CHEMOTHERAPY OF RODENT MALARIA
EVALUATION OF DRUG ACTION AGAINST NORMAL AND RESISTANT STRAINS INCLUDING EXO-ERYTHROCYTIC STAGES

FINAL REPORT

by

WALLACE PETERS, MD, DSc

December 1978

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Blood schizontocidal action of 5 WRAIR compounds and tissue schizontocidal action of 33 WRAIR compounds is summarised in this report. WR 226296 and WR 232584 and WR 235485, five-substituted 8-aminoquinolines, are highly active blood schizontocides. WR 235485 was active against chloroquine resistant lines but inactive against a primaquine resistant line. Of the 8-aminoquinolines tested WR 221527 is the most active tissue schizontocide but does not possess residual action.

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A procedure has been developed in conjunction with WHO for the screening of blood and tissue schizontocides with prolonged activity. Details of the Screening procedure are included with this report. A fluorescent technique is being developed to identify long acting compounds which possess tissue schizontocidal activity.

Investigations of polymer matrix preparations to prolong the antimalarial activity of pyrimethamine and sulphadiazine continue. A more reliable and technologically simpler method of preparing the drug-matrix polymers has been developed.

Further studies on the mode of action of chloroquine are reported.

The present programme in Liverpool will terminate at the end of September 1979 when the Principal Investigator will transfer his activities to the London School of Hygiene and Tropical Medicine.

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1. INTRODUCTION

During the year under review we have continued to evaluate new WRAIR compounds with special reference to causal prophylactic agents, to drug potentiation and to the development of a screening procedure to detect agents with prolonged activity. We have continued the investigation of WRAIR compounds received in 1977 together with a further 12 compounds sent this year. (This makes a total of 371 compounds examined to date.)

Biochemical work has been delayed during the year because of technical difficulties that have necessitated the cloning of our rodent malaria strains that are being employed in this work, and a shortage of small animal accommodation pending reconstruction work to improve our animal rooms.

In October 1978 the Principal Investigator took the opportunity of his presence in Washington to visit WRAIR for discussions on the progress of this programme.

2. CYCLICAL PASSAGE OF RODENT MALARIA STRAINS

In order to carry out work on long-acting compounds we are now maintaining P. yoelii yoelii 17X as well as P. y. nigeriensis in cyclical passage. Every precaution is taken to ensure that there is no accidental cross contamination, including a periodical check on enzyme markers.

3. CHEMOTHERAPY STUDIES

3.1 Blood schizontocides

Apart from the specially selected compounds used in the development of the screen for long-acting compounds we have examined 3 8-aminoquinolines and 2 other compounds of structures so far unidentified to us. WR 226,296 was highly active sc and po against P. berghei in the 4-day test. WR 232,584 was also active but less po than sc. WR 235,485 was very active sc and po against the N, NS and RC lines, but the P line was markedly resistant to it, especially sc. WR 212,293 and 233,637 showed insignificant activity at 30 mg/kg and will be examined at higher doses. These data are summarised in Table 1 and detailed in Tables 2 through 6.

3.2 Causal prophylaxis

We have examined the causal prophylactic properties of 33 WRAIR compounds. The data on these are summarised in Table 7, and detailed in Tables 8 through 58. Of the 8-aminoquinolines, the most active was WR 221,527 when given po. WR 228,456 is another salt of this compound which is slightly less active. Note that the data given have not been adjusted to take account of the molecular weights, and no primaquine index has therefore been calculated yet. Included in the compounds studied are several, such as the quinazolines WR 141,871, 159,412 and 180,872 that were provided primarily for studies on repository activity (see Addendum). It will be noted from the individual data sheets that many of these compounds did exhibit residual activity in the causal prophylaxis test, e.g. the Mannich bases WR 194,965 and 228,258.

3.3 Screening system for drugs with prolonged activity

A procedure has now been worked out for the detection of prolonged antimalarial activity in candidate antimalarials. Details are given in an Annex to this report. A further development of the procedure is being examined at the present time to distinguish between true action on exoerythrocytic schizogony from delayed activity against first (or later) generation asexual erythrocytic stages.

We were fortunate in being able to benefit from discussions with Dr. A. Ager of Miami on this project during his visit to Liverpool in April this year. It is hoped that Dr. Ager's laboratory will take over this system or modify it if necessary for use in screening the large number of candidate compounds with possible repository activity in the WRAIR inventory.

An examination of the series of compounds provided by WRAIR in this procedure, using diformyl dapsone (DFD) as a control, has shown clear residual activity in the pyridine methanol WR 172,435 (4 x DFD), the phenanthrene methanol WR 171,669 (3 x DFD) and the quinazoline WR 180,872. (It is encouraging to note that in this work which was carried out "blind", i.e. the nature of the compound was unknown to the staff performing the tests, WR 6798 gave precisely the same result as the DFD control.)

3.4 New drug delivery systems

We have continued our studies on the use of drug-polymer matrix preparations to obtain a prolongation of antimalarial effect with standard antimalarial compounds. Our original experimental system, employing implants prepared from silastic tubing filled with the powdered antimalarial compound has been discontinued, since such capsules were profligate in the use of compounds, up to 50 mg being used in each. Comparison of the results obtained with 'tubing' implants and polymer-drug 'mixture' implants also showed that the latter were more effective.

3.4.1 Implants prepared from siloxane-drug mixtures

Siloxane-drug mixtures have been prepared with a number of standard antimalarials as described in the last Annual Report. Further work has continued with pyrimethamine, sulphadiazine and latterly, sulphadoxine incorporated into silicone rubber matrices and employed experimentally. Attention has been paid to the design of experiments for the evaluation of residual antimalarial action since two major aspects of the protocol previously employed were considered unreliable; the first related to the fact that during the course of an experiment mice were of different ages and body weight at the time of challenge (all mice received implants on Day 0 and were challenged at intervals thereafter) and the second was the possible effect of host immunity on parasitaemia in animals which were repeatedly challenged with infected mouse erythrocytes. In the revised protocol which has been adopted during the past year, groups of mice receive implants on Days 0, +28 to + 140 at 28 day intervals and all groups are challenged on Day + 168. Groups of control, untreated mice are also set up on Day 0. Thus all mice are of the same age at the time of infection and receive a single parasite challenge. With this system it has been found that a 200 mg implant containing 1 mg pyrimethamine base protects mice for $> 5 < 6$ months.

3.4.2 Implants prepared from biodegradable polymer-drug mixtures

Mixtures of pyrimethamine, sulphadiazine and cycloguanil in biodegradable matrices have been prepared by Professor Graham , Strathclyde University, Scotland. Difficulties were encountered initially in preparing mixtures with pyrimethamine but 24 mg implants of this mixture (30% pyrimethamine base) protected mice against P. berghei challenge for > 3 months.

A more reliable and technologically simpler method of preparing matrix-pyrimethamine mixtures has now been developed and preliminary tests have revealed that 50 mg implants containing 20% pyrimethamine base protect mice for > 56 days. A full trial of these preparations is in progress.

Preparations containing 10% and 30% sulphadiazine in a biodegradable matrix have been obtained. Preliminary tests with these mixtures have given encouraging results and further evaluation is in progress.

Considerable attention has been focussed on the use of injectable, powdered formulations of biodegradable polymers containing sulphadiazine and pyrimethamine The different grades of particle supplied were of > 53 < 96 μ, > 96 < 250 μ and > 100 < 250 μ diameter. Colloidal preparations of particles were prepared in carboxymethyl cellulose and administered sc at doses from 0.5-5 mg/20 g body weight. The results obtained with the injectable biodegradable matrix-drug powders have shown that the residual effect of these preparations is much less than that obtained with an equivalent dosage in pellet form. This is probably related to a more rapid release of the antimalarial from such powders, and agrees with results obtained by Wise et al. (J. Pharm. Pharmac. (1978), 30, 686-689). Quantitative studies on the rates of release of antimalarials from the various preparations employed have not been possible because radio-labelled compounds have not been available. A source of radio-labelled sulphadoxine has now been obtained and it is hoped that radio-labelled pyrimethamine will be made available for our use through the WHO TDR Programme.

It is also intended to develop an in vitro bioassay for the determination of the serum levels of pyrimethamine, sulphadiazine and sulphadoxine using P. falciparum in vitro cultures.

In addition to work on pyrimethamine and sulphadiazine a limited amount of work has also been performed with cycloguanil hydrochloride-biodegradable polymer mixtures. No powder preparations have been tested but with solid implants the residual effect of ~50 mg implants containing 30% cycloguanil was < 14 days.

3.4.3 Sustained release from Alzet^{R} osmotic minipumps

Experiments using WR 99,210 (LIV/1019) and primaquine phosphate released from osmotic minipumps were described in the previous Annual Report (December 1977).

A comparison has been made between the antimalarial effects of equivalent dosages of primaquine phosphate administered once daily by sc injection and continously by constant release from the osmotic minipumps to determine if the use of a slow release preparation could result in a reduction in the total dosage of primaquine required to control parasitaemia.

On D+3 of infection with P. berghei N strain, Alzet^{R} osmotic minipumps (of 170 µl capacity and a flow rate of 1 µl/hr) containing solutions of 4.125, 8.25 and 16.5 µg/µl respectively of primaquine phosphate were implanted in three groups of mice. Three further groups of mice received primaquine at 5, 10 and 20 mg/kg, sc, daily from D+3 for 7 days. A release of 4.125 µg/hr from osmotic minipumps in a 20 g mouse is equivalent to a total daily dosage of 5 mg/kg. The experiment therefore included three paired groups of mice receiving primaquine phosphate at daily dosages of 5, 10 and 20 mg/kg for a 7 day period.

The results of this experiment (graphically illustrated in Figures 1, 2 and 3) demonstrate that the antimalarial effect of primaquine phosphate was similar in mice treated daily and in those which received drug continuously. A fulminating infection was observed in mice receiving 5 mg/kg daily and 4.125 µg/hr, there being a slightly greater antimalarial effect in mice receiving the drug by daily injection. A plasmodistatic effect was observed during the period of treatment at 10mg/kg daily and 8.25 µg/hr and a plasmodicidal effect with elimination of parasites by D+7 resulted from treatment with 20 mg/kg and 16.5 µg/hr.

These results and those from a duplicate experiment indicate that no reduction in the total dosage of primaquine phosphate required for the treatment of malaria infections may be achieved by the employment of slow release preparations.

3.5 Drug potentiation

We have completed studies on the potentiation of the blood schizontocidal activity of WR 158,122 by dapsone and by sulphadoxine, both of which are shown in Tables 59 and 60, and Figures 4 and 5 exhibit a marked degree of potentiation. In view of research that has been undertaken elsewhere (Dynatech R/D Corp) on the incorporation of WR 158,122 and sulphadiazine into biodegradable polymers these data give encouragement for the extension of polymer studies with one or other mixtures of these compounds.

3.6 Mode of action of chloroquine and mefloquine

It has been suggested that the death of the chloroquine-treated malarial parasite is caused by intercalation of chloroquine into the parasite's nucleic acid. To investigate this, parasites were treated with radioactively-labelled chloroquine for one hour in vitro and the amount of radioactivity associated with the TCA-insoluble fraction of the parasitised cells was measured. The first two experiments of this kind indicated substantial retention of chloroquine in the TCA-insoluble fraction with more of the chloroquine associated with protein than with nucleic acid. However, in three further experiments carried out in identical manner, virtually no radioactivity was found in either the protein or the nucleic acid fractions. Whether these conflicting

results were due to artefacts or to a change in the chloroquine sensitivity of the parasite due to the abnormally high temperature in the animal house cannot at present be determined. At the end of these experiments it was found that the enzymes of the parasite were no longer those of the chloroquine-sensitive N strain, but those of the chloroquine-resistant NS line. Experiments will be resumed when improvements to the animal house permit the preparation of an indisputably cloned strain.

4. CONCLUSIONS AND RECOMMENDATIONS

Our current year's work has continued to provide useful data concerning the value of the newer 8-aminoquinolines as causal prophylactic agents. Further work is required on a technique to distinguish definitively in rodents between true causal prophylaxis and the delayed blood schizontocidal action of some of these compounds. This will link in well with the extension of our work on the technique of evaluating long-acting drugs which has made good progress during the current year.

With the pending completion of construction work on improved small animal accommodation and the production of clones of the strains of Plasmodium needed for further biochemical studies on drug resistance, it is anticipated that experiments on the mode of action of chloroquine and mefloquine using radiolabelled material will continue early in the new year.

A fluorescent technique is being developed for the detection of small numbers of tissue schizonts as part of the screening procedure referred to above. Sera obtained in immunised rabbits have so far not been of sufficiently high titre to give consistent results.

Our studies on the prolongation of antimalarial action of various drugs by their incorporation in polymers will be continued, using any WRAIR compounds that may be suggested. Potentiating drug combinations will also be examined in such formulations.

The Principal Investigator will transfer his activities in October 1979 when he leaves Liverpool to take over the Chair of Medical Protozoology at the London School of Hygiene and Tropical Medicine. Funds have been requested from WRAIR to permit completion of the present programme up to the end of September 1979 in Liverpool. Early in the new year it is hoped to have a further meeting with WRAIR to negotiate possible further collaboration.

5. PAPERS PUBLISHED

5.1 Already published

Chance, M. L., Momen, H., Warhurst, D. C. and Peters, W. (1978). The chemotherapy of rodent malaria, XXIX. DNA relationships within the subgenus Plasmodium (vinckeia). Ann. trop. Med. Parasit., 72, 13-22.

Homewood, C. A. (1978). The biochemistry of rodent malaria parasites. In: "Malaria Parasites of Rodents", Academic Press, London. pp. 169-211.

Killick-Kendrick, R. and Peters, W. (1978). Malaria Parasites of Rodents. Academic Press, London.

Peters, W. (1978). Models for the study of antiprotozoal drugs. In: "Current Chemotherapy", Proceedings of the 10th International Congress of Chemotherapy, Vol. 1 (Eds. Siegenthaler, W. and Luthy, R.) p. 10-. American Society of Microbiology: Washington DC.

Peters, W. and Howells, R. E. (1978). Chemotherapy. In: "Malaria Parasites of Rodents" (Eds. Killick-Kendrick, R. and Peters, W.), Academic Press, p. 345-391.

Peters, W., Chance, M. L., Lissner, R., Momen, H. and Warhurst, D. C. (1978). The chemotherapy of rodent malaria, XXX. The enigmas of the NS lines of P. berghei. Ann. trop. Med. Parasit., 72, 23-36.

Cont. No. 1462

Peters, W., Howells, R. E., Judge, B. and Schofield, P. (1978). Studies on screening techniques using animal models. WHO Working paper for SWG on the Chemotherapy of Malaria, held in Geneva, July 1978.

Warhurst, D. C. and Thomas, S. C. (1978). The chemotherapy of rodent malaria, XXXI. The effect of some metabolic inhibitors upon chloroquine-induced pigment clumping (CIPC) in Plasmodium berghei. Ann. trop. Med. Parasit., 72, 203-211.

Cont. No. 1474

5.2 In press

Homewood, C. A. and Neame, K. D. (1979). Biochemistry of malaria parasites. In: "Malaria in Man and Experimental Animals", (Ed. J. P. Kreier), Academic Press.

Merkli, B., Richle, R. and Peters, W. (1979). The inhibitory effect of a drug combination on the development of mefloquine resistance in Plasmodium yoelii yoelii. Ann. trop Med. Parasit.

Peters, W. (1979). The research sphere. Paper presented at the WHO Working Group on Receptivity to Malaria and Other Parasitic Diseases, held in Izmir, October 1978.

Peters, W. (1979). Chemotherapy of malaria. In: "Malaria in Man and Experimental Animals" (Ed. J. P. Kreier), Academic Press.

