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ANTIMALARIAL DRUGS IN NIGERIA: RESULTS OF A NEW SURVEY

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The first survey of the use of antimalarial drugs in Nigeria (Bruce-Chwatt and Bruce-Chwatt, 1950) provided data on some special aspects of prophylaxis and treatment of malaria in this the largest British dependency in West Africa. A similar investigation by Nicol (1953) reported on the experience of the expatriate population in Lagos and discussed the value of various protective antimalarials in Nigeria.

Chemotherapy of malaria has progressed a great deal during the past decade, and a resurvey of the situation in Nigeria was called for. It was especially timely, because the difficulties of malaria eradication in holo-endemic areas of tropical Africa by residual insecticides alone have aroused more interest in the possibilities offered by chemotherapy (W.H.O., 1957). Moreover, it was thought that an assessment of the situation might be of value, as some new trends in the use of antimalarial drugs in Nigeria reflect the profound socio-economic changes seen in West Africa to-day.

This paper deals mainly with the small and transient but well-defined group of the non-immune expatriate population; problems of malaria in the indigenous population of Nigeria will be presented at a future date. Nevertheless, a considerable amount of information pertaining to chemotherapy of malaria in Africans was collected and is reported here.

The total population of Nigeria at the 1952-3 census was 31½ millions, and it was estimated that it increases at the rate of nearly 2% per annum.

The non-African population in Nigeria is distributed unevenly and its composition is constantly changing because of an estimated turnover (due to home leave) of about 30% during the year. This population numbered 16,700 in 1953 and nearly 18,000 in 1956. Of the total of 17,953 expatriates (in mid-1956), 30% were residents in the Federal Territory of Lagos, 31% were in the Northern Region, 20% in the Western Region, and 20% in the Eastern Region and the Southern Cameroons. The overall national composition of the non-African civilian population of Nigeria at the census was approximately as follows: 60% were British; 3% Commonwealth citizens, including Indians; 6% Americans; 9%

Syrians and Lebanese; 3% French; 3% Dutch; 3% Irish; and the remaining 13% belonging to various other nationalities (Nigeria, 1954).

There are few reliable figures referring to the incidence of malaria in the expatriate population of the Federation of Nigeria. The reasons for it were discussed before (Bruce-Chwatt and Bruce-Chwatt, 1950), and the situation has not changed.

Reliable diagnosis of malaria in non-immunes in West Africa is not easy for reasons opposite to those discussed with regard to malaria of the indigenous population. The attitude of the individual medical officer towards this problem varies considerably between two extremes: (a) labelling as malaria any disease with vague clinical symptoms which might or might not be due to the plasmodial infection, and (b) recognizing malaria only on the basis of a confirmatory report of a blood examination. Errors are bound to be committed in either case, and some striking differences between two successive annual rates of malaria in the same locality are often due to a change of medical officers.

An additional difficulty arises from the universal use of antimalarial drugs by the expatriate population; this greatly decreases the chance of finding parasites in the blood, and the diagnosis is then made by presumption when the symptoms respond to a tentative specific treatment. Thus the records of malaria incidence among expatriates in Nigeria are not more than estimates subject to many errors.

INFORMATION ON MALARIA AND ANTI-MALARIAL DRUGS FROM TWO QUESTIONNAIRES

Two years ago it was decided that some more reliable information on the incidence of malaria in Nigeria and on the value of modern antimalarial drugs could perhaps be obtained through suitably designed questionnaires, similarly to what had been done in 1950. It was intended to have two polls of opinion: one addressed to the medical profession in Nigeria, the other to a large though selected group of the residential population of Lagos which relies on routine drug prophylaxis for individual protection against malaria.

The medical questionnaire asked the following ques-

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tions: number, sex, and age of expatriates in the relevant station; number of cases of malaria during the year; type of prophylactic drug taken by the patients and regularity of administration; type of treatment favoured by the medical practitioner; evidence of toxic effects during prophylactic or therapeutic regimen; views on malaria prophylaxis and treatment in Africans and expatriates.

The non-medical questionnaire asked for information on the following: nationality, age, and sex; duration of stay in Nigeria and in Lagos; type of antimalarial drug taken and dosage; on whose advice and how regularly; reasons for change of drug if any; incidence of malaria and by whom diagnosed.

In July, 1956, the Federal Malaria Service dispatched two questionnaires. One, numbering 380 copies, was addressed to medical officers in Government stations and medical missions, and to private practitioners; the other was sent to 3,200 householders whose names appeared in 1956 in the official "residential list" of Lagos township.

The response to the questionnaire forwarded to 380 medical officers in Nigeria produced 146 complete replies, an overall percentage of 38.5. Of these replies, 128 came from the three Regions of Nigeria and 18 from Lagos. The expatriate population, under the medical care of 128 medical officers stationed outside the Federal Territory of Lagos, who answered the questionnaire, amounted to 6,859, which represents approximately 54% of the total expatriate population of Nigeria residing outside the Federal Territory in 1956.

Of the 3,200 questionnaires sent out to the "residential" population of Lagos, 1,026 were returned. Of these, 1,016 gave information in respect of 2,222 persons, distributed as shown in Table I.

TABLE I.—"Residential" Population of Lagos. Replies to the Questionnaire by Race and Age Group

	Adults (15 Years and Over)	Children 2-14 Years	Infants Under 2 Years	Total
Europeans (=Caucasians) ..	1,557	395	75	2,027
Africans	103	56	12	171
Others	20	3	1	24
Total ..	1,680	454	88	2,222

The collected data were coded, put on marginal punch-cards, and numerically assessed; they constitute the main subject of this paper and represent two polls of opinion—one medical, covering the whole country, and the other non-medical, limited to Lagos.

Incidence of Malaria

The two questionnaires provided some interesting data on the incidence of malaria in the expatriate population on a sample which amounts to 49% of the total 1956 population of expatriates in Nigeria (Table II).

