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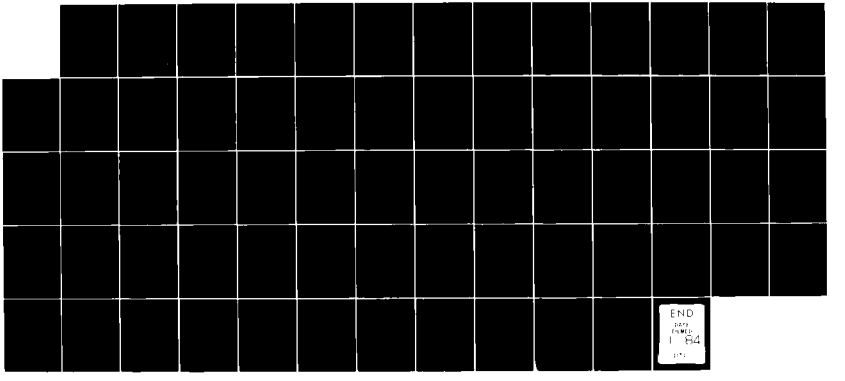

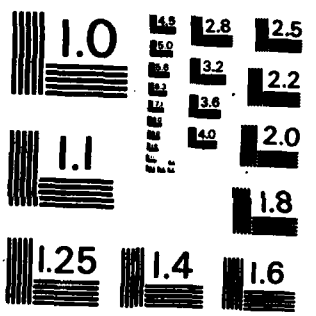

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CHEMOTHERAPY OF RODENT MALARIA
EVALUATION OF DRUG ACTION AGAINST NORMAL AND RESISTANT STRAINS INCLUDING EXO-ERYTHROCYTIC STAGES

ANNUAL REPORT

by

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1. INTRODUCTION

This is the last Annual Report to be issued by the Principal Investigator from Liverpool and concludes a period of collaboration in the US Army antimalarial drug programme that commenced with the first Contract in October 1967. A separate Final Report is in preparation. A further four WRAIR compounds have been examined since the last Report issued in December 1978 for blood schizontocidal activity, and another 21 have been examined as tissue schizontocides.

Further biochemical studies have been made on the mode of action of various drugs including mefloquine, in spite of a continuing problem with animal accommodation due to tightening Home Office regulations concerning animal care in research laboratories. It is understood that the new regulations that are being drawn up take guidance from FDA requirements as well as those in other EEC countries, and this will necessitate a major reconstruction of the animal accommodation in Liverpool.

The Principal Investigator is moving to the London School of Hygiene and Tropical Medicine where he will inaugurate a programme of antiprotozoal chemotherapy research after October 1st 1979.

In June 1979 the writer took the opportunity of being in transit through Florida to visit Dr. Arba Ager's laboratory at the University of Miami where he was able to discuss matters of joint interest in relation to the drug testing programme, and notably the new system for detecting residual drug activity.

2. CYCLICAL PASSAGE OF RODENT MALARIA STRAINS

Both P. yoelii yoelii and P. y. nigeriensis were maintained in regular cyclical transmission through Anopheles stephensi. The parasite strains will be transferred to the London laboratories where a colony of A. stephensi is already established, as well as numerous other species and strains of Anopheles.

3. CHEMOTHERAPY STUDIES

3.1 Blood schizontocides

The main interest this year has been to examine the activity of compounds in the highly mefloquine resistant line (N/1100), although in fact few compounds were received for this purpose. One compound of particular interest because of its broad activity against strains resistant to pyrimethamine and chloroquine is the triazine, WR 99210. The Mannich base WR 228258 was significantly less active against the N/1100 line. Of two other compounds of which the structures are not yet known to us, WR 212293 proved toxic and appeared less active against the N/1100 line. WR 233637 was moderately active by the sc route but much less active orally, and also showed less activity against the mefloquine-resistant line. A summary of these data is annexed as Table 1, and detailed information in Tables 2 through 5.

3.2 Causal prophylaxis

In Tables 6 through 8 are summarised causal prophylactic test data on 21 WRAIR compounds. The structures of 2 compounds are not yet known to us. WR 212293 was fully active at the screening dose of 30 mg/kg sc or po, without any residual activity. WR 233637 was inactive at this dose sc but showed some activity without residual activity po.

Several 8-aminoquinolines were examined. WR 231350 was inactive sc and po at the screening dose, whereas WR 237264 showed some activity sc (but not po). WR 236066 was active po and sc at 30 mg/kg without residual activity; WR 231530 has a Minimum Fully Active Dose (MFAD) of $>$ 30 mg/kg and shows marked residual action; the MFAD of WR 219423 is between 3 and 10 mg/kg while no residual activity is detectable at 30 mg/kg sc or po; WR 233627 is less active, with a MFAD between 10 and 30 mg/kg sc or po but also with no residual activity at 30 mg/kg; WR 231633 is inactive sc or po at the screening dose.

The Mannich base WR 225449 appears to have an MFAD between 3 and 10 mg/kg sc or po but has marked residual activity at 30 mg/kg. This is an unexpected finding for a Mannich base. The most active compound tested this time was a hydroxyquinoline WR 96345 which has an MFAD between 1 and 3 mg/kg sc with a trace of residual action at 3 mg/kg. Orally it was inactive at 30 mg/kg. Another quinoline derivative, WR 194905 had an MFAD of 3-10 mg/kg sc or po with some residual action at 30 mg/kg sc but none at this dose po. The bis-pyrimidine WR 234749 was inactive sc or po at 30 mg/kg. Two quinazolines which were fully active at the screening dose were WR 150017 which had a trace of residual activity po, and WR 155004 which had a marked residual action at 30 mg/kg sc. Three quinazolones, WR 237233, 237234 and 237227 were all inactive sc and po at 30 mg/kg, as were two furan derivatives WR 235780 and WR 235781, as well as a pyridine, WR 156949.

These data are summarised in Tables 6, 7 and 8 and given in detail in Tables 9 through 29.

3.3 New drug delivery systems

Further studies have been completed with antimalarials incorporated into polydimethylsiloxane (Silastic rubber^{R}) which is implanted surgically in the form of pellets each 150-200 mg weight. Pyrimethamine in a concentration of 0.5% base protected mice from challenge with P. berghei for 5 to 6 months. Each mouse received only a single challenge to avoid the possibility of their acquiring active immunity. Sulphadiazine implants in repeat experiments were unsuccessful and even a 3% implant failed to protect for more than a week. Implanted mice however had a longer prepatent period than controls (8 compared with 2 days) and longer mean survival time (18 days compared with 8 days for controls).

A preliminary study was made in which subeffective concentration implants of pyrimethamine and sulphadiazine were implanted simultaneously. The combination exhibited a potentiation effect and led to radical cure in challenged mice. Untreated controls and those receiving the single drugs had a prepatent period of about 2 days followed by a fulminating infection.

Other compounds studied in silastic implants were WR 99210 HBr and mefloquine. A 5% implant of WR 99210 was ineffective and irritant. A 5% mefloquine implant produced a plasmodistatic effect for 7 days post-challenge, but was no longer protective in mice challenged 14 days after implantation. A 15% sulphadoxine implant completely suppressed P. berghei challenge infections for more than 21 days.

Dr. R. E. Howells and Ms Judge have also extended their studies on the incorporation of various drugs in biodegradable polymers. Mice given a single implant containing 45 mg of which 30% was pyrimethamine base or sulphadiazine 40 mg (also 30% in polymer) have been protected against challenge with blood stages of a virulent strain of P. berghei for as long as 10 months. In these experiments also each group of mice has been challenged only once so that acquired immunity can be excluded. Moreover, mice suriving 10 months have been challenged after the implants have been surgically excised, and these animals have developed a heavy parasitaemia.

