in human sera. It is, however, probable that as blood transfusion and serological testing become commoner in Africans such human antibodies will be found, and it is not improbable that there will be occasional clinical manifestations of incompatible blood transfusion and even of haemolytic disease of the newborn arising from the corresponding antigen-antibody reactions.

Summary

An investigation has been carried out into the distribution in West Africa and the genetics of the Hunter antigen of Landsteiner, Strutton, and Chase (1934) and of the newly discovered Henshaw antigen. The genes for both of these antigens appear to be closely linked to those of the MNSs blood-group system.

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USE AND EFFECTIVENESS OF ANTIMALARIAL DRUGS

EXPERIENCE OF NON-NATIVE RESIDENT POPULATION OF NIGERIA, WEST AFRICA

BY

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The question most often put to the medical profession by European and other expatriates resident in West Tropical Africa is, "What antimalarial drug should I and my children take, and in what dosage?" The claims made in advertisements, the advice of friends, and the recommendations of employers conflict and confuse. More often than not the doctors themselves disagree, and recent comment in the medical press is even more confusing and conflicting (*British Medical Journal*, 1949; Colonial Med. Res. Com., 1949; Covell, Nicol, Shute, and Maryon, 1949a, 1949b; Davey and Smith, 1949; Garnham, 1949; Bruce-Chwatt, 1951; MacLeod, 1951; Messent, 1951; Manson-Bahr, 1952).

In view of this present disagreement on the part of the medical profession an inquiry into the use and effectiveness of antimalarial drugs was conducted in Lagos in 1951 and 1952, employing the past and present experience of a group of non-natives resident in Nigeria as a yardstick. A study with the same object in view was carried out in 1948 and 1949 by the Bruce-Chwatts (1950). They collected data by sending questionnaires to all doctors practising clinical medicine within the Colony and Protectorate. The investigation here reported was carried out by personal interview with a group of expatriates, many of whom lived in and around Lagos.

Method

The group investigated was composed of all the non-natives who reported to my out-patient clinic at the Creek Hospital, Lagos, between November 1, 1951, and March 31, 1952, irrespective of the complaint which brought them to hospital. Each individual was questioned regarding the following particulars:

Nationality, age, sex.

Antimalarial drug at present being taken: name of drug, dose, duration, and regularity of taking it.

Previous history of malaria while taking this drug. If present, was malaria diagnosed by a doctor, with or without laboratory confirmation, or by the individual himself?

Antimalarial drug, if any, used in the past: name, dose, duration, and regularity of taking it, previous history of malaria, grounds for diagnosis (see above), and reason for changing to another drug.

The age, sex, and nationality distributions of the sample of the non-native population of Nigeria, numbering 531 in all, are set out in Table I.

An estimate of the incidence of malaria in the group at the time of interview was made as follows. If a patient was found to be pyrexial or to present any clinical feature raising the question of the differential diagnosis of malaria, a thick blood film was made and sent to the laboratory. "Clinical malaria" was diagnosed on those occasions when the report on the film was negative, but the history and examination suggested malaria and the response to therapeutic doses of mepacrine or chloroquine was satisfactory. The possibility that cases of influenza and other short-term spontaneously remitting fevers were included as clinical malaria cannot be ruled out, nor can it be stated that all cases of parasitaemia were discovered by these simple methods; it is believed, however, that a reasonably good estimate of the incidence of overt malaria was obtained.

Blood films were made for the reasons mentioned above from 78 of the 441 patients aged 10 and over, and from 17 of the 90 children under 10 years. The infecting organism in all the blood films reported as positive was stated to be *Plasmodium falciparum*.

Results

The antimalarial drugs in use by the individuals forming the sample of the non-native population at the time of interview are shown in Table II; it will be seen that proguanil was used at all ages more often than any other drug. Proguanil was the drug chosen by the majority of all races except the Lebanese, Syrians, and French, who prefer quinine to any other antimalarial drug. A bigger proportion of the French (16%) than of any other race took chloroquine.

