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1. USE OF CHLORTHION AS A LARVICIDE IN THE "PROBLEM AREAS" IN GUATEMALA

The following note is a summary of three papers presented to the Eleventh Meeting of Directors of National Malaria Eradication Programmes of Central America, Mexico and Panama held at Guatemala in May 1961.

In Guatemala total coverage spraying in the malaria eradication programme was started in 1956 using dieldrin, but it became obvious in 1958 from epidemiological evidence that transmission was not being interrupted and, on investigation, it was found that both the principal vector, A. albimanus and also A. pseudopunctipennis, had become resistant to dieldrin. A change was made to DDT in October 1958, and there followed a considerable improvement over most of the country. However, in certain areas there was little change in the number of malaria cases and in August 1959 it was found that A. albimanus was showing resistance to DDT as well as to dieldrin; in addition there was a rapid inactivation of the DDT due, it was thought, to the acid mud with which the walls of the buildings were made.

In September 1959, staff was increased in these "problem areas" with double resistant A. albimanus and an all-out effort made to organize mass treatment of the population, the village of Sanarate being chosen for a pilot scheme. However, despite an intensive educational campaign and continuous supervision the results obtained were not satisfactory due to the attitude and habits of the population. There were objections to taking medicine when they felt well and to the number of tablets to be taken, and many of the inhabitants could not be traced despite repeated visits including calls in the evening.

Consideration was therefore given to trying antilarval measures. Initially a mixture of heavy oil and kerosene was used, but this was inefficient and investigations were made into the use of organophosphorus compounds.

It was considered that chlorthion (O,O-dimethyl O-(3-chloro-4-nitro phenyl) phosphorothioate) would be suitable as it has a low toxicity to vertebrates (LD₅₀ oral for rats 1500 mg/kg compared with 150-250 mg/kg with DDT). Although crustacea are very sensitive, fish and amphibians are little affected at the concentrations in use.

The basic level of susceptibility of A. albimanus larvae was tested using a one-hour exposure. 97 per cent. mortality was obtained with 0.5 p.p.m. technical chlorthion and 100 per cent. with 1.0 p.p.m.; the LD₅₀ was approximately 0.09 p.p.m.

The chlorthion was supplied as a 50 per cent. emulsion and 60 ml of the emulsion were diluted with 10 litres of water to give a 0.6 per cent. solution of the 50 per cent. emulsion. Larviciding was carried out using a Hudson X-pert WHO-02 compression sprayer with old eroded 8002 Teejet nozzles, which gave a nozzle output of 1 litre/minute at 25/35 p.s.i. The nozzle was held at 60-75 cm above the water surface giving a swath of about one metre. The operator was trained to walk at the speed of 200 metres in 10 minutes (1.2 km/hr). It was found that the chlorthion penetrated and acted on the larvae to a depth of 40-50 cm.

The following formula was employed to estimate the p.p.m. of chlorthion in water.

$$\text{p.p.m.} = \frac{63d}{166.67 VP + 1}$$

- (d = volume of emulsion concentrate in millilitres/10 litre pump charge)
- (V = pace of operator in km/hr)
- (P = depth of water in centimetres)

Spraying was carried out weekly as the breeding cycle of A. albimanus was found to average 12 days.

The results of this larviciding in two areas are as follows:

Month	MOCA			SANARATE		
	Number of applications of larvicide	Larval density larvae/dip	AAI*	Number of applications of larvicide	Larval density larvae/dip	AAI*
1960						
October	3	1.7	13.3	-	-	-
November	4	0.6	0.3	2	3.1	0.2
December	5	0.3	0.0	4	0.3	0.0
1961						
January	4	0.3	0.0	5	0.01	0.0
February	5	0.01	0.0	4	0.04	0.0
March	4	0.006	0.0	4	0.00	0.0
April	4	0.000	0.0	4	0.03	0.0

It was considered that antilarval measures as employed in Guatemala with chlorthion may have a place in malaria eradication operations where house spraying and other measures have been unsuccessful.

2. HUMAN RESISTANCE IN MALARIA ERADICATION PROGRAMMES

The following article by Dr N. I. D. Sharma, Assistant Director, Malaria Institute of India, and S. K. Jain, Publicity Officer, National Malaria Eradication Programme, has been extracted from "National Malaria Eradication News" (Volume 1, No. 5, November 1960), which is issued by the Director, National Malaria Eradication Programme, Delhi.