We have also, as anticipated, preliminary evidence of potentiation when mixed silastic implants have been given with these two compounds. While earlier work had shown that a good repository action could be obtained with pyrimethamine in a silastic rubber implant, this was not the case with sulphadiazine.

3.4 Drug potentiation

Using the simple (uncompounded) drugs sulphadiazine and WR 158122 (a quinazoline under study in repository formulations by WRAIR and Dynatech), we have shown marked potentiation in the 4-day test of blood schizontocidal action. These data are summarised in Table 30 and Figure 1, and may be compared with those for WR 158122 with dapsone or sulphadoxine presented in our December 1978 Report.

In addition to this study just mentioned we have tested a hypothesis concerning the possible reliance of chloroquine-resistant P. berghei on enhanced mitochondrial function by administering various combinations of chloroquine and chloramphenicol to mice infected with the RC line. In strong contrast to the combination to chloroquine with erythromycin which demonstrated a marked potentiation, not even an additive action was seen in the present experiment. The data are presented in Table 31.

3.5 Mode of action of chloroquine and mefloquine

Dr. Carol Homewood and Dr. Ken Neame (Department of Physiology) have continued their investigation of the modes of action of chloroquine and mefloquine. Attention has been focussed recently on two parameters of drug action, firstly the kinetics of drug incorporation and, secondly, the influence of drug on the incorporation of radioactive adenosine into parasite nucleic acid. We reported some time ago that experiments carried out while the N strain of P. berghei was changing to NS sometimes showed an apparent incorporation of radioactive chloroquine into nucleic acid during one hour incubation in vitro, but other experiments showed no incorporation. We felt that this variability might be related to the change to resistance to chloroquine. However, these experiments were repeated earlier this year and no radioactive chloroquine was found associated with the nucleic acid/protein fraction of the parasite.

Experiments were restarted on the uptake and concentration of chloroquine by P. berghei-infected red cells in vitro. We found that at low concentrations, accumulation was directly proportional to the concentration of chloroquine in the medium, with no evidence for saturation kinetics. The detection of a k_m for uptake of about 10^{-8}M thus apparently depends upon the conditions under which uptake is measured. We are presently investigating this.

A comparison of mefloquine and chloroquine shows that mefloquine acts more rapidly. The rate of incorporation of radioactive adenosine into nucleic acids by P. berghei-infected red cells is unaffected by preincubation for 1 hour with chloroquine at 10^{-6}M, but is reduced by about 20% by incubation for the same time with 10^{-6}M mefloquine. This reduced rate of incorporation is probably not due to an effect on carbohydrate metabolism, and hence energy production, as neither mefloquine nor chloroquine affect the rate of glucose utilisation (although results with mefloquine have been slightly erratic).

In one sense we have gone full circle in relation to the uptake of chloroquine, to the time in fact where we proposed that this compound passes into the parasite by means of a simple pH gradient, rather than by attachment to specific "high affinity binding sites". It is clear that the results of uptake experiments reported in the past by other workers as well as ourselves are barely comparable since so many experimental conditions can radically influence the outcome of such measurements.

4. PAPERS PUBLISHED

4.1 Already published

Judge, B. M. and Howells, R. E. (1979) A comparison of the response of Plasmodium berghei to primaquine diphosphate following drug administration by repeated daily infections and by a constant release system. Trans. R. Soc. trop. Med. Hyg., 73, 327-328. (Laboratory Demonstration).

Peters, W. (1978). Current concepts in the treatment of malaria with particular reference to drug resistance. SEAMEO Reg. Trop. Med. & Public Hlth Proj., Bangkok, 55-57.

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4.2 In press

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

Judge, B. M. and Howells, R. E. (1979). The use of drug-polymer mixture implants to produce sustained antimalarial effects in mice. Paper presented at BSP Spring Meeting, Parasitology.

Knight, D. J. and Peters, W. (1980). The antimalarial activity of N-benzyloxydihydrotriazines. I. The activity of clociguanil (BRL 50216) against rodent malaria and studies on its mode of action. Ann. trop. Med. Parasit.

Merkli, B., Richle, R. and Peters, W. (1980). 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, Izmir, September 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: "Manual of Chemotherapy of Malaria", (Eds. R. H. Black, L. J. Bruce-Chwatt, C. J. Canfield, D. F. Clyde, W. Peters, W. Wernsdorfer), WHO: Geneva.

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

Peters, W. (1979). Problems of chemotherapy in relation to drug resistance. Paper presented at Malaria Symposium held in New Delhi, November 1977 Contribution No. 1482

Peters, W. and Ramkaran, A. E. (1980). The chemotherapy of rodent malaria, XXXII. The influence of para-aminobenzoic acid on the transmission of Plasmodium yoelii and P. berghei by Anopheles stephensi. Ann. trop. Med. Parasit., Contribution No. 1535

5. APPENDICES

Table 1	Summary of blood schizontocidal studies in 4-day test against Plasmodium berghei.
Tables 2 through 5	Detailed 4-day tests of blood schizontocidal action.
Tables 6, 7 and 8	Summaries of causal prophylactic tests against Plasmodium yoelii nigeriensis
Tables 9 through 29	Details of causal prophylactic tests.
Table 30	ED_{90} of WR 158122 and sulphadiazine alone or in combination. Data in mg/kg sc in 4-day test (see Figure 1)
Table 31	ED_{90} of chloramphenicol and chloroquine alone or in combination against blood infection of P. berghei RC line in 4-day test. No additive or potentiating action is seen.
Figure 1	WR 158122 and sulphadiazine ED_{90} values when compounds are used alone or in combination in varying proportions (see data in Table 30).

SUMMARY OF BLOOD SCHIZONTOCIDAL (4 DAY TEST) DATA.

L I V No.	Suppliers No.	Route	N		NS		RC		P		B		PYR		ORA		N/1100		
			ED_{50}	ED_{90}	ED_{90}	I_{90}	ED_{90}	I_{90}	ED_{90}	I_{90}	ED_{90}	I_{90}	ED_{90}	I_{90}	ED_{90}	I_{90}	ED_{90}	I_{90}	
1511	WR99210AB AW 23628	s.c.	<1	<1															
		p.o.	7.6	19.0															
1516	WR228258AB B485640	s.c.	4.8	10.3													>30	>3.0	Mannich Base
		p.o.	1.2	2.6													>30	>11.5	
1590	WR212293AB BW49943	s.c.	10.0	>MTD													18.5	<1.0	Toxic
		p.o.	28.0	>MTD													93.0	<1.0	
1591	WR233637AB BW49596	s.c.	15.0	29.0													64.0	2.2	
		p.o.	<10?	<10?													76.0		

TABLE 1

ED_{50} / ED_{90} = mg/kg x 4 MTD = maximum tolerated dose

SUMMARY OF ANTIMALARIAL DRUG TESTS (BLOOD SCHIZONTOCIDES) TABLE 2

COMPOUND NAME or NUMBER WR99210 AE AW 29628 LIV.1511

PARASITE (SUB) SPECIES P.b.bergei

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
N s.c.	1·0	5	1	–	0
	3·0	5		–	0
	10·0	5		–	0
	30·0	5		–	0
	Ø	10		36·6	
ED_{50} (range)	<1·0				
ED_{90} (range)	<1·0				
	Resistance factor 90				
N p.o.	1·0	5	1	–	97·2 ± 2·4
	3·0	5		–	91·9 ± 5·0
	10·0	5		–	82·7 ± 5·3
	30·0	5		–	2·5 ± 2·4
	Ø	10		36·6	
ED_{50} (range)	7·6 (3·5–21)				
ED_{90} (range)	19·0 (8·5–50)				
	Resistance factor 90				

