

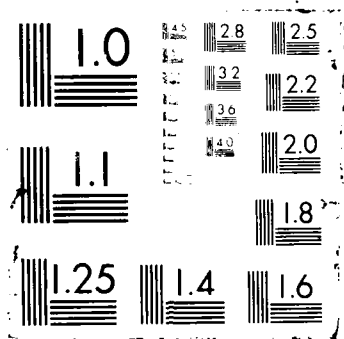
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CHEMOTHERAPY OF RODENT MALARIA

FINAL REPORT

WALLACE PETERS MD DSc

JULY 1985

Supported by

US ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

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1. INTRODUCTION

During the first half of the period since the submission of the Final Report for DAMD-17-83-G-9518, the emphasis of our studies was on vector orientated investigations of causal prophylactic, gametocytocidal and sporontocidal activity. However, in August 1984, it became necessary to close the Winches Farm insectaries as the Anopheles stephensi colony had become infected with a microsporidian parasite Pleistophora (Vavraia) culicis. Since there is no practical way of eliminating this organism from an infected colony, it was decided that this essential closure should be used as an opportunity to refurbish the insectaries and install an effective environmental control system. During the course of this work, it was found that a considerable amount of building repair was needed as the roof timbers were affected by dry rot. This work is now complete and it is anticipated that mosquito linked studies will recommence within the next two months.

The latter part of the contract period and the three months between the conclusion of the extension period and the commencement of the new contract has been concerned primarily with blood schizontocidal activity and in particular with studies on the development of resistant strains. Rodent malaria strains resistant to Halofantrine and to quinine have been developed and these will be included in future blood schizontocidal activity tests.

2. ADMINISTRATIVE EVENTS

Staff employed on US Army funds are as follows:

Senior Technologist/ Research Assistant	- Mr B L Robinson	50 % time
Junior technician	- Ms A West	100 % time
Junior technician	- Ms J R Cox	100 % time
Secretary	- Mrs T Sargeaunt	25 % time

Other staff associated with the project but paid from from London School sources are:

Professor W Peters (Principal Investigator)	20% time
Dr D C Warhurst (Biologist)	20% time
Dr D S Ellis (Electron Microscopist)	10% time
Dr W E Ormerod (Biologist-Pharmacologist)	20% time

In the period covered by the contract we have received seven compounds from WRAIR (including an additional supply of Halofantrine for resistance studies).

The collection of cryopreserved strains of rodent malaria continues to expand with the inclusion of strains resistant to Halofantrine, quinine and artemisinin. In addition, we are producing clones of our standard strains which are being included. Lysates have now been prepared from many of the stabilates for use in isoenzyme characterization studies. When completed, these studies will allow us to use defined cloned strains in our test systems.

Currently we have a battery of thirteen strains (derived from Plasmodium berghei or P.yoelii), which are resistant to

standard antimalarials, and one drug-sensitive P.berghei available for use in blood schizontocidal tests. Studies involving mosquito and exo-erythrocytic stages will in future employ P.yoelii 17X as well as P.y.nigeriensis.

An official visit was made to the School and Field Station by Dr Ho Chung and Ms Maxine Losee of USAMRDC in June 1984.

A close liaison has been maintained between the Principal Investigator and Colonel Davidson of WRAIR.

3. CHEMOTHERAPY STUDIES

3.1 Blood schizontocides

Data are summarised in Table 15 and detailed report sheets are appended as Tables 16 through 21.

3.1.1 WR 251855 AA

This lepidine, an analogue of primaquine, is very active against the drug-sensitive N strain of P.berghei possessing an ED₉₀ of 0.67 mg/kg X 4 sc. Further studies, involving our full battery of resistant lines, are to be carried out and results will be included in a subsequent report.

3.1.2 BK 74491 (WR number not known)

This compound has an ED₉₀ of 3.4 mg/kg X 4 sc against P.berghei N strain, a level of activity comparable with that of primaquine. Further studies involving the resistant lines are scheduled.

3.1.3 BK 73127 (WR number not known)

BK 73127 is slightly more active than the preceding compound against the N strain with an ED₉₀ of 2.1 mg/kg X 4 sc. Data from tests with resistant lines will be included in a later report.

3.1.4 Amodiaquine

In view of a recent resurgence of interest in this compound, it was decided to examine amodiaquine for activity against some of our resistant lines. In the drug sensitive N strain amodiaquine has an ED₉₀ of 2.7 mg/kg X 4 sc, a value very similar to that of chloroquine.

When used against the moderately chloroquine-resistant NS line, the ED₉₀ value increased significantly to 25.5 mg/kg - a resistance factor of 9.4. Our highly chloroquine-resistant RC strain was also highly resistant to amodiaquine, the resistance factor being considerably in excess of 22 (ED₉₀ = >60 mg/kg). A similar result was obtained with the quinine-resistant N/1923 strain where the ED₉₀ was also in excess of 60 mg/kg.

The mefloquine-resistant N/1100 line was also markedly insensitive to amodiaquine and the ED₉₀ against this strain was 75 mg/kg X 4 sc. This represents a resistance factor of 27.8 for the N/1100 when compared with N strain.

3.2 Causal prophylaxis

Causal prophylactic test data for 8-aminoquinolines and quinine analogues are summarised in Tables 1 and 2, detailed results from all tests are included in Tables 22 through 34.

3.2.1 Putative metabolites and analogues of primaquine

Results of earlier studies on all of the above compounds, with the exception of RCGJM-97, have been reported previously and the current tests have been performed to confirm earlier conclusions or to extend the dose range. The results obtained with WR 6890 and 15081 confirm our earlier findings of activity and illustrate the slightly lower level of activity of WR6890.

TABLE 1 A summary of causal prophylactic activity in some 8-aminoquinolines.

LON	WR Number	MFED	Residual activity
1801	15081	10 - 30	Nil at 30
1802	6890	30 - 100	Nil at 100
1877	199508AD	> 100	Nil at 100
1783	ANC-IX-19	Inactive at 100	Nil at 100
1908	RCGJM-97	30 - 100	Present at 30

MFED = Minimum fully effective dose. All doses expressed in mg/kg.

WR 199508 AD and the McChesney compound, ANC-IX-19, have been examined at higher dose levels and slight activity at 100 mg/kg is demonstrable with WR 199508 AD. No evidence of activity was found at this dose with ANC-IX-19.

A further compound, RCGJM-97 (3-bromo-primaquine, received from Dr McChesney) was found to be fully active at 100 mg/kg but this activity is at least partially due to the residual action of the compound.

3.2.2 Quinine analogues

These four quinine analogues showed no significant activity at 100 mg/kg in our preliminary tests (previously reported). In the current studies at higher dosage, Ph 4007 and pH 4901 show activity at 300 mg/kg associated with residual activity in the

case of Ph 4007. Neither Ph 4017 nor Ph 4900 show any activity at 300 mg/kg.

TABLE 2 A summary of causal prophylactic activity of four quinine analogues.

LON	WR Number	MFED	Residual activity
1884	Ph 4007	> 300	Nil at 300
1885	Ph 4017	Inactive at 300	Nil at 300
1886	Ph 4900	Inactive at 300	Nil at 300
1887	Ph 4901	> 300	Nil at 300

3.2.3 Floxacrine analogue

The floxacrine analogue, WR 250547 AA, had previously been reported to be fully active at 3 mg/kg with evidence of residual activity being present. From the new data presented here it is apparent that residual activity is the major component in the overall activity. At a dose of 1 mg/kg the residual element accounts for all the demonstrable activity. The minimum fully effective dose in the causal prophylaxis test is the same as that of floxacrine (1.0 - 3.0 mg/kg x 1 sc).

3.2.4 Antibiotics

In the preliminary causal prophylactic test, spiramycin has a minimum fully effective dose of 30 - 100 mg/kg. Lincomycin hydrochloride was less active (MFED = > 100 mg/kg). Both of these compounds are to be re-examined, when causal prophylactic testing recommences, to establish the presence or absence of residual

activity.

3.3 Gametocytocidal activity

Data from gametocytocidal activity tests are summarised in Tables 3 to 7 and detailed results are given in Tables 35 through 61. An innovation in this test system is the inclusion of a GD (gametocytocidal dose)₅₀ and GD₉₀ obtained from a dose response curve plotted on log : probit graph paper. The GD₉₀ is compared with that of primaquine and expressed as a Primaquine Index (PI₉₀).

3.3.1 8-aminoquinolines

Twelve 8-aminoquinolines, including primaquine diphosphate, have been examined in the gametocytocidal activity test. Primaquine was included as a reference standard for use with all tests and was found to have a GD₉₀ of 33 mg/kg. This value has been used throughout for calculation of Primaquine Indices.

WR 182234 and WR 211814 were found to be almost as active as primaquine with PI₉₀ values of 0.9 and 0.6 respectively. WR 228708 was the only other 8-aminoquinoline to show a reasonable degree of activity (PI₉₀ = 0.24). The remaining eight compounds in this group were all appreciably less active.

TABLE 3 Gametocytocidal activity of 8-aminoquinolines.

WR	BN	LON	GD ₅₀	GD ₉₀	PI ₉₀
2975AW ¹	BJ 08241	1711	1.3	33.0	1.0
182234	BE 17580	1720	12.3	38.5	0.86
211814	ZP 12775	1721	8.0	59.0	0.56
215295	ZN 43444	1722	230	1100*	0.03
238605	BH 69990	1727	135	2700*	0.01
243789	BJ 08189	1728	150	950*	0.03
246315	BJ 45691	1729	27.0	1100*	0.03
247705	BJ 51779	1730	300	3900*	<0.01
248412	BJ 59202	1731	>300	>>300	<<0.1
237375	BH 58120	1732	60.0	3500*	<0.01
228708	BG 66798	1733	36.0	138	0.24
194343	ZN 41968	1751	>300	>>300	<<0.1

¹ Primaquine dipnosphate; * = interpolated graphically

3.3.2 Primaquine metabolites

TABLE 4 Gametocytocidal activity of some primaquine analogues.

WR	BN	LON	GD ₅₀	GD ₉₀	PI ₉₀
ANC-IX-19 ¹	(McChesney)	1783	180	440	0.08
249725	BK 69990	1931	NA100	-	-
15081	AY 15653	1801	>300	>>300	<<0.1
6890	BK 12713	1802	100	340	0.1
RCGJM-53 ²	(McChesney)	1810	105	460	0.07
199508 AD	BK 56500	1877	220	3250*	0.01

¹ = WR 249725; ² = WR 199507 (5-hydroxyprimaquine)

NA = no activity; * = interpolated graphically

None of the six primaquine metabolites examined possess any marked degree of gametocytocidal activity. The best of these, WR 6890, had a PI₉₀ of 0.1.

3.3.3 Quinine analogues

TABLE 5 Gametocytocidal activity of some quinine analogues.

WR	BN	LON	GD ₅₀	GD ₉₀	PI ₉₀
Ph 4007	BK 64306	1884	31.0	365	0.09
Ph 4017	BK 64315	1885	20.0	90.0	0.37
Ph 4900	BK 64324	1886	13.5	92.0	0.36
Ph 4901	BK 64333	1887	>300	>>300	<<0.1

Our earlier observation of activity with the four quinine analogues has been confirmed in the current series of tests. The least active of the four was Ph 4901 and the flat nature of the dose response curve precluded us from obtaining a meaningful GD_{90} . A little more active was Ph 4007 with a GD_{90} of 365 (PI_{90} = 0.09) but Ph 4017 and Ph 4900 were very much more active. Ph 4017 had a GD_{90} of 90.0 mg/kg (PI_{90} = 0.37) and Ph 4900 had the same degree of activity with a GD_{90} of 92.0 mg/kg (PI_{90} = 0.36).

3.3.4 Floxacrine analogues

TABLE 6 Gametocytocidal activity of two floxacrine analogues.

WR	BN	LON	GD_{50}	GD_{90}	PI_{90}
245082	BK 02771	1752	70.0	2100*	0.02
246976	BK 02780	1753	11.0	255	0.13

* = interpolated graphically

Two floxacrine analogues, WR 245082 and WR 246976, have been examined for gametocytocidal activity. WR 246976 has approximately six times the activity of WR 245082 (PI_{90} values are 0.13 and 0.02 respectively).

3.3.5 Quinolines/quinoline-methanols

One quinoline-methanol, mefloquine, and two quinolines were tested in the gametocytocidal test system. Neither of the quinolines, WR 44450 AD and WR 102796 AD, show high levels of activity, and although mefloquine was active in this system, the GD_{90} level was not reached in this test. Further investigations of mefloquine and other amino-alcohols are planned.

TABLE 7 Gametocytocidal activity of mefloquine and two quinolines.

WR	BN	LON	GD ₅₀	GD ₉₀	PI ₉₀
44450 AD	AY 29540	1740	215	2000*	0.02
102796 AD	BC 78878	1741	34.0	>300	<0.1
142490 ¹	BH 10371	1100	11.0	>60	<0.55

¹ Mefloquine ; * graphically interpolated

3.4 Sporontocidal activity

Summarised results are included in Tables 8 through 14 and detailed test results are presented in Tables 62 through 101. As with the gametocytocidal test, it should be possible to quantify the sporontocidal effect and express it as a sporontocidal dose (SD₅₀ and SD₉₀) when an extended test is done. In the current report, however, we are presenting preliminary test data and activity in this single dose test can only be expressed qualitatively. Since no positive drug control has been included in this preliminary test series, and no extended dose range tests have yet been performed, the classification of activity is necessarily arbitrary. Further studies may indicate that other contributory factors, such as generalised cytotoxicity, are playing a significant part in oocyst suppression and the criteria currently employed in determining activity levels may require revision. Full tests, using an extended dose range and including pyrimethamine and/or cycloguanil as positive drug controls, will be performed on those compounds which have shown activity in the preliminary test.

3.4.1 8-aminoquinolines

TABLE 8 Sporontocidal activity of 8-aminoquinolines.

WR	BN	LON	ACTIVITY	% SUPPRESSION
225448 AG	BH 58522	1709	INACTIVE	15.1
5990	AG 99266	1715	ACTIVE	43.4
181023	BE 50003	1719	SLIGHTLY ACTIVE	39.1
182234	BE 17580	1720	INACTIVE	9.8
211814	ZP 12775	1721	SLIGHTLY ACTIVE	27.7
215295	ZN 43444	1722	ACTIVE	41.5
228000	ZN 81499	1723	INACTIVE	14.5
228583	ZN 78910	1724	ACTIVE	51.7
233627	BH 13989	1725	ACTIVE	58.5
235485	BH 35770	1726	ACTIVE	48.3
238605	BH 69990	1727	INACTIVE	21.3
243789	BJ 08189	1728	ACTIVE	44.9
246315	BJ 45691	1729	ACTIVE	55.1
247705	BJ 51779	1730	ACTIVE	67.1
248412	BJ 59202	1731	INACTIVE	1.7
237375	BH 58120	1732	INACTIVE	9.7
228708	BG 66798	1733	INACTIVE	23.1
242511 AA	BH 89438	1734	INACTIVE	0
242511 AB	BJ 78592	1736	ACTIVE	47.8
194343	ZN 41968	1751	SLIGHTLY ACTIVE	27.9
249725	BK 69990	1931	ACTIVE	57.4
251855 AA	BK 71178	1932	ACTIVE	39.8

A total of twenty-two 8-aminoquinolines have been examined in the preliminary screening test. Eight of these show no significant activity at the standard concentration (0.05%) used in this test. Three compounds (WR 181023, WR 211814 and WR 194343) show slight activity and the remaining ten compounds are active. None of the 8-aminoquinolines tested have been fully active at the dose used. The highest levels of activity were found with WR 249725 and WR 247705 which produced approximately 60 and 70 per cent suppression of oocysts respectively.

3.4.2 Putative primaquine metabolites

TABLE 9 Sporontocidal activity of some putative primaquine metabolites.

WR	BN	LON	ACTIVITY	% SUPPRESSION
199508 AD	BK 56500	1877	SLIGHTLY ACTIVE	29.0
199508	ZP 43350	1940	SLIGHTLY ACTIVE	30.7

Two samples of putative metabolites of primaquine have been submitted for sporontocidal activity testing. Both of these samples (WR 199508 AD and 199508) proved to be 6-hydroxy primaquine and gave almost identical results in the test, demonstrating slight activity.

3.4.3 Quinine analogues

All four of the quinine analogues submitted demonstrated a marked toxicity to mosquitoes, with Ph 4007 killing all of the mosquitoes exposed to the 0.05 per cent concentration used in our

preliminary test. The remaining three compounds also exhibited toxicity in varying degrees at this dose and, consequently, even the low level of activity shown by Ph 4900 must be regarded as probably resulting from a generalised cytotoxicity.

TABLE 10 Sporontocidal activity of some quinine analogues.

WR	BN	LON	ACTIVITY	% SUPPRESSION
Ph 4007	BK 64306	1884	LETHAL TO MOSQUITOES	
Ph 4017	BK 64315	1885	INACTIVE	0
Ph 4900	BK 64324	1886	ACTIVE	39.3
Ph 4901	BK 64333	1887	INACTIVE	0

3.4.4 Floxacrine analogues

TABLE 11 Sporontocidal activity of some floxacrine analogues.

WR	BN	LON	ACTIVITY	% SUPPRESSION
245082	BK 02771	1752	INACTIVE	0
246976	BK 02780	1753	SLIGHTLY ACTIVE	37.7
249684 AB	BK 51550	1870	ACTIVE	69.0
250548 AA	BK 51621	1871	SLIGHTLY ACTIVE	39.3
250547	BK 51630	1872	ACTIVE	58.6

Four of the five floxacrine analogues tested showed some degree of sporontocidal activity. The most active, WR 249684 AB,

showed almost 70 per cent suppression of oocysts, WR 250547 was nearly as active, producing approximately 60 per cent suppression, whilst WR 246976 and WR 250548 AA suppressed oocyst development by almost 40 per cent. The fifth analogue, WR 245082 was totally inactive at the test concentration, probably as a consequence of the extreme insolubility of this compound.

3.4.5 Mannich bases

TABLE 12 Sporontocidal activity of two Mannich bases.

WR	BN	LON	ACTIVITY	% SUPPRESSION
194965 AG	BG 56327	1707	ACTIVE	39.8
228258 AH	BJ 30663	1708	INACTIVE	9.2

No significant activity was demonstrable with WR 228258 AH but WR 194965 produced almost 40 per cent suppression.

3.4.6 Quinolines

TABLE 13 Sporontocidal activity of two quinolines.

