treatment. In no case was there a significant lowering of the white-cell count. A rising eosinophilia, reaching a peak at an average of five days after treatment, was noted in seven cases: in three of these the proportion of eosinophils rose from 1% to 5%; in two cases it reached 13%; and in two it exceeded 25%. No toxic phenomena unequivocally attributable to daraprim were noted.

Discussion

Daraprim is clearly a powerful schizonticide. A single dose of 0.5 mg. per kg. of body weight causes the disappearance of asexual forms of *P. falciparum* and *P. malariae* from the blood in the great majority of cases, at a rate which is not dependent on the degree of immunity possessed by the host. While in a minority of cases there is some evidence of action upon ring trophozoites, the drug seems to exert its effect mainly at the stage of plasmodial development, when the chromatin is in active division. The evidence presented suggests that after a single dose the concentration of the drug in the blood remains high enough to be lethal to all the asexual forms, even if some do not reach the vulnerable phase of schizogony for 72 hours after treatment, as in the quartan cases.

In two cases asexual parasites persisted in the blood stream. It seems reasonable to attribute the first of these failures (Case 11) to underdosage, since a second treatment at a higher dosage (0.5 mg. per kg.) was rapidly effective. The cause of the second failure (Case 10) is more obscure. In this case the infant on admission had a severe generalized exfoliative dermatitis, and on examination the edge of a very hard liver was palpable a hand's breadth below the costal margin. A considerable degree of metabolic disorder, including impairment of liver function, may be inferred. Should the antimalarial activity of daraprim depend upon the disintegration of the drug into some metabolite, it may be that the impaired liver function interfered with this process and prevented the establishment of an adequate concentration of the active substance in the blood. However, the possibility that the failure was due to the presence of a naturally resistant strain or to the establishment of drug resistance by previous inadequate treatment—in this case at a dosage level of 0.25 mg. per kg.—cannot be excluded.

Our experience is that daraprim promises to prove a valuable antimalarial drug. Its action seems to parallel closely that of proguanil ("paludrine"), while the rate at which it eliminates parasitaemia seems to be intermediate between that of proguanil and chloroquine. Its small effective dosage and tasteless character may well make this the drug of choice in the treatment of malaria in infants and children. It certainly merits extended trials, both therapeutic and prophylactic, against the known strains of plasmodia infecting man.

Summary

Cases of clinical malaria with high parasitaemia and pyrexia, due in 29 cases to *P. falciparum*, and in three to *P. malariae*, were treated with daraprim in single oral doses of 0.25 or 0.5 mg. per kg. of body weight.

The drug has a powerful destructive action on dividing schizonts and a lesser and inconstant effect on trophozoites. The blood was free of asexual parasites within 72 hours in all but two cases of *P. falciparum* infection and within 96 hours in all cases of *P. malariae* infection. No toxic effects were observed.

The drug seems to act just as swiftly in non-immunes as in subjects who possess considerable immunity.

As daraprim is tasteless it is particularly suitable for the treatment of malaria in infants and children.

Daraprim well merits extended trial as a therapeutic drug effective in very small single doses, and its efficacy as a suppressive deserves investigation.

We gratefully acknowledge our indebtedness to Brigadier J. S. K. Boyd, Director of the Wellcome Laboratories of Tropical Medicine, for his help and advice throughout this investigation and for making available to us supplies of daraprim and early information about its properties; and to Professor B. S. Platt, Director of the Medical Research Council Field Research Station, Gambia, for making it possible for us to do this work and for permission to publish this paper.