Table II quotes for the three regions of Nigeria the number of cases of malaria duly diagnosed and reported by medical practitioners. The incidence of malaria in the

Federal Territory of Lagos is quoted from the replies forwarded by the "residential" population and refers only to malaria diagnosed by a medical officer. Reports of "suspected malaria" (a total of 97) not seen or not confirmed by a doctor were not included, as it was felt that many of the symptoms could have been easily confused with undetermined or minor ailments.

As pointed out previously, the diagnosis of malaria in expatriates in tropical Africa is, paradoxically enough, not easy (even when made by medical practitioners), and the figures quoted must be interpreted with caution, although they are the best data that can be obtained in the circumstances.

Table II indicates that, as one would expect, the incidence of malaria in non-immunes is much less in the mainly urban population of the Federal Territory of Lagos than in the regions, which, with the exception of a few main centres, are predominantly rural areas. Moreover, the overall figures indicate that the incidence of malaria in the expatriate population of Nigeria fell from 225 per 1,000 in 1949 to 142 per 1,000 in 1956. The low mortality from malaria in the expatriate population is striking. There was one fatal case of blackwater fever in a Syrian merchant, following an intramuscular injection of quinine. One death due to cerebral malaria was recorded in a European child, but no details of this case are available.

With regard to the "residential" population of Lagos the data collected during the present survey indicate that the malaria incidence of expatriates decreased during the past eight years from 149 per 1,000 in 1948 to about 60 per 1,000 in 1956.

Thanks to the ready co-operation of the Army medical authorities, it was possible to obtain valuable data on the incidence of malaria in the British military personnel serving in Nigeria and in their families. This group numbers about 1,000, of whom 60% are male adults. The incidence of malaria in the British Army personnel, including the families, was 25 per 1,000 in 1956 (data incomplete) and 35 per 1,000 in 1957. Both figures are well below the rates estimated for the civilian expatriate population and confirm the impression that a number of cases of malaria in expatriates are due to a lapse in the regular routine of drug taking.

Comparative Therapeutic Value of Antimalarial Drugs

From the 146 replies to the questionnaire sent by the members of the medical profession there seems to be nothing approaching a standard treatment of malaria in Nigeria. Although the replies revealed many variations of treatment and a large number of combinations of antimalarial drugs a general pattern was discernible.

For the emergency treatment of severe malaria mepacrine and chloroquine are used with equal frequency, mainly by intramuscular injection; quinine is also used, though somewhat less often, by the intramuscular and occasionally by the intravenous route. The most common single adult dose of quinine injections is 10 gr. (650 mg.); the relevant doses of chloroquine and mepacrine are 200 mg. of base and 300 mg. of base respectively. Because of the frequency of toxic reactions in infants and small children, quinine and chloroquine (in suitably graded dosage) are preferred to mepacrine in paediatric practice.

For peroral treatment of moderately severe malaria chloroquine is the most-favoured single drug, selected by 60% of all medical practitioners, with mepacrine second (24%), amodiaquine third (14%), and quinine fourth (2%).

TABLE II.—Malaria Morbidity in the Expatriate Population in Nigeria in 1956

	Men			Women			Children			Total		
	No.	Malaria	Per 1,000	No.	Malaria	Per 1,000	No.	Malaria	Per 1,000	No.	Malaria	Per 1,000
Regions	3,565	628	176	1,977	311	157	1,317	202	153	6,859	1,141	166
Lagos	895	69	78	662	30	45	470	19	40	2,027	118	58
Total ..	4,460	697	157	2,639	341	129	1,787	221	124	8,886	1,259	142

A few correspondents placed much faith in the therapeutic value of proguanil, and two among them regarded pyrimethamine (at 100 mg. in 36 hours) as a good drug for the treatment of malaria.

Many medical practitioners treat ordinary attacks of malaria by a single intramuscular injection of quinine or mepacrine followed by oral administration of chloroquine or mepacrine or amodiaquine. A few use such combinations as amodiaquine-pyrimethamine, mepacrine-proguanil, etc.

The mean dosage of oral chloroquine is 1.8–2.1 g. of base in three to five days, of mepacrine 1.6–3.0 g. in three to five days, and of amodiaquine 1.2–1.4 g. in four days.

Many medical men adopt the logical principle that the drug used for treatment must be different from that used for prophylaxis. All of them agree that malaria in Africans past early childhood responds well to a less-sustained treatment than the disease seen in non-immunes.

Comparative Value of Prophylactic Antimalarial Drugs

(1) Medical Questionary

Out of 146 replies to the medical questionary, 97 (67%) favoured proguanil; of these, 52 advocated the standard dosage at 100 mg. daily, while 45, mainly from the Northern Region, preferred the daily dosage of 200 mg. Twenty-two replies (15%) gave pyrimethamine at 25 mg. or 50 mg. once a week as the best protective antimalarial. Twenty (14%) advocated chloroquine at two doses once a week totalling 300 mg., though a few preferred a weekly dosage of 600 mg. Three medical men considered that mepacrine and amodiaquine were the most reliable protective antimalarials, while two correspondents were staunch defenders of the "good old quinine."

In attempting to assess the protective value of antimalarials it was found from the medical questionary that the number of so-called "break-throughs" reported in people who were taking various drugs was roughly the same as the different ratios of their uses. Thus, of the break-throughs, 75% were reported in takers of proguanil (mainly in those whose daily dose was 100 mg.), 8% in takers of pyrimethamine, 10% in takers of chloroquine, 4% in takers of quinine, and 1% in takers of mepacrine or amodiaquine. In other words, it was alleged that none of the drugs was 100% effective in preventing attacks of malaria.

As the regularity and adequacy of prophylactic drug administration was not always certain, the reports on break-throughs should not be taken too literally. The fact that these break-throughs occurred roughly in proportionately the same number of people taking various antimalarials suggests that many of them were due to an inadequate prophylactic regimen, while others were due to various febrile conditions.