WR	BN	LON	ACTIVITY	% SUPPRESSION
44450 AD	AY 29540	1740	SLIGHTLY ACTIVE	24.3
102796 AD	BC 78878	1741	SLIGHTLY ACTIVE	34.9

Both of the quinolines tested, WR 44450 AD and WR 102796 AD, were slightly active in the preliminary test.

3.4.7 Miscellaneous compounds

a) WR 9792 (guanyldrazone) demonstrated no significant

activity against oocysts of P.y.nigeriensis.

b) WR 158124 had a reasonable level of activity and caused approximately 40 per cent suppression of oocyst development.

c) WR 203659 (clindamycin) is totally inactive in this test system at the dose tested.

TABLE 14 Sporontocidal activity of three miscellaneous compounds.

WR	BN	LON	ACTIVITY	% SUPPRESSION
9792	AJ 63248	1716	INACTIVE	14.2
158124	ED 22997	1718	ACTIVE	40.6
203659	ZN 39913	1909	INACTIVE	0

3.5 Combination studies

The bulk of the studies on drug interactions in this department are carried out under the terms of a WHO contract. Since, however, some of the compounds employed were supplied originally to us by WRAIR, the relevant results are summarised here for information.

Detailed data sheets are appended as Tables 102 through 194 and isobolograms are shown in Figures 1 to 14.

3.5.1 Mefloquine/spiramycin

This combination appears to produce a low degree of synergism.

3.5.2 Mefloquine/tetracycline

This combination was at best additive when tested using fixed ratios.

3.5.3 Mefloquine/minocycline

An additive effect resulted from this combination.

3.5.4 Mefloquine/clindamycin

When tested using fixed ratios, this combination was found to be more than additive.

3.5.5 Halofantrine/spiramecin

There is some suggestion of enhancement of the activity of halofantrine when using a combination of these compounds.

3.5.6 Halofantrine/chloroquine

The results obtained with this combination are indicative of a substantial degree of antagonism. This situation, when taken together with the rapidity with which halofantrine resistance may be induced experimentally in a chloroquine-resistant strain of P. yoelii and the blood schizontocidal test data on the halofantrine resistant line (reported in 3.6), is strongly suggestive of a shared receptor site for the two compounds.

3.5.7 Halofantrine/primaquine

Marked antagonism also occurs between halofantrine and primaquine. This is reflected in a reduced sensitivity to

primaquine in halofantrine resistant lines (see 3.6).

3.5.8 Halofantrine/pyrimethamine

The use of this combination results in a reasonable degree of synergism.

3.5.9 Halofantrine/sulfadiazine

This combination produces no more than an additive effect.

3.5.10 Halofantrine/clindamycin

There is no evidence of anything more than an additive effect with this combination.

3.5.11 Halofantrine/spiramycin

The combination of these two compounds apparently produces a degree of potentiation.

3.5.12 Halofantrine/tetracycline

At best an additive effect results from this combination and a further experiment is required to eliminate the possibility of antagonism.

3.5.13 Halofantrine/minocycline

This combination produces a clear synergistic response.

3.5.14 Floxacrine/cycloguanil

Although this combination has been claimed to be possibly synergistic in a patent claim (HOECHST AG 1979), the evidence

obtained in our test indicates that it is additive . Further studies are to be undertaken to resolve this contradiction.

3.5.15 Floxacrine/quinine

This combination also appears to have at best an additive effect and is possibly even slightly anagonistic, in spite of a patent claim (vide supra) for synergism.

3.5.16 Floxacrine/tetracycline

Results of our interaction study indicate an additive effect.

3.5.17 Floxacrine/erythromycin

There is at least an additive effect obtained with this combination and, possibly, slight synergism occurs.

3.5.18 Floxacrine/chloroquine

The combination of these two compounds produces a slightly antagonistic effect.

3.5.19 Floxacrine/primaquine

This combination produced an additive effect in our test system.

3.6 Development of drug resistance

During the period covered by this report, studies have been made on the acquisition of resistance by strains of rodent

malaria to two compounds, halofantrine and quinine, using our relapse technique.

In the case of halofantrine, resistant lines were developed from a drug sensitive strain of P.berghei (N strain) and also from the moderately chloroquine-resistant NS strain of P.yoelii. This latter strain is, however, insufficiently sensitive to quinine to allow the serial passage of the strain under drug pressure for the purpose of developing resistance since there is not a long enough delay produced by even the maximum tolerated dose to permit evaluation of change. Therefore, we developed quinine resistance only in the drug sensitive N strain.

3.6.1 Halofantrine resistance

Two lines of halofantrine resistant rodent malaria have been developed. The line derived from P.berghei N strain (N/HAL) showed a rapid acquisition of resistance to the maximum dose permitting recrudescence (5 mg/kg) with complete resistance being apparently reached by the eighth passage. This resistance was unstable as it was promptly lost as a result of freezing at this stage and it required a further six passages after retrieval from liquid nitrogen to restore this level of resistance. The strain was then passaged under drug pressure for eighteen more passages, during which time the resistance remained consistent, prior to the removal of drug pressure. When passaged without drug the delay to 2 % parasitaemia rapidly reverted to that of the original sensitive parent line (Figure 15).

The resistance level of the N/HAL strain was checked in the four day test at passage 31 and, at that stage, possessed a resistance factor of 2.8 ($ED_{90} \approx 3.6 \text{ mg/kg} \times 4 \text{ sd}$) compared with

the parent strain which had an ED_{90} of 1.3 mg/kg.

The NS derived strain, NS/HAL, showed an even greater propensity for developing resistance to halofantrine with almost complete resistance to a dose of 30 mg/kg being apparent after a single passage under drug pressure. This resistance was not lost in cryopreservation but withdrawal of drug pressure after 37 passages caused rapid reversion to the original level of sensitivity as measured by the 2 % delay time (Figure 16). Resistance was checked by the four day test technique at passage 35 and at that point the NS/HAL had a resistance factor of 13.2 (ED_{90} = 560 mg/kg, interpolated graphically). The parent NS strain had an ED_{90} of 42 mg/kg.

Both the N/HAL and the NS/HAL were also tested for sensitivity to chloroquine, primaquine, mefloquine and quinine in the four day test. There was a reduced sensitivity to each of these compounds in both strains.

These data are summarised in Table 195, together with those of the quinine-resistant line, and detailed reports are included in Tables 196 through 210.

3.6.2 Quinine resistance

Owing to the innate insensitivity of the NS strain to quinine, it was only possible to utilise the drug sensitive N strain for the development of a quinine-resistant line (N/1923). A preliminary experiment showed that the N strain would recrudesce following a single dose of 600 mg/kg of quinine given orally. Resistance to quinine developed relatively slowly, requiring more than thirty passages under drug pressure before a reasonably consistent, high level of resistance was attained. The

development of quinine resistance is depicted graphically in Figure 17.

The level of resistance in the N/1923 strain was assessed by the four day test for blood schizontocidal activity at passage 56. The parent strain was included as a direct comparison and it was found that the ED₉₀ of quinine in the parent strain was 85 mg/kg X 4 po, whilst in the N/1923 strain a dose of 600 mg/kg X 4 orally produced virtually no effect.

After withdrawal of drug pressure (Figure 18), the resistance level remained constant for eighteen passages before the strain began to revert to sensitivity. Even after fifty-two passages without drug pressure, this strain has still not stabilised as a completely sensitive line comparable with the parent strain.

3.7 Mode of action studies

A corollary to the idea that haemin, released during the digestion of haemoglobin, is a site for binding of antimalarial schizontocides is the proposition that resistance to these drugs may involve changes in quantity or structure of the protein(s) involved in the complexation of haemin as malaria pigment (Warhurst, 1981). We have investigated the composition of malaria pigment in two strains of P.falciparum, NF54 (chloroquine sensitive) and K1 (chloroquine-resistant), with the following results.

The major polypeptide detected on SDS-PAGE was present in all preparations of both strains and had a molecular weight (M_r) of 14.3 ± 0.8 K in NF54 and 14.6 ± 0.55 K in K1. It comprised 73 and 78 per cent of the total Coomassie blue staining protein and 40 and 55 per cent of the total labelled (³H-phenylalanine) protein.

The metabolic labelling of this component in vitro indicates that it is parasite derived.

Another polypeptide was found in eighty per cent of NF54 and all K1 pigment preparations. The M_r values were 30 K and 29.7 ± 0.56 K respectively. This polypeptide comprised 13.4 per cent (NF54) and 3.9 per cent (K1) of total protein and 12.9 per cent and 11.6 per cent of total labelled protein. In addition, a third polypeptide was found in eighty per cent of preparations of both strains. This had a M_r of 66.6 ± 0.48 K in NF54 and 66.5 ± 0.05 K in K1 derived material. When labelled (K1 only) it had 2.5 per cent of the total radioactivity.

Depending on the preparation's purity and the stages labelled, other minor bands were seen with molecular weights of 73 - 76 K and 20 - 22 K. These were not consistently present and are considered to represent contamination of the pigment preparation with membranes, etc.

Purified pigment from NF54 and K1 strains was subjected to protein (Lowry) and haemin (pyridine haemochrome) estimations to determine the relative proportions of haemin and protein. Combined data from eight estimations indicated that the relative proportions in NF54 were 52.32 per cent protein plus 10.03 per cent haemin. Similar estimations on a series of six K1 pigment preparations gave a result of 45.11 per cent protein plus 2.32 per cent haemin.

A 14 K polypeptide was reported as being precipitated from P.falciparum schizont preparations by a (? monoclonal) antibody (TDR/IMMAL/SWG(6)84.3). This may be the same polypeptide that we are finding, which would seem to be the major haemin-binding protein of P.falciparum.

Yamada and Sherman (1979) reported a 15 K pigment associated polypeptide in P. lophurae, which they suggested was a degraded monomer of globin. This was probably also a parasite derived haemin-binding protein.

Our observations would indicate that haemin is released in the digestive vacuoles and is available in trace amounts to bind to blood schizontocides such as chloroquine and quinine.

Studies on the aminoacid composition of the 14 K polypeptide indicate marked differences between the chloroquine-sensitive NF54 and the chloroquine-resistant K1 strains of P. falciparum.

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5. APPENDICES

5.1 BLOOD SCHIZONTOCIDAL TEST DATA

Summary of Observations on Bacteriological and Low Test Data

LON	WR & BN	SC	ED	RC		N/1100		N/1923		ED		ED		ED	
				ED	ED	ED	ED	ED	ED	ED	ED	ED	ED	ED	ED
1932	251855AA BK 71178	SC	0.25 0.67												
1956	BK 74491	SC	0.6 3.4												
1957	BK 73127	SC	0.5 2.1												
2022	Amodiaquine	SC	0.8 2.7 25.5 9.4 >60 >222 750 378 >60 >222												

TABLE 15

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OR NUMBER LON 1932 PARASITE SUBSPECIES P. eugene

MAXIMUM TOLERATED DOSE (MTD) ..30... MG/KG X 4.

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

BK 7443;

1950-1951 1952-1953 1954-1955 1956-1957 1958-1959 1960-1961 1962-1963 1964-1965 1966-1967 1968-1969 1970-1971 1972-1973 1974-1975 1976-1977 1978-1979 1980-1981 1982-1983 1984-1985 1986-1987 1988-1989 1990-1991 1992-1993 1994-1995 1996-1997 1998-1999 2000-2001 2002-2003 2004-2005 2006-2007 2008-2009 2010-2011 2012-2013 2014-2015 2016-2017 2018-2019 2020-2021 2022-2023 2024-2025 2026-2027 2028-2029 2030-2031 2032-2033 2034-2035 2036-2037 2038-2039 2040-2041 2042-2043 2044-2045 2046-2047 2048-2049 2050-2051 2052-2053 2054-2055 2056-2057 2058-2059 2060-2061 2062-2063 2064-2065 2066-2067 2068-2069 2070-2071 2072-2073 2074-2075 2076-2077 2078-2079 2080-2081 2082-2083 2084-2085 2086-2087 2088-2089 2090-2091 2092-2093 2094-2095 2096-2097 2098-2099 2100-2101 2102-2103 2104-2105 2106-2107 2108-2109 2110-2111 2112-2113 2114-2115 2116-2117 2118-2119 2120-2121 2122-2123 2124-2125 2126-2127 2128-2129 2130-2131 2132-2133 2134-2135 2136-2137 2138-2139 2140-2141 2142-2143 2144-2145 2146-2147 2148-2149 2150-2151 2152-2153 2154-2155 2156-2157 2158-2159 2160-2161 2162-2163 2164-2165 2166-2167 2168-2169 2170-2171 2172-2173 2174-2175 2176-2177 2178-2179 2180-2181 2182-2183 2184-2185 2186-2187 2188-2189 2190-2191 2192-2193 2194-2195 2196-2197 2198-2199 2200-2201 2202-2203 2204-2205 2206-2207 2208-2209 2210-2211 2212-2213 2214-2215 2216-2217 2218-2219 2220-2221 2222-2223 2224-2225 2226-2227 2228-2229 2230-2231 2232-2233 2234-2235 2236-2237 2238-2239 2240-2241 2242-2243 2244-2245 2246-2247 2248-2249 2250-2251 2252-2253 2254-2255 2256-2257 2258-2259 2260-2261 2262-2263 2264-2265 2266-2267 2268-2269 2270-2271 2272-2273 2274-2275 2276-2277 2278-2279 2280-2281 2282-2283 2284-2285 2286-2287 2288-2289 2290-2291 2292-2293 2294-2295 2296-2297 2298-2299 2300-2301 2302-2303 2304-2305 2306-2307 2308-2309 2310-2311 2312-2313 2314-2315 2316-2317 2318-2319 2320-2321 2322-2323 2324-2325 2326-2327 2328-2329 2330-2331 2332-2333 2334-2335 2336-2337 2338-2339 2340-2341 2342-2343 2344-2345 2346-2347 2348-2349 2350-2351 2352-2353 2354-2355 2356-2357 2358-2359 2360-2361 2362-2363 2364-2365 2366-2367 2368-2369 2370-2371 2372-2373 2374-2375 2376-2377 2378-2379 2380-2381 2382-2383 2384-2385 2386-2387 2388-2389 2390-2391 2392-2393 2394-2395 2396-2397 2398-2399 2400-2401 2402-2403 2404-2405 2406-2407 2408-2409 2410-2411 2412-2413 2414-2415 2416-2417 2418-2419 2420-2421 2422-2423 2424-2425 2426-2427 2428-2429 2430-2431 2432-2433 2434-2435 2436-2437 2438-2439 2440-2441 2442-2443 2444-2445 2446-2447 2448-2449 2450-2451 2452-2453 2454-2455 2456-2457 2458-2459 2460-2461 2462-2463 2464-2465 2466-2467 2468-2469 2470-2471 2472-2473 2474-2475 2476-2477 2478-2479 2480-2481 2482-2483 2484-2485 2486-2487 2488-2489 2490-2491 2492-2493 2494-2495 2496-2497 2498-2499 2500-2501 2502-2503 2504-2505 2506-2507 2508-2509 2510-2511 2512-2513 2514-2515 2516-2517 2518-2519 2520-2521 2522-2523 2524-2525 2526-2527 2528-2529 2530-2531 2532-2533 2534-2535 2536-2537 2538-2539 2540-2541 2542-2543 2544-2545 2546-2547 2548-2549 2550-2551 2552-2553 2554-2555 2556-2557 2558-2559 2560-2561 2562-2563 2564-2565 2566-2567 2568-2569 2570-2571 2572-2573 2574-2575 2576-2577 2578-2579 2580-2581 2582-2583 2584-2585 2586-2587 2588-2589 2590-2591 2592-2593 2594-2595 2596-2597 2598-2599 2600-2601 2602-2603 2604-2605 2606-2607 2608-2609 2610-2611 2612-2613 2614-2615 2616-2617 2618-2619 2620-2621 2622-2623 2624-2625 2626-2627 2628-2629 2630-2631 2632-2633 2634-2635 2636-2637 2638-2639 2640-2641 2642-2643 2644-2645 2646-2647 2648-2649 2650-2651 2652-2653 2654-2655 2656-2657 2658-2659 2660-2661 2662-2663 2664-2665 2666-2667 2668-2669 2670-2671 2672-2673 2674-2675 2676-2677 2678-2679 2680-2681 2682-2683 2684-2685 2686-2687 2688-2689 2690-2691 2692-2693 2694-2695 2696-2697 2698-2699 2700-2701 2702-2703 2704-2705 2706-2707 2708-2709 2710-2711 2712-2713 2714-2715 2716-2717 2718-2719 2720-2721 2722-2723 2724-2725 2726-2727 2728-2729 2730-2731 2732-2733 2734-2735 2736-2737 2738-2739 2740-2741 2742-2743 2744-2745 2746-2747 2748-2749 2750-2751 2752-2753 2754-2755 2756-2757 2758-2759 2760-2761 2762-2763 2764-2765 2766-2767 2768

MAXIMUM TOLERATED DOSE (MTD) 1000 MG/KG (4

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

BK 73.27

[illegible]

MAXIMUM TOLERATED DOSE (MTD) 2.000 mg/kg/d

Principal Investigator: Professor Walter
Department of Medical Microbiology
University of Toronto & Imperial College

SUMMARY OF ANTIMALARIAL DRUG TESTS
(Blood schizonticide)

TABLE 10

COMPOUND NAME

DR NUMBER ... AMODIAQUINE ... PARASITE (SUB)SPECIES ... *P. berghei* ...

