we need a controlled experiment in proguanil prophylaxis, comparing proguanil-sensitive and proguanil-resistant strains of human malaria parasites, to decide whether there is in fact any significant difference in their response to regular prophylactic doses.

Summary

Fresh infections of falciparum and vivax malaria occurred late in the year 1950 among British troops in the Tampin district of Negri Sembilan, Federation of Malaya, shortly after they had started night patrols in one particular locality.

A similar incidence of malaria occurred in 1951 among troops from a different unit operating in the same areas.

The troops were on an official suppressive dosage of 100 mg. of proguanil daily, and suppressive discipline was thought to be good.

Treatment of some of the vivax infections revealed that their erythrocytic parasites were only temporarily suppressed by doses of 300 mg. of proguanil daily for 7 to 10 days. Parasitological and clinical relapses occurred 7 to 17 days after reverting to the normal suppressive dose of 100 mg. daily. One of these patients had been only three months in Malaya, and had been on regular suppressive proguanil from the day after arrival.

Possible explanations for these findings are discussed. Irregular dosage cannot be excluded as a possible cause of the incidence of malaria in the Tampin units, but it is thought that some infections may have developed in men who took their suppressive doses regularly. It is suggested that the proguanil-treated vivax patients may have been infected with a strain whose erythrocytic parasites were already partially resistant. If this may happen, as seems possible, then controlled experiments are needed to determine whether resistance of erythrocytic forms also implies that pre-erythrocytic forms may complete their development, and produce clinical attacks of malaria, despite regular prophylactic dosage from the time of infection.

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REFERENCES

- Bruce-Chwatt, L. J., and Bruce-Chwatt, J. M. (1950). *British Medical Journal*, 2, 7.
 Clua, M., Baliff, L., and Chelaresco, M. (1948). *Bull. World Hlth Org.*, 1, 297.
 Cooper, W. C., Coatsney, G. R., and Imboden, C. A. (1950a). *J. nat. Malar. Soc.*, 9, 59.
 ———, Jeffrey, G. M., and Imboden, C. A. (1950b). *Ibid.*, 9, 366.
 Covell, G., Nicol, W. D., Shute, P. G., and Maryon, M. (1949). *British Medical Journal*, 1, 88.
 Davey, F., and Smith, M. (1949). *Ibid.*, 1, 956.
 Edeson, J. F. B., and Field, J. W. (1950). *Ibid.*, 1, 147.
 Fairley, N. H., et al. (1946a). *Trans. roy. Soc. Med. Hyg.*, 40, 105.
 ——— (1946b). *Ibid.*, 40, 229.
 Hawking, F., and Thurston, J. P. (1951). *Ibid.*, 44, 695.
 Institute for Medical Research, Federation of Malaya (1950). *Third Interim Report to Colonial Medical Research Committee. (Mimeographed Report.)*
 ——— (1951). *Annual Report for the year 1950. In press.*
 MacLeod, R. C. (1951). *British Medical Journal*, 1, 282.
 Seaton, D. R., and Adams, A. R. D. (1949). *Lancet*, 2, 323.
 ——— and Lourie, E. M. (1949). *Ibid.*, 1, 394.

The production of films covering the field of medicine and surgery is being encouraged in Spain by a newly created Association of Medical Cinematography. Exchange of similar films with foreign countries is planned. The general secretarial work is being undertaken by Dr. don Juan Fernán Pérez, calle de Fuencarral, No. 113, Madrid. He is director of *Vida Sana* and medical editor of the daily paper *Madrid*.

CHEMOTHERAPY AND CHEMOPROPHYLAXIS OF MALARIA

CLINICAL TRIALS IN 500 CASES AND
MASS PROPHYLAXIS IN A HYPERENDEMIC AREA

BY

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During the past three or four years a number of new drugs have been tested at the Calcutta School of Tropical Medicine for their therapeutic and suppressive values in malaria. The patients admitted to the attached hospital were utilized for the purpose, but the main work on the suppressive therapy was carried out in a rural area about 40 miles from Calcutta. A summary of the work is given in Tables II and III.

I. CHEMOTHERAPY

Only those patients who had fever with parasites in the blood and had no antimalarial drug outside were selected for the trials. The blood was examined twice daily (thick film method, using Field (1941) or J. S. B.* stain) until it became negative for asexual parasites, and thereafter once daily throughout the period of hospital observation. Of the 500 cases examined 51% had *P. vivax* and 42% *P. falciparum* infection; the rest had mixed (4.4%) or *P. malariae* (2.6%) infection. The following drugs were tried:

TABLE I.—Schedules of Treatment

No.	Compound Used	Route of Administration	No. of Cases
1	Proguanil (paludrine)	(A) Oral	209
		(B) Intravenous*	12
		(C) Intramuscular	12
2	Proguanil + pamaquin	Oral	30
3	Quino-pamaquin	"	13
4	M.5943	"	18
5	Chloroquine	"	75
6	Chloroquine + proguanil	"	13
7	Camoquin	"	80
8	Camoquin + proguanil	"	8
9-13	Neochin and other 4 indigenous drugs	"	30
			500

* One patient also had oral and intramuscular proguanil in addition to intravenous therapy.