LIVERPOOL SCHOOL OF TROPICAL MEDICINE DATE ..... PRINCIPAL INVESTIGATOR PROF. W. PETERS

SUMMARY OF ANTIMALARIAL DRUG TESTS (BLOOD SCHIZONTOCIDES) TABLE 3A

COMPOUND NAME or NUMBER WR228258AB BG85640 LIV/1516 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
N	1.0	5		–	95.3 ± 5.9
	3.0	5		–	83.6 ±
	10.0	5	1	–	7.8 ±
	30.0	5		–	0.2 ±
	Ø	10		37.6	
ED_{50} (range)	4.8(3.6-6.0)				
ED_{90} (range)	10.3(7.6-12.5)				
	Resistance factor 90				
N/1100	1.0	5		–	55.0 ± 18.3
	3.0	5		–	51.3 ± 15.9
	10.0	5	1	–	39.1 ± 4.5
	30.0	5		–	31.9 ± 5.4
	Ø	10		6.4	
ED_{50} (range)	2.5(<1 - 6.5)				
ED_{90} (range)	» 30				
	Resistance factor $_{90}$ » 3				

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SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE3B

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER WR228258AB BG85640 / LIV/1516

PARASITE (SUB) SPECIES P.b.beghei

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
N	1·0	5		–	54.0 ± 15.0
	3·0	5		–	15.4 ± 11.2
	10·0	5	1	–	0
	30·0	5		–	0
	~~Ø~~	10		37·6	
ED_{50} (range)	1·2(0·8–2·1)				
ED_{90} (range)	2·6(1·8–4·4)				
	Resistance factor 90 1·0				
N/1100	1·0	5		–	88·4 ± 7·2
	3·0	5		–	56·3 ± 6·9
	10·0	5	1	–	49·1 ± 11·4
	30·0	5		–	55·9 ± 9·0
	~~Ø~~	10		6·4	
ED_{50} (range)	>30				
ED_{90} (range)	≫30				
	Resistance factor 90 ≫11·5				

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SUMMARY OF ANTIMALARIAL DRUG TESTS — TABLE 4A

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER WR212293AB BH49943 LIV.1590 PARASITE (SUB) SPECIES P.b.beghei

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	10.0	5		–	50.5 ± 6.0
	30.0	5 *		–	35.6 ±
	60.0	5 **	1	–	–
	100.0	5 **		–	–
	∅	10		37.6	
ED_{50} (range)	10 (6.5 - 15.0)	* 2/5 DIED			
ED_{90} (range)	> MTD	** 5/5 DIED			
	Resistance factor 90				
N/1100	10.0	5		–	29.4 ± 4.8
	30.0	5		–	3.8 ± 1.8
	60.0	5 *	1	–	0
	100.0	5 **		–	–
	∅	10		6.4	
ED_{50} (range)	7.5 (6 - 10)	* 2/5 DIED			
ED_{90} (range)	18.5 (14.5 - 24.5)	** 5/5 DIED			
	Resistance factor 90				

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SUMMARY OF ANTIMALARIAL DRUG TESTS (BLOOD SCHIZONTOCIDES) TABLE 48

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 %	Treatec PR% / Control PR% x 100
N	10.0	5		-	68.8 ± 1.5
	30.0	5		-	48.7 ± 6.3
	60.0	5	1	-	35.0 ± 9.0
	100.0	5 *		-	28.1 ± 8.7
	ø	10		37.6	
ED_{50} (range)	28 (16 - 50)	* 1/5 DIED			
ED_{90} (range)	> MTD				
	Resistance factor 90				
N/1100	10.0	5		-	100 ± 14.1
	30.0	5		-	100 ± 3.6
	60.0	5	1	-	47.2 ± 15.9
	100.0	5 *		-	9.4
	ø	10		64	
ED_{50} (range)	66 (46 - 82)	* 3/5 DIED			
ED_{90} (range)	93 (63 - 115)				
	Resistance factor 90				

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SUMMARY OF ANTIMALARIAL DRUG TESTS (BLOOD SCHIZONTOCIDES) TABLE 5A

COMPOUND NAME or NUMBER WR 238637AB BH49536 LIV.1591 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
N	10.0	5		—	61.4 ± 2.5
	30.0	5		—	7.5 ± 4.7
	60.0	5	1	—	0.9 ± 0.6
	100.0	5		—	0
	Ø	10		37.6	
ED_{50} (range)	15(11 - 20)				
ED_{90} (range)	29(21 - 38)				
	Resistance factor 90 1.0				
N/1100	10.0	5		—	100 ± 15.6
	30.0	5		—	55.9 ± 6.9
	60.0	5	1	—	39.1 ± 18.0
	100.0	5		—	0.8 ± 0.6
	Ø	10		64	
ED_{50} (range)	40(29 - 64)				
ED_{90} (range)	64(48 - 103)				
	Resistance factor 90 2.2				

LIVERPOOL SCHOOL OF TROPICAL MEDICINE DATE ..... PRINCIPAL INVESTIGATOR PROF. W. PETERS

SUMMARY OF ANTIMALARIAL DRUG TESTS TABLE 5B

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME WR 233637 AB BH49696
or NUMBER .LIV/1591..... 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
N	10·0	5		–	0
	30·0	5		–	0
	60·0	5	1	–	0
	100·0	5		–	0
	Ø	10		37·6	
ED_{50} (range)	<10				
ED_{90} (range)	<10				
	Resistance factor 90				
N/1100	10·0	5		–	86·6 ± 13·8
	30·0	5		–	52·8 ± 18·6
	60·0	5	1	–	14·4 ± 6·6
	100·0	5		–	8·1 ± 1·8
	Ø	10		6·4	
ED_{50} (range)	28(21 – 40)				
ED_{90} (range)	76(48 – 108)				
	Resistance factor 90				

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	WR No.	LIV No.	Minimum fully active dose (mg/kg x 1)	Residual action at active dose	COMMENT	Type of Compound
BG94630	231350 AA	1531	–	–	NA 30 mg/kg x 1 sc	8-aminoquinoline
			–	–	NA 30 mg/kg x 1 po	"
BH57392	237264	1614	>30	NIL AT 30	ACTIVE 30 mg/kg x 1 sc	"
			–	–	NA 30 mg/kg x 1 po	"
BH39634	236066	1619	>30	NIL AT 30	ACTIVE 30 mg/kg x 1 sc	"
			>30	NIL AT 30	ACTIVE 30 mg/kg x 1 po	"