There is evidence of two widely differing attitudes of the medical profession in Nigeria with regard to the use of prophylactic antimalarials in Africans. While 20 doctors maintained that mass prophylaxis for the indigenous population is neither necessary nor beneficial because of the possible loss of acquired tolerance to malaria, 25 doctors were strongly in favour of drug prophylaxis, especially in some selected indigenous groups such as expectant mothers, schools, labour camps, etc.

An interesting observation came from a large leprosy centre directed by a mission: 500 patients were kept for one year on a weekly pyrimethamine prophylaxis, and this not only reduced the incidence of malaria but apparently also that of lepra reaction after sulphones. For prophylactic administration in African communities mepacrine, proguanil, or pyrimethamine once a week was favoured.

A few industrial organizations have adopted the policy of regular drug prophylaxis of their indigenous staff, and reported satisfactory results either because of apparent decrease of sickness or on account of better public relations. The Army has recently introduced a regular prophylactic

regimen for all Nigerian members of the Forces, including their families. The drug selected was pyrimethamine at 25 mg. once a week.

(2) Non-medical Questionary

The results of the non-medical "residential" questionnaire are shown in Table III and refer to 2,027 European (=Caucasian) residents. The replies of 171 African and

TABLE III.—*Selection of Protective Antimalarial Drugs by the "Residential" Population of Lagos in 1956*

	Adults		Children		Infants		Total	%
	No.	%	No.	%	No.	%		
Europeans:								
Proguanil ..	1,141	73.3	254	64.3	33	44.0	1,428	70.4
Chloroquine ..	92	5.9	9	2.3	2	2.7	103	5.1
Pyrimethamine ..	245	15.7	126	31.9	36	48.0	407	20.1
Mepacrine ..	12	0.8	—	—	—	—	12	0.6
Quinine ..	59	3.8	6	1.5	4	5.3	69	3.4
Amodiaquine ..	3	0.2	—	—	—	—	3	0.1
No drug ..	5	0.3	—	—	—	—	5	0.2
Total ..	1,557	100	395	100	75	100	2,027	100
Africans and Indians:								
Proguanil ..	56	45.5	23	39.0	3	23.0	82	42.1
Chloroquine ..	21	17.1	7	11.8	1	7.7	29	14.9
Pyrimethamine ..	17	13.8	5	8.5	5	38.4	27	13.7
Mepacrine ..	7	5.7	3	5.1	—	—	10	5.2
Quinine ..	6	4.9	13	22.0	4	30.9	23	11.8
Amodiaquine ..	6	4.9	3	5.1	—	—	9	4.6
No drug ..	10	8.1	5	8.5	—	—	15	7.7
Total ..	123	100	59	100	13	100	195	100

24 Indian residents represent a very small group, and for the sake of convenience were grouped together. The replies showed that proguanil was used by 68% of the residential population of Lagos. It was the most popular drug in all races, except for infants and to a less extent for children, in whom it was replaced by pyrimethamine, used by 20% of the public. Chloroquine was the third (6%) most popular prophylactic, while amodiaquine was used by 0.5% of people; mepacrine, which in a previous survey was still being taken by 10.6% of the population, has almost completely dropped out of favour, being taken by only 22 persons (1%). Quinine, which in 1950 was taken by 18.7% of expatriates, has dropped to 4%—mostly "old coasters," though it is still favoured by some, particularly for children and infants. No drug, except perhaps mepacrine, showed any significant difference by sex: this antimalarial is rarely taken by women.

Thus proguanil is shown to be the drug of choice; but where ease of administration is of particular importance, as in children and infants, pyrimethamine replaces it as a favourite. It will be noted from Table III that five Europeans and 15 Africans stated that they take no antimalarials at all. Of the Europeans, one man said that "mosquitoes did not seem to bite him," another said it "was not required in Lagos," one woman put her faith in homoeopathic remedies, and two women stated that all antimalarials upset their digestion.

The "residential" questionnaire attempted to investigate the incidence of malaria in the non-immune population of Lagos on the basis of the information received from 2,027 expatriates.

The reported cases of illness attributed to malaria were divided into three groups: (1) malaria diagnosed as such by a doctor; (2) suspected malaria—not seen by a doctor; and (3) "fever." The results are set out in Table IV, which shows that the so-called "break-throughs" of malaria occur with all drugs in about 6% of persons.

The first and second most favoured dosage schedules of the main drugs taken by adults of the sample of the Lagos residential population are shown in Table V. The percentages in this table refer to the number of people taking the particular drug. The dosage for children is lower by approximately one half.

TABLE IV.—Incidence of "Malaria" in Expatriate Takers of Antimalarials in Lagos

	Diagnosed Malaria		Suspected Malaria		"Fever"		Protected	
	No.	%	No.	%	No.	%	No.	%
Proguanil:								
Adults ..	72	6.3	51	4.5	146	12.8	872	76.4
Children ..	15	5.9	12	4.2	32	11.2	228	79.5
All ages ..	87	6.1	63	4.4	178	12.5	1,100	77.0
Chloroquine:								
Adults ..	5	5.4	4	4.3	10	10.9	73	79.4
Children ..	2	22.2	—	—	—	—	9	77.8
All ages ..	7	6.8	4	3.9	10	9.7	82	79.6
Pyrimethamine:								
Adults ..	18	7.4	20	8.2	24	9.8	183	74.6
Children ..	2	1.6	6	3.7	22	13.5	132	81.5
All ages ..	20	4.9	26	6.4	46	11.3	315	77.4
Mepacrine:								
Adults ..	—	—	1	8.3	3	25.0	8	66.7
Children ..	—	—	—	—	—	—	—	—
All ages ..	—	—	1	8.3	3	25.0	8	66.7
Quinine:								
Adults ..	4	6.8	3	5.1	5	8.5	47	79.6
Children ..	—	—	—	—	—	—	10	100.0
All ages ..	4	5.8	3	4.3	5	7.2	57	82.7
Amodiaquine:								
Adults ..	—	—	—	—	—	—	3	100.0
Children ..	—	—	—	—	—	—	—	—
All ages ..	—	—	—	—	—	—	3	100.0
Total:								
Adults ..	99	6.4	79	5.1	188	12.1	1,186	76.4
Children ..	19	4.1	18	3.8	54	11.5	379	81.0
All ages ..	118	5.8	97	4.8	242	12.0	1,565	77.4