1. Proguanil

Effect on Temperature and Parasite.—The usual route of administration was by mouth, and in only a small number of cases was the parenteral method used. Orally, various dosage schedules were tried either in a single dose of 0.1 to 0.8 g. or in divided doses of 0.3 to 0.8 g. given daily over 4 to 10 days. With any of these regimes an acute attack was terminated on the third day in most cases. A daily dose of 0.3 to 0.6 g., however, seemed to produce the best results, and we think that a course of 1.8 g. given over five

*Jaswant Singh and Bhattacharji (1944).

TABLE II.—*Chemotherapy of Malaria*

Drug	Group	Dosage	No. of Cases					Total	Time for Fever to Subside		Time for Asexual Parasites to Disappear		Relapse Rate	Observation Period
			F.	V.	M.	A + M	W + F		1-3 Days	4 Days or More	1-3 Days	4 Days or More		
Proguanil hydrochloride (87% base)	1	Single dose: 0.1 g. (salt)	7	2	1	1	0	11	8 (72%)	3 (28%)	9 (81%)	2 (19%)	6 (4 F., 1 M., 1 F.+V.) out of 8 (5 F., 1 V.) = 75%	14-55 days in hospital
	2	Single dose: 0.3 g. (salt)	26	16	0	0	0	42	37 (88%)	5 (12%)	37 (88%)	5 (12%)	6 (5 F., 1 V.) out of 22 (13 F., 9 V.) = 27%	14-30 days in hospital
	3	Single dose: 0.5 g. (salt)	12	12	0	1	0	25	21 (84%)	4 (16%)	21 (84%)	4 (16%)	9 (5 F., 4 V.) out of 22 (11 F., 10 V., 1 F.+V.) = 41%	14-120 days (7 cases relapsed within a month)
	4	Single dose: 0.6 g. (salt), 4 cases 0.8 g. (salt), 8 cases Divided dose: 0.1 g. t.d.s. 4 days = 1.2 g. Divided dose: 0.6 g. (in 2 doses) on 1st day and 0.3 g. daily for next 3 or 4 days = 1.5 to 1.8 g. Divided dose: 0.2 g. (salt) 6-hourly for 4 days = 3.2 g. Divided dose: 0.1 g. (salt) t.d.s. for 10 days = 3 g. Divided dose: 0.3 g. (salt) b.d. for 10 days = 6 g.	6	6	0	0	0	12	8 (67%)	4 (33%)	8 (67%)	4 (33%)	4 out of 12 = 33%	{ Average: 3 weeks in hospital 4-6 months
	5		20	21	1	2	0	44	35 (80%)	9 (20%)	41 (93%)	3 (7%)	5 out of 12 = 42%	
	6		4	14	0	0	0	18	16 (89%)	2 (11%)	18 (100%)	Nil	No relapse	
	7		3	7	1	1	0	12	8 (67%)	4 (33%)	8 (67%)	4 (33%)	2 vivax relapse	Average: 3 weeks in hospital—9 followed up for 2 months
	8		12	13	0	0	0	25	21 (84%)	4 (16%)	23 (92%)	2 (8%)	2 falciparum relapse	Average: 3 weeks in hospital
	9		14	6	0	0	0	20	16 (80%)	4 (20%)	18 (90%)	2 (10%)	1 relapse	Average: 3 weeks in hospital
	10													
Proguanil lactate (74% base)	11	Single dose: 0.1-0.3 g. (lactate) intramuscularly	3	6	2	0	1	12	8 (67%)	4 (33%)	11 (92%)	1 (8%)	4 (3 F., 1 V.) out of 12 (3 in hospital and 1 after discharge) = 33%	8-42 days in hospital
Proguanil acetate (79% base)	12	Divided dose: 0.2-0.6 g. (acetate) intravenously	9	2	0	1	0	12	10 (83%)	2 (17%)	10 (83%)	2 (17%)	1 (F.+V.) out of 3 (2 F., 1 F.+V.)	6-8 months
Proguanil hydrochloride and pamaquin naphthoate (45% base)	13	Proguanil 0.3 g. (salt) and pamaquin 0.01 g. (base) b.d. for 10 days	0	30	0	0	0	30	27 (90%)	3 (10%)	29 (97%)	1 (3%)	4* out of 14 = 29%	Average 3 months
Quinine sulphate (82% base) and pamaquin naphthoate	14	Quinine sulphate 0.33 g. (5 gr.) and pamaquin 0.01 g. (base) t.d.s. for 10 days	0	13	0	0	0	13	13 (100%)	Nil	13 (100%)	Nil	1 out of 13 = 8%	Average 3 months
M. 5943 (88% base)	15	Divided dose: 0.02 g. t.d.s. for 10 days	0	17	1	0	0	18	17 (94%)	1 (6%)	16 (89%)	2 (11%)	3 out of 18 = 17%	Average 3 months
Chloroquine diphosphate (62% base)	16	Divided dose: 1.25 g. (base), 42 cases												
	17	Single dose: 1.5 g. (base), 8 cases	18	27	1	4	0	50	50 (100%)	Nil	49 (98%)	1 (2%)	4 (2 F., 2 V.) out of 20 = 20%	1-7 months
	18	Single dose: 0.5 g. (base)	10	15	0	0	0	25	25 (100%)	Nil	25 (100%)	Nil	2 (1 F., 1 V.) out of 12 = 17%	1-3 months
Chloroquine diphosphate and proguanil hydrochloride	19	Chloroquine: single dose of 0.5 g. (base) on 1st day and proguanil hydrochloride 0.3 g. b.d. for next 6 days	11	0	0	2	0	13	13 (100%)	Nil	13 (100%)	Nil	No relapse in hospital	15-53 days in hospital
Camoquin dihydrochloride dihydrate (77% base)	20	Single dose: 0.5 g. (base)	20	25	5	2	1	53	53 (100%)	Nil	53 (100%)	Nil	8 (3 F., 5 V.) out of 33 = 24%	1-8 months
	21	Divided dose: 0.1 g. (base) b.d. for 3 days = 0.6 g.	12	11	0	4	0	27	26 (96%)	1 (4%)	27 (100%)	Nil	6 (1 F., 5 V.) out of 8 = 75%	1-8 months
Camoquin dihydrochloride dihydrate and proguanil hydrochloride	22	Camoquin: single dose of 0.5 g. (base) on 1st day and proguanil hydrochloride 0.3 g. b.d. for next 6 days	6	2	0	0	0	8	8 (100%)	Nil	8 (100%)	Nil	One falciparum relapse after three weeks	21-50 days