TABLE 6

	WR No.	LIV No.	Minimum fully active dose (mg/kg x 1 s.c.)	Residual action at active dose	COMMENT	Type of Compound
BG94916	231530AA	1533	>30	MARKED AT 30	MAINLY RESIDUAL ACTIVITY	8-aminoquinoline
			>30	MARKED AT 30	RESIDUAL ACTIVITY ONLY	"
BG94925	225449AB	1634	3-10	MARKED AT 30	FULLY ACTIVE AT 10 mg/kg x 1 sc	Mannich base
			3-10	MARKED AT 30	FULLY ACTIVE AT 10 mg/kg x 1 po	" "
BE73480	219423AA	1560	3-10	NIL AT 30	FULLY ACTIVE AT 10 mg/kg x 1 sc	8-aminoquinoline
			3-10	NIL AT 30	FULLY ACTIVE AT 10 mg/kg x 1 po	"
BC65489	96345 AB	1561	1-3	TRACE AT 3	FULLY ACTIVE AT 3 mg/kg x 1 sc	Hydroxyquinoline
			—	NIL AT 30	NA 30 mg/kg x 1 p.o	"
BG00754	194905 AB	1562	3-10	MARKED AT 30	FULLY ACTIVE AT 10 mg/kg x 1 sc	Quinoline
			3-10	NIL AT 30	FULLY ACTIVE AT 10 mg/kg x 1 po	"
BH13989	233627AA	1563	10-30	NIL AT 30	FULLY ACTIVE AT 30 mg/kg x 1 sc	8-aminoquinoline
			10-30	NIL AT 30	FULLY ACTIVE AT 30 mg/kg x 1 po	"
BH49943	212293AB	1590	<30	NIL AT 30	FULLY ACTIVE AT 30 mg/kg x 1 sc	
			<30	NIL AT 30	FULLY ACTIVE AT 30 mg/kg x 1 po	
BH49596	233637AB	1591	—	—	NA 30 mg/kg x 1 sc	
			>30	NIL AT 30	ACTIVE AT 30 mg/kg x 1 po	

TABLE 7A

	WR No.	LIV No.	Minimum fully active dose (mg/kg x 1 s.c.)	Residual action at active dose	COMMENT	Type of Compound
BW67503	234749 AB	1641	–	–	NA 30 mg/kg x 1 sc	bispyrimidine
			–	–	NA 30 mg/kg x 1 po	"

Table 7B

	WR No.	LIV No.	Minimum fully active dose (mg/kg x 1)	Residual action at active dose	COMMENT	Type of Compound
BG 94907	231633 AA	1532	-	-	NA 30 mg/kg x 1 sc	8-aminoquinoline Amodiaquine analogue
			-	-	NA 30 mg/kg x 1 po	" "
BH 30097	150017 AC	1567	< 30	NIL AT 30	FULLY ACTIVE AT 30 mg/kg x 1 sc	Quinazoline antifol.
			< 30	TRACE AT 30	FULLY ACTIVE AT 30 mg/kg x 1 po	" "
BH 30104	155004 AC	1568	< 30	MARKED AT 30	MAINLY RESIDUAL ACTIVITY	" "
			< 30	NIL AT 30	FULLY ACTIVE AT 30 mg/kg x 1 p	" "
BH 57025	237233	1610	-	-	NA 30 mg/kg x 1 sc	Quinazolone
			-	-	NA 30 mg/kg x 1 po	"
BH 57043	237234	1611	-	-	NA 30 mg/kg x 1 sc	"
			-	-	NA 30 mg/kg x 1 po	"
BH 57052	237227	1612	-	-	NA 30 mg/kg x 1 sc	"
			-	-	NA 30 mg/kg x 1 po	"
BH 37514	235780	1585	-	-	NA 30 mg/kg x 1 sc	Furan derivative
			-	-	NA 30 mg/kg x 1 po	" "
BH 37532	235781	1586	-	-	NA 30 mg/kg x 1 sc	" "
			-	-	NA 30 mg/kg x 1 po	" "

TABLE 8A

	WR No.	LIV No.	Minimum fully active dose (mg/kg x 1)	Residual action at active dose	COMMENT	Type of Compound
AN 99850	156949	1618	-	-	NA 30 mg/kg x 1 sc	Pyridine
			-	-	NA 30 mg/kg x 1 po	"

TABLE 8B

CAUSAL PROPHYLAXIS TEST NO. BR 702 DATE 3/10/78

DRUG: I.V. 1531 WR 231350 AA BOTTLE NO. BQ 94630

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: [illegible] TIME AFTER INFECTION: 2 hr

VERTEBRATE HOST: CFW MICE PARASITE (SBM) SPECIES: P. [illegible] 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 $(h-f)-\left[\frac{(h-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	COMMENT
ϕ	5/5		5/5	5.05		4.41				
3.0	3/3			5.38					NIL	INACTIVE
10.0	3/3			6.23					NIL	INACTIVE
300	3/3			5.18		3.95		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 9A

CAUSAL PROPHYLAXIS TEST NO. BR 702 DATE: 3/10/78

DRUG: L.V.: 1531 WR 231350 AA BOTTLE NO.: BG 94630

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~s.c.~~ p.o. TIME AFTER INFECTION: 2 hrs

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 $(h - f) - \left\| \frac{(b-a)(e-a)}{(c-a)} - (b \quad a) \right\|$	Residual Activity	Prophylactic Activity	COMMENT
∅	5/5		5/5	5.05		4.41				
3.0	3/3			4.84					NIL	INACTIVE
10.0	3/3			5.22					NIL	INACTIVE
30.0	3/3			5.58		4.15		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 9B

CAUSAL PROPHYLAXIS TEST NO. BR752 DATE. 8/6/79

DRUG. I.V./ 1614 WR 237264 BOTTLE NO. BH 59392

PREPARATION: [illegible] H_2O ROUTE OF ADMINISTRATION: [illegible] TIME AFTER INFECTION: 2 h

VERTEBRATE HOST: O.F.W MICE PARASITE (SPECIES): P. [illegible] 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 $(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(h-a)\right]$	Residual Activity	Prophylactic Activity	COMMENT
Ø	8/8	3/3	5/5	4.87	4.12	4.12				
30.0	2/3		3/3	>8.46		3.68		NIL	3.59	ACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 10A

CAUSAL PROPHYLAXIS TEST NO. BQ753

DATE 8/6/79

DRUG: LEV 1614 WR 237264 BOTTLE NO. BH 57392

PREPARATION: [illegible] H2O

FOOT OF ADMINISTRATION: [illegible] p

TIME AFTER INFECTION: [illegible]

FEBRILE HOST: [illegible]

PARASITES IN [illegible]

SMEARS: [illegible]

DOSE mg/kg	PATENCY RATE C^o/T^o	XC	C^x/T^y	GMP % P f/l_1	b	c/e	(a - 2) ACTIVITY VALUES $(h-f)-\left\{(b-a)\frac{(r-n)}{(c-a)}-(b-a)\right\}$	Residual Activity	Prophylactic Activity	COMMENTS
Ø	5/5	3/3	5/5	5·26	3·73	3·73				
30·0	3/3		3/3	5·36		3·70		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 108

CAUSAL PROPHYLAXIS TEST NO. **BR752** DATE **8/6/79**

DRUG: LOT **1619** WR **236066** BOTTLE NO. **BH 39634**

PREPARATION: [illegible] H_2O TIME AFTER INFECTION: [illegible]

VERTEBRATE HOST: **O** [illegible] MICE PARASITE (SUB) SPECIES: P. [illegible] 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 $(h - f) - \left[\frac{(h-a)(e-a)}{(c-a)} - (b - a)\right]$	Residual Activity	Prophylactic Activity	COMMENT
Ø	8/8	3/3	5/5	4.87	4.12	4.12				
30·0	2/3		3/3	>8.63		3.70		NIL	3.76	ACTIVE

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

RESIDUAL ACTIVITY: **NIL AT 30 mg/kg x 1 s.c.**

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 11A

CAUSAL PROPHYLAXIS TEST NO: BR753 DATE: 8/6/79

DRUG: LIV/ 1619 WR 236066 BOTTLE NO. BH39634

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip/sc~~/po TIME AFTER INFECTION: 2 Hrs

