ORIGINAL ARTICLES

POSSIBLE CHLOROQUINE RESISTANT MALARIA IN ZAMBIA

B. HIMPOO, M.B.,CH.B.(Rand)
Mine Medical Officer

and

J. B. MacCALLUM, M.B.CH.B.(EDIN.)
Government Medical Officer
Broken Hill General Hospital

In the fight against malaria the synthetic anti-malarials were greeted with great hopes. However, since their introduction there has been the disturbing evolution of strains of malaria resistant to them. In 1947 resistance was reported to proguanil in Malaya and the Far East. In 1954 pyrimethamine resistance was reported in Kenya and afterwards in West Africa, South America and the Far East (Jones 1954, Lasch and N’Guyen 1965, W.H.O. Tech. Ser. 266). The devaluation of these potent prophylactic drugs was to be regretted, but far more alarming was the emergence of resistance to chloroquin. This was first reported in 1961 when, in Columbia, strains of Plasmodium falciparum were discovered to be resistant to therapeutic doses of chloroquin. Later it was reported in the Far East and more recently in West and Central Africa (Harinas uta et al. 1965).

The size of the problem can be gauged from the report (Montgomery and Eyles) in 1962 of 10% evidence of resistance in Commonwealth troops in Malaya, and in 1963 Contactos et al. confirmed that 4 out of 5 Asian strains suspected of resistance were definitely resistant to chloroquin in normally curative doses.

In Central Africa the first report of malarial resistance to chloroquin came in 1966 from Malawi (Stevenson 1966) and we would like to report on a further three cases that we feel may well come under this category. These cases were all observed in the latter half of 1966 at the General Hospital in Broken Hill, Zambia.

CASE I

The first patient was a European male aged 25 who complained of fever, sweats, headache, and generalized aches and pains. He lived in Broken Hill, but a fortnight prior to the onset of the illness he had been fishing in the Lukanga Swamps, some 30 miles west of Broken Hill. He said he had been badly bitten by mosquitoes there and it was suspected he may have been infected there. He had had malaria previously, On examination the only significant findings were the pyrexia and sweating. An oral chloroquin course of 600mg at once followed by 300mg in 6hrs. and 300mg daily for two days was prescribed after identification of malarial parasites. Two days after the completion of the course the patient still manifested signs of profuse sweating and an occasional pyrexial paroxysm. After identification of parasites in a blood smear, chloroquin 5ml intramuscularly for three doses at eight-hourly intervals was given. The temperature persisted. After 72hr. with no response a course of quinine was started with a careful watch on his temperature, blood pressure, and urine. He received 300mg of quinine hydrochloride four times a day. After three doses of quinine the temperature responded and the patient discharged after the full ten-day course.

CASE II

The second patient was an African female aged about 30 and 36 weeks gravid. She had attended a rural clinic with generalized aches and had received an injection, possibly of chloroquin, but not feeling any better had attended the hospital out-patients clinic. Her complaints were of a stiff neck, fever, headache, and generalized pains. She said she had not been out of Broken Hill in the past two years. On examination she was pyrexial-104F with marked neck stiffness and a positive Kernigs sign. A lumbar puncture was performed and clear fluid under normal pressure was obtained. The fluid chemistry was normal and the cell count was 6 per cu. mm. A blood slide showed a heavy infestation with plasmodium falciparum. She was given an intramuscular course of chloroquin. Despite this she showed signs of a continued infection with persisting fever and symptoms. She was given an oral chloroquin course two days later. The temperature persisted and a full blood count was performed, a chest X-ray taken, her Widal measured, and urine inspected. Apart from the blood count these showed no abnormality. The blood picture gave a haemoglobin of 65%, white-cell count of 10,700 per cu. mm. and an occasional malarial trophozoite. She was started on a therapeutic regime of proguanil with a daily check blood slide. This appeared to have no effect on the pyrexia nor on the blood slide in which malarial trophozoites persisted. At this stage she was delivered of her child. It was a normal vertex delivery of a male child, who was in good health. There was very little blood loss. As she was rather ill she was given prophylactic penicillin cover in the puerperium. A blood culture was taken before it started and the report came back later as sterile. Another chloroquin course was given. She remained very ill and a further blood picture revealed a drop in haemoglobin to 38% and persisting trophozoites. She was given packed cells to restore her red cells and was started on an oral quinine course, in the first instance a sub optimal dosage to test her sensitivity. A very careful watch was kept on her urine and blood pressure. The blood slides taken after the initiation of the course were all negative and the pyrexia responded at once to the curative dosage of quinine. After a full course she was discharged well and at review two weeks later she remained in good health. A repeated blood picture showed a haemoglobin of 70% and a negative slide.