TABLE V

Drug	Modal Dose	Second Mode
Proguanil	7 tablets weekly—86%	14 tablets weekly—7%
Chloroquine	2 tablets weekly (300 mg.)—51%	3-4 tablets weekly (450-600 mg.)—42%
Pyrimethamine	1 tablet weekly—74%	2 tablets weekly—22%

Optimum Dose of Antimalarial.—It was found that there was no clear-cut correlation between the incidence of "malaria" and variation in the weekly dosage. Chloroquine, of which the most popular doses are two and three tablets a week for adults, and one and two tablets a week for children, shows the expected result—that is, 92.3% protection on the higher dose and 74.5% on the lower dose. This difference, however, just fails to reach statistical significance at the 5% level ($p=0.0543$ by Fisher's exact test). Amongst adults taking proguanil the converse is the case: those taking the modal dose of seven tablets a week are 77.2% protected, whereas those taking 14 tablets a week show 67.5% protection. This difference again just misses significance at the 5% level ($t=1.93$, with 1,051 degrees of freedom). Similar unexpected findings refer to samples of children taking proguanil at half-tablet (50 mg.) daily or one tablet (100 mg.) daily respectively. The same applies to two groups of adults: one on one tablet (25 mg.) of pyrimethamine and the other on two tablets (50 mg.) once a week. In children pyrimethamine shows the expected trend: 80.1% protection on the lower dose, and 84.7% on the higher.

The paradox of the higher dose giving the lower degree of protection is of interest though of limited importance. The ambiguous results of this part of the investigation are obviously due to neglect of numerous variables such as body weight, exposure to infection, and, last but not least, vagaries in the diagnosis of malaria.

Regularity in taking a drug is of prime importance for successful chemoprophylaxis, and a specific point was included in the questionnaire. Only 10 Europeans out of 2,022 confessed to irregularity in taking their antimalarials (from our personal experience, one might express some doubts about the reliability of this particular information). Amongst Africans, no fewer than 56 (32.7%) were irregular takers.

Reasons for choice of a particular drug were asked for, and the answers showed two primary reasons: proguanil was "officially recommended" to 57% of people by a doctor or an employer, while pyrimethamine was recommended to 11% and chloroquine to 16%. "Ease of administration" favoured pyrimethamine in 67% of its takers and proguanil in 33%.

(3) Toxic Effects of Antimalarial Drugs

Replies referring to side-effects of antimalarial drugs were of considerable interest. The results of the survey are discussed on the basis of data from the two questionnaires grouped separately for therapeutic and suppressive usage.

Medical observations on toxic reactions due to the therapeutic or protective administration of antimalarials are summarized below. It must be admitted that many side-effects associated with the prophylactic regimen (headache, insomnia, gastro-intestinal disturbances, depression, etc.) were so vague that the relationship between their frequency and the taking of a specific antimalarial was unconvincing.

Quinine.—The symptoms of cinchonism after high dosages of this drug are so well known that they need not be reported here. There was one case, however, of a sciatic nerve injury and paralysis after an intramuscular injection and one fatal case following an intravenous administration of the drug to a child. Intramuscular injections of quinine, nowadays much less common than before, were still advocated by 25 medical officers, particularly in severe malaria in children, apparently with very few local abscesses following the injection. There was one fatal case of blackwater fever following an intramuscular injection of quinine in a Syrian patient and five cases of "blackwater fever" in African children given irregular doses of quinine.

Mepacrine.—The most striking toxic effect of this drug, when given to infants and children up to 3 years of age, was an epileptiform seizure after the intramuscular injection of 100-150 mg. of mepacrine musonate. A total of 37 of these dramatic sequelae with 29 deaths were reported by 18 medical officers, including one case in the Army. The symptoms set off within 10 to 15 minutes after the injection, and consist of sudden clonic and tonic convulsions, dyspnoea, cyanosis, loss of consciousness, and either death or recovery within one to two hours. Two such cases with clonic convulsions of legs or one arm lasting for 20 minutes were observed in adults soon after the injection of 300 mg. of mepacrine. Cases of psychosis, mainly in adults, following the oral administration of mepacrine were reported by 36 medical officers. The incidence of this side-effect cannot be computed, but two correspondents assessed that it averaged 2% of people treated with mepacrine given at the standard dosage. In one small station four patients who were given rather high but not excessive doses of mepacrine developed mental symptoms, some of them of maniacal nature. Other side-effects ascribed to mepacrine were gastric symptoms with vomiting (4), gluteal abscess after intramuscular injection (3), and dermatitis (3).

Chloroquine.—Two epileptiform fits similar to those observed after parenteral mepacrine were reported following an intramuscular injection of 100 mg. of chloroquine—one in an infant, the other in a child of 18 months; one case recovered. The standard therapeutic regimen of chloroquine was followed by a number of side-effects. Vomiting and abdominal discomfort were most commonly reported; the next two common complaints were pruritus and blurring of vision (due probably to a paresis of accommodation). Either one or the other side-effect was seen, according to several correspondents, in 2 to 4% of all patients treated with chloroquine at full dosage. Pruritus seems to have been especially common in women, and was either general or localized in the perineal region or on hands and feet. Antihistamine drugs relieved this symptom, but in a few cases were without effect. Both these side-effects were temporary and abated within one week after the drug had been discontinued. Other minor complaints following

the administration of chloroquine were urticaria and oedema (4 cases), dizziness (8 cases), insomnia (3 cases), mental depression and abdominal discomfort (3 cases).

Amodiaquine.—Except for one case of vomiting, dizziness, and collapse in a child given 600 mg. of amodiaquine by mouth, no other side-effects were recorded, but the number of cases when this drug was used was small.

