The African Journal of MEDICAL SCIENCES

Volume 3

1972

BLACKWELL SCIENTIFIC PUBLICATIONS
Oxford London Edinburgh Melbourne

Afr. J. med. Sci. (1972) **3**, 77–91.

REVIEW ARTICLE

The Present Status of Chloroquine in the Drug Treatment of Malaria

I. A. OLATUNDE

Department of Pharmacology, University of Ibadan, Ibadan, Nigeria.

(*Received* 23 *March* 1971)

Summary. Chloroquine is the drug of first choice in the suppression of an acute attack of malaria, being more effective and less toxic than any of its predecessors. For prophylaxis, pyrimethamine, proguanil or cycloguanil is appropriate where strains of malaria parasites are sensitive to these; any of them may be combined with sulphadiazine or dapsone for better prophylaxis. Primaquine remains the only drug clinically useful in eliminating the tissue stages of relapsing malaria.

The development of toxic eye lesions, particularly on the retina was unveiled when high doses of chloroquine for prolonged periods were used for non-malaria conditions like rheumatoid arthritis and discoid lupus erythematosus. From south-east Asia and South America had come many reports of the development of chloroquine-resistance by strains of *Plasmodium falciparum*. Resistance to chloroquine has not been a feature of falciparum malaria in West Africa yet. In places where chloroquine-resistance had been established, various combinations of chloroquine with quinine, pyrimethamine, sulphormethoxine or dapsone were found effective.

Malaria prophylaxis with chloroquine is not advisable in view of the possibility of ocular toxicity on prolonged use and the danger of inducing chloroquine-resistance in malaria parasites. West Africa should be on their guard against chloroquine-resistant *P. falciparum*.

Résumé. La chloroquine est le médicament de premier choix dans le traitement du paludisme aigu, car elle est plus efficace et moins toxique que ses prédécesseurs. Pour la prophylaxie, la pyriméthamine, le proguanil ou le cycloguanil sont indiqués là où les parasites leur sont sensibles: chacun peut être associé avec la sulfadiazine ou le dapsone pour obtenir une meilleure prophylaxie. La primaquine demeure le seul médicament cliniquement utile dans l'élimination des stades tissulaires du paludisme récurrent.

L'évolution de lésions toxiques de l'oeil, particulièrement sur la rétine, a été

Correspondence: Dr I. A. Olatunde, Department of Pharmacology, University of Ibadan, Ibadan, Nigeria.

décelée là où de hautes doses de cloroquine avaient été adminstrées pendant des périodes prolongées dans des états non-paludéens tels que l'arthrite rhumatoïde ou le lupus discoïde érythémateux. Du sud-Est asiatique et de l'Amérique du Sud étaient parvenus de nombreux rapports de résistance à la chloroquine chez certaines variétés de *Plasmodium falciparum*. Cette résistance n'est pas encore signalée en Afrique occidentale. Dans les localités où la résistance à la chloroquine a été établie, diverses combinaisons de la chloroquine avec la quinine, la pyriméthamine, la sulforméthoxine ou le dapsone se sont révélées efficaces.

La prophylaxie du paludisme par la chloroquine n'est pas indiquée, en raison de la possibilité de toxicité oculaire à l'usage prolongé et du danger de résistance à la chloroquine chez les parasites du paludisme.

L'Afrique occidentale doit se garder du *P. falciparum* résistant à la chloroquine.

INTRODUCTION

Malaria constitutes the highest single major cause of morbidity in Africa and in various parts of the tropics and sub-tropics the world over (Manson-Bahr, 1960; Adams & Maegraith, 1960). Over the centuries, malaria has affected the destiny of nations in war and in peace. In the present century, the major land-marks in the chemotherapy of malaria were made during the two World Wars (Gaddum, 1959; Wiselogle, 1946). Mepacrine was discovered in 1930 as a result of intensive research stimulated by inavailability of quinine to the Germans during World War I; chloroquine was introduced following the extensive programme of antimalaria research in the United States during World War II (Rollo, 1965; Wiselogle, 1946; Loeb *et al.*, 1946).

Chloroquine is at present the most potent antimalarial agent in clinical use. However, the development of ocular toxicity on long-term use at high doses, and the appearance of chloroquine resistance in certain strains of falciparum malaria parasite, appear to be adversely affecting the position of this potent schizontocidal drug.

This review outlines the historical development of chloroquine and the other antimalarials in clinical use, summarizes the use of the other antimalarial agents and discussed the present status of chloroquine and its combination with other agents in the treatment of chloroquine-resistant *Plasmodium falciparum* malaria.

THE STORY OF CHLOROQUINE

Chloroquine was first synthesized by Andersag in Germany in 1934 (Lane, 1951) as chloroquine phosphate under the name of 'Resochin', but this fact was not known to other countries till after the end of the second World War (Rollo, 1965). It was not thoroughly investigated for its antimalarial potentialities at the time of its first synthesis probably because mepacrine which was discovered only a few years earlier dominated the field. Meanwhile, Russian investigators were reported to have described the 4-aminoquinolines as potential antimalarials (Berliner *et al.*, 1948) and French workers reported sontoquin, 3-methyl-7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline (SN-6911), as having a high activity against human malaria parasites (Rollo, 1965). The extensive co-operative programme of antimalarial drugs research which operated in the United States of America during World War II took notice of the French workers report and synthesized a sub-

stantial number of 4-aminoquinoline compounds (Wiselogle, 1946), of which chloroquine was finally selected as the most effective and the least toxic of the series of 4-aminoquinoline derivatives investigated (Loeb, 1946; Wiselogle, 1946). It was this re-discovery of chloroquine under the survey number 7618 or SN-7618 that brought it into the fore-front in the war against malaria (Fig. 1.).

By 1948 the superiority of chloroquine to mepacrine had been well established (Pullman *et al.*, 1948; Berliner *et al.*, 1948). At about the same time the therapeutic value of chloroquine in another morbid tropical disease came into light, for Conan (1948) from New York made his preliminary report on the success of chloroquine in hepatic amoebiasis.

