Papers and Originals

Cycloguanil Pamoate in the Treatment and Suppression of Malaria in the Gambia, West Africa

IAN A. MCGREGOR,* O.B.E., M.R.C.P., D.T.M.&H. ; K. WILLIAMS,* A.I.M.L.T.
G. H. WALKER,* M.B., CH.B. ; A. K. RAHMAN,* M.B.E.

Brit. med. J., 1966, 1, 695-701

Cycloguanil pamoate is an antimalarial drug recently developed by Thompson *et al.* (1963) in the United States. It is closely allied to the existing drugs, proguanil and pyrimethamine, and when administered intramuscularly is slowly released and thus maintains an effective antiparasmodial blood level for a prolonged period. The advantages offered by a repository drug become obvious when consideration is given to the difficulties of affording protection against diseases characterized by high rates of transmission to populations who live in small, isolated communities. A reliable antimalarial which remained effective for several months after administration in a single dose could materially enhance the role of chemoprophylaxis in campaigns undertaken to eradicate malaria. The present trial was made in 1964 to determine, in a hyperendemic West African environment, the antimalarial properties of cycloguanil pamoate at dosage levels known to be both safe and effective against malaria induced experimentally in Caucasian volunteers.

Cycloguanil Pamoate

Cycloguanil pamoate (Camolar ; CI-501) is a pamoic acid salt of dihydrotriazine suspended in a lipid vehicle. The dihydrotriazine moiety has been described as the active metabolite of proguanil by Carrington *et al.* (1951), and its soluble hydrochloride salt is known to possess high suppressive activity against the blood forms of the genus *Plasmodium*. Animal experiments indicated that repository action was achieved against challenge with trophozoites or sporozoites of *P. cynomolgi* and that the duration of action was influenced by the particulate nature of the preparation ; longest protection followed dosage with coarse rather than fine particles (Thompson *et al.*, 1963 ; Schmidt *et al.*, 1963).

The therapeutic and prophylactic value of cycloguanil pamoate in man has been tested against infections with *P. vivax* and *P. falciparum*. Protection was conferred for at least six months, and often for more than a year, against trophozoite and sporozoite challenges made intermittently with *P. vivax*, while parasitaemia patent at the time of treatment cleared within 72 hours (Coatney *et al.*, 1963). Alving (1963) showed that full protection was conferred against trophozoite and sporozoite challenge with proguanil-sensitive strains of *P. falciparum* but not to proguanil-resistant ones. Further studies by Lunn *et al.* (1964) have suggested that so far as *P. falciparum* is concerned the drug may act as a true causal prophylactic.

As is to be suspected from its similarity to proguanil, cycloguanil pamoate is antifolic and probably disrupts normal nuclear division in plasmodia by inhibiting folic-acid metabolism. At effective dosage levels in man slight temporary

reduction has been noted in haematocrit and haemoglobin values, and in erythrocyte density in some individuals.

Field Trial

Objectives

The principal objectives were to determine by controlled trial: (1) the acceptability of the drug to representatives of all age groups of a rural African population ; (2) the incidence and importance of side-effects, both local and systemic, that followed drug injection ; (3) the response of existing parasitaemia to therapy ; and (4) the duration of subsequent protection against natural challenge.

Selection of Subjects

Kafuta, a moderately prosperous village in the Kombo East district of the Gambia, was selected as the site after preliminary survey had confirmed its suitability, and 245 suitable subjects were allocated according to randomization tables to either drug-treated or control groups. Little effort was made to balance the groups according to sex. The eventual distribution of the subjects studied was as shown in Table I.

TABLE I.—Distribution of Subjects in Control and Treated Groups

Age (Years)	Treated			Controls		
	Male	Female	Total	Male	Female	Total
6/12-2	8	14	22	6	12	18
3-5	8	8	16	10	7	17
6-13	22	19	41	16	25	41
14+	21	24	45	16	29	45
Total	59	65	124	48	73	121

Timing of Therapy

The results of a trial of any long-acting drug are singularly apt to be influenced by season. In the Gambia transmission of malaria is frequent in the wet months July to November, and much less common in the remaining dry months. To minimize the effects of this variation in the present study three separate series were created within both the treated and the control groups. The first of these (44 drug, 41 control) received their appropriate injections in February 1964, the next (45 drug, 45 control) two months later in April, and the final series (35 drug, 35 control) in June. In this way members of the February series were dosed at a time when they could expect to experience some four months of relative freedom from severe plasmodial challenge, while those of the April series

* From the Medical Research Council Laboratories, Gambia.

could expect a similar reprieve of some two months' duration. Members of the June series, however, received their injections just prior to the onset of heavy malarial transmission.