Proguanil and Pyrimethamine.—These are rarely used for treatment of malaria, and most of the side-effects reported were connected with the prophylactic regimen. Only 13 medical officers noticed any side-effects of proguanil taken in daily dosage of 100–200 mg. Most of these symptoms consisted of abdominal discomfort, diarrhoea, anorexia; there were, however, five cases in which proguanil was apparently causing stomatitis and mouth ulcers in adults, two cases of haematuria in children after an administration of 200 mg. of the drug, and one case of dermatitis resembling erythema nodosum. No side-effects were reported following the administration of pyrimethamine at standard doses, but there were seven cases of acute accidental poisoning of children. Five of these (four in European children and one in an African) proved to be fatal. The history of most of these cases was essentially the same: a child between 2 and 5 years of age found a bottle of pyrimethamine tablets and swallowed a number (15–25) of them. Within 30 minutes to 2 hours the child developed convulsions, occasionally vomited, collapsed, and either died one to three hours later or recovered. In two of these cases prompt medical action saved the child. In one case pyrimethamine could not be incriminated with any certainty. Apart from acute poisoning there were five cases of chronic toxicity of pyrimethamine given to one infant and four children at gross overdosage—for example, three tablets a week for six weeks or one tablet daily for three weeks). This was followed by asthenia, severe megaloblastic anaemia, and, in the case of two African children, death from a condition diagnosed tentatively as agranulocytosis.

Although the medical questionnaire brought some evidence of the type and frequency of side-effects in regular takers of antimalarial drugs for prophylaxis it was thought that more direct information could be obtained from the large residential group in Lagos. A few specific points in the questionnaire designed for the lay public called for definite answers which could be of value in this investigation.

As it was well known that some people keep changing their antimalarial prophylactic drug while others are faithful to one for a long time, an appropriate point calling for a reply was inserted in the questionnaire addressed to the residents in Lagos. The results are shown in Tables VI and VII.

A total of 527 residents of Lagos stated that they had changed at one time from one drug to another. This change was more frequent among adults (29%) than among children (17.5%) or infants (15%), with no significant difference between sexes.

Of all people changing drugs, the greatest number (279) changed from proguanil, forming 52.9% of those who changed drugs and 13.8% of the total in this survey; 75.6% of these went over to pyrimethamine—more children (87.0%) and infants (85.7%) than adults (72.5%). Chloroquine was the next most popular choice (55 persons, 19.7%).

Mepacrine and quinine—the two “old-fashioned” drugs—were both abandoned by 19.5% of those who changed. Of those who stopped mepacrine, 75.7% went on to proguanil and 11.7% to pyrimethamine. Of the erstwhile quinine-takers, 68.9% preferred proguanil and 21.4% pyrimethamine. People who took chloroquine and pyrimethamine *ab initio* seem to be well satisfied with these drugs, changes occurring in only about 1% of the series.

The reason for a change of drug was also asked for. The answers were tabulated under the following headings: “Not effective,” “personal preference or other reasons,” “ill effects” (Table VII). Noticeable is the number of persons

TABLE VII.—Reasons for Changing Antimalarial Drugs in Lagos, 1956

Drug Changed from	Reason for Changing						Total	
	Not Effective		Personal Preference		Ill Effects			
	No.	%	No.	%	No.	%	No.	%
Proguanil ..	52	18.6	114	40.9	113	40.5	279	100
Chloroquine ..	3	13.0	9	39.1	11	47.8	23	100
Pyrimethamine ..	6	31.6	1	5.3	12	63.1	19	100
Mepacrine ..	31	30.1	—	—	72	69.9	103	100
Quinine..	24	23.3	36	34.9	43	41.8	103	100
Total ..	116	22.0	160	30.4	251	47.6	527	100

Note.—The percentages refer to the relative proportions of the different reasons in the number of people changing from that particular drug.

who abandoned proguanil from personal preference—mostly for pyrimethamine, on account of the convenience of a weekly dose as opposed to a daily one, particularly in children. Nevertheless it is worth remarking that some people gave the contrary reason for changing from pyrimethamine to proguanil, because they found the daily dose easier to remember than the weekly one. As regards the incidence of ill effects, there were no significant differences between the various drugs, except in the case of mepacrine, which always was notoriously unpopular because it stained the skin yellow.

Gastro-intestinal upset was the commonest ill effect attributed to any drug; the usual symptoms were anorexia and nausea, often accompanied by dyspepsia and flatulence. Pyrimethamine appears to be the least offensive in this respect. Headache, insomnia, depression, together with lassitude, forgetfulness, and irritability—a syndrome for long popularly recognized as “coast-head”—was attributed to a drug by 40 people (15.9%) complaining of ill effects; all stated or implied that their symptoms disappeared on changing their drug. As was to be expected, mepacrine was the principal cause of skin trouble, and quinine of symptoms referred to the ears; other complaints, often vague and unconvincing, accounted for 10% of “ill effects,” fairly randomly divided between the various drugs.

(4) Consumption of Antimalarial Drugs in Nigeria

A brief reference to the consumption of antimalarial drugs in Nigeria was made in a previous paper (Bruce-Chwatt, 1951), but the changing trends in the demand for these drugs can be assessed best from total amounts issued by the medical departments stores every year. Table VIII quotes the total number of tablets (in thousands) of each of the five main antimalarials indented during the period

TABLE VI.—Numbers of Residents in Lagos Changing Their Drug

Drug Changed from	Drug Changed to											
	Proguanil		Chloroquine		Pyrimethamine		Mepacrine		Quinine		Amodiaquine	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Proguanil ..	17	3.2	55	10.4	211	40.0	6	1.1	6	1.1	1	0.2
Chloroquine ..	10	1.9	8	1.5	5	0.9	—	—	1	0.2	—	—
Pyrimethamine ..	78	14.8	5	0.9	12	2.3	—	—	8	1.5	1	0.2
Mepacrine ..	71	13.5	8	1.5	22	4.2	2	0.4	—	—	—	—
Quinine ..	—	—	—	—	—	—	—	—	—	—	—	—
Total ..	176	33.4	76	14.4	250	47.5	8	1.5	15	2.8	2	0.4

1952-7 by medical officers of the Federal and the three Regional Governments. It should be pointed out that this table does not show the straight consumption of antimalarials; during the past five years the number of hospitals and dispensaries opened in Nigeria had increased very considerably, and the figures in Table VIII reflect to some extent the ordering of new supplies for the greater number of treatment centres. Data concerning the consumption of drugs by private persons and commercial firms are not included in this table as they are not easily available.