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DARAPRIM (B.W. 50-63)—A NEW ANTIMALARIAL

TRIALS IN HUMAN VOLUNTEERS

BY

L. G. GOODWIN, M.B., B.S., B.Sc., B.Pharm.

(From the Wellcome Laboratories of Tropical Medicine,
183-93, Euston Road, London, N.W.1)

2:4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine, "B.W. 50-63," or "daraprim," is a new antimalarial drug of high potency. Laboratory tests have shown it to be 60 times as active as proguanil against *Plasmodium gallinaceum* in chicks and 200 times as active against *P. berghei* in mice (Falco *et al.*, 1951). A single dose of 5 mg. was found by Archibald (1951) to clear *P. falciparum* schizonts from the blood of Lagos schoolchildren. Daraprim worked rather more slowly than mepacrine, but the 5-mg. dose was approximately equivalent to a dose of 300 mg. of mepacrine tested under the same conditions. Toxicity tests in the laboratory showed that the drug was less toxic than proguanil to mice; doses of 5 mg. per kg. of daraprim given twice daily to a rhesus monkey for five days every week for six weeks had no effect on the general health, appetite, or the blood picture. We estimated that if it could be assumed that human malaria parasites were as sensitive to daraprim as *P. cynomolgi*, an effective suppressive dose for a 70-kg. man would be of the order of 5 mg. once weekly. This is not, of course, a justifiable assumption, but we thought it reasonable to expect that a dose of 25 mg. once weekly would be effective as a suppressant in human malaria. The present paper is an account of a personal trial of the drug as a malaria suppressant, and of toxicity studies in a group of human volunteers.

A Personal Trial

From January to June, 1951, I was working in Africa, and therefore had the opportunity of making personal trials with daraprim. The aims of the trial were (a) to take the drug at a dose level higher than was necessary for the suppression of malaria and watch carefully for any toxic effects; and (b) to ensure that I came into contact with infected mosquitoes.

Dose of Drug.—A beginning was made by taking 50 mg. of daraprim twice weekly. This dosage was continued from December 5, 1950, until February 11, 1951, and no ill effects of any kind were observed. The blood picture and the urine were normal throughout. As I was spending a good deal of time in the bush and it needed an effort to remember which days to take the drug, I changed to a higher total dose of 25 mg. daily, which was continued from February 12 until April 4. Again no ill effects were observed. On February 5 I had diarrhoea after an expedition to Kankara, in Katsina Province; this responded rapidly to treatment with sulphaguanidine. I had two boils, which appeared on

Key to Chart.—The time in malarious areas was spent at Vom, Plateau province, Nigeria, with the exception of: (1) Lagos; (2) Kaduna (Zaria province) and Kankara (Katsina province); (3 and 4) Shendam (Plateau province); (5) trek from Vom to Kaduna (Plateau and Zaria provinces); (6) Lagos, Ibadan, and Kaduna; (7) Lumu (Zaria province); (8) Wase, Shendam, Makurdi, Nassarawa (Plateau and Benue provinces); (9) Belgian Congo (Leopoldville, Elisabethville, Stanleyville, and Costermansville); (10) East Africa (Entebbe, Nairobi); (11) Khartoum; (12) Italy.

March 18 and April 19, and blood counts made at each of the times showed a good leucocyte response, with a high proportion of young polymorphonuclear cells. By April 4 Dr. Archibald reported to me the preliminary results with daraprim in schoolchildren, and it was clear that 25 mg. daily was more than sufficient for malaria suppression. The dose of drug was therefore reduced to 5 mg. daily, and this I continued to take until the end of the year. On February 16, 17, and 18 doses of 50 mg. were taken, and on October 1 and November 26 doses of 25 mg. Doses of 100 mg. were taken on December 4 and 19 for the purpose of estimating blood levels of the drug. A full blood count made by Dr. M. Maizels at University College Hospital confirmed that the blood picture was normal after the year's experiment, and a sternal puncture showed a normal bone marrow. There was no abnormality of the urine at any time, and the drug had no effects at any dose level tried upon appetite or digestion. Some figures obtained from routine blood examinations are recorded in Table I.

TABLE I.—Blood Counts Made During a One-year Course of Daraprim

Date	Total Dose of Drug (g.)	Hb %	Red Cells ($\times 10^6$)	White Cells ($\times 10^3$)	Differential Count				
					Poly.	Lymph.	Mono.	Baso.	Eo.
5/12/50	0	105	4.9	10.0	66	24	10	1	0
6/1/51	0.450	102	5.1	7.3	56	32	10	2	0
20/2/51	1.250	120	5.0	9.1	63	31	4.5	0.5	1
18/3/51*	1.900	110	5.0	12.4	68	20	10	1	1
19/4/51*	2.700	110	5.0	16.0	72	23	4	0	1
3/12/51	3.785	110	5.1	9.7	56	33	9.5	1	0.5
4/12/51†		104	5.2	6.8	55.5	37.5	6	0.5	0.5

* Polymorphonuclear leucocytosis due to boils.

