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## 1. PROBLEMS OF RESISTANCE OF MALARIA PARASITES TO DRUGS

Among the points discussed at the Technical Meeting on Chemotherapy of Malaria, held in November 1960 at Geneva, was the increasingly important problem of resistance of malaria parasites to drugs.

The fact that after the administration of an adequate dose of the proper drug, parasites do not disappear from the blood of a person infected with malaria may be due either to drug failure or to drug resistance. Drug failure may result from defective absorption or unusual rates of metabolism and excretion of the drug. On the other hand, in drug resistance, while the absorption and metabolism of the drug appear normal, the parasite itself is insensitive to the action of the drug.<sup>1</sup>

Although sporadic observations of lessened sensitivity of some strains of malaria parasites to quinine, pamaquine and mepacrine have been reported in the past, the problem of drug resistance of human malaria parasites became significant only since 1948-1950 with the discovery of proguanil resistance of P. falciparum and P. vivax in Malaya. Further observations on proguanil resistance were reported in local strains of P. malariae and P. falciparum in Indonesia, and of P. falciparum in Assam, in New Guinea, in Viet Nam and in several parts of Malaya.

High resistance to proguanil develops most readily against the asexual forms but extends also to all developmental stages of the parasites; the speed of its appearance in the field depends probably on the strain of the parasite but it is believed that it is mainly due to prolonged and irregular treatment of populations living in highly endemic areas. Once developed the proguanil resistance appears to be fairly stable and this characteristic of the parasite is transmitted by mosquito passage. The latter fact underlines the importance of the phenomenon of resistance from the point of view of malaria eradication.

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<sup>1</sup> The definition of drug resistance of malaria parasites given by Covell, Coatney, Field & Singh (1955), World Health Organization Monograph Series No. 27, is as follows:

"Resistance (is the ability) of the parasite species to withstand the action of drugs which, administered to the vertebrate host in adequate and safe doses, normally destroy or contribute to the destruction of malaria parasites at some stage of their life cycle."

Considering the wide use of proguanil and the relative ease with which experimental resistance to this drug can be produced, the number of confirmed cases of resistance to proguanil reported from the field has been relatively small and usually limited to conditions when the dosage of the drug was low and its administration irregular.

The evidence of cross-resistance to pyrimethamine of proguanil-fast strains of P. falciparum was produced as long ago as 1952 in East Africa.

A recent field trial carried out in Ghana with chlorproguanil showed that in weekly doses of 20 mg the drug protected a group of African children from P. falciparum infection for a month, but thereafter irregular dosage produced, at the end of six months, resistance to this drug. The resistant strain of P. falciparum was also resistant to pyrimethamine.

Since 1954, when pyrimethamine-resistant strains of P. falciparum and P. malariae were reported from the field from Kenya and Tanganyika, the number of such records kept increasing every year. Most of these reports pertain to P. falciparum and come from Africa; they refer to generally small areas in the following countries and territories: Kenya, Tanganyika, Cameroun Republic, Voltaic Republic, Northern Nigeria, South-Western Nigeria and Ghana. Outside tropical Africa pyrimethamine resistance was reported in P. falciparum and P. vivax from Venezuela and in P. falciparum from the Netherlands New Guinea. In Venezuela the resistance was reported from a relatively large area in the western part of Venezuela inhabited by 38 000 people given a weekly or fortnightly adult dose of 50 mg of pyrimethamine for over one year. In the Netherlands New Guinea the signs of resistance appeared after six months of distribution of medicated salt containing pyrimethamine. Resistance to pyrimethamine or proguanil has not been recorded in USSR and Romania although these drugs have been widely used for "mass prophylaxis" together with other antimalarials.

