inoculation from each of the five children whose stools have so far been tested. The rhesus monkeys used all developed a disease similar to experimental poliomyelitis, and lesions pathognomonic of the disease were found in the brain and cord at necropsy.

Case 1.—R. R., aged 10 years. June, 1949. Revaccinated with smallpox lymph with "mild take" 12 days previous to the onset of symptoms. Developed meningo-encephalitis with evidence of paresis of the seventh cranial nerve four days after onset. Stool collected on the sixth day of illness.

Case 2.—S. S., aged 9½ months. September, 1949. Combined diphtheria-pertussis vaccine injected 17 days previous to onset. Paralysis of both arms three days after onset. Stool collected on the fourth day of illness.

Case 3.—D. M., aged 1 year. October, 1949. A.P.T. vaccine injected nine days previous to onset of symptoms. Paralysis, localized to inoculated arm, 12 days after injection. Stool collected on the 14th day of illness.

Case 4.—J. R., aged 1 year. December, 1949. Pertussis vaccine injected four days previous to onset of "cold." Paralysis, confined to inoculated limb, seven days after onset of "cold." Stool collected on the tenth day of illness.

Case 5.—R. W., aged 1 year 7½ months. December, 1949. Pertussis vaccine injected five days previous to onset of symptoms. Could not swallow two days after onset, and paralysis of neck muscles occurred on the following day. Stool collected on the 20th day of illness.

Cases 3 and 4 appear to be examples of the "double event" under discussion. In Cases 1, 2, and 5 the association between inoculation and poliomyelitis-like illness was present, but paralysis was not confined to the inoculated limb.

Summary

Poliomyelitis virus has been isolated from the stools of two children who had paralysis of a limb inoculated 11 and 12 days previously with certain vaccines.

The virus has also been isolated from the stools of three children who developed poliomyelitis or encephalitis 5 to 17 days after receiving a prophylactic inoculation without localization of paralysis in the inoculated limb.

It is recognized that the poliomyelitis virus is widespread during epidemic times, and no suggestion is made here that the viruses isolated were necessarily responsible for the present illness of the patients. These strains will be used, however, for experimental investigation of the problem of the effect of peripheral trauma in precipitating poliomyelitis or localization of paralysis in patients infected with or carrying poliomyelitis viruses.

The National Insurance Advisory Committee has been asked to consider and report on the preliminary draft of regulations which would modify the time limits for giving notice of incapacity and claiming sickness benefit for persons in hospital and for those who have not claimed that benefit before under the National Insurance Act. The proposals in the draft regulations are that a person claiming sickness benefit for the first time would have 21 days to put in his claim and would not be disqualified for having failed to give notice of incapacity. Long-stay patients in hospital would be treated as having good cause for failure to claim sickness benefit within the normal time limits while they are in hospital up to a maximum of three months; for short-stay patients this period would instead be the time spent in hospital and the three weeks after discharge. Copies of the preliminary draft of these regulations (the National Insurance (Claims and Payments) Amendment (No. 2) Regulations, 1950) can be purchased from H.M.S.O. for 3d. or from any bookseller. The committee will consider written objections to them if sent before July 18 to the secretary, National Insurance Advisory Committee, 30, Euston Square, London, N.W.1.

ANTIMALARIAL DRUGS IN WEST AFRICA, WITH PARTICULAR REFERENCE TO PROGUANIL

RESULTS OF A SURVEY IN NIGERIA

BY

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The traditional bottle of quinine tablets disappeared from the breakfast table of every European resident of West Africa soon after the outbreak of the last war. Mepacrine ("quinacrine," "atebrin"), introduced in 1943 by the armed Forces and adopted of necessity by the non-African civilian population, reigned supreme during the war, to be succeeded soon after the end of it by proguanil ("paludrine").

The use of proguanil for the prevention and treatment of malaria in West Africa dates from 1946, but the general adoption of the new drug was not achieved until well into 1947. The originally advocated dosage of proguanil in West Africa was 0.1 g. twice a week for prophylaxis, and 3 g. in fractional doses over 10 days for a radical cure of infections with *Plasmodium falciparum*, the prevalent parasite species.

In consequence of reports of field trials from other parts of the world the officially advocated prophylactic dosage was soon raised to 0.1 g. three times a week. By the end of 1947 several medical officers in Nigeria expressed their concern about the value of proguanil taken in the above dosage for prevention of malaria. The slow curative action of proguanil caused a good deal of disappointment, especially in severe clinical cases which eventually responded to quinine or mepacrine. The early cautious reports on the value of proguanil in Nigeria were met with a good deal of disbelief.

An important investigation carried out during 1948 by Covell, Nicol, Shute, and Maryon (1949) on neurosyphilitic patients at Horton revealed that infections with the Lagos strain of *P. falciparum* are causally prevented by the prophylactic administration of proguanil in fractional doses varying between 0.3 and 0.7 g. a week. On the other hand, proguanil used alone for treatment of infections with this strain failed to effect a radical cure when given in total doses varying between 2.1 g. in seven days and 4.2 g. in 14 days. Yet Maegraith and Andrews (1949) were able to report constant radical cures with proguanil given in a total dose of 3 g. in 10 days. Their latest results did not materially differ from those obtained in 1945, when the first therapeutic trials of proguanil were being carried out in Liverpool.

Experimental data obtained by Covell and his associates tacitly implied that medical reports referring to the failure of proguanil in the prophylaxis of West African malaria were based on insufficient evidence. None the less, during 1948-9 several medical officers in tropical Africa continued to express their conflicting views on proguanil. While Walls (1948), Bostock (1949), and Abbott (1949) were on the whole satisfied with its prophylactic value, Best (1949), Davey and Smith (1949), Shearer (1949), and Jelliffe (1949) quoted cases of overt *P. falciparum* malaria in subjects taking regularly 0.1 g. of proguanil a day.