Peters, W. (1979). Pharmacology of antimalarials. In: "Chemotherapy of Malaria", Second Edition, WHO Geneva.

Peters, W. (1979). Drugs against parasitic diseases. Paper to be presented at IOM-sponsored Conference on Pharmaceuticals for Developing Countries, Washington DC, January 1979.

6. APPENDICES

Table 1	Summary of blood schizontocidal studies in 4 day test against Plasmodium berghei.
Tables 2-6	Detailed 4-day tests of blood schizontocidal action
Table 7	Summary of causal prophylactic tests against Plasmodium yoelii nigeriensis
Tables 8-58	Details of causal prophylactic tests
Table 59	ED_{90} of WR 158,122 and DDS alone or in combination. Data in mg/kg sc in 4-day test (see Figure 4)
Table 60	ED_{90} of WR 158,122 and sulphadoxine alone or in combination. Data in mg/kg sc in 4-day test (see Figure 5).
Figures 1-3	A comparison of the response of Plasmodium berghei to primaquine phosphate following drug administration by repeated daily injections via mini osmotic pumps.
Figure 4	WR 158,122 and DDS - ED_{90} values when compounds are used alone or in combination in varying proportions.
Figure 5	WR 158, 122 and sulphadoxine - ED_{90} values when compounds are used alone or in combination in varying proportions.

COMPOUND		STRAIN														COMMEN
WR NO.	LIV NO.	Route	N ED_{50}	N ED_{90}	NS ED_{90}	NS I_{90}	RC ED_{90}	RC I_{90}	P ED_{90}	P I_{90}	B ED_{90}	B I_{90}	P.A ED_{90}	P.A I_{90}	ORA ED_{90}	ORA I_{90}	
226296AA BG44452	1391	sc	0.3	0.8													
		po	0.1	0.4													
232584 AA BH 05361	1541	sc	0.8	3.8													
		po		>1													
235485 AA BH 35570	1571	sc	0.7	2.5	2.4	1.0	2.5	1.0	65.0	26.0							
		po	1.0	2.3	2.3	1.0	1.5	0.7	11.0	4.8							
212293 AB BH 49943	1590	sc		>30													
233637 AB BH 49596	1591	sc		>30													

TABLE 1

SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 2

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER WR 226296 AA BG 44452 LIV/1391 PARASITE (SUB) SPECIES P.b.berghei

Route of administration : ~~i.p.~~/s.c./p.o.

Strain	Daily dose mg/kg D0 - D +3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% / Control PR% x 100
N sc	0.03	5		-	100 ± 2.5
	0.1	5		-	88.9 ± 7.3
	0.3	5	1	-	75.5 ± 13.3
	1.0	5		-	8.8 ± 3.6
	Ø	10		36.0	
ED_{50} (range)	0.3 (0.1 - 0.7)				
ED_{90} (range)	0.8 (0.3 - 1.8)				
	Resistance factor 90				
N p.o.	0.03	5		-	73.2 ± 11.4
	0.1	5		-	65.0 ± 11.2
	0.3	5	1	-	50.1 ± 12.1
	1.0	5		-	1.0 ± 0.3
	Ø	10		36.0	
ED_{50} (range)	0.1 (0.04 - 0.4)				
ED_{90} (range)	0.4 (0.1 - 1.2)				
	Resistance factor 90				

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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 3

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 232584 AA BH05361 HV/1541

PARASITE (SUB) SPECIES: P.b.berghei

Route of administration : ~~i.p.~~/s.c./p.o.

Strain	Daily dose mg/kg D0 - D +3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% / Control PR% x 100
N sc	0.03	5		-	100 ± 2.2
	0.1	5		-	90.2 ± 4.3
	0.3	5	1	-	68.1 ± 3.0
	1.0	5		-	51.3 ± 5.1
	Ø	10		36.0	
ED_{50} (range)	0.8 (0.4 - 1.3)				
ED_{90} (range)	3.8 (1.9 - 6.2)				
	Resistance factor 90				
N po.	0.03	5		-	93.5 ± 3.6
	0.1	5		-	96.3 ± 2.6
	0.3	5	1	-	99.8 ± 5.2
	1.0	5		-	85.4 ± 5.9
	Ø	10		36.0	
ED_{50} (range)					
ED_{90} (range)	> 1.0				
	Resisiance factor 90				

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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 4a

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 235485AA BH 35570 LIY/1571

PARASITE (SUB) SPECIES: P.b.berghei

Route of administration : ~~i.p.~~/s.c./~~p.o.~~

Strain	Daily dose mg/kg D0 - D +3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% / Control PR% x 100
N	0.1	5		-	93.9 ± 3.9
	0.3	5		-	85.4 ± 4.7
	1.0	5	1	-	50.7 ± 16.6
	3.0	5		-	4.2 ± 2.9
	Ø	10		36.5	
ED_{50} (range)	0.7 (0.4-1.5)				
ED_{90} (range)	2.5 (1.4-5.7)				
	Resistance factor 90 1.0				
NS	0.1	5		-	96.3 ± 6.9
	0.3	5		-	97.9 ± 5.6
	1.0	5	1	-	61.3 ± 17.1
	3.0	5		-	5.3 ± 2.7
	Ø	10		45.6	
ED_{50} (range)	1.1 (0.8-1.6)				
ED_{90} (range)	2.4 (1.7-3.7)				
	Resistance factor 90 1.0				

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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 4b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER WR 235485AA BH 35570 LIV/1571 PARASITE (SUB) SPECIES P.b.berghei

Route of administration : ~~i.p./s.c./p.o.~~

Strain	Daily dose mg/kg D0 - D +3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% / Control PR% × 100
RC	0.1	5		–	94.4 ± 10.4
	0.3	5		–	88.3 ± 9.6
	1.0	5	1	–	73.5 ± 13.4
	3.0	5		–	6.5 ± 2.9
	∅	10		4.6	
ED_{50} (range)	0.8(0.5-2.6)				
ED_{90} (range)	2.5(1.5-7.0)				
	Resistance factor 90 1.0				
P	0.1	5		–	87.3 ± 16.3
	0.3	5		–	62.1 ± 18.8
	1.0	5	1	–	62.3 ± 19.0
	3.0	5		–	53.0 ± 1.9
	∅	10		19.0	
ED_{50} (range)	2.2(0.5-5.8)				
ED_{90} (range)	65(14->100)	[Interpolated graphically]			
	Resistance factor $_{90}$ 26				

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SUMMARY OF ANTIMALARIAL DRUG TESTS. TABLE 4c

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR 235485 AA / BH 35570 / LIV/1571 ..... PARASITE (SUB) SPECIES: P.b.berghei .....

Route of administration : i.p./s.c./p.o.

Strain	Daily dose mg/kg D0 - D +3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% / Control PR% x 100
N	0·1	5		-	100 ± 4·3
	0·3	5		-	91·1 ± 5·3
	1·0	5	1	-	78·3 ± 5·1
	3·0	5		-	5·4 ± 2·2
	∅	10		36·5	
ED_{50} (range)	1·0 (0·6 - 1·9)				
ED_{90} (range)	2·3 (1·3 - 4·2)				
	Resistance factor 90 1·0				
NS	0·1	5		-	93·5 ± 4·5
	0·3	5		-	91·0 ± 4·5
	1·0	5	1	-	61·4 ± 13·1
	3·0	5		-	4·4 ± 2·0
	∅	10		45·6	
ED_{50} (range)	0·9 (0·6 - 1·7)				
ED_{90} (range)	2·3 (1·5 - 4·1)				
	Resistance factor $_{90}$ 1·0				

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SUMMARY OF ANTIMALARIAL DRUG TESTS (BLOOD SCHIZONTOCIDES) TABLE 4d

COMPOUND NAME or NUMBER WR235485AA BH 35570 LIV.1571..... PARASITE (SUB) SPECIES P.b.berghei....

Route of administration : i.p./~~s.c./~~p.o.

Strain	Daily dose mg/kg D0 - D +3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% / Control PR% × 100
RC	0.1	5		-	82.6 ± 10.9
	0.3	5		-	76.5 ± 12.5
	1.0	5	1	-	59.1 ± 18.0
	3.0	5		-	1.3 ± 0.8
	∅	10		4.6	
ED_{50} (range)	0.5(0.3-1.7)				
ED_{90} (range)	1.5(0.9-4.7)				
	Resistance factor 90 0.7				
P	0.1	5		-	100 ± 2.2
	0.3	5		-	93.0 ± 4.4
	1.0	5	1	-	94.1 ± 8.4
	3.0	5		-	65.2 ± 9.4
	∅	10		19.0	
ED_{50} (range)	3.4(0.9-5.7)				
ED_{90} (range)	11.0(3.2-18.8)				
	Resistance factor $_{90}$ 4.8				

LIVERPOOL SCHOOL OF TROPICAL MEDICINE DATE 5 - DEC 1978 PRINCIPAL INVESTIGATOR PROF. W. PETERS

SUMMARY OF ANTIMALARIAL DRUG TESTS — TABLE 5

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER: WR212293AB BH49943 LIV/1590 — PARASITE (SUB) SPECIES: P. b. berghei

Route of administration: i.p./s.c./p.o.

Strain	Daily dose mg/kg D0 - D +3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% / Control PR% x 100
N	1.0	5		-	84.3 ± 6.1
	3.0	5		-	88.6 ± 4.2
	10.0	5	1	-	75.0 ± 7.7
	30.0	5		-	86.6 ± 4.7
	Ø	10		49.0	
ED_{50} (range)					
ED_{90} (range)	> 30.0				
	Resistance factor 90				
ED_{50} (range)					
ED_{90} (range)					
	Resistance factor 90				

LIVERPOOL SCHOOL OF TROPICAL MEDICINE — DATE: DEC 1978 — PRINCIPAL INVESTIGATOR: PROF. W. PETERS

SUMMARY OF ANTIMALARIAL DRUG TESTS (BLOOD SCHIZONTOCIDES) TABLE 6

COMPOUND NAME or NUMBER: WR 233637 AB BH49596 .LIV/1591..... PARASITE (SUB) SPECIES: P.D. berghei.....

Route of administration : ~~I.P./S.C./P.O.~~

Strain	Daily dose mg/kg D0 - D +3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% / Control PR% x 100
N	1.0	5		-	97.6 ± 3.8
	3.0	5		-	74.2 ± 7.8
	10.0	5	1	-	80.1 ± 7.7
	30.0	5		-	78.3 ± 9.4
	~~Ø~~	10		49.0	
ED_{50} (range)					
ED_{90} (range)	>30.0				
	Resistance factor 90				
ED_{50} (range)					
ED_{90} (range)					
	Resistance factor 90				

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

DATE 7 - DEC 1978

PRINCIPAL INVESTIGATOR PROF. W. PETERS

WR No.	LIV No.	Minimum fully active dose (mg/kg x 1)	Residual action at active dose	Comment	Type of Compound
218335AA BE66930	1348	10-30 po	Nil		8-aminoquinoline
218335AA BE66930	1437	10-30 po	Nil		"
227681AA BG56612	1399	-	-	Inactive at 30 mg/kg po	"
228002AA BG58199	1402	3 po	-		"
228456AA BG62807	1413	3-10 po	Nil		"
212579AB BG48969	1428	-	Ni	Inactive at 30 mg/kg po	"
221527AB BG48898	1439	3 po	Nil		"
203608AA ZN42125	1449	-	-	Inactive at 30 mg/kg sc	"
203608AA ZN42125	1449	-	-	Inactive at 30 mg/kg po	"
219874AA ZN42821	1451	3-10 sc	Nil		"
219874AA ZN42821	1451	3-10 po	Nil		"
215761AA BE16967	1392	3-10 po	Nil		"
215761AA ZN44030	1455	30 po	Nil at 30		"
230388AA BG81580	1476	3-10 po	Nil		"
180409AC BE99420	1504	30 po	Present at 3 Marked at 30	Residual activity only	pyridine methanol
448AG AG28874	1505	30 po	Nil at 30		dapsone
6798AL AF50013	1506	30 po	Nil at 30		DFD
93133AC BB59627	1507	30 po	Nil at 30		furan

TABLE 7

WR No.	LIV No.	Minimum fully active dose (mg/kg x 1)	Residual action at active dose	Comment	Type of Compound
179305 AD BB47734	1508	10-30 po	Nil		furan
49808AC AJ32298	1509	10-30 po	Nil		menoctone
38839-B AM33272	1510	10-30 po	Nil		clociguanil
99210 AE AW 23628	1511	3 po	Nil		triazine
141871 AB AX26848	1512	0.3-1 sc	Nil		quinazoline
141871 AB AX26848	1512	0.3-1 po	Nil		"
159412AC BB59823	1513	1- 3 sc	Nil at 1		"
159412AC BB59823	1513	0.1-0.3 po	Nil at 1		"
180872AC BD09556	1514	3 sc	Present at 1		"
180872 AC BD09556	1514	3 po	Nil at 3		"
194965AG BG56327	1515	10-30 sc	Marked at 30	Residual activity only	Mannich base
194965 AG BG56327	1515	30 po	Marked at 30	Residual activity only	"
228258 AB BG85640	1516	10-30 sc	Present at 10 Marked at 30		"
228258 AB BG85640	1516	10-30 po	Present at 10 Marked at 30		"
81844AD ZF92291	1517	30 sc	Nil at 30		miscellaneous
81844AD ZF92291	1517	30 po	Nil at 30		"
87781AB AB 34313	1518	3-10 sc			minocyc...ie
87781AB AB 34313	1518	3-10 po			"

TABLE 7 (contd.)

WR No.	LIV No.	Minimum fully active dose (mg/kg x 1)	Residual action at active dose	Comment	Type of Compound
231033AA BG89086	1520	10-30 sc	Marked at 10	Residual activity only	8-aminoquinoline
231033AA BG89086	1520	10-30 po	Present at 10 Marked at 30	Residual activity only	"
231138AA BG89362	1521	30 sc	Nil at 30		naphthyridinone
231138AA BG89362	1521	30 po	Nil at 30		"
199507AB BD24062	1522	-	-	Inactive at 30 mg/kg sc	8-aminoquinoline
199507AB BD24062	1522	-	-	Inactive at 30 mg/kg po	"
230837AA BG85408	1524	30 sc	Nil at 30		miscellaneous
230837AA BG85408	1524	10-30 po	Nil		"
27653AD AH07834	1525	-	-	Inactive at 30 mg/kg sc	RC_{12}
27653AD AH07834	1525	-	-	Inactive at 30 mg/kg po	RC_{12}
232584AA BH05361	1541	10-30 sc	Nil		8-aminoquinoline
232584AA BH05361	1541	10-30 po	Nil		"

TABLE 7 (contd.)

CAUSAL PROPHYLAXIS TEST NO: BR649 DATE: 12/1/78

DRUG: L.V. 1348 WR 218335 AA BOTTLE NO: BG6692

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~ip~~/po TIME AFTER INFECTION

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. v. nigeriense STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMM
	C^c/T^c	XC	C^x/T^x	f/h	b	g/e	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	
Ø	5/5		5/5	5·68		3·98				
3·0	3/3			5·11					− 0·57	Inactive
10·0	3/3			5·51					− 0·17	Inactive
30·0	0/3		3/3	>14		3·80		NIL	> 8·32	Fully active

MINIMUM FULLY ACTIVE DOSE ....10-30.... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg.

PRINCIPAL INVESTIGATOR: PROFESSOR W

TABLE 8

CAUSAL PROPHYLAXIS TEST NO: BR649. DATE: 12.1.78

DRUG: I.V./ 1437 WR 218335 AA BOTTLE NO: BE6693

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~i.p.~~ p.o. TIME AFTER INFECTION

INFECTED HOST: CFW MICE PARASITE (NEM) SPECIES: P. c. chabaudi STRAIN: N/G

DOSE mg/kg	PATENCY RATE C^o/T^o	XC	C^x/T^x	GMP 2% P f/h	b	f/e	(a = 2) ACTIVITY VALUES $(h-f)-\left\lvert\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\rvert$	Residual Activity	Prophylactic Activity	COM
∅	5/5		5/5	5.68		3.98				
3.0	3/3			5.35					−0.33	Inactive
10.0	3/3			4.90					−0.78	Inactive
30.0	0/3		3/3	>14		4.63		NIL	> 8.32	Fully active

MINIMUM FULLY ACTIVE DOSE ....10-30..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg.

