Examples of successful interruption of residual-insecticide spraying on carefully pre-arranged lines were reported to the committee from the USA, Greece, and British Guiana, the first two following malaria elimination, and the last following vector eradication. The subject was also discussed at an informal meeting of several members of the Expert Advisory Panel, convened in Istanbul for the purpose. Experience now clearly shows that the objective of malaria elimination to a degree when routine insecticide application can be ended is a feasible one.

The widespread successful use of insecticides has reduced malaria to an extremely low level throughout many countries, for example, Ceylon, Greece, British Guiana, Italy, Mauritius, and Venezuela, and to comparably low levels in large areas of others, and guidance on policy after apparent elimination is therefore urgently needed. It is not likely that any single policy will be generally applicable, as the problem is affected by the original form of control, vector eradication or malaria eradication, and by local circumstances including the previous epidemiology of the disease.

There are places in which the collateral effects of residual-insecticide spraying, chiefly reduction in alimentary infection, are so great that continuation of the programme is desirable to maintain them. The committee considers that where this is not the case, and when suitable criteria of full elimination of malaria are met over any considerable area such as a country, discontinuation of spraying is justifiable subject to certain safeguards discussed below.

In reaching this conclusion the committee was much impressed by the plan of interruption in Greece, carried out after the authorities were satisfied that malaria was practically at an end. Spraying was discontinued in a progressive manner starting in the areas most remote from reinfection, and replaced by close observation of anopheline densities and detection of cases of malaria. Some work was continued in limited areas thought to be potential foci of spread of the disease. Emergency spraying was undertaken in areas indicated by periodical inspection as needing it, but they have proved to be extremely few. In the Island of Crete no spraying has been necessary for three years.

The criteria of full elimination already referred to must ensure that transmission has been completely interrupted for a sufficient time to eliminate the risk of its renewal by local gametocyte carriers. Criteria for the establishment of this end-point in the USA were specified by a committee called by the National Malaria Society and are reproduced in Annex 4 to this report (see page 32). This reproduction is for general guidance. Other countries might well devise criteria based on this general example but suitable to their own needs on the advice of competent observers.

Safeguards, however, will always be required, their chief objective being to ensure rapid detection of recurrence of malaria and its prompt elimination. An adequate scheme of close continuous observation to detect cases and of entomological survey should be instituted; the clinical disease should be made compulsorily notifiable; decentralized laboratory facilities should be provided on a sufficient scale to undertake routine surveys and to make rapid examination of blood-smears from any suspected cases; and an emergency organization supplied with insecticides and drugs should be kept in being to undertake control in an appropriate area around any detected cases. Experience has shown that outbreaks recognized at their early stages can be suppressed by such an organization before serious harm is done.

The general policy of interruption has been the subject of much discussion concerning the relative merits of progressive reduction of the dosage of the insecticide, the prolongation of intervals between applications, and discontinuation with or without spraying in barrier areas or other selected places. The successful examples reported and discussed were all of the last

type and it has been shown that this policy can be successful under more than one set of circumstances. A simultaneous discontinuation over great areas has not yet been attempted and it seems desirable to continue spraying in known potential epidemic foci for longer periods than in the general countryside.

Other circumstances may demand selective spraying, as for instance in places where it is known that there is an immigration of potential gametocyte carriers from unsanitated areas. Such places must remain fairly numerous so long as malaria control in neighbouring territories is uncoordinated, and this is the principal reason for the recommendation in a later section (see page 20) that WHO should interest itself in international co-ordination of this work.

The process of barrier spraying in places where vector eradication has been carried out, and to the development of which the committee looked forward in its second report, has been successfully developed in British Guiana, where it has been shown that natural barriers against the migration of *A. darlingi* can be recognized, and that by taking advantage of such barriers it is possible to restrict the areas in which barrier spraying must be practised.

#### 2.1.5 *Third and fourth reports of the Expert Committee on Insecticides*<sup>6</sup>

The committee has reviewed these reports, produced since its last meeting, and records its appreciation of their great value. The specifications of materials and equipment given in them have already considerably facilitated malaria control and will be of continuing use. The committee supports recommendation No. 3 of the fourth report, namely :

“ The committee, calling attention to the paucity of published data on the relationship between biological activity and particle size of DDT formulations, and to the almost complete absence of such data for BHC and other insecticides, recommends that WHO initiative work in this direction.”<sup>7</sup>

The committee also notes with satisfaction that the Expert Committee on Insecticides is considering the maintenance of the properties of water-dispersible powders after storage, as it knows of examples of rapid deterioration of suspensibility in approved supplies. It also looks forward to detailed specifications for dieldrin water-dispersible powders comparable with those given for DDT and BHC.

#### 2.1.6 *Toxic hazards of insecticides*

In several previous reports the committee has emphasized the harmlessness of DDT when used in the intended way, and later experience has

<sup>6</sup> *Wld Hlth Org. techn. Rep. Ser.* 1952, **46**, 54

<sup>7</sup> *Wld Hlth Org. techn. Rep. Ser.* 1952, **54**, 35

confirmed past opinion, for which there is now very considerable evidence. The committee also considers that BHC is quite safe and can be routinely applied without the use of special precautions. It welcomes the interest shown by WHO in the toxicity of pesticides of all types and particularly the production of a monograph by Dr. J. M. Barnes on this subject.<sup>8</sup> It concurs with the opinion expressed in that monograph that new insecticides which on laboratory trial appear to have a toxicity of the general order of DDT and BHC may justifiably be brought into routine use, if reasonable precautions, not amounting to excessive protection of workers which might impede their activities, are taken. It further considers that dieldrin may well be brought into use for malaria control, and that the original normal precautions advised should consist of emphasis on the employment of well-maintained apparatus which does not leak or bespatter the worker, the provision of special working overalls (which should be regularly washed), where these are normally used, and the provision of soap and facilities for washing after work in all cases. Eye-guards should be provided where requested, but respirators do not appear necessary. The committee further endorses Dr. Barnes' recommendation that an opportunity should be taken to make special medical examination and keep medical records of workers on a selected scheme when new insecticides are used, with the object of detecting unexpected ill effects.

## 2.2 Malaria Control by Methods other than Residual Insecticides

There is a risk that preoccupation with the power of residual insecticides could result in derogation of other methods which have considerable remaining utility. In some epidemiological circumstances control by prevention of breeding remains the method of choice, as is sometimes the case where the disease is carried by the *Kerteszia* group or by *A. melas* or *A. aquasalis*. It is always desirable to prevent unnecessary or excessive breeding by the practice of environmental sanitation and by avoiding the making of breeding-places. It is particularly desirable that public works and irrigation schemes should be carried out in such a way as to avoid the creation of breeding-places for possible vectors, since these undertakings still throw an unnecessary load of responsibility on health departments which should be borne by the works themselves. There also appears to be a remaining need in some limited and special cases for larvicidal practice to supplement or occasionally replace imagocidal work, as in some urban conditions, and in the case of *A. sergenti* in the Jordan Valley.

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<sup>8</sup> Barnes, J. M. (1953) *Toxic hazards of certain pesticides to man*, Geneva (World Health Organization : Monograph Series, No. 16)

While these are special cases, the more general desirability of supporting imagocidal campaigns by supplementary measures should not be overlooked. Success may be accelerated by selective therapeutic schemes. The maintenance of elimination may be made more easily attainable by drainage, by general mosquito control, and by developments in the practice of agricultural and animal husbandry and in social habits, since these lead to decreased breeding and to deviation of anophelines from man to animals. Experimental work on these lines is continuing and is to be encouraged as a contribution to formation of ultimate policy.