* One other case had subclinical parasitic relapse detected by subinoculation.

TABLE III.—*Chemoprophylaxis of Malaria*

Drug	Group	Parasite Rate										1949-50 Malaria Incidence Rate bet Sept 30 and Dec 30, 1949	Spleen Rate			
		1948-9				1949-50							1948-9		1949-50	
		May, 1948	Sept., 1948	Nov., 1948	Feb., 1949	May, 1949	July, 1949	Sept., 1949	Nov., 1949	Feb., 1950	May, 1950		May, 1948	Feb., 1949	Oct., 1949	Feb., 1950
Proguanil hydrochloride, 0.1 g. twice weekly	I	11.20 (235)	3.15 (222)	4.48 (223)	1.36 (221)	4.10 (167)	4.58 (153)	7.73 (194)	2.86 (175)	2.15 (186)	6.16 (211)	21.54*	55.4	24.4	33.0	26.8
Proguanil hydrochloride, 0.3 g. once weekly	II	9.42 (276)	9.13 (219)	5.73 (227)	3.09 (259)	9.56 (241)	12.50 (216)	8.00 (200)	7.65 (196)	5.31 (207)	11.6 (190)	12.28	72.8	35.6	33.5	26.0
Camoquin, 0.2 g. base once weekly	III	10.57 (246)	9.02 (212)	1.89 (212)	0.63 (159)	5.95 (84)	16.13 (155)	6.17 (162)	0.67 (149)	0.66 (151)	3.2 (217)	3.12	64.2	16.4	26.3	12.4
Chloroquine, 0.25 g. base once weekly	IV	7.90 (227)	5.90 (101)	2.60 (193)	1.60 (261)	1.87 (190)	7.09 (141)	0.00 (149)	0.00 (146)	2.16 (139)	2.0 (200)	3.27	57.7	18.2	25.7	8.8
Quinine sulphate, 0.33 g. (5 gr.) twice weekly	V	—	—	—	—	—	5.19 (289)	6.05 (21)	4.04 (198)	4.23 (189)	—	26.15*	—	—	53.4	43.1
Control (quinine for acute attacks only)	VI	11.32 (265)	15.03 (173)	36.87 (179)	14.57 (199)	17.4 (224)	6.82	9.32	15.57	13.33	22.2 (216)	62.98	61.2	50.6	54.2	55.4

The drugs were administered for 26 weeks from July to December in the first five groups and the sixth group served as a control. The observations were carried out through two transmission seasons and are referred to here as 1948-9 and 1949-50 experiments. The parasite rate, malaria incidence rate, and spleen rate are all expressed in percentages. The figures in parentheses indicate the number of cases examined at different stages of the experiment.

* The higher incidence rate in these two groups may be partly due to the mode of collection of data; they were paid two visits a week as compared with one visit a week in the other groups.

days—that is, 0.6 g. in two doses on the first day and 0.3 g. on the next four days—is sufficient to terminate a malarial attack in an average case unless one encounters a refractory strain. A higher dose has not been of any advantage either in controlling the acute attack or in preventing relapses. For reducing the relapse rate of vivax or malariae infection, however, it should be combined with pamaquin, or be followed by weekly proguanil (0.3 g.) as long as possible. We found the drug about equally active, though relatively slow, against falciparum and vivax types of parasites. It has no influence on the appearance of crescents in the peripheral blood; these tend to persist for a long time, the maximum period noted being two months.

Absorption and Excretion.—For determination of proguanil concentration in the blood the hydrolytic method of Spinks and Tottey (1946) was used. The level of proguanil varied with different individuals, but in general it was proportionate to the dose of the drug. There was a rapid rise in the concentration of the blood after four hours; it was reduced nearly to half on the second day, and usually by the fourth day it was down to negligible figures. About the same kind of result was obtained after intramuscular administration. It was also observed that the drug disappeared from the urine generally in four to five days, most of it being excreted during the first 48 hours. The total excretion varied from 37 to 54% of the drug administered.

Toxicity.—No toxic reactions were noticed except in patients who were having large amounts of the drug. With 0.8 g. given in a single dose or in daily divided doses, gastrointestinal irritation with nausea, vomiting, diarrhoea, and griping was the commonest untoward reaction, but renal irritation was noticed in two patients (0.2 g. six-hourly for four days), one of them having frank haematuria with pain in the loins. The withdrawal of the drug gave prompt relief, but in some patients the treatment was continued without any ill effect. In a few cases (0.3 g. twice daily for 10 days) gastric irritation was noticed towards the end of the course, and on this account treatment was discontinued about the seventh day.