The workers in the field of malariology are quite conversant with the problem of resistance in the malaria parasites to the antimalarials and in mosquitos to the insecticides.

One factor, however, that appears to have received scant attention in the planning of eradication operations has been the problems of resistance in man to the malaria eradication programme. When viewed through wider perspective this resistance phenomenon (if one can so term it) can at a future date present the possibilities of a threat serious enough to affect the success of the entire programme. As things stand it is already becoming obvious that the root cause of many of the present-day shortcomings in the country-wide eradication programme could easily be traced to one or the other form of human resistance.

Expatriating a little more about this problem one can say that since the man vis-a-vis the malaria eradication programme has three roles to play, i.e. an administrator, a malaria worker and a common man or the public, it is in these three distinct groups of individuals that various forms of human resistance can be discerned.

Although, by and large, the administrators are "goody-goody" fellows who are fully conscious of the fact that the National Malaria Eradication Programme has to run according to a predetermined schedule and in conducting the operation attention has to be paid to even the minutest details, as is done in conducting a war;

yet occasionally one has to encounter individuals who need to be educated about the salient features of the work with the implied urgency and necessity of maintaining the schedule of operations. This normally results in either reducing appreciably or completely eliminating such resistance.

Similarly, amongst the technical personnel responsible for running the programme there are many who even though fully trained in their duties and competent in their work, after a lapse of time start showing symptoms of callousness with the result that their work, measured in quantitative and qualitative terms, is not of the desired standard. The reason obviously is complacency with consequent loss of interest, enthusiasm and drive. But since these people are well saddled in their jobs they just do not care. The supervisory staff should pay particular attention to this aspect of the problem. It is well to remember by all of us that there is neither any short cut, nor any compromise, in the standard of work for achieving the eradication of malaria.

Another, and perhaps a more important form of increasingly apparent resistance amongst the technical staff is the outcome of a feeling that they are "working themselves out of the job". This false sense of future insecurity does nobody any good except resulting in inefficiency. Logically considered no one should really have any anxiety on this score for the central and the state governments would naturally not like to forget about the claims of experienced public health workers for work in other public health programmes.

But this is not the end of our troubles, for there is yet another category of people amongst the malaria workers who, for one reason or the other, have landed in the malaria eradication organization though their interest lies elsewhere. Enough to say that they are like a "square peg in a round hole" and the only alternative to remove this resistance is for these people to walk out and make room for those who have a greater interest in this type of work and in all respects are qualified to deliver the goods.

And now we come to the most important link in this chain of human resistance to the programme - the common man. As time passes it is being increasingly felt that in the past this important link has remained neglected through absence of any health education activities. With malaria already being in the disappearing

phase, in a major proportion of the country, and the collateral benefits like freedom from mosquito nuisance, houseflies and bed-bug on the decline, these things having become partially or completely resistant to the insecticides, the common man sees today little in the programme to be enthusiastic about to offer co-operation. Sometimes in dealing with the public one comes across a religious group which is opposed to killing any living thing, and, therefore, they refuse to get their houses sprayed. In approaching them points like heavy morbidity and mortality in India due to malaria, before the programme was launched, and the fact that by residual spraying of houses with insecticides interception of transmission of the disease is mainly due to reduction in the longevity of the mosquito vector, can be used convincingly. Their co-operation can be won over easily when approached tactfully.

To overcome any type of human resistance, therefore, it is the duty of all malaria eradication workers to propagate to the lay public the main objectives of the programme, the strategy of achieving the goal, and emphatically underline the fact that the present final stage of the programme is the most difficult phase of this campaign and one which cannot succeed without their fullest co-operation. The Malaria Officers and Inspectors should also pay particular attention to the training of field and surveillance workers since these people are our most important contact with the public. However, let it be clearly understood to the field staff that they should not make any claims or promises that are exaggerated and that cannot be substantiated or fulfilled technically. We are already paying rich dividends on this account from the past.

From the foregoing it is clear that various forms of human resistance that exist are capable of adversely affecting our programme. It is reality that has to be faced and for this the remedy lies in not only recognizing immediately the malaise but in initiating suitable action.

3. PRACTICAL PROBLEMS OF MASS DRUG ADMINISTRATION

At the Technical Meeting on Chemotherapy held in Geneva in November 1960, the practical problems of mass drug administration were discussed¹.