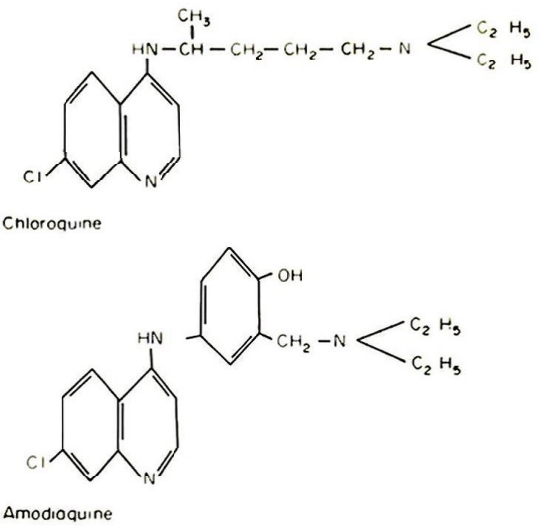

FIG. 1.

Soon after Page (1951) described the use of mepacrine in the treatment of chronic discoid lupus erythematosus, chloroquine was demonstrated to be equally effective and less toxic (Goldman, Cole & Preston, 1953). Since then chloroquine had been used to treat a variety of 'collagen diseases' and dermatoses (Ayres & Ayres, 1953; Morse *et al.*, 1961; Knox & Freedman, 1963). Chloroquine has been shown to have anti-inflammatory properties (Van Cauwenberge *et al.*, 1958) and this had lent support to its extensive use in the therapy of rheumatoid arthritis (Bagnall, 1957; Fuld & Horwich, 1958; Young, 1959).

Chloroquine has had two major set-backs; first, its long-term use in the treatment of discoid lupus erythematosus (DLE) and other chronic conditions at relatively high doses has unveiled retinopathy as a real danger. The second defect being the discovery of strains of Plasmodia resistant to chloroquine.

However, the administration of ammonium chloride or of dimercaprol (BAL) may obviate chronic toxicity with chloroquine by promoting increased excretion (Rubin, Bernstein & Zvaifler, 1963). Regular ophthalmological examination when chloroquine is given over a prolonged period is also essential to early recognition and treatment of chloroquine retinopathy (Hobbs & Calnan, 1959; Okun *et al.*, 1963).

The fact that quinine had been found effective in the treatment of chloroquine-resistant cases of falciparum malaria makes the evolution of chloroquine resistance not entirely hopeless. It has been suggested that combination of chloroquine with quinine in such cases may be very effective (Sheeby & Reba, 1967) besides making the development of resistance to either drug more remote (see page 85 below).

A BRIEF HISTORICAL REVIEW OF OTHER ANTIMALARIAL DRUGS

Quinine, the oldest antimalarial drug known was introduced into Europe from South America in 1639 as Peruvian or Jesuit's bark for the treatment of 'fevers and tertians'. Though included in the London Pharmacopeia as 'Cortex Peruanus' in 1677, it was not

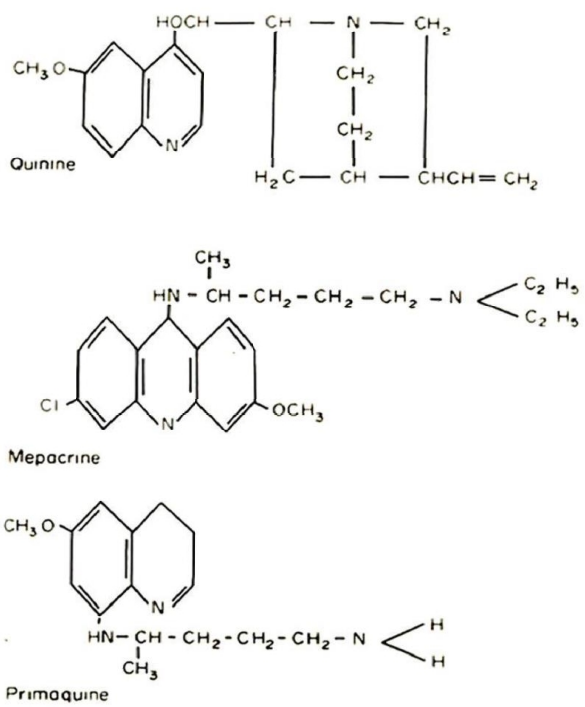

FIG. 2.

until 1820 that Pelletier and Caventon isolated it as an alkaloid of cinchona (Rollo, 1965). Quinine and the other cinchona alkaloids remained the sole specific chemotherapeutic agents for treating malaria till after World War I. During World War II, the superiority of mepacrine was clearly established over quinine. The primary antimalarial action of quinine is schizontocidal on all types of human malaria with an additional gametocidal effect for *Plasmodium vivax* and *P. malariae*. Like mepacrine and chloroquine it is effective as a suppressive, in the control of overt clinical attacks of malaria, but it is less well tolerated and less effective than mepacrine and much less so than chloroquine. Nevertheless, quinine now still has an important role in the treatment of malaria because it was recently shown to be effective against strains of *P. falciparum* resistant to chloroquine therapy

(Ebisawa *et al.*, 1966; Sheehy & Reba, 1967). At present the reasonable use of quinine is either in combination with primaquine to effect a radical cure in relapsing vivax malaria or alone for treating falciparum malaria produced by strains resistant to chloroquine and other antimalarial drugs (Fig. 2).

Mepacrine (Quinacrine) was synthesized in Germany in 1930 by Mauss and Mietzsch as a result of an extensive research programme which was stimulated by the unavailability of quinine to the Germans during World War I. With the large scale production of mepacrine when quinine was no longer available to the Allies during World War II, and the subsequent field experiences gained, it soon became the official antimalarial drug having proved to be much better than quinine. The toxicity of mepacrine and the fact that it lacks a true causal prophylactic action initiated the search for more potent antimalarial drugs.

The toxic and side-effects of mepacrine include yellow pigmentation of the skin and mucous membranes, dermatitis, gastro-intestinal upset, headache, excitation of the central nervous system with restlessness and insomnia, visual defects, blood dyscrasias, degenerative changes in tissues and less commonly toxic psychoses. Mepacrine enhances the toxicity of the 8-aminoquinoline antimalarial drugs (Pamaquine, Pentaquine and Primaquine) by increasing their concentrations in the blood and delaying their excretion, thus accentuating the tendency to methaemoglobinaemia and haemolysis (Zubrod, Kennedy & Shannon, 1948). Soon after the end of the second World War the superiority of chloroquine was unequivocally demonstrated over mepacrine (Loeb *et al.*, 1946; Pullman *et al.*, 1948; Berliner *et al.*, 1948).

