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FIRST FIELD TRIAL OF 377 C 54, A NEW ANTIMALARIAL COMPOUND

BY

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AND

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The action of modern antimalarials is such that they provide a reasonably satisfactory range of chemotherapeutic weapons at the disposal of the clinician. The public health worker in endemic malarious areas is less fortunate.

Difficulties encountered in many parts of Tropical Africa in achieving malaria eradication have renewed the interest in possibilities of mass chemotherapy, and several recent W.H.O. malaria conferences recommended that drugs be used in conjunction with residual insecticides wherever this combined attack may lead to the rapid elimination of malaria.

Mass chemotherapy of malaria with drugs available at the present time has two disappointing features. One is the possibility of development of resistant strains to otherwise excellent protective drugs such as proguanil and pyrimethamine. The other is the fact that all available antimalarials are excreted relatively rapidly and have a short "carry over" value. Thus any "mass treatment" of malaria aimed at elimination of the infection in the community and consequent interruption of transmission must be based on giving the drug at intervals of one to four weeks but not greater than one month (Bruce-Chwatt, 1956).

The more frequent the regimen the greater the chances of its irregularity, also the greater the difficulties and the higher the costs of correct administration over large areas with a low population density, poor communications, primitive educational level, and inadequate rural health service organization. The length of action of the drug required for mass chemotherapy of malaria should be at least equal to the "carry over" period of pentamidine, which when administered in a dose of 200–250 mg. will protect an individual from trypanosomiasis for three to six months.

The ideal antimalarial combining the virtues of causal prophylaxis, suppression, rapid and complete curative action, sporontocidal effect and inability to create parasite resistance, absence of toxic effects, slow excretion, palatability, and (last but not least) low cost is still wait-

ing to be discovered. Any new advances of synthetic chemistry applicable to chemotherapy of malaria are therefore of considerable practical importance.

The finding of Rollo and Duffin (1957) that the compound known under a code number, 377 C 54, belonging to a series of hydroxynaphthalenes, has a pronounced action against malaria parasites is of particular interest. It introduces an entirely new group of drugs and opens for the synthetic chemist the possibility of many variations on the main theme in the hope of producing, if not an ideal antimalarial, an improvement on present drugs.

Characteristics of 377 C 54

Coatney and his associates (1952), who tested nearly 4,000 chemical compounds for antimalarial activity, reported that naphthalene derivatives had some effect on the experimental infection of chickens with *P. gallinaceum*. Nevertheless in the final table of tested products with a significant therapeutic index, the halogenated naphthalene amino-alcohols occupied only a modest place in the middle of the range of just over 200 chemical compounds.

377 C 54, a new compound, synthesized recently in the laboratories of the Wellcome Foundation in London, is 2:5-bis(cyclo-hexylaminomethyl)naphthalene-1:6-diol dihydrochloride. It belongs to a series of mono- and dihydroxynaphthalenes which were first tested for antimalarial activity against *P. gallinaceum* infections in young chicks and *P. berghei* in mice (Rollo and Duffin, 1957). In further trials use was made of *P. cathemerium* in canaries and *P. knowlesi* in a rhesus monkey.

Screening tests showed that the activity of 377 C 54 against the two avian plasmodia was of a high order. In *P. gallinaceum* infections the median effective dose was about twice that of chloroquine. The therapeutic index of the new compound, calculated according to the method used by Coatney *et al.* (1952), is of the order of 60–70, and thus in the first third of the American table of compounds with a significant plasmodicidal activity. In single-dose experiments the speed of action of the new compound was of the same order as that of chloroquine. Its action on a virulent strain of *P. knowlesi* in the rhesus monkey was fast and complete.

The early pharmacological tests of 377 C 54 on chicks and man showed that the drug is rapidly absorbed; it appeared that its excretion is slow owing to retention in the liver and lungs. Its toxicity in laboratory animals and in man seemed to be low.

Method of Field Trial

Prior to the large-scale field trial of the new drug it was taken by each of us for seven days at the daily dose of 600 mg. This high dosage having produced only nausea and fatigue, it was decided to use the drug for a field trial.