A number of facts reported from the field are of interest. In an area of East Africa where pyrimethamine resistance of P. falciparum had developed, the proportion of resistant infections declined after the drug administration had ceased. In an area of Tanganyika where pyrimethamine resistance of P. falciparum was observed there was no significant resistance to proguanil. In Cameroun the combined administration of pyrimethamine and chloroquine did not prevent the development of P. falciparum resistance but the doses of the two drugs were very small. Administration of a single

dose of chloroquine as a preliminary step to the regular distribution of pyrimethamine in Tanganyika and Netherlands New Guinea did not prevent the development of resistance of P. falciparum to the latter drug.

Some recent experimental work on drug resistance of simian and human malaria parasites is of considerable interest but reference will be made here only to human plasmodia. It has been shown in the United States of America that the Chesson strain of P. vivax can develop resistance to pyrimethamine when given repetitive small doses of the drug over two months. Later work showed however that a high resistance by three strains of P. vivax (Chesson, Korea, St. Elizabeth), by a strain of P. malariae and by a Panama strain of P. falciparum could be produced rapidly after the administration of either a single dose or a few doses of pyrimethamine given during the peak of parasitaemia.

A review of all the known information regarding pyrimethamine resistance reported from the field showed that the conditions for the development of this resistance were not related to geographical distribution of the population involved, to the dosage of the drug, to the intervals between the doses or to the duration and mode of administration. Pyrimethamine resistance appeared in areas where the drug administration was the only antimalarial measure and in areas where the transmission was greatly decreased by simultaneous residual insecticide spraying.

A recent observation of a primaquine-resistant substrain (Marvel) of the Chesson strain of P. vivax was reported to the meeting. The case originated from a breakdown of drug discipline in a therapeutic trial and the substrain was subinoculated into volunteers. After the 25th passage there was no effect of high doses of primaquine. The drug did not affect the development of gametocytes of the resistant strain and the production of oocysts and sporozoites by mosquitos, but the attempt at infecting non-immune volunteers by the bites of such mosquitos was not successful. Resistance to primaquine might therefore be considered a possibility, but the fact that it has not been seen in practice in spite of the wide use of this drug should be stressed.

Although Indian workers showed a few years ago that a 200-fold increase of the level of chloroquine tolerance could be produced experimentally in P. berghei the likelihood of such occurrence in human malaria was generally discounted.

Some new evidence of the possibility of such an event was recently reported and much attention of the meeting was concentrated on the problem of possible chloroquine resistance in human malaria parasites. It has been pointed out that in the course of experimental studies an increased tolerance to chloroquine of a strain (El Limon) of P. falciparum known to be resistant to pyrimethamine was reported some years ago in the United States of America.

It was noted in Northern Nigeria, during a drug trial carried out in 1959 in the course of which pyrimethamine resistance of P. falciparum had developed, that the action of chloroquine was slow or incomplete when this drug was subsequently given at the usual dose to individuals with persisting parasitaemia.

A similar observation was made in the Haute Volta area in tropical Africa, and it was reported that in some individuals harbouring pyrimethamine-resistant P. falciparum there was evidence of increased tolerance of the relevant strain to chloroquine and to amodiaquine. In a limited area of Western Venezuela instances of alleged failures of chloroquine to clear pyrimethamine resistant trophozoites of P. falciparum were brought to notice in early 1960. Moreover, during the second half of 1960 it has been reported that in the state of Tachira in Venezuela at the border with Colombia, out of 41 cases of P. falciparum treated with 1 500 mg of chloroquine and a single dose of 45 mg primaquine, no less than 14 showed recurrences of the infection after a short period.

The recent observation of possible chloroquine resistance in P. falciparum concerns a strain which seems to have originated in Colombia, South America, and has been investigated by a team from the National Institute of Health in the United States of America. This strain was first discovered in two non-immune patients working in Colombia who had recurrent attacks of P. falciparum malaria in spite of oral and parenteral treatment by chloroquine. The strain obtained from one of these patients was transmitted by blood inoculation into six neurosyphilitic patients, and in five of them the disappearance of parasites from the bloodstream under the action of various, usually effective, doses of chloroquine was slow or incomplete. In four of these cases the clearance of parasitaemia was followed by a recurrence of the infection.<sup>1</sup>

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<sup>1</sup> A recent report indicates that the strain of P. falciparum from Magdalena valley in Colombia is also resistant to amodiaquine and to hydroxychloroquine.