Primaquine is the only 8-aminoquinoline drug now used against malaria. Pamaquine was introduced in 1926 by Muhlens as a direct result of Paul Ehrlich's original observation in 1891 that methylene blue exhibited a weak activity against *Plasmodium*. During World War II, part of the extensive research programme on antimalarial drugs in the United States worked on several 8-aminoquinoline derivatives (Wiselogle, 1946) and selected Pentaquine, Isopentaquine and Primaquine for further investigations. The value of primaquine is that it effects a radical cure in vivax malaria. It is highly active against the exo-erythrocytic forms of *P. vivax* and the primary exo-erythrocytic form of *P. falciparum*, but is ineffective against the erythrocytic forms of *P. falciparum*; and though active against the asexual blood forms of *P. vivax* its therapeutic effect as such is unreliable.

The acquired resistance of Plasmodia to Primaquine which had been demonstrated in the laboratory (Hill, 1963; Rollo, 1964) is probably of no practical importance. Primaquine is still the only chemotherapeutic agent capable of eliminating the primary and late tissue stages of relapsing malaria, the other 8-aminoquinolines being too toxic to be valuable. It is recommended that Primaquine should always be used with a 4-aminoquinoline schizontocide so as to curtail the possibility of inducing resistant strains of Plasmodia (Rollo, 1965).

Proguanil (chloroguanide) was synthesized by Curd and co-workers in 1945 (Curd, Davey & Rose, 1945a, b) and it represents the British contribution to antimalarial research during World War II. Being a biguanide its chemical structure is quite different from that of other previously known antimalaria drugs. It is metabolized to a triazine ring, which is the active form, in the body (Fig. 3). Proguanil was shown to be not only more potent than quinine but much safer to use. It is the nearest known drug to a causal prophylactic and though a slow-acting suppressive against falciparum malaria, is able to control a clinical attack. It controls an overt attack of vivax malaria by a slow suppressive activity,

but is not a true prophylactic against this infection. It is ineffective against the exo-erythrocytic forms of relapsing malaria. The action of proguanil on the asexual blood forms is very slow compared with that of the 4-aminoquinolines. While not destroying the gametocytes in the blood, it arrests their further development after being taken up and encysted in the gut wall of the mosquito (Rollo, 1955). Rollo (1955) had proposed that proguanil acts by inhibiting the reduction of folic acid thereby causing inhibition of nucleic acid synthesis. Chronic administration does not result in accumulation of the drug in the plasma and only slight cumulation occurs in the tissues. It has the further advantage of being the least toxic of the currently used antimalarial agents (Fig. 3).

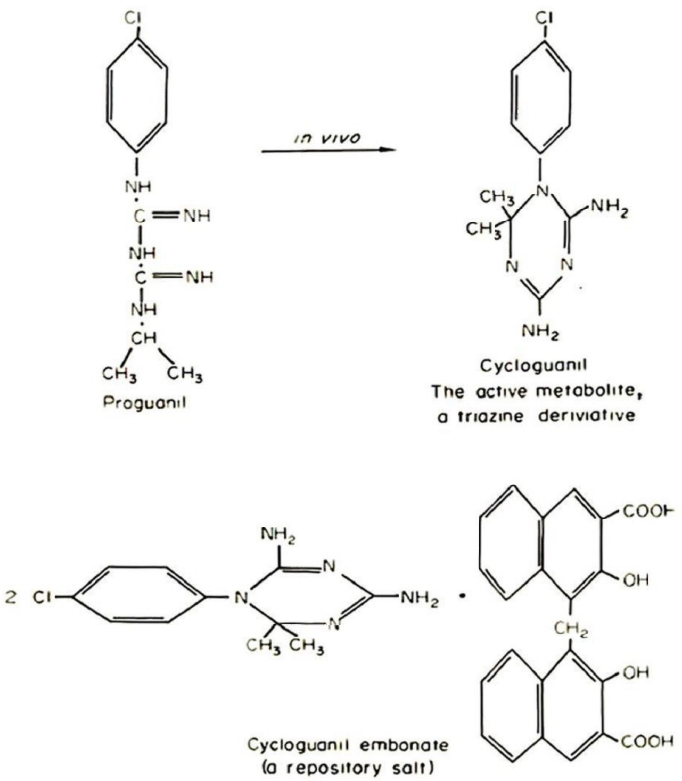

FIG. 3.

The main set-back has been the development of resistant strains, especially of *P. falciparum*, and there is evidence that strains of *P. vivax* and *P. malariae* resistant to proguanil exist (World Health Organization, 1965). These strains exhibit some degree of cross-resistance to pyrimethamine but remain sensitive to chloroquine, acridines and primaquine (Thompson, 1968).

Pyrimethamine was introduced in 1951 (Falco *et al.*, 1951; Symposium on Daraprim, 1952) as the most active of the series of 2, 4, diaminopyrimidines studied in experimental animals infected with malaria. The antimalarial actions of pyrimethamine and proguanil are identical, but pyrimethamine is more potent and of longer duration of action. Toxicity

studies have demonstrated antagonism to folic acid action. Sulphadiazine potentiates the antimalarial action of pyrimethamine and this synergism could used to advantage in preventing the development of resistant strains of Plasmodia (Rollo, 1955; Hurly, 1959). At the recommended prophylactic dose of 25 mg a week, little or no toxic symptoms occur; large doses produce megaloblastic anaemia similar to that of folic acid deficiency. Pyrimethamine is not recommended for the treatment of an acute attack of malaria in view of its slow onset of action; it is a useful prophylactic antimalarial agent. It can be expected to effect a suppressive cure in vivax malaria if continued weekly for at least 10 weeks after leaving a malarious area. Pyrimethamine structure is shown in Fig. 4.

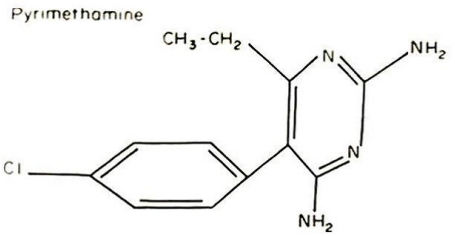

FIG. 4.