Relapses.—The working of the relapse rate is rather difficult in India, where people are constantly exposed to the risk of infection. Many of the relapse cases, however, developed the attack in the hospital or under conditions where the chance of reinfection was unlikely. Owing to the unavoidable uncertainty, we have lately laid more stress on the early relapses and kept most of our patients in hospital for at least a month under observation. Judging in this way, we found that early relapses were more infrequent with divided proguanil dosage given for 4 to 10 days than with single doses. But even with proper dosage the cases that have been followed up for three to six months have shown a relapse rate of the order of 40%. The actual relapse rates for different observation periods are shown in Table I, from which it will be evident that the single-dose treatment

always leads to a high early relapse rate, indicating the inadequacy of that method of treatment. We are therefore of the opinion that the single-dose treatment with proguanil should be abandoned.

Resistance to Proguanil.—We have encountered some cases of falciparum infection that proved refractory to proguanil. In one case the drug had no effect on the fever and parasites, and resistance of the particular strain was also shown in a second volunteer who was inoculated with the blood of the first patient and developed malaria which did not respond to intensive proguanil therapy. In another case there were repeated early relapses, indicating that the parasite was resistant and could not be completely eradicated with proguanil. Besides these we had two fatal cases of malaria: (1) a girl of 9 admitted in a restless and delirious state; and (2) a man of 75 with 35.6% of red cells infected with falciparum rings (some red cells containing two, three, or four rings) and a few schizonts and crescents. The girl had two intravenous injections, 0.1 g. each, before she died 16 hours after admission, while the old man had 1.4 g. of proguanil (parenterally and orally) in the course of the 34 hours he was alive in the hospital. A necropsy in this case showed intense proliferation of the parasites in the internal organs, though their number in the peripheral blood had been reduced. The first patient was severely ill and the second had a very heavy infection, so it is difficult to say what would have happened if more potent antimalarial drugs had been used.

Parenteral Proguanil.—This was given intravenously or intramuscularly, 12 cases by each method, and the results are shown in Table IV.

TABLE IV.—*Parenteral Proguanil: Effect on Temperature and Asexual Parasites*

Route	Total Cases	Infection					Last Day of Fever					Last Day of Parasites				
		F.	V.	M.	F. + V.	F. + M.	1	2	3	4	5	1	2	3	4	5
I.V.	12	9	2	0	1	0	1	4	5	0	0	2	0	7	3	0
I.M.	12	3	6	2	0	1	2*	1	5	3	1	0	1	5	5	0

* One of these patients, a case of quartan malaria, received the drug in the apyrexial period and the next paroxysm was suppressed.

Intravenous Proguanil.—Proguanil acetate or lactate was tried as an experimental measure in a series of 12 cases of malaria, all except two of which had falciparum infection. Two of the patients in this series, already mentioned above, died. The injections (up to 400 mg. at a time) were well tolerated by some, but two patients had phlebitis of the injected vein (which subsided in a few days), one had a severe reaction (collapse) after the injection, and another developed

symptoms suggestive of encephalitis, though it could not be definitely said whether it was the effect of the drug or of the disease. The symptoms eventually cleared up within about two months.

Intramuscular Proguanil.—Proguanil lactate (0.1 g. in 2-ml. ampoules) was tried in a single dose varying from 0.1 to 0.3 g. The results were somewhat like those obtained with oral proguanil. All the three *P. malariae* cases in this series responded to a single injection of 0.1 g., and no recrudescence occurred within four to six weeks while they were in the hospital. One of them had regular paroxysms for one year interrupted only for a fortnight by quinine, with a splenic enlargement to 9 in. (23 cm.) below the costal margin. The injection controlled the paroxysm and the patient was discharged after a month with a spleen reduced to only 3 in. (7.5 cm.) below the costal margin. The intramuscular injections were painful (more than with quinine), but the pain, local induration, and tenderness did not usually persist beyond the third day and left no sequelae, except in one case in which there was a local blister formation which gradually dried up.

2. Quino-Pamaquin, Proguanil-Pamaquin, and M.5943

These drugs were tried in 60 vivax and one malariae infection, mainly with the object of ascertaining the relapse rates. Quino-pamaquin is already a well-known remedy for the radical cure of recurring vivax malaria, and was adopted as a standard for comparison. M.5943 is a new synthetic compound. During their study of the antimalarial properties of diguanide substances related to proguanil, Curd, Davey, Hendry, and Rose (1950), of the Research Laboratories of Imperial Chemical Industries, Manchester, obtained the impression that weighting the benzene ring augmented activity. They therefore prepared a number of compounds in which *di*-substitution was made in the benzene ring. Dihalogen substitution in positions 3 and 4 proved particularly favourable for antimalarial activity. A representative compound, *N*,3:4-dichlorophenyl-*N*,5-isopropyl diguanide (given the laboratory number M.5943), was chosen for trial in human malaria. M.5943 differs from proguanil only in having an extra Cl group in position 3 of the benzene ring. Its constitution is:

M.5943 was tested against *P. gallinaceum* and *P. relictum* (Algerian strain) by Davey (1946a, 1946b) and was found to be much more active than proguanil against both the blood forms and the exoerythrocytic forms of these parasites. We are reporting here the results of treatment with M.5943 in vivax malaria as compared with combined courses of quino-pamaquin and proguanil-pamaquin.