† Independent determination by Dr. M. Maizels.

Bone marrow on December 11 (Dr. E. Graves): neutrophils, 24; eosinophils, 1; basophils, 0; lymphocytes, 10; monocytes, 0; myelocytes, 28; "blast" cells, 2.5; plasma cells, 1; reticulum cells, 0; proerythroblasts, 2.5; normoblasts, early 3.5, intermediate 9, late 18.5; megaloblasts, 0; megakaryocytes in normal numbers.

Infection with Malaria.—Most of my stay in Africa took place during the dry season and was spent on the Jos Plateau; mosquitoes were not very plentiful. However, several expeditions were made into the bush, and on three of these occasions I slept without a mosquito net. I very seldom wore socks during the evening and never wore mosquito boots. There is little doubt that I met the infection on more than one occasion. On my way back to England I took the opportunity of receiving an inoculation of *P. falciparum* sporozoites from four *Anopheles gambiae* mosquitoes at the I.C.I. research station in Nairobi prison. Sporozoites were shown to be present in the salivary glands of the mosquitoes when the insects were dissected after biting. No malarial attack followed this infection.

It is unjustifiable to draw far-reaching conclusions from observations upon a single experimental animal. However, the results described show that daraprim at a dose level of 5 mg. daily proved to be a satisfactory suppressant of *P. falciparum* malaria, and produced no ill effects of any kind when given continuously for a year.

Toxicity Trials in England

Thirteen volunteers in England took 50-mg. doses of daraprim twice weekly for three months. In 11 persons there were no unpleasant symptoms of any kind; in two there were complaints of slight gastro-intestinal upset, which was not experienced when the daraprim tablets were replaced by dummies without the knowledge of the volunteers. However, a further trial of two doses of either daraprim or dummy tablets in a fresh group of 40 persons showed that complaints were made by a higher proportion of the 20 who took dummies than by the 20 who took daraprim.

In the people who took daraprim no significant changes were observed in red or white cell counts, sedimentation rates, or in the urine (Table II).

TABLE II.—Blood Examinations upon Normal Volunteers taking Daraprim (50 mg. twice daily for 3 months)