FORMULATION ... Tween 80 / H₂O ... ROUTE OF ADMINISTRATION : SC / IP / PO / IV

MAXIMUM TOLERATED DOSE (MTD) > 600 MG/KG X 4

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated $\frac{P \pm S}{Control \frac{P \pm S}{\times 100}}$
	0.1	5		-	94.4 $\pm$ 2.7
	0.3	5		-	72.1 $\pm$ 7.6
N	1.0	5	1	-	61.4 $\pm$ 5.5
	3.0	5		-	37.0 $\pm$ 3.3
	10.0	5		-	0.1 $\pm$ 0.1
	30.0	5		-	0
	$\emptyset$	10		20.3	
ED ₅₀ (range) 0.8 (0.4 - 1.5)					
ED ₉₀ (range) 2.7 (1.3 - 5.4)					
	0.1	5		-	71.3 $\pm$ 7.2
	0.3	5		-	55.5 $\pm$ 4.6
	1.0	5		-	50.9 $\pm$ 3.9
NS	3.0	5	1	-	43.3 $\pm$ 2.8
	10.0	5		-	14.0 $\pm$ 4.2
	30.0	5		-	9.3 $\pm$ 2.7
	60.0	5		-	7.8 $\pm$ 2.6
	$\emptyset$	10		20.9	
ED ₅₀ (range) 0.6 (0.3 - 1.4)					
ED ₉₀ (range) 25.5 (11.5 - 54)					
Resistance factor I ₉₀ 9.4					

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
 (BRIDGES SCHLINTGENS)

TABLE 20

COMPOUND NAME

OR NUMBER AMODIAQUINE PARASITE (SUB)SPECIES P. berghei

FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION : SC/42/P0/IV

MAXIMUM TOLERATED DOSE (MTD) > 60 MG/KG X 4

Strain	Daily dose mg/kg D0-D+3	No. of mice	No. of experiments	Mean control parasite rate %	Treated PR% Control PR%
	1.0	5		-	100
	3.0	5		-	84.7 ± 12.2
RC	10.0	5	1	-	95.6 ± 1.5
	30.0	5		-	65.7 ± 17.7
	60.0	5		-	62.3 ± 15.0
	Ø	10		7.7	
ED ₅₀ (range) > 60					
ED ₉₀ (range) > 60					
Resistance factor I ₉₀ > 22.2					
	3.0	5		-	100 ± 2.5
	10.0	5		-	44.4 ± 4.4
N 1100	30.0	5	1	-	30.4 ± 3.9
	60.0	5		-	20.0 ± 5.3
	Ø	10		10.8	
ED ₅₀ (range) 9.5 (6.0 - 18.5)					
ED ₉₀ (range) 75.0 (49.0 - 150)					
Resistance factor I ₉₀ 27.8					

Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

- 140 - 21

OR NUMBER AMODIAQUINE PARASITE (SUB)SPECIES P. cagnei

FORMULATION : Tween 80 / H₂O... ROUTE OF ADMINISTRATION : SC/ID/PO/IV

MAXIMUM TOLERATED DOSE (MTD) > 60..... MG/KG X 4..

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

5.2 CAUSAL PROPHYLACTIC TEST DATA

SUMMARY OF CAUSAL PROPHYLACTIC TESTS

PRINCIPAL INVESTIGATOR: PROFESSOR W. J. LINTERS
DEPARTMENT OF MEDICAL PROTOZOLOGY
LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE

DATE: 26.3.84

LAB. NO. 2624

CONTAINER NO. 1801

BOTTLE NO. BK 12713

EXPERIMENTAL: Tween 80 dil.

TIME AFTER INFECTION: 2 HOURS

NO. OF MICE

PARASITE: *P. yoelii nigeriensis*

STRAIN: NIG

Dose	INFECTION RATE		SPP 2 nd Y		ACTIVITY VALUES			COMMENT
	Infected	Sporozoite and blood infected	Sporozoite infected (a)	Sporozoite and blood infected (d)	Total activity (b-a)	Residual activity (d-e)	Prophylactic activity (b-a)-(d-e)	
0	5/5	5/5	4.87	2.92				
3.0	3/3	3/3	4.61	2.90	0	0	NIL	INACTIVE
10.0	2/3	3/3	>8.20	2.87	>3.33	0	>3.33	ACTIVE
30.0	0/3	3/3	>14.00	2.96	>9.13	0.04	>9.09	FULLY ACTIVE
			(b)	(d)				
			(a)	(d)				
			(b)	(d)				

TABLE 2.3

EXPERIMENTAL: 10.0 - 30.0
 CONTAINER NO. 1801
 BOTTLE NO. BK 12713
 PARASITE: *P. yoelii nigeriensis*
 STRAIN: NIG

ORIENTAL PATENT LABORATORY
 Department of Microbiology
 100, Robinson Road, Singapore

DATE: 26.3.84

CAUSAL PROPYLAXIS TEST NO: 2624

BOTTLE NO: AY 15653

WR 6890

TIME AFTER INJECTION: 7 HOURS

ROUTE: sc ~~4444~~FORMULATION: Tween 80/H₂O

STRAIN: N16

PARASITE: *P. yoelii nigricans*

HOST: ♂ HM mice

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected (a)	Sporozoite and blood infected (c)	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a-d-c)	
Ø	5/5	5/5	4.87 (b)	2.92 (c)				
10.0	3/3	3/3	4.89 (b)	2.90 (c)	0.02	0	NUL	INACTIVE
30.0	2/3	3/3	>7.90 (b)	3.25 (c)	>3.03	0.33	>2.70	ACTIVE
100.0	0/3	3/3	>14.00 (b)	2.93 (c)	>9.13	0.01	>9.12	FULLY ACTIVE

TABLE 21

SPOROZOITE ACTIVITY INDEX: 30.0 - 100

SPOROZOITE ACTIVITY: 50

~~4444~~ AT 100

GMP 2% P AT

PRINCIPAL INVESTIGATOR: PROFESSOR N. F. L. F.
Department of Medical Microbiology
London School of Hygiene & Tropical Medicine

DATE: 20 1 55

CAUSAL PROPHYLAXIS TEST NO: 2465

COMPOUND: LON/ 1783 ANC - IX - 19

BOTTLE NO:

FORMULATION: Tween 80/H₂O

ROUTE: sc 47/40

TIME AFTER INJECTION: 2 HOURS

HOST: ♂ TFW mice

PARASITE: *P. yoelii nigeriensis*

STRAIN: NID

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	5/5		(a) 5 16	(c)				
60.0	3/3		(b) 4 95	(d)	0	NIL	NIL	INACTIVE
100.0	3/3		(b) 4 49	(d)	0	NIL	NIL	INACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

TABLE

MINIMUM FULLY ACTIVE DOSE mg/kg
 RESIDUAL ACTIVITY: NIL
 PRESENT AT 100.0
 MARFID AT mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETERS
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

DATE: 13.2.84

CAUSAL PROPHYLAXIS TEST NO: 2542

COMPOUND: LON/ 1908 3-bromo-phenazine diphenylate BOTTLE NO: RCGJM 97

FORMULATION: Tween 80/H₂O

ROUTE: sc/ipt/m TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice

PARASITE: P. yoelii nigeriensis

STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2 nd P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected (a)	Sporozoite and blood infected (c)	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
0	5/5	5/5	5.89 (a)	3.35 (c)				
10.0	3/3	3/3	4.88 (b)	3.17 (d)	0	0	0	INACTIVE
30.0	3/3	3/3	5.79 (b)	4.14 (d)	0	0.79	0	SOME RESIDUAL ACTIVITY ONLY
100.0	0/3	3/3	>14.00 (b)	5.18 (d)	>8.11	1.83	>6.28	FULLY ACTIVE - SOME RESIDUAL ACTIVITY

MINIMUM FULLY ACTIVE DOSE 30.0 - 100.0 mg/kg

RESIDUAL ACTIVITY: +++ PRESENT AT 30.0 mg/kg

MARSHAL AT 100.0 mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W. L. L. L.
Department of Medical Microbiology
London School of Hygiene & Tropical Medicine

DATE: 19 3 84

CAUSAL PROPHYLAXIS TEST NO: 2608

COMPOUND: LON/ 1884 Ph 4007

BOTTLE NO: BK 64306

FORMULATION: Tween 80/H₂O

TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TEW mice

PARASITE: *P. yoelii nigeriensis*

STRAIN: NIG

ROUTE: sc/4474

TABLE 25

DOSE mg/kg	PATENCY RATE		CMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	5/5	5/5	4.87 (a)	3.86 (c)				
100.0	3/3	3/3	4.93 (b)	3.57 (d)	0.06	0	NIL	INACTIVE
300.0	1/3	3/3	> 11.61 (b)	3.62 (d)	> 6.74	0	> 6.74	ACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

MINIMUM FULLY ACTIVE DOSE > 300 mg/kg

RESIDUAL ACTIVITY: NIL

~~PARASITE~~ AT 300

MARFED AT mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETERS
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

CAUSAL PROPHYLAXIS TEST NO: 2608
 COMPOUND: LON/ 1885
 FORMULATION: Tween 80/H₂O
 HOST: ♂ TFW mice

DATE: 19. 3. 84
 BOTTLE NO: Bk 64315
 ROUTE: sc/47/40
 TIME AFTER INFECTION: 2 HOURS
 STRAIN: NIG

PARASITE: *P. yoelii nigeriensis*

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	5/5	5/5	4/87 (a)	3/86 (c)				
100.0	3/3	3/3	5/42 (b)	3/54 (d)	0.55	0	0.55	INACTIVE
300.0	3/3	3/3	5/40 (b)	3/54 (d)	0.53	0	0.53	INACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

TABLE 29

MINIMUM FULLY ACTIVE DOSE mg/kg
 RESIDUAL ACTIVITY: NIL
~~PRESENT~~ AT 300 mg/kg
 MARKED AT mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W. FLERS
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

DATE: 19.3.84

CAUSAL PROPHYLAXIS TEST NO: 2608

BOTTLE NO: BK 64324

Ph 4900

TIME AFTER INFECTION: 2 HOURS

ROUTE: sc/44/44

STRAIN: NIG

PARASITE: *P. yoelii nigeriensis*

COMPOUND: LON/ 1886

FORMULATION: Tween 80/H₂O

HOST: ♂ TFW mice

TABLE 39

DOSE mgm/kg	PATENCY RATE		GNP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected (a)	Sporozoite and blood infected (c)	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
Ø	5/5	5/5	4.87	3.86				
100.0	3/3	3/3	5.12	3.53	0.25	0	NIL	INACTIVE
300.0	3/3	3/3	4.92	3.58	0.05	0	NIL	INACTIVE

MINIMUM FULLY ACTIVE DOSE: mg/kg

RESIDUAL ACTIVITY: NIL

MARKED AT 300 mg/kg

MARKED AT mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

CAUSAL PROPHYLAXIS TEST NO: 26008

DATE: 19 3 84

COMPOUND: LON/ 1887 Ph 4901

BOTTLE NO: BK 64333

FORMULATION: Tween 80/H₂O

TIME AFTER INFECTION: 7 HOURS

HOST: ♂ TFW mice

PARASITE: E. poellii nigricans

STRAIN: N10

DOSE mg/kg	PATENCY RATE		GMP 27 P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected (d)	Sporozoite and blood infected (d)	Total activity (b-a)	Residual activity (d-b)	Prophylactic activity (b-a)-(d-b)	
Ø	5/5	5/5	4/5	3/5				
100.0	3/3	3/3	6/85	3/80	1.98	0	1.98	SLIGHTLY ACTIVE
300.0	2/3	3/3	> 8.88	3.00	> 3.99	0	> 3.99	ACTIVE

Table 31

MINIMUM FULLY ACTIVE DOSE 300 mg/kg

RESIDUAL ACTIVITY: NIL

AT 300 mg/kg

MARFED AT mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W PETERS
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

DATE: 13.2.84

CASAL PREPARATION: 2542

COMPONENT: LON 1872 WR 250547 AA BOTTLE NO: BK 51630

FORMULATION: Tween 80-H₂O ROUTE: sc/ ~~iv~~ TIME AFTER INFECTION: 2 HOURS

host: 3 IFM mice PARASITE: *P. yoelii nigeriensis* STRAIN: NIG

Dose mg/kg	PATENCY RATE		GMP 27 P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
0.5	5/5	5/5	5/5	3/35				
0.1	3/3	3/3	5/13	3/48	0	0.13	NIL	INACTIVE
0.3	3/3	3/3	5/69	4/66	0	0.71	NIL	RESIDUAL ACTIVITY ONLY
1.0	3/3	3/3	7/36	5/69	1.47	2.34	NIL	RESIDUAL ACTIVITY ONLY

TABLE 1

PRIMUM FULLY ACTIVE DOSE mg/kg
RESIDUAL ACTIVITY: ~~+++~~
PRESENT AT 0.3.....mg/kg
MARKED AT mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W. L. F. F.
Department of Medical Parasitology
London School of Hygiene & Tropical Medicine

DATE: 19 6 84

CAUSAL PROPHYLAXIS TEST NO: 2821

COMPOUND: LON/ 1941 Spiramycin

FORMULATION: Tween 80/H₂O

HOST: ♂ TFW mice

PARASITE: *P. yoelii nigeriensis*

ROUTE: s.c./i.p.

STRAIN: NIG

TIME AFTER INFECTION: 2 HOURS

STRAIN: NIG

BOTTLE NO:

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
0	3/3		(a) 5.46	(c)				
30.0	2/3		(b) > 9.75	(d)	> 4.29			ACTIVE
100.0	0/3 *		(b) > 14.00	(d)	> 8.54			FULLY ACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

MAXIMUM FULLY ACTIVE DOSE 30.0 mg/kg
 RESIDUAL ACTIVITY: ALL PRESENT AT mg/kg
 MARKED AT mg/kg

* 1/3 USED

PRINCIPAL INVESTIGATOR: PROFESSOR W PETERS
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

DATE: 19.6.84

CAUSAL PROPHYLAXIS TEST NO: 2821

COMPOUND: LON/ 1944 *Lincomycin hydrochloride* BOTTLE NO:

FORMULATION: Tween 80/H₂O ROUTE: sc/4p/100 TIME AFTER INFECTION: 2 HOURS

HOST: ♂ TFW mice PARASITE: *P. yoelii nigeriensis* STRAIN: NIG

DOSE mg/kg	PATENCY RATE		GMP 2% P		ACTIVITY VALUES			COMMENT
	Sporozoite infected	Sporozoite and blood infected	Sporozoite infected	Sporozoite and blood infected	Total activity (b-a)	Residual activity (d-c)	Prophylactic activity (b-a)-(d-c)	
0	3/3		(a) 5.46	(c)				
30.0	2/3 *		(b) 6.87	(d)	1.41			SLIGHTLY ACTIVE
100.0	1/3		(b) > 11.65	(d)	> 6.19			ACTIVE
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				
			(b)	(d)				

TABLE 3

MINIMUM FULLY ACTIVE DOSE > 100. mg/kg

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

RESIDUAL ACTIVITY: NIL PRESENT AT mg/kg

MARFED AT mg/kg

5.3 GAMETOCYTOCIDAL TEST DATA

SUMMARY OF ANTIMALARIAL TESTS

TABLE 3.5

ANTI-TOXOPLASMA ACTIVITY

COMPONENT : LW 1711 WR 2975 AW BJ CS241 Primaquine diphosphate

FORMULATION : TAEN 50 (mg)

ROUTE : ~~IP~~ ~~SC~~ ~~IV~~

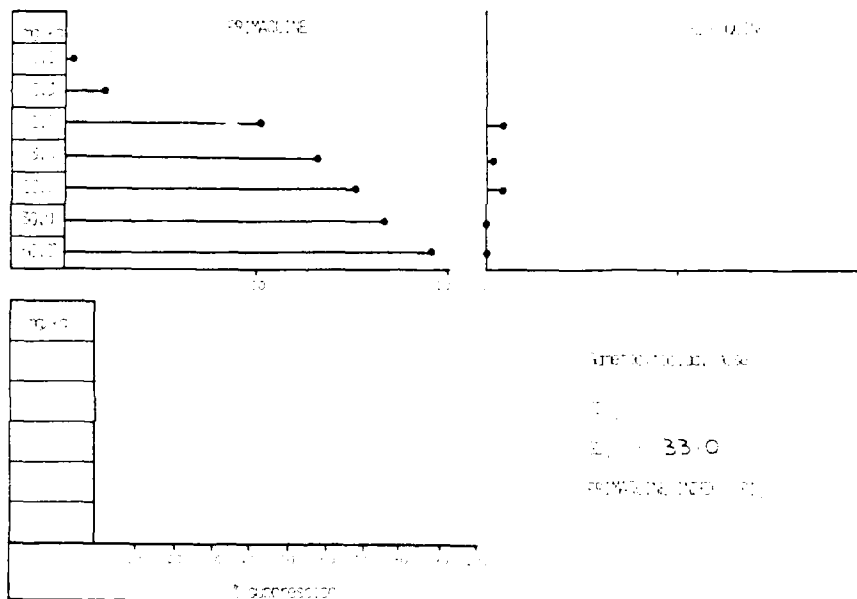
MAXIMUM BODY TOLERATED DOSE : > 60 mg/kg (1) EXPERIMENT NO. 2393 DATE 23 83

PARASITE : *Plasmodium jelski nigrescens*

VERTEBRATE HOST : ♂ FEA MICE

INVERTEBRATE HOST : Acinetobacter baumannii

DOSE mg/kg	DOSE GROUPS 1-10										11.0	12.0
2	45	16	13	14	13	3	21	10	48	16	17.8	18
	15	11										
1.0	13	3	10	8	3	6	4	7	13	20	37	43.9 ± 3.3
3.0	8	5	6	7	5	2	2	3	18	5	61	34.2 ± 9.9
10.0	2	1	4	6	5	5	2	8	9	1	43	24.2 ± 4.5
30.0	1	1	1	6	3	4	7	3	1	2	29	6.3 ± 3.4
60.0	0	0	2	1	1		2	0	0	0	27	1.2 ± 1



SUMMARY OF ANTIMALARIAL TESTS

TABLE 3.6

GAMETOCYTOCIDAL ACTIVITY

COMPOUND : LON 1720 WR 182234 BE 17580

FORMULATION : TWEEN 80 / H₂OROUTE : SC / ~~IP~~ / ~~IV~~ / ~~IM~~

MAXIMUM FULLY TOLERATED DOSE : > 100 mg / kg X 1

EXPERIMENT No.: 2422

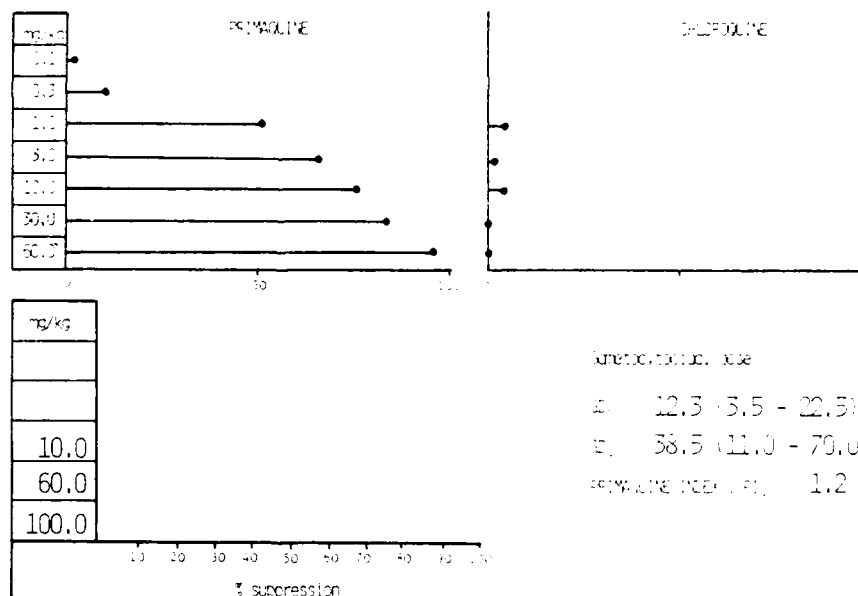
DATE : 7.12.83

PARASITE : *Plasmodium yoelii* nigeriensis

VERTEBRATE HOST : ♂ FFW MICE

INVERTEBRATE HOST : *Anopheles stephensi*

DOSE mg/kg	OOCYST COUNTS 0+7										MEAN	% CONTROL
0	15	16	12	7	16	11	14	16	18	10	14.0	100
	16	14	19	16	10							
10.0	7	4	8	4	8	5	8	6	4	10	6.4	45.7 ± 4.3
60.0	4	3	0	1	0	1	3	2	2	1	1.7	12.0 ± 2.9
100.0	0	0	1	2	0	2	1	0	0	1	0.7	0.5 ± 0.5