The method of the trial was that used for the past five years for several similar investigations (Bruce-Chwatt, 1951; Archibald, 1951; Bruce-Chwatt and Archibald, 1953; Charles and Bruce-Chwatt, unpublished). It was based on a selection of two or more volunteer groups of African schoolchildren naturally infected with malaria. Preliminary screening was followed by the administration to each group of a suitable therapeutic dose of the tested drug. The speed of disappearance of parasitaemia in each group was used as an indication of the respective activity of the tested drug and its dosage. It is fully realized that this method has its disadvantages. It cannot serve as a substitute for a well-controlled laboratory experiment in which all the variables of the infection are well assessed and the toxicity of the drug can be gauged during the investigation. Nor can this trial claim to give more information than a true therapeutic trial on non-immune patients with acute clinical malaria.

The method adopted by us stands half-way between the two mentioned above. It provides rapidly a good deal of

information on the comparative value in human malaria of drugs known to be active and non-toxic. Moreover, it uses reasonably good samples of subjects naturally infected with a variety of species and strains of the parasite and, after a judicious preliminary screening, permits us to standardize to some extent the composition of each group, though at times a random sampling might be preferred. Furthermore, this method approximates the conditions under which mass administration of antimalarials is most likely to be carried out in a given area.

The present investigation was carried out on 316 African children attending five elementary schools in the Mushin-Shomolu suburban area of Lagos. Its purpose was carefully explained to the teachers, to the parents, and to the children, and it was made clear that taking part in the trial was voluntary. It is a tribute to the intelligence of the teachers and parents and to the confidence of the children that refusals to take part in the trial were extremely rare.

After an initial screening the children were divided into two series of three groups, each to be given 377 C 54 at the following regimens: (I) single dosage at 300 mg., 200 mg., and 100 mg. respectively; (II) repeated dosage for two consecutive days at 300 mg., 200 mg., and 100 mg. respectively. In addition, one separate group was given a single dose of 100 mg. of chloroquine, and one small group of 20 children, given a placebo, served as control. All the drugs were administered by one of us and, apart from the initial selection for positive parasitaemia, the children were allotted at random to the six treatment groups. The observations were made at the height of the rainy season during the period June to October.

Thick blood films were collected daily from D-day to D+3 and weekly thereafter to week 4, stained with Giemsa, and examined for 200 microscopical fields on each occasion. A parasite density index was computed on the basis of grouped parasite densities per c.mm. (Bruce-Chwatt, 1951), parasite counts being made from the parasite/leucocyte ratio. Spleen and liver palpation was made a few days before D day at the time of the preliminary survey and again at the end of the observations at week 4.

The usual malariometrical indices were calculated for each group from the results of these investigations. The time of disappearance of the initial parasitaemia (exclusive of crescents) in each group of children was calculated as a "mean clearance time" and used for comparison of schizontocidal activity of the investigated drug.

Results of the Investigation

The preliminary screening of children showed that the two main series and the two additional groups were malariometrically comparable in all major respects (Table I). Their overall mean age was 7.2 years; liver enlargement rate, 31.3%; spleen rate, 75.3%; average enlarged spleen 1.54; parasite density index, 3.31; mean weight of children, 45 lb. (20.4 kg.).

As usual in Southern Nigeria, the predominant parasite species was *P. falciparum*, which occurred in 96.5% of the selected positive sample. *P. malariae*, generally in associa-

tion with *P. falciparum*, ranged between 20.7 and 32.2% in the group parasite formula, while *P. ovale* occurred irregularly with an overall frequency of 2.1%.

The gross parasite densities, which because of the general low counts of *P. malariae* and *P. ovale* principally reflect *P. falciparum*, centred around 500–1,000 parasites per c.mm. to give an overall parasite density index of 3.31. Gametocytes of *P. falciparum* were evenly distributed among the various groups at a comparatively high overall rate of 36.4%.

Effects of Treatment

The effects of the several regimens of the compound 377 C 54 and that of chloroquine are described here mainly with reference to parasite findings in the peripheral blood.