### 2.3 Appraisal of Results

Much of the material of this report is concerned with insecticide work, is correspondingly couched in entomological terms, and refers to entomological techniques. The committee must, however, emphasize that, as the objective is the elimination of malaria, the ultimate criteria of success must be in malariometric terms. The incidence and epidemiological features of malaria should be investigated by standard malariometric techniques, which should be used to collect as much information as is possible before the start of control. Though valuable in defining epidemiology, the parasite- and spleen-rates, in children and adults, are of less value in measuring the progress of control, because they sometimes react relatively slowly to changes in transmission. The most sensitive measure of changes in incidence is undoubtedly the parasite-rate among infants, and its routine measurement before and periodically during control is strongly advised.

## 3. CHEMOTHERAPEUTICS OF MALARIA

### 3.1 Report of the Working Party

At its fourth session, the committee recommended the preparation of an authoritative brochure on the antimalarial drugs in common use.<sup>9</sup> The task was entrusted to a small working party selected from the Expert Advisory Panel on Malaria.<sup>10</sup> For various reasons, chief among them being a serious illness of one of the working party, it was not possible to complete the brochure in time for it to be laid before the present session. However, the

<sup>9</sup> *Wld Hlth Org. techn. Rep. Ser.* 1951, 39, 18 (section 4.2)

<sup>10</sup> The members of the working party are : Sir Gordon Covell (Chairman), Dr. G. R. Coatney, Dr. J. W. Field, and Lieutenant-Colonel Jaswant Singh.

work is far advanced and the committee hopes that the brochure when completed will be printed in monograph form.

Since the last meeting of the committee, the search for a drug which would fulfil unaided the conditions required for an ideal antimalarial agent has continued. No compound has yet been found which possesses all these qualities, but a number of important chemotherapeutic studies have been carried out which have added substantially to our knowledge of the properties and limitations of the drugs then available and several new compounds have been developed. The views of the committee as to the current status of the antimalarial drugs now in use have been summarized in Annex 5 (see page 33), and discussion here will be confined to a consideration of the two most important newly developed compounds, namely, pyrimethamine (Daraprim)<sup>11</sup> and primaquine.

Pyrimethamine is a member of the 2-4-diaminopyrimidine group of drugs and is believed to owe its efficacy to an antimetabolic action against one or more members of the folic-folinic acid conversion series. In many respects its action resembles that of proguanil, and its chemical structure is not unlike that of a metabolite produced in the body by the latter drug.

As a therapeutic agent, its action is not sufficiently rapid to warrant its use in the treatment of acute malaria, at any rate in non-immune subjects, and its chief value is likely to be in prophylaxis. It is highly effective as a suppressant in all forms of malaria, and is a causal prophylactic of falciparum infections. The suppressive dose is very small, the recommended adult dose being only 25 mg weekly, which makes it a relatively inexpensive drug for mass prophylaxis. It is also highly active in rendering gametocytes incapable of attaining full development in the mosquito, a property which may be of considerable value in particular circumstances.

Studies carried out in a New Guinea strain of *Plasmodium vivax*, which does not present the phenomenon of late relapse, have shown that, when given in weekly doses of 25 mg over 8-12 weeks, pyrimethamine produces suppressive cure in a high proportion of cases. A similar régime tested on a late relapsing strain of *P. vivax* had no apparent effect in reducing the relapse rate, but it is possible that, had the administration of the drug been continued so as to cover the usual period of late relapse, suppressive cure might have resulted.

The drug has the advantage of being without a bitter taste, a property not possessed by any other antimalarial at present available.

It is obvious that pyrimethamine has remarkable, though selective, antimalarial properties, but, as is the case with proguanil, it has been shown that, by planned administration of attenuated doses, drug resistance may

<sup>11</sup> A list of synonyms (proprietary names) is given in Annex 5, page 42.

be produced experimentally. Cross-resistance with proguanil has also been demonstrated. The committee is not aware of any authenticated instance of resistance to pyrimethamine having been produced under field conditions.\* The possibility that this may occur cannot, however, be overlooked, and every effort should be made to ensure that if the drug is used it should be administered regularly in the dosage recommended.

As regards toxicity, serious side-effects have been recorded in monkeys when the drug has been given in doses many times greater, relative to the weight of the animal, than that recommended for man. But extended field observations have thus far failed to disclose any toxic side-effects attributable to pyrimethamine. The possibility that too prolonged continuous administration of the drug might interfere with haematopoiesis has, however, not yet been excluded.

Primaquine belongs to the 8-aminoquinoline group, of which the first to be used in the chemotherapy of malaria was pamaquin. Because of the tendency of the latter drug to produce serious toxic symptoms, such as methaemoglobinaemia, cyanosis, abdominal cramps, and in some cases acute intravascular haemolysis, an intensive search has been carried out during recent years to discover a compound which would ensure radical cure of vivax and malariae infections without the production of dangerous side-effects.

Of the compounds studied, pentaquine and isopentaquine both proved to be less toxic than pamaquin, but primaquine has been shown to be both more effective and less toxic than either of them. The drug has been used on a large scale with excellent results for troops returning from Korea, where the chief characteristic of vivax malaria is the occurrence of relapses in a very high proportion of cases several months after the infection has been contracted.

### **3.2 Part that Newly Synthesized Antimalarials might play in Malaria Control**

3.2.1 While recognizing that, on the evidence so far available, measures directed against the mosquito vector must retain priority in antimalaria campaigns, the committee believes that the newly synthesized antimalarials may play an important part in certain special circumstances. First, where the behaviour of the local vector or the constant movement of the population and influx of infected persons from outside the protected zone, or any other factors, render the response to mosquito control unsatisfactory, the use of antimalarial drugs might be of value in accelerating the reduction of

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\* See, however, Annex 5, p. 35.

malarial incidence brought about by antimosquito measures. This would apply particularly to circumscribed areas where the distribution and administration of the drugs can be effectively organized.

Secondly, where a malaria eradication campaign has reached a stage at which vector control has been interrupted, the radical cure of cases which may arise locally by relapses or by influx of infected immigrants will be one of the essential measures to limit the extension of the disease. In such cases primaquine given under supervision might play an important part.

Thirdly, where malaria has appeared in epidemic form, mass treatment by schizontocidal drugs is necessary. It should not, however, be used to the exclusion of antimosquito measures.

Fourthly, where a community is living under conditions which totally preclude the application of antimosquito measures, the use of antimalarial drugs may be the only practicable method of controlling the disease. An ingenious method of distribution by mingling the drug with table salt has been used in an area where the latter commodity is scarce and is issued under government control. The committee recognizes, however, that this method is applicable only under such exceptional circumstances.

3.2.2 Having regard to the importance of chloroquine, and other members of its group, and of primaquine in the treatment and control of malaria, and to the difficulty encountered in obtaining these drugs in sufficient quantity at moderate cost, the committee suggests that WHO explore the possibilities of increasing the production of these drugs and of securing a reduction in their price.

#### 4. RECENT SCIENTIFIC DEVELOPMENTS

##### 4.1 Utilization of *Plasmodium berghei* in the Current Study of Malaria

The committee considers that the isolation of *P. berghei* has opened up a fresh field of research in malaria which has far-reaching possibilities. Investigations so far carried out have resulted in a definition of the conditions under which this parasite is transmitted in nature, and of the variation in susceptibility of many species of rodents to it. Extensive studies have also been made on the course of the infection, on the mechanism of immunity, and on the response to diet and chemotherapeutic agents.

