CHLOROQUINE-RESISTANT FALCIPARUM MALARIA IN MALAYA*

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From the clinician's point of view *Plasmodium falciparum* is the most important of the malaria parasites of man since it causes the most severe symptoms and has the highest mortality rate, being responsible for 87.3 per cent of deaths from malaria in Malaya. Chloroquine has remained the drug of choice in the treatment of the acute malaria attack especially after it was shown that falciparum malaria could become resistant to paludrine and pyrimethamine and that mepacrine could produce disconcerting side effects.

Although it has no effect on the sporozoites, the pre-erythrocytic cycle or the gametocytes of *P. falciparum* chloroquine is highly effective against the asexual blood forms and produces not only a clinical cure but also radical cure. The dose recommended by WHO (1955) for an adult weighing 70 kg. is 600 mg. on the first day followed 6 hours later with a "loading dose" of 300 mg. and daily for the next two days of 300 mg. of chloroquine base. Fever generally comes down within 24 hours and parasites disappear from the blood stream in from 2 to 3 days' time. Chloroquine is also an excellent suppressive drug against *P. falciparum* and if it is continued to be taken for 3 or 4 weeks after exposure to infection it results in suppressive cure. The recommended suppressive dose is 300 mg. once a week.

DRUG-RESISTANCE IN MALARIA

It may be profitable at this stage to consider what is meant by drug resistance in malaria and how it may be brought about. It may be briefly defined as the ability of a species of malaria parasite, or a strain of it, to tolerate drugs in concentrations which would normally destroy it. A particular strain of a species of *Plasmodium* may be inherently non-susceptible to the drug in question. If this strain was the only one in a country, the inability of the drug to affect the course of the disease in the normal way would become evident very early. If this resistant strain, however, was present in the same area together with normal sensitive strains its presence may not become evident until after exposure to the drug for a certain length of time. In this case, the drug sensitive strains would tend to die out as the result of vigorous treatment leaving untouched the resistant strain which would establish itself as the dominant strain in the area. It is also conceivable that as a result of intermittent exposure to the drug in small doses over a period of time the malaria parasite alters its metabolism and develops the ability to withstand higher and higher doses of the drug in question. It is also possible for mutant strains which are drug-resistant to arise spontaneously or be induced by pressure of exposure to the drug and survive by selection as a result of the continued use of the drug.

Cross resistance or the transferability of resistance developed to one drug to another drug does occur. It is likely to be more pronounced in the case of drugs which have a similar chemical formula and whose mode of action on the parasites is the same. Thus, it would be natural, for instance, to expect a chloroquine-resistant strain to be cross resistant to other drugs related to the 4-amino-quinolines such as amodiaquine, and mepacrine.

CHLOROQUINE-RESISTANT FALCIPARUM MALARIA

Chloroquine has generally been regarded as not inducing drug resistance until Moore and Lamar (1961) and Young and Moore (1961) showed the existence in Columbia, S. America of a strain of *P. falciparum* which responded poorly to normal and even above-normal doses of this drug. There had been no previous administration of chloroquine in this locality and the drug resistance to this drug was evidently not an acquired phenomenon.

Later, Rodrigues (1961) and Box *et al* (1962) independently reported similar resistance as occurring in Brazil, S. America. As long as these reports of drug resistance were isolated and from distant countries they made no serious impact on us.

Last November, at the Unesco Symposium on Tropical Parasitology held in Singapore Dr. (Mrs.) Harinasuta of the University of Medical Sciences, Bangkok described several cases of

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falciparum infection from different parts of Thailand in which relapses occurred at about 12 days' interval in the absence of reinfection in spite of treatment with high doses of chloroquine. The presence of a chloroquine-resistant falciparum strain in Thailand has since been confirmed by transmission to volunteers by Young *et al* (1962).

