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The Chief of the Malaria Section
has the honour to communicate hereunder
the following note

PLACE OF CHEMOTHERAPY IN
MODERN MALARIA CONTROL PROGRAMMES

by

Dr I. H. Vincke ✓
"Médecin Hygiéniste Inspecteur"
"Institut pour la Recherche Scientifique en
Afrique Centrale", Bukabu, Belgian Congo

In the Report of its third session, the Expert Committee on Malaria expressed the following view:

"A considerable amount of new evidence has recently accumulated about many of the new drugs, but the Committee feels that none of these agents satisfies the ideal conditions, namely: that it be a causal prophylactic against all species of human malaria parasites; that it be a good therapeutic agent and, at the same time, be truly curative; that it possess low toxicity, and that it be readily available at moderate cost. In these circumstances, it is essential to point out that all the available antimalarial drugs have various limitations which must be kept in mind when considering the suitability of a chemotherapeutic agent."

In the Committee's fifth Report it is stated:

"... 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..."

MINISTRY OF HEALTH
Lagos

Nevertheless, the results of important research on chemotherapy and of numerous experiments in the field and in the clinics have made it possible to assign an increasingly important place to chemotherapy in programmes for the control of malaria.

1. Antimalarials in current use

Quinine. The inferiority of quinine in comparison with the synthetic drugs was established many years ago, but it can still be useful - particularly in the countries where it is produced. Moreover, at least in the Belgian Congo, it seems to be popular with the indigenous population on account of its stimulating properties. Its use should be controlled, however, in view of the possibility of accidents and of haemoglobinuria.

Mepacrine has been used with success and, it would seem, without any serious inconvenience in prophylactic doses; in therapeutic doses it has provoked accidents (psychoses, yellowing of the skin, dermatitis). It should only be used under close supervision.

Chloroquine appears to be more effective and has the advantage of being more easily handled.

Amodiaquine seems, on the basis of recent experiments, to be more potent than chloroquine and less toxic, dose for dose.

Plaquenil is related to chloroquine and appears to have a similar action.

Proguanil has the reputation of being a very effective prophylactic and it also has the advantage of inhibiting sporogonic development of P. falciparum. It acts as a real causal prophylactic against P. falciparum (Lagos strain).

Pyrimethamine, dose for dose, is the most potent suppressive agent known; it has the same power in preventing the completion of sporogony in the anopheles. Nevertheless, on account of its very slow action its use should be limited to prophylaxis. It appears also to be a true causal prophylactic against P. falciparum infections. Whereas paludrine, chloroquine and camoquine are only active schizonticides with respect to the Chesson strain of P. vivax, pyrimethamine will frequently prevent relapses.

Primaquine. The drugs belonging to the 8-aminoquinoline group are active against the exoerythrocytic forms and prevent P. vivax relapses. Primaquine has been found to be the most effective and least toxic of the group.

1.1 Doses recommended by the Expert Committee on Malaria (fifth session)

These were as follows:

Prophylaxis (causal and clinical)

- (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.

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 children up to five years of age, and in half the adult dose for children between six and twelve years.

1.2 Development of resistance to antimalarials

Only proguanil and pyrimethamine have been found to provoke the appearance of resistant Plasmodium strains.

This resistance is easily induced experimentally in a number of Plasmodium species affecting animals by the administration of definitely insufficient doses.

In the field, cases of resistance to proguanil have been notified in various parts of the world - particularly, it would seem, after inadequate dosage. This resistance is said to be stable. Strains resistant to pyrimethamine have appeared in East Africa but only after administration of spaced-out doses and in regions where proguanil seems to have been used on a large scale in the past. The existence of cross-resistance to these two drugs has been experimentally demonstrated.

It has been said also that resistance to pyrimethamine is 'labile' - disappearing as quickly as it appears, and that treatment must be constant if a high degree of tolerance is to be maintained.

Furthermore, a strain which has become resistant will multiply at the expense of the others for as long as the treatment lasts, and only within the geographical limits where it is applied; when treatment ceases, the sensitive strains will become uppermost again. At Katanga, in a region with about 20,000 inhabitants, treated once a year with DDT, a first campaign of chemoprophylaxis (15 to 20 weeks; 25 mg once a week) was organized in 1953, and a second in 1954. The results in both years were identical: maintenance of parasite rates at a negligible level for eight months.

The possible resistance to proguanil and pyrimethamine is a danger against which hygienists should be constantly on their guard.

2. Experiments carried out in malarious regions

It may be useful to summarize the results of the numerous experiments made in the field, although there must be certain reservations with regard to interpretation.