Details of the consumption of parenteral preparations of antimalarial drugs are of less interest, but it might be added that the estimated number of ampoules of mepacrine (at 100 and 300 mg.) ordered by the governments in 1956 was 40,000, while the respective figure for quinine ampoules (at 6 and 10 gr. (400 and 650 mg.) was 30,000, and for ampoules of chloroquine 15,000.

The estimated cost to the governments of all antimalarial drugs used in 1956 for both prevention and treatment of malaria was approximately £60,000.

TABLE VIII.—*Amounts of Antimalarial Drugs in Tablet Form (in Thousands) Purchased by the Government Medical Departments in Nigeria During the Period 1952-7*

Year	Quinine Tablets (All Salts) at 5 gr. (650 mg.) Each	Mepacrine Tablets at 100 mg. Each	Chloroquine Tablets at 150 mg. Base Each	Proguanil Tablets at 100 mg. Each	Pyrimethamine Tablets at 25 mg. Each	Amodiaquine Tablets at 200 mg. Base Each
1952	636	12,089	—	5,000	—	—
1953	242	8,647	91	2,007	11	—
1954	155	9,350	368	3,278	44	—
1955	240	9,424	1,042	10,018	121	59
1956	171	10,153	1,831	8,466	213	168
1957 (Approx.)	92	10,291	3,115	8,522	701	376

DISCUSSION

Difficulties in the correct diagnosis of malaria mainly from clinical symptoms, with little help from the blood examination, are considerable in West Africa, and are responsible to some extent for the unreliable malaria morbidity statistics of Africans and Europeans in Nigeria.

Information obtained through two questionnaires provided some new data on the incidence of malaria in the expatriate non-African population. It appears that the overall annual malaria morbidity in this population in the Federation of Nigeria fell from 225 per 1,000 in 1950 to 142 per 1,000 in 1956. Improvements in methods of malaria control in urban areas might have contributed to this gratifying decrease in morbidity, but the main cause of this is probably better individual protection and particularly the widespread use of more active prophylactic antimalarials. The disappearance of blackwater fever following the substitution of suppressive quinine by synthetic antimalarials is striking.

A survey of the therapeutic use of antimalarials in Nigeria revealed that as a whole the clinical medical practice in this country reflects creditably the remarkable advances achieved by experimental chemotherapy during the past ten years. Several interesting points were gathered from the answers to the medical questionnaire.

Chloroquine, given orally and parenterally, has become a drug of choice for the treatment of malaria in Nigeria. There can be little doubt that this drug is most effective and that the administration of the "loading dose," which averages two-thirds of the total dose, over three to five days is a correct procedure.

In spite of the popularity of chloroquine, quinine and mepacrine are still used; the former mainly for parenteral administration in severe malaria, the latter both by mouth and intramuscularly, somewhat indiscriminately, especially in rural areas.

The survey revealed a disturbing number of grave side-effects of intramuscular administration of mepacrine in

infants and young children. This disadvantage has been known for some time, but the frequency of these often fatal incidents was underestimated, as they were not widely known. It might be argued that 29 fatal sequelae of the intramuscular injection of mepacrine in children constitute a small proportion of all cases in which this treatment was beneficial, but it should be remembered that the number of accidents quoted above is probably only a proportion of all cases.

Similar observations were made in East Africa a few years ago (Dockeray, 1951) and confirmed in Uganda by Trowell (personal communication) and by Luder (1957). One such case, of toxic mepacrine encephalopathy in a child given a mepacrine injection in the absence of malaria, was described by one of us (Bruce-Chwatt, 1955). The experience in Nigeria is not in agreement with that of Covell *et al.* (1955), who maintain that mepacrine convulsions are alarming but seem to have no serious effects.

It must be admitted that chloroquine is not entirely blameless in this respect, and the two cases of acute toxic effects of intramuscular chloroquine, quoted by our medical correspondents, are similar to those described in Ghana by Harris (1955). Nevertheless at the present time the general consensus of medical opinion is that intramuscular chloroquine is safe when properly administered. It is certain that the danger of parenteral administration of any antimalarial will be greatly decreased if the drug is given in two or three fractional doses, over one to one and a half hours. Attention should be drawn to the importance of calculating the dosage of intramuscular chloroquine in relation to the actual weight of children and not by a rule of thumb referring only to the age of the child (Harris, 1957). Oral administration should be preferred whenever feasible.

Serious side-effects after chloroquine given by the mouth were uncommon; on a full therapeutic dose of about 2 g. over four to five days pruritus and temporary blurring of vision might be quite troublesome in about 1% of patients. Amodiaquine has gained some favour among the medical profession in spite of the fact that there is no evidence that it is superior to chloroquine. A comparative study of the schizontocidal effect of both drugs (Charles, 1958) confirmed Davey's (1955) opinion "that amodiaquine cannot be used in any way—that is, in any particular dosage regimen—which is significantly different from a way in which chloroquine might be used."

The results of the medical questionnaire were of interest with regard to some important points mentioned by Covell *et al.* (1955). (1) Dosage of antimalarial drugs necessary for treatment of malaria in semi-immunes was about one-third to a half of that needed for the non-immune subject, and a short treatment consisting of 600 mg. of chloroquine in a single dose or 800 mg. of mepacrine over two days was usually effective. Good effects were also reported by those who used single-dose treatment of 600 mg. of amodiaquine. (2) There was no evidence of any strain of *Plasmodium falciparum* in Nigeria being resistant to therapeutic doses of chloroquine, mepacrine, or amodiaquine. However, some indirect and inconclusive reports have been quoted of increased tolerance by malaria parasites of proguanil or pyrimethamine given as suppressives. (3) There were justified complaints of the ever-increasing confusion created by the profusion of various proprietary names for the same active drug and by the varying dosages expressed either as a salt or as a base. Need was expressed for a reliable active drug without a bitter taste, suitable for paediatric practice.

