Regular Review

Chemoprophylaxis of malaria in Africa: the spent "magic bullet"

L J BRUCE-CHWATT

Only a year ago a group of specialists convened by the Ross Institute in London prepared a comprehensive and well-reasoned report on the prevention of malaria in travellers from Britain.[1] Though plasmodia had become more resistant to common antimalarial drugs, said the report, a judicious selection of the available compounds should still provide adequate protection from malaria. It added, however, that complete safety from infection could not be expected, even if the existing drugs were taken regularly and at the appropriate dosage, in view of our lack of precise information on the type and degree of resistance of the three main species of plasmodia in most parts of the tropical world. Within each species of human malaria parasites are many geographical "strains" with great differences in their biological characters and especially in their susceptibility to specific drugs. Our knowledge of the genetic variations is still embryonic, but the results of new studies show the extreme complexity of the problem.[2]

Much has been written recently on resistance to antimalarial drugs.[3-8] Foci of resistance of *Plasmodium vivax* or *P malariae* in a few areas (Colombia, Venezuela, Pakistan, Malaysia, Taiwan, Vietnam) are still restricted to antifolic compounds (proguanil and pyrimethamine) and also (in one geographical area of the south-west Pacific) to primaquine, an 8-aminoquinoline used mainly for radical cure of relapsing malaria. No resistance to 4-aminoquinolines has been seen in *P vivax* and *P malariae* in the field. On the other hand, the resistance of *P falciparum* to chloroquine, hitherto our most reliable antimalarial of the 4-aminoquinoline group, has now been reported from various parts of 21 countries of America, Asia, and the south-west Pacific. In addition to countries quoted in the report of the Ross Institute[1] the new records comprise Sabah, the state of Orissa in India, including its western borders, and Sumatra.[9]

The combination of pyrimethamine and sulfadoxine at a fixed ratio of 1:20 (Fansidar; Falcidar) has become a valuable alternative to treatment of chloroquine-resistant falciparum malaria and is also increasingly used (with or without justification) for prophylaxis against the disease. A similar combination of sulphalene with pyrimethamine (Metakelfin) has been introduced but it is less widely known[8]; and Maloprim, a combination of pyrimethamine and sulphone at a fixed 1:8 ratio, is essentially a prophylactic drug which, despite reservations about its pharmacokinetics, is also of value in areas of chloroquine resistance.

Recently much clinical and other evidence has been accumulating of resistance of *P falciparum* to the combination of pyrimethamine and sulfadoxine in Indonesia, Thailand, Papua New Guinea, and Brazil. During the past three years signs of an impending change have also appeared in Africa, where previously there had been little cause for alarm. Resistance of *P falciparum* to pyrimethamine had often been reported since 1960 from various parts of Africa[10,11]; its distribution was well investigated only in East Africa,[10] but it probably occurred patchily over large tropical areas. Cross-resistance to proguanil may well also have been common in these places; no clear evidence was forthcoming. Reports of alleged foci of chloroquine-resistant falciparum malaria in Africa were, however, mostly discounted after proper investigations. Usually such claims were due to genuine technical errors or to non-compliance by patients, though in some cases authors may have been overambitious to secure a medical "scoop."[12] Nevertheless, a few studies in Ethiopia and in the Sudan indicated low degrees of resistance of local strains of *P falciparum*, but this was regarded as of little practical importance.[13-16]

Then in 1978 and 1979 appeared a series of clinical observations of *P falciparum* malaria in American, German, Scandinavian, and other tourists in East Africa (Kenya, Tanzania, Uganda), the Comoro Islands, and Madagascar.[17-22] Since the plasma of some of these patients contained adequate concentrations of chloroquine the problem of resistance was seen to be of greater importance than had previously been thought. Furthermore, a substantial degree of chloroquine resistance has been induced in an African strain of *P falciparum* maintained in a serial in-vitro culture in the laboratory.[23]

At the end of 1979 an extensive clinical and experimental investigation by Campbell *et al*[24] of malaria in an American tourist returning from Tanzania proved (on the basis of an induced infection in aotus monkeys and through culture in the laboratory) that this strain had some characteristics of chloroquine resistance greater than the low (RI) degree. Nevertheless, at that time chloroquine remained the best available prophylactic and therapeutic antimalarial drug in Africa.[25] Another decisive observation of resistance came in a Swedish study of two patients who had acquired their infection in Madagascar and one whose malaria had originated from Kenya; their response to chloroquine, including the assay of the amount of the drug in the sera, was consistent with clinical reports.[26,27]