PRINCIPAL INVESTIGATOR: PROFESSOR W

TABLE 9

CAUSAL PROPHYLAXIS TEST NO: BR649 DATE: 12.1.78

DRUG: I.V.' 1399 WR 227681 AA BOTTLE NO: BG56612

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: [illegible]/p/. TIME AFTER INFECTION:

VERTEBRATE HOST: CFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMM
	C^c/T^o	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left\lvert\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\rvert$	Residual Activity	Prophylactic Activity	
∅	5/5		5/5	5·68		3·98				
3.0	3/3			5·68					0	Inactive
10.0	3/3			6·13					0·45	Inactive
30.0	3/3		3/3	5·63		4·20		NIL	−0·05	Inactive

MINIMUM FULLY ACTIVE DOSE .... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W.

TABLE 10

CQ USAI PROPHYLAXIS TEST NO. BR 646 DATE 18.1.78

DRUG LOT 1402 WR 228002 AA BOOK NO. B45818

PREPARATION Tween 80, H2O ROUTE OF ADMINISTRATION i.p. TIME AFTER INFECTION

VERTEBRATE HOST: C TFW MICE PARASITE (SOME) SPECIES: P. c. chabaudi STRAIN NHG

DOSE mg/kg	PATENCY RATE C^c/T^o	XC	C^x/T^x	GMP 2% P f/h	b	c/e	(a - 2) ACTIVITY VALUES $(h-f)-\left\|\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\|$	Residual Activity	Prophylactic Activity	COMM
Ø	4/5			5.82						
0.3	1/3*			>8.96						Active
1.0	2/3			>9.02						Active
3.0	2/3			>9.90						Active

MINIMUM FULLY ACTIVE DOSE ....>3.0..... mg/kg

RESIDUAL ACTIVITY:

PRINCIPAL INVESTIGATOR: PROFESSOR W.

* 1/3 DIED

TABLE 11

CAUSAL PROPHYLAXIS TEST NO: BR 647 DATE: 5-1-78

DRUG: I.V/ 1413 WR 228456AA BOTTLE NO. BG 6280

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip/im~~/po TIME AFTER INFECTION

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: *T. v. nigeriense* STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^c/T^o	XC	C^x/T^x	GMP 2% P f/h	b	c/e	(a = 2) ACTIVITY VALUES $(h-f)-\left\lvert\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\rvert$	Residual Activity	Prophylactic Activity	COMM
Ø	5/5		5/5	6.17		5.77				
3.0	1/3			>11.26					> 5.09	Active
10.0	0/3		3/3	>14		3.51		NIL	> 7.83	Fully active
30.0	0/3*			.						>LD_{100}

MINIMUM FULLY ACTIVE DOSE ....3-10..... mg/kg

RESIDUAL ACTIVITY: Nil at 10 mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W.

* 3/3 DEAD

TABLE 12

CAUSAL PROPHYLAXIS TEST NO: BR649 DATE: 12.1.78

DRUG: I.V.: 1428 WR 212579 AB BOTTLE NO.: BG48965

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~s.c.~~/p.o. TIME AFTER INFECTION

VERTEBRATE HOST: C.F.W. MICE PARASITE (SPECIES): P. c. vinckei STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^c/T^o	XC	C^x/T^x	GMP 2% P f/h	b	c/e	(a - 2) ACTIVITY VALUES $(h-f)-\left\{\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\}$	Residual Activity	Prophylactic Activity	COM
Ø	5/5		5/5	5.68		3.98				
3.0	3/3			5.67					-0.01	Inactive
10.0	3/3			6.16					0.48	Inactive
30.0	3/3		3/3	6.17		4.58		NIL	0.49	Inactive

MINIMUM FULLY ACTIVE DOSE .... 30 ..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg.

PRINCIPAL INVESTIGATOR: PROFESSOR W.

TABLE 13

CAUSAL PROPHYLAXIS TEST NO. BR647 DATE 5/1/78

DRUG L.V.' 1439 WR 221527 AB BOTTLE NO. BG488

PREPARATION: Tween 80, H$_2$O ROUTE OF ADMINISTRATION: ~~i.p.~~/p.o. TIME AFTER INFECTION

VERTEBRATE HOST: ♂ TFM MICE PARASITE (SUB) SPECIES: P. v. nigeriensis STRAIN NIG

DOSE mg/kg	PATENCY RATE C^c/T^c	XC	C^x/T^x	GMP 2% P f/h	b	c/e	(a = 2) ACTIVITY VALUES $(h-f)-\left\|\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\|$	Residual Activity	Prophylactic Activity	COM
∅	5/5		5/5	6.17		3.77				
3.0	0/3*			>14					>7.83	Fully active
10.0	0/3**		3/3	>14		4.03		NIL	>7.83	Fully active
30.0	0/3***									>LD$_{100}$

MINIMUM FULLY ACTIVE DOSE ....<3..... mg/kg

RESIDUAL ACTIVITY: Nil at 10 mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W

* 1/3 DIED

** 2/3 DIED

*** 3/3 DIED

TABLE 14

CAUSAL PROPHYLAXIS TEST NO: BR656 DATE: 27/1/78

DRUG: L.V./ 1449 WR 203608 AA BOTTLE NO: ZN42125

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ip/sc/po TIME AFTER INFECTION:

VERTEBRATE HOST: 6 TEW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMM
	C^c/T^c	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left\|\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\|$	Residual Activity	Prophylactic Activity	
ϕ	4/4		3/3	5·73		3.62				
3.0	3/3			5·17					-0·56	Inactive.
10.0	3/3			5·50					-0·23	Inactive.
30.0	3/3		3/3	5·45		3.74		NIL	-0·28	Inactive.

MINIMUM FULLY ACTIVE DOSE .... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W.

TABLE 15

CAUSAL PROPHYLAXIS TEST NO. BR656 DATE. 27/1/78

DRUG. I.V./ 1449 WR 203608 AA BOTTLE NO. ZN 42125

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip/im~~/po TIME AFTER INFECTION:

VERTEBRATE HOST: O TFW MICE PARASITE (SUB) SPECIES: P. v. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMME
	C^c/T^o	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left\|\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\|$	Residual Activity	Prophylactic Activity	
Ø	4/4		3/3	5·73		3.62				
3.0	3/3			5·48					-0.25	Inactive.
10.0	3/3			5·38					-0.35	Inactive.
30.0	2/3		3/3	5.44		3.58		NIL	-0·29	Inactive.

MINIMUM FULLY ACTIVE DOSE ..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg.

PRINCIPAL INVESTIGATOR: PROFESSOR W. P

TABLE 16

CAUSAL PROPHYLAXIS TEST NO: BR646 DATE: 18.1.78

DRUG: L.V./ 1451 WR 219874AA BOTTLE NO.: ZN42821

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~ip~~/sc TIME AFTER INFECTION:

VERTEBRATE HOST: ♂ TFW MICE PARASITE (Strain) SPECIES: P. v. nigeriense STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^o/T^o	XC	C^x/T^x	GMP 2% P f/h	b	c/e	(a = 2) ACTIVITY VALUES $(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	COMM
Ø	4/5			5.82						
3.0	1/3			>11.48						Active
10.0	0/3			>14						Fully active
30.0	0/3*			>14						Fully active

MINIMUM FULLY ACTIVE DOSE .... 3-10 ..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 (previous data)

PRINCIPAL INVESTIGATOR: PROFESSOR W.

* 2/3 DIED

TABLE 17

CAUSAL PROPHYLAXIS TEST NO. BR 646 DATE 18.1.78

DRUG: LV 1451 NR 219874 AA BOTTLE NO: ZN42821

PREPARATION: Tween 80, H_2O POINT OF ADMINISTRATION: ~~s.c.~~ p.o. TIME AFTER INFECTION:

VERTEBRATE HOST: C TFW MICE PARASITE (GENUS) SPECIES: P. [illegible] STRAIN NGG

DOSE mg/kg	PATENCY RATE C^c/T^o	XC	C^x/T^y	GMP 2% P f/h	b	c/e	(a - 2) ACTIVITY VALUES $(h-f)-\left\|\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\|$	Residual Activity	Prophylactic Activity	COMM
∅	4/5			5.82						
3.0	2/3			>847						Active
10.0	0/3			>14						Fully active
30.0	0/3			>14						Fully active.

MINIMUM FULLY ACTIVE DOSE ...3 - 10..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 (previous data)

PRINCIPAL INVESTIGATOR: PROFESSOR W.

TABLE 18

CAUSAL PROPHYLAXIS TEST NO: BR647 DATE: 5/1/78

DRUG I.V.: 1392 WR 215761 AA BOTTLE NO.: BE16967

PREPARATION: Tween 60, H_2O ROUTE OF ADMINISTRATION: ~~i.p.~~ p.o. TIME AFTER INFECTION:

VERTEBRATE HOST: CFW MICE PARASITE (SEX) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENTS
	C^c/T^c	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left\|\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\|$	Residual Activity	Prophylactic Activity	
Ø	5/5		5/5	6.17		3.77				
3.0	3/3			5.62					− 0.55	Inactive
10.0	0/3			>14					> 7.83	Fully active
30.0	0/3		3/3	>14		3.62		NIL	> 7.83	Fully active

MINIMUM FULLY ACTIVE DOSE ....3-10..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PE

TABLE 19

CAUSAL PROPHYLAXIS TEST NO: BR 647 | DATE: 5/1/78

DRUG: LV' 1455 | WR 215761 AA | BOTTLE NO. ZN4403[illegible]

PREPARATION: Tween 80, H_2O | ROUTE OF ADMINISTRATION: p.o. | TIME AFTER INFECTION:

VERTEBRATE HOST: ♂ TFW MICE | PARASITE (SUB) SPECIES: P. y. nigeriensis | STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^o/T^o	PATENCY RATE XC	PATENCY RATE C^x/T^x	GMP 2% P f/h	GMP 2% P b	GMP 2% P c/e	(a = 2) ACTIVITY VALUES $(h - f) - \left[\frac{(b - a)(e - a)}{(c - a)} - (b - a)\right]$	Residual Activity	Prophylactic Activity	COMMENTS
Ø	5/5		5/5	6.17		3.77				
3.0	3/3			5.55					-0.62	Inactive
10.0	3/3			6.13					-0.04	Inactive
30.0	1/3		3/3	>11.67		3.54		NIL	> 5.50	Active

MINIMUM FULLY ACTIVE DOSE .... >30 .... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W. P[illegible]

TABLE 20

CAUSAL PROPHYLAXIS TEST NO: BR 647 DATE: 5/1/78

DRUG: LIV/ 1476 WR 230388 AA BOTTLE NO. BG 81580

PREPARATION: Tween 80/ H_2O ROUTE OF ADMINISTRATION: ~~ip/im~~/po TIME AFTER INFECTION:

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^o/T^o	XC	C^x/T^x	GMP 2% P f/h	b	c/e	(a = 2) ACTIVITY VALUES $(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	COMME
ø	5/5		5/5	6.17		3.77				
3.0	2/3			>8.42					> 2.25	Active
10.0	0/3			>14					> 7.83	Fully active
30.0	0/3			>14		3.42		NIL	> 7.83	Fully active

MINIMUM FULLY ACTIVE DOSE ....3-10..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg PRINCIPAL INVESTIGATOR: PROFESSOR W.

TABLE 21

AUSAI PROPHYLAXIS TEST NO. BR652 DATE 18/1/78

DRUG I.V.' 1504 WR 180409 Ac BOTTLE NO. BE99420

PREPARATION Tween 80, H₂O ROUTE OF ADMINISTRATION: ~~sprinkle~~ p.c. TIME AFTER INFECTION

VERTEBRATE HOST: CFW MICE PARASITE (SEM) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMM
	C^c/T^c	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	
Ø	5/5	3/3	5/5	5·41	4·50	4·60				
3·0	2/3*			9·60		7·35	$4.19-\left[\frac{2.50\times5.35}{2.60}-2.50\right]$	2·65	1·54	}
10·0	3/3			9·26		7·60	$3.85-\left[\frac{2.50\times5.60}{2.60}-2.50\right]$	2·89	0·96	} Activity mainly resid
30·0	3/3			11·01		10·50	$5.60-\left[\frac{2.50\times8.50}{2.60}-2.50\right]$	5·68	−0·08	}

MINIMUM FULLY ACTIVE DOSE .... >30 ..... mg/kg

RESIDUAL ACTIVITY: Present at 3 mg/kg .

PRINCIPAL INVESTIGATOR: PROFESSOR W. P

* 1/3 DICD

TABLE 22

CAUSAL PROPHYLAXIS TEST NO: BR 652 DATE: 18·1·78

DRUG: L.V./ 1505 WR 448 AG BOTTLE NO: AG 28874

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~s.c.~~/p.o. TIME AFTER INFECTION:

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: *P. y. nigeriensis* STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMM
	C^o/T^o	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	
∅	5/5		5/5	5.41		4.60				
3.0	3/3			6.29					0.88	Inactive.
10.0	3/3			7.78					2.37	Active.
30.0	2/3		3/3	>9.32		4.29		NIL	3.91	Active.

MINIMUM FULLY ACTIVE DOSE ...> 30..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W.

TABLE 23

[illegible] PROPHYLAXIS TEST NO. BR 652 — DATE 18.1.78

DRUG [illegible] 1506 — WR 6798 AL — BOTTLE NO. AF 5001[illegible]

PREPARATION [illegible] 80, H_2O — ROUTE OF ADMINISTRATION: p. [illegible] — TIME AFTER INFECTION [illegible]

VERTEBRATE HOST: C [illegible] W MICE — PARASITE (S/B) SPECIES: P. [illegible] — STRAIN N[illegible]

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMM[ENTS]
	C^c/T^o	XC	C^c/T^x	$^f/_h$	t	$^c/_e$	$(h - f) - \left[\frac{(b - a)(e - a)}{(c - a)} - (b - a)\right]$	Residual Activity	Prophylactic Activity	
∅	5/5		5/5	5.41		4.60				
3.0	3/3			5.56					0.15	Inactive
10.0	3/3			6.22					0.81	Inactive
30.0	3/3		3/3	8.58		4.06		NIL	3.17	Active

MINIMUM FULLY ACTIVE DOSE ..> 30........ mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W.

TABLE 24

CARDIAC PROPHYLAXIS TEST NO. BR652 DATE 18.1.78

DRUG LOT Liv/1507 WR 93133 AC BOTTLE NO. BB 5962

PREPARATION [illegible] ROUTE OF ADMINISTRATION [illegible] TIME AFTER INFECTION [illegible]

ARTERIAL BLOOD: C 7 W MICE PARASITE (VIR) SPECIES: [illegible] STRAIN Nic

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMM
	C^c/T^c	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left\|\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\|$	Residual Activity	Prophylactic Activity	
Ø	5/5		5/5	5.41		4.60				
3.0	3/3			5.91					0.50	Inactive
10.0	3/3			5.38					-0.03	Inactive
30.0	3/3		3/3	7.95		4.48		NIL	2.54	Active

MINIMUM FULLY ACTIVE DOSE .... >30 ..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg.

PRINCIPAL INVESTIGATOR: PROFESSOR W.