Principal Investigator : Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

TABLE 3

GAMETOCYCIDAL ACTIVITY

COMPOUND : LON 1721 WR 211814 ZP 12775

FORMULATION : TWEEN 80 / H₂O

ROUTE : SC / ~~40-60-70-80~~

MAXIMUM FULLY TOLERATED DOSE : >100 mg / kg X 1

EXPERIMENT No.: 2422

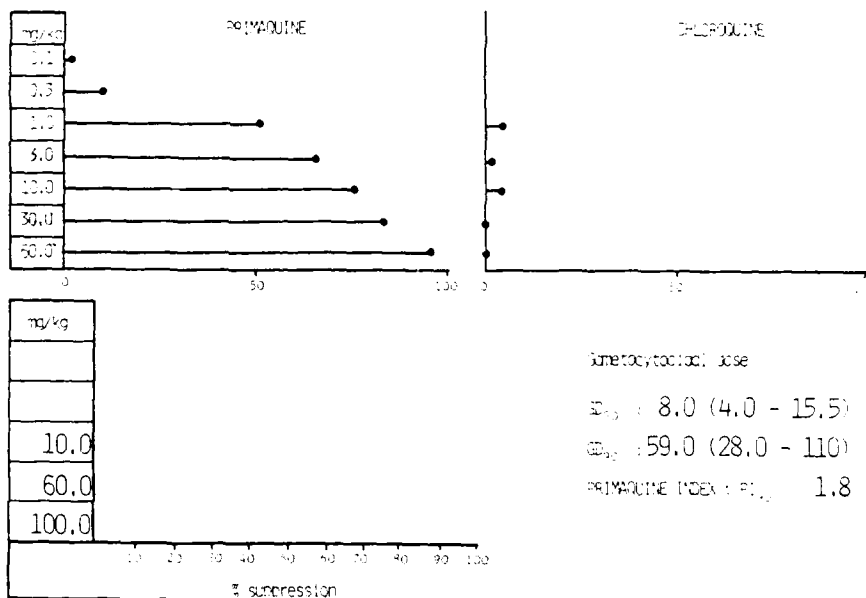
DATE 7.12.85

PARASITE : *Plasmodium yoelii* nigriensis

VERTEBRATE HOST : 5⁺ FEM MICE

INVERTEBRATE HOST : *Anopheles stephensi*

DOSE mg/kg	OOCYST COUNTS D+7										MEAN	% CONTROL	
2	15	16	12	7	16	11	14	16	18	10	14.0	100	
	16	14	19	16	10								
10.0	8	0	0	6	5	4	5	9	5	6	4.8	34.3	6.4
60.0	7	2	1	2	0	3	1	3	1	0	2.0	14.3	5.0
100.0	2	1	2	1	2	0	0	0	1	0	0.75	5.4	1.4
	0	0											



Principal Investigator : Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

TABLE 3/5

GAMETOCYTOCIDAL ACTIVITY

COMPOUND : LW 1722

WR 215295

ZN 43444

FORMULATION : TWEEN 80 / H₂O

ROUTE : SC / ~~IP~~ ~~PO~~ ~~IV~~

MAXIMUM FULLY TOLERATED DOSE : > 300 mg / kg X 1

EXPERIMENT No. : 2422

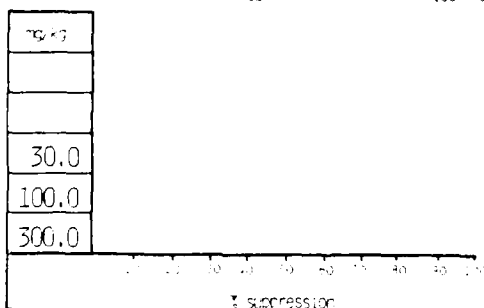
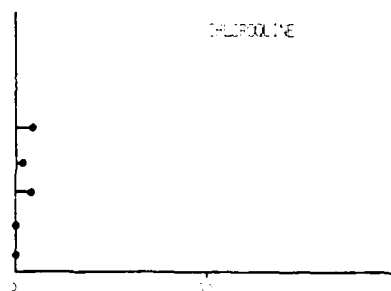
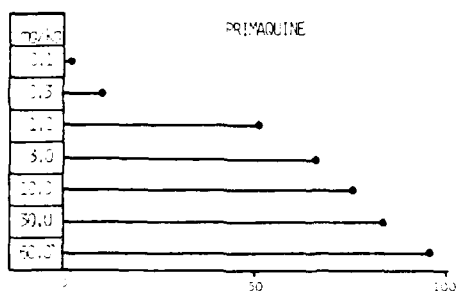
DATE : 7.12.83

PARASITE : *Plasmodium yoelii* nigeriensis

VERTEBRATE HOST : ♂ FFW MICE

INVERTEBRATE HOST : *Anopheles stephensi*

DOSE mg/kg	GAMETOCYTE COUNTS D+7										MEAN	% SUPPRESSION
0	15	16	12	7	16	11	14	16	18	10	14.0	100
	16	14	19	16	10							
30.0						From Experiment 2151						96.8
100.0	14	13	14	8	9	8	7	13	15	6	9.9	70.7 ± 6.4
300.0	8	9	6	7	3	9	5	5	7	6	6.5	46.4 ± 4.3



Gametocytocidal dose

ED₅₀ : 230 (160 - 330)

ED₉₀ : 1100 (740 - 1500)

PRIMAQUINE INDEX : FI₅₀ 33.3

Principal Investigator : Professor W. Peters

Department of Medical Parasitology

London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

TABLE 3.9

SANETOCYTOCIDAL ACTIVITY

COMPOUND : LON 1727

WR 238605

BH 69990

FORMULATION : TWEEN 80 / H₂O

ROUTE : SC / ~~IP~~ / ~~PO~~ / ~~IV~~

MAXIMUM FULLY TOLERATED DOSE : >300 mg / kg x 1

EXPERIMENT NO.: 2453

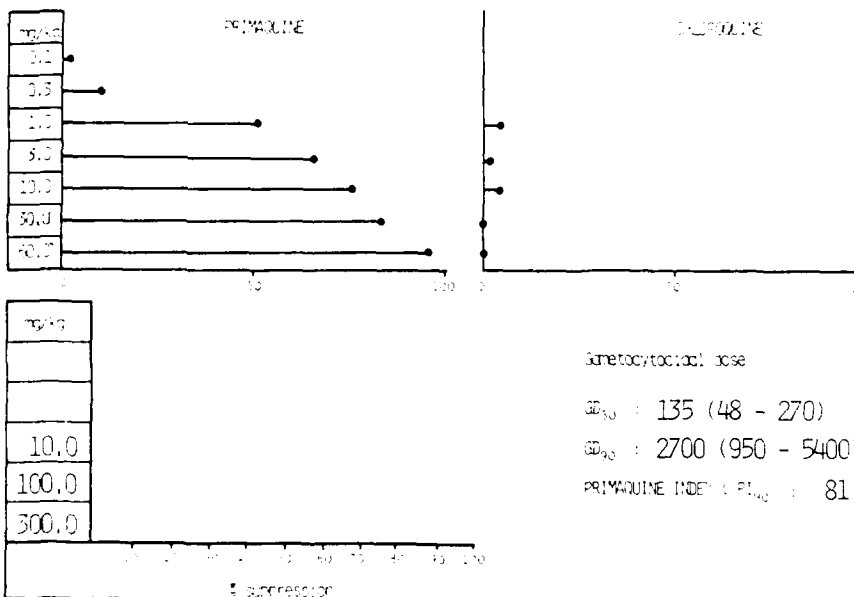
DATE 11.1.84

PARASITE : *Plasmodium yoelii* yoelii

VERTEBRATE HOST : ♂ TFW MICE

INVERTEBRATE HOST : *Anopheles stephensi*

DOSE mg/kg	DOCYST COUNTS D+7										MEAN	% CONTROL
0	47	73	38	35	20	38	30	28	29	16	33.5	100
15												
10.0	20	36	28	30	22	31	28	50	37	22	30.4	90.7 ± 4.0
100.0	19	14	7	27	23	2	20	17	14	23	16.0	47.8 ± 7.5
	12	14										
300.0	10	16	16	20	20	11	12	16	21	15	14.7	43.9 ± 3.5



Principal Investigator : Professor A. Peters

Co-investigator : Medical Entomology

Principal Investigator : Professor A. Peters

SUMMARY OF ANTIMALARIAL TESTS

TABLE 10

GAMETOCYTOCIDAL ACTIVITY

COMPOUND : LON 1728

WR 243789

BJ08189

FORMULATION : TWEEN 80 / H₂O

ROUTE : SC ~~IP~~ ~~IV~~ ~~IM~~ ~~IT~~

MAXIMUM FULLY TOLERATED DOSE : >300 mg/kg

EXPERIMENT No. : 2453

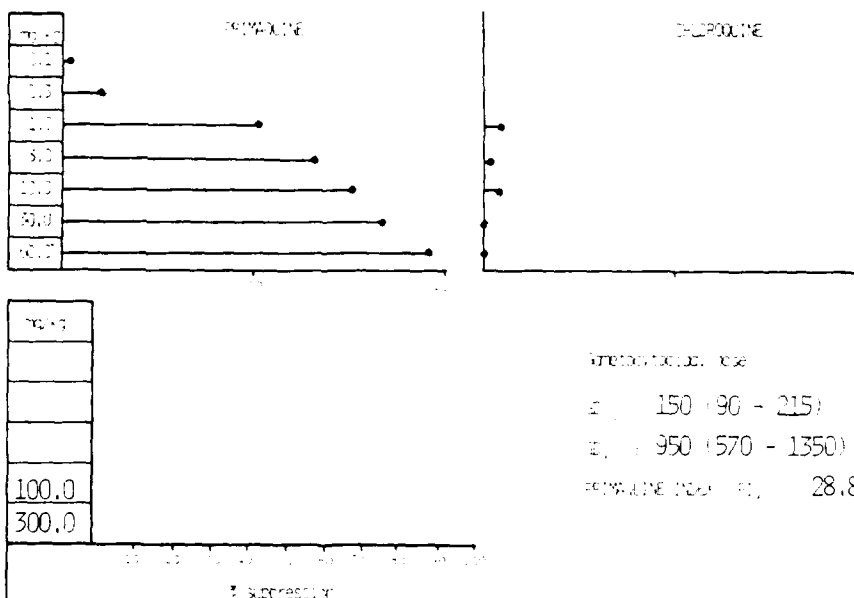
DATE : 11.1.84

PARASITE : *Plasmodium yoelii* nigripennis

VERTEBRATE HOST : STRA MICE

(INVERTEBRATE HOST : *Anopheles stephensi*)

DOSE mg/kg	DOCT COUNTS D+7										MEAN	% CONTROL
0	47	73	38	35	20	38	30	28	29	16	33.5	100
	15											
100.0	19	11	18	13	20	38	16	12	11	32	18.6	55.6 ± 7.0
	15											
300.0	7	20	14	8	11	6	11	15	13	12	12.4	37.0 ± 4.2



SUMMARY OF ANTIMALARIAL TESTS

TABLE 11

GAMETOCYTOCIDAL ACTIVITY

COMPOUND : LON 1729

WR 246315

BJ 45691

FORMULATION : TWEEN 80 / H₂OROUTE : SC / ~~IP / PO / IV~~

MAXIMUM FULLY TOLERATED DOSE : > 300 mg / kg X 1

EXPERIMENT No.: 2453

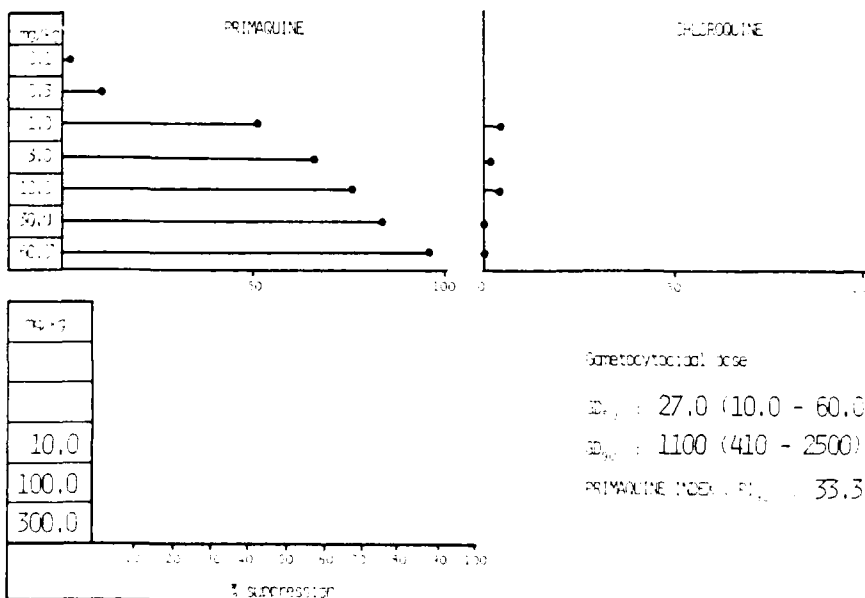
DATE : 11.1.84

PARASITE : *Plasmodium yoelii* nigeriensis

VERTEBRATE HOST : ♂ TFW MICE

INVERTEBRATE HOST : *Anopheles stephensi*

DOSE mg/kg	OOCYST COUNTS 0+7										MEAN	% CONTROL
a	47	73	38	35	20	38	30	28	29	16	33.5	100
	15											
10.0	18	26	24	12	20	18	33	18	21	28	22.5	67.0 ± 6.3
	29											
100.0	16	12	18	14	17	10	17	12	19	8	13.6	40.7 ± 3.6
	7											
300.0	5	13	6	4	5	2	12	13	9	12	7.8	23.4 ± 3.3



Principal Investigator : Professor W. Peters
 Department of Medical Parasitology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

TABLE 12

GAMETOCYCIDAL ACTIVITY

COMPOUND : LW 1730

WR 247705

BJ 51779

FORMULATION : TWEEN 80 / H₂OROUTE : SC / ~~100-100-100~~

MAXIMUM FULLY TOLERATED DOSE : >300 mg / kg X 1

EXPERIMENT No.: 2501

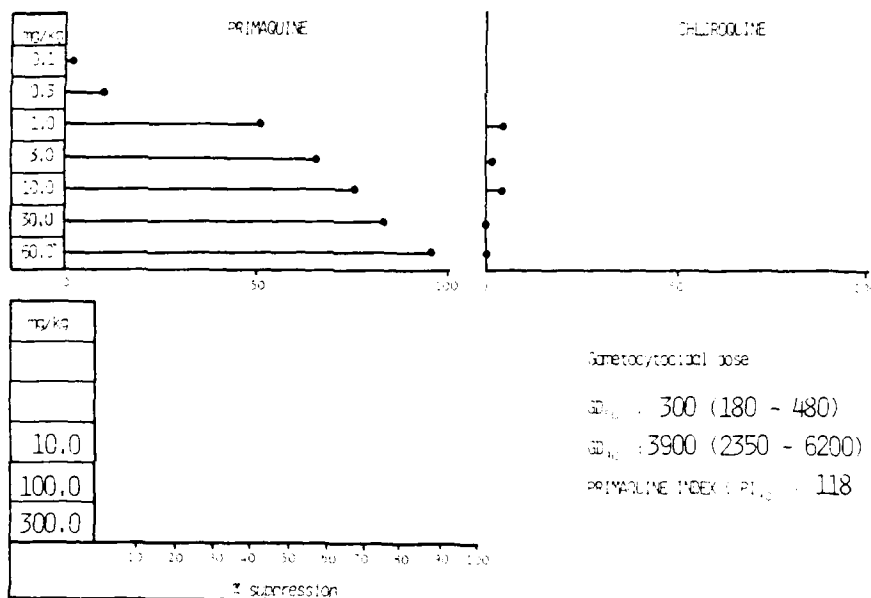
DATE : 1.2.84

PARASITE : *Plasmodium yoelii* nigeriensis

VERTEBRATE HOST : ♂ TFW MICE

INVERTEBRATE HOST : *Anopheles stephensi*

DOSE mg/kg	OOCYST COUNTS D+7										MEAN	% CONTROL
a	29	10	28	20	11	24	22	17	30	10	21.1	100
	10											
10.0	22	19	20	12	16	20	17	18	13	17	16.7	79.1 ± 4.3
	14	12										
100.0	17	23	13	18	9	27	17	21	6	0	15.1	71.6 ± 10.0
300.0	19	6	9	12	11	14	7	9	13	5	10.5	49.8 ± 6.6