Changes from One Drug to Another

Many individuals, regular takers of an antimalarial drug, were found to have changed for various reasons from one drug to another during the course of their stay in West Africa. Among adults the swing was away from quinine or mepacrine to proguanil or chloroquine (Table III). An increase in the dosage of proguanil from 100 mg. to 200 mg. daily had also occurred. Such changes indicate dissatisfaction with the drug initially taken.

The reasons given for stopping quinine were repeated attacks of "fever" (80%), dyspepsia, and tinnitus. In 89% of cases the reason given for relinquishing mepacrine was the yellow staining of the skin, but gastric upsets were also blamed by a small number of patients. The sole reason given for increasing the dose of proguanil, or for changing to another drug, was the occurrence of fever while taking the lower dose. Proguanil was never given up as a result of loss of appetite (*British Medical Journal*, 1949; Shearer, 1949). Proguanil in doses of 200 mg. daily and chloroquine 300 mg. twice or thrice a week were found satisfactory by the few who have taken them regularly and without change since starting to live in the Tropics.

Incidence of Malaria Discovered at the Interview

The overall incidence of malaria among the group of adult patients who had taken one or other of the antimalarial drugs regularly was found to be 8% (Table V). The figure of 8.2% for those taking 100 mg. of proguanil daily agrees well with that reported by the Bruce-Chwatts (1950). A significant difference does not exist between the

TABLE IV.—*Incidence of a Past History of Malaria in Non-native Residents in Nigeria 20 Years of Age and Over, Regular Takers of Only One Antimalarial Drug, Time the Drug has been Taken, and the Distribution of Malaria Throughout this Period*

Antimalarial Drug and the Daily Dose*	No. Taking	% Reporting Proved Malaria	% Reporting Clinical Malaria	Mean Duration of Taking Antimalarial Drug			
Proguanil:							
100 mg.	203	6	9	3.6 years			
200 "	15	0	0	0.7 year			
Mepacrine:							
100 mg.	21	14	3	4.9 years			
Quinine:							
4 or 5 gr.	55	35	15	7.1 ..			
Chloroquine:							
300 mg.	3	0	0	0.5 year			
		Percentage in which Malaria had Occurred after					
		Less than 1 Yr.	1-2 Yrs.	3-4 Yrs.	5-9 Yrs.	10-19 Yrs.	20 Yrs. and Over
Proguanil:							
100 mg.	203	7	13	14	15	—	—
Mepacrine:							
100 mg.	21	0	0	9	17	—	—
Quinine:							
4 or 5 gr.	55	20	17	26	37	48	49

* Dose of chloroquine is taken twice or thrice weekly, not daily.

TABLE V.—*Incidence of Malaria in Non-natives 20 years of Age and Over Resident in Nigeria Found at the Interview, and the Antimalarial Drug being Taken at the Time*

Antimalarial Drug and Dose	No. Taking	No. with Positive Blood Film	No. with Diagnosis of Clin. Malaria	% with Positive Films	Total % Malaria
Proguanil:					
100 mg. daily ..	245	11	9	4.5	8.2
200 mg. " ..	48	0	0	0	0
Mepacrine:					
100 mg. daily ..	30	1	2	3.3	10.0
Quinine:					
4 or 5 gr. daily ..	59	4	4	6.8	13.6
Chloroquine:					
300 mg. twice or thrice weekly ..	8	0	0	0	0
Intermittent:					
Proguanil	29	5	3	17.3	27.6
Mepacrine	6	1	2	16.7	50.0
Quinine	9	1	2	11.1	33.3
Nothing	1	1	0	100.0	100.0
	435	24	22	5.7	10.6

TABLE VI.—*Incidence of Malaria in Non-native children Resident in Nigeria Less than 10 Years of Age, as Diagnosed at the Interview, and the Antimalarial Drug being Used at the Time*

Antimalarial Drug and Dose*	No. Taking	No. with Positive Blood Film	No. with Diagnosis of Clin. Malaria	% with Positive Films	Total % Malaria
Children 1 to 9 years					
Proguanil:					
25 mg.	1	0	0	0	0
50 "	17	1	3	6	24
100 "	35	0	1	0	3
Quinine:					
1½ to 2½ gr. ..	17	1	3	6	24
4 or 5 gr.	2	0	0	0	0
Chloroquine:					
150 mg.	1	0	0	0	0
Children under 1 year of age					
Proguanil:					
25 mg.	4	1	0	25	25
50 "	6	0	0	0	0
Quinine:					
1 or 1½ gr. ..	2	0	0	0	0
Lacquin:					
½ or 1 dr. ..	5	0	0	0	0