Dosage

Cycloguanil pamoate in oily suspension was administered to each age group at the following dosage: 6 months to 2 years 0.6 ml. (84 mg. base), 3 to 5 years 1 ml. (140 mg. base), 6 to 13 years 1.8 ml. (250 mg. base), and over 14 years 2.5 ml. (350 mg. base). Controls received only the drug-free vehicle in precisely the same volumes according to age.

Administration was by intramuscular injection, the buttock being constantly the site of choice. Care was taken to ensure that the drug particles were in uniform suspension. As cycloguanil pamoate is heat stable, the ampoules were warmed in boiling water, thoroughly shaken, and allowed to cool to body temperature before administration.

Methods

Two days prior to injection all members of the treatment and control groups were re-examined. The height and weight of each were recorded, and distinguishing features, including state of dentition, noted. Oxyhaemoglobin values were determined from capillary blood with the M.R.C. grey-wedge photometer (Macfarlane *et al.*, 1948). Microhaematocrit readings were made after spinning in a Hawksley microhaematocrit centrifuge for five minutes at 12,000 *g*. Thin blood films were stained by Giemsa's method and thick ones by Field's. In the case of members of the February-treated and control series, the supernatant plasma was retained after haematocrit readings had been made and was used for subsequent assessment of fluorescent malarial antibody titre by the method described by McGregor *et al.* (1965).

At day seven post injection all subjects were again examined and the state of the injection site was noted. Complaints volunteered were recorded, but no information was sought by direct questioning. Thick and thin blood films were again made and capillary blood samples taken for haemoglobin and microhaematocrit determination. These examinations were repeated at the end of each month after injection.

Parasite density counts were made by enumerating parasites against leucocytes, and, on the assumption of a standard leucocyte count of 8,000/c.mm., the density per c.mm. was estimated.

Results

Injection Site Reaction

February Series.—The members of this series were injected in the right gluteus maximus. In the days immediately after injection drug-treated subjects frequently complained of pain at the site, and some emphasized the point by hobbling or walking with the aid of a stick. Pain seemed to be maximal on days two and three, and thereafter rapidly abated. In contrast, few members of the control group complained or showed evidence of incapacitation.

Over the first two months 12 of the 44 drug-treated subjects complained of abscess development with subsequent pointing and discharge. In all but one inspection confirmed the history and the presence of a discharging sinus was noted. These complications usually developed in the second and third weeks following injection, but in one instance occurred nine weeks after what seemed to be entirely satisfactory drug administration. In four subjects the progress of abscess formation was observed during hospitalization. Cultures made from the discharge on

the day of rupture yielded negative results, while stained smears showed no organismal content but revealed the presence of drug crystals.

No abscess developed, late or early, in any member of the control group.

April and June Series.—The incidence of serious local reaction in the drug-treated series was alarming. Observation suggested that abscess formation might be the result of cycloguanil pamoate gaining access to fatty tissue and it was decided to change the site of injection. The gluteus minimus was selected as the new site, and injection in the subsequent series was made into a V-shaped space formed between the fingers when the first finger of the left hand was placed on the right anterior superior iliac spine with the second finger, abducted, on the crest of the ilium.

No further instance of abscess formation was observed, while the incidence of pain and tenderness at site after cycloguanil pamoate administration decreased markedly. Drug-treated subjects still showed a higher reaction incidence than did the control group but in none was reaction considered so severe as to have jeopardized acceptability.