Disappearance of parasitaemia (exclusive of crescents) was complete in Series I only for the 300-mg. group. Failure of such clearance was recorded in five children (11.4%) of the 200-mg. group, while only 21 of 44 children (47.7%) were cleared in the single-dose 100-mg. group. In these two groups failure of clearance occurred both against *P. falciparum* in single infections and against *P. falciparum* and *P. malariae* in mixed infections. The parasite density of these failures did not differ from that of the groups as a whole. Where one species only was cleared in a mixed infection it was included in calculating the clearance time for that species. In Series II all three regimens of 377 C 54 produced total clearance, as also did the single 100-mg. dose of chloroquine. No change was noticeable in the control group, the 100% parasite rate of which remained at this level throughout the investigation.

TABLE II.—Clearance Time Obtained in Two Series of Children Given 377 C 54 Compared with One Group on Chloroquine

	No. of Infections	Percentage Cleared	Clearance Time (Mean Days $\pm$ S.E.)		
			Gross	<i>P. falciparum</i>	<i>P. malariae</i>
377 C 54 Series I:					
300 mg. } Single dose	43	100.0	2.73 $\pm$ 0.52	1.41 $\pm$ 0.10	6.50 $\pm$ 1.55
200 " } dose	44	88.6	2.28 $\pm$ 0.46	1.66 $\pm$ 0.09	4.78 $\pm$ 0.95
100 " } dose	44	47.7	2.62 $\pm$ 0.34	1.90 $\pm$ 0.42	2.42 $\pm$ 0.68
377 C 54 Series II:					
300 mg. } Two doses	41	100.0	2.60 $\pm$ 0.39	1.51 $\pm$ 0.08	4.96 $\pm$ 1.05
200 " } doses	45	100.0	2.51 $\pm$ 0.34	1.77 $\pm$ 0.08	4.66 $\pm$ 0.98
100 " } doses	42	100.0	3.78 $\pm$ 0.51	2.15 $\pm$ 0.07	5.68 $\pm$ 0.95
Chloroquine 100 mg. Single dose	37	100.0	2.53 $\pm$ 0.24	2.08 $\pm$ 0.12	2.77 $\pm$ 0.97

Clearance time set out in Table II is shown for all species combined and for the two main species separately. As previously observed by us (Charles and Bruce-Chwatt, unpublished) in relation to chloroquine and amodiaquine, the relatively prolonged gross clearance times recorded here are due principally to the persistence of fully grown pre-segmenters of *P. malariae*. These parasites with poorly staining cytoplasm and clumped pigment were seen in the peripheral blood for upwards of a week without any evidence of further development.

The irregular nature of this phenomenon is reflected in the long mean clearance times (2.42 ± 0.68 to 6.50 ± 1.55 days) and the large standard error of the means recorded for *P. malariae* alone.

TABLE I.—Malarimetrical Findings on 316 Children Taking Part in the Field Trial

	No.	Mean Age (Years) $\pm$ S.E.	Spleen Enlarged		Liver Enlarged %	Blood Examination				P.D.I.
			Rate %	A.E.S.		<i>P. falciparum</i>	<i>P. malariae</i>	<i>P. ovale</i>	<i>P. falciparum</i> gametocytes	
377 C 54 Series I:										
300 mg. } Single dose	43	7.0 $\pm$ 0.09	60.5	1.42	23.2	73.6	20.7	5.7	34.9	3.49
200 " } dose	44	7.1 $\pm$ 0.23	85.6	1.74	34.1	72.9	25.4	1.7	43.2	3.66
100 " } dose	44	7.3 $\pm$ 0.06	72.7	1.56	31.8	69.8	30.2	0	40.9	3.05
377 C 54 Series II:										
300 mg. } Two doses given	41	7.3 $\pm$ 0.17	85.4	1.46	31.7	74.5	21.8	3.7	39.0	3.44
200 " } in two days	45	7.1 $\pm$ 0.04	68.8	1.64	40.0	78.2	21.8	0	37.7	3.02
100 " } doses	42	7.2 $\pm$ 0.18	83.3	1.37	35.7	67.8	32.2	0	45.2	3.19
Chloroquine 100 mg. single dose	37	7.0 $\pm$ 0.16	73.0	1.55	21.6	72.5	21.6	5.9	45.9	3.51
Control group	20	7.5 $\pm$ 0.07	65.0	1.47	30.0	75.0	25.0	0	30.0	2.60
Total	316	7.2 $\pm$ 0.04	75.3	1.54	31.3	72.8	25.1	2.1	36.4	3.31

A.E.S. = Average enlarged spleen. P.D.I. = Parasite density index.