In 1949 the Colonial Office and the Medical Research Council, on the advice of the Colonial Medical Research Committee, amended the previous recommendations for the use of proguanil in prophylaxis and treatment of malaria by increasing the prophylactic daily dose to 0.1 g. daily and advising the combined mepacrine-proguanil treatment.

Since the trend of Nigerian medical opinion with regard to the prophylactic and therapeutic value of proguanil and to the frequency and type of side-effects continued to be somewhat at variance with results obtained by recent experimental investigations, it was thought that a collection of a considerable amount of information from medical practitioners and from the non-immune population would be of value.

The non-African population in Nigeria is distributed very unevenly and its composition is extremely varied. Of the total of approximately 11,000 non-Africans in 1948 over 40% were residents of Lagos and of the small area of the Lagos Colony; the remaining 60% were distributed in groups varying between 2 and 500 all over the 373,000 square miles of the Protectorate. The overall racial composition of the non-African civilian population of Nigeria is: Europeans (including Americans), 82%; Syrians and Lebanese, 16%; Indians and others (Egyptians, Arabs, Iraqis), 2%.

The data relevant to the non-African population of the Protectorate could be obtained best through the agency of medical practitioners, more than 300 of whom are distributed over the area and in Government stations, medical missions, and to a very small extent in private practices. The same method of collecting data was not practicable in Lagos with its large mixed non-African community, and it was decided to make a direct approach to this part of the population, but at the same time to obtain some relevant information from the records of the Creek Hospital, which serves the non-African community.

Two suitably designed questionnaires were sent—one in August, 1949, to 313 medical officers in Nigeria, and the second in October to 1,400 accessible non-African householders of Lagos. The information thus gathered constitutes the main subject of this paper. The results of the two polls of opinion, medical and non-medical, are analysed and presented separately.

Results of Questionnaire Sent to Medical Officers

The response to the questionnaire forwarded to all qualified medical practitioners in Nigeria is shown in Table I.

TABLE I.—Results of Questionnaire Sent to Medical Officers

	No. Sent	Replies Received
Government medical officers ..	196	99 (50.5%)
Mission " " ..	85	24 (28.2%)
Private practitioners ..	32	3 (9.5%)
Total ..	313	126* (40.2%)

* Of 126 replies received 116 came from outside Lagos.

TABLE II.—Composition of Non-African Population in the Protectorate Relevant to the Medical Questionnaire

	Europeans (including Americans)	Syrians, Lebanese, Indians, and Others
Men ..	2,206	488
Women ..	1,145	280
Children ..	593	257
Total ..	3,944	1,025

The composition of the non-African population of the Protectorate of Nigeria, under the medical supervision of 116 medical officers who co-operated in this investigation, is shown in Table II.

The above sample is satisfactorily representative of the overall composition of the non-indigenous population of the Protectorate and constitutes approximately 70% of it.

Incidence of Malaria in Non-Africans

The importance of information on the incidence of malaria in non-immunes residing in a highly endemic area is quite obvious, and yet great difficulty is experienced in attempting to obtain any reliable data in West Africa. The reasons for this are many and not necessarily due to circumstances beyond control. Although reliable statistical records of malarial morbidity in non-Africans are difficult to obtain, approximate evaluation of the incidence of this disease was possible on the basis of data supplied by the medical officers in their replies.

All cases diagnosed as malaria and recorded during the period January 1, 1947, to January 1, 1949, by 116 medical officers from the Protectorate are classified in Table III.

TABLE III.—Annual Distribution of Cases of Malaria Amongst a Part of the Non-African Population of the Protectorate During 1947–8

	Europeans				Syrians and Indians			
	Out-patients		In-patients		Out-patients		In-patients	
	Clini- cal	Pos. Blood	Clini- cal	Pos. Blood	Clini- cal	Pos. Blood	Clini- cal	Pos. Blood
Men ..	618	164	253	87	124	9	64	7
Women ..	309	86	131	27	99	10	28	5
Children ..	75	11	40	13	58	2	7	3
Men ..	782		340		133		71	
Women ..	395		158		109		33	
Children ..	86		53		60		10	
	1,263		551		302		114	
Total ..	1,814				416			

The comparative annual incidence of malaria in men, women, and children of the two racial groups, the ratio of out-patients to in-patients, and the ratio of "clinical malaria" to "blood-positive malaria" are shown in Table IV.

TABLE IV.—Comparative Annual Incidence of Malaria in Two Main Racial Groups of the Part of the Non-African Population of the Protectorate During 1947–8

	Europeans				Syrians and Indians			
	Men	Women	Children	Total	Men	Women	Children	Total
Annual incidence of malaria per 1,000	253	241	114	228	210	245	136	222
Ratio of in-patients to out-patients	1:2.3	1:2.5	1:1.6	1:2.3	1:1.9	1:3.3	1:6	1:2.6
Ratio of "blood positive malaria" to "clinical malaria"	1:3.6	1:2.9	1:2.6	1:3.2	1:11.8	1:8.5	1:13	1:10.5
Deaths due to malaria ..	2*				1‡			
Blackwater fever ..	4†							

* Due to cerebral malaria. † 1 fatal. ‡ No details.

Malaria in Takers of Prophylactic Drugs

Information on the type of suppressive drugs taken by the non-African population in the Protectorate is summarized in Table V.