Further progress in research has been gravely hampered by the difficulties encountered in effecting mosquito transmission of the parasite in the laboratory. Recently, however, encouraging reports have been received which appear to indicate that, by the adoption of a special technique, this obstacle might be overcome. If this turns out to be the case, *P. berghei*

should prove a valuable additional means of clarifying the problems of exo-erythrocytic schizogony, immunity, experimental epidemiology, and chemotherapy under controlled conditions. The chief advantage would be that investigation of this nature could be prosecuted on small laboratory mammals which are inexpensive and easy to handle. Should the life-cycle of this parasite on fuller investigation prove to resemble that of the mammalian plasmodia rather than that of the avian, its value would be correspondingly enhanced.

The committee considers that, in addition to concentrating research activities on developing an effective technique for laboratory mosquito transmission of *P. berghei*, efforts to isolate new species of rodent plasmodia should be continued. The recent detection of *P. vinckei* encourages the hope that such efforts may not be in vain. The committee considers that WHO might well promote the co-ordination of such research activities.

#### 4.2 Cytogenetic Methods Applied to the Classification of Anophelines

The growing importance of knowledge of the strain composition of anopheline species and of genetic characters of anophelines has been referred to in section 2.1.1 (see page 6). A new method of chromosome analysis has been devised which appears to be a valuable tool in such work, as indicated by recent studies in Italy and Brazil.<sup>12</sup> The committee wishes to encourage the development and use of this technique in all WHO Regions. It suggests that a selected biologist from each Region should be granted a fellowship to enable him to study the technique, and that he should be given facilities for its practical application on his return.

#### 4.3 Changes in Anopheline Fauna Following Successful Control

Four examples of material change in anopheline fauna following successful control have been reported to the committee; the usurpation of the breeding-places of (a) *A. labranchiae* by *A. hispaniola* and *A. sacharovi* in Sardinia and by *A. claviger* in the Pontine marshes; (b) *A. superpictus* by *A. claviger* in Greece; and (c) *A. sacharovi* by *A. hyrcanus* in the Jordan Valley. These happenings demonstrate an unexpected relationship between the species which may be antagonistic to each other, one successfully vying with another for breeding-space. They do not appear to present great practical problems, but the phenomenon is of considerable interest and could have practical implications, advantageous as well as disadvantageous. The

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<sup>12</sup> Frizzi, G. (1953) *Bull. Wld Hlth Org.* 9, 335

committee does not make any recommendations, but draws the attention of entomologists to the happenings which may have parallels elsewhere, and which deserve study.

#### **5. POSSIBLE EXTENSION OF INTERNATIONAL MALARIA-CONTROL ACTIVITIES**

In some regions, malaria control is now practised very extensively and the objective of elimination of malaria as a public-health problem is foreseeable. Its attainment, however, may be delayed and the interruption of spraying in individual countries postponed by a lack of co-ordination of effort, resulting in the possibility of reinfection of malaria-free areas from neighbouring ones where the disease is less adequately controlled, or even uncontrolled. The time has now been reached when co-ordination of effort may be more valuable than demonstration or local aid and could produce considerable economy of effort and increase in success.

WHO has a unique capacity to encourage such co-ordination, and an exceptional opportunity in doing so. Its actions in this respect would necessarily be mainly regional, although inter-regional and central action would also be needed. The regional conferences already arranged are a useful preliminary step in this direction, and advantage could be taken of them for early discussions on co-ordination and tentative agreements. Full agreement would require more formal occasions and elaborate preparation, for which it is suggested that WHO offer its technical help. The ideal to be aimed at is the uniform practice of control throughout all malarious parts of a Region, or throughout large contiguous areas with similar malarious conditions even though they fall into two or more national territories or WHO Regions. For this purpose, co-ordination of control in method, timing, and boundaries would first be necessary, while later close integration would be necessary in interruption of control and subsequent practice of safeguards against recurrences.

#### **6. STANDARDIZATION OF PROCEDURE IN EPIDEMIOLOGICAL INQUIRIES ON MALARIA (REPORT ON MALARIA TERMINOLOGY)**

The committee notes with satisfaction that the reports concerning the standardization of methods to be followed in epidemiological inquiries on malaria have now been achieved, according to the conditions set forth by the third and fourth sessions of the committee.

The English text has already been published as No. 13 in the Monograph Series of the World Health Organization,<sup>13</sup> and the committee suggests a similar publication of the French text which has recently been completed.<sup>14</sup>

The members of the committee who worked these texts wish to record their appreciation of the assistance given them by Dr. P. C. C. Garnham, as well as by Sir Rickard Christophers, Professors H. Galliard, E. Roubaud, and E. Sergent, Doctors H. Jonchère, E. J. Pampana, and D. Bagster Wilson, and Mr. H. S. Leeson. The committee wished to express its special thanks to Professor N. H. Swellengrebel, who not only acted as chairman of the group responsible for the English text, but also collaborated in the preparation of the French version.

Lastly, the members of the committee, and the authors of the two reports, wish to express their admiration for the work accomplished by their distinguished predecessors, the authors of the *Report on terminology in malaria*,<sup>15</sup> published in 1940 by the Malaria Commission of the League of Nations, which has served as a model and a basis for their work.

## 7. FOURTH AWARD OF THE DARLING MEDAL AND PRIZE

The Expert Committee on Malaria has examined the various nominations submitted for the award in conformity with the second paragraph of Article 3 of the Regulations. As the Darling Foundation Committee decided that only one prize should be awarded in 1951, the second paragraph of Article 3 of the Regulations was not applied. In consequence, the committee was requested to recommend two candidates, so that two awards could now be made.

Having discussed in private session the relative merits of the candidates nominated, the committee, in conformity with Article 7, has sent its recommendations by letter to the Secretary of the Darling Foundation Committee, the Director-General of WHO.

## 8. OTHER MATTERS

The committee considered a proposal referred to it by a meeting of some members of the Expert Advisory Panel on Malaria, in Istanbul, that workers

<sup>13</sup> Covell, G., Russell, P. F. & Swellengrebel, N. H. (1953) *Malaria terminology. Report of a drafting committee appointed by the World Health Organization*, Geneva (*World Health Organization: Monograph Series*, No. 13)

<sup>14</sup> Vaucel, M. A., Roubaud, E. & Galliard, H. (1954) *Terminologie du paludisme*, Geneva (*Organisation Mondiale de la Santé: Série de Monographies*, N° 24) (in press)

<sup>15</sup> League of Nations, Malaria Commission (1940) *Bull. Hlth Org. L.o.N.* 9, 131

should combine in describing and classifying the characteristics of strains of human plasmodia. While in sympathy with the objective, the committee considered that knowledge on which to distinguish strains was now so incomplete, and existing procedures so difficult, that it could not make a recommendation of practical value, but decided to circulate the proposal to all members of the Expert Advisory Panel for their consideration.

The committee also considered a classification of the ways in which repellent action of insecticides on mosquitos is manifested, together with a request that it should express an opinion on the types encountered in insecticidal practice. The classification was discussed with other relevant matters under section 2.1.3 (see page 11). The committee considered that present knowledge does not provide a sufficient basis for the expression of the opinion requested.

## 9. CONCLUSIONS AND RECOMMENDATIONS

### 9.1 Principles and Progress of Malaria Control

Having reviewed the principles of malaria control on a nationwide basis as currently followed so successfully in so many countries by the use of modern toxicants possessing residual insecticidal effect,

The Expert Committee on Malaria

1. REAFFIRMS its confidence in the original aim of WHO to work towards the elimination of malaria from the world as a public-health problem ;
2. NOTES with satisfaction the very considerable inspiration and guidance that have been derived from WHO through its malaria-control demonstration schemes, informational and advisory service, malaria fellowships, international malaria courses, and assistance to malaria institutes ;
3. NOTES with deep appreciation the very substantial aid for malaria control that has been provided by various bilateral and multilateral agencies ;
4. CONSIDERS that there is still pressing need for further reduction of costs of malaria control in underdeveloped areas ; and
5. RECOMMENDS that experimentation in methods of organization, training, and insecticidal practice be encouraged by WHO, in order to reduce the cost of malaria control.