Sulphonamides and sulphones have moderate but usually incomplete blood schizontocidal action and are not recommended for use alone (World Health Organization, 1967). In combination with certain potentiating drugs such as pyrimethamine or proguanil, the sulphones and sulphonamides may prove of more value as antimalarial agents. The disadvantages when used alone which include narrow spectrum of antimalarial activity, slow clinical response, the risk of emergence of resistant strains and the need for frequent administration are more or less overcome by mixtures of pyrimethamine with sulphadiazine, sulphormethoxine or diaminodiphenyl sulphone (DADS). Some success has attended the use of these mixtures in chloroquine-resistant and pyrimethamine-resistant falciparum malaria (Bartelloni, Sheehy & Tigertt, 1967; Sheehy *et al.*, 1967). The prophylactic advantage of dapsone or sulphormethoxine combined with pyrimethamine had recently been demonstrated by Lucas and his colleagues (1969). In a double-blind control trial sulphormethoxine—or dapsone-pyrimethamine combination was shown to sustain a virtually complete suppression of malaria parasitaemia throughout a year while pyrimethamine alone gave incomplete suppression.

Cycloguanil, a dihydrotriazine metabolite of chlorguanide was introduced by Thompson *et al.* in 1963. It was found to have protective properties against vivax and falciparum malaria for periods up to 1 year or more following a single intramuscular dose 5 mg/kg body weight (Coatney, Contacos & Lunn, 1964, Contacos *et al.*, 1964, Lunn *et al.*, 1964). Studies in West Africa showed the period of protection to be much shorter than the American studies, being about 4–6 months (McGregor *et al.*, 1966). Cycloguanil was only effective on strains sensitive to proguanil or pyrimethamine; it is not desirable to use the drug where the local strain is resistant to the biguanide and diaminopyrimidine derivatives (Contacos *et al.*, 1964; Lunn *et al.*, 1964). In a village study by Fasan (1970) on school

children aged 6–10 years in a holoendemic malaria region (Western State of Nigeria), cycloguanil pamoate was used in a dose range from 7·3 to 10·8 mg/kg body weight. Results of this preliminary study were not encouraging; protection conferred by chloroquine and cycloguanil given together in single doses was for 6 weeks, and was about the same as that given by chloroquine alone. Moreover, the immunity of the children under treatment appeared to have been depressed at 12 weeks following this prophylactic drug treatment. The poor response of malaria infection to cycloguanil in this Nigerian study is hardly surprising in view of the known resistance of *P. falciparum* infection to proguanil and pyrimethamine in West Africa (Archibald, 1960; Dodge, 1966; Lucas *et al.*, 1969). The other important factor mitigating against a good response to cycloguanil prophylaxis is the high rate of re-infection in such a holoendemic region.

THE PRESENT TREATMENT OF MALARIA AND THE STATUS OF CHLOROQUINE

Chloroquine is the drug of first choice in the treatment of an acute clinical attack of malaria (Rollo, 1965; World Health Organisation, 1967). Though like quinine and mepacrine it is primarily a schizontocide, it is not only more potent and more rapidly effective, but is less toxic and better tolerated than either of its predecessors (Berliner *et al.*, 1948). Its activity is quite high against the asexual erythrocytic forms of *Plasmodium vivax*, *P. falciparum* and the gametocytes of *P. vivax*. Most patients with acute attacks of malaria become free of symptoms within 24–48 hr and the peripheral blood cleared of parasites within 48–72 hr. Chloroquine is neither a true causal prophylactic nor a radically curative agent in vivax malaria, just like quinine and mepacrine; but the interval between relapses is much longer after chloroquine than after the two older drugs (Pullman *et al.*, 1948). Unlike mepacrine, chloroquine may be combined with Primaquine to effect a radical cure in vivax malaria without the danger of toxic synergism.

Quinine has been shown to be effective in treating malaria caused by strains of *P. falciparum* resistant to chloroquine and the other antimalarials (Montgomery & Eyles, 1963; Ebisawa *et al.*, 1966; Sheehy *et al.*, 1967). Amodiaquine ('Camoquin'), another 4-aminoquinoline derivative may be used instead of chloroquine but it is known to be more expensive and appears to cause more generalized weakness (personal observation).

For prophylaxis both proguanil and pyrimethamine should first be considered before chloroquine. Proquanil in a dose of 100–200 mg daily or pyrimethamine taken in a dose of 25 mg once a week is virtually free from any toxic side-effect (Goodwin & Rollo, 1955; Falco *et al.*, 1951; Symposium on Daraprim, 1952). They are effective in most cases in suppressing vivax malaria and may 'suppressively cure' falciparum malaria. Break-through may more often be due to irregular medication than to acquired resistance (Grounds, 1954).

Sulphadiazine, sulphormethoxine or dapsone combined with either pyrimethamine or proguanil increases the antimalarial potency (Rollo, 1955; Hurly, 1959; Lucas *et al.*, 1969), and may lessen the incidence of the development of resistant strains of *P. vivax* and *P. falciparum*. Where natural insensitivity occurs to either proguanil or pyrimethamine a change of antimalarial therapy is indicated.

Cycloguanil may be used for protection against vivax, falciparum or malariae malaria where the strains are sensitive to proguanil. Under such a situation, it has the advantage of long-term duration of action following a single intramuscular dose (Coatney *et al.*, 1964;

Contacos *et al.*, 1964; Lunn *et al.*, 1964). The experience of Fasan (1970) with cycloguanil shows what could happen when the drug is used in a holoendemic region with strains of falciparum malaria resistant to proguanil. The untoward effects of the oleaginous suspension of cycloguanil pamoate include pain at the site of injection radiating to the legs, also pain and swelling which may occasionally give rise to induration abscess (Babione, 1968; Fasan, 1970). It should be possible to obviate these physical inconveniences, which are important in mass eradication campaigns, by compounding a more fluid suspension which would be easier to inject intramuscularly. The adverse effects of its antifolic action should be watched for in susceptible and malnourished persons. These untoward effects are not enough to recommend a discontinuation of the prophylactic use of cyclyoguanil especially when there are proper indications for its use in environments without existing proguanil-resistance. It is conceivable that combination of cycloguanil with dapsone or sulphormethoxine would produce an enhanced antimalarial activity and delay or prevent the genesis of resistance strains of *Plasmodium* just as their combinations with pyrimethamine have done.