Sex and Age	Date	Hb %	R.B.C. ($\times 10^6$)	Packed Cell Volume (%)	W.B.C. ($\times 10^3$)	Differential Count				
						Poly.	Lymph.	Mono.	Eo.	Baso.
F 28	*6/12/50	95	4.6		7.0	62	29	6.0	2	1
	18/12/50	96	4.7		5.8	52	42	5.5	0	0.5
	16/1/51	98	4.5		8.0	54	37	7.5	0.5	1
	25/4/51	98	4.8		6.8	51	43	3.5	1	1.5
M 26	*6/12/50	106	4.9		7.3	61	32.5	4.5	2	0
	18/12/50	108	5.2		7.8	59	33	5.0	1	2
	4/5/51	108	5.2		7.2	61	33.5	6.5	2	2
M 25	*4/1/51	108	5.5		6.6	65.5	30.5	2.5	0.5	1
	1/5/51	108	5.3		7.2	52.5	39.5	4.5	2	1.5
	18/12/50	100		44	9.6	52	32	5	1	—
M 35	17/1/51	97		45	6.0	52	38	9	1	—
	*18/12/50	102		44	5.4	60	30	8	2	—
	17/1/51	100		44	5.4	59	33	7	1	—
M 39	5/2/51	98		44	4.8	60	33	5	2	—
	*18/12/50	98		44	10.0	71	22	3	4	—
	17/1/51	104		44	12.0	74	20	6	0	—
	5/2/51	100		44	12.6	68	24	6	2	—
M 46	19/3/51	105		44	11.0	67	29	3	1	—
	*18/12/50	108		49	5.8	61	32	5	2	—
	17/1/51	105		48	5.0	59	33	8	0	—
	5/2/51	104		48	6.4	56	36	8	0	—
†M 44	19/3/51	102		47	9.8	62	29	5	4	—
	*18/12/50	112		47	6.5	63	27	8	2	—
	17/1/51	106		46	7.6	66	29	4	1	—
	19/3/51	105		47	6.6	58	36	4	2	—
M 47	*18/12/50	96		46	9.6	65	23	7	5	—
	5/2/51	95		44	6.8	62	32	5	1	—
	*18/12/50	102		48	6.2	57	29	6	8	—
	17/1/51	106		45	5.4	55	33	8	4	—
M 30	5/2/51	102		47	5.6	59	33	8	0	—
	19/3/51	100		45	7.0	48	40	10	2	—
	*18/12/50	98		46	9.0	59	27	8	6	—
	17/1/51	102		44	8.8	54	40	5	1	—
†M 47	5/2/51	100		43	6.6	59	36	4	1	—
	19/3/51	98		44	9.8	65	30	4	1	—
	*18/12/50	98		48	5.2	53	37	9	1	—
	17/1/51	98		44	6.4	62	30	6	2	—
M 45	5/2/51	98		45	5.2	55	37	8	0	—
	19/3/51	105		45	6.8	52	44	4	0	—
	*18/12/50	105		46	6.0	52	36	6	6	—
	5/2/51	106		45	5.0	57	35	7	1	—
	19/3/51	105		45	6.6	55	34	9	2	—

* Blood counts made before beginning course of daraprim.

† Slight gastro-intestinal symptoms in these two volunteers.

Summary

Daraprim (2:4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine) has been shown to be an effective malaria suppressant in one individual when given in doses of 5 mg. daily. No toxic symptoms of any kind were observed, and no abnormalities were produced in the blood or bone-marrow picture or in the urine during one year's continuous administration of the drug.

In a group of volunteers in England, doses of 50 mg. given twice weekly produced no significant effects upon

the blood picture, sedimentation rate, or urine, and the only symptoms recorded were slight gastro-intestinal disturbances in two persons.

I am indebted to Dr. H. M. Archibald for his interest and co-operation; to Dr. Robertson at the I.C.I. Unit in Nairobi for the infected mosquito bites; to Dr. J. C. Hawksley, Dr. M. Maizels, and Dr. E. Graves, of University College Hospital, for the final count upon my blood and the sternal puncture; to Dr. J. C. Broom and Dr. S. R. M. Bushby for the determinations recorded in Table II; to the volunteers who submitted to trials with the new drug; and to Brigadier J. S. K. Boyd for his encouragement and advice at all times during the experiments.

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HYPNOSIS IN CHILDBIRTH

BY

A. M. MICHAEL, M.B., F.R.C.Sed., M.R.C.O.G.
M.M.S.A.

*Late Senior Registrar, Department of Obstetrics and
Gynaecology, St. Helier Hospital, Surrey*

Considerable interest has been aroused in recent years, both in this country and in the United States, in the phenomenon of hypnosis, with special reference to its application in the relief of pain during childbirth. Unfortunately the attitude of the general public and some medical practitioners towards this phenomenon has been, and too often still is, one of superstition, fear, and even open hostility. No doubt this is the result of witnessing lay demonstrations by medically ignorant and often completely irresponsible people making extravagant claims for hypnosis.

From time to time reports of cases of childbirth while under hypnosis have appeared in the lay press, arousing interest and discussion. An attempt has therefore been made to investigate these claims on a scientific basis, so far as this is possible, and it is with this idea in mind that this preliminary objective evaluation of the effects of hypnosis as an anaesthetic agent in childbirth has been undertaken.