The meeting considered the evidence available on the present status of resistance of human malaria parasites to drugs and fully endorsed the recent statement of the WHO Expert Committee on Malaria, eighth session (Geneva, August 1960) on this subject.<sup>1</sup> It appears that where strains resistant to pyrimethamine and proguanil have occurred, they do not spread rapidly, perhaps because they are not so readily transmitted by the mosquito. Although pyrimethamine resistance has appeared in many instances in various parts of the world, in both P. falciparum and P. vivax, there are nevertheless many areas where this drug has been used for a long time without recorded appearance of resistance. Treatment of established infections in these areas has usually been carried out with 4-aminoquinolines. Nevertheless, the fact that reports of pyrimethamine resistance have been numerous indicates the need for insistence that in malaria eradication programmes this drug should be used only for its intrinsic causal prophylactic and sporontocidal qualities.

It is evident that instances of drug failure demand the fullest and strictest investigation, before reports on them are circulated or published. The relevant investigation should cover all the circumstances under which the alleged failure appeared, its degree, geographical distribution and transmissibility through the vector. Evidence of resistance of malaria parasites to any drug can only be obtained if the response of the relevant strain to the specific drug is assessed under rigorous conditions excluding reinfection and assuring that the drug has been ingested and reached adequate blood level. Final proof of resistance requires the transfer of such strain of malaria parasite to an uninfected, non-immune host.

Whatever the mechanism of the drug resistance of malaria parasites it is now clear that whenever such resistance occurs in the field it may seriously interfere with malaria eradication programmes which rely to the greater or lesser extent on chemotherapy. Most observations from the field indicate that the resistance develops when the selection of drugs used for a particular chemotherapeutic purpose is not properly considered. Thus the sole use at any dosage of essentially prophylactic or sporontocidal drugs for treatment of acute cases of malaria or for suppression of high parasitaemia should be condemned.

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<sup>1</sup> "The resistance developed by some strains and species of human malaria parasites against such drugs as pyrimethamine and proguanil ... presents serious potential obstacles in some malaria eradication programmes, and particularly in those which rely to any extent on the sporontocidal action of these drugs. The importance, range, geographical distribution and spread under field conditions of specific drug resistance in human malaria parasites should be fully assessed." Report of the WHO Expert Committee on Malaria, eighth session, Wld Hlth Org. techn. Rep. Ser., 205 (1961)

Although recent experimental work has shown that single or few large doses of some drugs given at the height of parasitaemia may be followed by development of resistance by parasites, most observations from the field suggest that the administration of unduly low or widely spaced doses of antimalarials increases the probability of drug resistance. With drugs having a relatively long duration of action it is important that regularity and adequacy of dosage be maintained.

Generally speaking, it seems that the combined use of drugs with different types of action and at adequate dosage may prevent the development of resistance.

Each area in which chemotherapy is used for malaria eradication should be viewed as a separate problem, with due regard to the species of parasite and vector, intensity of transmission, selection of proper drug or drugs, practicability of regular, frequent dosage and the extent and nature of previous drug administration. Due precautions should be taken for the early discovery of resistance and for a rapid change to a drug belonging to a different group. The increase of the dosage of the drug against which the specific resistance has developed, with the hope of maintaining the therapeutic effect of the drug, is a serious error.

Practical points with regard to some currently used drugs are as follows. Pyrimethamine, biguanides or 8-aminoquinolines given for the purpose of gametocytocidal, sporontocidal or anti-relapse action should always be used together with a schizontocidal drug (4-aminoquinoline). Pyrimethamine alone should not be used for mass drug administration and especially not in medicated salt. For treatment of established infections 4-aminoquinolines are undoubtedly the best drugs (followed by 8-aminoquinoline when a radical cure of relapsing malaria is aimed at). More field research on the prevention of the development of resistance by the use of combined antimalarials is urgently needed.