Meanwhile in West Africa, despite a single clinical observation from one locality in Nigeria suggesting a slow response of *P falciparum* infection to a standard dose of chloroquine, tests on a large group of naturally infected children showed normal response to the usual (10 mg/kg) dose of chloroquine.[28,29] A single report from Zambia of a child whose symptoms did not yield to a high dosage of chloroquine lacked proof of absorption of chloroquine.[30] A recent hospital report from the Ivory Coast, however, described some expatriate and indigenous patients who had not responded to the usual dosage of chloroquine

because of the presence of a drug-resistant strain of *P falciparum*.[31]

Further reports on chloroquine resistance in travellers returning to Europe and the United States from East Africa appeared in 1980-1.[32-36] Some as yet unpublished but fairly authentic cases of drug-resistant malaria have occurred in temporary residents in East Africa, who were apparently taking proper chloroquine prophylaxis; some deaths have occurred. Resistance was confirmed at the Hospital for Tropical Diseases in London, where patients who had acquired their infection in Tanzania were treated.[37]

A further predicament arose this year when the first reports of resistance of *P falciparum* to the pyrimethamine-sulfadoxine combination were signalled from East Africa. These observations were supported by biochemical evidence of adequate concentrations of the drug in the sera of patients who had developed symptoms despite a proper prophylactic regimen.[38-40] Another recent report also from East Africa described a patient taking pyrimethamine-sulphone prophylaxis who developed falciparum malaria.[41] Yet a well-conducted field study, though confirming pyrimethamine resistance in *P falciparum* from Kisumu (Kenya), emphasised the good clinical response of local strains to the pyrimethamine-sulfadoxine combination.[42]

Individual prophylaxis

At present, therefore, the picture is complex and ominous and is causing much concern both among the general population and within the medical profession. A few weeks ago a group of American experts recommended for areas with chloroquine resistance a new prophylactic regimen consisting of 300 mg of chloroquine base and a tablet of pyrimethamine-sulfadoxine once a week.[43] No doubt such triple regimen may have greater protective effect if the strains of *P falciparum* resistant to one or the other compound are not too prevalent. This recommendation, however, caused some controversy: surely the combination of chloroquine with pyrimethamine and sulphone would have been more logical since the latter has a prophylactic action, even if its composition has been questioned and its preventive effect is less than expected. Any wider use of pyrimethamine with sulfadoxine may increase the selection pressure on the malaria parasite. This would contribute to a further spread of resistance to the combination—which is essentially a therapeutic drug of particular value when chloroquine loses some of its antiplasmodial action.

Other possibilities, such as increasing the protective dosage of chloroquine to the 600 mg a week regimen, widely used in French-speaking parts of West Africa, might have been considered, since the side effects of this dosage taken for a limited time are no greater than those of the present 300 mg base dosage. Other possible drug combinations include proguanil-chloroquine and proguanil-amodiaquine.

This, then, is the present confused and unsatisfactory state of chemoprophylaxis of malaria generally and especially in Africa. Much of the confusion stems from the presence of unknown numbers of strains of *P falciparum* with different degrees of susceptibility to antimalarials, and from the virtual impossibility of constant monitoring of actual or potential resistance. The value of one drug regimen or another depends largely on the place and degree of exposure to the infection and also on another (most uncertain and fallible) factor: the compliance of the drug user. This uncertainty is compounded by the unpredictability of the side effects of present drugs taken by persons of varied age and sex, nutritional levels with different genetic characteristics, metabolic aberrations, and immunological states.

The main trouble is that the current prophylactic regimens are not based on well-established scientific criteria, such as those worked out during the second world war by Hamilton Fairley in Australia on many hundreds of volunteers from the armed Services or by the Americans and the British on civilian volunteers. Many new or amended preventive drug regimens are relics of past experience, when the susceptibility of strains of malaria parasites was different; moreover, some of our expert advice on chemoprophylaxis is derived from limited experience on groups of people whose degree of exposure to the infection was not quantified, whose adherence to the drug regimen was not supervised, and whose response to the infective challenge was often unknown.