TABLE 25

CAUSAL PROPHYLAXIS TEST NO. BR680 DATE 27/4/78

DRUG I.V./ 1508 WR 179305 AD BOTTLE NO. BB47734

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~s.c.~~/p.o. TIME AFTER INFECTION:

VERTEBRATE HOST: O TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^o/T^o	XC	C^x/T^x	GMP 2% P f/h	b	c/e	(a = 2) ACTIVITY VALUES $(h-f)-\left\|\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\|$	Residual Activity	Prophylactic Activity	COMME
Ø	5/5		3/3	6.73		3.86				
3.0	3/3			4.43					-2.30	Inactive.
10.0	1/3*			>9.54					>2.81	Active.
30.0	0/3		3/3	>14		3.92		NIL	>7.27	Fully active.

MINIMUM FULLY ACTIVE DOSE ...10 – 30... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W.

* 1/3 DIED

TABLE 26

CAUSAL PROPHYLAXIS TEST NO: BR680 DATE: 27/4/78

DRUG: I.V./1509 WR 49808 AC BOTTLE NO. AJ 32298

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~i.p./i.v.~~/p.c. TIME AFTER INFECTION:

VERTEBRATE HOST: O TFW MICE PARASITE (SUB) SPECIES: P. v. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMME
	C^o/T^o	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left\|\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\|$	Residual Activity	Prophylactic Activity	
∅	5/5		3/3	6.73		3.86				
3.0	3/3			5.83					-1.90	Inactive.
10.0	2/3			>8.72					>1.99	Active.
30.0	0/3		3/3	>14		3.82		NIL	>7.27	Fully Active.

MINIMUM FULLY ACTIVE DOSE ....10-30..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg PRINCIPAL INVESTIGATOR: PROFESSOR W. P

TABLE 27

CAUSAL PROPHYLAXIS TEST NO. BR680 DATE. 27/4/78

DRUG: L.V. 1510 WR 38839-B BOTTLE NO. AM 33272

PREPARATION: Tween 60, H_2O ROUTE OF ADMINISTRATION: ~~ip/im~~/po TIME AFTER INFECTION:

VERTEBRATE HOST: O TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMM
	C^o/T^o	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	
∅	5/5		3/3	6.73		3.86				
3.0	3/3			6.48					−0.25	Inactive.
10.0	3/3			5.65					−1.08	Inactive.
30.0	0/3		3/3	>14		3.98		NIL	>7.27	Fully active.

MINIMUM FULLY ACTIVE DOSE ...10-30..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W.

TABLE 28

CAUSAL PROPHYLAXIS TEST NO: BR680 DATE: 27/4/78

DRUG: I.V.' 1511 WR 99210 AE BOTTLE NO. AW2362

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~i.p./s.c.~~/p.o. TIME AFTER INFECTION

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^o/T^o	XC	C^x/T^x	GMP 2% P f/h	b	c/e	(a = 2) ACTIVITY VALUES $(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	COMM
∅	5/5		3/3	6·73		3·86				
3·0	0/3			>14					>7·27	Fully active
10·0	0/3			>14					>7·27	Fully active
30·0	0/3		3/3	>14		3·78		NIL	>7·27	Fully active

MINIMUM FULLY ACTIVE DOSE ....<3..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W.

TABLE 29

CAUSAL PROPHYLAXIS TEST NO. BR 658 DATE 3.2.78

DRUG: L.V./ 1512 WR 141871 AB BOTTLE NO. AX2684

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~ip/sc/po~~ TIME AFTER INFECTION

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. v. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMM
	C^o/T^o	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left\lvert\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\rvert$	Residual Activity	Prophylactic Activity	
Ø	4/5			5.69						
3.0	0/3			>14						Fully active.
10.0	0/3			>14						Fully active.
30.0	0/3			>14						Fully active.

MINIMUM FULLY ACTIVE DOSE ....<3.0..... mg/kg

RESIDUAL ACTIVITY:

PRINCIPAL INVESTIGATOR: PROFESSOR W.

TABLE 30

CAUSAL PROPHYLAXIS TEST NO: BR667 DATE: 1/3/78

DRUG: I.V. 1512 WR 141871 AB BOTTLE NO: AX 26848

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~s.c./i.v./p.o.~~ TIME AFTER INFECTION

VERTEBRATE HOST: C.F.W. MICE PARASITE (SUB) SPECIES: P. v. nigeriense STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a - 2) ACTIVITY VALUES			COMMENTS
	C^c/T^c	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	
∅	5/5	3/3	3/3	6.48	4.33	4.28				
0.1	2/3*		3/3	5.43		4.34	$-1.05-\left[\frac{2.83\times2.34}{2.28}-2.33\right]$	0.07	-1.12	INACTIVE
0.3	2/3*		3/3	5.80		5.15	$-0.68-\left[\frac{2.33\times3.15}{2.28}-2.33\right]$	0.89	-1.57	INACTIVE
1.0	0/3		3/3	>14		4.61	$7.52-\left[\frac{2.33\times2.61}{2.28}-2.33\right]$	0.35	7.17	FULLY ACTIVE

MINIMUM FULLY ACTIVE DOSE ....0.3 - 1.0.... mg/kg

RESIDUAL ACTIVITY: NIL AT 1 mg/kg PRINCIPAL INVESTIGATOR: PROFESSOR W

* 1/3 DIED

TABLE 31

CAUSAL PROPHYLAXIS TEST NO. BR 658 DATE 3·2·78

DRUG: I.V. 1512 WR 141871 AB BOTTLE NO. Ax2684

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~s.c.~~ p.o. TIME AFTER INFECTION

VERTEBRATE HOST: ♂ TFW MICE PARASITE (STRAIN) SPECIES: *P. y. nigeriensis* STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^o/T^o	XC	C^x/T^x	GMP 2% P f/h	b	c/e	(a = 2) ACTIVITY VALUES $(h-f)-\left\|\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\|$	Residual Activity	Prophylactic Activity	COMM
∅	4/5			5·69						
3·0	0/3			>14						Fully active.
10·0	0/3			>14						Fully active.
30·0	0/3			>14						Fully active.

MINIMUM FULLY ACTIVE DOSE ...<3·0..... mg/kg

RESIDUAL ACTIVITY:

PRINCIPAL INVESTIGATOR: PROFESSOR W.

TABLE 32

CAUSAL PROPHYLAXIS TEST NO: BR667 DATE: 1/3/78

DRUG: I.V./ 1512 WR 141871 AB BOTTLE NO. AX 268

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~s/c~~ po TIME AFTER INFECTION

VERTEBRATE HOST: C TFW MICE PARASITE (SUB) SPECIES: P. v. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COM
	C^o/T^o	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	
ϕ	5/5	3/3	3/3	6.48	4.33	4.28				
0.1	3/3		2/3*	6.25		4.65	$0.23-\left[\frac{2.33 \times 2.65}{2.28}-2.33\right]$	0.38	-0.15	INACTIVE
0.3	2/3		2/3*	>8.43		4.70	$1.95-\left[\frac{2.33 \times 2.70}{2.28}-2.33\right]$	0.44	1.51	ACTIVE
1.0	0/3		3/3	>14		4.76	$7.52-\left[\frac{2.33 \times 2.76}{2.28}-2.33\right]$	0.49	7.03	FULLY ACTIVE

MINIMUM FULLY ACTIVE DOSE ...0.3-1.0.... mg/kg

RESIDUAL ACTIVITY: NIL AT 1 mg/kg PRINCIPAL INVESTIGATOR: PROFESSOR W

* 1/3 DIED

TABLE 33

CAUSAL PROPHYLAXIS TEST NO. BR 658 DATE 18.1.78

DRUG: I.V. 1513 WR 159412 AC BOTTLE NO. BB5997

FORMULATION: [illegible] H_2O ROUTE OF ADMINISTRATION: [illegible] TIME AFTER INFECTION

INFECTIVE DOSE: C TFW MICE PARASITE (NMR) SPECIES: P. [illegible] STRAIN: NMR

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COM
	C^c/T^c	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	
ϕ	4/5			5·69						
3·0	0/3			>14						Fully active
10·0	0/3			>14						Fully active
30·0	0/3			>14						Fully active

MINIMUM FULLY ACTIVE DOSE ... < 3·0 ..... mg/kg

RESIDUAL ACTIVITY:

PRINCIPAL INVESTIGATOR: PROFESSOR W.

TABLE 34

CAUSAL PROPHYLAXIS TEST NO: BR670 DATE: 21/3/78

DRUG: I.V/ 1513 WR 159412 AC BOTTLE NO. B869

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~ip~~/~~sc~~/~~po~~ TIME AFTER INFECTION

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. v. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			CO
	C^o/T^o	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left\lvert\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\rvert$	Residual Activity	Prophylactic Activity	
ϕ	5/5	3/3	3/3	5.72	3.74	3.79				
0.1	3/3		3/3	5.87		3.85	$0.15-\left[\frac{1.74\times1.85}{1.79}-1.74\right]$	0.06	0.09	Inactive.
0.3	3/3		3/3	6.58		3.67	$0.86-\left[\frac{1.74\times1.67}{1.79}-1.74\right]$	-0.11	0.97	Inactive.
1.0	2/3		3/3	>10.87		3.70	$>5.15-\left[\frac{1.74\times1.70}{1.79}-1.74\right]$	-0.04	>5.19	Active.

MINIMUM FULLY ACTIVE DOSE ....1-3..... mg/kg

RESIDUAL ACTIVITY: Nil at 1 mg/kg PRINCIPAL INVESTIGATOR: PROFESSOR W

TABLE 35

CAUSAL PROPHYLAXIS TEST NO. BR658 DATE 18.1.78

DRUG LAB 1513 WR 159412 AC BOTTLE NO. 88598[illegible]

PREPARATION Tween 80, H_2O ROUTE OF ADMINISTRATION: [illegible] p.

VERTEBRATE HOST: C TFW MICE PARASITE (SUB) SPECIES: P. [illegible] TIME AFTER INFECTION

STRAIN NG

DOSE mg/kg	PATENCY RATE C^o/T^o	XC	C^x/T^x	GMP 2% P f/h	b	c/e	(a = 2) ACTIVITY VALUES $(h-f) - \left[\frac{(b-a)(e-a)}{(c-a)} - (b-a)\right]$	Residual Activity	Prophylactic Activity	COM[illegible]
ϕ	4/5			5.69						
3.0	0/3			>14						Fully active
10.0	0/3			>14						Fully active
30.0	0/3			>14						Fully active

MINIMUM FULLY ACTIVE DOSE ....<3.0....... mg/kg

RESIDUAL ACTIVITY:

PRINCIPAL INVESTIGATOR: PROFESSOR W[illegible]

TABLE 36

CAUSAL PROPHYLAXIS TEST NO: BR 670 DATE: 21/3/78

DRUG I.V. 1513 WR 159412 Ac BOTTLE NO. 88 69823

PREPARATION: Tween 80 H_2O ROUTE OF ADMINISTRATION: ~~s.c.~~/p.o. T.M.I. AFTER INFECTIONS

VERTEBRATE HOST: C.F.W. MICE PARASITE (SUB) SPECIES: *P. y. nigeriensis* STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^o/T^o	XC	C^x/T^x	GMP 2% P f/h	b	s/e	(a = 2) ACTIVITY VALUES $(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	COMM
∅	5/5	3/3	3/3	5.72	3.74	3.79				
0.1	2/3		3/3	>8.33		3.39	$>2.61-\left[\frac{1.74\times1.39}{1.79}-1.74\right]$	Nil	>2.61	Slightly active.
0.3	0/3		3/3	>14		3.96	$>8.28-\left[\frac{1.74\times1.96}{1.79}-1.74\right]$	0.17	>8.11	Fully active.
1.0	0/3		3/3	>14		4.09	$>8.28-\left[\frac{1.74\times2.09}{1.79}-1.74\right]$	0.30	>7.98	Fully active.

MINIMUM FULLY ACTIVE DOSE ...0.1 - 0.3... mg/kg

RESIDUAL ACTIVITY: Nil at 1 mg/kg.

PRINCIPAL INVESTIGATOR: PROFESSOR W. P

TABLE 37

CAUSAL PROPHYLAXIS TEST NO: BR665 DATE: 24/2/78

DRUG: L.V/ 1514 WR 180872AC BOTTLE NO. BD09

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ip/sc/po TIME AFTER INFECTIO

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. v. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			CO
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	f/h	b	c/e	$(h-f)-\left\lvert\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\rvert$	Residual Activity	Prophylactic Activity	
Ø	4/5	3/3	5/5	6.29	3.91	3.91				
3.0	0/3		3/3	>14		5.30	$>7.71-\left[\frac{1.91 \times 3.30}{1.91}-1.91\right]$	1.39	>6.32	Fully active. Some resi
10.0	0/3		3/3	>14		8.40	$>7.71-\left[\frac{1.91 \times 5.40}{1.91}-1.91\right]$	3.49	>4.22	Marked residual activ
30.0	0/3		0/3	>14		>14	$>7.71-\left[\frac{1.91 \times 12.00}{1.91}-1.91\right]$	>10.09	–	Prophylactic activity ma
										residual activity.

MINIMUM FULLY ACTIVE DOSE ...≤ 3.0..... mg/kg

RESIDUAL ACTIVITY: Present at 1 mg/kg. PRINCIPAL INVESTIGATOR: PROFESSOR W

TABLE 38

CAUSAL PROPHYLAXIS TEST NO: BR665 DATE: 24/2/78

DRUG: I.V./ 1514 WR 180872 Ac BOTTLE NO. BD09

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~sc/im~~/po TIME AFTER INFECTIO

VERTEBRATE HOST: OTFW MICE PARASITE (SUB) SPECIES: P. v. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE $C^o/_{T^o}$	XC	$C^x/_{T^x}$	GMP 2% P f/h	b	c/e	(a = 2) ACTIVITY VALUES $(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	CO
Ø	4/5	3/3	5/5	6.29	3.91	3.91				
3.0	0/3		3/3	>14		4.30	$>7.71-\left[\frac{1.91\times 2.30}{1.91}-1.91\right]$	0.39	>7.32	Fully active.
10.0	0/3		3/3	>14		5.10	$>7.71-\left[\frac{1.91\times 3.10}{1.91}-1.91\right]$	1.19	>6.52	Fully active. Some res
30.0	0/3		3/3	>14		6.19	$>7.71-\left[\frac{1.91\times 4.19}{1.91}-1.91\right]$	2.28	>5.43	Fully active. Marked res

MINIMUM FULLY ACTIVE DOSE ....<3.0..... mg/kg

RESIDUAL ACTIVITY: Nil at 3 mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR

TABLE 39

CAUSAL PROPHYLAXIS TEST NO. BR665 DATE 24/2/78

DRUG: I.V. 1513 WR 194965AG BOTTLE NO. BG563

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~ip/sc~~/po TIME AFTER INFECTION

VERTEBRATE HOST: O TFW MICE PARASITE (SUB) SPECIES: *P. v. nigeriensis* STRAIN: NIG

DOSE mg/kg	PATENCY RATE $C^c/_{T^o}$	XC	$C^x/_{T^x}$	GMP 2% P f/h	b	c/e	(a = 2) ACTIVITY VALUES $(h-f)-\left\lvert\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\rvert$	Residual Activity	Prophylactic Activity	COM
∅	4/5	3/3	5/5	6.29	3.91	3.91				
3.0	3/3		3/3	5.49		3.95	$-0.80-\left[\frac{1.91\times1.95}{1.91}-1.91\right]$	0.04	-0.84	Inactive
10.0	3/3		3/3	5.99		4.20	$-0.30-\left[\frac{1.91\times2.20}{1.91}-1.91\right]$	0.29	-0.59	Inactive
30.0	0/3		3/3	>14		12.11	$>7.71-\left[\frac{1.91\times10.11}{1.91}-1.91\right]$	8.20	-0.49	All activity residual

MINIMUM FULLY ACTIVE DOSE ..10.-30..... mg/kg

RESIDUAL ACTIVITY: Marked at 30 mg/kg.