## **9.2 Quantitative Needs of Insecticides for Malaria Control**

Having considered the quantitative needs of insecticides for malaria control in various areas and in diversified conditions of climate, vector, and wall-surface,

The Expert Committee on Malaria

1. RECOMMENDS that WHO continue to stimulate and support fundamental research on the physical and chemical properties of insecticides, their interaction with wall-surfaces, and their mode of action on insects ; and
2. RECOMMENDS that WHO continue to stimulate and support fundamental research on the behaviour characteristics of malaria-carrying mosquitos in reference to residual spraying.

## **9.3 Malaria Control in Areas where Houses have Mud Walls**

Having considered the available evidence,

The Expert Committee on Malaria

CONCLUDES that mud walls do not constitute a barrier to the successful control of malaria by residual spraying.

## **9.4 Development of Resistance to Insecticides by Anophelines**

Realizing that there is evidence of both physiological and behavioural resistance to insecticides by some anophelines,

The Expert Committee on Malaria

1. CONSIDERS nevertheless that in no case has such resistance so far constituted an important barrier to malaria control or a reason for abstaining from insecticidal work ; and
2. RECOMMENDS that WHO consider the possibility of supporting reference laboratories that would undertake precise tests on the susceptibility of anophelines to insecticides in order to detect the occurrence of resistance and to measure its degree.

## **9.5 Interruption of Residual Spraying**

Having considered the available evidence,

The Expert Committee on Malaria

CONCLUDES that the practice of discontinuing residual spraying, under proper safeguards, after several years of achieved malaria control, is both logical and feasible, and should be given careful consideration by administrations that have carried out malaria control to a satisfactory end-point in all or the major parts of their territories.

#### **9.6 Third and Fourth Reports of the Expert Committee on Insecticides**

The Expert Committee on Malaria

1. NOTES with satisfaction, and appreciates the value of, the third and fourth reports of the Expert Committee on Insecticides, and
2. HOPES that, in continuation of their work, the experts will further consider :
  - (a) The maintenance of the properties of water-dispersible powders after storage, and
  - (b) Detailed specifications for dieldrin water-dispersible powders.

#### **9.7 Toxic Hazards of Insecticides**

Having considered the available evidence and the monograph on *Toxic hazards of certain pesticides to man* by J. M. Barnes,

The Expert Committee on Malaria

CONCLUDES that DDT and BHC are quite safe in routine use, and that dieldrin may well be brought into routine use with some caution until its properties are more fully understood.

#### **9.8 Malaria Control by Methods other than Insecticides**

Having considered the possibility of the utilization in malaria control of methods other than insecticides,

The Expert Committee on Malaria

CONCLUDES that, despite the great success of the newer forms of insecticidal work, there still remains room for the use of the more traditional methods, such as antimalarial drugs, prevention of breeding and especially of the creation of man-made breeding-grounds, and the fostering of changes in the practice of agriculture and animal husbandry, and in social conditions, which have by themselves eliminated malaria from large territories in Europe and America.

### 9.9 Chemotherapeutics of Malaria

Having considered the available evidence on the therapeutic efficiency of the various antimalarial drugs,

The Expert Committee on Malaria

1. BELIEVES that neither proguanil nor pyrimethamine is sufficiently rapid in action to warrant its use for the treatment of acute malaria in non-immune subjects without reinforcement with some rapidly acting schizontocide ;
2. NOTES that primaquine is a particularly effective and relatively non-toxic drug for the radical cure of *P. vivax* infections ;
3. DRAWS attention to the fact that in some areas resistance of malaria parasites to proguanil has been reported and that, experimentally, resistance to pyrimethamine has been produced ;
4. CONSIDERS that it is advisable to reserve both proguanil and pyrimethamine for prophylactic purposes ;
5. NOTES the difficulty encountered in obtaining some of the antimalarial drugs, such as chloroquine and primaquine, in sufficient quantity at moderate cost ; and
6. RECOMMENDS that WHO explore the possibilities of increasing the production of these drugs and of securing a reduction in their price.

### 9.10 Part that Newly Synthesized Antimalarials might play in Malaria Control

While recognizing that, on evidence so far available, measures directed against the mosquito vector must retain priority in antimalaria campaigns,

The Expert Committee on Malaria

CONSIDERS that the newly synthesized antimalarials may have special control value in the following circumstances :

- (1) where any factor precludes the application of antimosquito measures or renders the response to them unsatisfactory ;
- (2) where residual spraying has been discontinued but there is still need to deal effectively with relapsing cases or infected immigrants ; and
- (3) where malaria has appeared in an epidemic form.

### 9.11 Recent Scientific Developments

1. Considering that the isolation of *Plasmodium berghei* and *P. vinckei* has opened up a fresh field of research in malaria, and

Considering that further progress in research is gravely hampered by the difficulties encountered in effecting mosquito transmission in the laboratory,

The Expert Committee on Malaria

RECOMMENDS that WHO promote the co-ordination of research activities on these plasmodia, more particularly those directed to the development of an effective technique of experimental mosquito transmission.

2. Noting the development of an additional technique for the distinction of varieties of mosquitos by chromosome analysis, and having regard to the increasing importance of such distinction in relation to the problems of malaria control,

The Expert Committee on Malaria

RECOMMENDS that WHO encourage this type of research by facilitating the granting of a fellowship to a biologist from each WHO Region to enable him to study the technique of chromosome analysis in mosquitos.

### 9.12 Possible Extension of International Malaria-Control Activities

Having considered the geographical distribution of the major control schemes and the degree of co-ordination between them in this respect,

The Expert Committee on Malaria

1. NOTES with satisfaction that major control schemes have been instituted in most of the malarious areas in some WHO Regions, and that malaria elimination in them is foreseeable ;

2. CONSIDERS that this objective of malaria elimination could be made more readily attainable and that the possibility of discontinuation of spraying would be increased if work in different national territories were co-ordinated to secure simultaneous action on similar principles in neighbouring territories ;

3. RECOMMENDS that WHO make efforts and offer its technical help to promote and encourage international co-ordination of malaria-control programmes.

### 9.13 Report on Malaria Terminology

Having noted with satisfaction that a report on malaria terminology in English has been published, and that a comparable but not identical report in French is completed,

The Expert Committee on Malaria

RECOMMENDS that the French version be similarly published by WHO.

### 9.14 Award of the Darling Medal and Prize

Having considered the nominations submitted as stipulated in the Regulations of the Darling Foundation for the Award of the Darling Medal and Prize,

The Expert Committee on Malaria

RECOMMENDS that its report on the selection of the candidates, as well as its request for a revision of the present Regulations, be submitted by the Director-General of WHO to the Darling Foundation Committee, during the next session of the Executive Board, for consideration and for final decision on the awards proposed.