Chloroquine being the most potent known drug in the control of an overt attack of malaria is better reserved for such and should only be used for prophylaxis when local strains of malaria parasites are known to be unaffected by pyrimethamine, proguanil or combinations of these with sulphadiazine or dapsone. Moreover, the chronic use of chloroquine, though in more frequent dosages than those recommended for malaria suppression has been shown to adversely affect the eyes (Hobbs, Sorsby & Freedman, 1959; Okun *et al.*, 1963). Mass eradication of malaria by the use of chloroquine medicated table salt has been attempted (Clyde, 1966; Giglioli, Rutten & Ramjattan, 1967). Though successes have been claimed, this type of chronic use of chloroquine at unknown individual doses should not be encouraged in view of the reasons given above.

Primaquine is yet unrivalled in effecting a radical cure in relapsing vivax malaria. It is not only highly active against the primary exo-erythrocytic forms of *P. vivax* and *P. falciparum* and the late tissue stages of *P. vivax* but exerts a marked gametocidal action against all the four species of human malaria. It has to be combined with chloroquine or quinine to effect a radical cure because of its relative inactivity against the blood asexual forms of plasmodia. Primaquine is not popular in malarious areas such as West Africa for two reasons: a sizeable percentage of Africans are sensitive to its haemolytic toxic effect because of the deficiency of glucose-6-phosphate dehydrogenase (Allison, 1960; Allison & Clyde, 1961); secondly, the rate of re-infection with malaria is very high in these parts. It is therefore only advisable to use primaquine for immigrants staying temporarily in these environments after they had left for non-malarious areas.

CHLOROQUINE RESISTANCE

Young & Moore reported resistance to chloroquine in *Plasmodium falciparum* in 1961; since then cases of chloroquine-resistant falciparum malaria had been observed in Thailand (Young *et al.*, 1963), Malaya (Montgomery & Eyles, 1963), South America (Box, Box & Young, 1963), and Vietnam (Legsters *et al.*, 1965). In Africa a number of unconfirmed reports on the suspected existence of chloroquine-resistant strains of *P. falciparum* have been made from Upper Volta (Lasch & N'Guyen, 1965), Ghana (Schwendler, 1965) and Zambia (Himpoo & MacCallum, 1967).

The World Health Organization expert Committee on Resistance of Malaria Parasites to Drugs (1965) had defined the resistance of human malaria parasites to drugs: it is the ability of a parasite strain to survive and/or to multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within the limits of tolerance of the subject. In the World Health Organization Technical Report Series (1967) the schizontocidal activity of the 4-aminoquinolines in falciparum malaria was further described as varying from full sensitivity to complete resistance as shown in Table 1.

TABLE 1. Sensitivity of falciparum malaria to the 4-aminoquinolines (World Health Organization, 1967)

Response	Recommended symbol	Evidence
Sensitivity	S	Clearance of asexual parasitaemia within 7 days of the first day of treatment, without recrudescence
Resistance	R I	Clearance of asexual parasitaemia as in sensitivity followed by recrudescence
	R II	Marked reduction of asexual parasitaemia but no clearance
	R III	No marked reduction of asexual parasitaemia

More cases have recently been reported from Vietnam (Legsters *et al.*, 1965; Eppes *et al.*, 1966) and from Japan (Ebisawa *et al.*, 1966).

Palecek, Palecekova & Aviado (1967) studied experimentally the pathological physiology of chloroquine resistant *P. berghei* in mice. The blood from mice infected with chloroquine resistant strain of *P. berghei* showed essentially the same features as the blood collected from mice inoculated with sensitive strain with the following minor differences: the anaemia was more severe but the parasitaemia was less intense in the mice with chloroquine-resistant strain; the curve for oxyhaemaglobin (shifted to the right) was between the curve from non-infected mice and that from mice infected with sensitive strain. Warhurst & Killick-Kendrick (1967) observed spontaneous resistance to chloroquine in a strain of rodent malaria—*P. berghei yoelli*. The strain named 17X was as resistant as laboratory strains of *P. berghei* which was produced by treatment of infected animals with chloroquine. The resistance appeared to be stable unlike the artificially produced chloroquine resistance. Hahn *et al.* (1966) had explained that the basis of chloroquine resistance is a reduced uptake or concentration of chloroquine in resistant cells.

In their studies on cycloguanil, sulphone, and chloroquine-resistant *P. berghei* in mice, Thompson *et al.* (1967) indicated five groupings for antimalarial drugs which could serve as a rational basis for dealing with various types of resistant strains as well as help in the development and recognition of drugs with new modes of action:

(i) Cycloguanil hydrochloride, proguanil and pyrimethamine.
(ii) Chloroquine, amodiaquine, amopyroquine, acridine N-oxide CI-423, quinacrine, naphthalene BW 377-C54, quinine.
(iii) DDS and sulphadiazine.
(iv) Primaquine.
(v) Oxophenarsine.

Fortunately, the treatment of chloroquine-resistant malaria have not proved hopeless or very difficult. Much older drugs especially quinine have been found effective in many cases of chloroquine-resistant falciparum malaria (Ebisawa *et al.*, 1966).

Even when quinine alone has not been entirely effective, a combination of drugs was found curative; for example:

(i) Chloroquine and quinine (Sheehy & Reba, 1967; Bartelloni *et al.*, 1967).
(ii) Chloroquine and dapsone (De Gowin *et al.*, 1966).
(iii) Quinine and pyrimethamine (Sheehy & Reba, 1967).
(iv) Pyrimethamine and sulphormethoxine or sulphadiazine (Bartelloni *et al.*, 1967; Sheehy & Reba, 1967; Neves *et al.*, 1968).
(v) Chloroquine, quinine and dapsone (Sheehy *et al.*, 1967).
(vi) Quinine, sulphadiazine or sulphormethoxine and pyrimethamine (Hunter *et al.*, 1968; Sheehy & Reba, 1967; Bartelloni *et al.*, 1967).

The importance of vigorous treatment of chloroquine-resistant falciparum malaria has been emphasized by Blout (1967). That there is no room for complacency or careless drug combinations is also brought out by the fact that the incidence of relapse cases have only been reduced and not completely eliminated. Also, isolated cases of resistance to chloroquine as well as to quinine (Eppes *et al.*, 1966) or to chloroquine, pyrimethamine and quinine combinations (Legsters *et al.*, 1965) have been observed in Vietnam.