PRINCIPAL INVESTIGATOR: PROFESSOR W

TABLE 40a

CAUSAL PROPHYLAXIS TEST NO: BR690 DATE: 5/6/78

DRUG I.V. 1525 WR 27653 AD BOTTLE NO: AH07834

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~s.c.~~ p.o. TIME AFTER INFECTION:

VERTEBRATE HOST: O TFW MICE PARASITE (SUM) SPECIES: *P. y. nigeriensis* STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^o/T^o	XC	C^x/T^x	GMP 2% P f/h	b	s/e	(a = 2) ACTIVITY VALUES $(h-f)-\left\|\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\|$	Residual Activity	Prophylactic Activity	COMM
ϕ	5/5		5/5	5.40		3.82				
3.0	3/3			5.26					-0.14	Inactive
10.0	3/3			6.21					-0.19	Inactive
30.0	3/3		3/3	5.73		3.88		Nil	0.33	Inactive

MINIMUM FULLY ACTIVE DOSE .... ~~.....~~ ..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg.

PRINCIPAL INVESTIGATOR: PROFESSOR W.

TABLE 40b

CAUSAL PROPHYLAXIS TEST NO: BR665 DATE: 24/2/78

DRUG: I.V. 1515 WR 194965 AG BOTTLE NO. BG5632

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~i.v.~~ p.o TIME AFTER INFECTION:

VERTEBRATE HOST: C TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^c/T^o	XC	C^x/T^x	GMP 2% P f/h	b	c/e	(a = 2) ACTIVITY VALUES $(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	COMM
∅	4/5	3/3	5/5	6.29	3.91	3.91				
3.0	1/3			5.21		3.98	$-1.08-\left[\frac{1.91\times1.98}{1.91}-1.91\right]$	0.07	−1.15	Inactive.
10.0	3/3			6.35		5.20	$0.06-\left[\frac{1.91\times3.20}{1.91}-1.91\right]$	1.29	−1.23	Inactive.
30.0	2/3		2/3	5.56		>11.44	$-0.73-\left[\frac{1.91\times9.44}{1.91}-1.91\right]$	7.53	− 8.26	All activity residual.

MINIMUM FULLY ACTIVE DOSE ....>30..... mg/kg

RESIDUAL ACTIVITY: Marked at 30 mg/kg.

PRINCIPAL INVESTIGATOR: PROFESSOR W.

TABLE 41

CAUSAL PROPHYLAXIS TEST NO: BR662 DATE: 15/2/78

DRUG: i.v./ 1516 WR 228258 AB BOTTLE NO. BG8564

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~ip/sc/po~~ TIME AFTER INFECTION:

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^o/T^o	XC	C^x/T^x	GMP 2% P f/h	b	c/e	(a = 2) ACTIVITY VALUES $(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	COMM
∅	8/8	3/3	5/5	5.82	3.86	3.91				
3.0	3/3		3/3	7.32		4.02	$1.50-\left[\frac{1.86\times 2.02}{1.91}-1.86\right]$	0.11	1.39	Slightly active.
10.0	3/3		3/3	>13.09		6.32	$>7.27-\left[\frac{1.86\times 4.32}{1.91}-1.86\right]$	2.35	>4.92	Active, Some residual
30.0	0/3*		3/3	>14		10.09	$>8.18-\left[\frac{1.86\times 8.03}{1.91}-1.86\right]$	6.02	>2.16	? Fully active. Marked residual activity

MINIMUM FULLY ACTIVE DOSE ....10-30..... mg/kg

RESIDUAL ACTIVITY: Marked at 30, present at 10 mg/kg. PRINCIPAL INVESTIGATOR: PROFESSOR W.

* 2/3 DIED

TABLE 42

CAUSAL PROPHYLAXIS TEST NO. BR662 DATE. 15/2/78

DRUG. I.V./ 1516 WR 228258 AB BOTTLE NO. BG8564

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~ip/im~~/po TIME AFTER INFECTION:

VERTEBRATE HOST: O TFW MICE PARASITE (SUB) SPECIES: P. v. nigeriense STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^o/T^o	XC	C^x/T^x	GMP 2% P f/h	b	e/e	(a = 2) ACTIVITY VALUES $(h-f)-\left\lvert\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\rvert$	Residual Activity	Prophylactic Activity	COMM
∅	8/8	3/3	5/5	5.82	3.86	3.91				
3.0	2/3		3/3	10.74		4.81	$4.92-\left[\frac{1.86\times2.81}{1.91}-1.86\right]$	0.88	4.04	Active.
10.0	1/3*		3/3	13.90		5.90	$8.08-\left[\frac{1.86\times3.90}{1.91}-1.86\right]$	1.95	6.13	Active. Some residual a
30.0	0/3		2/3	>14		>10.67	$>8.18-\left[\frac{1.86\times8.67}{1.91}-1.86\right]$	>6.59	> 1.59	Fully active. Marked residua

MINIMUM FULLY ACTIVE DOSE ....10-30.... mg/kg

RESIDUAL ACTIVITY: Present at 10 mg/kg, marked at 30 mg/kg. PRINCIPAL INVESTIGATOR: PROFESSOR W.

* 2/3 DIED

TABLE 43

CAUSAL PROPHYLAXIS TEST NO: BR663 DATE: 15/2/78

DRUG: L.V. 1517 WR 81844 AD BOTTLE NO. ZF9229

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ip/sc/ps TIME AFTER INFECTION

VERTEBRATE HOST: O TFW MICE PARASITE (SUB) SPECIES: P. v. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMM
	C^c/T^c	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	
∅	8/8		5/5	5.82		3.91				
3.0	2/3*			5.24					-0.58	Inactive.
10.0	2/3*			9.36					3.54	Active.
30.0	2/3*		3/3	10.05		4.48		Nil	4.23	Active.

MINIMUM FULLY ACTIVE DOSE .... >30 ..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg.

PRINCIPAL INVESTIGATOR: PROFESSOR W

* 1/3 DIED

TABLE 44

CAUSAL PROPHYLAXIS TEST NO: BR663 DATE: 15/2/78

DRUG: L.V./ 1517 WR 81844 AD BOTTLE NO. ZF922

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip~~/po TIME AFTER INFECTION

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: *P. v. nigeriensis* STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^o/T^o	XC	C^x/T^x	GMP 2% P f/h	b	e	(a = 2) ACTIVITY VALUES $(h-f)-\left\|\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\|$	Residual Activity	Prophylactic Activity	COM
∅	8/8		5/5	5.82		3.91				
3.0	3/3			6.27					0.45	Inactive.
10.0	3/3			5.54					-0.28	Inactive.
30.0	3/3		3/3	5.99		3.78		Nil	0.17	Inactive.

MINIMUM FULLY ACTIVE DOSE ...> 30..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg.

PRINCIPAL INVESTIGATOR: PROFESSOR W

TABLE 45

CAUSAL PROPHYLAXIS TEST NO: BR682 DATE: 8/5/78

DRUG: L.V./ 1518 WR 87781 AB BOTTLE NO. AB34313

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ip/sc/po TIME AFTER INFECTION:

VERTEBRATE HOST: ♂ TEW MICE PARASITE (SUB) SPECIES: *T. v. nigeriense* STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMM
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	f/h	b	c/e	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	
∅	5/5			6·41						
3·0	3/3			6·39						Inactive
10·0	0/3			>14						Fully active
30·0	0/3			>14						Fully active

MINIMUM FULLY ACTIVE DOSE ....3-10..... mg/kg

RESIDUAL ACTIVITY:

PRINCIPAL INVESTIGATOR: PROFESSOR W.

TABLE 46

CAUSAL PROPHYLAXIS TEST NO: BR682 DATE: 8/5/78

DRUG: LIV/ 1518 WR 87781 AB BOTTLE NO: AB3431

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip/im~~/po TIME AFTER INFECTION

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: *T. v. nigeriensis* STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^o/T^o	XC	C^x/T^x	GMP 2% P f/h	b	c/e	(a = 2) ACTIVITY VALUES $(h-f)-\left\lvert\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\rvert$	Residual Activity	Prophylactic Activity	COM
∅	5/5			6.41						
3.0	1/3			>11.45						Active
10.0	0/3			>14						Fully active
30.0	0/3			>14						Fully active

MINIMUM FULLY ACTIVE DOSE ....3-10..... mg/kg

RESIDUAL ACTIVITY:

PRINCIPAL INVESTIGATOR: PROFESSOR W

TABLE 47

CAUSAL PROPHYLAXIS TEST NO: BR669 DATE: 16/3/78

DRUG: L.V/ 1520 WR 231033 AA BOTTLE NO. BG89086

PREPARATION: Tween. 80, H_2O ROUTE OF ADMINISTRATION: sp/sc/po TIME AFTER INFECTION

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: *P. y. nigeriensis* STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COM
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	f/h	b	c/e	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	
∅	5/5	3/3	5/5	5.51	3.54	3.54				
3.0	3/3		3/3	6.49		4.26	$0.98-\left[\frac{1.54\times 2.26}{1.54}-1.54\right]$	0.72	0.26	Inactive
10.0	1/3		3/3	>11.02		7.82	$>5.51-\left[\frac{1.54\times 5.82}{1.54}-1.54\right]$	4.28	1.23	Active - mainly residua
30.0	0/3		0/3	>14		>14	$>8.49-\left[\frac{1.54\times 12.00}{1.54}-1.54\right]$	> 10.46	- 1.97	Fully Active. Residual activity only

MINIMUM FULLY ACTIVE DOSE ...10-30..... mg/kg

RESIDUAL ACTIVITY: Marked at 10 mg/kg.

PRINCIPAL INVESTIGATOR: PROFESSOR W

TABLE 48

CAUSAL PROPHYLAXIS TEST NO: BR669 DATE: 16/3/78

DRUG: L.V./ 1520 WR 231033 AA BOTTLE NO. BG 890

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip/sc~~/po TIME AFTER INFECTION

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: *T. v. nigeriensis* STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COM
	C^o/T^o	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	
∅	5/5	3/3	5/5	5.51	3.54	3.54				
3.0	3/3			5.86		4.16	$0.35-\left[\frac{1.54\times 2.16}{1.54}-1.54\right]$	0.62	−0.27	Inactive
10.0	3/3			6.82		4.60	$1.31-\left[\frac{1.54\times 2.60}{1.54}-1.54\right]$	1.06	0.25	Slight residual activity
30.0	0/3		0/3	>14		>14	$>8.49-\left[\frac{1.54\times 12.00}{1.54}-1.54\right]$	>0.46	−1.97	Fully active. Residual activity only

MINIMUM FULLY ACTIVE DOSE ....10-30..... mg/kg

RESIDUAL ACTIVITY: Present at 10 mg/kg, marked at 30mg/kg. PRINCIPAL INVESTIGATOR: PROFESSOR W

TABLE 49

CAUSAL PROPHYLAXIS TEST NO: BR669 DATE: 16/3/78

DRUG: L.V./ 1521 WR 231138 AA BOTTLE NO: 86893

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~im/sc/po~~ TIME AFTER INFECTIO

VERTEBRATE HOST: O TFW MICE PARASITE (SUM) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			
	C^c/T^c	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	CO
∅	5/5		5/5	5.51		3.64				
3.0	3/3			5.61					0.10	Inactive.
10.0	3/3			5.88					0.37	Inactive.
30.0	2/3		3/3	>8.45		3.64		NIL	> 2.94	Active.

MINIMUM FULLY ACTIVE DOSE ...> 30..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg.

PRINCIPAL INVESTIGATOR: PROFESSOR

TABLE 50

CAUSAL PROPHYLAXIS TEST NO. BR669 DATE 16/3/78

DRUG L.V./ 1521 WR 231138AA BOTTLE NO. BG 89362

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~i.p.~~/po TIME AFTER INFECTION:

VERTEBRATE HOST: O TFW MICE PARASITE (SUB) SPECIES: *P. y. nigeriensis* STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMM
	C^c/T^c	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left\|\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\|$	Residual Activity	Prophylactic Activity	
Ø	5/5		5/5	5.51		3.54				
3.0	3/3			6.28					0.77	Inactive
10.0	3/3			6.02					0.51	Inactive
30.0	2/3		3/3	>8.40		4.17		NIL	>2.89	Active

MINIMUM FULLY ACTIVE DOSE ....>30..... mg/kg

RESIDUAL ACTIVITY: Nil at 30mg/kg.

PRINCIPAL INVESTIGATOR: PROFESSOR W. P

TABLE 51

CAUSAL PROPHYLAXIS TEST NO: BR 690 DATE: 5/6/78

DRUG: I.V./ 1522 WR 199507 AB BOTTLE NO: BD2400

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip~~ ~~sc~~/~~po~~ TIME AFTER INFECTION

VERTEBRATE HOST: C TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^c/T^c	XC	C^x/T^x	GMP 2% P f/h	b	e/e'	(a = 2) ACTIVITY VALUES $(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	COM
∅	5/5		5/5	5.40		3.82				
3.0	3/3			5.24					-0.16	Inactive
10.0	3/3			6.05					0.65	Inactive
30.0	2/3*		3/3	5.87		3.68		Nil	0.47	Inactive

MINIMUM FULLY ACTIVE DOSE ..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg.

PRINCIPAL INVESTIGATOR: PROFESSOR W

* 1/3 DIED

TABLE 52

CAUSAL PROPHYLAXIS TEST NO: BR690 DATE: 5/6/78

DRUG: L.V. 1522 WR 199507 AB BOTTLE NO. BD240

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~s.c.~~/po TIME AFTER INFECTIO

VERTEBRATE HOST: O TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^c/T^c	XC	C^x/T^x	GMP 2% P f/h	b	c/e	(a - 2) ACTIVITY VALUES $(h-f)-\left\{\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\}$	Residual Activity	Prophylactic Activity	COI
∅	5/5		3/3	5.40		3.82				
3.0	3/3			5.27					-0.13	Inactive
10.0	3/3			5.35					-0.05	Inactive
30.0	3/3		3/3	5.65		3.77		Nil	0.25	Inactive

MINIMUM FULLY ACTIVE DOSE .... — ..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W

TABLE 53

CAUSAL PROPHYLAXIS TEST NO: BR686 DATE: 26/5/78

DRUG: L.V./ 1524 WR 230837AA BOTTLE NO. BG854

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip/sc/po~~ TIME AFTER INFECTION

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. v. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COM
	C^o/T^o	XC	C^x/T^x	f/h	b	e/e	$(h-f)-\left\{\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\}$	Residual Activity	Prophylactic Activity	
∅	5/5		3/3	5.92		3.85				
3.0	3/3			5.51					-0.41	Inactive.
10.0	3/3			6.86					0.94	Inactive.
30.0	3/3		3/3	>8.83		4.03		Nil	>2.91	Active

MINIMUM FULLY ACTIVE DOSE .... > 30 ..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W

TABLE 54

CAUSAL PROPHYLAXIS TEST NO: BR686 DATE: 26/5/78

DRUG: LV/ 1524 WR 230837 AA BOTTLE NO. BG854C

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip/im~~/po TIME AFTER INFECTION

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. v. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^o/T^o	XC	C^x/T^x	GMP 2% P f/h	b	c/e	(a = 2) ACTIVITY VALUES $(h-f)-\left\lvert\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\rvert$	Residual Activity	Prophylactic Activity	COMM
∅	5/5		3/3	5.92		3.85				
3.0	2/3			>8.77					>2.85	Active
10.0	1/3			>11.80					>5.88	Active
30.0	0/3		3/3	>14		3.95		Nil	>8.08	Fully active

MINIMUM FULLY ACTIVE DOSE ..10-30..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg.

PRINCIPAL INVESTIGATOR: PROFESSOR W.