TABLE V.—Comparative Number of Non-Africans Taking Various Prophylactic Drugs in the Protectorate in 1948-9

	No. of Takers	%
Proguanil	1,978	69.5
Mepacrine	302	10.6
Quinine	534	18.7
Chloroquine	28	1.0
Total on antimalarial drugs	2,842	100.0
Unknown	1,102	
Grand total	3,944	

The information gathered with regard to the dosage of antimalarial drugs taken regularly by the non-African population is not precise enough to be tabulated. It reveals, however, that most of the proguanil takers during 1947 and 1948 were on the dosage 0.1 g. two to four times a week. By the end of 1948 and at the time of this investigation 87% of adults were following the daily 0.1 g. regimen, 8% were still on the obsolete dosage of 0.1 g. two to four times a week, and 5% were taking either 0.2 g. every day throughout the year, or 0.2 g. daily during the rainy season, or combined the 0.1 g. daily dose of proguanil with 0.1 to 0.3 g. of mepacrine or with 10 to 30 gr. (0.65 to 2 g.) of quinine a week.

Quinine is still taken—in daily doses of 5 gr. (0.32 g.)—by a considerable number of people, particularly by the “old coasters,” who are used to it and dislike a change. It is also the favourite suppressive drug given to children. Mepacrine, 0.1 g. three to seven times a week, is still taken by some; these are mostly men who acquired the habit in the Army and do not mind the yellow discoloration of the skin. The most interesting information—namely, the comparative incidence of malaria in large groups of non-Africans taking different antimalarial drugs—was also the most difficult to collect.

Table VI gives relatively small but fairly reliable figures representing the grouped numbers of Europeans on various prophylactic drugs, together with the corresponding number of cases among them diagnosed as malaria during the period 1947-8.

TABLE VI.—Comparative Numbers of Cases of Malaria in Four Groups of Europeans in the Protectorate Taking Various Suppressive Drugs

	Antimalarial Drug			
	Quinine.	Mepacrine	Proguanil	Chloroquine
Weekly dose ..	35 gr. (2.3 g.)	0.4-0.7 g.	0.2-0.7 g.	0.5 g.
No. of takers ..	288	160	956	34
Cases of malaria ..	68 (23.6%)	33 (20.6%)	122* (12.8%)	8 (23.5%)

*Out of 122 cases of malaria in persons on suppressive proguanil 28 were either irregular takers or on 0.1 g. twice a week. If they are excluded the percentage of cases of malaria in takers of proguanil at 0.1 g. four to seven times a week is 9.85.

A few illustrative cases of the apparent failure of proguanil given in the dose of 0.1 g. a day should be quoted. They have been reported and personally observed by experienced medical officers, and some of them occurred in their own families.

Report 68.—“During the past year I have been taking proguanil regularly, 0.1 g. a day, having previously taken mepacrine. In May I ran short of it and took nothing for three days: overt malaria resulted at once. In June, when on 0.1 g. daily, I entered upon a period of hard work and a good deal of mental strain. Again overt M.T. malaria resulted, requiring intramuscular mepacrine.”

Report 74.—“Own child, aged 1 month, proceeded to West Africa by sea. Proguanil was started 12 days before landing

in West Africa. On board 0.05 g. given every second day and on arrival regularly every day. Three months later acute feverish condition: malaria parasites found by myself; later confirmed in hospital. Treated by quinine intramuscularly; good response; rapid recovery.”

Report 107.—“Proguanil taken by me personally, 0.1 g. daily, regularly for a year; two break-throughs with subtertian and quartan parasites in blood.”

Opinion with regard to the comparative suppressive value of antimalarial drugs was expressed in 99 replies to the questionnaire and in 30 replies to a circular letter sent in March, 1949 (Table VII).

TABLE VII.—Comparative Suppressive Value

No. of Replies	Best Drug				Equally Good			Not Favoured		
	P	Q	M	C	P=Q	P=M	P=Q=M	P	Q	M
129	60	23	18	1	2	12	8	10	8	6

The most favoured dosage of proguanil is 0.1 g. daily, but six medical practitioners are of the opinion that 0.2 g. daily is better, either permanently or at least during the malaria transmission period, and four advocated taking regular proguanil in conjunction with either mepacrine 0.1 g. two or three times a week or quinine 5 gr. (0.32 g.) a day.

Comparative Therapeutic Value of Antimalarial Drugs

The same poll of medical opinion with regard to the therapeutic value of antimalarials produced 110 replies, which, together with the 30 replies to the circular letter of March, 1949, are classified in Table VIII.

TABLE VIII.—Comparative Therapeutic Value

No. of Replies	Best Single Drug				Equally Good		Not Favoured		
	P	Q	M	C	Q=M	P=Q=M	P	Q	M
140	8	67	46	1	16	2	14	2	1

For the immediate treatment of acute malaria with hyperpyrexia, signs of cerebral involvement, distressing vomiting, and massive parasitaemia, quinine holds the first place, and is given intravenously or intramuscularly in doses varying between 5 and 30 gr. (fractional) in the first 24 hours. As an alternative and in less severe forms intramuscular mepacrine is used in doses varying between 0.3 and 0.9 g. during the first 24-48 hours.

Proguanil alone has often proved to be disappointingly slow. The following is a typical comment: “European official, 35 years of age, on regular proguanil, two tablets a week since 1947. Acute fever with intense headache; temperature 101° F. (38.3° C.); blood-slide positive, showing rings of *P. falciparum*. Put on proguanil 0.2 g. three times a day for three days. Little improvement, and on the fourth day the temperature rose to 104° F. (40° C.). Symptoms of cerebral irritation. 10 gr. of quinine hydrochloride diluted in 10 ml. of normal saline given intravenously. Within three hours the temperature dropped to 99.4° F. (37.4° C.), and after six hours was 98° F. (36.7° C.). Next day much improved; kept on oral quinine; made uneventful recovery.”

The treatment of attacks of malaria of average severity leaves scope for more varied types of treatment according to the personal views and past experience of every medical officer. The types of treatment favoured by 113 medical practitioners are shown in Table IX.

TABLE IX.—Type of Treatment Favoured

No. of Replies	Single Drug				Combined Treatment		
	Q	M	P	C	Q+M	Q+P	M+P
113	18	27	8	1	24	23	13

There is a good deal of variation in the dosage of these drugs, but the average range used in Nigeria is as follows:

Quinine: 30–60 gr. (2–4 g.) daily for 5 to 10 days.