TABLE V.—*M.5943, Quino-Pamaquin and Proguanil-Pamaquin in Vivax Malaria*

No. of cases	Quinine 5 gr. (0.32 g.) + Pamaquin 10 mg. (Base) t d s. for 10 Days	Proguanil hydrochloride 0.3 g. + Pamaquin 10 mg. (Base) b d. for 10 Days	M.5943 20 mg t d s. for 10 Days
13 (V.)	14 (V.)	18 (17 V. + 1 M.)	
Average duration of fever (days)	1.1	1.8	1.8
Average duration of parasite in blood (days)	1.8	2.0	2.2
Gametocytes:			
Cleared in 3 days	100%	86%	67%
Persisted for 4 or 5 days	Nil	14%	33%
Relapse rate (average period of observation, 3 months)	8%	29%	17%

Table V shows that the best immediate result was obtained with quino-pamaquin, both proguanil-pamaquin and M.5943 being slower and equal in action. M.5943 appears to be

rather slowly active against *P. malariae*, the temperature and parasites in the single case having persisted for five days. All the three drugs cleared the peripheral blood of the vivax or malariae gametocytes, and this property was most marked with quino-pamaquin, which was also better than the other two in respect of both immediate action and relapses. The difference in the gametocidal property of the first two combinations, however, may be due to the higher dose of pamaquin—namely, 30 mg. daily used in the first as compared with 20 mg. in the second.

Relapses.—The relapse rate in a follow-up for an average period of three months in the 45 cases observed in 1949 worked out at 17% (3 cases) for M.5943, 29% (4 cases) for proguanil-pamaquin, and 8% (1 case) for quino-pamaquin. Another subclinical relapse in the second series was detected accidentally by the development of febrile malaria in the recipient of a blood transfusion from the said case. If this is included the relapse rate in the proguanil-pamaquin series rises to 36%. If all the 30 cases (including 16 cases treated in the previous year) of the proguanil-pamaquin series are taken together, however, the relapse rate works out at 20%. There is no significant difference in the interval of freedom of attack prior to relapse in the three groups.

Toxicity.—Two cases in the proguanil-pamaquin series showed rather severe toxic reactions (nausea, vomiting, palpitation, and depression) and could not take the full course. No significant side-effect was noticed with quino-pamaquin. In the M.5943 group seven patients had toxic reactions—namely, nausea, vomiting, and/or abdominal pain. One patient complained of bleeding from the gums and another of dysuria during the course, but it cannot be definitely stated that they were entirely due to the drug. The treatment had to be interrupted for a day or two in a few cases for these reactions, and was then resumed in the same or slightly reduced dosage.

3. Chloroquine

Effect on Temperature and Parasites.—Chloroquine was tried in either single or divided doses in a series of 75 patients. The clinical response was very prompt with each regime, and fever and parasitaemia were controlled by the third day in all except one case. With 1.5 g. (base) in a single dose or 1.25 g. in divided doses, 96% became afebrile and 80% parasite-free in two days in a series of 50 patients: these figures were 84% and 100%, respectively, in another series of 25 patients treated with a single dose of 0.5 g. We have not had such an excellent result with any other antimalarial drug. We found it somewhat more active against vivax than against falciparum infection.

TABLE VI.—*Action of Chloroquine on P. falciparum and P. vivax*

Infection	No. of Cases	Last Day of Fever				Last Day of Asexual Parasite			
		1	2	3	4	1	2	3	4
<i>P. falciparum</i>	29	17 59%	7 24%	5 17%	0	12 41%	11 38%	5 17%	1 3%
<i>P. vivax</i>	41	23 56%	17 41%	1 3%	0	20 49%	17 41%	4 10%	0

It will be seen from Table VI that, while fever had subsided in 83% and asexual parasites disappeared in 79% in two days in falciparum infection, the corresponding figures from vivax infection are 97% and 90%. The drug has little or no action on gametocytes, the crescents having been found up to 22 days after treatment.

Toxicity.—Some untoward effect of the drug was observed in 5 of the 50 cases (10%) treated with 1.25 or 1.5 g. of the basic drug. Complaint was made of one or more of the following symptoms, which usually disappeared in two days; insomnia, gastro-intestinal irritation, pruritus (especially in the hands and feet), and pain in the lower abdomen, genitalia, and thighs (1 case). Another patient, not included in this series, had epileptiform fits after taking the drug.

Relapses.—Four patients relapsed out of 20 who had 1.5 g. (single dose) or 1.25 g. (divided doses) and who could be followed up for one to seven months: two with falciparum infection after 30 and 45 days, and two with vivax infection after 45 and 210 days. Two (one falciparum and one vivax) out of 12 patients given a single dose of 0.5 g., and who were followed up to three months, relapsed after 53 and 49 days respectively. None of the patients had an early recrudescence in the hospital with either regime, unlike the cases under proguanil. In fact, relapses were much less common with chloroquine.

4. Camoquin

Camoquin is almost as potent a drug as chloroquine. A single dose of 0.5 g. of the basic drug terminated fever and cleared the parasites in two days in 86% and 83% of the 52 cases respectively. This single-dose treatment was better than the divided dose of 0.1 g. twice daily for three days, which in a series of 27 cases gave the corresponding figures as 74% and 81%. It is almost equally effective against vivax, falciparum, and malariae infections. It has no action on crescents, which were seen in the blood up to 26 days, but the vivax and malariae gametocytes disappeared in one to five days.