TABLE 55

CAUSAL PROPHYLAXIS TEST NO: BR680 DATE: 5/6/78

DRUG: L.V. 1525 WR 27653 AD BOTTLE NO. AH07

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~ip/sc~~/p TIME AFTER INFECTION

VERTEBRATE HOST: O TFW MICE PARASITE (SUB) SPECIES: P. v. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			CO
	C^o/T^o	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left\{\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\}$	Residual Activity	Prophylactic Activity	
Ø	5/5		5/5	5.40		3.82				
3.0	3/3			5.24					-0.16	Inactive
10.0	3/3			5.91					0.51	Inactive
30.0	3/3		3/3	5.60		3.82		Nil	0.20	Inactive

MINIMUM FULLY ACTIVE DOSE ..... — ..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W

TABLE 56

CAUSAL PROPHYLAXIS TEST NO: BR656 DATE: 27/1/78

DRUG: LIV/ 1541 WR 232584 AA BOTTLE NO. BH053

PREPARATION: Tween. 80/H_2O ROUTE OF ADMINISTRATION: ip/sc/po TIME AFTER INFECTION

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			CON
	C^o/T^o	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	
∅	4/4		3/3	5·73		3.62				
3.0	3/3			5·35				-	−0.38	Inactive.
10.0	2/3			>8·55					> 2·82	Active.
30.0	0/3		3/3	>14		3.80		NIL	> 8·27	Fully Active

MINIMUM FULLY ACTIVE DOSE ...10-30..... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg PRINCIPAL INVESTIGATOR: PROFESSOR W

TABLE 57

CAUSAL PROPHYLAXIS TEST NO: BR656 DATE: 27/1/78

DRUG: LiV/ 1541 WR 232584 AA BOTTLE NO. BHOS

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip/im~~/po TIME AFTER INFECTIO

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. y. nigeriensis STRAIN: NIG

DOSE mg/kg	PATENCY RATE $C^o/_{T^o}$	XC	$C^x/_{T^x}$	GMP 2% P f/h	b	c/e.	(a = 2) ACTIVITY VALUES $(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	CO
ϕ	4/4		3/3	5·73		3.62				
3.0	3/3			5·16					−0.57	Inactive.
10.0	2/3			>8.48					> 2.75	Active
30.0	0/3		3/3	>14		3.71		NIL	> 8·27	Fully active

MINIMUM FULLY ACTIVE DOSE ...10-30.... mg/kg

RESIDUAL ACTIVITY: Nil at 30 mg/kg PRINCIPAL INVESTIGATOR: PROFESSOR W

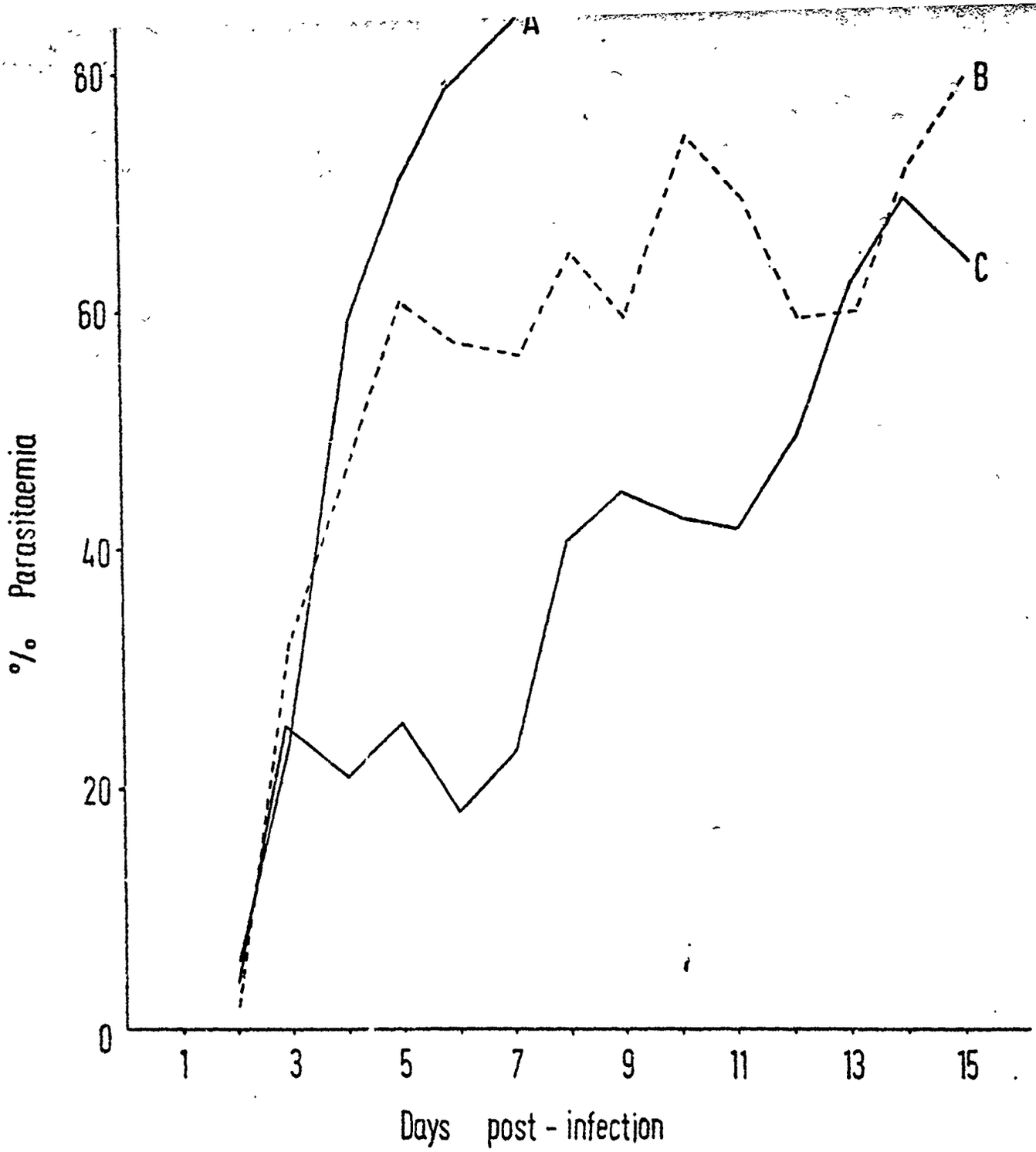
TABLE 58

		LIV/1342 (WR 158,122)					
DDS		Ø	0.03	0.1	0.3	1.0	ED_{90}
	Ø		100 ± 2.3	95.7±3.2	68.5 ±5.9	30.9±9.8	1.6
	0.03	77.5 ±7.4	73.7 ±6.9	17.6±5.4	1.3 ±0.7	0	0.14
	0.1	63.6 ±8.2	49.6 ±11.4	6.7±2.7	0.4 ±0.3	0	0.09
	0.3	59.4±16.2	14.5± 6.7	5.3±3.8	0.3± 0.2	0	0.08
	1.0	23.7± 8.5	0.7 ± 0.4	0.1 ± 0.1	0	0	0.004
	ED_{90}	4.0	0.32	0.12	0.009	-	

TABLE 59

		LIV/1342 (WR 158,122)					
SULPHADOXINE		Ø	0.03	0.1	0.3	1.0	ED_{90}
	Ø		100 ±3.2	95.8±2.1	71.9± 8.2	31.1± 8.2	1.6
	0.003	96.0±3.3	69.3±3.1	50.4±11.1	6.1±3.4	0	0.18
	0.01	78.5±4.8	63.8±5.2	57.2±5.0	6.5± 4.3	0	0.16
	0.03	65.0±2.3	59.0±5.7	24.9±5.7	0.2± 0.2	0	0.12
	0.1	52.6±4.5	41.9±2.4	2.8±1.6	0	0	0.05
		0.6	0.4	0.05	0.006	-	

TABLE 60



A Control Animals

B 4·125 µg/µl/hour D+3 - D+9

C 5 mg/kg/day D+3 - D+9

FIGURE 1

A comparison of the response of Plasmodium berghei to primaquine phosphate following drug administration by repeated daily injections via mini osmotic pumps (at 4.125 µg/µl/hr. v. 5 mg/kg/day).

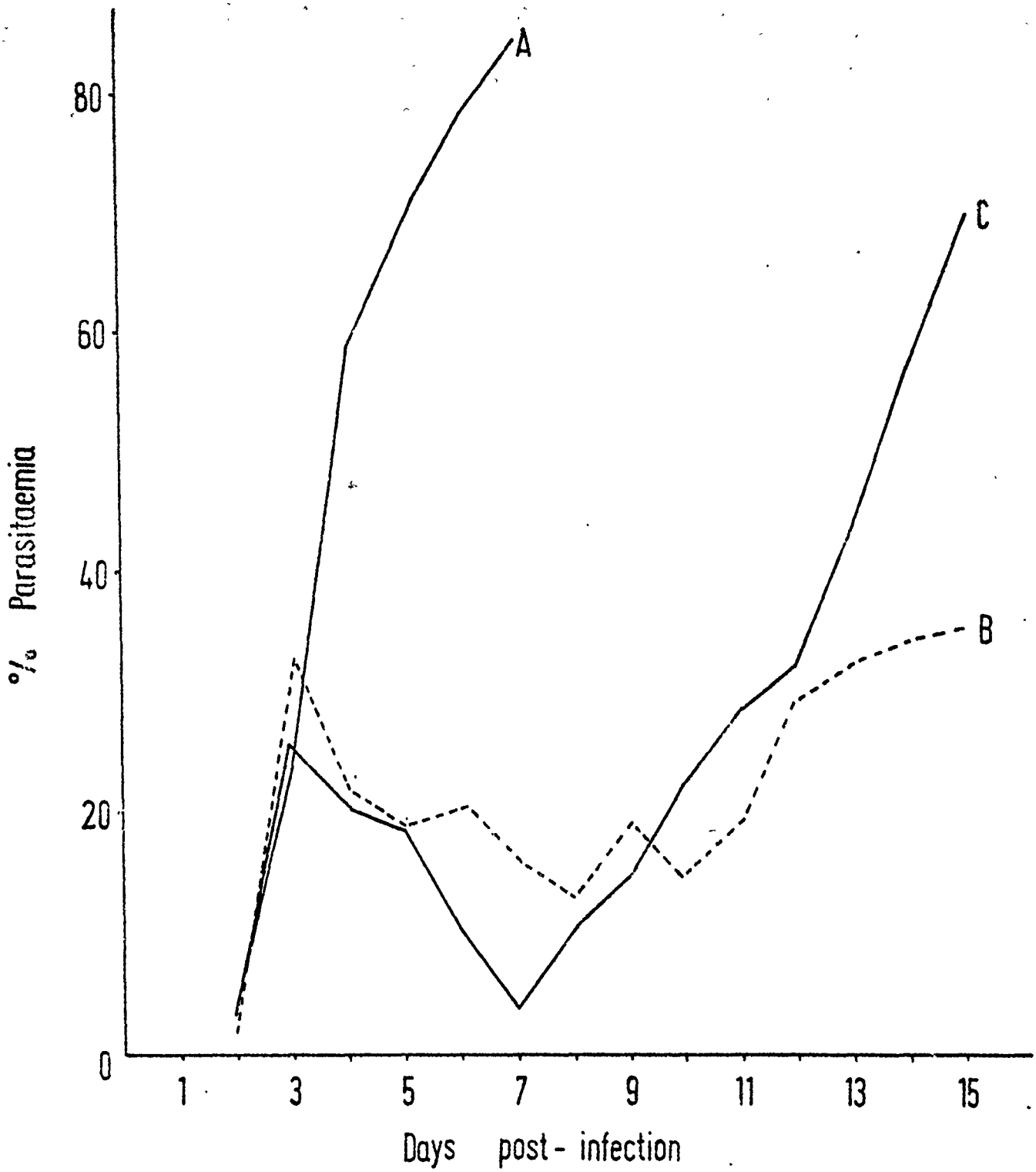


FIGURE 2

A comparison of the response of Plasmodium berghei to primaquine phosphate following drug administration by repeated daily injections via osmotic minipumps (at 8.25 µg/µl/hr. v. 10 mg/kg/day).

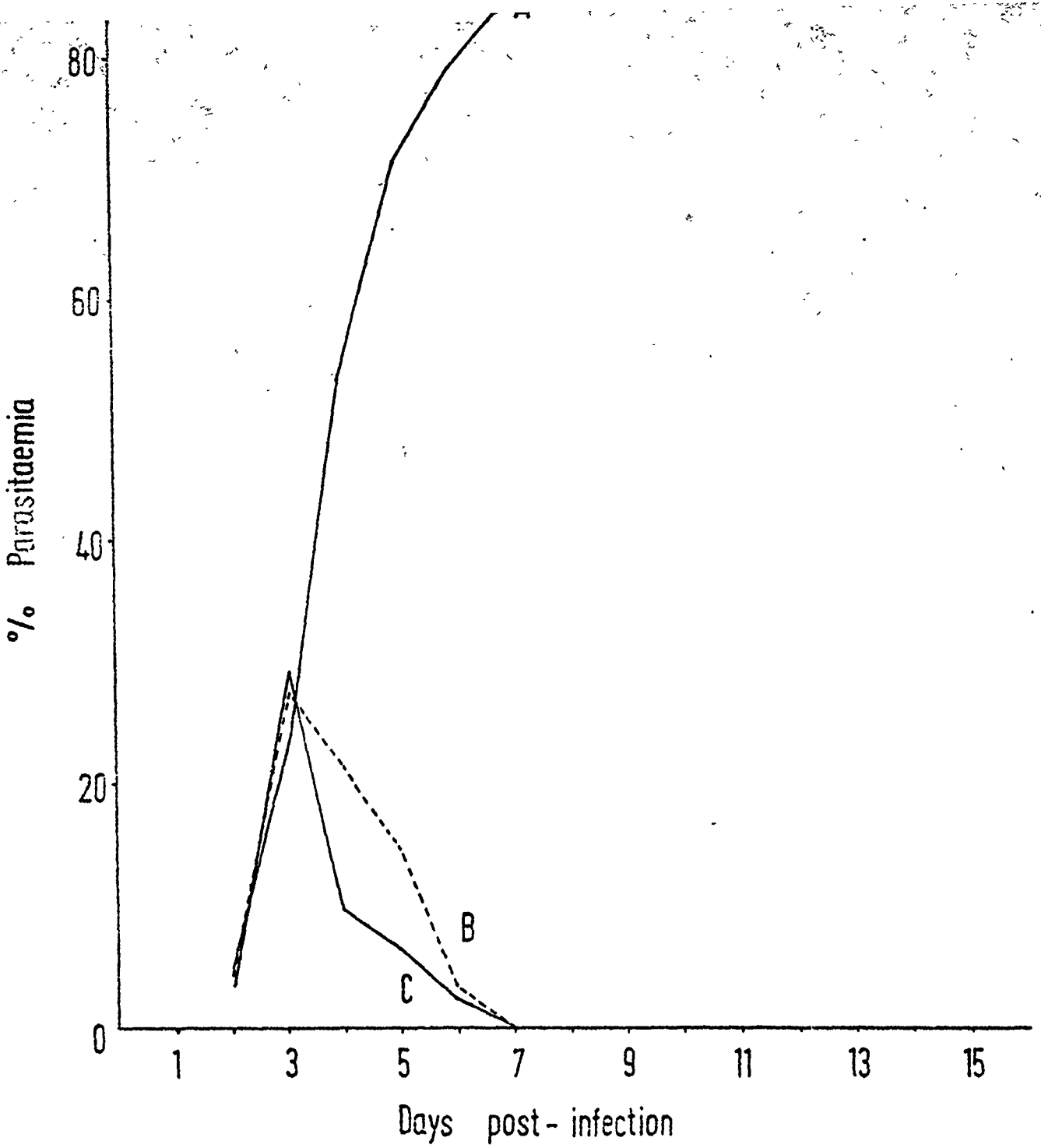


FIGURE 3

A comparison of the response of Plasmodium berghei to primaquine phosphate following drug administration by repeated daily injections via osmotic minipumps (at 16.5 µg/µl/hr. v. 20 mg/kg/day).

