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Observations on an Apparent Chloroquine-resistant Strain of *Plasmodium falciparum* in West Africa

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Since their development as synthetic antimalarial drugs during the second world war the 4-aminoquinolines have enjoyed a role of expanding importance throughout the world and are now regarded as the drugs of choice, both for suppression and for therapy, in malaria (Coatney, 1963). Though resistance of human plasmodia to pyrimethamine and proguanil has long been known, the recognition of 4-aminoquinoline-resistant strains of *Plasmodium falciparum* is of relatively recent occurrence. Since 1961, strains showing abnormal response to chloroquine have been reported from Colombia (Young and Moore, 1961; Young, 1962; Moore and Lanier, 1963; Powell et al., 1963), and Brazil (Rodrigues Da Silva et al., 1961; Box et al., 1963) in South America, and from Thailand (Young et al., 1963), Vietnam (Powell et al., 1963), Cambodia (Contacos et al., 1963), and Malaya (Montgomery and Eyles, 1963; Sandosham et al., 1963) in South-east Asia. To date, chloroquine resistance, though suspected (Chemotherapy of Malaria,

1961), has not been reported from the African Continent, where the use of chloroquine as an antimalarial drug is widespread.

In this paper we report the results of some observations which, while not pretending to furnish an absolute and final proof of resistance of *P. falciparum* to chloroquine, do tend to strengthen suspicion of its existence. These observations lead us to believe that there exists in this part of West Africa (Upper Volta) a strain or several strains of *P. falciparum* less sensitive to chloroquine than usually admitted.

Material and Methods

The present report is based on a study of 15 patients from Upper Volta, West Africa, who either developed malignant tertian malaria while taking chloroquine sulphate (Nivaquine) as a suppressive (nine cases) or failed to respond to treatment by this drug or by chloroquine phosphate (Aralen) (six cases).

The patients were children hospitalized in the paediatric ward of the Ouagadougou Hospital. All are African children

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who have lived only in the central part of Upper Volta, and it may be safely presumed that their malaria infections were locally acquired. Doses were directly given by responsible nursing personnel under medical supervision. The stomach-tube was used when the children could not take the drug orally or when they were uncooperative. In two cases the chloroquine was given intramuscularly. Urines were collected and tested to detect the presence of chloroquine by the method described by Wilson and Edeson (1959). All slides were personally examined by one of us. (T. L. N.).

Part I—Failure of Suppressive Therapy

The routine at the Ouagadougou Hospital calls for chloroquine to be administered as a suppressive to all children admitted to the paediatric ward. The drug is given daily, and because of the lowered resistance of the sick children the dosages used exceed those usually recommended for suppressive treatment in the young. A generally accepted regimen of suppressive therapy in healthy children calls for 25 mg.¹ of chloroquine every other day until 1 year of age, 33 mg. daily at 1 to 3 years, 50 mg. daily at 4 to 6 years, and 75 mg. at 7 to 12 years; but at the Ouagadougou Hospital children up to 2 years of age receive 50 mg. daily; children of 2 to 5 years receive 75 mg., and those over 5 years receive 100 mg. daily. These are the doses given routinely, but they are not always followed to the letter, all depending on the particular patient.

All patients in our series were admitted to the hospital for treatment of diseases other than malaria. In one case (No. 9) there was an associated malaria on admission, and it is probable that subclinical infection with *P. falciparum* was present in at least some of the other children.

As Table I shows, all nine children received regular daily doses of chloroquine sulphate for periods ranging from 6 to 55 days before developing a typical attack of malaria. These children were free of fever for several days or several weeks before the attack. Blood smears were taken at the time of the attack. Asexual parasites of *P. falciparum* were found in all patients. In cases 8 and 9 a qualitative test for chloroquine in the urine, with the method of Wilson-Edeson, was carried out at the time the blood smears were taken. These two urine tests were positive, indicating that the drug had been absorbed.

When malaria was diagnosed each child was treated with therapeutic doses of quinine or amodiaquine, or a combination of the two. Temperatures dropped promptly, clinical signs abated, and blood smears were negative for parasites within 24 to 72 hours.

Discussion

The absorption of chloroquine is known to be relatively complete and rapid when the drug is taken by mouth, and its suppressive effect appears early. Yet seven out of nine patients

¹ All quantities are expressed in chloroquine base.

developed malaria, confirmed by a thick blood smear, after having regularly received the drug in daily doses for periods ranging from 15 to 55 days.