Against *P. falciparum* the clearance times observed for 377 C 54 were generally less than two days. In both series the speed of clearance appeared to be directly proportional to dosage, ranging from 1.41 to 1.90 days for 300 mg. and 100 mg. respectively in Series I, and from 1.51 to 2.15 days for the same doses in Series II. In both series analysis of this relationship by the chi-square test suggested the improbability of this finding occurring by chance alone ($P < 0.001$). The apparent faster action of the single-dose regimens in Series I than that of the corresponding repeated dose regimens in Series II was in no instance statistically significant. The difference between the fastest (1.41 days) *P. falciparum* clearance time for 377 C 54 and that for chloroquine (2.08 days) was, however, highly significant $P < 0.001$.

All but one of the nine *P. ovale* infections included in the groups were cleared by D+1, and that exception was cleared by D+2.

Analysis of the speed of clearance of *P. falciparum* in relation to the pre-treatment density of that species per c.mm. was made for Series II. For this purpose the usual 10 parasite density groups were consolidated into two groups below and above the level of 500 parasites per c.mm. There was no significant association of clearance time with the parasite density.

Reappearance of Parasitaemia.—In assessing the time of reappearance of parasitaemia, the small number of *P. malariae* pre-segmenters persisting from the original infections were discounted in both series, and in Series I only those children in whom total clearance had been attained were taken into consideration. The results of these observations are summarized in Table III and illustrated in the graph. Most of the recurrences were due to

TABLE III.—Weekly Parasite Rates Following Initial Therapeutic Clearance of Parasitaemia

Treatment Group	Week After Treatment			
	1	2	3	4
377 C 54 Series I:				
300 mg. {No. examined ..	42	40	41	40
{ % positive ..	0	2.5	24.4	51.2
200 " {No. examined ..	36	36	36	37
{ % positive ..	0	2.8	27.7	51.3
100 " {No. examined ..	41	40	41	41
{ % positive ..	14.3	47.6	85.0	90.5
377 C 54 Series II:				
300 mg. {No. examined ..	41	40	41	41
{ % positive ..	0	0	7.3	19.5
200 " {No. examined ..	45	45	43	44
{ % positive ..	0	0	4.6	13.6
100 " {No. examined ..	42	42	41	41
{ % positive ..	0	7.1	19.5	46.3
Chloroquine				
100 mg. {No. examined ..	36	37	37	37
{ % positive ..	0	0	2.7	13.5

Parasite rates in African schoolchildren all infected with malaria prior to administration of 377 C 54. The drug was given in three doses of 100 mg., 200 mg., and 300 mg. once (Series I) or twice (Series II). The graph shows the different speed of the reappearance of parasitaemia after a clearance on week 1 or week 2.

P. falciparum, but a small number (five and six) pertained to *P. malariae* and *P. ovale* respectively. In the 200-mg. and 300-mg. groups of Series I the first reappearance of parasites was observed by week 2. Although by week 4 approximately half of the children in these two groups showed positive blood films, 90% of the 100-mg. group were already positive.

Gametocytocidal Action.—Although 377 C 54 appeared to act on all the erythrocytic forms of *P. malariae* and *P. ovale*, it had no immediate and direct action on the gametocytes of *P. falciparum*. There was evident, however, a gradual and indirect reduction of crescents over a period of time after clearance of the asexual forms (Table IV).