* The dose in the case of chloroquine is taken thrice weekly.

incidence of malaria discovered in the groups of patients taking 100 mg. of proguanil, 100 mg. of mepacrine, or 4 or 5 gr. (260 or 320 mg.) of quinine. The evil effects of using any of these drugs intermittently are clearly demonstrated in Table V.

The data obtained from children under 10 years are set out in Table VI. Although few in number, the figures suggest that proguanil in adequate doses is a satisfactory antimalarial drug for this group. For infants 1 to 1½ gr. (65 to 100 mg.) of quinine seems to be an efficient prophylactic dose.

Discussion

Past experience with antimalarial drugs in Nigeria has led many of the individuals included in this investigation to relinquish quinine or mepacrine in favour of proguanil or chloroquine. The high incidence of a previous history of malaria in the group initially taking quinine provides good reason for the swing away from this drug, but no such reason exists in the case of mepacrine. The yellow discoloration of the skin associated with the regular use of mepacrine provided most of the Europeans with a ready excuse for changing to something else.

The incidence of malaria discovered in those patients taking quinine at the time of the interview was not significantly higher than that among patients taking 100 mg. of proguanil or of mepacrine. This fact cannot be used as an argument to offset the high incidence of the disease in the past histories of those taking quinine. It was impossible to decide if the cases of malaria encountered at the time of the interview were fresh infections or were relapses of earlier infections.

The information disclosed by this investigation indicated that malaria will occur in about 10% of those using a daily dose of 100 mg. of proguanil, but that daily doses of 200 mg. of proguanil or doses of 300 mg. of chloroquine twice or thrice a week provide efficient prophylaxis against the subtertian malaria endemic in Nigeria. In the experience of the group of people which has been studied, and in my own and that of my family, the higher dose of proguanil causes no unpleasant side-effects.

It is impossible to say whether the high dosage of proguanil recommended as a result of this investigation is necessitated by a developing resistance of the local strains of plasmodium to this drug or if the dosage used in the past was too small to accomplish efficient prophylaxis.

Conclusions

The data presented and discussed lead to the general conclusion that, in the present state of knowledge and in view of past experience, proguanil in adequate dosage is the most satisfactory drug to use in Nigeria at the present time for the prevention of malaria. Chloroquine has been taken by so few people, and for such a short time, that it would be unwise to draw any premature conclusions about its efficiency, but the information so far available is of a satisfactory nature. The conclusion that a daily dose of 100 mg. of proguanil or of mepacrine is more effective as a suppressive than 5 gr. (320 mg.) of quinine against the local strains of *P. falciparum* is based upon good evidence.

Proguanil, in daily doses of 200 mg. for those 10 years of age and over and 50 mg. for children under the age of 1 year, with proportionate intermediate doses, is an efficient prophylactic. Quinine in daily doses of 1 to 1½ gr. (65 to 100 mg.) is satisfactory for infants.

These conclusions are not intended to belittle the importance of applying all the other means available to prevent infection being acquired by the non-immune population of Nigeria.

Summary

An account is given of an investigation carried out in Lagos, Nigeria, which was designed to discover which of the many available antimalarial drugs are being, and

have been, used by a group of non-native residents in that country, and what is the past and present incidence of malaria in this group.

The group was composed of all the non-native residents in Nigeria who reported to my out-patient clinic between November 1, 1951, and March 31, 1952.

The following antimalarial drugs were being used at the time these patients were interviewed: proguanil by 68%; quinine by 16%; mepacrine by 6%; chloroquine by 2%. Of the whole group, 6% admitted to being, or were known to be, intermittent in their habits. One individual did not take any antimalarial drug.