An observation made ten years ago that some strains of malaria parasites with a higher tolerance to quinine show an increased susceptibility to 8-aminoquinolines is of interest. Such a "negative correlation" between two compounds may provide new possibilities for prevention of the development of resistance and research in this field of experimental chemotherapy should be encouraged.

## 2. PARTICIPATION OF SOCIAL WELFARE WORKERS IN MALARIA ERADICATION PROGRAMMES

In the first quarter's report 1961 from Burma, Dr G. L. Adan, Project Leader and WHO Malariologist at the Malaria Institute, Rangoon, describes a plan for co-operation with social welfare workers of the Burma Social Welfare Service during the malaria eradication programme.

He suggests social welfare workers could assist the malaria eradication programme in the following ways:

### During the spraying campaign:

(i) Advance information to the villagers on the date the village will be sprayed. In the villages, the village social workers will show to the villagers how they could help the spray programme, such as in the preparation of houses, the supply of water to mix the insecticide, carrying the insecticide from one place to another, keeping infants, children, domestic pets, etc., away from the house during spraying, reporting to the spray team houses that are not properly sprayed or not yet sprayed.

(ii) The village social worker will also give the correct information about the programme, how malaria is acquired, and the need to have every house in the community properly sprayed; that a house left unsprayed is a danger to the entire community. They should impart to the people the need to protect the sprayed surfaces from washing, rubbing, so that they are protected from malaria until the next spray season.

### During surveillance:

(i) To form the nucleus of voluntary collaborators in surveillance.

(ii) To search for suitable villagers who may be trained to act as voluntary collaborators.

(iii) The village social workers and villagers interested in the work of voluntary collaborators will be given training in:

- (a) enquiry of fever and history of fever amongst villagers;
- (b) taking blood smears;
- (c) administering antimalaria drugs;
- (d) packing and transporting blood slides to the laboratory;
- (e) making the necessary forms;

- (f) keeping records;
- (g) keeping fever registry;
- (h) making follow-up of confirmed cases;
- (i) giving the correct information to the malaria supervisor about the village when asked to give such as the number of fever cases, number of houses, number of population, etc.

At a meeting held at the Malaria Institute, Rangoon, on 14 March 1961 between the Deputy Director (Public Health), the Senior Malariologist, Malaria Eradication, the Deputy Director, Social Welfare Service, and Dr Adan, WHO, discussions were held on how the Malaria Eradication Organization and the Social Welfare Service could best co-operate and it was decided to adopt the following lines of action:

(i) Team leaders should send copies of the spray programme (plan and action) to the social welfare officials in various districts of the regions. By this means, the social welfare officials can visit the villages in advance and give prior information and education to the headmen and villagers on such points as how to help, see that every house is sprayed and also to find fever cases at the time of surveillance work.

(ii) In places where there are township social workers, and village social welfare workers, the District Social Welfare Officer will personally visit these social welfare workers and brief them on how to put the plan into effect in the villages.

(iii) The two departments concerned will issue directives for the implementation of the plan to their respective staff in the districts. The Malaria Institute will send such directives to the regional team leaders, malaria assistants, malaria inspectors, malaria supervisors, and also the district health officers. In the same way, the Social Welfare Services Department will also issue similar directives to their district personnel.

(iv) In the regions and districts, the team leaders, malaria assistants and malaria inspectors will, on receipt of the directives, contact the social welfare workers and conduct discussions for carrying out the plan.