## Annex 1

### LIST OF SUPPORTING DOCUMENTS

- Andrews, J. M. & Grant, J. S. (1954) "Effects of suspended residual spraying and of imported malaria on malaria control in the USA", *Bull. Wld Hlth Org.* **10** (in preparation)
- Covell, G. (1954) "Chemotherapy of malaria", *Bull. Wld Hlth Org.* (to be published)
- Farid, M. A. (1954) "Non-effectiveness of DDT residual spraying in stopping malaria transmission in the Jordan Valley", *Bull. Wld Hlth Org.* **10** (in preparation)
- Georgopoulos, G. (1954) "Extension to other insecticides of DDT resistance observed in *Anopheles sacharovi*", *Bull. Wld Hlth Org.* **10** (in preparation)
- Giglioli, G. (1954) "Methodology of malaria control", *Bull. Wld Hlth Org.* **10** (in preparation)
- Livadas, G. A. & Georgopoulos, G. (1953) "Development of resistance to DDT by *Anopheles sacharovi* in Greece", *Bull. Wld Hlth Org.* **8**, 497
- Macdonald, G. & Davidson, G. (1953) "Dose and cycle of insecticide applications in the control of malaria", *Bull. Wld Hlth Org.* **9**, 785
- Trapido, H. (1954) "Recent experiments on possible resistance to DDT by *Anopheles albimanus* in Panama", *Bull. Wld Hlth Org.* **10** (in preparation)
- Vaucel, M. A., Roubaud, E. & Galliard, H. (1954) *Terminologie du paludisme*, Geneva, (*Organisation Mondiale de la Santé: Série de Monographies*, N° 24) (in press)

### Unpublished Working Documents

WHO/Mal/79	} Is it necessary to continue indefinitely DDT residual-spraying programmes ? by G. Livadas
WHO/Mal/79 Add. 1	
WHO/Mal/79 Add. 2	} Provisional agenda
WHO/Mal/81	
WHO/Mal/81 Add. 1	} Cytogenetic methods in the systematics of anopheles, by P. F. Russell
WHO/Mal/83	
WHO/Mal/84	Malaria control by methods other than insecticides : malaria carried by <i>Anopheles leucosphyrus</i> in Borneo, by J. McArthur
WHO/Mal/86	Malaria control in areas where the houses are made of mud, by Jaswant Singh
WHO/Mal/87	Changes of anopheline fauna and intra-species changes following the application of modern insecticides, by H. Trapido & T. H. G. Aitken
WHO/Mal/88	The role and importance of the new synthetic antimalarial drugs in the prevention of malaria, by M. A. Vaucel
WHO/Mal/89	On the possibility of specific differences in resistance-development-potential in anopheles, by R. A. Senior-White
WHO/Mal/90	Malaria control in areas where houses have mud walls, with a note on malaria control in the Transvaal, by S. Annecke
WHO/Mal/91	A bibliographical list of papers dealing with the utilization of <i>Plasmodium berghei</i> in the current study of malaria
WHO/Mal/93	} The application of pyrimethamine in rural areas, by I. H. Vincke
WHO/Mal/93 Add. 1	
WHO/Mal/94	Malaria control in areas where houses have mud walls (Ceylon), by S. Rajendram
WHO/Mal/97	The fate of DDT sprayed on mud walls of houses in Venezuela, by A. L. Berti, A. Gabaldón, S. J. Carrillo & H. Mazzari
WHO/Mal/99	List of members of the Expert Advisory Panel on Malaria

In addition, 26 "working papers" were distributed. These contained extracts from communications by members of the Expert Advisory Panel and other workers to the committee. The contributors included : Annecke, S. ; Bordas, E. ; Bruce-Chwatt, L. J. ; Covell, G. ; Farinaud, M. E. ; Frizzi, G. ; Garnham, P. C. C. ; Husain, M. Z. Y. ; Pinotti, M. ; Rodhain, J. ; Schmidt, L. H. ; Singh, Jaswant ; Thiel, P. H. van ; Vargas, L. ; Vincke, I. H. ; and Young, M. D.

## Annex 2

## THE MEASUREMENT OF LONGEVITY OF MOSQUITOS

The direct measurement of longevity of mosquitos under natural conditions is perhaps practically impossible, although an approach to it has been made by Russell & Rao<sup>1</sup> under conditions closely resembling nature.

Indirect approaches in which the age composition of anopheline populations is determined hold more prospect of success and may take the form of either (a) estimation of the age of individual specimens composing the population or (b) estimation of the proportion of a population falling within a known age-group ; this latter method can be adopted if it is assumed that the mortality does not vary greatly with age, which it often appears justifiable to assume.

The techniques of the first method, estimation of the age of individuals, are still undeveloped and need further research before they can be usefully applied. The approach now favoured involves measurement of the time of the gonotrophic cycle, and estimation of the degree of parity of anophelines and of their ovarian development. Measurement of parity remains uncertain and research on it turns largely on measurement of the ampulla of the oviduct.

The second method, estimation of the proportion of the population within a given age-group, can be used with a reasonable approach to accuracy if large numbers of mosquitos are available, the inflow of newly hatched ones is believed to be fairly regular, a notable proportion show sporozoites in their salivary glands, and the mean period of completion of the extrinsic cycle of the prevalent malaria parasite is known. A considerable number are captured and divided into two groups, a sporozoite-rate being immediately measured on one group. The other group is maintained under ideal laboratory conditions, and a sporozoite-rate determined on the survivors after the lapse of 12 days or the period of the extrinsic cycle. Two sporozoite-rates are thus secured, immediate and delayed, the latter exceeding the former by that proportion of mosquitos which were incubating parasites but had not yet developed sporozoites when originally captured.

The ratio of the immediate to the delayed rate is directly related to the mosquito mortality in a simple logarithmic form. If the probability of

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<sup>1</sup> Russell, P. F. & Rao, T. R. (1942) *Amer. J. trop. Med.* 22, 417, 517

survival through one day is termed  $p$  and the period of the extrinsic cycle  $n$ , then

$$\log p = \frac{\log \text{ratio}}{n - 1}$$

an equation which can be easily solved with the aid of simple logarithm tables.

Expression of longevity in this form, as probability of survival through one day, is often the most convenient form, but if the expectation of life is required in days, it is equivalent to  $\frac{1}{p}$ .

This method has been successfully used in practice, though more experimentation on such lines is desirable. Although probably reasonably accurate, it has the disadvantage that considerable numbers of mosquitos are needed to avoid significant statistical error, and for this reason it may be inapplicable once even moderate control has been established. The further development of the first method, which has not this disadvantage, is therefore much to be desired.

### Annex 3

#### TECHNIQUE FOR ASSESSING SUSCEPTIBILITY OF ANOPHELINES TO INSECTICIDES \*

##### 1. Impregnation of Filter-Papers

The insecticide is dissolved in a non-volatile, clear, mineral oil (Shell "Risella" oil) and diluted to a suitable range of concentrations. (For measuring out small quantities of oil solutions, 10-ml, 5-ml, and 1-ml "Record"-type syringes should be used; the oil is too viscous to measure accurately by pipette or measuring cylinder.) The concentrations tested should be at approximately equal logarithmic intervals. For *Anopheles gambiae*, the following should be of the right order: DDT at 2.0%, 1.0%, and 0.5%; gamma-BHC at 0.04%, 0.02%, and 0.01%; dieldrin at 0.4% and 0.2%.

To treat a batch of papers, 3-10 ml of any selected solution is taken and diluted with twice its volume of a volatile solvent.<sup>1</sup> Ethylene dichloride or

\* This technique, which was originally described by Busvine, J. & Nash, R. (*Bull. ent. Res.* 1953, 44, 371), has been slightly modified by Dr. J. Busvine (personal communication, 1954).

<sup>1</sup> Ether, which was originally advised by Busvine & Nash, may be found unsuitable under tropical conditions.

trichlorethylene (Trilene) will be found most convenient. One millilitre of this mixture is then applied to each paper in a spiral way so as to wet the paper as evenly as possible.

The filter-papers used are Whatman No. 1, 11 cm in diameter. They are treated in groups of 4-6, each paper being laid on the points of 4 vertical pins projecting from a board. It will be found that most of the volatile solvent evaporates within a minute. After this, the papers may be taken off the pins and hung up, so that a further group can be impregnated. Papers should be hung for at least 3 hours to allow of further drying and spreading of the oil residue. They may then be used for 2 or 3 days after treatment.