TABLE IV.—*P. falciparum* Gametocyte Rates in Seven Groups of Treated Children and One Control Group

	D	D+1	D+2	D+3	Wk 1	Wk 2	Wk 3	Wk 4
377 C 54 Series I:								
300 mg. ..	34.9	44.2	29.5	34.9	38.1	31.7	19.5	12.5
200 " ..	43.2	43.2	45.5	52.3	56.1	51.2	29.3	19.0
100 " ..	40.9	43.2	43.2	38.6	38.6	25.0	30.2	25.0
377 C 54 Series II:								
300 mg. ..	39.0	31.7	41.5	39.0	41.5	25.0	17.1	9.7
200 " ..	37.7	31.1	42.2	46.6	40.0	32.5	32.5	9.3
100 " ..	45.2	38.1	35.7	47.6	42.8	26.2	24.4	12.2
Chloroquine:								
100 mg. ..	45.9	48.6	48.6	48.6	41.6	40.5	32.4	18.9
Control group ..	30.0	35.0	30.0	30.0	35.0	40.0	35.0	35.0

TABLE V

	Before Drug Administration	5 Days After Receiving 300 mg. of 377 C 54
No. of <i>P. falciparum</i> gametocytes ..	180/c.mm.	40/c.mm.
No. of <i>A. gambiae</i> infected on 10th day ..	3 out of 10 dissected	1 out of 9 dissected
Total No. of oocysts of <i>P. falciparum</i> ..	14	2

Thus in Series II, where all asexual forms of *P. falciparum* were cleared by D+3 in all three groups, crescents were still found in about 10% of children at week 4, though about 40% of the children showed them at the start of the observation period.

Sporontocidal Action.—Four children with *P. falciparum* gametocytes varying in density between 80 and 180 per c.mm. were each exposed to bites of 20–30 *A. gambiae*. Immediately after this they were each given a single dose of 300 mg. of 377 C 54. On the fifth day after receiving the drug the children were again examined for crescents and exposed to bites of new batches of *A. gambiae*. The mosquitoes were dissected for oocysts and sporozoites between the 9th and the 11th day after the infective meal. Infections were obtained from three children before the drug administration and from one child after it. The results pertaining to this child aged 6 are shown in Table V. The result suggests that 377 C 54 is not a sporontocidal drug, but that it acts indirectly on gametocytes, decreasing their number by attrition, similarly to the 4-aminoquinolines.

Effects on Splenomegaly.—No significant changes in spleen rate or average enlarged spleen were observed in any of the groups under review.

Toxic Effects.—Among 259 children treated with the dosage regimens described above, nausea and vomiting, usually within two hours after taking the drug on an empty stomach, was reported by eight. No other side-effects were noted, although many of the youngest children, having to crush the tablets before swallowing, were obviously conscious of the bitter taste of the drug.

Discussion

The results of these first field trials indicate that the compound 377 C 54 has an appreciable schizontocidal action on *P. falciparum*, *P. malariae*, and *P. ovale* infections.

Of the *P. falciparum* infections cleared by 100 mg. of 377 C 54, the speed of clearance did not differ statistically from that for chloroquine. But at the higher single doses of 200 and 300 mg. respectively the clearance times for the new drug was significantly faster ($P < 0.001$) than that for chloroquine at 100 mg. This is of particular interest, since in a previous field trial the clearance times for single-dose chloroquine at 100, 200, and 300 mg. respectively did not differ significantly one from another (Charles and Bruce-Chwatt, unpublished).

Judging by the comparative clearance rate with single doses of the new drug and of chloroquine it appears that 377 C 54 is approximately one-half to one-third as active on *P. falciparum* as chloroquine. This is reasonably consistent with the experimental findings of the activity of 377 C 54 against *P. gallinaceum*.

The fact that at week 4 there was no evidence of a significant decrease of the spleen rate or of the average enlarged spleen in any of the six dosage groups of 377 C 54 suggests that the action of the drug is not as complete as that of 4-aminoquinolines given at single doses of 200 or 300 mg. (Charles, in print). Apart from the single doses of 100 mg. and 200 mg. of 377 C 54 which did not completely clear the parasitaemia in the respective groups, the clearance time for the other dosages was directly proportional to the amount of the drug administered. The steepness of the dose response curve on human malaria parasites is of interest and in accordance with experimental findings in *P. gallinaceum*. The rate of reappearance of parasitaemia indicates that 377 C 54 is a quick-acting and rapidly excreted antimalarial.