The results, in fact, may be different according to the strains, the degree of immunity of the population, the number of infective bites and, as far as P. vivax is concerned, the duration of incubation - all factors which it is sometimes difficult to estimate.

In addition, it is not easy to assess the radical cures in an endemic or hyper-endemic region, in view of the risks of reinfection.

Placed as they are midway between clinical experiments in the prisons and psychiatric homes, and the implementation of large-scale malaria control programmes, these experiments in the field are essential because only through them is it possible to evaluate the practical difficulties to be overcome later.

It is, therefore, not superfluous to review them.

These experiments have been conducted in various ways.

2.1 Single dose or short-interval doses

In most cases this method has been applied to patients with febrile attacks. In a short time the asexual forms disappear from the circulation in nearly all cases, but the gametocytes persist in the presence of amodiaquine, chloroquine, hydroxychloroquine, paludrine, and pyrimethamine. The drug exerts its effect for a certain time but some relapses have been observed, particularly for P. vivax.

Administration of the single dose can nevertheless be a very valuable method for, with the decrease of the number of asexual forms, the gametocytes must also be reduced, and in this way the population is immediately relieved (this can be most easily effected during DDT operations).

The most rapid results are obtained with camoquine and chloroquine.

Radical cures have been obtained with camoquine against P. falciparum infections (adult dose 0.8 g) with subjects not exposed to reinfection (Bolivia).

2.2 Weekly doses for subjects having acquired variable degrees of immunity

The conditions of the experiment were as follows:

- (a) subjects under strict control and followed up individually;
- (b) disciplined groups such as persons in workers' camps, schools, etc.;
- (c) inhabitants of villages or groups of villages with limited population in a malarious region, combined or not with residual insecticide treatment;
- (d) wider regions with 20,000 to 25,000 inhabitants, combined with application of insecticides;
- (e) regions free of malaria vectors in which malaria-infected populations have settled.

The observations covered several weeks, several months or several years.

In general, results are very favourable for chloroquine, amodiaquine and pyrimethamine, less so for mepacrine and paludrine.

During the treatment period, the parasites disappeared from the blood in the immense majority of cases, and the spleen rates showed a very marked drop.

Complete negativity cannot be expected in a population which has not been followed up case by case. For example, when the parasite rate is about 1-5 per cent., this may be explained by the arrival of persons coming from a neighbouring region. This may be compared with what happens at high altitudes where there are no malaria vectors (2,000 metres) and where the plasmodium index is about the same.

As a general rule, the parasite rate rises again one or two months after discontinuance of treatment. Some believe that here it is a case of relapses, in view of the simultaneous small anopheline population. This phenomenon has been observed in particular in connexion with pyrimethamine.

However, these "relapses" were observed only in relatively small populations (a few hundreds) in malarious country. In two cases the surrounding villages had been treated with DDT but certainly not with 100 per cent. success; in a third case the treatment had ceased during the season which is least favourable to the anopheles.

Might this sudden rise in the blood index not be caused by even a small number of infected anopheles, in the light of the under-mentioned experiments?

- (1) A malaria-infected population which settled in a non-infected region was treated with 15-20 weekly doses of pyrimethamine (25 mg dose) and no such relapses were observed (Belgian Congo).
- (2) The same observation was made in a region with about 150,000 inhabitants protected (imperfectly) with DDT and where 20,000 of them also received the same treatment (Belgian Congo).
- (3) In New Guinea, radical cures were obtained against P. vivax infections in a large proportion of cases which were given similar treatment.

3. Present status of chemotherapy in malaria control

According to the answers to questionnaires addressed to the various countries of South-East Asia and Africa south of the Sahara, it may be said that anti-imago

campaigns are the foundation of all malaria control. Nevertheless, chemotherapy is also an important factor. This latter may be applied in a number of forms and the answers (sometimes rather short) received may be summarized as follows

(44 replies):

- (1) treatment of patients in hospitals and dispensaries . . . all countries do this;
- (2) wide and more or less organized distribution of drugs . . . 10 countries;
- (3) organized distributions in case of epidemics and during peak transmission periods 3 countries;
- (4) prophylaxis in clearly-defined groups such as those found in schools, infant dispensaries, the armed forces, plantations, administrative services 10 countries;
- (5) prophylaxis during spraying operations 2 countries.

The drugs employed are: quinine, mepacrine, proguanil, pyrimethamine, camoquine.

4. Recent proposals on the same subject

We cannot do better here than quote the views expressed by the Working Party at the fifth session of the Expert Committee on Malaria and the report of the Malaria Conference for the Western Pacific and South-East Asia Regions (Baguio, Philippines).

4.1 Expert Committee on Malaria (Istanbul)

"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 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."