Principal Investigator : Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

TABLE 4.3

ANTI-TOXICOCIDAL ACTIVITY

COMPOUND : LUN 1731

WR 248412

BJ 59202

FORMULATION : TWEEN 80 / H₂O

ROUTE : SC / IP / PO / IV

MAXIMUM FULLY TOLERATED DOSE : > 300 mg / kg X 1

EXPERIMENT No. : 2501

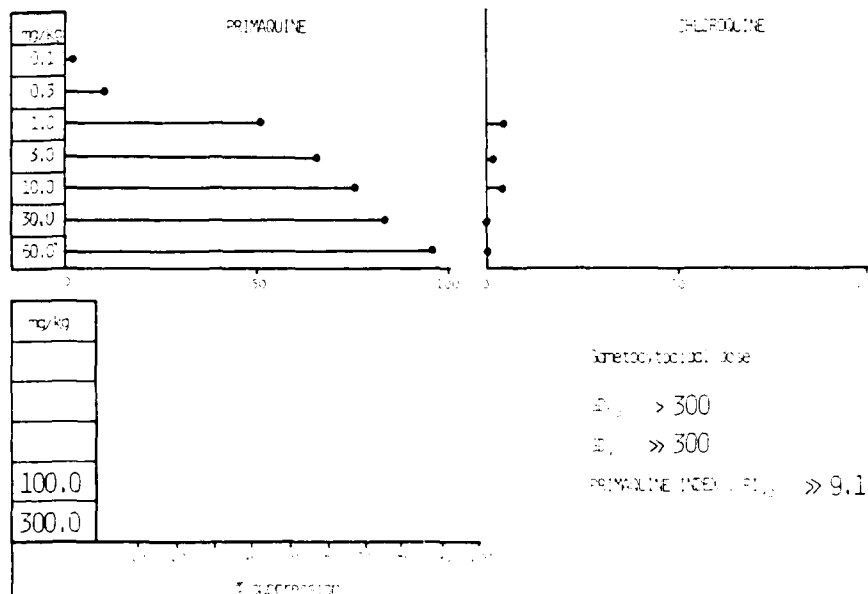
DATE : 1.2.84

PARASITE : *Plasmodium yoelii* nipertensis

VERTEBRATE HOST : ♂ FFW MICE

INVERTEBRATE HOST : *Anopheles stephensi*

DOSE mg/kg	DOCYST COUNTS D+7										MEAN	% CONTROL
0	29	10	28	20	11	24	22	17	30	10	21.1	100
	10											
100.0	21	13	13	17	20	18	12	16	10	18	16.0	75.8 ± 5.2
	18											
300.0	19	17	25	18	20	16	18	3	8	18	15.3	72.4 ± 8.6
	6											



Principal Investigator : Professor W. Petent
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIPROTOZOAL ACTIVITY

TABLE 1.1

ANTIPROTOZOAL ACTIVITY

COMPOUND : LON 1732

WR 237375

BH 58120

FORMULATION : TWEEN 80 / H₂O

ROUTE : SC / IP / ORAL

MAXIMUM FULLY TOLERATED DOSE : > 300 mg/kg (1)

EXPERIMENT NO. 2501

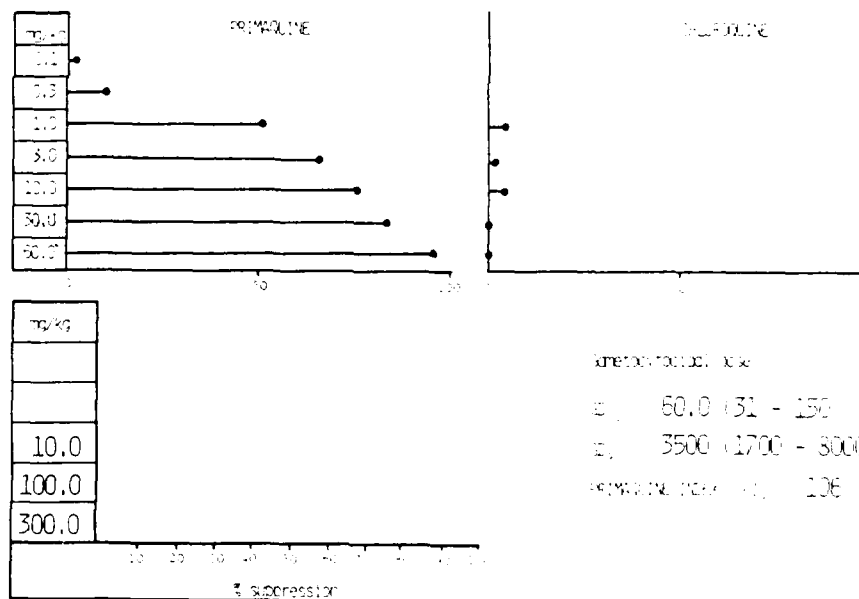
DATE : 1.2.84

PARASITE : *Plasmodium yoelii* (Nigeriensis)

VERTEBRATE HOST : ♂ FWH MICE

INVERTEBRATE HOST : *Anopheles stephensi*

DOSE mg/kg	OOCYST COUNTS D+7										MEAN	* CONTROL
a	29	10	28	20	11	24	22	17	30	10	21.1	11
	10											
10.0	16	18	11	13	16	12	14	18	19	10	15.0	71.1 ± 4.3
	21	12										
100.0	13	11	26	5	8	23	22	7	5		13.3	63.0 ± 7.6
300.0	13	16	7	15	10	0	11	5	10	7	9.2	43.6 ± 7.6



Principal Investigator : Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANIMAL EXPERIMENT

TABLE 1.5

ANETHROCYCLOL ACETATE

MINDEN 1733

NR 228708

BG 60798

ANESTHESIA TAKEN > 100

ROUTE: 10-10-10-10-10-10

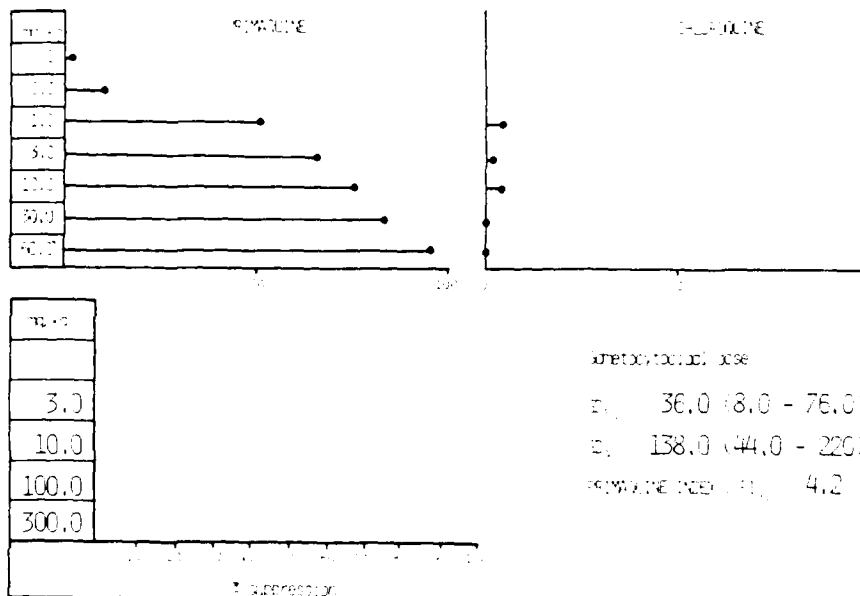
MAXIMUM TOLERATED DOSE > 300 mg/kg

EXPERIMENT NO. 2519

DATE: 8.2.84

PARASITE: Plasmodium falciparumINVERTEBRATE HOST: A. TA. MUIINVERTEBRATE HOST: Agoutis stephens

DOSE mg/kg	DOSE COUNT D+7										MEAN	STANDARD	
1	15	12	18	16	18	14	17	16	18	18	16.5	1.0	
	19												
3.0	27	22	12	14	14	20	19	19	16	18	18.1	100	1.5
10.0	12	9	8	7	10	11	3	6	10		8.4	50.9	5.5
100.0	7	7	6	0	5	0	0	7	5	0	3.7	22.4	4.2
300.0	3	0	0	0	5	2	0	0	0	1	1.7	10.3	5.5



Principal Investigator: Professor W. Peters
 Department of Medical Parasitology
 London School of Hygiene & Tropical Medicine

REFERENCES

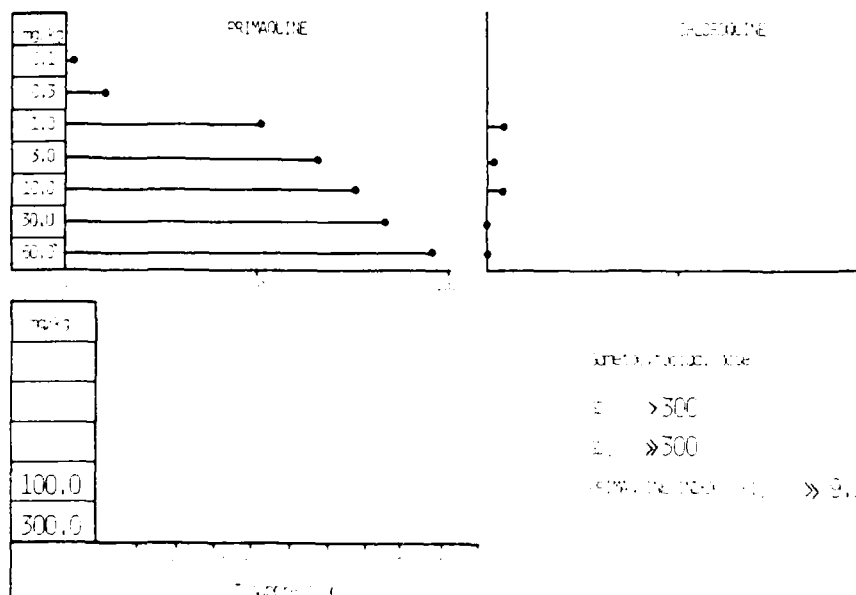
© 2004 Blackwell Publishing Ltd *Journal of Internal Medicine* 255: 101–107

FILE NO. ~~100-441101-100~~

PARAFINE PLASTICUM OELI EXPERIMENTA

LEGATE AT ROME

DEPARTMENT OF AGRICULTURE

[illegible]

DEPARTMENT OF THE ARMY
WASHINGTON, D. C. 20315

1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2150, 2151, 2152, 2153, 2154, 2155, 2156, 2157, 2158, 2159, 2160, 2161, 2162, 2163, 2164, 2165, 2166, 2167, 2168, 2169, 2170, 2171, 2172, 2173, 2174, 2175, 2176, 2177, 2178, 2179, 2180, 2181, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2190, 2191, 2192, 2193, 2194, 2195, 2196, 2197, 2198, 2199, 2200, 2201, 2202, 2203, 2204, 2205, 2206, 2207, 2208, 2209, 2210, 2211, 2212, 2213, 2214, 2215, 2216, 2217, 2218, 2219, 2220, 2221, 2222, 2223, 2224, 2225, 2226, 2227, 2228, 2229, 2230, 2231, 2232, 2233, 2234, 2235, 2236, 2237, 2238, 2239, 2240, 2241, 2242, 2243, 2244, 2245, 2246, 2247, 2248, 2249, 2250, 2251, 2252, 2253, 2254, 2255, 2256, 2257, 2258, 2259, 2260, 2261, 2262, 2263, 2264, 2265, 2266, 2267, 2268, 2269, 2270, 2271, 2272, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2284, 2285, 2286, 2287, 2288, 2289, 2290, 2291, 2292, 2293, 2294, 2295, 2296, 2297, 2298, 2299, 2300, 2301, 2302, 2303, 2304, 2305, 2306, 2307, 2308, 2309, 2310, 2311, 2312, 2313, 2314, 2315, 2316, 2317, 2318, 2319, 2320, 2321, 2322, 2323, 2324, 2325, 2326, 2327, 2328, 2329, 2330, 2331, 2332, 2333, 2334, 2335, 2336, 2337, 2338, 2339, 2340, 2341, 2342, 2343, 2344, 2345, 2346, 2347, 2348, 2349, 2350, 2351, 2352, 2353, 2354, 2355, 2356, 2357, 2358, 2359, 2360, 2361, 2362, 2363, 2364, 2365, 2366, 2367, 2368, 2369, 2370, 2371, 2372, 2373, 2374, 2375, 2376, 2377, 2378, 2379, 2380, 2381, 2382, 2383, 2384, 2385, 2386, 2387, 2388, 2389, 2390, 2391, 2392, 2393, 2394, 2395, 2396, 2397, 2398, 2399, 2400, 2401, 2402, 2403, 2404, 2405, 2406, 2407, 2408, 2409, 2410, 2411, 2412, 2413, 2414, 2415, 2416, 2417, 2418, 2419, 2420, 2421, 2422, 2423, 2424, 2425, 2426, 2427, 2428, 2429, 2430, 2431, 2432, 2433, 2434, 2435, 2436, 2437, 2438, 2439, 2440, 2441, 2442, 2443, 2444, 2445, 2446, 2447, 2448, 2449, 2450, 2451, 2452, 2453, 2454, 2455, 2456, 2457, 2458, 2459, 2460, 2461, 2462, 2463, 2464, 2465, 2466, 2467, 2468, 2469, 2470, 2471, 2472, 2473, 2474, 2475, 2476, 2477, 2478, 2479, 2480, 2481, 2482, 2483, 2484, 2485, 2486, 2487, 2488, 2489, 2490, 2491, 2492, 2493, 2494, 2495, 2496, 2497, 2498, 2499, 2500, 2501, 2502, 2503, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2513, 2514, 2515, 2516, 2517, 2518, 2519, 2520, 2521, 2522, 2523, 2524, 2525, 2526, 2527, 2528, 2529, 2530, 2531, 2532, 2533, 2534, 2535, 2536, 2537, 2538, 2539, 2540, 2541, 2542, 2543, 2544, 2545, 2546, 2547, 2548, 2549, 2550, 2551, 2552, 2553, 2554, 2555, 2556, 2557, 2558, 2559, 2560, 2561, 2562, 2563, 2564, 2565, 2566, 2567, 2568, 2569, 2570, 2571, 2572, 2573, 2574, 2575, 2576, 2577, 2578, 2579, 2580, 2581, 2582, 2583, 2584, 2585, 2586, 2587, 2588, 2589, 2590, 2591, 2592, 2593, 2594, 2595, 2596, 2597, 2598, 2599, 2600, 2601, 2602, 2603, 2604, 2605, 2606, 2607, 2608, 2609, 2610, 2611, 2612, 2613, 2614, 2615, 2616, 2617, 2618, 2619, 2620, 2621, 2622, 2623, 2624, 2625, 2626, 2627, 2628, 2629, 2630, 2631, 2632, 2633, 2634, 2635, 2636, 2637, 2638, 2639, 2640, 2641, 2642, 2643, 2644, 2645, 2646, 2647, 2648, 2649, 2650, 2651, 2652, 2653, 2654, 2655, 2656, 2657, 2658, 2659, 2660, 2661, 2662, 2663, 2664, 2665, 2666, 2667, 2668, 2669, 2670, 2671, 2672, 2673, 2674, 2675, 2676, 2677, 2678, 26

DOI: 10.1002/for

SUMMARY OF ANTIMALARIAL TESTS

TABLE 4.7

DACTEOCYTICIDAL ACTIVITY

Compound: LW1783 ANC-IX-19 (McChesney) - WR 249725

Formulation: Tween 80 / H₂O

Route: i.p. / i.p. / i.p.

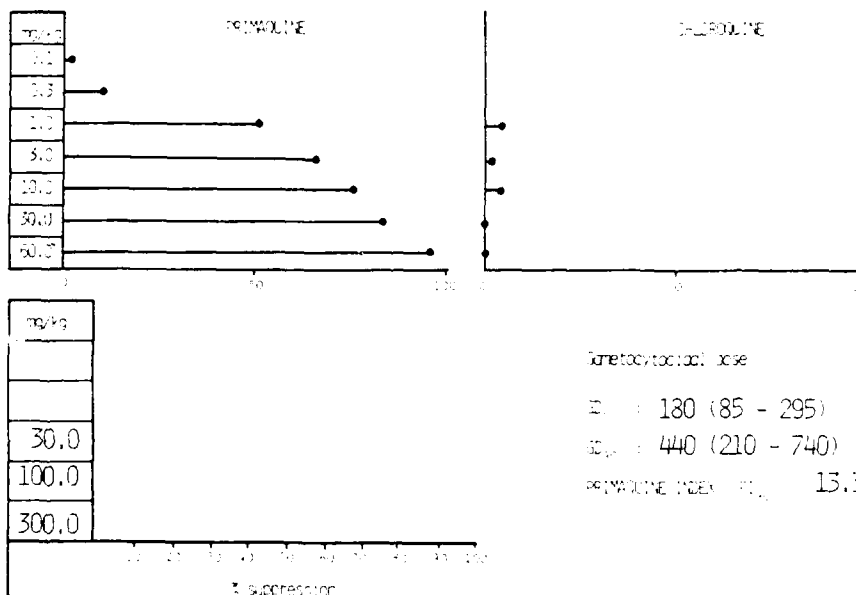
Maximum fully tolerated dose: >300 mg/kg x 1 Experiment No. 2481 Date: 25.1.84

Parasite: *Plasmodium yoelii* (Nederlands)

Vertebrate host: J. TRA WICE

Invertebrate host: *Anopheles stephensi*

DOSE mg/kg	DOCT COUNTS 0-7										MEAN	% CONTROL
	15	18	17	19	20	24	18	23	17	25		
	14	12	23	21								
30.0	21	25	20	27	26	14	25	18	8	15	19.9	100 ± 10.0
100.0	5	14	13	3	1	10	13	14	9	14	9.6	50.5 ± 6.8
300.0	7	14	2	5	8	12	8	7	10	8	8.1	42.6 ± 6.3



Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

TABLE 1-5

ANTI-PROTECTORIAL ACTIVITY

COMPOUND: LA 1801

WR 15031

AY 15653

FORMULATION: TWEEN 80 + H₂O

ROUTE: SC (400/200/100)

MAXIMUM TOLERATED DOSE: >300 mg/kg (1)

EXPERIMENT NO.: 2632

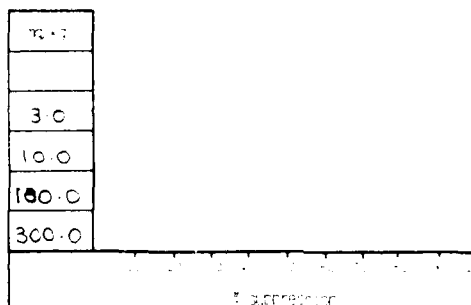
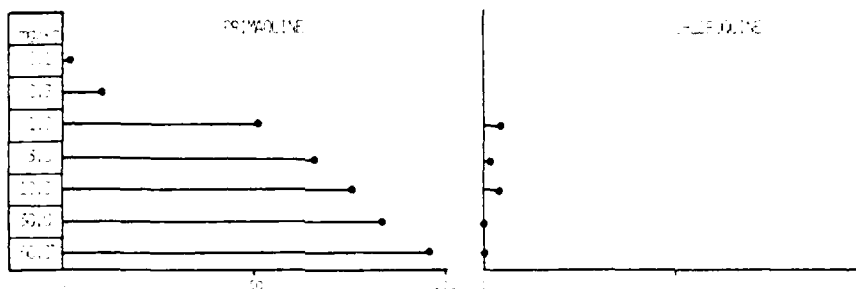
DATE: 4-4-64