Summary

The results of the first field trial on African children of 377 C 54, a new antimalarial compound belonging to a series of mono- and di-hydroxynaphthalenes, indicate that the drug has a pronounced schizontocidal effect on *P. falciparum*, *P. malariae*, and *P. ovale*. There is no evidence of any direct gametocytocidal or sporontocidal action on *P. falciparum*. The new compound is well tolerated in a dosage of about 30 mg. per kg. given in two days.

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Which Way Now? is a leaflet issued by the National Association for Mental Health for parents of mentally handicapped children. The leaflet describes how such children, for whom ordinary schools are unsuitable, are placed under "supervision" by a mental welfare officer or a health visitor, who will help and advise the parents as necessary. Occupation centres, which are similar to special schools, may be provided by the local health authority. If there is no occupation centre the health authority may employ a "home teacher" at regular intervals. This leaflet (price 3d. net), and others also concerned with the training of mentally handicapped children, are obtainable from the National Association for Mental Health, 39, Queen Anne Street, London, W.1.

ANTIVENENE REACTION FOLLOWING ACCIDENTAL SEA-SNAKE BITE

BY

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The following personal experience illustrates some problems in snake-bite and its treatment.

Case Report

On September 23, 1955, sea-snakes were being manipulated to obtain venom. At that time the technique used was to grasp the neck of the sea-snake with a long pair of forceps and lift it from the glass bowl in which the snakes swam. The snake was then laid on a table and seized by the left thumb and index finger either between the head and forceps or just behind the forceps (depending on how near the forceps were to the head). The forceps were then released and venom was taken on a plastic spoon. An adult *Enhydrina schistosa* (Daud)—total length 810 mm. (32 in.)—was being held thus by forceps on the table, but as my finger approached to grasp the snake, it managed to turn its head quickly (with far greater speed than I thought possible in this usually sluggish species) and bite the tip of my finger. This was at 2.50 p.m.

The snake was rapidly returned to its bowl and the index finger, bleeding slightly, sucked with much dismay. Amputation was considered, but the means were not immediately to hand. It was therefore decided to "take a chance." At the same time, I thought that if the chance did not come off, inactivity would not appear—even posthumously—to have been masterly. Without faith in the procedure, antivenene therapy was therefore given as follows: 3.10 p.m., 250 mg. of cortisone by intramuscular injection; 3.20 p.m., 10 ml. of antivenene intramuscularly; 3.25 p.m., a further 10 ml. of antivenene together with 1,000 units of hyaluronidase intramuscularly. The antivenene was polyspecific against *Naja naja*, *Bungarus coerulesus*, *Vipera russelli*, and *Echis carinatus* and concentrated by sulphate. It has negligible *in vitro* neutralizing power against *E. schistosa* venom (Savoor, 1955).

Until 6 p.m. there were no symptoms suggesting sea-snake poisoning. The bite mark was painless and there was no objective sensory loss over the index finger. Neurological and general physical examinations were negative. Routine venom-taking was resumed, the *E. schistosa* specimen which bit me giving an unusually high yield (after drying, it weighed 27 mg.; the average maximum for this species is 15 mg.). At 6 p.m. generalized aches, stiffness, and some muscular weakness started. Sleep that night was disturbed, but no further symptoms of sea-snake poisoning developed. The next morning the stiffness was much better although still present. Both palms were red and swollen. On September 25 and 26 I felt quite well but had a pricking sensation at the site of the bite. X-ray examination showed an opacity in the finger pulp. With the help of a dissecting microscope I extracted a grooved fang.

On September 27 urticaria started, the next day general aches, and on September 29 lip-swelling and conjunctival congestion developed. Promethazine, 50 mg. twice daily, temporarily relieved these symptoms, but malaise remained severe. At 6 p.m. on September 30 the neck was stiff and painful. At 9 p.m. twinges were passing down both arms. At 1 a.m. on October 1, I was woken by violent shooting pains down the arms and over the left buttock: they were agonizing and were not significantly relieved by 100 mg. of promethazine and 8 tablets of aspirin. Further sleep was impossible. Throughout that day severe pains continued despite 8 codeine compound tablets and 100 mg. of pethidine. Nausea was constant.