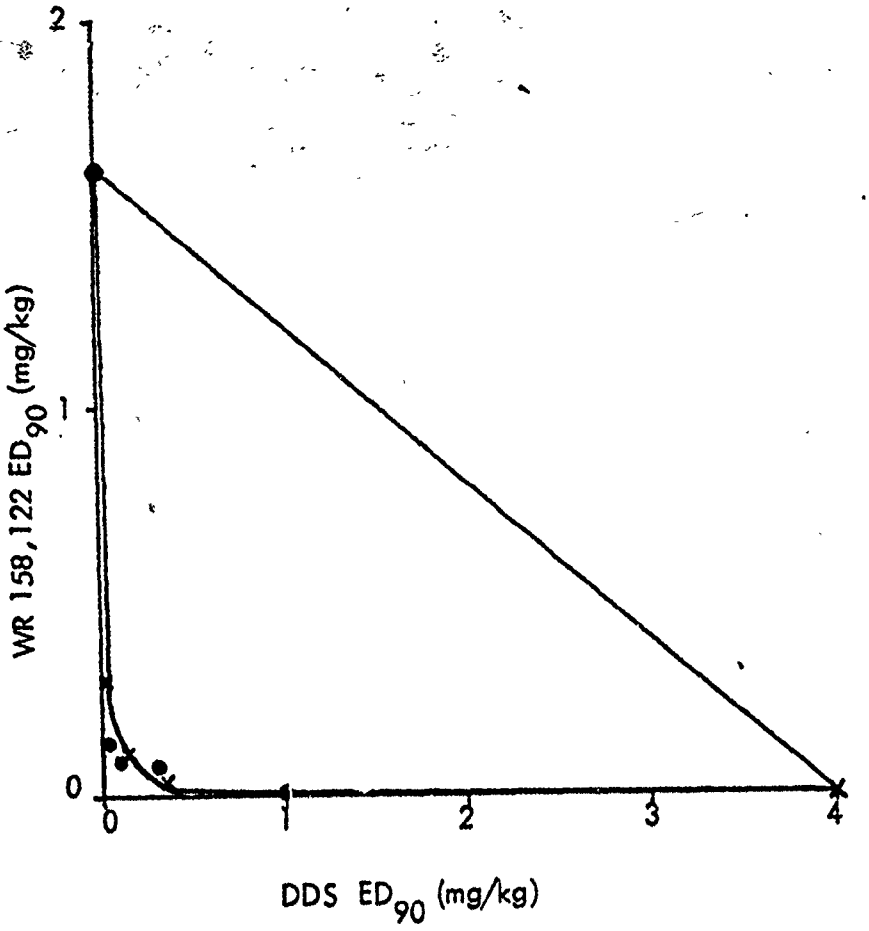


FIGURE 4

WR 158,122 and DDS - ED_{90} values when compounds are used alone or in combination in varying proportions. (See data in Table 59). The graph shows a very strong potentiation between two compounds.

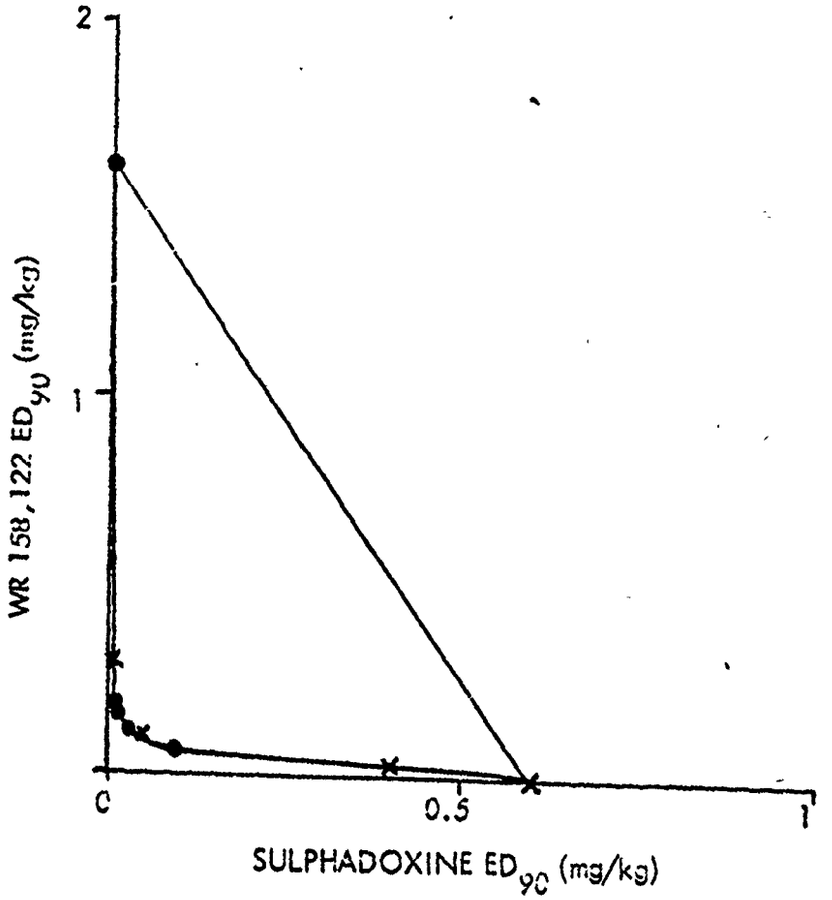


FIGURE 5

WR 158,122 and sulphadoxine - ED_{90} values when compounds are used alone or in combination in varying proportions. (See data in Table 60). The graph shows a very strong potentiation between the two compounds.

ADDENDUM

A technique for screening of drugs with residual antimalarial action

P. Schofield, R. E. Howells and W. Peters

The method described here for the screening of long-acting antimalarial agents in a rodent malaria system represents a primary screening system with limited objectives. The screen is designed to detect compounds which may possess either residual causal prophylactic or residual blood schizontocidal activity or both and which may act following administration either orally (po) or subcutaneously (sc). The technique employs a single dosage level of test compounds and this dosage is that which, in a series of preliminary experiments using selected candidate compounds, has proven optimal in terms of demonstrable residual activity and minimal local tissue reaction at the site of administration. The test is limited to a 35 day period of observation.

Materials and methods

Plasmodium y. yoelii (17X) is employed in this screen. The parasite is maintained by cyclical passage through Anopheles stephensi and albino mice. Mice are maintained at 22°C + 2°C and supplied with Dixon's 41B diet and water ad libitum. Mosquitoes are maintained at 26°C + 2°C and at 75%-85% R.H. All experimental procedures are performed in random-bred male albino mice (Tuck, TFW) which are of 20 g body weight on the first day of an experiment. The mice are employed in groups of five. Sporozoites are obtained from mosquitoes twelve days after the infective blood meal. Whole mosquitoes are homogenised in tissue culture medium 199 containing 1% bovine serum albumin (BSA) and the crude homogenate is centrifuged at 500 rpm for 1 minute to sediment the mosquito tissue. The supernatant, containing sporozoites, is removed and stored on ice until required. Sporozoite numbers are determined in a haemocytometer and the sporozoite suspension is diluted with TC 199 and 1% BSA to give a final count of 40,000 sporozoites/0.2 ml. Mice are infected by the intravenous (iv) injection of 0.2 ml of the sporozoite suspension.

All experimental compounds are prepared in suspension or solution with 0.2% Tween 80. Ager (personal communication) has observed that Tween 80 and hydroxyethyl cellulose are equally effective, and superior to arachis oil, as vehicles for experimental agents in the screening of residual antimalarial activity. The screen has been developed with a series of compounds provided by WRAIR (Table 1).

Experimental procedure

The screening method involves a preliminary stage designed to eliminate from the screen those compounds which possess no appreciable residual activity and a second stage, performed on selected compounds, which is designed to detect compounds which have a residual action of <7 days, >7 days and <14 days, >14 <21 days, and of greater than 21 days. The observation period is limited to 35 days.

The preliminary stage

In this stage, mice are treated po and sc with 80 mg/kg body weight of the test compound on Day 0 (D0). Thus the total dosage per mouse is 160 mg/kg Three days later (D+3) the mice are infected by iv inoculation of 40,000 sporozoites of P. y. yoelii 17X. Blood films are prepared from the mice on D+10 and the parasitaemia determined. On D+17 the number of surviving mice are recorded.

All experiments include groups of control animals which receive 0.2 ml of 0.2% Tween 80 po and sc and groups which receive a standard, long-acting antimalarial compound. Diformyl dapsone (DFD) is an appropriate standard compound for inclusion in this screen. DFD has no demonstrable residual activity following administration po but has a marked residual effect sc, even at 20 mg /kg. To ensure uniformity in the test, however, DFD is employed po and sc at 80 mg /kg

The parasitaemia of mice on D+10 is determined from Giemsa-stained blood films and scored 0 through +++++. The following system is used in scoring parasitaemia (using a microscope fitted with x 100 objective and x 10 eyepiece).

0	= negative	(no parasites in 10 fields)
+	= very scanty	($\leq$ 5 infected cells in 10 fields)
++	= scanty	($\leq$ 5 infected cells per field)
+++	= moderate	($<$ 20 per cent of erythrocytes infected)
++++	= heavy	($<$ 50 per cent of erythrocytes infected)
+++++	= very heavy	($>$ 50 per cent of erythrocytes infected)

Examples of the results obtained in this preliminary test are appended (Table III). Compounds which possess some demonstrable antimalarial activity in this screen are selected for further evaluation.

The secondary stage

A further evaluation of the residual antimalarial activity of selected compounds is performed in a secondary stage. In this stage of the procedure three groups of mice receive po and sc 80 mg/kg body weight (total 160 mg/kg) of the test compounds on D0, +7 and +14 respectively. Groups of control animals are also treated on these days, one with 0.2% Tween 80 alone (untreated control) and a second with DFD at 80 mg/kg, po and sc.

All mice are infected on D+21 by the inoculation iv of 40,000 sporozoites of P. y. yoelii 17X. Blood films are prepared from mice on D+28 and D+35, parasitaemia being scored 0 through ++++, as described in the preliminary stage. Mortalities on D+28 and D+35 are recorded.

The results obtained with a series of selected antimalarial compounds are presented in Tables IV and V. These results demonstrate that DFD is an ideal standard compound for inclusion in this test, giving at the dosage employed a marked residual effect, but one that is a shorter duration than the observation period. It is therefore convenient to express the residual effect observed with other compounds relative to that of DFD. In this DFD Index (DFDI) the residual effect of DFD is considered as 1. Candidate compounds in the secondary screening stage may be expected to vary from those with no demonstrable residual activity to those which totally suppress, for a period of 14 days (to D+35), the parasitaemia of mice challenged 21 days post-treatment. The performance of such compounds and those with intermediate residual activities has been scored from 0 through 4 on the basis of comparison with the residual activity of DFD, as illustrated in Table II.

Examples of the interpretation of results in DFDI terms are presented in Table IV. A simplified system for the presentation of results in terms of DFDI is represented in Table V.

It should be noted that in our laboratory, few untreated mice die within 14 days of infection with 40,000 sporozoites of P. y. yoelii 17X. The DFDI presented here is consequently based on parasitaemia scores. In other laboratories where the strain of parasite may be of greater virulence, or the mice of greater susceptibility to infection than those presently employed, significant mortality rates may be expected within this period. It is considered highly improbable however, that the death of mice will occur by seven days post infection (D+28). Under these circumstances both mouse survival and parasitaemia scores will be considered in the interpretation of results, but should not influence the applicability of the index and the scoring of individual compounds.

Observations

The methods which are described in this document are designed for the primary screening of compounds for long-acting antimalarial activity and enable compounds with varying degrees of residual activity to be selected. The tests are limited in that they employ a single dosage level of the test compound, do not differentiate between compounds which are active po or sc or both, and will select compounds with both causal prophylactic and blood schizontocidal activity. A flow-chart outlining the sequential stages for the further evaluation of long-acting antimalarial compounds is appended (Figure A).

The results obtained with cycloguanil pamoate in the secondary screening stage, at first sight appear enigmatic and might be considered to cast doubt upon the validity of the test. As indicated in Table IV 3/5, 1/5 and 4/5 mice were negative 7 and 14 days post-challenge (on D+21), following treatment on days 0, 7 and 14

respectively. The compound does therefore demonstrate a marked residual effect and would therefore be selected for further study, particularly since no sign of induration or ulceration was observed at the injection site at the dosage level of 80 mg/kg. The results furthermore are consistent with those reported by Thompson et al. (Am. J. trop. Med. Hyg., 1963, 12, 481-493) who described the repository action of cycloguanil pamoate in mice, following injection sc at dosages from 24 mg/kg to 1317 mg/kg. In that study 2/3, 3/5 and 3/3 mice exhibited patent parasitaemias seven days after challenge at 3, 4 and 5 weeks respectively post-treatment with 189 mg/kg sc in lipid and aqueous suspensions. We conclude that even were the secondary screening stage to employ cycloguanil pamoate at a dosage level of approximately 200 mg/kg, essentially similar results would be obtained to those at 80 mg/kg.

TABLE I

EXPERIMENTAL AGENTS EMPLOYED IN THE DEVELOPMENT OF THE SCREENING TECHNIQUE

Standard Agents (11)

WR 1544	Chloroquine
WR 5473	Cycloguanil (Pamoate)
WR 2978	Pyrimethamine
WR 7557	Sulphadiazine
WR 4629	Sulphalene
WR 5949	Trimethoprim
WR 2977	Amodiaquine
WR 1543	Atebrin
WR 2975	Primaquine
WR 2976	Quinine
WR 25979	Nitroguanil

Experimental Agents (20)

Quinoline Methanols

WR 30090	AV 07996	LIV 1499
WR 184806	ZN 37115	LIV 1500

Phenanthrene Methanols

WR 33063	AW 43746	LIV 1501
WR 171669	BB 43914	LIV 1502

Pyridine Methanols

WR 172435	AY 98670	LIV 1503
WR 180409	BE 99420	LIV 1504

Sulphones

WR 448	AG 28874	LIV 1505
WR 6798	AF 50013	LIV 1506

Furans

WR 93133	BB 59627	LIV 1507
WR 179305	BB 47734	LIV 1508

AR 20613	LIV 1488	
AU 76138	LIV 1489	
AG 65046	LIV 1490	
ZN 32629	LIV 1491	
AU 72569	LIV 1492	
AF 87341	LIV 1493	
AG 64870	LIV 1494	
AR 78360	LIV 1495	
AH 24988	LIV 1496	
AW 23860	LIV 1497	
AH 78744	LIV 1498	

Naphthoquinones

WR 49808	AJ 32298	LIV 1509

Triazines

WR 38839	AM 33272	LIV 1510
WR 99210	AW 23628	LIV 1511

Quinazolines

WR 141871	AX 26848	LIV 1512
WR 159412	BB 59823	LIV 1513
WR 180872	BD 09556	LIV 1514

Mannich Bases

WR 194965	BG 56327	LIV 1515
WR 228258	BG 85640	LIV 1516

Miscellaneous

WR 81844	ZF 92291	LIV 1517
WR 87781	AB 34313	LIV 1518

TABLE II

THE PARAMETERS EMPLOYED IN THE CONSTRUCTION OF THE DFD INDEX (DFDI)

TREATMENT DAY	PARASITAEMIA ON DAY +28	PARASITAEMIA ON DAY +35	DFDI	COMMENTS
0	+++	++++	1	Residual activity (RA) of DFD standard. RA < 21 days Animals challenged 14 days post treatment (pt) negative at 7 days but positive at 14 days post challenge (pi).
7	0	++++		
14	0	0		
0	0	0	4	RA > 21 days Total suppression of parasitaemia for duration of test.
7	0	0		
14	0	0		
0	0	+	< 4	RA intermediate between 3.0 and 4.0
7	0	0		
14	0	0		
0	0	+++	3	RA > 21 days Animals challenged 21 days pt negative at 7 days but positive at 14 days pi.
7	0	0		
14	0	0		
0	+	+++	< 3	RA intermediate between 2.0 and 3.0
7	0	0		
14	0	0		
0	+++	++++	2	RA < 21 days Animals challenged 14 days pt negative at 7 and 14 days pi.
7	0	0		
14	0	0		
0	+++	++++	<2	RA intermediate between 1.0 and 2.0
7	0	+		
14	0	0		

TABLE II (ctd.)