Among the adults who had taken only one antimalarial drug daily with regularity since starting to live in Nigeria, a past history of malaria was reported as follows: those taking 100 mg. of proguanil, 15%; 200 mg. of proguanil, 0%; 100 mg. of mepacrine, 17%; 4 or 5 gr. (260 or 320 mg.) of quinine, 50%. Chloroquine in doses of 300 mg. twice or thrice weekly had been taken regularly by three individuals, none of whom reported having had malaria.

The overall incidence of malaria in the group at the time of interview was found to be 11%, of which total 10.9% occurred in those 10 years of age and over and 12.2% in children below this age. Excluding all individuals self-admittedly irregular takers of any antimalarial drug, the incidence of malaria was found to be 9%, and if children are excluded the incidence in adults 20 years of age and over was 8%.

It is concluded that the most satisfactory prophylactic to use at the present time against the subtertian malaria endemic in Nigeria is proguanil, taken in doses of 200 mg. daily by those 10 years of age and over and 50 mg. daily for babies under 1 year. Quinine in doses of 1 to 1½ gr. (65 to 100 mg.) daily is a satisfactory suppressive for infants.

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The perennial problem of over-population is again stressed in the report for 1951 of the health conditions in the Maltese Islands and of the work of the Medical and Health Department, which was published recently. Cardiac conditions and cerebral vascular accidents accounted for the highest proportion of deaths, the figures being 148 and 102 per 1,000 respectively. Research is being carried out on the radical cure of malignant growths; deaths from this cause increased during the year under review. Progress is reported in the fight against tuberculosis: a good proportion of the population is being radiographed, and the incidence of the disease has shown a considerable decrease. An attempt has been made to integrate the laboratory services in Malta, which are at present divided into several sections and spread over a wide area. All this and much more information is contained in the report, which is available from the office of the Chief Government Medical Officer, Malta.

FEMALE FERTILITY

BY

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In 1866 Matthews Duncan noted that "whilst a large number [of women] are fertile for a first time in each of the first three years of married life, only 7% of the fertile bear children after three years of marriage." From this it has been concluded by most British authors that sterility should be investigated after three years of marriage. In the United States of America most of the gynaecological textbooks suggest that two years of potentially fertile coitus should elapse before investigation. This may well be due to the work of Pearl (1939), who concluded, after investigating the case records of 199 white American women, that it took a woman, on an average, 24 months to conceive.

Recent editions of American and British textbooks voice this confusion. Four give four years as the time which should elapse before investigation of sterility, five give three years, three give two years, and two give one year. The others give no time. It is noted that those writers who have made a special study of the problem tend to investigate infertility after a shorter time than the others. As an example of this, Meaker's (1934) definition of infertility may be quoted. He defines sterility as "the inability to initiate the reproductive process on the part of a couple who have desired and attempted to reproduce for a reasonable length of time, ordinarily at least one year."

The incidence of infertile couples is estimated variously as between 8.5 and 15% of all marriages. In these unsettled times it becomes more important to determine the average length of time between the desire to conceive and the actual conception, so that those who exceed this average may be investigated with the minimum of delay. For nowadays, with poor housing conditions, voluntary contraception, occupations which entail longer or shorter periods of separation of the couple, later age of marriage, and impending separation for military reasons, those who are anxious to conceive should be helped as much as possible. As time passes and a woman still finds herself barren, much marital unhappiness and stress (which Stallworthy (1948) contends is itself a factor in infertility) accrues, and it is little comfort to her to be told by her doctor to "go away and don't worry, for you are still young."

That the fertility of a woman is related to her age has been believed from the time of Matthews Duncan onwards. In his investigations in Glasgow in 1866 he found that while 90% of women between the age of 20 and 24 would conceive for a first time within two years of marriage, only 63% of women between the ages of 30 and 34 and only 15% of women between the ages of 40 and 44 would do so. The Royal Commission on Population (1949) also gives interesting figures regarding the decline of fertility and the duration of marriage. It appears that the risk of conception in the second five years of marriage is reduced to about 50% of the risk in the first five years, and is again halved in the third five years.

Fertility in Salford

This survey was therefore undertaken in order to determine the average interval between the desire to conceive