PARASITE: *Plasmodium yoelii nigritensis*

INTESTINE HOST: 3 WEEK MICE

INTESTINE HOST: *Anopheles stephensi*

DOSE mg/kg	OOCYST COUNTS 3+7										MEAN	% CONTROL
0	11	39	14	22	16	24	15	14	13	33	20.1	100
3.0	15	5	20	12	13	11	22	21	12	21	15.2	75.6 ± 7.5
10.0	25	10	16	18	10	9	14	12			14.3	70.9 ± 6.8
100.0	11	7	12	19	22	13	28	12	8	18	15.0	74.6 ± 6.5
300.0	7	11	17	12	17	16	21	14			14.4	71.5 ± 9.1



Antiprotozoal dose

0 > 300

10 > 300

PRIMAQUINE DOSE: 100 > 9.1

Principal Investigator: Professor W. Peters
Department of Medical Parasitology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

PAGE 1/1

ANTI-PROLIFERATIVE ACTIVITY

IMPACT: 1802

WR 6890

BK 12713

FORMULATION: 100% H₂O

ROUTE: 100% H₂O

MAXIMUM TOLERATED DOSE: > 300

EXPERIMENT NO.: 2560

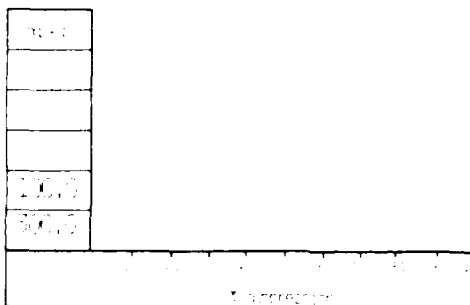
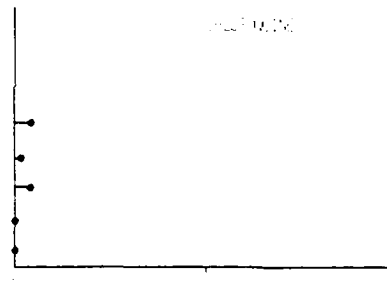
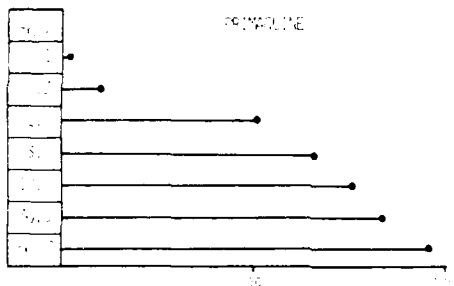
DATE: 29.2.84

PASASITE: *Plasmodium falciparum* (F3D7)

TESTERATE HOST: 100% H₂O

TESTERATE HOST: 100% H₂O

DOSE (mg)	DOSE COUNTS (n=7)											MEAN	ST. DEV.
0	30	33	29	39	17	18	30	24	20	17	25.7	1.1	
100.0	8	9	16	10	13	20	13	10	15	17	13.1	51.0 ± 2.3	
300.0	6	2	2	1	7	2	3	1	2	5	3.1	12.1 ± 1.4	



CHLOROQUINE DOSE

100(90 - 110)

340(290 - 370)

PRIMAQUINE DOSE: 10.3

Principal Investigator: Dr. Antonio M. Petroni

Co-Investigator: Dr. Antonio M. Petroni

Principal Investigator: Dr. Antonio M. Petroni

• 4500

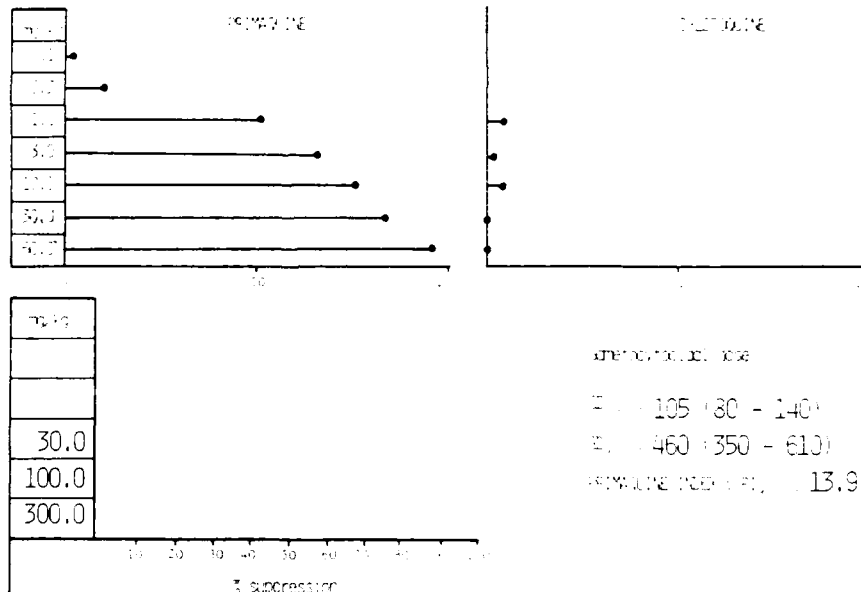
FORMULATION : TWEEN 80 / H₂O

ROUTE : 20 / 42 → 46 → 49

PARASITE : Plasmodium yoelii nigeriensis

VERTEBRATE HOST : ♂ FWH MICE

INVERTEBRATE HOST : Anomelies sternalis.

[illegible]

Principal Investigator : Professor W. Peters
Department of Medical Protozoology,
London School of Hygiene & Tropical Medicine

51

BK 56500

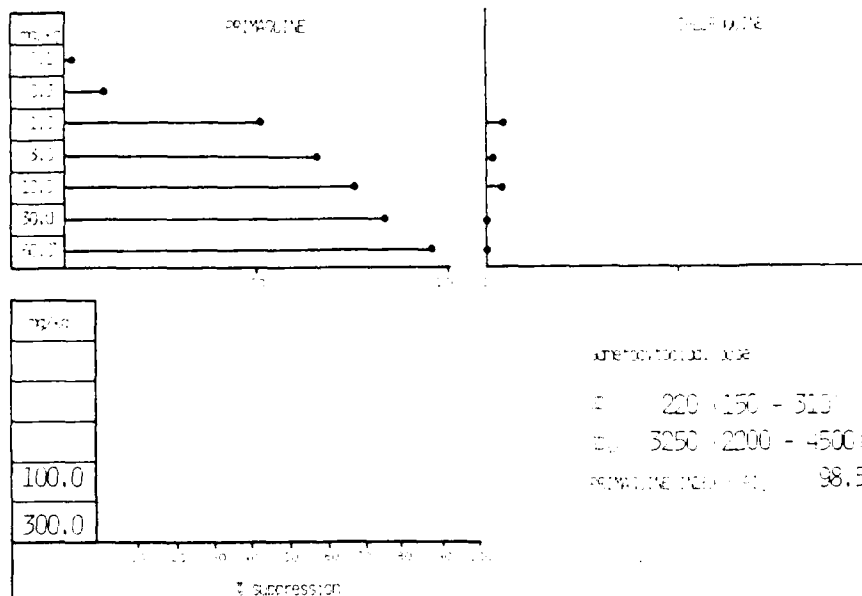
21 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54 56 58 60 62 64 66 68 70 72 74 76 78 80 82 84 86 88 90 92 94 96 98 100

EXPERIMENT NO. 2560

29.2.84

PARASITE : *Plasmodium falciparum* nigeriensis

INTERSTATE - OCT. ACCIDENT REPORT.

[illegible]

Principal Investigator : Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIPYRETIAC TEST

Page 5 of 2

ANTIPYRETIAC ACTIVITY

Compound: LA 1931 WR 249725 BK 69990

Formulation: Tween 80 + H₂O Route: Oral (100 mg/kg)

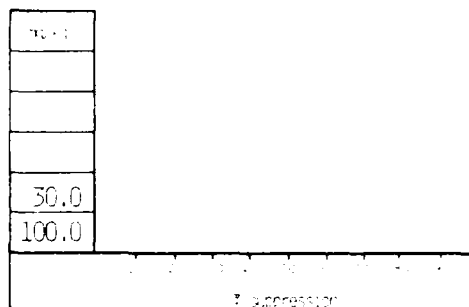
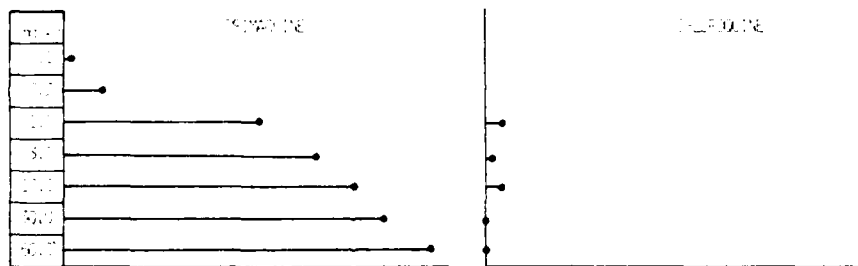
Maximum Tolerated Dose: >100 mg/kg Experiment No.: 2645 Date: 11.4.85

Parasite: *Plasmodium berghei* (289/85)12

Temperature Host: 37 °C (Femur)

Overtemperature Host: Antipyretic (phenol)

Dose (mg/kg)	Individual Data (°C)										Mean	Control
0	21	13	18	8	20	24	6	11	14	12	15.5	16
	23											
30.0	19	12	21	11	18	13	23	18	20	19	16.9	100 ± 2.9
	12											
100.0	22	14	18	11	16	20	14	13	19	8	15.5	100 ± 4.8



Antipyretic Dose

1 >> 100

4 >> 100

Antipyretic Dose >> 3.0

Principal Investigator: Professor W. Peters
Department of Medical Pharmacology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TEST

SLIDE 5-1

ANTI-PROTOZOAL ACTIVITY

MPHIC 1884 Ph 4007 BK 64306

FORMULATION: TABLETS

ROUTE: PO (48-48-48-48)

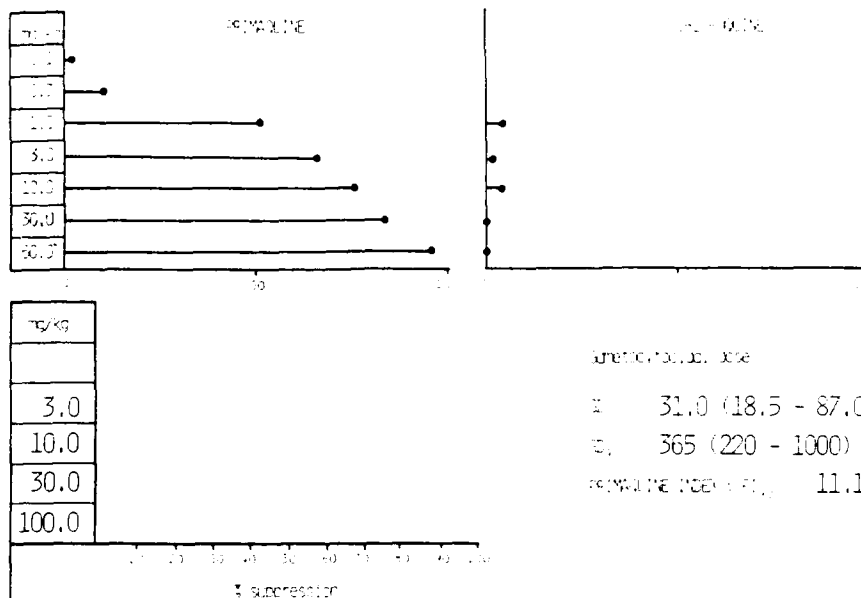
MAXIMUM FULLY TOLERATED DOSE: >100mg/kg/day EXPERIMENT NO. 2589 DATE: 14.3.84

PARASITE: Plasmodium falciparum

INVERTEBRATE HOST: A. stephensi

INVERTEBRATE HOST: Anopheles stephensi

DOSE (mg/kg)	XOXYSTUARTS 1-7										MEAN	STANDARD DEVIATION
7	12	16	23	16	20	16	17	18	17	24	17.9	1.7
3.0	18	13	16	18	15	10	21	17	20	16	16.4	91.6 ± 4.4
10.0	13	22	15	15	8	11	14	7	12	15	13.2	73.7 ± 6.1
30.0	8	6	7	11	9	8	14	4	9	8	8.4	46.9 ± 5.6
100.0	7	0	3	9	7	5	9	8	4	0	5.8	32.4 ± 5.0



Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

ANTHELMINTIC ACTIVITY

REFERENCE No. 1885

Ph 4017 BK 64315

FORMULATION: TWEEN 80 + H₂O

PURITY: 100% (estimated)

MAXIMUM FULLY TOLERATED DOSE: >100 mg/kg

EXPERIMENT No. 2589

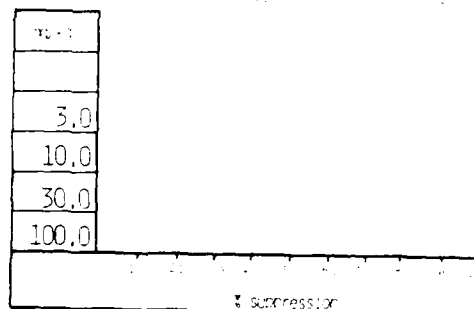
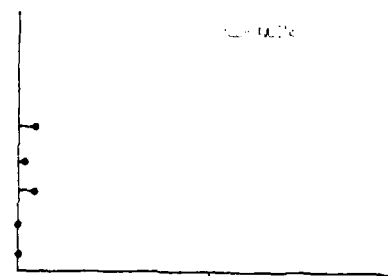
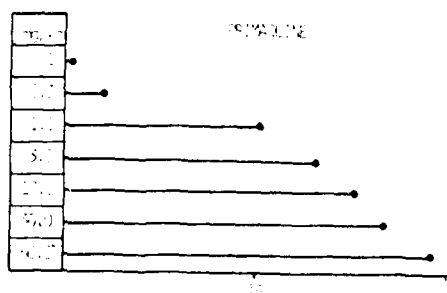
DATE: 14.3.84

PARASITE: *Plasmodium falciparum* (K1)

TEST STRAIN: 100% (K1)

TEST STRAIN: 100% (K1)

DOSE (mg/kg)	DOCKET COUNTS (n=10)										MEAN	ST. DEV.
0	12	16	23	16	20	16	17	18	17	24	17.9	1.1
3.0	19	16	14	10	20	25	18	14	11	16	16.3	91.1 ± 4.4
10.0	13	16	14	18	21	15	16	11	14	10	14.8	82.7 ± 4.4
30.0	2	3	6	4	3	8	4	9	5	1	4.5	25.1 ± 4.5
100.0	4	2	5	0	4	3	0	3	6	6	3.3	18.4 ± 3.4



ANTHELMINTIC ACTIVITY

1. 20.0 (10.5 - 39.0)

2. 90.0 (47.0 - 175)

ANTHELMINTIC ACTIVITY: 2.7

Principal Investigator: Professor W. Peters
Department of Medical Parasitology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

TABLE 5.71

GAMETOCYTOCIDAL ACTIVITY

COMPOUND : LW 1886

Ph 4900

BK 64324

FORMULATION : TWEEN 80 + H₂O

ROUTE : SC / TP / PO / IT / IV

MAXIMUM FULLY TOLERATED DOSE : >100 mg/kg x 1

EXPERIMENT No.: 2589

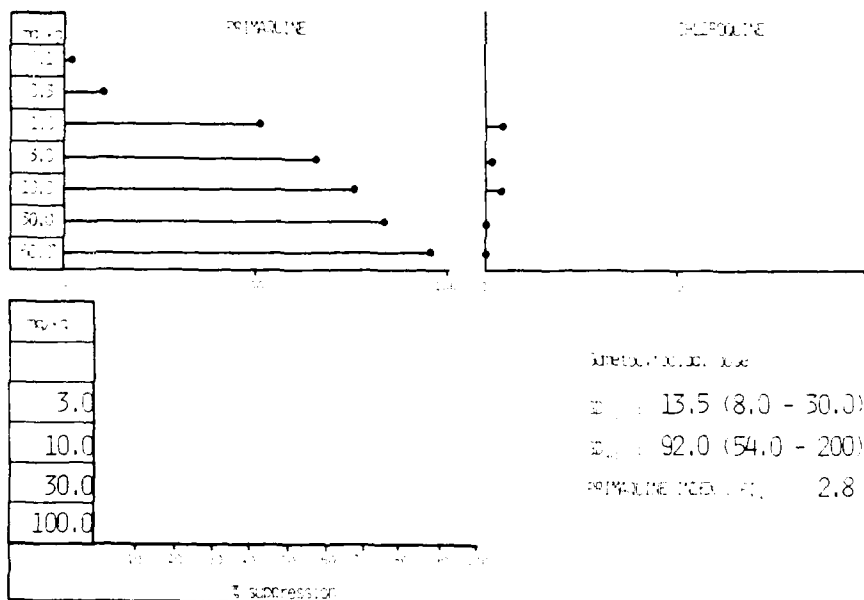
DATE : 14.3.84

PARASITE : *Plasmodium yoelii* nederlandsi

VERTEBRATE HOST : ♀ TPA MICE

INVERTEBRATE HOST : *Anopheles stephensi*

DOSE mg/kg	DOCYST COUNTS 0-7											MEAN	% CONTROL
0	12	16	23	16	20	16	17	18	17	24	17.9		100
3.0	14	13	16	20	10	28	11	22	9	18	16.1		89.0 ± 5.0
10.0	10	10	14	12	8	14	9	11	10	7	10.5		58.7 ± 3.9
30.0	4	1	2	3	6	4	3	6	5	8	4.2		23.5 ± 3.9
100.0	0	6	5	1	2	3	4	1	0	0	2.2		12.3 ± 3.4



Principal Investigator : Professor W. Peters
 Department of Medical Parasitology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

TABLE 5 (1)

GAMETOCYCIDAL ACTIVITY

COMPOUND : L-1887

Ph 4901

BK 64333

FORMULATION : TWEEN 80 / H₂OROUTE : SC / ~~IP~~ ~~IV~~ ~~IM~~

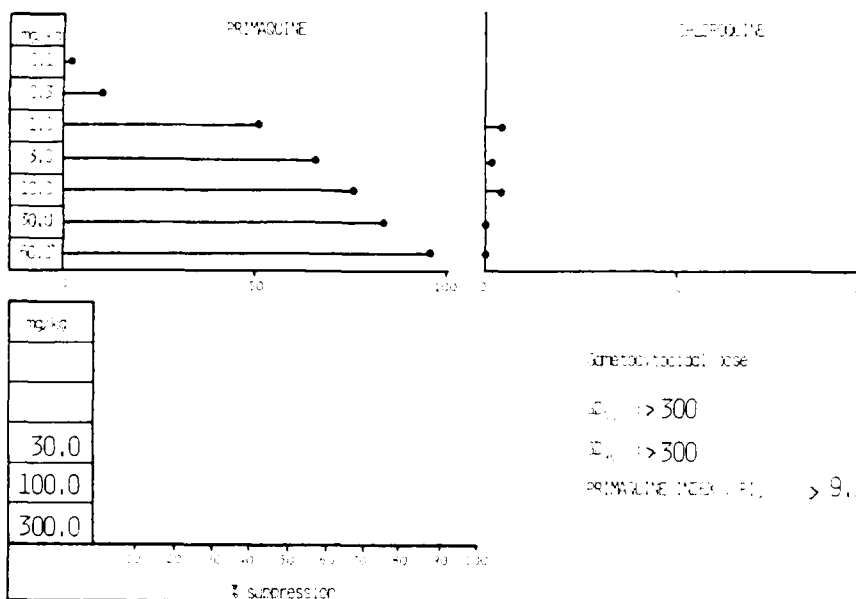
MAXIMUM TOLERATED DOSE : > 300 mg/kg x 1