Therapeutic Effect

Asexual parasitaemia was found in 81 (65%) of 124 drug-treated subjects two days before therapy. Of the infections 99% were with *P. falciparum*, 17% with *P. malariae*, and 4% with *P. ovale*. Seventy-six (63%) of 121 vehicle-injected subjects were similarly parasitized, the species frequency being *P. falciparum* 97%, *P. malariae* 22%, and *P. ovale* 8%. Table II shows the frequency and density of pre-injection parasitaemia by age and sex in both groups, children under 6 years of age being classified together.

TABLE II.—Incidence and Density of Malarial Parasitaemia in the Two Groups Prior to Injection

	Age		
	< 6 Years	6–13 Years	14+ Years
Drug treated:			
Infected	30/38 (79%)	39/41 (95%)	12/45 (27%)
Mean parasite density ..	7,949/c.mm.	1,919/c.mm.	160/c.mm.
Range	10–74,240/c.mm.	10–19,000/c.mm.	10–540/c.mm.
Control:			
Infected	28/35 (80%)	40/41 (98%)	8/45 (18%)
Mean parasite density ..	5,629/c.mm.	1,211/c.mm.	1,011/c.mm.
Range	80–50,000/c.mm.	30–10,560/c.mm.	20–6,200/c.mm.

Seven days after injection blood films were prepared from all but one of the drug-treated individuals and from all control subjects. After standard examination of 100 oil fields of each thick film no asexual parasites were detected in any drug-treated member, but 55% of the control subjects still showed circulating asexual parasites. The drug appeared to have no immediate effect upon gametocytes and no morphological change was noted in these following therapy; gametocytaemia persisted into the second month in 16 persons, and into the third month in one.

Chemoprophylaxis After First Injection

Of the 124 drug-treated subjects 44 were dosed in February, 45 in April, and 35 in June. Members of the February and April series maintained good attendance records throughout their respective observation periods but a high proportion of the June series refused to attend for further examination from the fourth month onwards. These non-attenders were all members of one religious minority recognized as the most uncooperative and unreliable section of the Gambian population. Freedom from asexual parasitaemia for each treatment

group is shown in Fig. 1, which illustrates the percentage of each group remaining parasite-free at week one, and at the end of each month, post injection. The figure gives the results in a cumulative manner, and to simplify presentation persons not seen, but not known to have been reinfected, are classified with those known to be parasite-free. Wherever this occurs the percentage of those non-attenders is shown. (For purposes of comparison it may be stated that the incidence of asexual parasitaemia in control subjects of all series did not fall below 48% at any month following injection.)

FIG. 1.—Duration of protection following cycloguanil pamoate.

Members of the February drug-treated series enjoyed longer freedom from malaria than did persons treated in April or June. At the end of the fourth month over 90% showed no evidence of asexual parasitaemia and the first major wave of reinfection did not occur until the fifth month. In contrast, a high incidence of breakthrough occurred in the third and fourth months both in the April and in the June series. This difference is further emphasized by the fact that about a quarter of the persons treated in February possibly lost some part of their drug inoculum through sinus formation.

Three drug-treated members of the February series and four of the April group, each with complete attendance records, were still trophozoite-free at the tenth and eighth months respectively. All but one, a boy of 7 years, were adults. The significance of this observation is not readily assessable, for the

examination of 100 fields of a single blood film each month does not constitute an exacting criterion of the absence of infection. If, however, these subjects were in fact malaria-free the role of acquired immunity in promoting prolonged drug action must be considered, for they belonged predominantly to the highly immune adult section of the population. One member of the February control series remained aparasitic for 10 months and two of the April series for eight months. All three subjects were adults.

The number of persons, treated and control, remaining unparasitized throughout the trial period is too small to justify statistical comparison. However, as the immune state of an individual is likely to influence the effectiveness of any anti-malarial drug, and since acquired immunity advances with age, a comparison by age of the groups treated with cycloguanil pamoate is presented in Fig. 2.

The earliest recurrence of parasitaemia was in an 18-month-old child who had been injected in June, and whether it represented a fresh infection or a recrudescence of a pre-existing infection it is impossible to say. *P. falciparum* trophozoites were found in low density (less than 10/c.mm.) in a blood film taken routinely at month one and in another taken 48 hours later. The parasitaemia responded to pyrimethamine therapy (12.5 mg. in single dose) and the child subsequently remained malaria-free until month three.

