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The Secretary of the Expert Committee  
on Malaria has the honour to communicate hereunder  
a report on

THE THERAPEUTICS OF MALARIA IN AFRICA

(Section 4 of the Agenda)

by

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The drugs in common use for the treatment of malaria may be classified as follows:

<u>Class</u>	<u>Examples</u>
I. Cinchona alkaloids	Quinine
II. 9-amino-acridines	Mepacrine (atabrine, quinacrine)
III. 4-amino-quinolines	Chloroquine (nivaquine B, aralen), camoquin
IV. 8-amino-quinolines	Pamaquin (plasmochin, praequine), pentaquine, isopentaquine
V. Biquanides	Proguanil (chlorguanide, paludrine)

#### 4.1 MODERN METHODS OF TREATMENT OF MALARIA IN AFRICA

##### (A) Treatment of the clinical attack in non-immunes

Of the 4 human malaria parasites, Plasmodium falciparum, P.vivax, P.malariae and P.ovale, the first two are by far the most common. The treatment of falciparum infections differs in some respects from that used against vivax. Generally speaking, regimes prescribed for the latter are also suitable for infections with P.malariae and for P.ovale.

##### (1) Treatment of falciparum infections

Quinine is now seldom used in the routine treatment of falciparum malaria, although it will control the clinical symptoms in most cases and will effect a high proportion of radical cure. It is, however, inferior in action to some of the synthetic antimalarials considered below. It also produces certain unpleasant side effects and has been known to act as a precipitating factor in blackwater fever. It is nevertheless still used parenterally in the emergent treatment of cerebral and "pernicious" cases of malaria (see below).

Mepacrine is generally superior to quinine in rapidity of action, provided that the initial loading dose is sufficiently high, and it effects a high proportion of radical cure. It has the disadvantage of producing in some subjects certain unpleasant side effects, and in rare cases alarming though temporary psychotic symptoms. It also tints the skin yellow in a proportion of cases. The dosage usually employed for adults is 0.6 to 0.9 g on the first day or first 2 days of treatment, followed by 0.3 g daily for the next 3 to 5 days.

Chloroquine has not as yet been used very extensively in Africa, but such reports as are available indicate that it is probably superior to mepacrine for the treatment of the clinical attack in falciparum infections as regards rapidity of action. It also effects a high proportion of radical cure. Moreover, it has not the disadvantage of tinting the skin, and is said to be comparatively free from other undesirable side effects. The dosage recommended for adults is 0.6 g initially followed by an additional 0.3 g 6 to 8 hours later, and a single dose of 0.3 g on each of the two following days.

Camoquin has an action similar to that of chloroquine, and the few reports available suggest that it is of approximately equal value. It has been employed in

doses up to 0.4 g thrice daily for 5 days for adults.

Proguanil, by itself, is not sufficiently rapid in action to warrant its use for the treatment of falciparum infections. It also fails to effect radical cure in a high proportion of cases. If reinforced with mepacrine (0.6 to 0.9 g) or chloroquine (0.6 g) on the first day of treatment, both these disadvantages are overcome, and since its toxicity is lower than that of any other antimalarial drug known, and since it also renders gametocytes non-infective to mosquitoes, this combined treatment is considered by some to be the best available for falciparum infections in non-immune subjects. The dosage of proguanil generally employed in Africa is 0.3 g twice daily for 10 days.

For emergent cases of falciparum malaria, where the patient is unable to take drugs by the mouth, quinine dihydrobromide or dihydrochloride, 10 grains (0.65 g) in 20 ml of normal saline may be injected very slowly intravenously, repeated 6 to 8 hours later if necessary. Mepacrine sulphonate (atabrine musonate) may also be given intravenously, but the margin of safety with this drug is low, and the intramuscular route is to be preferred, 0.2 g being injected into each buttock (total dosage 0.4 g).