¹ Chemotherapy of Malaria, Report of a Technical Meeting, WHO (1961)
Wld Hlth Org. techn. Rep. Ser. 226

In general, it was considered that the difficulties of administering drugs to large communities, regularly and in a sufficiently thorough manner to interfere with transmission, were considerable but perhaps not insurmountable if the programme is limited to a short duration of time. There are two types of drug administration: direct to the recipient by means of tablet or liquid preparations, or indirect by incorporating the drug in common salt. While the latter method is more easy to apply, the degree of its effectiveness on a large scale has yet to be demonstrated.

In areas with deficient public health services the difficulties that arise in connexion with direct mass drug administration may be enumerated as follows:

- (a) to ensure total coverage, mass drug administration must be based on an accurate census;
- (b) to ensure regular drug consumption and to overcome the apathy, or active antagonism, of the population;
- (c) the habits of the people, and their various beliefs;
- (d) the administration of treatment at short intervals;
- (e) the attainment of complete coverage of the population.

At the beginning of any mass drug administration campaign, the ground-work of public health education must be carefully laid, taking into account the interests, beliefs and the susceptibilities of the population. The public must be informed about the objects and the health benefits of the campaign, and what is required of them.

The work must be supported by the leading local people (village chiefs, religious chiefs, other people of influence) who will explain in a simple and usually vivid way the purpose of this drug administration, what are the benefits to be expected from it, and what must be done in order to obtain good results. The people should then be receptive to census-takers. Care must be taken in obtaining permanent names and in relating the people to heads of families and village housing blocks.

The first few doses of a new medicine are always accepted eagerly; but very soon, loss of interest will be reflected by increasing refusals to receive treatment. Therefore, while drug administration is in progress, attempts should be made to maintain the people's interest.

However, it is obvious that high attendance figures cannot be kept up through health education alone. After the initial enthusiasm has vanished, distribution of small presents to regular "drug-takers" may prove more successful.

Nevertheless, whatever the efforts made and the measures taken there is always a certain number of active or passive defaulters who resent taking drugs when they are not sick. In order to achieve the essential complete coverage, these defaulters must be located and persuaded to accept treatment. Legal measures and sanctions are most likely to change indifference, and even co-operation, into open opposition.

Defaulting is more likely with frequent drug administration than with widely-spaced treatments. Should a drug become available which after a single dose would give protection for six months or longer, many difficulties would be overcome.

Experience has shown that drug distribution teams going from house to house should be composed of full-time personnel without other responsibilities. The prestige and personality of the drug distributor contribute greatly to the success of the campaign.

It is important to adjust the time of drug distribution to the customs and beliefs of the people; for instance, during the sowing and harvesting seasons, treatment of the working population is possible only if night visits are made by the team.

Accuracy in administering the drug is essential. It should not be entrusted to community leaders or family heads, but given directly by the drug distributor who records each treatment on individual cards, or on a book register, and notes defaulters. Differential colouring of tablets or the packing of doses in over-printed cellophane strips have been suggested.

In order to simplify administration of drugs in mass campaigns, a standardization of dosage in terms of number of tablets is desirable. A two or three-step regimen (such as that advocated by the Technical Meeting on Malaria Eradication in Africa¹) may be convenient, for example:

<u>Age-group</u>	<u>Dosage</u>
3 months - 3 years	1 tablet
4 - 9 years	2 tablets
10 years and over	3 tablets

Such a regimen is readily understood by the drug distributor, and the actual content of the tablets may be decided depending on local needs.

In all mass drug administration programmes aiming at the interruption of transmission and final elimination of the disease, isolation of the protected area from outside sources of infection is essential. In practice, however, complete social and entomological isolation of the area where mass drug administration is carried out is seldom attainable, and unless the programme is extended far into the areas from which infections are imported, transmission will not be interrupted. In view of the practical difficulties which confront the efficient organization of mass drug administration on a large scale, it is doubtful if in any large hyperendemic area malaria can be eradicated by the sole use of drugs.

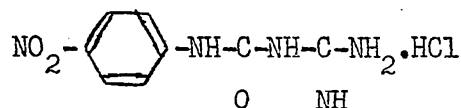
In areas where residual insecticides are not applicable or ineffective and drugs remain the only means of attack, mass drug administration in the form of medicated salt is a more practical and more efficacious method, provided that it can be applied to the best advantage.

4. ANTIMALARIAL PROPERTIES OF SOME DERIVATIVES OF PHENYL-AMIDINE-UREA

According to information received from the Polish Ministry of Health, a relatively new group of compounds - substituted amidine ureas - has recently been prepared in that country and has been investigated for antimalarial activity.