In general the protection conferred upon individuals of all ages by cycloguanil pamoate decayed slowest in those who received the drug in February. This difference can probably be attributed to the change in malarial endemicity that occurs with season in the Gambia. Protection persisted longest in adults irrespective of month of therapy. However, in the three treatment groups little difference in duration of protection was detected in the younger age groups. The similar behaviour of these younger age groups is of interest, for it suggests that some factor other than degree of acquired immunity is

TABLE III.—Mean Logarithmic Values for Fluorescent Antibody Concentration Prior to Injection in Members of the February Series

Age	Cycloguanil Group		Control Group	
	No.	Titre	No.	Titre
<3 years ..	6	1.81	7	1.98
3-5 " ..	8	2.18	5	2.19
6-13 " ..	14	2.65	14	2.63
14+ " ..	16	3.22	15	2.95

important in determining the duration of drug action. Epidemiologically, children aged 6 to 13 years in the Gambia exhibit greater acquired immunity than younger ones. They show a greater ability to restrict parasite density (see Table II), and, while apparently unable to eliminate parasitaemia, rarely suffer even moderately severe clinical illness. These general epidemiological observations were supported by the findings of fluorescent antibody assay in members of the February series, which showed a steady rise in titre with age (Table III).

Thus, despite evidence indicating that in this study children aged 6 to 13 years possessed substantially greater acquired immunity than younger children, this difference was not manifest in a prolongation of protection following drug treatment. It is therefore necessary to consider results in relation to level of drug dosage.

As has already been stated, cycloguanil pamoate was administered to each age group at a flat rate of dosage. Since each person was weighed before treatment, it was possible to calculate with accuracy the quantity of drug given per unit of body weight. Choosing four different dosage levels, 4<5 mg./kg., 5<10 mg./kg., 10<15 mg./kg., and 15+ mg./kg., the

FIG. 2.—Duration of protection following cycloguanil pamoate according to age.

response to therapy has been analysed. Results are shown in Fig. 3.

it possible to analyse by age and by dosage the 83 sinus-free subjects who were examined in consecutive months for six months (Fig. 5). This confirms the observation that, whereas the senior age group enjoyed the most prolonged freedom from asexual parasitaemia, no one younger age group was at an advantage over the others. Similarly, again it is not possible to correlate directly duration of protection with size of dosage.

Second Injection of Cycloguanil Pamoate

Seventy-two persons received a second injection because of renewed asexual parasitaemia. By predetermined policy none was re-treated with cycloguanil pamoate within four months of the first injection; patent infections that developed in the interval were treated with oral pyrimethamine or proguanil. Of the 72 re-treated individuals 34 were members of the February series, 34 of the April series, and four of the June series. Fifteen were aged less than 3 years, 12 were 3 to 5 years, 31 were 6 to 13 years, and 14 were 14 or more years of age.

Site reactions to second injections were not severe. Of the 72 subjects re-treated with cycloguanil pamoate none showed asexual parasitaemia on the seventh day after therapy. One, however, became infected at month one, five at month two, 17 at month three, four at month four, three at month five, and one at month six. Analysis by dose and age is shown in Fig. 6.

The results expressed in this figure broadly confirm those observed after the first injection. They also confirm the proneness of those aged 6 to 13 to reinfection despite relatively high drug dosage and despite substantial acquired immunity.

Of 31 individuals who showed recurrence of parasitaemia after each of two injections of the drug the second injection conferred longer protection in four, for the same period in six, and for a shorter period in 21. On average, the first injection protected into the fourth month, and the second into the third; but it is important to note that most of the second injections were given in the period of most intense malarial transmission.

Haematological Observations

In Table IV the mean pre-injection haemoglobin values of treated and control subjects are shown contrasted with mean values observed subsequently in the same individuals. Values for months four and later, other than for December 1964, are not given, since frequent malarial breakthrough in these months

Fig. 3.—Duration of protection following cycloguanil pamoate according to dosage.