Toxicity.—The drug was well tolerated and no untoward symptoms were noticed even in cases with severe anaemia.

Relapses.—Here also the single-dose treatment gave better results. Out of 33 patients who had a single dose of 0.5 g., 8 (3 falciparum and 5 vivax) relapsed, while 6 out of 8 patients who had 0.6 g. over three days relapsed, in each case after an interval varying from 2 to 30 weeks. All of them were under observation for one to eight months. The high relapse rate and lower potency of the divided dose would appear to be due to inadequacy of dosage, and will, we think, be improved by giving an initial loading dose.

5. Chloroquine or Camoquin in Combination with Proguanil

Since infections with *P. falciparum* may prove refractory to proguanil alone, we used that drug in combination with chloroquine or camoquin in two series of cases, and 21 patients have so far been treated in this manner. The effect on temperature and parasitaemia is shown in Table VII.

TABLE VII.—Effect of Combined Chloroquine-Proguanil and Camoquin-Proguanil on Temperature and Parasitaemia

Drug and Dose	Infection	No. of Cases	Last Day of Fever				Last Day of Parasitaemia (Asexual)			
			1	2	3	4	1	2	3	4
Chloroquine, 0.5 g. base on 1st day, and proguanil hydrochloride, 0.3 g. b.d., for next six days	F. V.	11	7	3	1	0	1	8	2	0
	F.V.	2	1	1	0	0	1	1	0	0
Total ..		13	8	4	1	0	2	9	2	0
			92.5%				84.6%			
Camoquin, 0.5 g. base on 1st day, and proguanil hydrochloride, 0.3 g. b.d., next 6 days	F. V.	6	1	4	1	0	3	1	2	0
	V.	2	0	1	1	0	0	1	1	0
Total ..		8	1	5	2	0	3	2	3	0
			75%				62.5%			

It will be seen that this method of treatment rapidly terminated the malarial attack. The results are comparable to those obtained with single doses of camoquin or chloroquine alone. But proguanil alone would have been slower in action, and its reinforcement on the first day by a single dose of chloroquine or camoquin seems to have had a greater effect than quinine or mepacrine in similar conditions.

There were no toxic reactions, and only one case in the camoquin-proguanil series out of the 21 cases treated relapsed after three weeks in a follow-up period of 15–53 days in the hospital.

6. Indigenous Drugs

Neochin, which is dicinchonine carbonate, had a poor antimalarial property, and the other drugs were useless.

Conclusion

Chloroquine and camoquin are the two outstanding drugs in the treatment of malaria. Even with a single dose they can effect a clinical cure in most cases in two days, with disappearance of asexual parasites. Proguanil is also effective, but has a slower action, and resistant falciparum cases are occasionally encountered. The optimum effective dose in our cases has been chloroquine (base), 0.5 g. immediately, 0.25 g. after six hours, and 0.25 g. on the second and third days; camoquin (base), 0.5 g. (or three 0.2 g. tablets) in a single dose; and proguanil hydrochloride, 0.3 g. twice daily on the first day and 0.3 g. once daily for the next four days. The toxic effects of proguanil are usually insignificant, but may result from large doses. So far no toxicity has been observed with camoquin, while about 10% of chloroquine cases had temporary untoward reactions in the doses used. These drugs, however, do not solve the problem of vivax relapses, which can at present be reduced by giving quino-pamaquin, which is more effective than proguanil-pamaquin, or suppressed by weekly doses of one of the above drugs. M.5943 has no advantage over other antimalarials.

II. CHEMOPROPHYLAXIS

Prophylactic trials were carried out in two successive years, 1948 and 1949, in a hyperendemic rural area, about 40 miles (64 km.) from Calcutta, comprising 10 villages with a population of 1,458. The people were mostly land workers in a poor nutritional condition. The overall spleen and parasite rates were 62.8% and 10.7% respectively, while the corresponding rates for children under 10, who formed nearly one-third of the population, were 58.5% and 17.4%. The work was started with five groups of the population each consisting of about 250 people—four having proguanil, camoquin, or chloroquine (groups I to IV, see Table III), and one serving as control (group VI). In 1949, in addition to these five groups, an extra group (V) was given bi-weekly quinine prophylaxis, and a subgroup (IIIA) of about 50 people had camoquin prophylaxis in a reduced dosage. The details are shown in Table VIII.

The drugs were administered throughout the transmission period from July to December. Blood was examined every two or three months, but the spleen was examined only at the beginning and end of the prophylactic period. The incidence of malaria in those taking the drugs was judged by examining the blood of those who had fever. To the control group no drug was administered except a few doses of quinine to control the acute attacks. No anti-mosquito measures were adopted in the whole area.