¹ Report of the Technical Meeting on Malaria Eradication in Africa (Brazzaville, November 1959), AFRO/Mal/4.

Screening tests using P. gallinaceum infections in chickens showed moderate antiplasmodial activity for one compound of the above group designated by the code number T.72 and for which the name "Nitroguanil" has been suggested. It is the hydrochloride of N₁-amidine-N₂-(p-nitrophenyl) urea and has the following structural formula:



Compounds in which the nitro group in the para-position of the benzene ring was replaced by other substituents (Br, SO₂NH₂) were inactive, or showed only very slight activity (NH₂·HCl).

In comparative tests with proguanil, T.72 was found to be only about one-quarter as active as proguanil against P. gallinaceum infections in chickens, whereas its toxicity in mice and rats was about 26 times less than that of proguanil.

Encouraged by the low toxicity of the compound and a certain structural similarity with proguanil, steps were taken to test T.72 also against human malaria infections.

Trials were carried out in Tanganyika by Dr D. F. Clyde who first took the drug himself to be certain of its lack of toxicity. About 350 children aged 7-10 years and infected mostly with P. falciparum (97.5 per cent.) but showing also P. malariae (14.6 per cent.) and P. vivax and P. ovale (4.0 per cent.) were treated with increasing doses of T.72.

Clyde found that in these semi-immune children the smallest dose of T.72 sufficient to clear asexual parasitaemia within a period of 7 days was 1333 mg. This is more than 3 times the dose of proguanil and more than 10 times the dose of chloroquine base required to achieve the same effect.

Comparative results obtained with T.72, proguanil and chloroquine are shown in the following table:

	T.72	Proguanil	Chloroquine base
Minimum effective dose to clear asexual parasitaemia within 7 days	1 333 mg	400 mg	120 mg
Mean clearance time	76 hours	64 hours	38 hours
Duration of protection (time from successful treatment to reappearance of trophozoites)	10 days	9 days	18 days

T.72 was given in two forms: gelatine capsules each containing 133 mg of T.72, and an orange-flavoured liquid. No signs of toxicity and no untoward symptoms were observed and the very wide margin of safety of T.72 was thus confirmed. But the large doses of T.72 required proved difficult to administer in the field. To provide the minimum effective dose, 10 capsules or a large quantity of the liquid was required, and this tended to alarm the subjects. Dr Clyde concludes that these inconveniently large amounts offset the lower toxicity of T.72, that accordingly this compound has no advantage over proguanil, but has some disadvantages principally in the quantity needed.

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(The Editor of WHO/Mal/Supplement feels that news on the development of new anti-malarials deserves some prominence at the present time. Nevertheless it is doubtful if compounds which, in experimental studies in animal malaria, show relatively little promise should be elevated to the rank of drugs that justify field trials on man.)

5. CO-ORDINATION OF THE WORK OF THE NMES AND THE WHO ADVISERS

In order to ensure that the fullest co-operation is obtained between the personnel of the National Malaria Eradication Service and WHO Advisers, it has been found desirable in some country programmes to make the following arrangements with the Chief of the NMES:

- (a) Each WHO team member should have an appointed counterpart of the NMES and he should be accompanied by this counterpart on all official visits to the project.
- (b) The Chief Officer of the NMES should send to the WHO/MEP team leader and the UNICEF country representative copies of all circulars and orders which are designed to implement the provisions of the plan of operations and of its addenda as they are issued.
- (c) The Chief Officer of the NMES should also send to the WHO/MEP team leader and the UNICEF country representative a summary of all circulars and orders relative to the working of the NMES, including any which may be at variance with the plan of operations or the addenda thereto.
- (d) Before issuing any circular or order containing provisions that are at variance with those contained in the plan of operations, the Chief of the NMES should discuss them with the WHO/MEP team leader and secure his agreement.
- (e) If a WHO team member considers that national field personnel should be advised on any matter which might be thought to differ from the procedures laid down in the plan of operations and its addenda, or from the orders of the Chief of the NMES which have previously been agreed to, he must first discuss these matters with the Chief of the NMES and secure his agreement.
- (f) All WHO team members must be permitted complete freedom to express to members of the NMES of all levels such constructive criticisms or suggestions which they deem necessary provided they comply with the provisions of the plan of operations and its addenda and the orders of the Chief of the NMES. A report on the advice and criticisms offered must be sent to the Chief of the NMES.
- (g) The Chief of the NMES should discuss budget proposals for the service with the WHO team leader before submitting them for approval at higher level.