Last October, seven members of the staff of the U.S. Pub. Health Service Research Team and the Institute for Medical Research went to the Paillin area of W. Cambodia on a field study of malaria. Three of them came down with falciparum malaria in spite of having taken prophylactic chloroquine and two of these relapsed thrice at about two-week intervals in spite of full dosage of chloroquine at each attack. Details of these cases are being reported in the medical press by Eyles *et al.*

More recently, there have been cases of falciparum malaria contracted in N. Perlis, near the Thai border, which relapsed in the same manner after chloroquine treatment. A team from the Institute for Medical Research and the U.S. Public Health Service Research Unit went to this area and found malaria incidence in some kampongs as high as 50 per cent with *P. falciparum* the most prevalent species. *A. balabacensis balabacensis* has been incriminated as one of the Malayan vectors of malaria for the first time. A report on this survey will be published in the local medical press shortly by Sandosham *et al.*

MEETING TO REVIEW EVIDENCE FOR CHLOROQUINE RESISTANCE IN S.E. ASIA

With the permission of the Director of Medical Services I convened at the Institute for Medical Research on December 1st 1962 a meeting of those likely to be able to throw light on this problem and Dr. J. W. Field, C.M.G. presided. I feel that the deliberations of the meeting will be of interest to the Physicians of this country who in turn will be in a position to help confirm the findings and prevent the general spread of this strain. The evidence for the existence of a chloroquine resistant strain of *P. falciparum* was sifted and the meeting agreed that there was a clear indication that we were confronted with a problem although it was not possible to assess how serious it was.

CRITERIA OF RESISTANCE

On the subject of the criteria that should be adopted in establishing that drug resistance was present the meeting summed up the position as follows: "A tolerance in malaria parasites to drugs which normally destroy them may range from a minor loss of sensitivity to a resistance so marked that the organisms tolerate doses which endanger the host. Reports of resistance should hence give some indication of the degree. There should also be safeguards against error. The criteria of resistance to chloroquine in *Plasmodium falciparum* provisionally accepted by the Committee are:

I. Appearance of asexual parasites in blood films, with or without fever, after one month or more of suppressive therapy at W.H.O. dosage (0.3 gm. base weekly), the administration of the drug having ceased.

II. Clinical or parasitological 'break-through' while the drug is being taken at W.H.O. suppressive dosage.

III. Relapse of infection after treatment of acute attacks at W.H.O. dosage (at least 1.5 gm. base in 3 - 5 days).

IV. Persistence of fever for more than 72 hours, or of asexual parasites in blood films for more than 86 hours after the start of therapy at W.H.O. dosage for acute attacks.

V. A rising asexual parasitaemia during the W.H.O. standard course of therapy.

Before reporting a possible resistance, medical officers should be reasonably sure (a) that the drug has been taken, and (b) that for I and III fresh infection can be excluded. For IV and V, blood films should be examined daily, and where possible the urine should be examined daily for the presence of chloroquine. Observation in hospital, with clinical and parasitological 'follow-up' should be arranged when practicable for patients carrying a falciparum strain suspected to be resistant".

ALTERNATIVE DRUGS

It was felt that where there was a possibility of resistant strains to chloroquine it was advisable to use a combination of drugs. The Cambodian strain was resistant to chloroquine and pyrimethamine and the Malayan strain has been shown (Field and Edeson, 1949) to be resistant to proguanil (paludrine) and is probably resistant also to pyrimethamine.

PRECAUTIONS TO BE TAKEN BY THOSE FROM ENDEMIC AREAS

It was agreed that everything should be done to prevent the establishment of the chloroquine-resistant strain of *P. falciparum* in the rest of

the country. There should be insistence on the continuation of drug prophylaxis for an adequate length of time after the return and on the strict adherence to the regimes of personal prophylaxis to prevent infecting mosquitoes.

COMMITTEE TO KEEP A WATCHING-BRIEF

It was unanimously agreed that a Standing Committee should be set up to operate informally within the orbit of the Malaria Advisory Board and keep a watching-brief on the situation. The Committee was formed with Dr. J.W. Field as Chairman, and Professor A.A. Sandosham as Secretary and representatives from the Federation Armed Forces, the Commonwealth Army, U.S. Army Research Unit, U.S. Public Health Service Research Unit, World Health Organization, Institute for Medical Research and the Malaria Eradication Pilot Project as members.

YOUR RESPONSIBILITY

As Senior Physicians of the State Hospitals of the country you will be in a better position than most medical practitioners to keep a lookout for the existence of this resistant-type of falciparum infection. A careful clinical and parasitological follow-up of all falciparum cases should help. It may be more widespread than we are aware of. The Committee welcomes any observations you may make on this problem and on our part we will give you any assistance you may need regarding examination of blood, urine etc. The spreading of the chloroquine-resistant strain of *P. falciparum* to the rest of the country may have serious consequences as we already have paludrine-resistance in Malaya and pyrimethamine-resistance in Cambodia and probably Malaya also. We may be forced to go back to quinine as a last resort as we have had to do with our relapsing falciparum infections contracted in Cambodia.

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