Mepacrine: 0.4–0.9 g. on day 1; 0.3–0.6 g. on days 2 and 3; 0.2–0.3 g. on days 4–6. Total dosage varying between 1.6 and 3 g.

Proguanil: 2–9 g. distributed over 5 to 10 days.

Chloroquine (diphosphate): 1 g. as initial dose, total 2.5 g. in 3 days.

The most popular combined treatments are used in the following dosage range:

Q+M: Quinine is given as a single intramuscular injection of 5 gr. or orally 30 gr. a day for 2–3 days, followed by 0.2 to 0.6 g. of mepacrine daily for 4–6 days.

Q+P: Quinine dosage as above followed by proguanil 0.3 to 0.6 g. daily for 7 to 10 days.

M+P: Mepacrine 0.3 to 0.9 g. on day 1, 0.3 to 0.6 g. on day 2, followed by proguanil 0.3 to 0.6 g. daily for 4 to 10 days.

Toxic Effects of Antimalarial Drugs

Medical reports on side-effects caused by antimalarial drugs were grouped separately for suppressive and therapeutic dosages respectively. In *suppressive* doses quinine seldom causes any degree of cinchonism or other complaints severe enough to be reported to the medical officer.

Mepacrine.—This causes many more side-effects, and the frequency of these symptoms reported by 122 medical officers is as follows: (a) slate-blue pigmentation of nails, hard palate, gums, tip of nose, ear lobes, tongue, or prepuce was reported 27 times; (b) dermatitis (lichenoid or eczematoid form) or simple pruritus, 19 times; (c) anorexia, nausea, vague gastro-intestinal troubles, 12 times; (d) mental depression, lassitude, insomnia, nightmares, 7 times; (e) hepatitis (?) was reported once. Most reports with regard to side-effects of suppressive mepacrine cover the pre-proguanil period, when practically everybody was on mepacrine, and refer to a civilian population of about 5,000 non-Africans. Calculation of the incidence of these toxic reactions in relation to the exposed population is not practicable.

Proguanil.—Reports on side-effects of prophylactic proguanil refer to the total number of 956 non-Africans and are grouped according to their overall frequency, but not to the weekly dose of the drug. They are as follows: (a) anorexia, nausea, mild gastro-intestinal upsets, 13 cases (1.35%); (b) headaches, 7 cases (0.72%); (c) depression, lassitude, 2 cases (0.21%); (d) giant urticaria, 1 case.

Medical observations on toxic reactions due to the *therapeutic* dosage of antimalarial drugs are summarized below:

Quinine.—The well-known symptoms of mild cinchonism are common and need not be reported here. There was one case of quinine amblyopia. Three of the five cases of blackwater fever reported during 1947–8 were associated with high doses of quinine.

Mepacrine.—The symptoms associated with therapeutic doses of mepacrine were: (a) of gastro-intestinal origin, 18; (b) transient but very disturbing toxic psychoses, usually of hypomanic excitement, more rarely of acute confusional states, 13; (c) tachycardia, 2; (d) aplastic anaemia, 1; blackwater fever, 1. Eleven cases of acute toxic reactions to the intramuscular administration of mepacrine were reported in infants or small children given normal therapeutic doses, between 0.05

and 0.15 g. The symptoms set off within 10–20 minutes after the injection, and consist of an epileptiform seizure with facial twitching, clonic convulsions, cyanosis, loss of control over the constrictors, and occasional vomiting. Recovery within one to two hours is the rule, but one fatal case was observed.

Proguanil.—Therapeutic doses of proguanil were associated with: (a) nausea, vomiting, epigastric pains, diarrhoea, 15 times (particularly in children); (b) headaches, 7 times. Haematuria was reported in 5 instances, of which 3 refer to children. The first observation of haematuria was reported by a medical officer who noticed it in his own child (4 years of age) 24 hours after every dose of 0.2–0.3 g. daily. This rather alarming symptom disappeared after the drug was discontinued, but it reappeared on two other occasions when proguanil was readministered. In another child haematuria with hyaline casts was noticed after a daily dose of 0.1 g. for three days. In one adult haematuria was accompanied by intense lumbar and abdominal pain. On the other hand, proguanil can be quite harmless, as demonstrated by the example of a European woman who took 40 tablets (4 g.) in 24 hours without any ill-effects.

Results of Questionary Sent to Non-African Residents of Lagos

A much-simplified questionnaire was sent to a representative section of the non-African population in Lagos in order to obtain first-hand information with regard to the type of drug and dosage taken, the age and length of residence in West Africa of each person, the incidence of malaria, such toxic effects as had been experienced, and any other relevant information that might be of interest. It should be noted that the non-African population of Lagos is extremely fluid on account of long periods of recuperative leave in Europe, and it is difficult to assess the exact number of non-African residents in Lagos at any particular time. For the purpose of this survey 1,400 households, corresponding to approximately one-third of the total non-African population of Lagos, were addressed. The comparative response is shown in Table X.

TABLE X.—Results of Questionary sent to Non-African Residents

	Europeans	Syrians	Indians	Total
No. sent	1,100	200	100	1,400
Replies received	582 (52.8%)	45 (22.5%)	14 (14%)	641 (46%)
No. of persons covered	1,035	57	44	1,136

Length of residence in Nigeria was divided into three groups in order to cover three distinct periods in the history of antimalarial drugs.

Group I: Less than 1 year to 2 years—proguanil period.

Group II: 2 to 7 years—mepacrine period.

Group III: 7 to 40 years—quinine period.

Those classified under Group I came to West Africa when all three drugs were readily available and were therefore able to make a free choice from the very outset. Those in Group II started taking antimalarial drugs at a time when mepacrine was the only available drug. Those in Group III belong to the period when quinine was the only prophylactic in use.