Parasite Rate

Compared with the control group malaria was definitely under check, the parasite rate remaining more or less low according to the drug used. In May, 1948, prior to the first experiment, the average infection rate in these villages was 10 per 100. In November, 1948, this rose to 37 in the control group (October and November are here the usual peak

TABLE VIII.—*Schedule of Chemoprophylaxis*

Group	No. of Subjects	Drug Used and Frequency of Administration	Dose			Year of Trial	Initial Spleen Rate %	Initial Parasite Rate %
			> 10 yrs.	4–10 yrs.	< 4 yrs.			
I	235	Proguanil hydrochloride twice weekly	0.1 g.	0.05 g.	0.03 g.	1948–9	55.4	12
II	276	Proguanil hydrochloride once weekly	0.3 „	0.2 „	0.1 „	1948–9	72.8	9.42
III	246	Camoquin* once weekly	0.2 „	0.1 „	0.05 „	1948–9	64.2	10.57
IV	227	Chloroquine* once weekly	0.25 „	0.125 „	0.062 „	1948–9	57.7	7.9
V	289	Quinine sulphate twice weekly	5 gr.	2½ gr.	2½ gr.	1949	53.4	5.19
VI	265	No drug—prophylaxis (control)				1948–9	61.2	11.32

* Dosage of camoquin and chloroquine is expressed in base.

period of malaria), while the parasite rates in the treated groups varied from 2 to 6, the best results being obtained with camoquin and chloroquine. As regards proguanil, there was some superiority of the bi-weekly group (I) to the weekly regime (II). In 1949 the results were still more remarkable. The control group showed a parasite rate of 15.57 in the month of November—a much lower peak than in the previous year owing to lessened severity of malaria that year or to unexplained factors, whereas the corresponding figures for chloroquine (IV), camoquin (III), and bi-weekly proguanil (I) were 0.00, 0.67, and 2.86 respectively. With the last regime, however, there was a rise in the parasite rate in September, 1949, by almost 50% above the rate in July, 1949, the cause for which is not understood.

In striking contrast to the results in the three groups mentioned above, the weekly proguanil regime (II) was less effective, with a parasite rate of 7.65 against the previous year's figure of 5.73, which in itself was high enough. As regards quinine, which was first used in 1949, the reduction of parasite rate from 5.19 in July to 4.04 in November is not itself significant, but there is no doubt that this drug exerted some control, for the parasite rate in the control group rose from 6.82 to 15.57 in the same period of time. The conclusion, confirmed statistically, was that chloroquine and camoquin prophylaxis offered the best protection. Of the two proguanil groups the bi-weekly regime (I) definitely gave better results than the weekly regime (II), though both were inferior to groups III and IV. The results obtained with bi-weekly quinine prophylaxis (V) were somewhat intermediate between the two proguanil regimes in respect of the parasite rate, but the difference was not statistically significant.

It has been mentioned that, in addition to the main camoquin group (III) receiving 0.2 g. of the basic drugs weekly, a subgroup was included in 1949 consisting of 50 subjects who were given 0.1 g. of camoquin (base) every week (IIIA). The parasite rates in the latter were similar to the main camoquin group (III). As the malaria incidence rate per 100 was 4.00 in group IIIA as compared with 3.12 in group III and 62.98 in group VI (control), it would appear that the effect of 0.1 g. of camoquin weekly is the same as that of 0.2 g. But, the number of subjects taken in group IIIA being very small, the similarity of its action with group III cannot be regarded as statistically significant. Nevertheless it shows that camoquin in such small dosage as 0.1 g. weekly can give considerable protection to persons exposed to malarial infection. It is possible, from the parasite rates in the control and treated groups, to calculate the degree of freedom from attacks afforded by each drug. Table IX gives the number of persons who would be freed from parasites by each of the drugs out of 100 who carry parasites in their blood.

The month of November has been chosen from each group, as this is the peak period for malaria.

TABLE IX.—*Percentage of Infected Persons Given Protection by Various Drugs*

	Nov., 1948	Nov., 1949
Proguanil (twice weekly) ..	88	82
„ (once weekly) ..	84	51
Camoquin (once weekly) ..	95	96
Chloroquine (once weekly) ..	93	100
Quinine (twice weekly) ..	—	74

Spleen Rate

The reduction of the spleen rate is best seen from Table X.

TABLE X.—*Showing Effects on the Spleen Rate*

Group	May, 1948	Feb., 1949	Oct., 1949	Feb., 1950
I	55.4	24.4	33.0	26.8
II	72.8	35.6	33.5	26.0
III	64.2	16.4	26.3	12.4
IV	57.7	18.2	25.7	8.8
V			53.4	43.1
VI	61.2	50.6	54.2	55.4

In keeping with their effects on the parasites, camoquin and chloroquine had considerably reduced the spleen rates—namely, to 12.4 and 8.8% respectively in February, 1950 (for convenience final spleen examination was made in February each year)—and these figures are lower than in the previous year. Curiously enough, though proguanil acted differently on the parasites according to the dosage scheme, the spleen rates in both groups were about the same—namely, 26% in February, 1950 (see Chart). Quinine was undoubtedly least effective in respect of the spleen rate, which was 43.1% in February, 1950, the initial rate being 53.4%. This would throw doubt on the efficacy of quinine prophylaxis in spite of its effect on the parasite rate. The control group, in accordance with our expectations, showed a persistently high rate, never falling below 50%.

* OCT. '49 in case of GROUP V.

To arrive at a proper evaluation of the drugs so far as the splenic enlargement is concerned, a statistical analysis was made of those subjects who had an enlarged spleen at the beginning of the experiment and those who had no such enlargement. The results in the former are similar to the overall figures shown above. In the latter, whose spleen was initially not palpable, all the treated groups showed prevention of splenic enlargement in varying degrees (see Table XI).