EXPERIMENT No : 2576

DATE : 7.3.84

PARASITE : *Plasmodium yoelii nigeriensis*INVERTEBRATE HOST : 3rd FWH MICEINVERTEBRATE HOST : *Anopheles stephensi*

DOSE mg/kg	DOCT COUNTS 0-7										MEAN	ST. DEV.
0	21	16	20	22	19	25	13	6	21		18.1	10
30.0	15	14	19	15	18	18	20	12	24	12	16.7	92.3 ± 3.4
100.0	18	15	23	19	11	13	16	11	10	14	15.0	82.9 ± 4.5
300.0	12	11	14	8	12	14	10	17	13	7	11.2	61.9 ± 6.6
	5											



Principal Investigator : Professor W. Peters

Department of Medical Protozoology

London School of Hygiene & Tropical Medicine

UNIVERSITY OF AUSTRALASIAN MEDICAL RESEARCH - CELL 57

ANTI-PROLIFERATIVE ACTIVITY

COMPOUND: LK 1752 WR 245082 BK 02771

FORMULATION: TAEN 80 H₂O ROUTE: i.p. *****

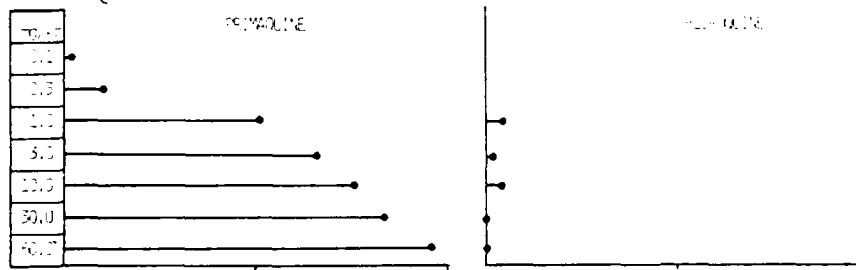
MAXIMUM FULLY TOLERATED DOSE: >300 mg/kg EXPERIMENT NO: 2532 DATE: 15.12.84

PARASITE: *Plasmodium falciparum* (Nobelsens)

VERTEBRATE HOST: 21 DAY MICE

INVERTEBRATE HOST: *Anopheles stephensi*

DOSE mg/kg	DOSEY POINTS D+7										MEAN	STANDARD
a	18	27	48	10	11	17	12	11	21	14	18.0	1.0
	9											
10.0	16	18	11	19	14	15	12	13	10	15	14.7	81.7 ± 4.4
	19											
100.0	24	14	4	5	5	12	2	4	3	2	7.3	40.6 ± 8.2
	6											
300.0	6	7	3	12	5	6	5	4	9	8	6.2	34.4 ± 5.0
	3											



DOSE mg/kg	10.0	100.0	300.0
10.0	100	80	60
100.0	100	80	60
300.0	100	80	60

ANTI-PROLIFERATIVE ACTIVITY

1. 70.0 - 28.0 - 185

2. 2100 - 850 - 5500

PRIMARY DOSE: 63.6

Principal Investigator: Professor A. R. G. G.
Department of Medical Microbiology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TEST

DATE: 5/8

EXPERIMENTAL DESIGN

COMPOUND: 1753 WR: 246976 BK: 02780

FORMULATION: Tween 80 + H₂O ROUTE: IP -----

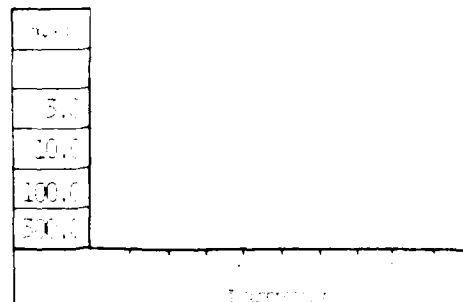
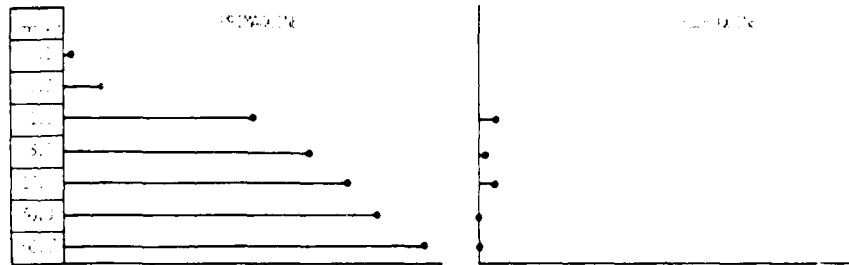
MAXIMUM FULLY TOLERATED DOSE: >300 mg/kg EXPERIMENT NO: 2532 DATE: 15.12.84

PARASITE: Plasmodium falciparum

TEST STRAIN: 3D7

INTERPRETATION: Antimalarial

DOSE (mg/kg)	NO. OF PARASITES										MEAN	ST. DEV.
0	18	27	48	10	11	17	12	11	21	14	18.0	0
	9											
3.0	10	12	13	17	9	16	8	15	12	10	12.0	67.8 ± 5.1
10.0	11	18	11	6	12	4	8	15	10	14	11.0	60.0 ± 5.0
100.0	4	4	4	3	5	6	6	4	7		4.6	25.7 ± 1.7
300.0	2	1	3	1	2	0	1	1	2		1.3	7.0 ± 1.7



INTERPRETATION:

1. 11.0 6.0 ± 23.1

2. 25.7 14.0 ± 5.1

3. 7.0 1.7 ± 1.7

Notes: 1. The test was performed in triplicate.

2. The test was performed in triplicate.

3. The test was performed in triplicate.

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1971

INSTITUTIONAL ADDRESS

MOORE 1741 WS 102796 AD EC 78878

NAME AND ADDRESS OF DONOR

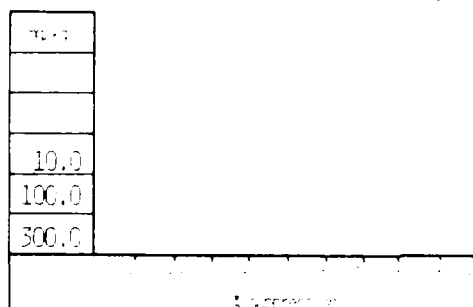
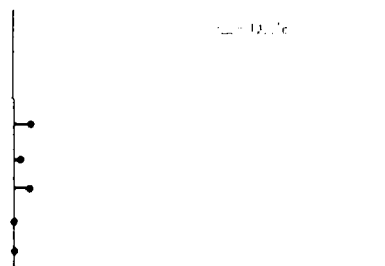
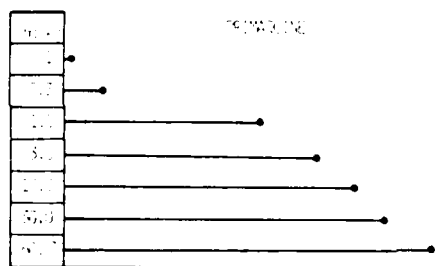
WISCONSIN DEPARTMENT OF AGRICULTURE

STATE OF WISCONSIN

UNIVERSITY OF WISCONSIN

UNIVERSITY OF WISCONSIN

DOSE (mg)	DOSE (mg)										MEAN	ST. DEV.
2	15	12	18	16	18	14	17	16	13	18	10.5	
	19											
10.0	22	13	18	7	9	11	14	10	18	3	12.8	60.1 ± 5.5
	8											
100.0	16	3	5	9	10	6	0	6			0.4	42.8 ± 3.5
300.0	2	7	7	9	4	5	6	4	5	0	4.3	29.7 ± 5.5



UNIVERSITY OF WISCONSIN

1971

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MOORE 1741 WS 102796 AD EC 78878

NAME AND ADDRESS OF DONOR

WISCONSIN DEPARTMENT OF AGRICULTURE

STATE OF WISCONSIN

UNIVERSITY OF WISCONSIN

UNIVERSITY OF WISCONSIN

- 2 - 61

208777 U.S. AIR FORCE

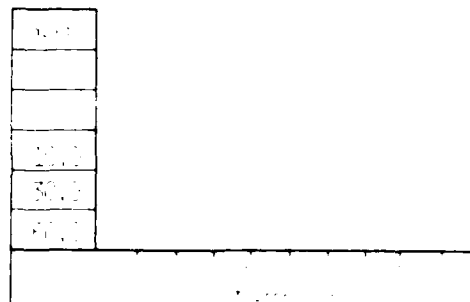
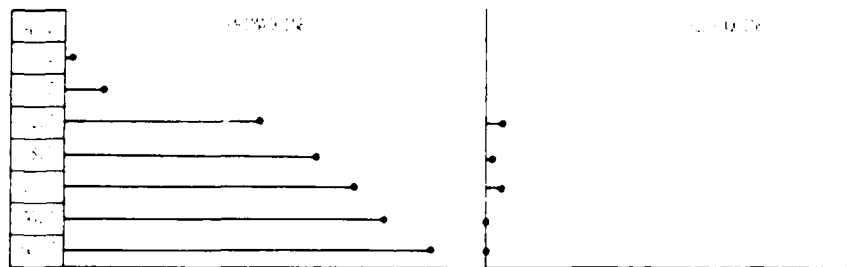
NAME: A-1100 WR 142490 BH 10371 Meflocaine

Figure 1. Schematic representation of the experimental design. The subjects were divided into two groups: the control group and the experimental group. The control group was divided into two subgroups: the control group and the control group. The experimental group was divided into two subgroups: the experimental group and the experimental group.

ADDITIONAL COMMENTS: 100% ≥ 60 mg/l. ≥ 60 mg/l. 2481 15.1.84

DATE RECEIVED

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[illegible][illegible]

11-40-240

1. $\frac{1}{2}$

 $\text{pH} = 1.8$

1. The first group of people who are not in the labor force are those who are not in the labor force because they are not in the labor force.

[illegible]

1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2150, 2151, 2152, 2153, 2154, 2155, 2156, 2157, 2158, 2159, 2160, 2161, 2162, 2163, 2164, 2165, 2166, 2167, 2168, 2169, 2170, 2171, 2172, 2173, 2174, 2175, 2176, 2177, 2178, 2179, 2180, 2181, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2190, 2191, 2192, 2193, 2194, 2195, 2196, 2197, 2198, 2199, 2200, 2201, 2202, 2203, 2204, 2205, 2206, 2207, 2208, 2209, 2210, 2211, 2212, 2213, 2214, 2215, 2216, 2217, 2218, 2219, 2220, 2221, 2222, 2223, 2224, 2225, 2226, 2227, 2228, 2229, 2230, 2231, 2232, 2233, 2234, 2235, 2236, 2237, 2238, 2239, 2240, 2241, 2242, 2243, 2244, 2245, 2246, 2247, 2248, 2249, 2250, 2251, 2252, 2253, 2254, 2255, 2256, 2257, 2258, 2259, 2260, 2261, 2262, 2263, 2264, 2265, 2266, 2267, 2268, 2269, 2270, 2271, 2272, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2284, 2285, 2286, 2287, 2288, 2289, 2290, 2291, 2292, 2293, 2294, 2295, 2296, 2297, 2298, 2299, 2300, 2301, 2302, 2303, 2304, 2305, 2306, 2307, 2308, 2309, 2310, 2311, 2312, 2313, 2314, 2315, 2316, 2317, 2318, 2319, 2320, 2321, 2322, 2323, 2324, 2325, 2326, 2327, 2328, 2329, 2330, 2331, 2332, 2333, 2334, 2335, 2336, 2337, 2338, 2339, 2340, 2341, 2342, 2343, 2344, 2345, 2346, 2347, 2348, 2349, 2350, 2351, 2352, 2353, 2354, 2355, 2356, 2357, 2358, 2359, 2360, 2361, 2362, 2363, 2364, 2365, 2366, 2367, 2368, 2369, 2370, 2371, 2372, 2373, 2374, 2375, 2376, 2377, 2378, 2379, 2380, 2381, 2382, 2383, 2384, 2385, 2386, 2387, 2388, 2389, 2390, 2391, 2392, 2393, 2394, 2395, 2396, 2397, 2398, 2399, 2400, 2401, 2402, 2403, 2404, 2405, 2406, 2407, 2408, 2409, 2410, 2411, 2412, 2413, 2414, 2415, 2416, 2417, 2418, 2419, 2420, 2421, 2422, 2423, 2424, 2425, 2426, 2427, 2428, 2429, 2430, 2431, 2432, 2433, 2434, 2435, 2436, 2437, 2438, 2439, 2440, 2441, 2442, 2443, 2444, 2445, 2446, 2447, 2448, 2449, 2450, 2451, 2452, 2453, 2454, 2455, 2456, 2457, 2458, 2459, 2460, 2461, 2462, 2463, 2464, 2465, 2466, 2467, 2468, 2469, 2470, 2471, 2472, 2473, 2474, 2475, 2476, 2477, 2478, 2479, 2480, 2481, 2482, 2483, 2484, 2485, 2486, 2487, 2488, 2489, 2490, 2491, 2492, 2493, 2494, 2495, 2496, 2497, 2498, 2499, 2500, 2501, 2502, 2503, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2513, 2514, 2515, 2516, 2517, 2518, 2519, 2520, 2521, 2522, 2523, 2524, 2525, 2526, 2527, 2528, 2529, 2530, 2531, 2532, 2533, 2534, 2535, 2536, 2537, 2538, 2539, 2540, 2541, 2542, 2543, 2544, 2545, 2546, 2547, 2548, 2549, 2550, 2551, 2552, 2553, 2554, 2555, 2556, 2557, 2558, 2559, 2560, 2561, 2562, 2563, 2564, 2565, 2566, 2567, 2568, 2569, 2570, 2571, 2572, 2573, 2574, 2575, 2576, 2577, 2578, 2579, 2580, 2581, 2582, 2583, 2584, 2585, 2586, 2587, 2588, 2589, 2590, 2591, 2592, 2593, 2594, 2595, 2596, 2597, 2598, 2599, 2600, 2601, 2602, 2603, 2604, 2605, 2606, 2607, 2608, 2609, 2610, 2611, 2612, 2613, 2614, 2615, 2616, 2617, 2618, 2619, 2620, 2621, 2622, 2623, 2624, 2625, 2626, 2627, 2628, 2629, 2630, 2631, 2632, 2633, 2634, 2635, 2636, 2637, 2638, 2639, 2640, 2641, 2642, 2643, 2644, 2645, 2646, 2647, 2648, 2649, 2650, 2651, 2652, 2653, 2654, 2655, 2656, 2657, 2658, 2659, 2660, 2661, 2662, 2663, 2664, 2665, 2666, 2667, 2668, 2669, 2670, 2671, 2672, 2673, 2674, 2675, 2676, 2677, 2678, 26

5.4 ORIENTATIONAL TEST DATA

62

2005 05 22

FORMULATION: DISSOLVED / SUSPENDED IN 5 % ALCOHOL / PROPYLENE GLYCOL

ROUTE - ORAL ADMINISTRATION TO YOUNGSTERS IN SUSPECTED FOR MALARIA

PARASITE : Plasmodium falciparum

WEBSITE: www.mccormick.com

TOXICITY : XXXXX ~~XXXXXXXXXXXX~~ XXXX, NO TOXIC EFFECTS OBS.

DATE : 30.5.84

DEFININARY TEST

[illegible]

~~XXXXXXXXXXXX / XXXXX / XXXXXX / XXXX / XXXX~~

[illegible][illegible]

1. *Journal of the American Medical Association*, 1997; 277: 1033-1038.

• • •

• • •

1. *Phragmites australis* (Cav.) Trin. ex Steud.