TABLE XI.—Number of Persons Taking Different Antimalarial Drugs Related to their Length of Residence in Nigeria

Residence	No. of Takers	Quinine	Mepacrine	Proguanil	Chloroquine	No Drug
—1 year	287	42 (14.6%)	14 (5.2%)	226 (78.7%)	3 (1%)	2 (0.7%)
1–2 years	215	42 (19.5%)	28 (13%)	141 (65.5%)	2 (0.9%)	2 (0.9%)
2–7 "	324	84 (24.3%)	37 (11.2%)	200 (62%)	1 (0.32%)	2 (0.6%)
7–15 "	153	76 (49.7%)	24 (15.6%)	53 (34.5%)		
15–40 "	157	92 (58%)	10 (6.2%)	55 (35%)		
Total	1,136	336 (29.7%)	113 (10%)	675 (59%)	6 (0.5%)	6 (0.5%)

The weekly dose of each drug taken by adults in Lagos is very similar to that taken in the Protectorate generally. In the case of children the dose (varying according to age) is on an average 10 gr. a week for quinine and 0.35 g. a week for proguanil. No children take mepacrine.

Incidence of Malaria in Non-Africans in Lagos

The reported cases of malaria among the non-African population were divided into three groups: (1) Malaria diagnosed as such by a medical officer. (2) Suspected malaria (fever, sweating, rigors, headache, with gastrointestinal upsets); case not seen or diagnosed by a doctor. (3) So-called "low fever" (persistent slight temperature and general feeling of low health): this group was eventually discarded, as it was felt that its symptoms were too easily confused with those of chill, general ill-health, or undetermined minor ailments.

The relative numbers of cases of diagnosed or suspected malaria reported during the two years in the three groups of drug-takers are shown in Table XII.

TABLE XII.—Number of Cases of Malaria Reported During 1947–9

	No.	Diagnosed Malaria	Suspected Malaria	Total
Quinine takers	336	41 (12.2%)	23 (6.8%)	64 (19%)
Mepacrine	113	21 (18.6%)	7 (6.2%)	28 (24.8%)
Proguanil	675	40 (5.9%)	28 (4.1%)	68 (10%)
Chloroquine	6	1 (16.6%)	—	1 (16.6%)
Total	1,130	103 (9.1%)	58 (5.2%)	161 (14.3%)

Cases of malaria, diagnosed or suspected, in persons admitting irregularity or known to have been on less than adequate dosage of any drug have been omitted.

Side-effects of Drugs Taken for Prophylaxis or Suppression of Malaria

The toxic effects which were produced are classified in Table XIII.

TABLE XIII.—Nature and Number of Toxic Effects Reported

Quinine	No. of Cases	Mepacrine	No. of Cases
Gastric symptoms	13	Gastric symptoms	61
Deafness, tinnitus	19	Blue pigmentation of nails, nose, etc.	28*
Shakiness, dizziness	9	Dermatitis	18†
Menorrhagia	6	Mental depression	9
Weakness, lassitude	7	General low health	5
Headaches	7		
Depression	6		

* 1 case of onychosis with loss of toenails. † 1 case of erythroderma.

Proguanil	No. of Cases	Per cent of all Proguanil Takers, Former and Present (750)
Gastric symptoms	35	4.67
Headaches	13	1.73
Depression	11	1.47
Lassitude	7	0.93
Dizziness	4	0.54
Dermatitis	2	0.27
No. of persons reporting toxic effects	58	7.75

Changes from one drug to another are not significant in the case of quinine or mepacrine, as both were taken of necessity at different times and subsequent changes or reversions to one or the other do not necessarily imply dissatisfaction. With proguanil, however, the choice of drugs was voluntary, and changes are noted here: 75 persons (6.3% of the total) took proguanil and changed either to quinine or mepacrine; 25 of these reported attacks of malaria (without stating the dosage they were taking), 25 had complaints shown in Table XIII, and 25 gave no definite reasons. It should be pointed out that the six persons who voluntarily take from 14 to 42 (!) tablets of proguanil every week have not reported any toxic effects of the drug.

Survey of the Incidence of Malaria at the Creek Hospital, Lagos

It was felt that the results of the inquiry obtained direct from a representative sample of the non-African population of Lagos should be supplemented and correlated with the statistical data recorded at the Lagos Creek Hospital.

Table XIV brings out some salient points with regard to the importance of malaria in non-African residents of Lagos and the Colony during the period 1946–9.

The overall mean incidence of malaria calculated on the basis of replies obtained direct from the population concerned is 47.7 per 1,000 per year during 1947–9 (Table XII). The respective figure obtained from the records of the Creek Hospital (Table XIV) is 41.3 per 1,000 per year. The difference between the two figures is relatively small, and is due to the inclusion of cases of "suspected malaria" not admitted to the hospital.

As a rule malaria in Lagos is a comparatively mild disease, easily yielding to adequate treatment. The average duration of the stay at the Creek Hospital is 5.2 days, and, generally speaking, less than 10% of patients can be regarded as seriously ill. However, every year there occur sporadic cases of fulminant infections, with enormous numbers of parasites in the blood, very early cerebral symptoms, and death within 8 to 24 hours after admission. It must be emphasized that all four fatal cases of cerebral malaria in adults during 1948–9 occurred in people who

TABLE XV.—Distribution of Antimalarial-drug Takers in 55 Cases of Malaria During 1949

	Antimalarial-drug Takers on Regular Daily Regimen			No Drug, or Very Erratic Takers
	Proguanil	Mepacrine	Quinine	
No. of cases of malaria	16 (3)	7 (2)	9 (2)	23 (14)
Average duration of stay in the hospital ..	3.7 days	5.1 days	5.5 days	4.7 days (fatal cases not included)
Total No. of cases ..	32			23
Deaths due to malaria ..	0			3

NOTE.—Figures in parentheses refer to the number of cases in which malaria parasites were found in the blood film taken on admission.