From this brief review a few conclusions emerge: there is today no absolute guarantee of an ideal chemoprophylaxis of malaria; some drug regimens will confer a high degree of protection, others will provide at best a partial one. However small may appear our present choice of antimalarial compounds, a judicious selection of them, singly or in combination, will in most cases prevent any severe infection. In most cases, even if there is a failure of protection, prompt and adequate treatment of an acute malaria infection with, when necessary, the use of quinine with or without sulphonamide-pyrimethamine or tetracycline, will effect a rapid recovery.

Population prophylaxis

The second current dilemma is whether or not to give out antimalarial drugs to large numbers of people in tropical countries to lessen their burden of disease—with the possible risk of increasing the selection pressure on the existing mutants within the population complex of the parasite species.[44] Unfortunately, unlike the clinical microbiologist with his large choice of potent antibiotics, the malariologist has at his disposal perhaps half a dozen compounds and only a few permutations in mixing them.

A balanced approach is needed with, perhaps, some enforced limitation of drug use and careful monitoring of any change, but this has to be linked with technical, administrative, social, and political considerations. In Kenya in July 1982 the medical authorities instructed all health institutions in the country to use medicines containing pyrimethamine as reserve drugs only: practitioners found prescribing these medicines for routine treatment or prophylaxis would face disciplinary action. More emphasis needs to be given to control of malaria transmission by attack on the anopheles vector, despite the difficulties in highly endemic tropical areas.

Indeed, planning the control of malaria within a given country or area demands a good knowledge of the epidemiological features of malaria transmission locally, and this entails an understanding of the behaviour of the population concerned. The observance of some time-honoured and relatively simple methods of individual protection from mosquito bites may be of great value—measures which are now being disregarded by newcomers to tropical countries.

New drugs

In our search for new antimalarial drugs, we have not made enough progress with the evaluation of all possible compounds. The immense effort of the American Army research group

screened some 250 000 compounds and produced several possible leads.[45] Mefloquine, a new drug remarkably effective against strains of *P falciparum* resistant to many other drugs, is now undergoing extended field trials under the aegis of the World Health Organisation. Six other compounds of three aminoalcohol series are being considered.[46] Various other derivatives of previously known compounds, such as the Chinese Qinghaosu, are being developed and tested under the aegis of the WHO Special Programme for Research and Training in Tropical Diseases.

Sadly, however, the search for new antimalarials has become steadily more difficult and more expensive. The often expressed hope that better knowledge of the biochemistry of plasmodia will lead to some tailor-made, highly active compounds has not yet been fulfilled.[47] On the other hand, the development of methods of culture of *P falciparum* in the laboratory has provided a reliable and simple means for screening various strains of parasites for the presence and degree of resistance to drugs, and aotus monkeys infected with human plasmodia have proved to be of great value for testing of candidate antimalarial drugs.[48 49] Hopefully, too, a malaria vaccine may eventually open new possibilities for immunoprophylaxis of malaria.[50]

In the mean time we must use all our experience and imagination to overcome the present difficulties, which, however daunting they may be, are not beyond solution.

L J BRUCE-CHWATT

Emeritus Professor of Tropical Hygiene,
University of London,
Wellcome Museum of Medical Science,
London NW1 2BP