With regard to the latter point, attention might be drawn to the recent confirmation by Clyde and Shute (1958), in Tanganyika, of the failure of the chloroquine methylene- β -hydroxynaphthoate reported by Bruce-Chwatt and Charles (1957).

Respective Values of Suppressives

When it comes to discussing the recent trends in the choice of suppressive antimalarials and their respective

values the conclusions deriving from the two questionnaires are on less objective grounds. The use of antimalarial drugs for individual protection has been almost general in the expatriate population of West Africa for the past 50 years.* All senior Government officials and most of the senior staff in commercial undertakings, missions, etc., are supplied with antimalarials free of charge. A few years ago only quinine, mepacrine, or proguanil could be obtained on demand, but nowadays this extends also to chloroquine and pyrimethamine. Since the taking of an antimalarial is a normal feature of everyday life no wonder that the discussion of favourite antimalarial drugs is a popular conversational topic at any social gathering in Nigeria. There are unfathomable "fashions" in drug-taking, and many more or less imaginary complaints connected with them tend to obscure the real incidence of specific side-effects. All this, stimulated by an increasing amount of advertising, has led to an undesirable situation, as many expatriates are experimenting on themselves, using one or several drugs, often at dangerously high dosages.

It appears from replies to both the medical and the "residential" questionnaire that proguanil is taken by nearly three-quarters of all expatriates and by an increasing number of educated Nigerians. Pyrimethamine and chloroquine are the next choice, with amodiaquine third. In comparing these findings with those of the 1950 questionnaire the remarkable though expected trend is the eclipse of quinine and mepacrine as protective drugs. The other interesting fact is the generally increased dosage of proguanil as compared with the modal dose in 1950.

The changing trend in prophylactic antimalarials taken by a representative sample of the expatriate population of Nigeria can be seen best from the comparative figures obtained successively by the Bruce-Chwatts (1950), Nicol (1953), and the present survey.

The percentages of expatriates taking one or the other prophylactic antimalarial were as follows:

	1950	1952	1956
Proguanil	65%	68%	70%
Quinine	23%	16%	3%
Mepacrine	10%	6%	0.6%
Chloroquine	1%	2%	5%
Pyrimethamine			20%

General Protection

The true comparative value of the main drugs for the "general protection," in the sense given to this term by Covell *et al.* (1955)—that is, suppression of clinical symptoms, suppressive cure of *P. falciparum*, and causal prophylaxis—cannot be established from replies given to the two questionnaires. Every drug, at whatever dosage taken, was alleged to have failed in approximately 6% of takers. This figure is in reasonably good agreement with the results obtained by Nicol (1953), who gave the percentage of "break-throughs" as 10.

Whether these break-throughs are genuine and due to the irregularity of drug-taking, or its underdosage, or an intercurrent gastro-intestinal illness interfering with the absorption of the drug, or unusually great exposure to infection, the presence of a resistant strain of the malaria parasite or other unknown factors is impossible to tell, though the first suspicion is justified and the following two causes are most likely. The possibility of relapsing infections with *P. malariae* or *P. ovale* of local origin cannot be dismissed, but is likely only in sporadic cases and not in nearly 10% *P. vivax*, usually responsible for relapses of malaria, is so extremely rare in Nigeria that one or two imported cases

*It is generally believed that the regular use of prophylactic quinine was introduced into West Africa in 1835. According to the late G. M. Findlay (*in litt.*), however, the "preventive quinine" was initiated on the West Coast in 1772 by Robert Robertson, a naval surgeon and a friend of James Lind, the promoter of the administration of "the bark for the cure of ague" in India. Robertson later became a Fellow of the Royal Society.

would not account for more than a fraction of the incidence of malaria quoted above.

There is no factual evidence that proguanil- and pyrimethamine-resistant strains of *P. falciparum* might be responsible for some of the "break-throughs." A few personal comments of medical officers who had experienced an attack of malaria (with a positive blood slide) while on proguanil or pyrimethamine prophylaxis are insufficient to support this presumption. The incidence of malaria in regular takers of antimalarials generally and proguanil and pyrimethamine in particular has not increased in comparison with 1950, and it can be safely said that for the time being no drastic changes in the choice of suppressive drugs in Nigeria are necessary (Nigeria, 1949-54).

In Nigeria there has been an obvious trend to substitute pyrimethamine for proguanil, especially in children. The main, and good, arguments in favour of pyrimethamine are the lack of taste and the ease of giving a tablet once a week (usually on Sunday) instead of every day. It is of interest that in several replies to the questionnaires correspondents admitted that they reverted to the daily proguanil regimen, as they found it difficult to remember to take pyrimethamine on only one particular day of the week and felt that the daily routine left much less margin for any possible errors of individual prophylaxis. On the other hand, the use of pyrimethamine once a week was most convenient in hospitals, schools, labour camps, antenatal clinics, etc., whenever a collective prophylaxis is carried out in a reasonably stable or supervised group. The problem of the best routine of prophylactic drug-taking is far from simple and must "take into account economics, human desires, and human failings" (Davey, 1955). This is of considerable importance with regard to the routine administration of prophylactic chloroquine, which is usually given twice a week at 300 mg. base; it is probable that a daily routine of 50-75 mg. would be a far better choice for individual prophylaxis.

It is of interest, therefore, that Davey and Robertson (1957) carried out a successful field trial of chemoprophylaxis with a daily dose of 50 mg. of chloroquine base because the daily regimen has been favoured by the Army authorities. Several years ago French workers adopted the daily prophylactic dosage of 100 mg. of chloroquine base, and since 1953 this method has been used throughout French West and Equatorial Africa with considerable success.