CASE III

The third patient was an African female aged 15 who came from a village 15 miles outside Broken Hill.
from which she had not moved in several months. She presented with a severe diarrhoea and a headache of three days' duration. She had been hospitalized with a severe attack of malaria the previous year. On examining her she was found to have a palpably enlarged spleen a suspicion of jaundice, some neck stiffness, and a temperature of 102F. She was dehydrated. The dehydration was corrected. A blood slide was found positive and a lumbar puncture showed normal cerebrospinal fluid. A chloroquin course was given by the intramuscular route. The temperature was reduced to 100F but she remained ill and a repeat blood slide three days later showed persistent trophozoites. She was given a course of quinine to which she responded immediately. Her haemoglobin on admission was 58% and this fell over the three days to 36%. She also was given packed cells after the response to treatment of her malaria.

DISCUSSION

The diagnosis of a chloroquin-resistant malaria must depend on the definite diagnosis of malaria after an adequate course of chloroquin treatment and, if possible, the laboratory isolation of the parasite and confirmation of its resistance. The mere prescription of a course of chloroquin is not sufficient to imply that a therapeutic course has been given, as besides the risk of an unreliable patient there is the risk of loss of the drug in vomitus or faulty absorption from the gut. It was for this reason that the first man was admitted to hospital. In hospital there can be supervision of the patient in the taking of the tablets and observation of any episodes of vomiting, but the problem of faulty absorption remains and it is for this reason that the injection is given to the hospital in-patient. Ideally one should test the urine during a course of treatment to be sure that chloroquin is getting into the circulation but we could find no reference to any method of doing this. We feel that the parenteral route in these cases should have delivered sufficient of the drug.

The diagnosis of malaria depended on the identification of the parasite in blood smears. In most cases this was in thin smears which were used to confirm the type of parasites also. The common parasite in the district is the falciparum and we have not seen any other type diagnosed in the hospital. Abnormal trophozoites have been seen in the smears of patients in the hospital after and during a chloroquin course, but these have responded to chloroquin tablets for three days after the course. Trophozoites are said to persist in the blood for several days after an adequate course of chloroquin treatment and gametocytes can persist for a number of weeks. These persistent parasitaemias should not be associated with a pyrexia. However, the pyrexia could have been due to some other cause, a factor which was only really investigated in the second case in which the diagnosis of chloroquin resistance was avoided as long as possible. In the other two cases the first one so obviously had clinical malaria that the diagnosis was far more readily entertained and the third coming within a couple of months after the second and starting with a rather low haemoglobin we felt justified in starting the quinine rather early. In all three cases it was the full blood count that was being done as the first step of an investigation of a P.U.O., which drew our attention to the persistent parasitaemia. As is usual, the chloroquin had been given 72 hr. to act before further investigations were begun. The persistent pyrexia and the persistent parasitaemia thus led us to suspect that we were dealing with a malaria refractory to chloroquin therapy, but we feel that the dramatic responses to quinine confirmed our tentative diagnoses.

The mechanisms of resistance of plasmodia to drugs has not been satisfactorily elucidated but it is thought that it may be the selection of drug-fast strains induced by spontaneous mutation. In this case it is probable that all over the world in malarious zones chloroquin resistance is bound to evolve and the more the use of chloroquin the more the likelihood of the development of the chloroquin-resistance problem.