[1] Ross Institute. Malaria prevention in travellers from the United Kingdom. *Br Med J* 1981;**283**:214-8.
[2] Walliker D. Genetic variation in malaria parasites. *Br Med Bull* 1982;**38**: 123-8.
[3] World Health Organisation. Chemotherapy of malaria and resistance to antimalarials. *WHO Technical Report Series* 1973; No 529.
[4] Wernsdorfer WH, Kouznetzov RL. Drug-resistant malaria, occurrence, control, surveillance. *Bull WHO* 1980;**58**:341-52.
[5] Wery M, Coosemans M. Drug resistance in malaria. *Ann Soc Belg Méd Trop* 1980;**60**:137-62.
[6] Peters W. In: Kreier JP, ed. *Malaria*. Vol 1. *Epidemiology, chemotherapy morphology and metabolism*. New York and London: Academic Press, 1980:145-283.
[7] Peters W. Antimalarial drug resistance: an increasing problem. *Br Med Bull* 1982;**38**:187-92.
[8] Bruce-Chwatt LJ, Black RH, Canfield CJ, Clyde DF, Peters W, Wernsdorfer WH. *Chemotherapy of malaria*. 2nd ed. Geneva: World Health Organisation, 1981.
[9] World Health Organisation. Chloroquine resistant malaria. *WHO Weekly Epidemiological Record* 1981;**56**:143.
[10] Clyde DF. *Malaria in Tanzania*. London: Oxford University Press, 1967.
[11] Michel R. Resistance to pyrimethamine in the anti-malaria 1-zone of Thiés (Senegal). *Med Trop (Mars)* 1961;**21**:876-8.
[12] Bruce-Chwatt LJ. Resistance of P falciparum to chloroquine in Africa: true or false? *Trans R Soc Trop Med Hyg* 1970;**64**:776-84.
[13] Dennis DT, Doberstyn EB, Sissay A, Terfal GK. Chloroquine tolerance of Ethiopian strains of P falciparum. *Trans R Soc Trop Med Hyg* 1974; **68**:241-5.
[14] Armstrong JC, Asfaha W, Palmer TT. Chloroquine sensitivity of Plasmodium falciparum in Ethiopia. I. Results of an in vivo test. *Am J Trop Med Hyg* 1976;**25**:5-9.
[15] Palmer TT, Townley LB, Yigzaw M, Armstrong JC. Chloroquine sensitivity of Plasmodium falciparum in Ethiopia. II. Results of an in vivo test. *Am J Trop Med Hyg* 1976;**25**:10-3.
[16] Kousnetzov RL, Rooney W, Wernsdorfer W, El Gaddal AA, Payne D, Abdalla RE. Assessment of the sensitivity of P falciparum to antimalarial drugs in Sennar, Soudan. *WHO/Mal* 1979;79/910. (Cyclostyled.)
[17] Goasguen J, Gentelet B, Moreau JP, Fourquet R, Coulanges P. P falciparum resistant to nivaquine. *Arch Inst Pasteur Madagascar* 1975;**44**: 143-5.
[18] Center for Disease Control. Chloroquine-resistant malaria acquired in Kenya and Tanzania—Denmark, Georgia, New York. *MMWR* 1978; **27**:463-4.
[19] Fogh S, Jepson S, Effersoe P. Chloroquine resistant P falciparum malaria in Kenya. *Trans R Soc Trop Med Hyg* 1979;**73**:228-9.
[20] Kean BH. Chloroquine-resistant malaria from Africa. *JAMA* 1979;**241**: 395.
[21] Stille W. Chloroquine-resistant malaria tropica after a visit to Kenya. *Dtsch Med Wochenschr* 1979;**104**:954-5.
[22] Eichenlaub D, Pohle HD. A case of falciparum malaria with RI chloroquine resistance from the East African Comoro Islands. *Infection* 1980; **8**:90-2.
[23] Nguyen-Dinh P, Trager W. Chloroquine resistance produced in vitro in an African strain of human malaria. *Science* 1978;**200**:1397-8.
[24] Campbell CC, Collins WE, Chin W, Teutsch S, Moss DM. Chloroquine-resistant Plasmodium falciparum from East Africa: cultivation and drug sensitivity of the Tanzanian I/CDC strain from an American tourist. *Lancet* 1979;ii:1151-4.
[25] Bruce-Chwatt LJ, Peters W. Chloroquine-resistant Plasmodium falciparum in Africa. *Lancet* 1979;ii:1374-5.
[26] Aronsson P, Bengtsson E, Björkman A, Peherson PO, Rombo L, Wahlgren M. Chloroquine-resistant falciparum malaria in Madagascar and Kenya. *Ann Trop Med Parasitol* 1981;**75**:367-73.