TABLE XI.—Showing the Effect of the Drugs on the Spleen of Patients who had no Initial Splenic Enlargement

Group	1948-9 Experiment		1949-50 Experiment	
	No. of Cases with No Palpable Spleen in May, 1948	Percentage Showing Enlargement in Feb., 1949	No. of Cases with No Palpable Spleen in Oct., 1949	Percentage Showing Enlargement in Feb., 1950
I	73	15	117	11.1
II	32	12	130	8.5
III	47	0	85	4.7
IV	31	0	90	1.1
V	—	—	68	6.3
VI	56	27	59	27.1

All the treated groups show significantly lower spleen rates compared with the control, in which 27% developed splenic enlargement after the transmission season. It was striking that in 1948-9 the spleen was not palpably enlarged at the end of the experiment in any of those subjects in the camoquin (III) and chloroquine (IV) groups who had not shown it at the beginning. In 1949-50 the lowest spleen rate was recorded in group IV, and is significantly less than all the other groups except III, which occupies an intermediate position between group IV and other treated groups. It may therefore be concluded that all the prophylactic regimes were effective in preventing splenic enlargement, chloroquine being most valuable in this respect.

Malaria Incidence

The data for malaria incidence during the prophylactic period were more accurately collected in the second experiment. Nevertheless they should be regarded as only approximate, because there were difficulties in obtaining correct information from the villagers. The incidence rate of malaria in those who were under prophylactic treatment was 21.54% with bi-weekly proguanil, 12.28% with weekly proguanil, 3.12% with camoquin, 2.27% with chloroquine, and 26.1% with quinine, as compared with 62.98% in the control group. It should be mentioned that only parasite-positive cases have been taken in the above analysis, and a person suffering more than once has been counted as one.

We might say that all the treatments were effective in reducing the incidence rate in so far as the rates recorded for these were significantly lower than that of the control group. Group III and group IV treatments were definitely better than all the others. There was no statistical evidence of difference amongst the other treated groups (I, II, and V). The higher rates in groups I and V may have been partly due to the method of collecting the data. These groups were paid two visits a week as compared with one visit in the other groups. This has undoubtedly inflated the figures in groups I and V to some extent. But, even taking this fact into consideration, camoquin and chloroquine show the best results in the prevention of malaria.

Conclusion

As in chemotherapy, so in chemoprophylaxis, chloroquine (base, 0.25 g. weekly) and camoquin (base, 0.2 g. weekly) have proved superior to proguanil (salt, 0.3 g. weekly or 0.1 g. bi-weekly). They afforded high protection and reduced splenomegaly, thereby improving the general health of the population and increasing the working capacity.

In spite of the fact that the people were living in poor economic conditions, and in the absence of any other

antimalarial measures, there was marked reduction in the incidence of malaria, which varied according to the drugs used. Until anti-mosquito measures are possible chemoprophylaxis should have an important place in the suppression of malarial fever. It causes no inconvenience—a dose once or twice a week is enough, and it need not be costly. What is wanted is malaria discipline, but, once impressed, the villagers are willing to co-operate.

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REFERENCES

- Curd, F. H. S., Davey, D. G., Hendry, J. A., and Rose, F. L. (1950). *Brit. J. Pharmacol.*, 5, 438.
 Davey, D. G. (1946a). *Ann. trop. Med. Parasit.*, 40, 52.
 — (1946b). *Ibid.*, 40, 453.
 Field, J. W. (1941). *Trans. roy. Soc. trop. Med. Hyg.*, 35, 35.
 Jaswant Singh and Bhattacharji, L. M. (1944). *Indian med. Gaz.*, 79, 102.
 Spinks, A., and Tottey, M. M. (1946). *Ann. trop. Med. Parasit.*, 40, 101.

ATYPICAL ABDOMINAL TUBERCULOSIS WITH HAEMATOLOGICAL MANIFESTATIONS

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Enlargement of the liver and spleen is an uncommon mode of presentation of abdominal tuberculosis. The four cases reported below illustrate the clinical appearance of this condition and, in addition, demonstrate the association of blood disorders with hepato-splenic tuberculosis.

Case 1

A woman aged 69 had had enlarged lymph nodes excised from her neck at the age of 6 years and a tuberculous right axillary lymph node removed when aged 36. For one year she had suffered from lassitude, haemorrhoids, and an uncomfortable swelling of the abdomen. The cardiovascular, respiratory, and nervous systems were normal. The spleen was hard, painless, and enlarged almost to the umbilicus, with a firm raised swelling 2½ by 1½ in. (6.4 by 4.4 cm.) in size palpable on its surface. The liver was enlarged 1-2 in. (2.5-5 cm.) below the costal margin. She was afebrile and of a steady weight. A blood count on admission showed: Hb, 63% (9.1 g.); red cells, 4,500,000 per c.mm.; white cells, 30,000 per c.mm. (neutrophils 86%, lymphocytes 4%, monocytes 3%, eosinophils 1%, metamyelocytes 2%, myelocytes 4%); platelets, 320,000 per c.mm. The blood film revealed hypochromia, microcytosis, and anisocytosis. The sternal marrow gave a total nucleated cell count of 200,000 per c.mm. (myeloblasts 3%, premyelocytes 2%, myelocytes 32%, metamyelocytes 10%, polymorphonuclears 38%, lymphocytes 1.5%, monocytes 0.7%). The myeloid/erythroid ratio was 9:1. These figures supported the clinical diagnosis of chronic myeloid leukaemia. After a course of deep x-ray therapy to the spleen her leucocyte count was 13,500 per c.mm., but rose subsequently to 28,000-50,000 per c.mm.