- (v) The departmental heads of the Social Welfare Service and Malaria Institute in Rangoon will periodically visit the districts wherever the plan is in progress, to see how far success has been achieved.
- (vi) The malaria assistants, malaria inspectors and malaria supervisors will mention in their monthly reports about the co-operation received from the social welfare officials and the villagers and also on the extent of success achieved.
- (vii) In the same way, team leaders will mention how much co-operation has been received and the success achieved in their monthly reports.
- (viii) Similarly, the social welfare officials will submit special monthly reports, during the spraying season, on the villages they visited and activities they have carried out according to the instructions contained in the directives.
- (ix) During the surveillance period, the social welfare workers will offer help in searching for fever cases, not necessarily only malaria, and give information whenever and wherever they come across such cases.

### 3. SOUTH-EAST AFRICAN MALARIA CO-ORDINATION BOARD

In August 1958 the first meeting was held in Lourenco Marques on the question of malaria eradication in South-East Africa.<sup>1</sup> At this meeting it was accepted that eradication in this area was feasible and it was recommended that a pilot scheme be instituted. It was considered that four pre-eradication survey teams would be necessary, working in Mozambique, Northern Transvaal and Bechuanaland Protectorate, Natal and Swaziland and in Southern Rhodesia. The meeting also recommended that a standing co-ordinating committee be set up which would be composed of representatives from the territories concerned, from WHO Regional Office and the field teams.

A further meeting of this Co-ordination Board took place at Salisbury, Southern Rhodesia, in January 1961 when progress reports from the representatives were received.

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<sup>1</sup> Reported in Mal/Inform/45 of 1 June 1959

In Mozambique, due to various delays, the Plan of Operations was only just being implemented. In Northern Transvaal transmission of malaria had been interrupted over the greater part of the territory except in areas adjacent to international boundaries, particularly in the east and north-east contiguous with Mozambique and Southern Rhodesia. Little further progress had taken place in Bechuanaland though the area bordering Transvaal is controlled by spraying teams of the Union of South Africa Malaria Service. Infection was still high along the Southern Rhodesian boundary. In Natal the malarious areas were found mainly in the north-eastern tip of the province adjoining Mozambique. During the period October 1959 to September 1960 spraying was carried out in this "transmission zone" with BHC but this insecticide was not found to be sufficiently long-lasting and a change has been made to DDT. Swaziland reported that spraying was stopped in 1958 and was replaced by surveillance, but an invasion of infection occurred early in 1960 and chemoprophylaxis was started. During the 1960-61 transmission season DDT spraying was started again. The eradication programme in Southern Rhodesia is restricted to an area in the south of the country with a population of 320 000. This area is divided into three sectors. The first sector, to the west, was already under surveillance; the second central sector is being brought under surveillance during 1961. In the third eastern sector bordering on Transvaal and Mozambique transmission is still continuing and spraying is still in operation.

All territories reported large population movements over their boundaries and several had schemes to deal with these migrants.

The following recommendations were made at the meeting:

- (i) After consideration of the minimum provisions laid down by WHO for the establishment and running of an effective eradication programme, the meeting recommended that these provisions, modified according to conditions prevailing in individual countries, should be implemented throughout the South-East African Malaria Eradication Programme regardless of the phase of eradication achieved.
  - (ii) The meeting, bearing in mind the recommendations of the WHO meeting on Malaria Eradication in South-East Africa held at Lourenco Marques in 1958, and having agreed to the establishment of a Co-ordination Board for the South-East African Programme, recommended that WHO should formally request Member governments to signify their approval.
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- (iii) The meeting, having discussed the functions and duties of such a Co-ordination Board, considered that, in order to ensure the efficient execution of its duties on behalf of the Member governments, the Board would require a small permanent secretariat which, for convenience, would be located at Salisbury. It further recommended that WHO should study the requirements of such a secretariat and notify Member governments of the cost involved to them, together with a proposal for individual contributions.
- (iv) The meeting recommended that the next session of the Co-ordination Board should be held in approximately one year's time, unless special circumstances should call for an earlier meeting.