[27] Bengtsson E, Björkman A, Brohult J, *et al*. Malaria prophylaxis when visiting areas of East Africa with chloroquine resistance. *Lancet* 1981;ii: 249.
[28] Eke RA. Possible chloroquine-resistant Plasmodium falciparum in Nigeria. *Am J Trop Med Hyg* 1979;**28**:1074-5.
[29] Aderounmu AF, Salako LA, Walker O. Chloroquine sensitivity of Plasmodium falciparum in Ibadan, Nigeria. II. Correlation of in vitro with in vivo sensitivity. *Trans R Soc Trop Med Hyg* 1981;**75**:637-40.
[30] Khan AA, Maguire MJ. Relative chloroquine resistance of P falciparum in Zambia. *Br Med J* 1978;i:1669-70.
[31] Mahoney JL. Malaria, breakthroughs and resistance to chloroquine in Africa: case reports. *S Afr Med J* 1981;**60**:786-8.
[32] Centers for Disease Control. Chloroquine-resistant Plasmodium falciparum malaria acquired in East Africa—Pennsylvania. *MMWR* 1981;**30**:525-6.
[33] Faehlmann M, Rombo L, Hedman P. Serum concentrations of chloroquine in a patient with a late recrudescence of Kenyan Plasmodium falciparum malaria. *Trans R Soc Trop Med Hyg* 1981;**75**:362-4.
[34] Gardner AL, Weinstein RA, Lincoln L. Failure of chloroquine prophylaxis in Plasmodium falciparum from East Africa. *JAMA* 1981;**246**: 979-80.
[35] Petterson T, Kyrönseppä H, Pitkänen T. Chloroquine-resistant falciparum malaria from East Africa. *Trans R Soc Trop Med Hyg* 1981;**75**:112-3.
[36] Varnai F, Banhenyi D, Miskovitz M. Chloroquine resistant malaria imported from Tanzania. *WHO/Mal* 1981;81/943. (Cyclostyled.)
[37] Hall AP. Quinine by intravenous infusion for falciparum malaria. *Br Med J* 1982;**285**:439.
[38] Markwalder KA, Meyer HE. Possible sulfadoxine-pyrimethamine resistance in Plasmodium falciparum malaria from Kenya. *Trans R Soc Trop Med Hyg* 1982;**76**:281.
[39] Stahel E, Degrémont A, Lagler U. Pyrimethamine sulfadoxine resistant falciparum malaria acquired at Dar es Salaam, Tanzania. *Lancet* 1982; i:1118-9.
[40] Timmermanns PM, Hess U, Jones ME. Pyrimethamine sulfadoxine resistant falciparum malaria in East Africa. *Lancet* 1982;i:1181.
[41] Herzog Ch, Lambert HP, Maudgal D, Warhurst DC, Rogers HJ. Pyrimethamine-dapsone resistant falciparum malaria imported from Kenya. *Lancet* 1982;i:1119-20.
[42] Nguyen-Dinh P, Spencer HC, Chemangey-Masaba S, Churchill FC. Susceptibility of Plasmodium falciparum to pyrimethamine and sulfadoxine/pyrimethamine in Kisumu, Kenya. *Lancet* 1982;i:823-5.
[43] Centers for Disease Control. Prevention of malaria in travellers—1982. *MMWR* 1982;**31**, suppl.
[44] Geddes AM. General antimicrobial prescribing. Introduction. *Lancet* 1982;ii:82.
[45] Canfield CJ, Heiffer MH. The US Army drug development programme. In: Adolphe M, ed. *Advances in pharmacology and therapeutics*. Vol 10. Oxford: Pergamon Press, 1978.
[46] Canfield CJ. Antimalarial aminoalcohol alternatives to mefloquine. *Acta Trop (Basel)* 1980;**37**:232-7.
[47] Howells RE. Advances in chemotherapy. *Br Med Bull* 1982;**38**:193-9.
[48] Schmidt LHP. Plasmodium falciparum and Plasmodium vivax infections in the owl monkey (Aotus trivirgatus). I. The courses of untreated infections. *Am J Trop Med Hyg* 1978;**27**:671-702.
[49] Schmidt LH. Plasmodium falciparum and plasmodium vivax infections in the owl monkey (Aotus trivirgatus). III. Methods employed in the search for new blood schizontocidal drugs. *Am J Trop Med Hyg* 1978; **27**:718-37.
[50] Cohen S. Progress in malaria vaccine development. *Br Med Bull* 1982;**38**: 161-5.