(ii) Treatment of vivax infections

If it is intended that the patient shall be placed on a suppressive regime for an indefinite period after the termination of the clinical attack, this may be treated with proguanil 0.3 g twice daily for 10 days, or with the same dosage of chloroquine or camoquin as prescribed for falciparum infections. If the patient is not to undergo suppressive treatment, the best chance of attaining radical cure is a course of quinine 20 to 30 grains daily for 14 days, combined with pamaquin, pentaquine or isopentaquine for the same period. The most effective and least toxic of these is isopentaquine, the dosage recommended for adults being 0.03 g daily. During this treatment the patient should remain in bed under close supervision.

(B) Treatment of the clinical attack in subjects partially immune

In most localities a standard treatment is administered to indigenous populations for all forms of malaria. The drugs most commonly used are proguanil and chloroquine, the choice being very largely governed by financial considerations. The dosage employed depends very largely on local experience. Excellent results have been

reported in some areas by the administration of a single dose treatment with either drug of 0.3 g. In other areas in which either the level of communal immunity is lower or the local strains of malaria parasite more resistant, it has been found necessary to extend the treatment over 3 or more days. Chronic relapsing cases of vivax malaria may be treated with combined quinine-pamaquin or quinine-isopentaquine courses similar to those prescribed in the case of non-immunes.

#### 4.2 MODERN METHODS OF SUPPRESSIVE TREATMENT IN AFRICAN CONDITIONS

##### (A) For non-immune subjects

Quinine is definitely inferior to proguanil, mepacrine, chloroquine or camoquin for the prophylaxis of malaria under African conditions, and is now seldom used for that purpose.

Mepacrine, 0.1 g daily, is an effective suppressant, provided that it is taken for 14 days before exposure to infection, but it has the disadvantage of turning the skin yellow, and in some subjects produces certain undesirable side effects, the commonest of which is a lichenoid dermatitis. The drugs of choice for prophylaxis are proguanil, 0.1 g daily or chloroquine 0.3 g once weekly. Reports have been received from certain areas in Africa that overt attacks of falciparum malaria have occurred in persons said to be taking proguanil regularly. This may be due to the existence of naturally resistant strains of the parasite, or even to the eventual development of acquired resistance. Break-throughs have also been reported in persons under chloroquine or mepacrine prophylaxis, but whatever drug is used, it is always difficult to be certain that it is in fact being taken with meticulous regularity.

##### (B) For subjects partially immune

The drugs most commonly used are proguanil and chloroquine, each administered in a single dose of 0.3 g weekly. Results reported with both these drugs among labour forces and other indigenous communities have been generally favourable. The deciding factor governing the choice of drug is in most cases the price at which it is made available for general use.

#### 4.3 SUGGESTED EXPERIMENTS WITH MODERN ANTIMALARIAL DRUGS

There are two types of experiment which might shed light on the relative efficacy of the various drugs available:

- (1) Experiments on non-immune subjects under conditions where local reinfection or superinfection is impossible;
- (2) Experiments on indigenous inhabitants of malarious areas.

There are few, if any, areas in Africa where local conditions allow experiments of the first type to be undertaken with any prospect of success. Generally speaking, they can only be carried out in non-malarious countries, the subjects being either inmates of mental hospitals, prisons or similar institutions, or volunteers derived from military personnel. It is exceedingly difficult to obtain volunteers from the last-named source under peacetime conditions.

An example of the second type of experiment is that recently carried out in West Africa by Dr. L.J. Bruce-Chwatt, among 4 "standardized" groups of school-children, all of whom at the commencement of the experiment had parasites in demonstrable numbers in the peripheral blood. Three of the groups received treatment with one or other of the drugs under study, the fourth being left untreated for comparison. All the subjects were observed over a period of two or more months, examinations being made in respect of the spleen rate, average enlarged spleen, temperature, parasite rate, parasite density, duration of parasitaemia, infectivity of gametocytes and relapse rate. It seems likely that results of considerable value might be achieved by further experiments in other parts of Africa conducted on similar lines.