## 2. Making the Exposure Chambers

### (a) *Non-volatile insecticides (DDT, dieldrin)*

A strip 3 inches (8 cm) wide is cut from each filter-paper and rolled up to form the lining of a 3 inch  $\times$  1 inch (8 cm  $\times$  2.5 cm) specimen tube. The strip is cut slightly eccentrically to leave a wider segment on one side, from which a 1-inch (2.5-cm) circle is cut and pinned to the base of the cork. Thus, with the cork in place, a cylindrical chamber is formed, with all surfaces lined with treated paper except the glass bottom of the specimen tube.

### (b) *Volatile insecticides (gamma-BHC, aldrin)*

The exposure is made in a treated paper cylinder as before ; but to avoid concentration of vapour, the ends are closed with netting only. For this purpose, paper or metal collars are made, supporting 1-inch (2.5-cm) circles of cotton mosquito netting. Each paper is rolled round a pair of these collars and fixed with a strip of adhesive tape.

## 3. Exposure

Mosquitos in any standard conditions may be used, but it seems advisable to test the least susceptible forms, namely, young females, a few hours after a blood-meal. They may be reared at 27°C (80°F).

Robust mosquitos like *Aedes aegypti* may be handled by sucking tube, but this causes mortality among some species such as *Anopheles gambiae*. It is best to collect these in groups of 2 or 3 in test-tubes. When a sufficient number has been collected, the exposure chambers are laid horizontally on the edge of a table with the cork (or one netting-covered collar) removed.

The test-tubes containing the mosquitos are opposed to the mouths of the chambers and are gently rotated so that the insects fly out and settle on the treated paper. With care, about 6 mosquitos can be introduced, and the cork (or netting-covered collar) replaced without loss.

The mosquitos are exposed for 1 hour at 27°C, in darkness, with the exposure cylinders upright. After this, the insects are transferred to clean, wire-mesh cages, supplied with pads of damp cotton wool. Mortality counts are made after 24 hours at 27°C (80°F).

While this technique does not expose the mosquitos to the sort of dry films they would experience in the field, it does ensure that the same sort of insecticide contact is duplicated in all tests, and the consistency of the results obtained on different trials has confirmed the validity of the test method. The space in which the mosquitos are confined is small enough so that fairly uniform contact with the treated surfaces is maintained throughout the exposure period. This method is intended, of course, to measure only the ability of the mosquitos to survive contact with the toxicant, not their ability to detect or avoid it.

#### 4. Replicates and Results

Tests at critical concentrations (i.e., those with partial mortality from which dose/kill graphs can be drawn) should be replicated six times if possible. Log-concentrations/probit regression lines are drawn using the average mortalities and the median lethal concentrations can be estimated graphically.

#### Annex 4

##### CRITERIA OF MALARIA ERADICATION \*

“Malaria may be assumed to be no longer endemic in any given area when no primary indigenous case has occurred there for three years, if reporting, including the name and address of the patient and diagnosing physician, and case finding are actively promoted and adequate investigations are carried out.

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\* Quoted from the Final Report of the National Malaria Society Committee on Criteria to Determine when Malaria Ceases to be an Endemic Disease (*J. nat. Malar. Soc.* 1951, 10, 195).

This opinion is rendered with the full knowledge that relapses of malaria may occur after periods of latency exceeding three years, but it is believed that these instances will be so infrequent as to be inconsequential.

#### DEFINITIONS

1. Primary indigenous malaria is defined as the first parasite-positive evidence of infection, resulting from natural (mosquito) transmission within the given area.

2. Adequate investigation is defined as the epidemiologic investigation and appraisal of each reported case by qualified personnel. This involves verifying the diagnosis and determining if possible where and when the transmission occurred.

#### RECOMMENDATIONS

1. All slides considered to be positive should be submitted to a national depository for review.

2. The Public Health Service (Communicable Disease Center) should be designated as the national depository.

3. Consultants, including non-governmental authorities, should be appointed to review all controversial slides.

4. Non-governmental consultants should periodically examine and review the epidemiologic appraisals.

5. Inasmuch as determining the cessation of malaria transmission is dependent upon adequate epidemiologic intelligence, it is essential that every effort should be made to stimulate morbidity reporting, parasitologic confirmation, and case appraisal."

#### Annex 5

#### CHEMOTHERAPEUTICS OF MALARIA

As is now generally recognized, considerable differences exist in the reaction of various strains of parasites to drug prophylaxis and therapy, and the state of premunition of the host may greatly affect the action of antimalarial drugs. The efficacy of individual compounds therefore varies considerably in different places and under different immunological conditions.

The demonstration of a pre-erythrocytic phase of *Plasmodium cynomolgi* in the liver of the monkey and of a similar phase of *P. vivax* and *P. falciparum* in man has shed new light on the chemotherapy of malaria. The mode of action of the various drugs must be considered in relation to the different phases in the life-cycle of the parasite.

#### Mode of Action of Antimalarial Drugs<sup>1</sup>

In theory a drug may act on the malaria parasite in any of the following ways: (i) against the sporozoites when first they enter the human body; (ii) against the primary tissue or pre-erythrocytic phase; (iii) against the asexual parasites in their erythrocytic phase; (iv) against the sexual parasites in their erythrocytic phase; (v) against the late exo-erythrocytic or secondary tissue phase, to which the phenomena of latency and late relapse in vivax malaria have been attributed (a phase apparently non-existent in falciparum malaria); (vi) against the gametocytes in the mosquito phase of the life-cycle.

The classes of drugs in common use are: (a) the cinchona alkaloids (quinine, totaquina); (b) the amino-acridines (mepacrine); (c) the 4-aminoquinolines (chloroquine, amodiaquine); (d) the 8-aminoquinolines (pamaquin, primaquine<sup>2</sup>); (e) the biguanides (proguanil); and (f) the diaminopyrimidines (pyrimethamine<sup>3</sup>).

No drug as yet tested has any demonstrable effect on the sporozoite stage of the malaria parasite. The cinchona alkaloids, amino-acridines, 4-aminoquinolines, biguanides, and diaminopyrimidines have a destructive action on the asexual forms of all species of human malaria parasites in the erythrocytic phase, though the action of the last two is too slow for treatment of the clinical attack in a non-immune subject. The 8-aminoquinolines do not affect the asexual parasites of *P. falciparum* in the erythrocytic phase, but have a powerful destructive action on the gametocytes of all species. They also act on the secondary exo-erythrocytic forms of *P. vivax*, and it is in this respect that they have their greatest value. They have an inhibitory effect on the pre-erythrocytic forms of both *P. falciparum* and *P. vivax*, but only when administered in dosage dangerously high for routine use.

The biguanides and the diaminopyrimidines are the only classes of drugs of which members can be used with safety against the pre-erythrocytic phase, and so far as is known they are fully effective only in falciparum

<sup>1</sup> A list of synonyms (proprietary names) is given on page 42.

<sup>2</sup> Primaquine: 8-(4-amino-1-methylbutylamino)-6-methoxy quinoline

<sup>3</sup> Pyrimethamine: 5-(4'-chlorophenyl)-2,4-diamino-6-ethyl pyrimidine

infections. They have no apparent action on the sexual forms of *P. falciparum* in the peripheral blood, but both have been shown to render them incapable of completing their development in the mosquito.

#### *Drug resistance in malaria*

The fact that some strains of malaria parasites are more resistant than others to the action of particular antimalarial drugs has long been recognized, but acquired resistance to malaria is a comparatively recent phenomenon. Such resistance to proguanil of *P. gallinaceum* was first reported in 1947. Subsequently, other species of *Plasmodium*, including *P. falciparum* and *P. vivax*, have been shown to share this capacity for adaptation to proguanil. More recently, resistance to pyrimethamine, whose behaviour resembles that of proguanil in many ways, has been demonstrated, and cross-resistance between the two drugs has been shown to exist. Drug resistance in malaria has thus become a major clinical problem.