It is apparent that increase in the amount of drug administered per unit of body weight was not followed by correspondingly prolonged protection. That the lowest dosage level employed produced best results is probably explained by the fact that those who received it were adults possessing substantial immunity. In estimating drug dosage no allowance was made for drug-loss in those members of the February series who developed discharging sinuses. Since duration of protection has no obvious direct correlation with drug dose per unit of body weight, its relationship to size of the drug inoculum should be considered. Fig. 2 gives the relevant details. Again it will be noted that, whereas the adults who received the largest inoculum did indeed experience longer protection, little difference is obvious in the three younger groups despite substantial differences in volume of drug administered; the age group 6 to 13 years in each series fared no better than the youngest group despite a threefold difference in volume of inoculum.

Of 95 persons examined in consecutive months for six months or until reinfected 12 developed sinuses. Duration of protection is contrasted in Fig. 4 between the sinus-free and sinus-afflicted individuals. The similar behaviour of the two groups does not suggest that sinus-free persons experienced any material advantage.

Elimination of subjects who developed sinuses, and of those who failed to attend for their follow-up examinations, makes

Fig. 4.—Duration of protection following cycloguanil pamoate in 12 sinus-positive and 83 sinus-free subjects examined monthly for six months.

Fig. 5.—Protection following cycloguanil pamoate (A) by age and (B) by dosage in 83 sinus-free subjects examined monthly for six months.

greatly influenced individual haemoglobin levels. It will be noted that at each observation after cycloguanil injection the mean values for the three youngest age groups exceed the pre-treatment mean value. Only in the oldest age group did the post-treatment values tend to fall below pre-treatment levels, but even here the treated group maintained values superior to those of their controls. These findings indicate either that cycloguanil pamoate did not depress erythropoiesis or that its antimalarial benefit more than balanced any possible depressant effect.

Mean haematocrit values behaved in a manner similar to those for haemoglobin. The mean haemoglobin values of the same subjects, before and after a second injection of cycloguanil, are shown in Table V. The slight falls in haemoglobin concentration recorded at week one are most likely due to malaria. The absence of any subsequent mean value lower than pre-injection levels again indicates that cycloguanil exerted no depressant haematological effect.

In no instance was any abnormality detected in leucocytes or erythrocytes in routine examination of thick and thin blood films.

TABLE V.—Mean Haemoglobin Values of the Same Individuals Before and After Second Injections

Age	No. of Persons	Mean Haemoglobin Values (g./100 ml.)					
		Pre-injection	Post-injection				
			Week 1	Month 1	Month 2	Month 3	December
> 3 years	14	9.56	9.50	10.97	10.47	10.94	10.70
	14	9.62					
	12	9.90					
	9	10.24					
	13	9.40					
3-5 years	10	10.51	10.63	11.74	11.71	11.00	12.12
	12	10.77					
	11	10.89					
	9	10.80					
	12	10.77					
6-13 years	31	11.79	11.44	11.80	11.97	12.33	12.82
	31	11.79					
	26	11.85					
	22	12.00					
	30	11.79					
14+ years	14	12.75	12.02	13.16	12.86	12.27	13.81
	13	12.82					
	9	12.43					
	4	12.12					
	14	12.75					

Treatment of Breakthroughs

In all, 160 malarial episodes developed in the 124 treated persons over the observation period: 142 were treated immediately after a second blood film confirmed the infection. Forty-two episodes were treated with single doses of pyrimethamine (12.5 mg. for children less than 6 years, others 25 mg.); 28 were treated with proguanil (300 mg. on each of three successive days for adults and proportionately less for children); and 72 were re-treated with cycloguanil pamoate at a dose identical to the earlier one. Thick and thin blood films were again examined on day seven post therapy; in no instance were asexual parasites found. Eighteen episodes remained untreated, either because the individuals were not available or because they occurred

FIG. 6.—(A) Duration of protection following second injection of cycloguanil pamoate according to dosage. (B) Duration of protection following second injection of cycloguanil pamoate according to age.