Explanations of apparent "breakthroughs" must take into account a number of variables: irregularity of drug-taking underdosage, intercurrent gastro-intestinal illness interfering with absorption of the drug, unusually great exposure to infection, fatigue and generally lowered host resistance from whatever cause, including climatic and altitude changes, the presence of resistant strains of malaria parasites, or other unknown factors (Bruce-Chwatt and Horn, 1958).

As it is notoriously difficult to be certain of the good faith of out-patients about taking suppressive medication, many of the so-called "breakthroughs" result probably from failure to take the drug regularly. However, it was possible to eliminate this variable as all the patients were in hospital and were under the direct supervision of the medical and nursing staff of the paediatric service. The drugs were personally administered by responsible nursing personnel, and in cases of vomiting or spitting the drug was administered by stomach-tube.

Malabsorption of the drug from the gastro-intestinal tract may accompany diarrhoeal and nutritional diseases. Children with diarrhoea or evidence of malabsorption were therefore excluded.

The positive urine tests confirm the absorption of the drug in at least two of the nine patients.

It is possible that these attacks of malaria may represent the relapse of an existing infection rather than a new infection or reinfection. However, the dosages of chloroquine given were large and were continued for a long period, presumably producing blood levels that should have eradicated any pre-existing infection. Cases 2 and 7 because of their amoebiasis received more than therapeutic doses for 17 and 6 days respectively; Case 9 because of the malaria infection on admission received very high doses for 37 days; and Cases 3 and 8 received high dosages by error. With dosage levels of this magnitude the question of reinfection *versus* relapse becomes academic: the chloroquine failed to suppress the attack of malaria.

Another possibility that must be excluded is the lowered resistance of children ill enough to require admission to hospital: could this have permitted these "breakthroughs"? Here it is significant to note that all the children responded satisfactorily to other antimalarial drugs administered in therapeutic dosages; this suggests that general debilitation and lowered host resistance did not play an important part.

Part II—Failure of Treatment

The drug chiefly used in the Ouagadougou Hospital for the treatment of malaria is Nivaquine (chloroquine sulphate), and dosages are based on those recommended by Schneider (1960).

According to this schedule children up to 1 year of age should receive 100 mg. of the drug daily for two days and 50 mg. daily for the next three days; those aged 1–3 years should receive 150 mg. daily for two days and 100 mg. daily

TABLE I.—Daily Doses of Chloroquine (Base), Duration of Suppressive Regimen Prior to Onset of Malaria, and Treatment of the Attack

Case No.	Diagnosis on Admission	Age (Years)	Weight (kg.)	Chloroquine (Base) (mg./day)	Suppressive Therapy before Onset of Parasitaemia (Days)	Average Daily Dosage of Chloroquine (mg./kg./day)	Treatment of Breakthrough			
							Drug Used	Quantity (mg./day)	No. of Days	Result
1	Urinary infection ..	6/12	4.9	50	55	10.2	Quinine	100	3	Cure
2	Amoebic abscess, liver ..	1½	9.3	200	17	21.5	Amodiaquine	100	1½	"
3	Abscess, axilla ..	10/12	7.4	100	10	13.5	Quinine	200	3	"
4	Typhoid ..	11	25.5	100	27	3.9	Amodiaquine	100	1½	"
5	Pyrexia of unknown origin ..	7/12	7.5	50	15	6.6	Quinine	300	2	"
6	Urinary infection ..	6/12	5.1	50	22	9.8	Amodiaquine	150	3	"
7	Amoebiasis ..	9	200	200	6	22.2	Quinine	100	1½	"
8	Tropical ulcer ..	2	8.5	100	18	11.7	Quinine	200	3	"
9	Malnutrition with associated malaria on admission	3	8.5	200 × 2 days 100 × 35 "	37	12.8	Amodiaquine	200	3	"
							Quinine	100	2	"

for the next three days; and those aged 4–6 years should receive 200 mg. daily for two days and 150 mg. daily for the following three days. The dosage for intramuscular therapy is 5 mg./kg. body weight, given once or twice daily.

As in suppression, also in treatment, the dosages advocated are not always followed to the letter. In certain instances the initial doses are higher than the recommended ones, and are often continued for more than two days, all depending on the particular patient. The intramuscular dosages, on the other hand, are rigorously maintained. Four of the six patients were admitted to hospital because of malignant tertian (*falciparum*) malaria. Two were admitted for other reasons (Case 12 for lobar pneumonia and amoebiasis, and Case 13 for bronchopneumonia). Both of them had associated malaria.