It will thus be understandable why the method of individual prophylaxis by amodiaquine—two tablets twice a month—is quite unrealistic and of doubtful value.

There is little evidence that any of the three commonly used prophylactic drugs (proguanil, chloroquine, pyrimethamine) produce any serious and consistent side-effects when taken at standard dosage. Pyrimethamine is probably the least responsible for any gastro-intestinal or other complaints commonly referred to other drugs. It is therefore all the more regrettable that during 1956 there were five fatal cases of poisoning due to pyrimethamine left within the reach of toddlers, attracted by the small size of the tablets and their lack of bitter taste.

All these cases are much the same as those of accidental pyrimethamine poisoning in children described by Taylor (1953), Davidson (1954), Gunther (1954), Peake (1954), Abbott (1955), Davies (1956), and in the Belgian Congo by Montauban *et al.* (1956), whose paper contains the best clinical description of acute pyrimethamine poisoning.

It should be added, in all fairness to the drug, that these accidents happened in Nigeria in 1956, before the introduction of the modern plastic strip pack of pyrimethamine, which should effectively prevent children from swallowing more than one or two tablets.

Five cases of long-term toxicity of pyrimethamine (megaloblastic type of anaemia), given at doses far in excess of those normally used, were more serious, as they were due to an error of judgment of the medical practitioner or to irresponsible self-medication by laymen. The main cause

of the medical errors of judgment was the lack of appreciation of the differences between proguanil (which has a wide margin of safety) and pyrimethamine, remarkably active in small doses but toxic when given to children at several times its standard dose.

It appears that the conclusions of Myatt *et al.* (1953) about the reversibility of megaloblastic anaemia of adult volunteers on 25 mg. of pyrimethamine daily for several weeks do not necessarily apply to the blood-forming organs of children. The Federal Government of Nigeria, justifiably alarmed at the excessive dosage of pyrimethamine used in 1956 by some medical practitioners and by the lay public, circularized at the end of that year a warning to the medical profession in Nigeria. It appears that this warning was duly heeded, as only one case of overdosage of pyrimethamine came to light during the past year.

The replies to the medical questionnaire showed that there is a considerable measure of disagreement between medical practitioners in Nigeria regarding the value of drug prophylaxis in the indigenous population. The fact that out of 146 replies 100 did not express any definite opinion on this controversial subject indicates the gap in our knowledge of the problem of malaria immunity and its relationship with individual or collective chemotherapy. In view of the absence of a concerted opinion of the medical profession in Nigeria on the value of drug prophylaxis in the African population we express our own point of view.

In discussing the value of protective drugs in the indigenous population three groups of people must be distinguished. The first is a small but growing group of African infants and children either born in Europe or having been away for a long time and who are returning to the malarious areas. These should be treated, especially for some time after their return, as non-immunes and protected by the same drug regimen. The second group is constituted by antenatal clinics, infant welfare centres, schools, labour camps, etc. Such groups can be supervised; and here the value of antimalarial drugs is considerable, since they reduce the amount of sickness and decrease the infectivity of the human reservoir of infection.

An ideal drug in these conditions should have a combined curative and long protective action similar to that shown by pentamidine for prevention of trypanosomiasis. Unfortunately there is no such antimalarial at present, and all known drugs are excreted rapidly and have a short "carry over" value, so that a once-weekly or, at least, once-monthly administration is necessary whenever a long-term effect is sought. The choice lies between proguanil and pyrimethamine on the one hand and mepacrine, chloroquine, and amodiaquine on the other.

The first two have the advantage of low toxicity, low cost, and a potent sporontocidal effect, but they may induce parasite resistance, especially when used for treatment as well as prevention of malaria.

Chloroquine and amodiaquine are excellent for both purposes; their cost is still relatively high. Mepacrine has the advantage of being cheap, but it has several undesirable side-effects. The general consensus of opinion is still rather in favour of proguanil and pyrimethamine, but it is possible that in the long run chloroquine or amodiaquine will be the best in conditions where protection from malaria must start with its cure and especially where resistance to the first two drugs had appeared.

An indigenous child continuously exposed to malarial infection need not be given a continuous uninterrupted protective regimen from its early infancy through its whole life. There is no doubt that the administration to these children of adequate doses of active antimalarial drugs, particularly at the peak of the transmission season, will help the growing organism by easing the load of heavy parasitaemia without thereby hampering the progressive building up of the individual acquired immunity to malaria.

In the third group of the indigenous, large, and scattered rural population mass distribution of antimalarials could

hardly achieve any permanent results (Bruce-Chwatt, 1956). Moreover, administrative difficulties of such mass distribution are enormous, and with the exception of some special circumstances, such as stopping an epidemic, the prevention of malaria by residual insecticides remains the only possibility, though mass treatment will speed up the interruption of transmission.

SUMMARY

Reliable data on the incidence of malaria are difficult to obtain in Nigeria, and the reported figures do not reflect the true situation.

The malaria morbidity of the expatriate population in Nigeria, which was estimated in 1950 at 225 per 1,000, had decreased in 1956 to 142 per 1,000. In an expatriate population of nearly 18,000 there was one death due to malaria and one to blackwater fever.

Information on antimalarial drugs obtained from two questionnaires showed that chloroquine is the most popular therapeutic drug, with mepacrine second, and amodiaquine third. For severe malaria, quinine injections are still frequently used.

As a protective drug proguanil was the most favoured, followed by pyrimethamine and chloroquine. In about 6% of takers of all protective drugs "break-throughs" of malaria were reported, but the reasons for these break-throughs, as well as their diagnosis, are uncertain.

Intramuscular injections of mepacrine in infants and small children may be followed by serious and often fatal sequelae. Both mepacrine and chloroquine given at a full therapeutic dose may produce a number of side-effects which are usually transient. Side-effects due to protective drugs are rare, though in 1956 there were several cases of accidental fatal poisoning of children by pyrimethamine.

An assessment has been made of the amount of antimalarial drugs consumed in Nigeria in 1956.

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