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	$c/_e$	(α 2) ACTIVITY VALUES $(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	COMMENT
Ø	5/5	3/3	5/5	5.26	3.73	3.73				
30.0	2/3		3/3	>8.10		3.76		NIL	>2.84	ACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 11B

CAUSAL PROPHYLAXIS TEST NO. BR 113 DATE: 12/12/75

DRUG: L.V. 1633 WR 231530 AA BOTTLE NO. BG94916

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: s.c./p.o. TIME AFTER INFECTION: 2 Hrs

VERTEBRATE HOST: O'TEW 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	c/e	(a - 2) ACTIVITY VALUES $(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b\ a)\right]$	Residual Activity	Prophylactic Activity	COMMENT
Ø	2/4	3/3	5/5	4·88	4·15	4·12				
10.0	3/3			5·58					NIL	INACTIVE
30.0	2/3		3/3	>12·95		9·89	$>8.07-\left[\frac{2.15\times 7.89}{2.12}-2.15\right]$	5·86	2·21	MAINLY RESIDUAL ACTIVITY

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

RESIDUAL ACTIVITY: MARKED AT 30 mg/kg × 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 12A

CAUSAL PROPHYLAXIS TEST NO: BR715 DATE: 12/12/78

DRUG: L.V./ 1533 WR 231530 AA BOTTLE NO. BQ94916

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: [illegible] po. TIME AFTER INFECTION: 2 hrs

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 $(h-f)-\left\lvert\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\rvert$	Residual Activity	Prophylactic Activity	COMMENT
Ø	2/4	3/3	5/5	4.88	4.15	4.12				
3.0	3/3			5.45					NIL	INACTIVE
10.0	2/3		3/3	>8.66		7.64	$>3.78-\left[\frac{2.15\times 5.64}{2.12}-2.15\right]$	3.58	NIL	RESIDUAL ACTIVITY ONLY
30.0	2/3		3/3	>12.53		12.18	$>7.65-\left[\frac{2.15\times 10.18}{2.12}-2.15\right]$	8.18	NIL	RESIDUAL ACTIVITY ONLY

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

RESIDUAL ACTIVITY: MARKED AT 10 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 12B

CAUSAL PROPHYLAXIS TEST NO. BR715 DATE: 12/12/78

DRUG: L.V./ 1534 WR 225 449 AB BOTTLE NO. BG 94925

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: sc TIME AFTER INFECTION: 2 Hrs

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

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a - 2) ACTIVITY VALUES			COMMENT
	$C^o/_{T^o}$	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	2/4	3/3	5/5	4.88	4.15	4.12				
3.0	3/3			11.20						ACTIVE
10.0	0/3			>14						FULLY ACTIVE
30.0	0/3		1/3	>14		>12.66	$>9.12-\left[\frac{2.15 \times 10.66}{2.12}-2.16\right]$	8.67	0.45	MAINLY RESIDUAL ACTIVITY

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

RESIDUAL ACTIVITY: MARKED AT 30.0 mg/kg x1 sc

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 13A

CAUSAL PROPHYLAXIS TEST NO: BR 715 DATE: 12/12/78

DRUG: LW/ 1534 WR 225449 AB BOTTLE NO. BC, 94925

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~ip~~ po TIME AFTER INFECTION: 2 Hrs

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 $(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	COMMENT
Ø	2/4	3/3	5/5	4.88	4.15	4.12				
3.0	3/3			10.60						ACTIVE
10.0	2/2			14.30						FULLY ACTIVE
30.0	0/3		1/3	>14.00		>14.20	$>9.12-\left[\frac{2.15\times 12.20}{2.12}-2.15\right]$	>10.23	NIL	RESIDUAL ACTIVITY ONLY

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

RESIDUAL ACTIVITY: MARKED AT 30 mg/kg x 1 po

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 138

CAUSAL PROPHYLAXIS TEST NO. BR743 DATE. 4/4/79

DRUG. LIV/ 1560 WR 219423 AA BOTTLE NO. BE73480

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~ip/sc/po~~ TIME AFTER INFECTION: 2 Hrs

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

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a - 2) ACTIVITY VALUES			COMMENT
	$C^o/_{T^o}$	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	5·32		3·64				
3.0	0/3			>14						FULLY ACTIVE
10.0	0/3			>14						FULLY ACTIVE
30.0	0/3		3/3	>14		3·82		NIL	> 8·68	FULLY ACTIVE

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

RESIDUAL ACTIVITY:

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 14A

CAUSAL PROPHYLAXIS TEST NO: **BR 743** DATE: **4/4/79**

DRUG: LAV/ **1560** WR **219423 AA** BOTTLE NO. **BE 73480**

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~spray~~ po TIME AFTER INFECTION: 2 Hrs

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	COMMENT
~~Ø~~	5/5		5/5	5·32		3·64				
3·0	1/3			>11·14					> 5·32	ACTIVE
10·0	0/3			>14					> 8·68	FULLY ACTIVE
30·0	0/3		2/3	>14		3·52		NIL	> 8·68	FULLY ACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 14B

CAUSAL PROPHYLAXIS TEST NO: BR743 DATE: 4/4/79

DRUG: LIV/ 1561 WR 96345 AB BOTTLE NO. BC 65489

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ip/sc/po TIME AFTER INFECTION: 2 Hrs

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	COMMENT
Ø	5/5		5/5	5·32		3·64				
3.0	0/3			>14						FULLY ACTIVE
10.0	0/3			>14						FULLY ACTIVE
30.0	0/3			>14		>12.75				FULLY ACTIVE

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

RESIDUAL ACTIVITY: MARKED AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 15A

CAUSAL PROPHYLAXIS TEST NO: BR743 DATE: 4/4/79

DRUG: LIV/ 1561 WR 96345 AB BOTTLE NO. BC 65489

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip/sc~~/po TIME AFTER INFECTION: 2 Hrs

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 $(h-f)-\left\|\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\|$	Residual Activity	Prophylactic Activity	COMMENT
Ø	5/5		5/5	5·32		3·64				
3.0	2/3			5·37					NIL	INACTIVE
10.0	2/3			5·54					NIL	INACTIVE
30.0	3/3		3/3	6·12		3·63		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 15B

CAUSAL PROPHYLAXIS TEST NO. BR745 DATE 25/4/79

DRUG: Lot 1562 WR 194905 AB BOTTLE NO. BG00754

PREPARATION: [illegible] H2O ROUTE OF ADMINISTRATION: [illegible] TIME AFTER INFECTION: [illegible]

VERTEBRATE HOST: OF1 MICE PARASITE (STRAIN) SPECIES: P. [illegible] STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP % P			(a - 2) ACTIVITY VALUES			COMMENT
	C^o/T^o	XC	C^x/T^x	f/l_1	b	c/e	$(h-f)-\left[\frac{(b-a)(\epsilon-a)}{(c-a)}-(h-a)\right]$	Residual Activity	Prophylactic Activity	
ø	4/4		5/5	5.04		3.87				
3.0	0/3			>14						FULLY ACTIVE
10.0	0/3			>14						FULLY ACTIVE
30.0	0/3		0/3	>14		>14				FULLY ACTIVE

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

RESIDUAL ACTIVITY: MARKED AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 16A

CAUSAL PROPHYLAXIS TEST NO. BR745 DATE 25/4/79

DRUG: LOT 1562 WR 194905 AB BOTTLE NO. BQ00754

PREPARATION: [illegible] H_2O ROUTE OF ADMINISTRATION: [illegible] p. TIME AFTER INFECTION: 24 h