Experience in south-east Asia suggests that the effective treatment of chloroquine-resistant falciparum malaria should be along the following lines:

(a) Early recognition of patients infected with chloroquine resistant strains of malaria by a careful history taking—those returning from south-east Asia and South America;
(b) early onset of quinine therapy after non-response to chloroquine;
(c) the quinine is given orally or parenterally for 14 days;
(d) medication with sulphadiazine or sulphormethoxine in the first 5 days and pyrimethamine in the first 3 days or within the last 3–5 days of quinine administration (Sheehy & Reba, 1967; Bartelloni *et al.*, 1967).

An alternative approach is to give a combined chloroquine and quinine therapy followed by dapsone 25 mg daily for 1 month. Relapse after such a course of supplemental sulphone was found to be less than 3% as compared with 41% relapse rate after chloroquine and quinine alone (Sheehy *et al.*, 1967).

Even though up to 30% of falciparum malaria infections acquired in south-east Asia is chloroquine-resistant (Sheehy & Reba, 1967), virtually all infections with *P. falciparum* in Africa are amenable to chloroquine medication. The experience of Lasch & N'Guyen (1965) and Himpoo & MacCallum (1967) have not been confirmed by other workers (Jeffery & Gibson, 1966; Wolf & Hudleston, 1969).

Chloroquine thus remains the most effective single agent in the treatment of an acute attack of falciparum malaria. Until malaria is eradicated or until a more effective and less

toxic drug is discovered chloroquine alone or in combination with other drugs will hold the pride of place in malaria treatment.

The future chloroquine does not appear to be bright, however; the two main set-backs, that of ocular toxicity and the emergence of chloroquine-resistant strains of *P. falciparum* have already affected the status of chloroquine in malaria and in the treatment of other diseases. The likelihood of a world-wide eradication of malaria is still remote but the prospects of synthesizing a better antimalarial drug are very high. Experiences with cycloguanil prophylaxis have been most variable (Contacos *et al.*, 1964; McGregor *et al.*, 1966; Babione, 1968; Fasan, 1970); however, as described above, drug combinations appear to be very effective both prophylactically and in the treatment of overt attacks of falciparum malaria strains resistant to chloroquine.

Chloroquine will continue to be effective in those parts of the world such as West Africa where little or no sign of chloroquine resistance have become obvious. Fast communication between various peoples in all parts of the world these days may mean that even West Africa will not be free for too long from these strains of resistant falciparum malaria parasites.

REFERENCES

Adams, A.R.D. & Maegraith, B.G. (1960) *Clinical Tropical Diseases*, 2nd edn. Blackwell Scientific Publications, Oxford.

Allison, A.C. (1960) Glucose-6-phosphate dehydrogenase deficiency in red blood cells of East Africans. *Nature (Lond.)* **186,** 431–432.

Allison, A.C. & Clyde, D.F. (1961) Malaria in African children with deficient erythrocyte glucose-6-phosphate dehydrogenase. *Brit. med. J.* **1,** 1346.

Archibald, H.M. (1960) The appearance of *P. falciparum* resistant to pyrimethamine in a northern Nigerian village. W. *Afr. med. J.* **9,** 21–25.

Ayres, S. & Ayres, S. Jr., (1955) Chloroquine in the treatment of lichen planus and other dermatoses. *J. Amer. med. Ass.* **157,** 136–139.

Babione, R.W. (1968) Malaria eradication in the Americas—a review of 12 years of effort. In: *Proceedings.* A report given at the 8th International Congress on Tropical Medicine and Malaria. Tehran, Iran. September 1968.

Bagnall, A.W. (1957) The value of chloroquine in rheumatoid disease: a 4-year study of continuous therapy. *Canad. med. Ass. J.* **77,** 182.

Bartelloni, P.J., Sheehy, T.W. & Tigertt, W.D. (1967) Combined therapy for chloroquine-resistant *Plasmodium falciparum* infection. Concurrent use of long acting sulphormethoxine and pyrimethamine. *J. Amer. med. Ass.* **199,** 173–177.

Berliner, R.W., Earle, D.P. Jr., Taggart, J.V., Zubrod, C.G., Welch, W.J., Conan, N.J., Bauman, E., Scudder, S.T. & Shannon, J.A. (1948) Studies on the chemotherapy of the human malarias. VI. The physiological disposition, antimalarial activity and toxicity of several derivatives of 4-aminoquinolines. *J. clin. Invest.* **27,** 98–107.

Blout, R.E. (1967) Management of chloroquine-resistant falciparum malaria. *Arch. intern. Med.* **119,** 557–560.

Box, E.D., Box, Q.T. & Young, M.D. (1963) Chloroquine-resistant *Plasmodium falciparum* from Porto Velho, Brazil. *Amer. J. trop. Med. Hyg.* **12,** 300–304.

Clyde, D.F. (1966) Suppression of malaria in Tanzania with the use of medicated salt (sodium chloride plus chloroquine) in man. *Bull. Wld Hlth Org.* **35,** 962–968.

Coatney, G.R., Contacos, P.G. & Lunn, J.S. (1964) Further observations on the antimalarial activity of CI-501 ('Camolar') against the Chesson strain of vivax malaria. *Amer. J. trop. Med. Hyg.* **13,** 383–385.

Conan, M.J., Jr. (1948) Chloroquine in amoebiasis. *Amer. J. trop. Med. Hyg.* **28,** 107–110.

Contacos, P.G., Coatney, G.R. Lunn, J.S. & Kilpatrick, J.W. (1964) The antimalarial activity of CI-501 ('Camolar') against falciparum malaria. *Amer. J. trop. Med. Hyg.* **13,** 386–390.

CURD, F.H.S., DAVEY, D.G. & ROSE, R.L. (1945a) Studies on synthetic antimalarial drugs. II. General chemical considerations. *Ann. trop. Med. Parasit.* **39,** 157.

CURD, F.H.S., DAVEY, D.G. & ROSE, R. L. (1945b) Some biguanide derivatives as new types of antimalarial substances with both therapeutic and causal prophylactic activity. *Ann. trop. Med. Parasit.* **39,** 208.

DE GOWIN, R.L., EPPES, R.B., CARSON, P.E. & POWELL, R.D. (1966) The effects of diphenyl-sulphone (DDS) against chloroquine-resistant *Plasmodium falciparum. Bull. Wld Hlth Org.* **34,** 671–681.