#### 4. EVALUATION SECTION IN IRAN

The monthly report for July 1960 from Mr Chen Kuo, Sanitary Engineer, reports the formation of an Evaluation Section in the Iran Malaria Eradication Project. The first report of the Section gives an outline of its plan of action. It points out that, although progress has on the whole been satisfactory, there have been some defects in the operations from the quantitative and qualitative points of view. The new Section is at present composed of four members of the antimalaria staff. It is likely to be enlarged as the programme proceeds. Transport and office equipment, including a calculating machine, will be needed.

The aims of the Evaluation Section are described as follows:

1. To find out in the field the various problems or deficiencies that exist with spraying and surveillance operations, laboratory performance, capability of field personnel, etc., and to investigate the causes.
2. To arrange the problems in the order of importance.
3. To find out solutions and to recommend measures for improving the situation and preventing recurrence of similar problems.
4. To follow up the subsequent progress.
5. Final evaluation of the accomplishment of the programme and of the work of the Section itself.

The work plan is divided into field investigations and office analyses. The former will involve visiting each Ostan Office to study its available records of spraying, surveillance and laboratory work, in order to gain a knowledge of (a) the quantity and quality of the records, and (b) the present malaria situation in that particular Ostan. Analysis of the records should provide the answers to questions such as the following:

Were all the villages actually sprayed as planned? If not, why not?

Were all the villages actually covered by surveillance as planned? If not, why not?

Did the surveillance agents carry out the planned number of visits? If not, why not?

Field investigations will be made of the quality of spraying and surveillance operations, the capability of the field personnel, and the reliability of field reports and records.

The office work will be directed towards three main objectives: first, the expression in terms of statistical measurements of the quantity of work performed; second, the expression, statistically if possible, of the quality of the work; third, an evaluation of the degree of importance of the various problems discovered.

The results of these investigations will be that the Section will obtain for itself a description of the malaria situation in each Ostan, as indicated in the available records. Where the expected progress has not been achieved, it will find out the reasons. If the local records are insufficient for a proper evaluation, recommendations will be made for an improvement of the recording system; if they are found to be unreliable, steps will be advised to rectify this. Corrective measures, to be taken in the field, will be worked out by the Section if it finds that spraying or surveillance operations are not entirely satisfactory; attention will also be paid to the quality of supervision procedures, so that proper techniques and complete coverage may be ensured in the future. Finally, the state of training of field personnel will be assessed. If men are found to have been inadequately trained, or to need refresher courses, recommendations for their training or re-training will be made to the authorities.

5. SOUTHERN ADVANCE OF DIELDRIN RESISTANT A. GAMBIAE IN AFRICA

The phenomenon of physiological resistance to dieldrin was first observed in A. gambiae in Western Sokoto, Northern Nigeria, in 1955. Following this initial observation, reports of similar resistance were made in 1956 from Kano, also in Northern Nigeria; in 1957 from Haute Volta, Ivory Coast and Liberia; and in 1959 from Cameroun, Dahomey, Togo and Ghana.

Until now it had appeared that this resistant strain was confined to the western part of the continent of Africa north of the Equator. Indeed, although dieldrin has been used for a considerable period in the Taveta Pare project and in Zanzibar, no evidence of dieldrin resistance of A. gambiae has been found in East Africa.

However, two new sites of resistance have recently (May 1961) been reported - at Pointe-Noire and at Brazzaville, both in the Republic of the Congo. In view of the proximity of Leopoldville to Brazzaville, there is a distinct possibility that the resistant gene exists over a wider area, covering both banks of the Congo river.

It is interesting to note that thus far neither in Libreville, the capital of Gabon, nor in Port Gentil some 350 miles north of Pointe-Noire, is there any evidence of a resistant strain, even though insecticides have been used in these two places for a long period.

There is now, however, a definite possibility of the introduction by air of dieldrin resistant A. gambiae to eastern and southern Africa, and this is causing concern to the national governments and to the World Health Organization. Appropriate steps are being taken to improve still further the measures of protection from the accidental introduction of mosquitos by aircraft.