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SSM) SPECIES: P. [illegible] STRAIN: NLG

DOSE mg/kg	PATENCY RATE C°/T°	XC	C^x/T^x	GMP 2% P f/h	b	c/e	(a - 2) ACTIVITY VALUES (h - f) - [(b - a)(e - a)/(c - a) - (b - a)]	Residual Activity	Prophylactic Activity	COMMENT
Ø	4/4		5/5	5.04		3.87				
3.0	2/3			>8.16					>3.11	ACTIVE
10.0	0/3			>14					>8.96	FULLY ACTIVE
30.0	0/3		3/3	>14		4.58		NIL	>8.96	FULLY ACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 168

CAUSAL PROPHYLAXIS TEST NO BR745 DATE 25/4/79

DRUG: Lot 1563 WR 233627 AA BOTTLE NO: BH13989

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

VERTEBRATE HOST: O TEW MICE PARASITE (SPM) SPECIES: P. [illegible] STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a - 2) ACTIVITY VALUES			COMMENT
	C^o/T^o	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left[\frac{(h-a)(e-a)}{(c-a)}-(h-a)\right]$	Residual Activity	Prophylactic Activity	
Ø	4/4		5/5	5.04		3.87				
3.0	3/3			4.84					NIL	INACTIVE
10.0	3/3			5.66					NIL	INACTIVE
30.0	0/3		3/3	>14		4.54		NIL	>8.96	FULLY ACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 sc.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 17A

CAUSAL PROPHYLAXIS TEST NO. **BR 745** DATE: **25/4/79**

DRUG: L.V./ **1663** WR **233627 AA** BOTTLE NO. **BH 13989**

PREPARATION: Water 60 H_2O ROUTE OF ADMINISTRATION: p.o. TIME AFTER INFECTION: 24 hr

VERTEBRATE HOST: O.F.W. MICE PARASITE (S.M.) SPECIES: P. yoelii 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 $(h-f)-\left\|\frac{(b-a)(e-a)}{(c-a)}-(h-a)\right\|$	Residual Activity	Prophylactic Activity	COMMENT
Ø	4/4		5/5	5.04		3.87				
3.0	3/3			5.14					NIL	INACTIVE
10.0	2/3			>8.07					> 3.03	ACTIVE
30.0	0/3		3/3	>14		4.29		NIL	> 8.96	FULLY ACTIVE

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

RESIDUAL ACTIVITY: **NIL AT 30 mg/kg x 1 p.o.**

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 17B

CAUSAL PROPHYLAXIS TEST NO. BR752 DATE: 8/6/79

DRUG: I.V.: 1590 WR 212293 AB BOTTLE NO.: BH49943

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

VERTEBRATE HOST: C.F.W. MICE PARASITE (S.M.) SPECIES: P. [illegible] STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^a/T^a	XC	C^x/T^y	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	COMMENT
Ø	8/8	3/3	5/5	4.87	4.12	4.12				
30.0	0/3		3/3	>14		4.18		NIL	>9.13	FULLY ACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 18A

CAUSAL PROPHYLAXIS TEST NO. BR 753 DATE. 8/6/79

DRUG. I.V./ 1590 WR 212293 AB BOTTLE NO. BH 49943

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: p.o. TIME AFTER INFECTION: 24 hrs

VERTEBRATE HOST: O.F.W. MICE PARASITE (SUB) SPECIES: P. [illegible] STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP % P			(a = 2) ACTIVITY VALUES			COMMENT
	C^o/T^o	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\left[\frac{(b-a)(e-a)}{(c-a)}-(h-a)\right]$	k critical Activity	Prophylactic Activity	
Ø	5/5	3/3	5/5	5·26	3.73	3.73				
30.0	0/3		3/3	>14		3.70		NIL	>8.74	FULLY ACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 18B

CAUSAL PROPHYLAXIS TEST NO. BR752 DATE 8/6/79

DRUG: L.V. 1591 WR 233637 AB BOTTLE NO. BH 49596

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

VERTEBRATE HOST: O.F.W. MICE PARASITE (S.M.) SPECIES: P. [illegible] 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	COMMENT
Ø	8/8	3/3	5/5	4.87	4.12	4.12				
30.0	3/3		3/3	5.10		4.44		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x1 s.c.

INVESTIGATOR: PROFESSOR W. PETERS

TABLE 19A

CAUSAL PROPHYLAXIS TEST NO: BR753 DATE: 8/6/79

DRUG: Lot 1581 WR 233637 AB BOTTLE NO: BH49596

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: p TIME AFTER INFECTION: 2 h

VERTEBRATE HOST: O TPW MICE PARASITE (SUB) SPECIES: P. [illegible] STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P				(a 2) ACTIVITY VALUES			COMMENT
	C^o/T^o	XC	C^x/T^x	f/h	b	c/e	$(h-f)-\frac{(b-a)(e-a)}{(c-a)}-(b\ a)$	Residual Activity	Prophylactic Activity	
Ø	5/5	3/3	5/5	5·26	3·73	3·73				
30·0	3/3		3/3	6·88		4·40		NIL	1·62	ACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg × 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 19B

CAUSAL PROPHYLAXIS TEST NO **BR 752** DATE **8/6/79**

DRUG. L.V. **1641** WR **234749 AB** BOTTLE NO. **BH67503**

PREPARATION. In ca. 60% H_2O ROUTE OF ADMINISTRATION: + / + TIME AFTER INFECTION: 2 hr

VERTEBRATE HOST: **O.F.W. MICE** PARASITE (SEX) SPECIES: P. [illegible] 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 $(h-f)-\left[\frac{(h-a)(e-a)}{(c-a)}-(b-a)\right]$	Residual Activity	Prophylactic Activity	COMMENT
Ø	8/8	3/3	5/5	4.87	4.12	4.12				
30.0	3/3		3/3	4.88		4.29		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: **NIL AT 30 mg/kg x1 s.c.**

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 20A

CAUSAL PROPHYLAXIS TEST NO: BR 753 DATE: 8/6/79

DRUG: LIV/ 1641 WR 234749 AB BOTTLE NO. BH 67503

PREPARATION: Tween 80/H_2O ROUTE OF ADMINISTRATION: ~~ip/se~~/po TIME AFTER INFECTION: 2 Hrs

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

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a = 2) ACTIVITY VALUES			COMMENT
	$C^o/_{T^o}$	XC	$C^x/_{T^x}$	$f/_h$	b	$c/_e$	$(h-f)-\left\lvert\frac{(b-a)(c-a)}{(c-a)}-(b-a)\right\rvert$	Residual Activity	Prophylactic Activity	
Ø	5/5	3/3	5/5	5.26	3.73	3.73				
30.0	3/3		3/3	4.94		3.87		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 20B

CAUSAL PROPHYLAXIS TEST NO: BR702 DATE: 3/10/78

DRUG: L.V.: 1632 WR 231633 AA BOTTLE NO.: BG 94907

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: [illegible] TIME AFTER INFECTION: 24h

VERTEBRATE HOST: O TEW MICE PARASITE (SUB) SPECIES: P. [illegible] 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	COMMENT
Ø	5/5		5/5	5.05		4.41				
3.0	3/3			5.17					NIL	INACTIVE
10.0	3/3			4.92					NIL	INACTIVE
30.0	3/3		3/3	5.09		3.95		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 sc

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 21A

CAUSAL PROPHYLAXIS TEST NO BR702 DATE 3/10/78

DRUG: L.V.' 1532 WR 231633 AA BOTTLE NO. BG 94907

PREPARATION: Tween 80 H_2O ROUTE OF ADMINISTRATION: [illegible] TIME AFTER INFECTION: 2 Hrs