DODGE, J.S. (1966) Some notes on the isolation of a strain of *P. falciparum* insensitive to pyrimethamine in Northern group of provinces. *J. Nigeria med. Ass.* **3,** 383–387.

EBISAWA, ISAO; NAMIKI, MASAO & IGARASHI, HIROSHI (1966) Imported falciparum malaria with inadequate response to chloroquine. *Jap. J. Exp. Med.* **36,** 601–607.

EPPES, R.B., DE GOWIN, R.L., POWELL, R.D. & LEGSTERS, J.J. (1966) Clinical studies with a drug-resistant strain of *Plasmodium* from Vietnam. *Milit. Med.* **131,** 362–370.

FALCO, E.A., GOODWIN, L.G., HITCHINGS, G.H., ROLLO, I.M. & RUSSELL, P.B. (1951) 2-4-Diamino pyrimidines, a new series of antimalarials. *Brit. J. Pharmacol.* **6,** 185.

FASAN, P.O. (1970) Field trial of cycloguanil pamoate in the treatment and suppression of malaria in Nigeria school children: A preliminary report. *Trans. roy. Soc. trop. Med. Hyg.* **64,** 839–849.

FULD, H. & HORWICH, L. (1958) Treatment of rheumatoid arthritis with chloroquine. *Brit. med. J.* **2,** 1199.

GADDUM, G.H. (1959) *Pharmacology*, 5th edn. Oxford University Press, London, New York and Toronto.

GIGLIOLI, G., RUTTEN, F.J. & RAMJATTAN, S. (1947) Interruption of malaria transmission by chloroquinized salt in Guyana; with observations on a chloroquine-resistant strain of *Plasmodium falciparum. Bull. Wld Hlth Org.* **36,** 283–301.

GOLDMAN, L., COLE, D.P. & PRESTON, R.H. (1953) Chloroquine diphosphate in treatment of discoid lupus erythematosus. *J. Amer. med. Ass.* **152,** 1428.

GOODWIN, L.G. & ROLLO, I.M. (1955) The chemotherapy of malaria, piroplasmosis, trypanosomiasis and leishmaniasis. In: *Biochemistry and Physiology of Protozoa* (Ed. by S. H. Hinter & A. Lwoff), Vol. II. Academic Press, Inc., New York.

GROUNDS, J.G. (1954) Occurrence of pyrimethamine-resistant strain of malaria in Teita district of Kenya. *E. Afr. med. J.* **31,** 51.

HAHN, F.E., O'BRIEN, R.L., CIAK, J., ALLISON, J.L. & OLENICK, J.G. (1956) Studies on modes of action of chloroquine, quinacrine and quinine and on chloroguine resistance. *Milit. Med.* **1316,** Suppl. 1071-1089.

HILL, J. (1963) Chemotherapy of malaria: Part 2, The antimalarial drugs. In: *Experimental Chemotherapy* (Ed. by R. J. Schnitzer & F. Hawking). Academic Press, Inc., New York.

HIMPOO, B. & MACCALLUM, J.B. (1967) Possible chloroquine-resistant malaria in Zambia. *Med. J. Zambia,* **1,** 31–35.

HOBBS, H.E. & CALNAN, C.B. (1959) Visual disturbances with antimalarial drugs; with particular reference to chloroquine keratopathy. *Arch. Derm.* **80,** 557.

HOBBS, H.E., SORSBY, A. & FREEDMAN, A. (1959) Retinopathy following chloroquine therapy. *Lancet,* **ii,** 478.

HUNTER, G.W. III, BATEY, L., MELENEY, H.E. & SANDERS, E. (1968). Apparent chloroquine-resistant falciparum malaria from coastal Brazil. *Amer. J. trop. Med. Hyg.* **17(3),** 364–368.

HURLY, M.G.D. (1959) Potentiation of pyrimethamine by sulphadiazine in human malaria. *Trans. roy. Soc. trop. Med. Hyg.* **53,** 412.

JEFFERY, G.M. & GIBSON, F.D. (1966) Studies on chloroquine-resistance of *Plasmodium falciparum* in Upper Volta and Liberia, West Africa. *Bull. Wld Hlth Org.* **35,** 441–449.

KNOX, J.M. & FREEMAN, R.G. (1963) Prophylactic use of chloroquine to prevent skin cancer. *Arch. Derm.* **87,** 315.

LANE, R. (1951) Treatment of hepatic amoebiasis with chloroquine. *J. Trop. med. Hyg.* **54,** 198–206.

LASCH, E.E. & N'GUYEN, T.L. (1965) Observations on an apparent chloroquine-resistant strain of *Plasmodium falciparum* in West Africa. *Brit. med. J.* **2,** 1219–1222.

LEGSTERS, L.J., WALLACE, D.K., POWELL, R.D. & POLLACK, S. (1965) Apparent refractoriness to chloroquine, pyrimethamine and quinine in strains of *Plasmodium falciparum* from Vietnam. *Milit. Med.* **130,** 168–176.

LOEB, R.F. *et al,* (1946) Activity of a new antimalarial agent, chloroquine (SN-7618). Statement approved by the Board for co-ordination of Malarial Studies. *J. Amer. med. Ass.* **30,** 1069.

LUCAS, A.O., HENDRICKSE, R.G., OKUBADEJO, O.A., RICHARDS, W.H.G., NEAL, R.A. & KOFIE, B.A.K. (1969) The suppression of malarial parasitaemia by pyrimethamine in combination with dapsone or sulphormethoxine. *Trans. roy. Soc. trop. Med. Hyg.* **63,** 216–229.

LUNN, J.S., CHIN, W., CONTACOS, P.G. & COATNEY, G.R. (1964) Cycloguanil pamoate (CI-501) as a casual prophylactic against a South Rhodesian strain of falciparum malaria. *Amer. J. trop. Med. Hyg.* **13,** 783–785.

MANSON-BAHR, SIR PHILIP H. (1960). *Manson's Tropical Diseases*, 15th edn. Baillière, Tindal and Cassell, Ltd, London.

MCGREGOR, I.A., WILLIAMS, K., WALKER, G.H. & RAHMAN, A.K. (1966) Cycloguanil pamoate in the treatment and suppression of malaria in the Gambia, West Africa. *Brit. med. J.* **1,** 695–701.