Resistance to proguanil may appear quickly or slowly, or indeed not at all, depending on the conditions of exposure to the drug. Under artificial conditions, with deliberate underdosage and careful gradation and timing, a high tolerance to the drug may appear within a few months. In clinical and preventive practice, with efficient treatment or thorough suppression, resistance thus far has not been recorded.

Thus, in the Tampin district of Malaya, where owing to disturbed local conditions administration of the drug was irregular and inadequately supervised, resistance to proguanil began to appear with *P. falciparum* after two years and with *P. vivax* after four years had elapsed. One hundred miles (approximately 160 km) away, on a malarious estate with good suppressive discipline, after continuous use for six years at 100 mg once or twice a week, proguanil is apparently still effective.

Certain preliminary unpublished work in East Africa suggests that periodic mass treatment with pyrimethamine may also result in the eventual appearance of resistance to this drug.

It seems that the primary factors in the causation of resistance are underdosage and significant parasitaemia operating together, and under field conditions are found particularly in the smouldering infections partially controlled by irregular or inadequate suppressive dosage.

The evidence as regards the production of resistance to pyrimethamine is as yet incomplete, but it seems probable that the same considerations will apply to this drug as to proguanil.

Significant drug resistance has never been reported in the case of chloroquine or amodiaquine. Experimental attempts to produce resistance in avian and mammalian malaria to mepacrine, chloroquine, and amodiaquine

have never been successful. In an isolated instance, however, Fairley<sup>4</sup> reported relative resistance to mepacrine in strains of *P. falciparum* observed in the Aitape-Wewak-Lae area of New Guinea.

Acquired resistance to quinine in human malaria is rare, if indeed it occurs at all, although southern European strains of *P. falciparum* tested at Horton have been found to require eight times as much of the drug to control the attack as strains from India and Africa, and even this amount proved ineffective in producing radical cure.

Thus, the risk of drug resistance to the antimalarial compounds at present in common use is apparently confined for all practical purposes to proguanil and pyrimethamine.

### Therapeutics of Malaria

The most important objectives are first, prompt alleviation of symptoms with minimum risk of toxic side-effects and secondly, radical cure of the infection. Interruption of sporogony, so that mosquitos which may feed upon the patient are unable to transmit the disease to others, is also desirable, and in certain circumstances may be a matter of considerable importance.

*Quinine sulfate or dihydrochloride*, given in a daily dose of 20-30 grains (1.3-2.0 g) will usually bring about rapid termination of the clinical attack and, in falciparum infections, a high rate of radical cure. This drug is, however, much less effective in the radical cure of certain European strains of *P. falciparum*. It has no effect on the infectivity of gametocytes to mosquitos, and in certain circumstances may act as a contributory factor in the precipitation of blackwater fever.

*Mepacrine*, when given with a loading dose of 600-900 mg on the first day or first two days of treatment followed by 300 mg daily for the rest of the week, will usually effect a rapid termination of the clinical attack in all forms of malaria, and a high rate of radical cure in falciparum infections. It does not affect gametocytes. Toxic effects, though of rare occurrence, are by no means negligible, as for example mepacrine psychosis, which may be attended with symptoms of mental aberration or even of maniacal excitement. Another drawback is the yellow discoloration of the skin which sometimes follows administration of this drug.

*Chloroquine* brings about rapid alleviation of clinical symptoms in all forms of malaria and a high rate of cure in falciparum infections. It has

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<sup>4</sup> Fairley, N. H. (1946) *Trans. roy. Soc. trop. Med. Hyg.* 40, 229

the advantage over mepacrine of not tinting the skin and of being less likely to induce disagreeable intestinal or psychotic manifestations. The regimen usually recommended is an initial dose of 600 mg of the base, followed by 300 mg six hours later and a single dose of 300 mg on each of the two following days. *Amodiaquine*, whose action resembles that of chloroquine, is probably equally effective. Neither of these drugs renders gametocytes non-infective to mosquitos.

*Proguanil*, in the absence of reinforcement with some more powerful schizontocidal drug, is too slow in action for treatment of acute malaria in a non-immune subject; moreover, it cannot be relied upon to effect radical cure even of falciparum infections in certain geographical areas. It effectively prevents the completion of sporogony of *P. falciparum*, a property not possessed by mepacrine, chloroquine, amodiaquine, or quinine. It is moreover by far the least toxic to man of all known antimalarial drugs.

*Pyrimethamine*, like proguanil, is too slow in action for treatment of an acute attack in non-immunes. It shares with proguanil the property of preventing the completion of sporogony of *P. falciparum*. Although no serious toxic effects have yet been reported in human subjects, animal experiments suggest that such effects might occur should the recommended therapeutic dosage be substantially exceeded.

#### *Treatment of the clinical attack in non-immune subjects*

For this class of patient it is necessary to employ one or other of the more powerful schizontocidal drugs, such as chloroquine, amodiaquine, mepacrine, or quinine. Considering the relative advantages and disadvantages which have been listed, chloroquine and amodiaquine are probably the most effective agents for terminating the clinical attack, and the toxic side-effects of a serious nature are rare in either case. These two compounds are generally recognized as the drugs of choice in the treatment of acute malaria.

Neither proguanil nor pyrimethamine is sufficiently rapid in action to warrant its use for the treatment of acute malaria in non-immune subjects without reinforcement by some more rapidly acting schizontocide.

For the treatment of comatose or other cases where for any reason it is impossible to administer antimalarial drugs by the oral route, they must be given parenterally. Quinine dihydrochloride, 0.65 g in 300-400 ml of normal saline, may be injected intravenously *very slowly* (not more than 50 mg of the salt per minute), repeated if necessary six hours later, or the drug may be given by continuous drip over a period of 24 hours or more. The latter procedure has been found particularly valuable in cases of

extreme malnutrition. Alternatively, mepacrine methane sulfonate may be given intramuscularly in a dosage of 300-400 mg, repeated if necessary after six hours. Chloroquine and amodiaquine have also been given intramuscularly and intravenously, but evidence is not yet to hand as to their efficacy in cases of extreme gravity. The intramuscular injection of quinine, still widely practised in many countries, has the disadvantage that it causes necrosis and may produce abscess. As soon as the patient is able to take drugs by the mouth, all further medication should be by the oral route.

#### *Radical cure of vivax malaria*

If it is intended to place the patient on a suppressive régime for an indefinite period after treatment of the clinical attack, no further medication is called for. If suppressive treatment is not contemplated, radical cure may be effected in a large proportion of cases by the use of one or other of the 8-aminoquinoline group of drugs. The first of these to be used for the prevention of relapse was pamaquin, in a dosage of 10 mg of the base thrice daily for 10 days. Recent work has shown that certain other members of the group—pentaquine, isopentaquine, and primaquine—are more effective and less toxic than pamaquin, primaquine being considered the best of the three in both respects. The dosage of primaquine recommended is 15 mg of the base daily for 14 days, reinforced with the standard chloroquine treatment if given during an acute attack.

The treatment recommended for radical cure of malariae infections is the same as that for vivax.

Careful supervision of the patient is called for with all members of the 8-aminoquinoline group of drugs, particularly in the case of dark-skinned races, because of the occasional unpredictable occurrence of acute intravascular haemolysis.

#### *Treatment of the clinical attack in subjects partially immune*

For the dispensary treatment of partially immune people, a single-dose treatment of 600 mg of chloroquine base, or of 600 mg of amodiaquine base, has proved efficient. Good results have also been reported with a single-dose treatment of 300 mg of proguanil. It has been suggested that pyrimethamine in a single dose of 50 mg might prove an efficient and economical therapeutic agent under similar conditions. But, for reasons already stated under the heading of drug resistance, it seems preferable to reserve both proguanil and pyrimethamine exclusively for prophylactic purposes, and to use chloroquine, amodiaquine, mepacrine, and quinine as therapeutic agents.