TABLE XIV.—Incidence of Malaria in Non-African Residents of Lagos During 1946–9 (Creek Hospital)

Year	Non-African Resident Population	Overall Morbidity of the Non-African Resident Population			Overall Morbidity per 1,000	Malaria Incidence in Non-African Residents. No. of Admissions				Deaths Due to Malaria	Overall Incidence of Malaria per 1,000	Malaria Incidence per cent Overall Morbidity	Ratio Blood-Positive Malaria to Clinical Malaria
		Men	Women	Total		Men	Women	Children	Total				
1946	1,842	509	247	756	410	67	23	1	91	1 ad. 1 child	49.0	12.0	1:2.1
1947	2,990	701	287	988	330	123	37	5	165	1 .. 1 ..	55.5	16.7	1:3.8
1948	4,305	661	340	1,001	234	109	26	8	143	1 adult	33.3	14.3	1:2.1
1949	4,900	667	354	1,021	208	139	44	12	195	3 ad. 3 inf.	39.8	19.2	1:2.1

were not taking any prophylactic drugs. The three fatal cases in newborn European infants were diagnosed as congenital malaria. Blackwater fever has practically disappeared since 1945 except for one fatal case that occurred in 1949 in an irregular quinine-taker.

Detailed past history of the prophylactic regimen was obtained from records of 55 cases of malaria in non-African residents of Lagos admitted to the Creek Hospital in 1949 (Table XV).

Discussion

The information with regard to the present trends of medical and lay opinion pertaining to the prophylactic and therapeutic use of antimalarial drugs in Nigeria, obtained by means of two questionnaires, revealed several important points.

The prophylactic efficacy of antimalarial drugs could not be assessed with any degree of certainty on account of the lack of reliable statistical data on malaria in West Africa. This regrettable situation has changed very little since Granville Edge (1937) drew attention to it, and even the figures for malaria incidence among the few thousand non-Africans in Nigeria are sketchy. This is due to several reasons.

The greater part of the European population in West Africa has an estimated turnover of about 30% during the year, and relatively few return to the same station after an 18-months tour. The medical facilities in different stations vary considerably, and while in a station with adequate hospital accommodation most of the non-African cases of malaria are recorded as in-patients, in other stations all these cases remain at home and are recorded as out-patients or remain unrecorded. Records themselves are often casual and lack continuity on account of frequent changes of station medical officers.

Another important reason for unsatisfactory statistics of malaria in West Africa is the fact that the diagnosis of this disease leaves a wide margin for personal interpretation of clinical symptoms and of results of the blood examination for parasites. Wartime experience has shown that in not a few stations in Nigeria the average technique for laboratory diagnosis of malaria is inadequate.

The attitude of the individual medical officer towards the problem of diagnosis of malaria varies considerably between two extremes. One, remembering the protean clinical picture of *P. falciparum* infections, diagnoses any case of headache, fever, gastro-intestinal upset, etc., as malaria, and records it as such. The other clinches the diagnosis of malaria only when it is confirmed by finding parasites in the thick or thin blood film (though this confirmation may come from a junior technician whose reports are seldom checked). That many clinical errors are bound to be committed in the first case is obvious. None the less it seems that the opposite attitude has something of a counsel of perfection and can also lead to mistakes. Some striking differences between two successive annual rates of malaria in the same locality could be traced to a change of medical officers, with dissimilar ideas on the problem of diagnosis of this disease.

There is little doubt that there exist in West Africa cases of subtertian malaria with severe clinical symptoms preceding by a day or two the appearance of scanty parasites in the peripheral blood. Hughes and Bomford (1944) found that in 968 hospital cases of West African malaria of five clinical types (febrile, gastro-intestinal, respiratory, myalgic, cerebral) parasites were found in the blood at the first examination in 57%, while in 13% parasites were not found

during the first few days and the condition had to be treated as clinical malaria. The occasionally late appearance of parasites in severe attacks of malaria in West Africa was more recently confirmed by Nelson-Jones (1944).

The supreme importance of the laboratory in the diagnosis of *P. falciparum* malaria and as a guide to its treatment is emphasized by Field (1949); a high standard should be aimed at but will be difficult to attain in tropical Africa.

It seems that the laboratory diagnosis of malaria in West Africa is handicapped by two facts, diametrically opposite in non-immune Europeans and in immune Africans. In non-immunes the habit of taking antimalarial drugs reduces to a considerable degree the chance of finding parasites in the blood (Table XV) and leaves the alternative—an anathema to a good clinician—of diagnosing malaria by the good result of a tentative specific treatment, which cannot be withheld for long. On the other hand, the symptomless presence of parasites in immune Africans is a common finding in children and (to a less degree) in adults, and does not necessarily indicate an overt clinically important infection, but may accompany any intercurrent disease.

In considering the epidemiology of malaria in non-immunes one more point must not be forgotten. Although *P. falciparum* is the main parasite in West Africa, *P. malariae*, *P. vivax*, and *P. ovale* are also present. The possibility of Europeans having a relapsing benign tertian or quartan malaria of West African origin is seldom considered, in spite of the fact that relapses of vivax malaria were seen in the U.K. in people who during the war spent a year or so in West Africa and nowhere else.

In Nigeria the mean overall ratio of records of "clinical malaria" to "blood-positive malaria" is 2.5 to 1 in Europeans. The embarrassingly large number of cases of so-called "clinical malaria" and the difficulty that these cases present for an evaluation of a suppressive or curative regimen is not new. During the war the same problem had to be faced by the Army Medical Services when collecting the annual statistical data for the West Africa Force. There, in spite of a far more standardized hospital treatment, better laboratory facilities, more adequate supervision, and less-variegated and more-disciplined patients, the mean ratio of "clinical malaria" to "blood-positive malaria" was 1:1.2 (in 1944).