4.2 Baguio Conference (Role of Drugs)

"In the Suppression and Cure of Malaria Infections"

"The role of drugs in the suppression and cure of malaria infections was well attested by the experience of the second world war. For the protection of armies in the field, for labour groups, survey parties, and similar groups moving through malarious territory, drugs give a high degree of protection; indeed no other method of comparable efficiency is known. But the role of drugs in the control of endemic rural malaria is less impressive. They are useful under particular conditions but they must take a second place to residual spraying. The Conference was informed of the imminent publication by WHO of a monograph on the Chemo-Therapeutics of Malaria, and the discussion was therefore restricted to the supplementary use of drugs in spraying programmes and in certain special situations.

"In Relation to Spraying Programmes"

"Residual spraying with insecticides cannot, of course, influence the reservoir of infection already present when spraying operations begin. Transmission will

usually be arrested but existing infections must either be left to die out, or else terminated by drugs. Left alone, falciparum infection will sometimes last for a year, vivax infections for about three years, and malariae infections even longer - a sustained source of periodic clinical activity. Broadly stated, the role of drugs in spraying programmes is the eradication of existing infections. The theoretical possibilities are good but practical difficulties impose limitations. Mass suppressive treatment is impractical and radical cure is difficult except in falciparum infections.

"If at the beginning of spraying programmes there is evidence of clinically active malaria, the Conference agreed that three courses are possible and practical:

"(a) To use drugs during spraying operations only for persons with fever at the time, a single dose of chloroquine or amodiaquine would be appropriate. Most falciparum infections would be terminated and all infections so treated would be clinically relieved.

"(b) To give single doses of chloroquine or amodiaquine to all persons at the time of spraying, a course for which the occurrence of many cases of fever would be a clear indication.

"(c) To give single-dose treatments repeated at short intervals for a few weeks. The most useful drugs are chloroquine, amodiaquine and pyrimethamine. Given in appropriate single doses once a fortnight for two months to children and pregnant women in regions of Viet-Nam seriously affected by malaria, Farinaud obtained a more rapid improvement in health conditions than was possible with spraying alone. Difficulties of organization place a limitation on this form of supplementary drug control but when the malaria is severe, as in the highlands of Viet-Nam, and the response to spraying alone is slow, the benefits are beyond doubt.

"Towards the end of spraying programmes, when transmission has been interrupted for a significant period, residual vivax and malariae infections are likely to pose a problem for which there is no simple answer, and in many areas with poor dispensary facilities there may be no alternative but to allow the infections to burn themselves out. The most useful drug is primaquine given daily for 14 days at a dosage of 15 mg.

Whether, with the particular vivax strains of the two regions, a shortened period of treatment may still be effective, is not yet known. After the interruption of the spraying programme, cases of malaria should be promptly dealt with. From available evidence the Conference suggested that a single dose of 600 mg chloroquine base with 15 mg of primaquine base, given together, would eliminate the immediate dangers to the community.

"In Special Situations

"Epidemics

"The Conference emphasizes that epidemics occurring in areas as yet unsprayed demand quick action and that drugs can best meet the immediate situation. The most useful drugs are chloroquine, amodiaquine, mepacrine, and pyrimethamine. Various patterns of administration have been recommended; one of the most effective is perhaps that which depends on an immediate single dose of 600 mg chloroquine or amodiaquine base, with a weekly follow-up of chloroquine, amodiaquine, mepacrine, or pyrimethamine at appropriate dosages and continued as appears necessary. The administration of drugs should not of course replace or delay an immediate attack on the adult vector mosquito. Spraying with insecticides should begin at once.

"New settlements

"A special situation arises when land is being opened up for settlement. Rational planning will normally provide houses which have been sprayed beforehand with residual insecticides. But if this has not been possible then drug suppression during the period of main risk is probably the best answer to the problem.

"Migration

"A malaria problem for which spraying is not a complete solution arises when populations are settled for only a part of the year - farmers, fisherfolk and the like who sometimes leave their homes for months at a time for distant farms and fishing grounds. In parts of Viet-Nam, for example, disappointing results from residual spraying have been attributed to this seasonal migration. This again is a situation which can be countered by drugs wherever it is possible to organize

their distribution. A single dose of 600 mg chloroquine or amodiaquine base given as a supplement to spraying at the first opportunity after they return home would go far to speed the clinical response to control.

"Stocks of quinine or mepacrine

"The attention of the Conference was drawn to the special situation of countries which hold large stocks of quinine or mepacrine and are hence reluctant to buy the newer drugs. The use of quinine imposes an extra burden of administrative difficulties on a national malaria control organization, but efficiently used in times of need the drug will usefully supplement residual spraying programmes. Though less effective than chloroquine or amodiaquine, mepacrine may replace these drugs at the same dosage when the newer drugs are not readily available."