As can be seen in Table II all patients received therapeutic doses of chloroquine for the usually prescribed number of days or more. Case 11 received the initial treatment intramuscularly because he was unconscious on arrival, and in Case 15 oral treatment was changed to a parenteral one, as owing to intractable vomiting there was some doubt concerning absorption of the chloroquine. Five out of six patients apparently reacted well to the treatment and were put on a preventive maintenance regimen at the end of it—a regimen which was usually higher than the prescribed one—but all of these patients relapsed soon afterwards, Case 10 even twice. All relapses but one could be controlled finally by treatment with quinine and amodiaquine. In Case 11 the relapse could not be controlled and the patient died.

In Case 14 there was no reaction whatsoever to treatment with chloroquine, and quinine had to be used to control the infection.

Blood smears were taken from all patients on admission, at the end of the treatment, and when a relapse was suspected to have occurred. All slides were examined personally by one of

us (T. L. N.) and in all patients asexual parasites of *P. falciparum* were present. Urine examinations for chloroquine were found to be positive in five out of six patients, proving that the chloroquine had been absorbed.

Discussion

Young and Eyles (1963) have listed certain conditions that should be fulfilled in order to detect if the parasites are resistant to chloroquine when *P. falciparum* fails to respond to it. The drug should be in good condition, medication should be given under supervision, and the patient be observed to swallow the drug and to have retained it. Blood smears should be taken and examined for density of parasites by a qualified technician. We believe these criteria have been met in the six reported cases. The drugs were stored under good conditions in a central warehouse, were used within a few months, and were given under the direct supervision of qualified staff. Laboratory facilities for the determination of plasma levels were not available, but the urine was tested in five patients and found to be positive for chloroquine. While this does not necessarily show the blood-level concentration, it does show that the drug has been absorbed from the intestinal tract. In Case 15 the drug was given intramuscularly. As it is well known that chloroquine is rapidly absorbed from the tissues, it can safely be postulated that, in this case at least, a satisfying blood level had been reached.

Blood smears were taken and the number of parasites per high-power field (oil-immersion) were counted by one of us at the beginning of treatment, at the end of it, and when it was suspected that treatment had failed or a relapse had occurred.

These conditions having been fulfilled, how do our cases compare with what has been thought to be the normal response of *P. falciparum* to treatment?

TABLE II.—Clinical and Parasitological Signs and Treatment

Case No.	Diagnosis on Admission	Age (Years)	Weight (kg.)	No. of Trophozoites per H.P.F.*	Initial Treatment			No. of Days	Response		Maintenance Suppressive Treatment (Nivaquine)	
					Drug Used	Method of Administration	Quantity (mg. Base/Day)		Clinical	Parasites No. per H.P.F.	mg. of Base/Day	No. of Days
10	Cerebral malaria ..	2	10	2–3	Nivaquine†	Oral	200	4	Temp. normal 4th day	Thick smear neg. 4th day	100 50	3 5
11	„ „ ..	3/12	5	4–6	Aralen‡ Nivaquine	I.M. Oral	30 100	1st dose 5	Temp. normal 3rd day	Thick smear neg. 3rd day	50	3
12	Malaria, amoebiasis/pneumonia lobar	5	15	7–9	Nivaquine	Oral	200	8	Temp. normal 8th day	Thick smear neg. 8th day	200	2
13	Bronchopneumonia, malaria	5/12	5.8	2–3	„	„	150	5	Temp. normal 4th day	—	100 50	9 6
14	Malaria	3 7/12	11.8	3–4	„	„	200	7	No response	4–5 7th day		
15	„	3/12	4.5	2–3	Nivaquine Aralen	Oral I.M.	50 50	7 5	No response Temp. normal 5th day	Thick smear neg. 5th day	50	2

TABLE II.—continued

Case No.	Relapse					Urine Examination for Chloroquine	Treatment of Relapse and/or Final Treatment			Final Outcome
	Yes	No	Which Day after Admission	Clinical Signs	Parasite Examination (No. per H.P.F.)		Drug Used	Quantity (mg./Day)	No. of Days	
10	(1) +		12	Temp. 39° C.	More troph. than on admission (4-5)	Pos.	Nivaquine	150	4	Not known§
	(2) +		16	Temp. 38.4° C.			Quinine	400	2	
11	+		9	Cerebral malaria (Temp. 38.6° C.)	5-6	„	Nivaquine Quinine	100 100	1	Died
12	+		10	Temp. 39.5° C.	4-5	„	Quinine Amodiaquine	300 200	3	Recovered
13	+		20	Temp. 39.1° C.	2-3	„	Quinine	100	3	„
14		+				„	„	400	3	„
15	+		15	Temp. 38° C.	3-4	—	Quinine Amodiaquine	100 100	3	„

* High-power field (oil-immersion). † Chloroquine sulphate. ‡ Chloroquine phosphate. § Left hospital against medical advice.