Thus in the present state of affairs in West Africa there are no criteria on the basis of which true statistical data of malarial morbidity can be separated from cases erroneously diagnosed as malaria. In the circumstances all cases labelled as malaria by the medical officers were taken into consideration for assessment of the comparative value of antimalarial drugs in Nigeria.

The pooled results of the two country-wide questionnaires, covering about 48% of the non-African population of Nigeria, revealed that proguanil is at the present time by far the most popular prophylactic drug, being used by 65% of all the non-Africans. The respective figures for quinine, mepacrine, and chloroquine are 22.5, 10.3, and 0.9%. The prevailing medical opinion in Nigeria is that proguanil is the best and least toxic antimalarial. This opinion was expressed by 60% of the medical officers. Percentages of opinions favouring quinine and mepacrine were 23 and 18 respectively.

On the assumption that every case reported as malaria was correctly diagnosed, the following figures of the incidence of malaria were obtained for four groups of non-Africans taking prophylactic antimalarial drugs in

1948-9. In the Protectorate, according to medical records, malaria occurred in 9.9% of those on regular proguanil regimen; 23.6% of quinine-takers; 20.6% of mepacrine-takers; and 23.5% of chloroquine-takers. The figures for Lagos and the Colony area, obtained direct from the population concerned, are 10% in proguanil-takers, 19% in quinine-takers, 24.7% in mepacrine-takers, and 16.6% in chloroquine-takers.

There can be little doubt that, in Nigeria, proguanil taken in a daily dose of 0.1 g. is far superior to mepacrine and quinine as a prophylactic. The difference between the malaria rates of the combined suppressive quinine-mepacrine group of non-Africans and the parallel group on prophylactic proguanil is 7.6 times the standard error of the difference and therefore highly significant.

In spite of the fact that 1 g. of proguanil daily is more efficacious than any other drug (including chloroquine) the percentage of cases of malaria in proguanil-takers amounts, according to both questionnaires, to about 10%. Some of these cases may be erroneously diagnosed or be due to carelessness in taking proguanil, or to both. None the less, even after discounting these errors, several break-throughs seen in regular proguanil-takers at 0.1 g. daily were reported by conscientious and experienced medical officers and have too authentic a ring to be lightly dismissed.

The causes of these relatively rare break-throughs of West African malaria in subjects who have apparently been taking regular and adequate doses of proguanil are not quite clear. They may be due to individual differences in the absorption of the drug, to its too rapid excretion, or to the transformation of the active principle into a non-active compound. The hypothesis of the chemical change or faster excretion of proguanil in some subjects has not been confirmed by Field and Edeson (1949), who demonstrated that the proguanil resistance of the Malayan strain of *P. falciparum* was inherent to it and not related to the fate of proguanil in the organism of the patient.

There remains the probability that occasional failures of proguanil prophylaxis in West Africa are caused by a particularly resistant strain of *P. falciparum*. The resistance to adequate therapeutic doses of proguanil was well demonstrated by Covell and his team, but the value of this drug in the prophylaxis of infections with the Lagos strain was confirmed.

It must be borne in mind that the Lagos strain of *P. falciparum* established at Horton is only one of the unknown number of strains which are bound to exist in a hyper-endemic zone with its unlimited possibilities for crossings and mutations. Other strains may behave differently in experimental infections and show a greater resistance to prophylactic proguanil. One sees no reason why this should be disturbing or surprising. The same facts were tacitly admitted or somewhat less discussed with regard to suppressive mepacrine in West Africa during the war. While the enforced and regularly supervised daily administration of mepacrine in the South-East Asia Command reduced the incidence of malaria within a few months to a practically negligible level, the same dose of mepacrine in the West Africa Force could not bring the number of malarial attacks in European personnel below 378.8 per 1,000 in 1943 or below 278 per 1,000 in 1944 (Findlay and Stevenson, 1944; Stevenson, 1945). One had to conclude with some reluctance that a daily dose of 0.1 g. of mepacrine is not a perfect suppressive for all strains in West Africa and that the facile explanation of carelessness in taking the drug could not be applied to all cases (Findlay and Stevenson, 1944). A similar occurrence was reported by

Fairley and his associates (1946) in New Guinea, where the Aitape-Wewak strain was found to be relatively resistant to mepacrine.

It is worth mentioning here that two European residents of Lagos who were in the Far East during the war and had no malaria while on suppressive mepacrine developed malaria in West Africa in spite of having remained on the same mepacrine regimen.

The other and most probable explanation of reported failures of prophylactic proguanil in West Africa may be due to the fact that in localities with a high infective density of anopheles a delay of one week before starting the prophylactic routine, or an interval of more than five though less than eight days in the otherwise regular regimen, may be sufficient to miss the essential causal action of proguanil on pre-erythrocytic forms of the parasite. Subsequent resumption of the regular prophylactic regimen will not prevent the first wave of erythrocytic merozoites from establishing the infection. With the proguanil unable to effect a radical cure of West African subtertian malaria, as shown by Covell and his associates, the "prophylactic" routine would then be not more than an imperfect cure with spontaneous recrudescences of the primary infection or occasional break-throughs during any intercurrent disease. The rapid rate of excretion of proguanil makes this explanation plausible.

Naturally, the theoretical blame for the failure to keep up an ideal prophylactic regimen would in this case lie with the human subject, but it seems that just as much responsibility remains with the drug, which because of its rapid rate of excretion has not sufficient "carry-over" value.

With regard to the therapeutic value of proguanil, the consensus of medical opinion in Nigeria emphasizes its slow action and its failure to bring about a radical cure of infections with *P. falciparum*. This fully corroborates the experimental results obtained by Covell and his team. The wide and early adoption of the combined treatment of acute malaria by medical officers in Nigeria seems to have anticipated the recent official recommendations of the Colonial Medical Research Committee (1949).