VERTEBRATE HOST: ♂ TFW MICE PARASITE (SUB) SPECIES: P. [illegible] 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	COMMENT
Ø	5/5		5/5	5.05		4.41				
3.0	3/3			5.03					NIL	INACTIVE
10.0	3/3			4.79					NIL	INACTIVE
30.0	3/3		3/3	5.26		3.95		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 21B

CAUSAL PROPHYLAXIS TEST NO. BR752 DATE. 8/6/79

DRUG: LOT 1567 WR 150017 AC BOTTLE NO. BH30097

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

VERTEBRATE HOST: OTEW MICE PARASITE (SUB) SPECIES: P. [illegible] STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a - 2) ACTIVITY VALUES			COMMENT
	C^c/T^n	XC	C^x/T^y	f/h	b	c/e	$(h-f)-\left\{\frac{(h-a)(e-a)}{(c-a)}-(b-a)\right\}$	Residual Activity	Prophylactic Activity	
Ø	8/8	3/3	5/5	4.87	4.12	4.12				
30.0	0/3			>14		4.15		NIL	> 9.13	FULLY ACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 s.c.

INVESTIGATOR: PROFESSOR W. PETERS

TABLE 22A

CAUSAL PROPHYLAXIS TEST NO. BR763 DATE. 8/6/79

DRUG. I.V.: 1567 WR 150017 AC BOTTLE NO.: BM 30097

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

VERTEBRATE HOST: OTTAWA MICE PARASITE (SUB) SPECIES: P. [illegible] 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 $(h-f)-\left[\frac{(h-a)(e-a)}{(c-a)}-(h\ a)\right]$	Residual Activity	Prophylactic Activity	COMMENT
Ø	5/5	3/3	5/5	5.26	3.73	3.73				
30.0	0/3	·	3/3	>14		5.26	$>8.74-\left[\frac{1.73\times3.26}{1.73}-1.73\right]$	1.53	> 7.21	FULLY ACTIVE

MINIMUM FULLY ACTIVE DOSE <30 mg/kg

RESIDUAL ACTIVITY: TRACE AT 30 mg/kg

[illegible] INVESTIGATOR: PROFESSOR W. PEIERS

TABLE 22B

CAUSAL PROPHYLAXIS TEST NO. BR752 DATE 8/6/79

DRUG: I.V. 1568 WR 155004-AC BOTTLE NO. BH30104

PREPARATION: [illegible] H_2O ROUTE OF ADMINISTRATION: [illegible] TIME AFTER INFECTION: 2 [illegible]

VERTEBRATE HOST: OF1 MOUSE PARASITE (SPH) SPECIES: P. [illegible] 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 $(h-f)-\left[\frac{(b-a)(e-a)}{(s-a)}-(h-a)\right]$	Residual Activity	Prophylactic Activity	COMMENT
∅	8/8	3/3	5/5	4.87	4.12	4.12				
30.0	0/3			>14		>14	$>9.13-\left[\frac{2.12\times12.0}{2.12}-2.12\right]$	>9.88	NIL	FULLY ACTIVE. ALL ACTIVITY RESIDUAL ?

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

RESIDUAL ACTIVITY: MARKED AT 30 mg/kg x 1 s.c.

TECHNICAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 23A

CAUSAL PROPHYLAXIS TEST NO: BR 753 DATE: 8/6/79

DRUG: I.V.: 1568 WR 155004 AC BOTTLE NO.: BH 30104

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~s.c.~~ p.o. TIME AFTER INFECTION: 2 hrs

VERTEBRATE HOST: 6 TEW MICE PARASITE (SUB) SPECIES: P. c. 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	COMMENT
Ø	5/5	3/3	5/5	5.26	3.73	3.73				
30.0	0/3		3/3	>14		4.59		NIL	>8.74	Fully Active

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 po

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 23B

CAUSAL PROPHYLAXIS TEST NO. BR752 DATE 8/6/79

DRUG: LAY 1610 WR 237233 BOTTLE NO. BH57025

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

VERTEBRATE HOST: O TEW MICE PARASITE (SUB) SPECIES: P. [illegible] 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	COMMENT
Ø	8/8	3/3	5/5	4.87	4.12	4.12				
30.0	3/3		3/3	5.14		3.91		NIL	NIL	INACTIVE

MINIMUM FULLY ACTIVE DOSE .... [illegible] ..... mg/kg

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 24A

CAUSAL PROPHYLAXIS TEST NO BR753 DATE 8/6/79

DRUG: I.V./ 1610 WR 237233 BOTTLE NO. BH57025

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: p.o. TIME AFTER INFECTION: 2 hrs

VERTEBRATE HOST: OTFW MICE PARASITE (SUB) SPECIES: P. [illegible] 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 $(h-f)-\left\|\frac{(h-a)(e-a)}{(c-a)}-(h-a)\right\|$	Residual Activity	Prophylactic Activity	COMMENT
Ø	5/5	3/3	5/5	5.26	3.73	3.73				
30.0	3/3		3/3	5.79		4.28		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 24B

CAUSAL PROPHYLAXIS TEST NO. BR752 DATE: 8/6/79

DRUG: I.V./ 1611 WR 237234 BOTTLE NO: BH57043

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

VERTEBRATE HOST: C.F.W MICE PARASITE (STAGE) SPECIES: P. [illegible] STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2% P			(a - 2) ACTIVITY VALUES			COMMENT
	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	8/8	3/3	5/5	4.87	4.12	4.12				
30.0	3/3		3/3	4.98		3.72		NIL	NIL	INACTIVE

MINIMUM FULLY ACTIVE DOSE .... [illegible] ..... mg/kg

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 25A

CAUSAL PROPHYLAXIS TEST NO. BR753 DATE 8/6/79

DRUG: I.V. 1611 WR 237234 BOTTLE NO. BH57043

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: p TIME AFTER INFECTION: 2 h

VERTEBRATE HOST: O.F.W. MICE PARASITE (SEX, SPECIES): P. [illegible] STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^o/T^o	XC	C^x/T^x	GMP 2% P $f_{/h}$	r	$^c/_e$	(0 2) ACTIVITY VALUES $(h-f)-\left[\frac{(b-a)(c-a)}{(c-a)}-(b\ a)\right]$	Residual Activity	Prophylactic Activity	COMMENT
Ø	5/5	3/3	5/5	5·26	3·73	3·73				
30·0	3/3		3/3	5·44		3·61		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 25B

CAUSAL PROPHYLAXIS TEST NO. BR 752 DATE. 8/6/79

DRUG. I.V. 1612 WR 237227 BOTTLE NO. BH57052

PREPARATION: Tween 80 H_2O ROUTE OF ADMINISTRATION: [illegible] TIME AFTER INFECTION: 2 hr

VERTEBRATE HOST: OTTAWA MICE PARASITE (S.M) SPECIES: P. [illegible] STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^o/T^o	XC	C^x/T^y	GMP 2% P f/h	b	c/e	(a 2) ACTIVITY VALUES $(h-f)-\left[\frac{(h-g)(e-a)}{(e-a)}-(b\ a)\right]$	Residual Activity	Prophylactic Activity	COMMENT
Ø	8/8	3/3	5/5	4.87	4.12	4.12				
30.0	3/3		3/3	5.26		3.58		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 26A