The use of chloroquin in the treatment of the confirmed case of malaria must be admitted to be proper, but unfortunately chloroquin is often misused. In this country there appears to be the practice of treating any pyrexia with firstly a dose of chloroquin, which is justified by the arguments that malaria is the most common cause of pyrexia and that the parasite is not always visible in the blood slide. Although this is true it may be worth while to reconsider this in the light of the potential devaluation of a potent and useful drug. In a country in which there are adequate medical and laboratory facilities this problem will not arise. The other doubtful use of chloroquin is as a prophylactic drug. Since in this country there has not been any report of any resistance to either of the standard prophylactics, namely proguanil and pyrimethane, it would seem unnecessary to use this drug for this purpose. As MacDonald (1965) points out, the development of resistance will be extremely serious for the treatment and eradication of malaria, and he felt that this use of chloroquin as a prophylactic could only aggravate the problem. For this reason we in Zambia could well take his advice to heart and use this, at present, valuable drug only in its field of proven worth, namely, the treatment of proven cases of malaria.

ACKNOWLEDGMENTS

We wish to thank Dr. M. M. Nalumango, Permanent Secretary, Ministry of Health, for permission to publish this report.

REFERENCES

The relatively frequent occurrence of multiple pregnancies in Zambia and the paucity of literature on the incidence and etiology of multiple births in the African prompted this investigation.

**MATERIAL AND INCIDENCE**

The material for this study includes every patient with multiple pregnancy who was admitted to the non-paying wing of the Obstetric Unit during 1966, either in labour or subsequent to delivery of one or more infants outside the Unit. Over the 12-month period there were 151 cases of twins and 4 cases of triplets in a total of 5,654 maternities. The hospital incidence of multiple pregnancy, therefore, is 1 in 37 for twins and 1 in 1,414 pregnancies for triplets. Because this is the only maternity unit in the region and an established district midwifery service is non-existent, there is no selection of patients and all cases are admitted. Consequently the true incidence is probably close to if not higher than the hospital incidence. Stocks (1952) gives the following figures for England and Wales which compare closely with those from Canada and the United States (Percival, 1959): twins 1 in 83 and triplets 1 in 10,050.

It is evident from Table I that the incidence of multiple births is considerably higher in the African than in Whites.

**TABLE I. INCIDENCE OF MULTIPLE PREGNANCY**

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Country</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debb, R. G.</td>
<td>1960</td>
<td>Nyasaland</td>
<td>1 in 32</td>
</tr>
<tr>
<td>Knox and Morley</td>
<td>1960</td>
<td>Nigeria</td>
<td>1 in 19</td>
</tr>
<tr>
<td>Farrell</td>
<td>1964</td>
<td>Natal</td>
<td>1 in 28</td>
</tr>
<tr>
<td>Lucas and Hassim</td>
<td>1966</td>
<td>Lusaka</td>
<td>1 in 37</td>
</tr>
<tr>
<td>Registrar General</td>
<td>1959</td>
<td>England &amp; Wales</td>
<td>1 in 84</td>
</tr>
</tbody>
</table>

**Maternal complications of multiple pregnancy.**

1. **Toxaemia of pregnancy.**

   This occurs more commonly in association with multiple than with single pregnancies. Bender (1952) in 472 cases of twin pregnancies reported an incidence of 24% compared to 6.4% in single pregnancies. In the present series 32% of cases were found to have at least 2 out of 3 signs of pre-eclampsia (hypertension, oedema, albuminuria). This high incidence is partly due to the almost complete lack of antenatal care in the majority of cases. Only 60% attended a clinic on one or more occasions. In 33 cases at least 1 twin was delivered outside hospital. Although pre-eclampsia is a common association it is of a milder form. This is in agreement with other workers (Percival, 1959).

2. **Hydramnios.**

   Moderate to gross hydramnios was clinically diagnosed in 8% of cases. Figures vary between 1.6% (Seski and Miller, 1963) and 12.5% (Farrell, 1964). Hydramnios occurred with equal frequency in mono- and dizygotic twins, other reports give a much higher incidence in the case of monozygotic twins. In no case was it found necessary to induce labour for the relief of symptoms.

3. **Ante-partum haemorrhage.**

   The incidence of accidental haemorrhage was not higher compared to single pregnancies. Placenta praevia, generally considered commoner in twins because of the larger placental area which may encroach on the lower segment, was in fact met with less commonly in the authors' series.

4. **Anaemia.**

   Anaemia is still one of the most important