Field and Edeson (1949) suggested that the Lagos strain obtained by Shute in 1947 has become resistant to the curative action of proguanil on account of some possible previous contacts with this drug, similarly to the proguanil resistance produced experimentally by Adams and Seaton (1949) or acquired naturally by the Negri-Sembilan strain. The suggestion is a plausible one, but its correctness is highly unlikely. The Lagos strain was isolated in November, 1947, from a child living in one of the suburbs of Lagos. In 1947 proguanil was mainly restricted to hospital use, and no attempts at mass prophylaxis of malaria in the African population by this drug were ever carried out in Lagos.

So far as side-effects of prophylactic regimen are concerned, the very low toxicity of proguanil was confirmed by the two pools of opinion. None the less, it was found that even a drug of very low toxicity can produce a certain amount of mild side-effects in Europeans, of both sexes, who are compelled to take it for years in physically and mentally trying climatic conditions.

In the therapeutic dosage proguanil seems to be remarkably well tolerated by an overwhelming majority of patients. Minor toxic symptoms include vomiting and epigastric pain, particularly with maximum daily doses taken on an empty stomach. Haematuria, an alarming though transient symptom, was recorded in five instances—four times in children.

Analysis of the present trend of medical and lay opinion in Nigeria suggests that lately there has been some increase in the popularity of quinine for suppression of malaria.

It is a matter for regret that the initial dosage of proguanil advocated at the time of its introduction in West Africa was so overcautiously low in spite of the unusually wide margin between its active and its toxic dosage. Subsequent changes of official recommendations have somewhat undermined the confidence of the non-African population. Occasional cases of malaria in persons taking supposedly adequate prophylactic dosage of proguanil and reports of its slow curative effect have produced a psychological reaction of "sales resistance" to proguanil and a tendency to return to the "good old quinine," particularly among the "old coasters."

This tendency is to be deplored and warned against because proguanil still remains the best and least toxic antimalarial drug. Quinine is not only an unsatisfactory suppressant of malaria but has also many melancholy associations with blackwater fever—an entity which had become so rare as to be almost forgotten. There is little doubt that, therapeutically, quinine is almost unanimously preferred on account of its rapidity of action and lack of any serious toxic effects.

With regard to chloroquine, although the present survey yielded a very limited amount of information it seems to have produced the first available data on the prophylactic use of this drug in West Africa. Until recently chloroquine diphosphate ("aralen") was available only to a few Americans residing in Nigeria, who were taking two tablets (0.5 g.) a week, corresponding to 0.3 g. of chloroquine base. According to the pooled information received direct from the persons concerned and from two experienced American medical missionaries, chloroquine taken regularly in the above dosage failed to prevent an infection with *P. falciparum* in 23.5% of cases—an incidence of malaria similar to that obtained in the quinine-taking group of non-Africans.

On the other hand, the few available medical reports on the therapeutic value of chloroquine in West Africa and the results of a field trial in progress seem to indicate that chloroquine is probably the most potent and rapid synthetic schizonticide known, achieving with a high degree of constancy what appears to be a radical cure of falciparum infections of West African origin and showing very few side-effects.

Sapero's (1947) remarks with regard to therapeutic postulates of antimalarial drugs can also be applied in West Africa to the evaluation of their prophylactic action: "Action of antimalarial drugs depends on the chemotherapeutic value, the efficacy of the immune mechanism, and the inherent characteristics of the causative species or strain. The ideal drug capable of effecting a causal prophylaxis and a radical cure of all infections with *P. falciparum* remains to be discovered. At the present time we have an adequate arsenal of antimalarial drugs of suboptimal efficacy, and one has to devise ways and means to attain the best possible effects from a combination of drugs not wholly effective."

Summary

A survey of the incidence of malaria in the non-African population of the Colony and Protectorate of Nigeria was carried out by means of two questionnaires sent to the medical officers throughout the country and to a representative sample of the non-indigenous residents of Lagos.

In spite of the difficulty in obtaining any reliable data with regard to the malaria morbidity in non-Africans, the survey revealed that during 1947 and 1948 the annual malaria morbidity of non-Africans was approximately 225 per 1,000 in the Protectorate and 44.5 per 1,000 in Lagos.

The pooled results of the two questionnaires have shown that prophylactic proguanil is used by 65% of the non-African population. The respective figures for quinine, mepacrine, and chloroquine are 22.5, 10.3, and 0.9%.

The comparative pooled figures of malaria incidence in four groups of non-Africans taking various antimalarial drugs or chloroquine are as follows: 10% in proguanil-takers, 21.8% in quinine-takers, 22.6% in mepacrine-takers, and 22.5% in chloroquine-takers.

The slow therapeutic effect of proguanil and its failure to produce a radical cure of *P. falciparum* malaria are confirmed.

With the exception of a small percentage of cases in which mild or transient side-effects of prophylactic and therapeutic proguanil were experienced, this drug has a very low toxicity.

The occasional failures of prophylactic proguanil are reported and their possible causes discussed.

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The Health Council of Greater New York has just celebrated its third anniversary. According to the *New York Times*, the council is "not just another agency that works with medical societies and health officers. It is more interested in positive health than in disease." Its activities are widespread. It has given help to local authorities to establish mental hygiene clinics; it has cleaned up vacant building lots and converted them into recreation grounds; it has operated a milk co-operative, reduced the smoke nuisance from large factories, participated in water conservation programmes, successfully insisted on better garbage collection, organized cooking classes, and seen that school-children have had midday meals. All this work is voluntary. The council teaches that citizens do not need to be forced by the Health Department into taking care of themselves, their neighbours, and their surroundings if they are taught by the Health Council to do so spontaneously.