TABLE IV.—Mean Haemoglobin Values of Those Patients, Treated and Control, Examined Before and After Injection

Age Group	No. of Persons		Mean Haemoglobin Values (g./100 ml.)									
			Pre-injection		Post-injection							
	Week 1				Month 1		Month 2		Month 3		December	
	T	C	T	C	T	C	T	C	T	C	T	C
< 3 years	21	18	9.98	9.82	10.66	9.83	11.11	10.48	11.35	10.20	10.79	10.25
	20	17	10.03	9.81								
	22	15	9.95	10.09								
	21	17	9.89	9.81								
	18	13	9.94	10.03								
3-5 years	16	17	11.28	10.43	11.82	10.96	12.19	10.42	12.38	10.78	12.27	10.83
	16	17	11.28	10.43								
	16	17	11.28	10.43								
	16	16	11.28	10.53								
	13	15	11.20	10.53								
6-13 years	41	41	11.94	11.93	12.19	11.97	12.03	11.60	12.44	12.00	12.02	11.74
	40	40	11.96	11.89								
	40	40	12.21	11.89								
	39	41	11.93	11.93								
	34	33	12.73	11.90								
14+ years	45	45	13.38	12.90	13.06	12.69	12.93	12.48	13.15	12.59	12.62	12.17
	44	43	13.39	12.97								
	42	43	13.32	13.25								
	44	42	13.32	12.88								
	36	35	13.28	12.90								

T = Cycloguanil pamoate-treated subjects. C = Control subjects.

in the last month of observation and clinically did not warrant treatment.

Teratogenic Effects

Three women were pregnant at the time of cycloguanil injection. Two progressed normally and were ultimately delivered of healthy, normal children. The third aborted two months after therapy. Two further women became pregnant post injection; both the pregnancies progressed without incidence and both have since been delivered of normal children. From date of delivery, conception in one instance appeared to have occurred around the fifth week post injection and in the other at the twelfth week.

Four vehicle-treated women were pregnant at time of injection and a further one became pregnant post injection. All have since been delivered of normal children.

The incidence of abortion in the Gambia is high, and its occurrence in one woman treated with cycloguanil pamoate is probably unlikely to have been attributable to the drug.

Discussion

Side-effects of Cycloguanil Pamoate

Thompson *et al.* (1963) were of the opinion that systemic toxicity was unlikely to follow the repository use of the drug, since low plasma levels were attained and no appreciable drug storage occurred in tissues other than at the injection site. Schmidt *et al.* (1963), however, drew attention to the potential effects of a folic-acid antagonist on undernourished communities. It is therefore of interest that in no drug-treated member of the present trial was there observed any evidence of systemic toxicity.

Of greater concern was the severity of injection-site reactions that developed early in the trial. This was unexpected and alarming, and had we been unable to modify the course of subsequent injections our interest in cycloguanil pamoate would have ceased abruptly. However, change of site to an area relatively free from fat eliminated serious reactions, and it must be emphasized that successful large-scale administration of this drug in its present form will be conditional upon the maintenance of a high standard of injection technique.

Despite the inauspicious start, the drug remained surprisingly popular among the villagers. No person refused a second injection when one was offered, and the pain and tenderness that commonly occurred in the first few days post injection were accepted with good humour.

Chemotherapeutic Results

Two-thirds of the drug-treated subjects showed asexual parasitaemia immediately before medication. By the seventh day after drug administration asexual forms had disappeared in all instances. Since the criterion of change was based solely on the study of 100 oil fields of a thick film, caution should be exercised in the interpretation of results. Nevertheless, the uniform response of asexual parasitaemia to both first and second injections indicates the cycloguanil pamoate is a powerful schizonticide and that the prevalent plasmodial species were susceptible to the drug at the beginning of the trial and remained so throughout. The choice of pyrimethamine or proguanil for the treatment of early breakthroughs was deliberate, for we wished to detect incipient parasite resistance at the earliest moment. In the event, no unsatisfactory response was noted in 42 breakthroughs treated with pyrimethamine or in 28 treated with proguanil. These findings indicate that the field use of cycloguanil in repository form did

not, within the time span of the trial, encourage the creation or selection of drug-resistant strains of plasmodia.