MONTGOMERY, R. COL. & EYLES, D.E. (1963) Chloroquine-resistant falciparum malaria in Malaya. *Trans. roy. Soc. trop. Med. Hyg.* **57,** 409.

MORSE, S.I., COHN, Z.A., HIRSCH, J.G. & SCHAEDLER, R.W. (1961) The treatment of sarcoidosis with chloroquine. *Amer. J. Med.* **40,** 779.

MUHLENS, P. (1926) Die Behand lung der naturlichen menschlichen Malaria—Infektion mit Plasmochin. Quoted by I. M. Rollo, (1965). *Naturwissenchaften*, **14,** 1162.

NEVES, J., MOURA, H.B., ARAUJO, F.G., COLEN, S.E.U. & LOIOLA, J.C. (1968) Resistance of *Plasmodium falciparum* to chloroquine. *Rev. Inst. Med. trop. S. Paulo*, **10,** 28–35. English Summary from *Biol. Abs.* 1968, **49,** No. 96478.

OKUN, E., GOURAS, P., BERNSTEIN, H. & VON SALLMAN, L. (1963) Chloroquine retinopathy. *Arch. Ophthal.* **69,** 59.

PAGE, F. (1951) Treatment of lupus erythematosus with mepacrine. *Lancet*, **ii,** 755.

PALECEK, F., PALECEKOVA, M. & AVIADO, D.M. (1967) Pathologic physiology and chemotherapy of *Plasmodium berghei*: Oxyhaemoglobin dissociation curve in mice infected with chloroquine-sensitive and resistant strains. *Exp. Parasitol.* **21,** 16–30.

PULLMAN, T.N., CRAIGE, B. JR., ALVING, A.S., WHORTON, C.M., JONES, R. JR. & EICHELBERGER, L. (1948) Comparison of chloroquine, quinacrine and quinine in the treatment of acute attacks of sporozoite-induced vivax malaria (Chesson strain). *J. clin. Invest.* **27,** Suppl. 46–50.

ROLLO, I.M. (1955) The mode of action of sulphonamides, proguanil and pyrimethamine on *Plasmodium gallinaceum*. *Brit. J. Pharmacol.* **10,** 208.

ROLLO, I.M. (1964) *Biochemistry and Physiology of Protozoa*, Vol. 3. Academic Press, Inc., New York.

ROLLO, I.M. (1965) Drugs used in the chemotherapy of Malaria. In: *The Pharmocological Basis of Therapeutics* (Ed. by L. S. Goodman & A. Gilman), 3rd edn. Macmillan, New York, London and Toronto.

RUBIN, M., BERNSTEIN, H.N. & ZVAIFLER, N.J. (1963) Studies on the pharmacology of chloroguine, *Arch. Ophthal.* **70,** 474–481.

SCHWENDLER, H.P. (1965) Chloroquine-resistant strains of *Plasmodium falciparum* in Ghana? *Ghana Med. J.* **4,** 20–22.

SHEEHY, T.W., NEFF, T.A., REBA, R.C., GAINTER, J.R. & TIGERTT, W.D. (1967) Supplemented sulfone (Dapsone) therapy: used in the treatment of chloroquine-resistant falciparum malaria. *Arch. intern. Med.* **119,** 561–566.

SHEEHY, T.W. & REBA, R.C. (1967) Treatment of chloroquine-resistant Plasmodium in Vietnam. *Ann. intern. Med.* **66,** 616–622.

SYMPOSIUM ON DARAPRIM (1952) *Trans. roy. Soc. trop. Med. Hyg.* **46,** 467–508.

THOMPSON, P.E. (1968) Drug resistance in malaria, and criteria in the selection of new agents for trial against drug-resistant strains. In: *Mode of Action of Anti-parasitic drug.* (Ed. by J. R. da Silva & M. J. Ferreira), pp. 69–75. Pergamon Press, Oxford.

THOMPSON, P.E., OLSZEWSKI, B., BAYLES, A. & WAITZ, J.A. (1967) Relations among antimalarial drugs: Results of studies with cycloguanil-, sulfone-, or chloroquine-resistant *Plasmodium berghei* in mice. *Amer. J. trop. Med. Hyg.* **16,** 133–145.

THOMPSON, P.E., OLSZEWSKI, B.J., ELSLAGER, E.F. & WORTH, D.F. (1963) Laboratory studies on 4,6-diamino-1-(p-chlorophenyl)-1, 2-dihydro-2, 2-dimethyl-S-triazine pamoate (CI-501) as a repository antimalarial drug. *Amer. J. trop. Med.* **12,** 481–493.

VAN CAUWENBERGE, PAR H., LECOMTE, J. & LAPIERE, C.H. (1958) Influence of chloroquine on the development of the granuloma round the cotton-wool tampon and on the granulomatous pouch of Selye. *Societe Belge de Biologie, Biologie comptes Rendus.* **152,** 1414–1417.

WARHURST, D.C. & KILLICK-KENDRICK, R. (1967). Spontaneous resistance to chloroquine in a strain of rodent malaria (*Plasmodium berghei yoelii*). *Nature* (*Lond.*), **213,** 1048.

WISELOGLE, F.Y.—Editor (1946). *A survey of antimalarial drugs 1941–1945.* J. W. Edwards Publisher Inc. Ann. Arbor, Michigan, U.S.A.

WORLD HEALTH ORGANIZATION (1965). Technical Report Series, No. 296. Resistance of malaria parasites to drugs.

WORLD HEALTH ORGANIZATION (1967) Technical Report Series, No. 375. Chemotherapy of malaria.

WOLF, H.L. & HUDLESTON, J.A. (1969) Investigation of suspected resistance of *P. falciparum* to chloroquine in Zambia. *Med. J. Zambia* **2,** 173–176.

YOUNG, J.P. (1959) Chloroquine in rheumatic disorders. *Ann. intern. Med.* **51,** 1159.

YOUNG, M.D., CONTACOS, P.G., STITCHER, J.E. & MILLAR, J.W. (1963) Drug resistance in *Plasmodium falciparum* from Thailand. *Amer. J. trop. Med.* **12,** 305–315.

ZUBROD, C.G., KENNEDY, T.J. & SHANNON, J.A. (1948) The physiological disposition of Pamaquine. *J. Clin. Invest.* **27,** 114–120.