5. Remarks and conclusions

The ideal antimalarial drug has not yet been discovered. Nevertheless, enormous progress has been made during recent years, especially from the point of view of prophylaxis. Publications of results obtained in the field are becoming more and more numerous and encouraging.

The general opinion at the present time is that chemotherapy can play an important role in malaria control but that its role is limited to particular eventualities such as epidemics, the protection of special groups, or the need to provide some immediate relief for populations which must necessarily wait for the results of control operations.

Considered from this angle, chemotherapy is not, strictly speaking, an important element in a malaria eradication programme.

The argument most often invoked is that the absorption of the drug cannot be sufficiently supervised among large groups of populations.

It is perhaps not so much a question of toxicity: as far as most of the medicaments dealt with here are concerned, few disadvantages have been reported from this point of view; the main apprehension seems to be caused by the possibility

that the least expensive and least toxic prophylactic substances (proguanil and pyrimethamine) may bring about the development of resistant strains if absorption is not strictly controlled.

This fear would seem to be justified with regard to proguanil, since the administration of this drug was not carefully supervised from the very beginning.

Pyrimethamine may still have a role to play: it might contribute to an eradication programme provided the programme is on a sufficiently large scale and provided the product is not used for acute cases (hospitals and dispensaries).

In an experiment which, it is true, was limited to 20,000 inhabitants, the results of an annual administration of 15-20 tablets for as many weeks, and of an annual spraying operation, were definitely better than those obtained from two campaigns for the control of the imago (Katanga).

It is above all a question of price! Here are the wholesale prices for the Belgian Congo:

	<u>centigrammes</u>	<u>Belgian francs</u>
Quinine	50	0.474
	25	0.255
Mepacrine	10	0.77
Amodiaquine	20	0.65
Chloroquine	10	0.33
Pamaquin	1	0.127
Pyrimethamine	25	0.34

The price per capita of one application of DDT in 1952-1953 in Katanga was 11 Belgian francs in the urban and 15 Belgian francs in the rural area (30 USA cents). This is a fairly high price, but it could now, we believe, be reduced to 15-20 USA cents on account of the fall in the price of insecticides.

In any case, 15 tablets of pyrimethamine cost only 5.10 Belgian francs, i.e. about 10 USA cents.

If the co-operation of the population is obtained, the cost of organization of distribution is negligible, so that the total price per capita (DDT + drug) becomes something just over 35 USA cents.

In this case, we may ask if it would not be preferable to concentrate on drug prophylaxis? If this were done, the distributions would have to be continued indefinitely and the price would still be about 35 USA cents.

We are of the opinion that the populations would tire very quickly, being deprived of the accessory benefits from the insecticides, which are the most important in their eyes.

We believe, moreover, that the combined imogocide-chemoprophylactic method is the best and the cheapest.

This does not exclude the possibility of employing other drugs, using a similar system, but here also the cost of the campaign should be given consideration.¹

In any case, therefore, experiments with the combined methods should be repeated on large population groups. The bigger the programme, the quicker will eradication be achieved and the less will be the risks of resistance. The efforts must not be indefinitely concentrated on innumerable small, scattered centres: this would be the surest way of compromising the future.

¹ The taenifuge properties of some compounds of the 4-aminoquinoline group should be borne in mind, as for some regions this might be of primary importance.

Antimalarial drugs and their synonyms

AMODIAQUINE

Cam-aqi
Camoquin
Flavoquine
Miaquin
SN 10751

CHLOROQUINE

Aralen
Nivaquine B
Resochin
Tanakan
SN 7618
3377 RP

MEPACRINE

Acriquine
Arichin
Atabrine
Atebrin
Chemiochin
Chinacrin
Crinodora
Erion
Haffkinine
Italchina

Malaricida
Methoquine
Metoquina
Metoquine
Palusan
Quinacrine

PAMAQUIN

Aminoquin
Beprochin
Fourneau-710
Gamefar
Pamaquine
Plasmochin
Plasmocide
Plasmoquine
Praequine
Quipenyl
Rhodoquine

PRIMAQUINE

SN 13272

PLAQUENIL

Hydroxychloroquine

FROGUANIL

Balusil
Bigumal
Chlorguanide
Chloriguane
Diguanyl
Drinupal
Guanatol
Paludrine
Palusil
Tirian
M4888
SN 12837
3359 RP

PYRIMETHAMINE

Daraprim
Malocide
B-W 50-63

SONTOQUINE

Nivaquine A
Nivaquine C
Santochin
Santoquine
Sontochin
SN 6911
3038 RP