CAUSAL PROPHYLAXIS TEST NO. BR753 DATE. 3/6/79

DRUG. UV/ 1612 WR 237227 BOTTLE NO. BH57052

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

VERTEBRATE HOST: [illegible] PARASITE [illegible] STRAIN: [illegible]

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	COMMENT
Ø	5/5	3/3	5/5	5·26	3·73	3·73				
30·0	3/3		3/3	5·31		3·67		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 26B

CAUSAL PROPHYLAXIS TEST NO. BR 752 DATE. 8/6/79

DRUG. L.V. 1585 WR 235780 BOTTLE NO. BH37514

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

VERTEBRATE HOST: C3H/HeN MICE PARASITE (STRAIN) SPECIES: P. [illegible] 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 $(h-f)-\left\lvert\frac{(b-a)(e-a)}{(c-a)}-(b-a)\right\rvert$	Residual Activity	Prophylactic Activity	COMMENT
Ø	8/8	3/3	5/5	4.87	4.12	4.12				
30.0	3/3		3/3	5.02		4.14		NIL	NIL	INACTIVE

MINIMUM FULLY ACTIVE DOSE .... [illegible] ..... mg/kg

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 27A

CAUSAL PROPHYLAXIS TEST NO. BR753 DATE. 8/6/79

DRUG. I.V./ 1685 WR 235780 BOTTLE NO. BH 37514

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: ~~i.v./~~p.o. TIME AFTER INFECTION: 2 d

VERTEBRATE HOST: ♂ TFW MICE PARASITE (S.M.) SPECIES: P. c. vinckei 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	COMMENT
Ø	5/5	3/3	5/5	5·26	3·73	3·73				
30·0	3/3		3/3	5·72		3·67		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg × 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 27B

CAUSAL PROPHYLAXIS TEST NO. BR752 DATE: 8/6/79

DRUG: I.V./ 1586 WR 235781 BOTTLE NO. BH37532

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: s.c. TIME AFTER INFECTION: 2 hr

VERTEBRATE HOST: OTFW MICE PARASITE (STAGE) SPECIES: P. c. nigeriense STRAIN: NIG

DOSE mg/kg	PATENCY RATE C^o/T^o	XC	C^x/T^y	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	COMMENT
Ø	8/8	3/3	5/5	4.87	4.12	4.12				
30.0	3/3			4.64		3.48		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 28A

CAUSAL PROPHYLAXIS TEST NO: BR 753 DATE: 8/6/79

DRUG: I.V. 1586 WR 235781 BOTTLE NO: BH 37532.

PREPARATION: Tween 80, H_2O ROUTE OF ADMINISTRATION: p TIME AFTER INFECTION: 2 hr

VERTEBRATE HOST: OF1 MICE PARASITE (S.M) SPECIES: P. [illegible] 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	COMMENT
∅	5/5	3/3	5/5	5.26	3.73	3.73				
30.0	3/3		3/3	5.06		3.80		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg × 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 28B

CAUSAL PROPHYLAXIS TEST NO. BR752 DATE 8/6/79

DRUG: I.V.: 1618 WR 156949 BOTTLE NO.: AV99850

PREPARATION: Lact. 60, H_2O ROUTE OF ADMINISTRATION: [illegible] TIME AFTER INFECTION: [illegible]

VERTEBRATE HOST: OTFW MICE PARASITE (SUB) SPECIES: P. [illegible] 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	COMMENT
Ø	8/8	3/3	5/5	4.87	4.12	4.12				
30.0	3/3		3/3	5.75		3.76		NIL	NIL	INACTIVE

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

RESIDUAL ACTIVITY: NIL AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 29A

CAUSAL PROPHYLACTIC TEST NO. **BR 753** | DATE **8/6/79**

[illegible] **1618** | [illegible] **156949** | BOTTLE NO. **AV 99850**

[illegible]

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

RESIDUAL ACTIVITY: **NIL AT 30 mg/kg x 1 p.o.**

DOSE mg/kg	PATENCY RATE			GMP 2% P			ACTIVITY VALUES			COMMENT
	C	XC	C^x/T^x	t/h	b	c/a	(b − f) − [(b − a)(c − a)/(c − a)] − (b − a)	Causal Activity	Prophylactic Activity	
Ø	5/5	3/3	5/5	5.26	3.73	3.73				
30.0	3/3		3/3	5.86		3.67		NIL	NIL	INACTIVE

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

TABLE 29B

		Sulphadiazine					
LIV/1342 s.c. WR158122		Ø	0.03	0.1	0.3	1.0	ED_{90}
	Ø		91.6±3.9	73.7±4.1	2.2±1.1	0.3±0.3	0.25
	0.03	87.2±4.4	69.2±5.0	4.1±2.5	0	0	0.08
	0.1	78.3±1.9	12.7±2.3	0	0	0	0.03
	0.3	71.8±4.7	5.9±8.3	0	0	0	0.02
	1.0	0	0	0	0	0	-
	ED_{90}	0.5	0.1	0.02	-	-	

TABLE 30

ED_{90} values of sulphadiazine and WR 158122, alone or in various combinations against N strain P. berghei in the 4-day test in mice. Note the marked potentiation.

RC	Chloramphenicol s.c.						
Chloroquine sc		Ø	30.0	100.0	300.0	600.0	ED_{90}
	Ø		92.3±8.9	100±16.3	94.4±6.4	75.9±9.4	
	3.0	65.7±7.9	100	100± 7.4	100±0.5	91.3±4.4	
	10.0	100±4.4	100±2.5	91.3±5.4	91.3±5.4	69.8±10.3	
	30.0	100±7.4	59.5±10.3	51.3±10.8	41.0±3.9	36.9±12.8	
	60.0	62.6±14.8	50.3±6.9	62.6±9.9	57.4±3.9	54.4±11.8	
	ED_{90}						

TABLE 31

ED_{90} values of chloramphenicol and chloroquine alone or in various combinations and RC line P. berghei in the 4-day test in mice. Note the complete lack of potentiation.

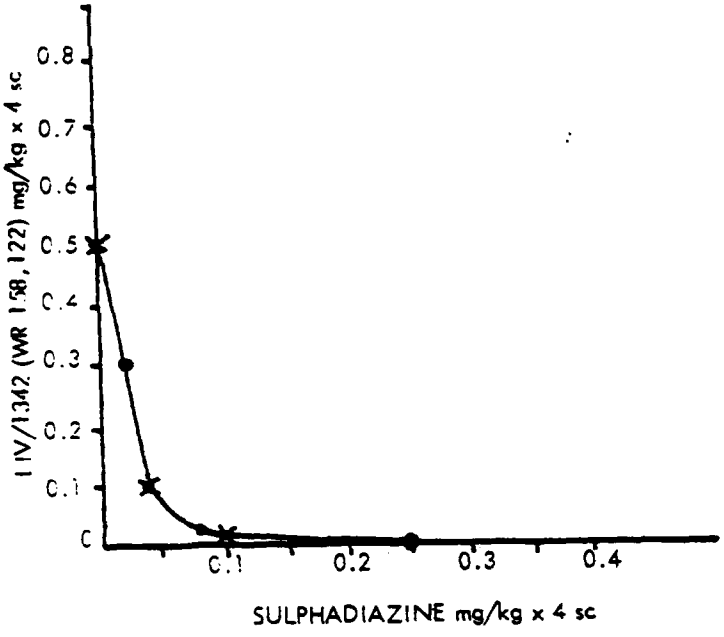

FIGURE 1

WR 158,122 and sulphadiazine - ED_{90} values when compounds are used alone or in combination in varying proportions. (See data in Table 67). The graph shows a very strong potentiation between the two compounds.

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