The curative action of chloroquine is usually thought to be very rapid; in the 46 cases summarized by Jeffery *et al.* (1956) 61% were clear of parasites in two days, and only two showed a parasitaemia five days after treatment. Symptoms abated even more rapidly, and in no case did a fever over 38° C. persist after two days of treatment. Young and Eyles (1963) give criteria for detecting resistance of *P. falciparum* to chloroquine. In their opinion prime evidence of resistance to the drug is the persistence of fever 72 hours after the beginning of treatment, a higher parasitaemia after 48 hours than before treatment, and the occurrence of parasites in the blood-stream after six days. If we apply these results and criteria to Case 14 we see that resistance of the infection to the drug was very probable, because not only had the fever not abated after seven days of treatment and after double the usual dose of chloroquine, but the parasitaemia was higher than before.

The second problem is that of relapse. If we again cite Jeffery *et al.* (1956) we see that among his cases only one out of 46 who received the normal dosage relapsed, and only three relapsed of the 18 patients who had received a single dosage of 400 mg. intramuscularly. Covell *et al.* (1955) state categorically that chloroquine produces radical cure of *P. falciparum*. Young and Eyles (1963) maintain that reappearance of parasites in the blood-stream within three weeks is indicative of resistance. In comparison with these findings our Cases 10 and 11 relapsed within a week while still under relatively high preventive dosages; in Case 12 there was a relapse while still receiving therapeutic dosages; in Case 13 a relapse occurred on the nineteenth day after the attack while still under a high preventive regime; and in Case 15 there was a relapse 24 hours after completion of intramuscular therapy. All of these patients relapsed after having received much larger dosages than those usually prescribed for their respective age groups; the relapse occurred very shortly after treatment, and while preventive treatment was still being given.

Another problem is posed by Case 11. It has always been thought that if there was a breakthrough of malaria under prevention it was usually mild and could easily be brought under control. But in this case the relapse, which occurred not only under preventive treatment but a short time after the end of treatment, took the form of a pernicious cerebral attack which ended with the patient's death.

Conclusions

The 15 cases reported demonstrate that in this part of West Africa chloroquine, even when given in high dosages, does not always prevent attacks of malaria (nine cases), does not cure all cases, and does not prevent relapses.

As already stated, the possibility that a strain of *P. falciparum* resistant to chloroquine exists in Upper Volta has been suspected, but to the best of our knowledge no systematic studies have yet been carried out.

The cases reported tend to strengthen these suspicions. Clinical considerations, however, did not always allow us to follow a rigorous experimental routine, and because of lack of certain laboratory facilities we do not regard our findings as an absolute proof of resistance. Therefore this report is presented as a preliminary one. Still, it does appear that the behaviour of the parasites towards the drug was abnormal in all the cases recorded, since they showed a sensitivity towards it which was lower than usual. In our opinion the most plausible explanation would be that there exists in these cases a resistance towards chloroquine.

On the other hand, this presumed resistance appears not to be universal; there are many cases which react favourably to chloroquine in the area under study. Even among the cases reported five out of six showed some response to chloroquine in that the infections could be controlled while not cured.

Resistance of this strain to other antimalarial drugs could not be demonstrated. All patients reacted promptly when given quinine, amodiaquine, or a combination of both.

As we have said, this paper, containing clinical but not experimental data, is to be regarded as a preliminary report. Epidemiological considerations are beyond its scope. Plans, however, are being drawn up for more detailed studies in co-operation with laboratories specializing in these problems.

Summary

In 15 African children from Upper Volta, West Africa, an abnormal response of *P. falciparum* to chloroquine has been observed. All cases were hospitalized and kept under close medical supervision.

Nine of the cases demonstrated breakthroughs while under massive suppressive doses. In six cases the *P. falciparum* infection could not be controlled by large dosages of chloroquine. In one of these cases there was no reaction whatsoever to treatment, and the other five relapsed soon after the infection had apparently been controlled.

There is reason to suspect, therefore, that one or several chloroquine-resistant strains of *P. falciparum* exist in this part of West Africa.

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