Duration of Chemoprophylaxis

The duration of protection against malaria that followed a single injection of cycloguanil was substantially greater than could reasonably have been expected to follow a single dose of any other known antimalarial. In general, however, chemoprophylaxis in this trial did not last as long as in American volunteers treated at comparable dosage rates with the same particle size. As the American volunteers had never previously experienced malarial infection, the Gambian subjects might have been expected to enjoy greater freedom from parasitaemia as a result of acquired immunity. There was no evidence that the Gambian plasmodia were less susceptible to cycloguanil, since no breakthrough failed to respond to further treatment with cycloguanil itself or to the allied drugs, proguanil and pyrimethamine. The American volunteers received heavy parasitic inocula and it seems unlikely that the Gambians were challenged more intensively.

Cycloguanil is a relatively insoluble substance and the maintenance of effective plasma levels following its intramuscular administration is probably affected by the amount of drug present in the inoculum and by the rate of blood flow around the injection site. Whereas the American volunteers were penitentiary prisoners, the Gambian adults and older children were actively engaged in prolonged arduous agricultural activity, and it is possible that in the Gambians the relatively short duration of chemoprophylaxis was principally the result of sustained muscular activity and hyperaemia causing a faster rate of absorption from the injection site. This may explain why African children aged 6–13 years appeared to possess substantial immunity and yet, despite a high rate of cycloguanil dosage, remained protected for no longer than younger children and for considerably less than their adult counterparts. There can be little doubt that many factors other than drug dosage and parasite susceptibility combine to render difficult the assessment of drug action in subjects of varying immune states, and we are of the opinion that, so far as repository drugs deposited in muscle are concerned, the degree of muscular activity and associated local hyperaemia may be an important factor in determining the duration of chemoprophylaxis.

Conclusions

The evaluation of a long-acting antimalarial employed in field conditions is complex. Precise assessment of the frequency and nature of challenging infection in individual members is not possible; medical observations must be restricted to what is acceptable to the population and should not disrupt everyday life; in hyperendemic environments the occurrence of individual differences in immune states introduces an almost unfathomable variable. In the long run the success of the trial varies with the criteria of its assessment.

Compared with findings in non-immune American volunteers treated with similar doses of cycloguanil the duration of chemoprophylaxis in the Gambian trial is disappointingly brief. However, compared with what could reasonably have been expected to follow a single dose of any known antimalarial it is encouraging. Since no signs of systemic toxicity were detected, extended trial of the drug at increased dosage is clearly indicated. Furthermore, in explanation of the discrepant results of the American and Gambian studies the influence of muscular activity on the rate of absorption of cycloguanil from intramuscular deposits merits study.

The frequency of site reactions following injection of the drug in the pamoate form may well affect its popularity in any mass application, though choice of a relatively fat-free site can

materially reduce the incidence of painful side-effects. Finally, if the Gambia can be considered as representative of communities in West Africa the hazard of swiftly creating widespread drug resistance in plasmodia through the result of a repository antimalarial in this area would seem to be smaller than has been feared by some authorities.

Summary

The repository antimalarial properties of single doses of cycloguanil pamoate were tested in hyperendemic field conditions in the Gambia, West Africa. The first subgroup of treated subjects developed pain, tenderness, induration, and swelling at the injection site in high incidence, and sterile abscess formation occurred in 27%. Change of injection site to one less closely associated with adipose tissue greatly reduced the incidence of local reaction in subjects treated subsequently. No signs indicative of systemic toxicity were detected in treated or control subjects and haemoglobin concentrations in the former tended to improve after dosage.

Asexual parasitaemia existed in 65% of treated subjects before dosage. At day 7 post therapy all were trophozoite-free, though gametocytaemia persisted. Before injection 63% of control subjects were similarly parasitized and by day 7 55% were still infected.

Chemoprophylaxis following cycloguanil administration was of substantially greater duration than would have been expected to follow a single dose of any known antimalarial. However, compared with results obtained in American volunteers its duration was disappointingly short. It is suggested that the

extreme muscular activity of Gambian subjects may have increased rates of drug absorption and excretion.

The occurrence of strains of plasmodia resistant to cycloguanil, pyrimethamine, or proguanil was not observed during the trial. The absence of signs of systemic toxicity following cycloguanil administration indicates that further field trials should be undertaken at higher dosage levels.