Relief of Pain During Childbirth

In our present civilization, women have been conditioned to expect pain during childbirth, and are convinced that it is a necessary adjunct to labour. Anticipation increases pain largely through muscular and nervous tension. Following on the publication of the work of Grantly Dick Read in educating the patient in the value of relaxation, and in attempting to remove the fear and apprehension of childbirth, efforts are being made to induce the parturient woman to regard childbirth as a natural function which should cause no more discomfort than any other physiological process of the body. Read's technique depends on the use of education, relaxation, and suggestion, and by employing trance states one only carries his method a stage further.

Kroger and De Lee (1943) believe that the only method of producing relief of pain with complete safety for mother and infant, without altering the normal mechanism of labour, is hypnosis. They further maintain "that hypnosis has unrealized possibilities for making childbirth not merely the equivalent of a surgical operation but rather a satisfying psychological experience, which may fulfil a deeply felt and unformulated need of the mother." Greenhill (1947) states that hypnosis should be employed more often than it is at

present. Even if complete hypnosis is not to be resorted to, physicians should remember that repeated suggestion, with or without the aid of medication, can accomplish a great deal in labour, particularly for the relief of fear, as well as the pain of childbirth.

Prior to 1775 the phenomenon of hypnosis was often described as a miracle performed by high priests of ancient civilizations, particularly in the East. The scientific history of hypnosis began with Anton Mesmer. In this country James Braid, in 1841, found that trance-like states could be induced by holding any bright object in front of, and slightly above, the subject, so as to strain the eyes and quickly fatigue them. He first coined the terms hypnosis and hypnotism. During the past 30 years there has been an increasing wealth of publications dealing with the effective use of hypnosis in the fields of psychiatry and experimental psychology. There have been papers advocating the use of hypnosis as an anaesthetic agent in surgery and dentistry. Sampimon and Woodruff (1946) described 29 surgical and dental operations successfully performed under hypnosis while in a prisoner-of-war camp in Singapore during the Japanese occupation.

Hypnosis has been used in obstetrics for many years, and Schultze-Rhönhof (1922) reported an 89.5% success rate in a series of 79 cases. He came to the conclusion that hypnosis was a useful and harmless anaesthetic agent. Isolated enthusiastic reports of labours conducted under hypnosis have appeared in recent years in the medical press, but, with the exception of papers by Kroger and De Lee (1943) and Abramson and Heron (1950), no large series of cases have been reported in the English language. It should be pointed out at this stage that in Abramson and Heron's series of 100 cases the experimental group of patients (receiving hypnosis) were each given a mean amount of 103.5 mg. of pethidine during labour, whereas the control group of patients (not receiving hypnosis) received a mean of 123.6 mg. of pethidine. In the series of 30 cases reported here only those cases which failed completely during labour received anaesthetic agents.

Present Investigation

Material.—All subjects in this series were volunteers and were obstetrically normal at the 34th–37th weeks of pregnancy. No attempt was made to select patients, and only one case was rejected during the antenatal period. This patient could not be hypnotized after three attempts, and, owing to pressure of work, it was not deemed practicable to continue with this case. Vogt, of Berlin, with typical Teutonic thoroughness, persevered with one case through 600 attempts and 700 with another before inducing hypnosis (Le Cron and Bordeaux, 1949). All volunteers were drawn from patients attending the antenatal clinics of this hospital, and no elaborate preparations were made to secure optimum conditions for hypnosis.

Antenatal Preparation.—Patients were seen at varying intervals during the antenatal period in order to hypnotize them and to accustom them to the routine. A semi-reclining position on the examination couch in an un-darkened room was adopted, and in order to secure fixation of attention the gaze was focused on a fixed point

TABLE I.—Analysis of Cases in Which Hypnosis Failed During Labour

Case	Age	Parity	No. of A.N. Training Sessions	Depth of Hypnosis* Obtained During A.N. Sessions	Stage of Labour Hypnosis Failed
A	19	1	10	4	1st
B	16	1	6	3	"
C	33	2	7	3	Beginning of 2nd
D	35	4	3	4	"
E	36	2	11	4	Crowning of head
F	23	2	2	3	"
G	27	2	11	5	"

* Depth of hypnosis referred to in this column is in accordance with Le Cron and Bordeaux's classification.