### Prophylaxis and Suppression

The onset of a clinical attack of malaria may be prevented (i) by a drug acting on the pre-erythrocytic phase of the parasite (causal or causative prophylaxis) or (ii) by a drug acting on the asexual erythrocytic phase.

The only classes of drugs of which members can achieve the former effect in non-toxic dosage are the biguanides and diaminopyrimidines, and in both cases their action is confined in this respect so far as is known at present to falciparum malaria. Since, however, they act also on the asexual erythrocytic forms in all species of malaria, their use in prophylaxis is by no means confined to falciparum infections. To guard against the production of resistant strains of *Plasmodium*, it is essential that these drugs be methodically administered.

The dosage of *proguanil* recommended for prophylactic or suppressive use is 100 mg daily for non-immune individuals, and 300 mg in a single dose once weekly for indigenous inhabitants of malarious countries. A great advantage of this drug is that it can be placed in the hands of laymen for distribution without risk of ill-effect, even should the prescribed dose be grossly exceeded.

The dosage of *pyrimethamine* recommended for this purpose is 25 mg in a single weekly dose. The very small amount used is a great advantage of this drug, while the fact that it is tasteless renders it particularly suitable for administration to children. For this very reason, however, it is necessary to keep the bottle out of reach, for instances have been recorded where children have swallowed a number of tablets in mistake for candy. Both proguanil and pyrimethamine have the further advantage of preventing sporogony.

For the effective suppression of falciparum malaria, *quinine* has to be administered in doses as high as 10 grains (0.65 g) daily. Against New Guinea strains of *P. falciparum* even this dosage has proved insufficient. Apart from the unpleasant side-effects liable to arise from prolonged administration of this amount of quinine, the association of this drug with the precipitation of blackwater fever renders it unsuitable for use as a suppressant in areas where falciparum infections are prevalent.

*Mepacrine*, in a dosage of 100 mg daily, is a very effective suppressant of all forms of malaria, provided that the drug is taken for 14 days before exposure to infection and continued for one month after leaving the endemic area, but it has certain disadvantages which militate against its routine use under peacetime conditions. When taking the drug over long periods, a proportion of individuals develop skin lesions, the most common of which

is a lichenoid dermatitis affecting chiefly the hands, wrists, feet, and ankles. Yellow discoloration of the skin, a comparatively common feature, is a further disadvantage.

*Chloroquine* is probably an even more powerful suppressant than mepacrine, the dosage usually prescribed being 300 mg of the base once weekly, or for non-immunes in some areas 100 mg daily. Its action resembles that of mepacrine, but it is generally less toxic and does not tint the skin. *Amodiaquine*, in a dosage of 400 mg of base weekly, is equally effective.

At present the choice of drug for prophylaxis seems to lie between proguanil, pyrimethamine, chloroquine, and amodiaquine. The first two have the advantage of preventing the completion of sporogony in the mosquito and, at the present time, of being low in cost; proguanil has, in addition, the advantage of extremely low toxicity. There is, however, the possibility of resistance appearing with either of these drugs, particularly if they are used indiscriminately as therapeutic agents. Should this occur, a switch-over to chloroquine, amodiaquine, or quinine is indicated.

### Summary of Dosage Recommended

#### *Treatment of clinical attack in non-immune subjects*

- (1) Chloroquine diphosphate or sulfate : 600 mg of base immediately, 300 mg six hours later, 300 mg on each of the next two days.
- (2) Amodiaquine dihydrochloride dihydrate : 600 mg of base immediately, 400 mg daily for next two days.
- (3) Mepacrine hydrochloride : 200 mg thrice daily for first two days, 100 mg thrice daily for next five days ; *or* 1 g (five doses of 200 mg) on first day, and 100 mg thrice daily for next six days.
- (4) Quinine sulfate or dihydrochloride : 20-30 grains (1.3-2.0 g) daily for 5-7 days.

#### *Emergency treatment*

- (1) Quinine dihydrochloride : 10 grains (0.65 g) in 300-400 ml of normal saline injected intravenously *very slowly* (not more than 50 mg of salt per minute), repeated after six hours if necessary ; *or* administered by intravenous drip at the rate of 2.0 g of the salt in 24 hours.

(2) Mepacrine methane sulfonate : <sup>5</sup> 300-400 mg injected intramuscularly, repeated after six hours if necessary.

Note : Chloroquine and amodiaquine have also been given both intramuscularly and intravenously with good results, but evidence is not yet to hand regarding their efficacy in cases of extreme gravity.

*Radical cure of vivax and malariae infections*

(1) Primaquine diphosphate : 15 mg of base daily for 14 days, reinforced with standard chloroquine treatment if given during an acute attack.

(2) Pamaquine naphthoate or dihydrochloride : <sup>6</sup> 10 mg of base thrice daily for 5-10 days, reinforced with standard chloroquine or quinine treatment if given during an acute attack.

*Treatment of clinical attack in semi-immune subjects*

(1) Chloroquine diphosphate or sulfate : 600 mg of base in a single dose.

(2) Amodiaquine dihydrochloride dihydrate : 600 mg of base in a single dose.

(3) Mepacrine hydrochloride : 600 mg in a single dose.

(4) Quinine sulfate or dihydrochloride : 15-25 grains (1.0-1.5 g) daily for two or more days.

Note : 1 g = 15 grains.

*Prophylaxis and suppression*

(1) Chloroquine diphosphate or sulfate : 300 mg of base once weekly, or 100 mg daily.

(2) Proguanil monohydrochloride : 100 mg daily ; or, for semi-immune subjects, 300 mg once weekly.

(3) Amodiaquine dihydrochloride dihydrate : 400 mg of base once weekly.

(4) Pyrimethamine : 25 mg of base once weekly.

Note : The doses given above are for adults of 70 kg body-weight. They should be adjusted according to the usual rules for weight and age. However, proguanil and pyrimethamine may be given in quarter the adult dose for those up to five years of age, and in half the adult dose for those between six and twelve years.

<sup>5</sup> 375 mg mepacrine methane sulfonate = 300 mg mepacrine hydrochloride.

<sup>6</sup> 18 mg naphthoate = 8 mg base = 10 mg dihydrochloride. For practical purposes, 2 naphthoate = 1 base = 1 dihydrochloride.

## Antimalarial Drugs and their Synonyms

AMODIAQUINE	Malaricida	Chlorguanide
Cam-aqi	Methoquine	Chloriguane
Camoquin	Metoquina	Diguanyl
Flavoquine	Metoquine	Drinupal
Miaquin	Palusan	Guanatol
SN 10751	Quinacrine	Paludrine
		Palusil
		Tirian
CHLOROQUINE	PAMAQUIN	M4888
Aralen	Aminoquin	SN 12837
Nivaquine B	Beprochin	3359 RP
Resochin	Fourneau-710	
Tanakan	Gamefar	
SN 7618	Pamaquine	PYRIMETHAMINE
3377 RP	Plasmochin	Daraprim
	Plasmocide	Malocide
	Plasmoquine	B-W 50-63
MEPACRINE	Praequine	
Acriquine	Quipenyl	
Arichin	Rhodoquine	SONTOQUINE
Atabrine		Nivaquine A
Atebrin	PRIMAQUINE	Nivaquine C
Chemiochin	SN 13272	Santochin
Chinacrin		Santoquine
Crinodora	PROGUANIL	Sontochin
Erion	Balusil	SN 6911
Haffkinine	Bigumal	3038 RP
Italchina		

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