We wish to acknowledge our gratitude to Mrs. R. Williams, for assistance of inestimable value in maintaining records and preserving village relations; to Drs. S. H. O. Jones and J. Mahoney, successive Directors of Health Services, Gambia, for their unfailing interest; to Dr. D. S. Harling, of the Medical Research Council Laboratories, Gambia, for his medical care of sick villagers, connected and unconnected with the trial; to Drs. K. O. Courtney and P. E. Thompson, of Parke Davis Co. Ltd., for making available full details of earlier experimental studies of the drug; and, above all, to the villagers of Kafuta whose trust and co-operation made possible a difficult project.

REFERENCES

- Alving, A. A. (1963). Unpublished summary of investigations.
Carrington, H. C., Crowther, A. F., Davey, D. G., Levi, A. A., and Rose, F. L. (1951). *Nature (Lond.)*, **168**, 1080.
Coatney, G. R., Contacos, P. G., Lunn, J. S., Kilpatrick, J. W., and Elder, H. A. (1963). *Amer. J. trop. med. Hyg.*, **12**, 504.
Lunn, J. S., Chin, W., Contacos, P. G., and Coatney, G. R. (1964). *Ibid.*, **13**, 783.
Macfarlane, R. G., King, E. J., Wootton, I. D. P., and Gilchrist, M. (1948). *Lancet*, **1**, 282.
Schmidt, L. H., Rossan, R. N., and Fisher, K. F. (1963). *Amer. J. trop. Med. Hyg.*, **12**, 494.
Thompson, P. E., Olszewski, B. J., Elslager, E. F., and Worth, D. F. (1963). *Ibid.*, **12**, 481.

Perforated Peptic Ulcer in the West of Scotland: a Survey of 5,343 Cases During 1954–63

COLIN MACKAY,* M.B., CH.B., F.R.C.S., F.R.C.S.ED., F.R.C.S.GLASG., B.SC.

Brit. med. J., 1966, **1**, 701–705

The incidence of perforated peptic ulcer in the West of Scotland has been studied from 1924 until 1953 (Illingworth, Scott, and Jamieson, 1944; Jamieson, 1955). This paper is concerned with the period 1954 to 1963.

As in the previous surveys, the area included the City of Glasgow and the Counties of Argyll, Dunbarton, Lanark, and Renfrew. This is a compact region and forms, surgically speaking, an isolated community. The hospitals in the area handle virtually all the emergencies occurring within the region and very few outside it. The population, which exceeds two million, is mainly industrial, being concentrated around Glasgow and Clydeside. The rural population, which is small, is located mainly in the highland county of Argyll.

The features of a perforated peptic ulcer are usually so dramatic that it was felt that few patients would fail to reach hospital. The study was therefore confined to a search of hospital case records, operation log-books, and post-mortem records. Only those cases in which the perforation was confirmed, either at operation or at necropsy, were included in the survey. The so-called "leaking ulcers" recovering without operation were excluded from the survey, as most clinicians

agree that such a diagnosis is difficult to establish with certainty.

All the hospitals which accept surgical emergencies were included in the survey. The information obtained from the case records was recorded on dual-purpose punch-cards to facilitate the subsequent analysis.

The area studied, the technique used, and the criteria adopted are the same as those in the previous surveys by Illingworth *et al.* (1944) and Jamieson (1955). The results are therefore comparable.

In this paper I wish to consider four aspects of perforated peptic ulcer: (1) the incidence, (2) the time, (3) the site, and (4) the treatment of perforation.

Incidence of Perforation

Fig. 1 shows the incidence of perforation in males and females over the 40-year period 1924–63. There was a fairly steady increase, except for the spike occurring in 1940 and 1941, up until the early 1950's. However, over the past 10 years the incidence has declined. There were 5,343 perforations in the period 1954–63, exactly 1,000 fewer than in the previous decade, and this despite a small increase in the popula-

* Hall Tutorial Fellow, University Department of Surgery, Western Infirmary, Glasgow. Now Registrar in Surgery, Western Infirmary, Glasgow.