THE PARAMETERS EMPLOYED IN THE CONSTRUCTION OF THE DFD INDEX

TREATMENT DAY	PARASITAEMIA ON DAY +28	+35	DFDI	COMMENTS
0	+++	++++		
7	0	++++	1.0	RA as DFD standard above
14	0	0		
0	+++	++++		
7	+	+++	< 1.0	RA intermediate between 0.5 and 1.0
14	0	0		
0	+++	++++		
7	+++	++++	0.5	RA < 14 days Animals challenged 7 days pt negative at 7 and 14 days pi
14	0	0		
0	+++	++++		
7	+++	++++	< 0.5	RA intermediate between 0.2 and 0.5
14	0	+		
0	+++	++++		RA < 14 days
7	+++	++++	0.2	Animals challenged 7 days pt negative at 7 days but positive at 14 days pi
14	0	++++		
0	+++	++++		
7	+++	++++	< 0.2	RA intermediate between 0 and 0.2
14	+	+++		
0	+++	++++		
7	+++	++++	0	No residual activity observed RA < 7 days
14	+++	++++		

Footnote Parasitaemia scores refer to mean parasitaemia obtained in a group of 5 mice and not number of mice positive

TABLE III

PRELIMINARY SCREENING STAGE FOR RESIDUAL ANTIMALARIAL ACTIVITY (3 DAY TEST)

DOSE: 80 mg/kg ROUTE: sc and po CHALLENGE: Sporozoites of P. y. yoelii 17X on Day +3

Compound LIV No.	WR No.	BN No.	Parasitaemia on D+10 following treatment	Survival on D+17 following treatment	Comment	
DFD	Control		++++	5/5	Control 0.2% Tween 80	
1499	30090	AV07996	0	5/5	Standard	
1500	184806	ZN37115	++	5/5	Quinoline methanol	Pass
1501	33063	AW43746	0	5/5	Quinoline methanol	Pass
1502	171669	BB43914	+++	5/5	Phenanthrene methanol	Reject
1503	172435	AY98670	0	5/5	Phenanthrene methanol	Pass
1504	180409	BE99420	0	5/5	Pyridine methanol	Pass
1505	448	AG28874	0	5/5	Pyridine methanol	Pass
1506	6798	AF50013	++	5/5	Sulphone	Pass
1507	93133	BB59627	0	5/5	Sulphone	Pass
1508	179305	BB47734	+++	5/5	Furan	Reject
1509	49808	AJ32298	+++	5/5	Furan	Reject
1510	38839	AM33272	0	5/5	Naphthoquinone	Pass
1511	99210	AW23628	+++	5/5	Triazine	Reject
1512	141871	AX26848	0	5/5	Triazine	Pass
1513	159412	BB59823	0	5/5	Quinazoline	Pass
1514	180872	BD09556	0	5/5	Quinazoline	Pass
1515	194965	BG56327	0	2/5	Quinazoline	Repeat
1516	228258	BG85640	0	5/5	Mannich base	Pass
1517	81844	ZF92291	+	5/5	Mannich base	Pass
1518	87781	AB34313	+++	5/5	Miscellaneous	Pass
			+	5/5	Miscellaneous	Pass
DFD	Control		++++	4/5	Control 0.2% Tween 80	
1488	1544	AR20613	0	5/5	Standard	
1489	5473	AU76138	++++	3/5	Chloroquine	Reject
1490	2978	AG65046	0	2/5	Cycloguanil pamoate	Repeat
1491	7557	ZN32629	0	3/5	Pyrimethamine	Pass
1492	4629	AU72569	0	5/5	Sulphadiazine	Pass
1493	5949	AF87341	+++	5/5	Sulphalene	Reject
1494	2977	AG64870	+++	5/5	Trimethoprim	Reject
1495	1543	AR78360	+++	5/5	Amodiaquine	Reject
1496	2975	AH24988	+++	3/5	Atebrine	Reject
1497	2976	AW23860	++++	5/5	Primaquine	Reject
1498	29579	AH78744	+++	5/5	Quinine	Reject

TABLE IV

SECONDARY SCREENING STAGE FOR RESIDUAL ANTIMALARIAL ACTIVITY

DOSE: 80mg/kg ROUTE: sc and po CHALLENGE: Sporozoites of P.y.yoelii 17X on day -21

COMPOUND			TREATMENT DAY	PARASITAEMIA (AND SURVIVAL) ON DAY				DFDI	COMMENTS
LIV NO	WR NO	BN NO		+28		+35			
			0	+++	(5/5)	+++++	(5/5)		
			7	+++	(5/5)	+++++	(5/5)	0	Control (0.2% Tween 80)
			14	+++	(5/5)	++++	(5/5)		
			0	++	(5/5)	+++	(5/5)		
DFD	CONTROL		7	0	(5/5)	++	(5/5)	1	Standard
			14	0	(5/5)	0	(5/5)		
1503	172435	AY98670	0	0	(5/5)	0	(5/5)		
			7	0	(5/5)	0	(5/5)	4	Pyridine methanol
			14	0	(5/5)	0	(5/5)		
1502	171669	BB43914	0	0	(5/5)	+++	(5/5)		
			7	0	(5/5)	+	(5/5)	< 3	Phenanthrene methanol
			14	0	(5/5)	0	(5/5)		
1514	180872	BD09556	0	+++	(5/5)	+++	(5/5)		
			7	0	(5/5)	0	(5/5)	2	Quinazoline
			14	0	(5/5)	0	(5/5)		
1516	228258	BG85640	0	+++	(5/5)	+++	(5/5)		
			7	0	(5/5)	++	(5/5)	1	Mannich base
			14	0	(5/5)	0	(5/5)		
1506	6798	AF50013	0	++	(5/5)	+++	(5/5)		
			7	0	(5/5)	++	(5/5)	1	Sulphone
			14	0	(5/5)	0	(5/5)		

(ctd

TABLE IV (ctd.)

SECONDARY SCREENING STAGE FOR RESIDUAL ANTIMALARIAL ACTIVITY
DOSE: 80mg/kg ROUTE: sc and po CHALLENGE: Sporozoites of P.y.yoelii 17X on day +21

COMPOUND			TREATMENT DAY	PARASITAEMIA (AND SURVIVAL) ON DAY				DFDI	COMMENTS
				+28		+35			
LIV NO	WR NO	BN NO							
1512	141871	AX26848	0	+++	(4/5)	++++	(4/5)	0.5	Quinazoline
			7	+++	(5/5)	+++	(5/5)		
			14	0	(5/5)	0	(5/5)		
1509	49808	AJ32298	0	+++	(5/5)	++++	(5/5)	0.5	Naphthoquinone
			7	+++	(5/5)	++++	(5/5)		
			14	0	(5/5)	0	(5/5)		
1515	194965	BG56327	0	+++	(5/5)	++++	(5/5)	0.2	Mannich base
			7	+++	(5/5)	++++	(5/5)		
			14	0	(5/5)	+	(5/5)		
1513	159412	BB59823	0	+++	(5/5)	+++	(5/5)	0.2	Quinazoline
			7	+++	(5/5)	++++	(5/5)		
			14	0	(5/5)	+++	(5/5)		
1504	180409	BE99420	0	+++	(5/5)	++++	(5/5)	<0.2	Pyridine methanol
			7	+++	(4/5)	+++++	(4/5)		
			14	++	(5/5)	+++	(5/5)		
1489	5473	AU76138	0	+++	(5/5)	+++	(5/5)	0	Cycloguanil pamoate Parasitaemia in individual mice variable - REPEAT
			7	+++	(5/5)	++++	(5/5)		
			14	+++	(5/5)	+++	(5/5)		
1490	2978	AG65046	0	++++	(1/5)	++++	(1/5)	0	Pyrimethamine - REPEAT
			7	+++	(3/5)	++++	(3/5)		
			14	++++	(2/5)	++++	(2/5)		

TABLE IV (ctd.)

SECONDARY SCREENING STAGE FOR RESIDUAL ANTIMALARIAL ACTIVITY
DOSE: 80mg/kg ROUTE: sc and po CHALLENGE: Sporozoites of P.y.yoelii 17X on day +21

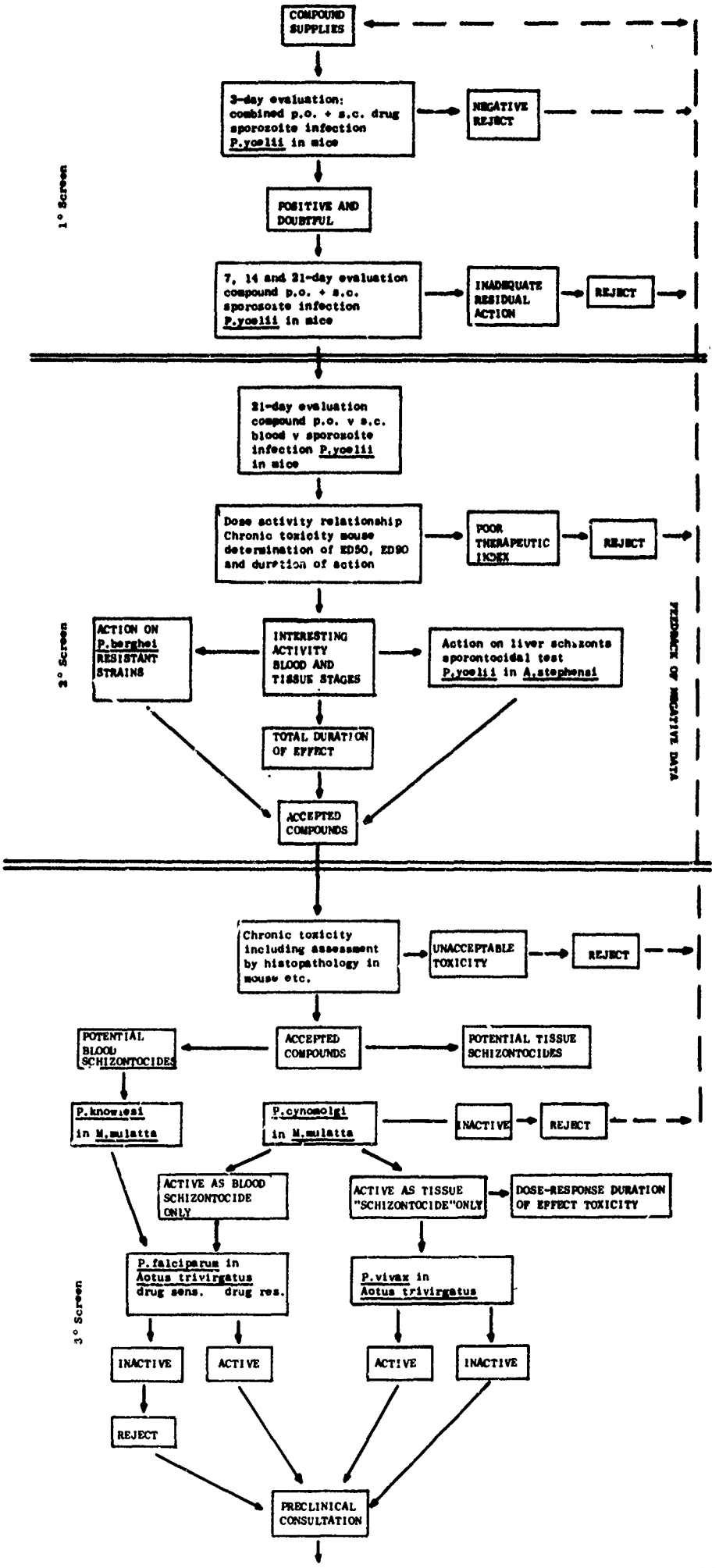
COMPOUND			TREATMENT DAY	PARASITAEMIA (AND SURVIVAL) ON DAY		DFDI	COMMENTS
LIV NO	WR NO	BN NO		+28	+35		
1491	7557	ZN32629	0	+++ (5/5)	++++ (5/5)	0	Sulphadiazine
			7	+++ (5/5)	+++++ (5/5)		
			14	+++ (5/5)	++++ (5/5)		
1499	30090	AV07996	0	++++ (5/5)	++++ (4/5)	0	Quinoline methanol
			7	+++ (5/5)	++++ (5/5)		
			14	+++ (5/5)	++++ (5/5)		
1500	184806	ZN37115	0	+++ (5/5)	+++++ (5/5)	0	Quinoline methanol
			7	+++ (5/5)	++++ (5/5)		
			14	+++ (5/5)	++++ (5/5)		
1505	448	AG28874	0	+++ (5/5)	++++ (5/5)	0	Sulphone
			7	++++ (5/5)	+++++ (4/5)		
			14	+++ (5/5)	++++ (5/5)		
1511	99210	AW23628	0	+++ (5/5)	++++ (5/5)	0	Triazine
			7	+++ (4/5)	++++ (4/5)		
			14	+++ (5/5)	++++ (5/5)		
1517	81844	ZF92291	0	++++ (5/5)	++++ (5/5)	0	Miscellaneous
			7	+++ (5/5)	++++ (5/5)		
			14	+++ (5/5)	++++ (5/5)		
1518	87781	AB34313	0	+++ (5/5)	++++ (5/5)	0	Miscellaneous
			7	+++ (5/5)	++++ (5/5)		
			14	+++ (5/5)	++++ (5/5)		

TABLE V

RESUME OF RESULTS OF SECONDARY SCREENING STAGE FOR RESIDUAL ANTIMALARIAL ACTIVITY

LIV No.	Compound WR No.	BN No.	Dosage mg/kg po	sc	DFDI	Comments
DFD	Control				0	Control 0.2% Tween 80
1503	172435	AY98670	80	80	1	Standard
1502	171669	BB43914	80	80	4	Pyridine methanol
1514	180872	BD09556	80	80	3	Phenanthrene methanol
1516	228258	BG85640	80	80	2	Quinazoline
1506	6798	AF50013	80	80	1	Mannich base
1512	141871	AX26848	80	80	1	Sulphone
1509	49808	AJ32298	80	80	0.5	Quinazoline
1515	194965	BG56327	80	80	0.5	Naphthoquinone
1513	159412	BB59823	80	80	0.2	Mannich base
1504	180409	BE99420	80	80	0.2	Quinazoline
1489	5473	AU76138	80	80	0.2	Pyridine methanol
1490	2978	AG65046	80	80	0	Cycloguanil pamoate
1491	7557	ZN32629	80	80	0	Pyrimethamine
1499	30090	AV07996	80	80	0	Sulphadiazine
1500	184806	ZN37115	80	80	0	Quinoline methanol
1505	448	AG28874	80	80	0	Quinoline methanol
1511	99210	AW23628	80	80	0	Sulphone
1517	81844	ZF92291	80	80	0	Triazine
1518	87781	AB34313	80	80	0	Miscellaneous
						Miscellaneous

FLOW CHART FOR THE SELECTION OF COMPOUNDS POSSESSING RESIDUAL ANTIMALARIAL ACTIVITY



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