1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2150, 2151, 2152, 2153, 2154, 2155, 2156, 2157, 2158, 2159, 2160, 2161, 2162, 2163, 2164, 2165, 2166, 2167, 2168, 2169, 2170, 2171, 2172, 2173, 2174, 2175, 2176, 2177, 2178, 2179, 2180, 2181, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2190, 2191, 2192, 2193, 2194, 2195, 2196, 2197, 2198, 2199, 2200, 2201, 2202, 2203, 2204, 2205, 2206, 2207, 2208, 2209, 2210, 2211, 2212, 2213, 2214, 2215, 2216, 2217, 2218, 2219, 2220, 2221, 2222, 2223, 2224, 2225, 2226, 2227, 2228, 2229, 2230, 2231, 2232, 2233, 2234, 2235, 2236, 2237, 2238, 2239, 2240, 2241, 2242, 2243, 2244, 2245, 2246, 2247, 2248, 2249, 2250, 2251, 2252, 2253, 2254, 2255, 2256, 2257, 2258, 2259, 2260, 2261, 2262, 2263, 2264, 2265, 2266, 2267, 2268, 2269, 2270, 2271, 2272, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2284, 2285, 2286, 2287, 2288, 2289, 2290, 2291, 2292, 2293, 2294, 2295, 2296, 2297, 2298, 2299, 2300, 2301, 2302, 2303, 2304, 2305, 2306, 2307, 2308, 2309, 2310, 2311, 2312, 2313, 2314, 2315, 2316, 2317, 2318, 2319, 2320, 2321, 2322, 2323, 2324, 2325, 2326, 2327, 2328, 2329, 2330, 2331, 2332, 2333, 2334, 2335, 2336, 2337, 2338, 2339, 2340, 2341, 2342, 2343, 2344, 2345, 2346, 2347, 2348, 2349, 2350, 2351, 2352, 2353, 2354, 2355, 2356, 2357, 2358, 2359, 2360, 2361, 2362, 2363, 2364, 2365, 2366, 2367, 2368, 2369, 2370, 2371, 2372, 2373, 2374, 2375, 2376, 2377, 2378, 2379, 2380, 2381, 2382, 2383, 2384, 2385, 2386, 2387, 2388, 2389, 2390, 2391, 2392, 2393, 2394, 2395, 2396, 2397, 2398, 2399, 2400, 2401, 2402, 2403, 2404, 2405, 2406, 2407, 2408, 2409, 2410, 2411, 2412, 2413, 2414, 2415, 2416, 2417, 2418, 2419, 2420, 2421, 2422, 2423, 2424, 2425, 2426, 2427, 2428, 2429, 2430, 2431, 2432, 2433, 2434, 2435, 2436, 2437, 2438, 2439, 2440, 2441, 2442, 2443, 2444, 2445, 2446, 2447, 2448, 2449, 2450, 2451, 2452, 2453, 2454, 2455, 2456, 2457, 2458, 2459, 2460, 2461, 2462, 2463, 2464, 2465, 2466, 2467, 2468, 2469, 2470, 2471, 2472, 2473, 2474, 2475, 2476, 2477, 2478, 2479, 2480, 2481, 2482, 2483, 2484, 2485, 2486, 2487, 2488, 2489, 2490, 2491, 2492, 2493, 2494, 2495, 2496, 2497, 2498, 2499, 2500, 2501, 2502, 2503, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2513, 2514, 2515, 2516, 2517, 2518, 2519, 2520, 2521, 2522, 2523, 2524, 2525, 2526, 2527, 2528, 2529, 2530, 2531, 2532, 2533, 2534, 2535, 2536, 2537, 2538, 2539, 2540, 2541, 2542, 2543, 2544, 2545, 2546, 2547, 2548, 2549, 2550, 2551, 2552, 2553, 2554, 2555, 2556, 2557, 2558, 2559, 2560, 2561, 2562, 2563, 2564, 2565, 2566, 2567, 2568, 2569, 2570, 2571, 2572, 2573, 2574, 2575, 2576, 2577, 2578, 2579, 2580, 2581, 2582, 2583, 2584, 2585, 2586, 2587, 2588, 2589, 2590, 2591, 2592, 2593, 2594, 2595, 2596, 2597, 2598, 2599, 2600, 2601, 2602, 2603, 2604, 2605, 2606, 2607, 2608, 2609, 2610, 2611, 2612, 2613, 2614, 2615, 2616, 2617, 2618, 2619, 2620, 2621, 2622, 2623, 2624, 2625, 2626, 2627, 2628, 2629, 2630, 2631, 2632, 2633, 2634, 2635, 2636, 2637, 2638, 2639, 2640, 2641, 2642, 2643, 2644, 2645, 2646, 2647, 2648, 2649, 2650, 2651, 2652, 2653, 2654, 2655, 2656, 2657, 2658, 2659, 2660, 2661, 2662, 2663, 2664, 2665, 2666, 2667, 2668, 2669, 2670, 2671, 2672, 2673, 2674, 2675, 2676, 2677, 2678, 26

1. *Journal of the American Medical Association*, 1997; 278: 1039-1044.

COMPARISON OF ANTIMALARIAL TESTS

Page 63

SPOROZOICIDAL ACTIVITY

COMPOUND : UN 1715 WR 5990 AG 99266

FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION

ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS

PARASITE : *Plasmodium yoelii* nigeriensis

VERTEBRATE HOST : 3 FEMALE MICE

INVERTEBRATE HOST : *Anopheles gambiae*

TOXICITY : ~~XXXXXXXXXXXX~~ NO TOXIC EFFECTS SEEN

EXPERIMENT NUMBER : 2760

DATE : 30.5.84

PRELIMINARY TEST

CONCENTRATION (%)	OOCYST COUNTS (5 + 5)										MEAN	ST. CONTROL
2	15	26	14	73	32	37	17	22	34	38	35.6	
0.05	27	25	14	10	20	28	31	19	12	24	20.6	66.6 ± 6.9
	13											

~~XXXXXXXXXX~~ = ACTIVE ~~XXXXXXXXXX~~ = INACTIVE AT 100% T

EXTENDED TEST

CONCENTRATION (%)	OOCYST COUNTS (5 + 5)										MEAN	ST. CONTROL
2												

2
0.05

POTENTIAL Dose 100

100g

100g

100g 100g 100g 100g 100g 100g 100g 100g 100g 100g

0 suppression

Principal Investigator : Professor W. Peters

Department of Medical Microbiology

London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

14-10-84

PROTENTOCICAL ACTIVITY

COMPOUND : JCN 1719 WR 181023 BE 50003

FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION

ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS

PARASITE : Plasmodium yoelii nigeriensis

VERTEBRATE HOST : 3 FEA MICE

INVERTEBRATE HOST : Anopheles stephensi

TOXICITY : ~~XXXXXXXXXXXXXXXXXXXX~~ NO TOXIC EFFECTS SEEN

EXPERIMENT NUMBER : 2760

DATE : 30.5.84

PRELIMINARY TEST

CONCENTRATION (%)	DOCYST COUNTS D + 7										MEAN	T. CONTROL
3	15	26	14	73	32	37	17	22	34	38	35.8	34
0.15	25	20	30	16	29	15	23	18	25	21	21.8	60.9 ± 4.1

~~XXXXXXXXXXXX~~ SLIGHTLY ACTIVE ~~XXXXXXXXXX~~ AT 0.15 %

EXTENDED TEST

CONCENTRATION (%)	DOCYST COUNTS D + 7										MEAN	T. CONTROL
3												34

3
0.05

PROTENTOCICAL INDEX : 1.0

AD₅₀

100%

10	20	30	40	50	60	70	80	90	100
T. suppression									

Principal Investigator : Professor W. Peters

Department of Medical Parasitology

London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS
SPOROZOICIDAL ACTIVITY

1961-67

COMPOUND : LUN 1720 WR 182234 BE 17580
FORMULATION : DISSOLVED & SUSPENDED IN 5% AQUEOUS SUCROSE SOLUTION
ROUTE : ORAL ADMINISTRATION TO MOSQUITOES ON SUCROSE FEED FOR 7 DAYS
PARASITE : Plasmodium falciparum
VERTEBRATE HOST : ♂ FWH MICE INVERTEBRATE HOST : Anopheles stephensi
TOXICITY : ~~XXXXXXXXXXXX~~ ; NO TOXIC EFFECTS SEEN
EXPERIMENT NUMBER : 2760 DATE : 30.5.84

PRELIMINARY TEST

CONCENTRATION (%)	OOCYST COUNTS D + 7											MEAN	% CONTROL
2	15	26	14	73	82	37	17	22	34	38	35.8	100	
0.05	45	16	41	21	50	16	32	14	66	22	32.3	90.2 ± 6.1	

~~XXXXXXXXXXXX~~ INACTIVE AT D+5 & 7

EXTENDED TEST

CONCENTRATION (%)	OOCYST COUNTS D + 7											MEAN	% CONTROL
2													100

2
0.05

SPOROZOICIDAL INDEX (%)

100

100

Suppression

Principal Investigator : Professor W. Peters
Department of Medical Parasitology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS
SPOROZOICIDAL ACTIVITY

Table 6.1

COMPOUND : LCN 1721 WR 211814 ZP 12775
FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION
ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS
PARASITE : Plasmodium yoelii nigritensis
VERTEBRATE HOST : ♂ FFW MICE INVERTEBRATE HOST : Anopheles stephensi
TOXICITY : ~~XXXXXXXXXXXXXXXXXXXX~~ NO TOXIC EFFECTS SEEN
EXPERIMENT NUMBER : 2760 DATE : 30.5.84

PRELIMINARY TEST

CONCENTRATION(%)	OOCYST COUNTS D + 7										MEAN	CONTROL
1	15	26	14	73	82	37	17	22	34	38	35.3	10
0.05	10	42	20	18	13	30	23	39	45	19	25.9	72.3 ± 7.0

~~XXXXXXXXXXXX~~ - SLIGHTLY ACTIVE ~~XXXXXXXX~~ AT 0.05 %

EXTENDED TEST

CONCENTRATION(%)	OOCYST COUNTS D + 7										MEAN	CONTROL
1												10

1
0.05

RESISTANCE INDEX

100

50

100	50	25	12.5	6.25	3.125	1.5625	0.78125	0.390625	0.1953125	0.09765625	0.048828125	0.0244140625	0.01220703125	0.006103515625	0.0030517578125	0.00152587890625	0.000762939453125	0.0003814697265625	0.00019073486328125	0.000095367431640625	0.0000476837158203125	0.00002384185791015625	0.000011920928955078125	0.0000059604644775390625	0.00000298023223876953125	0.000001490116119384765625	0.0000007450580596923828125	0.00000037252902984619140625	0.000000186264514923095703125	0.0000000931322574615478515625	0.00000004656612873077392578125	0.000000023283064365386962890625	0.0000000116415321826934814453125	0.00000000582076609134674072265625	0.000000002910383045673370361328125	0.0000000014551915228366851806640625	0.00000000072759576141834259033203125	0.000000000363797880709171295166015625	0.0000000001818989403545856475830078125	0.00000000009094947017729282379150390625	0.000000000045474735088646411895751953125	0.0000000000227373675443232059478759765625	0.00000000001136868377216160297393798828125	0.000000000005684341886080801486968994140625	0.0000000000028421709430404007434844970703125	0.00000000000142108547152020037174224853515625	0.000000000000710542735760100185871124267578125	0.0000000000003552713678800500929355621337890625	0.00000000000017763568394002504646778106689453125	0.000000000000088817841970012523233890533447265625	0.0000000000000444089209850062616169452667236328125	0.00000000000002220446049250313080847263336181640625	0.000000000000011102230246251565404236316680908203125	0.0000000000000055511151231257827021181583340451171875	0.00000000000000277555756156289135105907916702255859375	0.000000000000001387778780781445675529539583511279296875	0.0000000000000006938893903907228377647697917556396484375	0.00000000000000034694469519536141888238489587781982421875	0.000000000000000173472347597680709441192447938909912109375	0.0000000000000000867361737988403547205962239694549560546875	0.00000000000000004336808689942017736029811198472747802734375	0.000000000000000021684043449710088680149055992363739013671875	0.0000000000000000108420217248550443400745279961818695068359375	0.00000000000000000542101086242752217003726399809093475341796875	0.000000000000000002710505431213761085018631999045467376708984375	0.0000000000000000013552527156068805425093159995227336883544921875	0.00000000000000000067762635780344027125465799976136684417724609375	0.000000000000000000338813178901720135627328999880683422088623046875	0.0000000000000000001694065894508600678136644999403417110443115234375	0.00000000000000000008470329472543003390683224997017085552215576171875	0.000000000000000000042351647362715016953416124985085427761077880859375	0.0000000000000000000211758236813575084767080624925427138805389404296875	0.00000000000000000001058791184067875423835403124627135694026947021484375	0.000000000000000000005293955920339377119177015623135678470134735107221875	0.0000000000000000000026469779601696885595885078115783923506723675536109375	0.00000000000000000000132348898008484427797925390578919617533618377680546875	0.000000000000000000000661744490042422138989626952894598087668091888402734375	0.0000000000000000000003308722450212110694948134764472990438340459442013671875	0.00000000000000000000016543612251060553474740673822364952191702297210068359375	0.000000000000000000000082718061255302767373703369111824760958511486050341796875	0.0000000000000000000000413590306276513836868516845559123804792557430251708984375	0.00000000000000000000002067951531382569184342584227795619023962787151258544921875	0.000000000000000000000010339757656912845921712921138978095119813935756292724609375	0.0000000000000000000000051698788284564229608564605694894025996069678781463623046875	0.00000000000000000000000258493941422821148042823028474470149980348393907318115234375	0.000000000000000000000001292469707114105740214115142372350749940191969536590576171875	0.0000000000000000000000006462348535570528701070575711861753749700959847682952880859375	0.00000000000000000000000032311742677852643505352878559308768748504799238414764404296875	0.000000000000000000000000161558713389263217526764392796543843742523996192073822021484375	0.0000000000000000000000000807793566946316087633821963982719218712619980960369110107221875	0.000000000000000000000000040389678347315804381691098199135960935630999048018455505361015625	0.0000000000000000000000000201948391736579021908455490995679804678154995240092277576171875	0.00000000000000000000000001009741958682895109542277454977849023390774976200461387880859375	0.000000000000000000000000005048709793414475547711387274889245116953874881002306935904296875	0.0000000000000000000000000025243548967072377738556936374446225584769374405011534679521484375	0.00000000000000000000000000126217744835361888692784681872231127923846872025057673397607221875	0.000000000000000000000000000631088724176809443463923409361115563961934360125288366988036109375	0.000000000000000000000000000315544362088404721731961704680557781980967180062644183046875	0.0000000000000000000000000001577721810442023608659808523402788909904835900313220917724609375	0.0000000000000000000000000000788860905221011804329904261701394454952417950156610458984375	0.00000000000000000000000000003944304526105059021649521308506972274762089750783052294921875	0.000000000000000000000000000019721522630525295108247606542534861373810448753915261474609375	0.0000000000000000000000000000098607613152626475541238032712674306869052243769576307373046875	0.000000000000000000000000000004930380657631323777061901635633715343452612188478815368671875	0.000000000000000000000000000002465190328815661888530950817816857671726306094239407683359375	0.0000000000000000000000000000012325951644078309442654754089084288358631530471197038416796875	0.00000000000000000000000000000061629758220391547213273770445442141793157652355985192083984375	0.000000000000000000000000000000308148791101957736066368852227210708965788261779925960419921875	0.0000000000000000000000000000001540743955509788680331844261136053544828941308899629802099609375	0.00000000000000000000000000000007703719777548943401659221305680267724144706544498149401048046875	0.000000000000000000000000000000038518598887744717008296106528401338620723532722490747005240234375	0.0000000000000000000000000000000192592994438723585041480532642006693103617663612453735026201171875	0.00000000000000000000000000000000962964972193617925207402663210033465518088318062268675131005859375	0.000000000000000000000000000000004814824860968089626037013316050167327590441590311343375655029296875	0.0000000000000000000000000000000024074124304840448130185066580250836637952207951556716878275146484375	0.0000000000000000000000000000000012037062152420224065092533290125418318976103975778358439137573246875	0.00000000000000000000000000000000060185310762101120325462666450627091594880519878891792195687866234375	0.000000000000000000000000000000000300926553810505601627313332253135457974402599394458960978439331171875	0.0000000000000000000000000000000001504632769052528008136566661265677289872012996972294804892196655859375	0.00000000000000000000000000000000007523163845262640040682833306328386449360064984861472404460983279296875	0.000000000000000000000000000000000037615819226313200203414166531641932246800324924307362022304916396484375	0.000000000000000000000000000000000018807909613156600101707083265820966123400162462153681011152458198246875	0.0000000000000000000000000000000000094039548065783000508535416329104830617000812310768405055762290991234375	0.00000000000000000000000000000000000470197740328915002542677081645524153085004061553842025278811454956171875	0.000000000000000000000000000000000002350988701644575012713385408227620765425020307769210126394057274780859375	0.0000000000000000000000000000000000011754943508222875063566927041138103827125101538846050631970286373904296875	0.00000000000000000000000000000000000058774717541114375317834635205690519135625507694230253159851431869521484375	0.000000000000000000000000000000000000293873587705571876589173176028452595678127538471151265799257159347609375	0.0000000000000000000000000000000000001469367938527859378295865880142262978390637692355756328996285796738046875	0.00000000000000000000000000000000000007346839692639296891479329400711314891953188461778781644981428983690234375	0.000000000000000000000000000000000000036734198463196484457396647003556574459765942308889393224907144916846171875	0.000000000000000000000000000000000000018367099231598242228698323501778287229882971154444696612453572458423046875	0.000000000000000000000000000000000000009183549615799121114349161750889143614941485577222348306226786229421484375	0.0000000000000000000000000000000000000045917748078995605571745808754445718074707427886111741531133931147107246875	0.00000000000000000000000000000000000000229588740394978027858729043772228590373537139430558707655669655735536234375	0.000000000000000000000000000000000000001147943701974890139293645218861142951867685697152793538278348278677681171875	0.0000000000000000000000000000000000000005739718509874450696468226094305714759338428485763967691391741393388405859375	0.00000000000000000000000000000000000000028698592549372253482341130471528573796692142428819838456958706966942279296875	0.000000000000000000000000000000000000000143492962746861267411705652357642868983460712114409917284793534834711396484375	0.000000000000000000000000000000000000000071746481373430633705852826178821434491730356057204958642396767417355698246875	0.0000000000000000000000000000000000000000358732406867153168529264130894107172458651780286024793211983837086778491234375	0.00000000000000000000000000000000000000001793662034335765842646320654470535862293258901430123966059919185433892456171875	0.000000000000000000000000000000000000000008968310171678829213231603272352679311466294507150619830299595927169462280859375	0.0000000000000000000000000000000000000000044841550858394146066158016361763396557331472535753099151497979635847311404296875	0.00000000000000000000000000000000000000000224207754291970730330790081808816982786657362678765495757489898179236557201484375	0.00000000000000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2025 RELEASE UNDER E.O. 14176

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RECEIVED FROM THE U.S. DEPARTMENT OF JUSTICE INACTIVE AT CLOSE

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APPENDIX A

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SUMMARY OF ANTIMALARIAL TESTS

TABLE 16.9

SPOROZOICIDAL ACTIVITY

UNFACED : LCN 1724 WR 228583 ZN 78910
 FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION
 ROUTE : ORAL ADMINISTRATION TO MOSQUITOES ON SUCROSE FEED FOR 7 DAYS
 PARASITE : *Plasmodium yoelii* *yoelii*
 VERTEBRATE HOST : ♂ TFW MICE INVERTEBRATE HOST : *Anopheles stephensi*
 TOXICITY : ~~XXXXXXXXXXXXXXXXXXXX~~ NO TOXIC EFFECTS SEEN
 EXPERIMENT NUMBER : 2776 DATE : 6.6.84

PRELIMINARY TEST

CONCENTRATION (%)	DOCT COUNTS 0-7										MEAN	T. CONTROL
0	6	16	25	20	15	24	13	12	22	17	20.7	0
	58											
0.05	7	18	17	15	11	8	19	9	7	11	12.5	48.3 ± 5.1

~~XXXXXXXXXX~~ ACTIVE ~~XXXXXXXXXXXXXXXXXXXX~~ AT 0.05 %

EXTENDED TEST

CONCENTRATION (%)	DOCT COUNTS 0-7										MEAN	T. CONTROL
0												0

0
0.05

0 10 20 30 40 50 60 70 80 90 100
 % suppression

SPOROZOICIDAL ACTIVITY

0.05%

0.05%

Principal Investigator : Professor W. Peters
 Department of Medical Microbiology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS
SPOROZOICIDAL ACTIVITY

TABLE 7.0

COMPOUND : LDN 1725 WR 233627 BH 13989
FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION
ROUTE : ORAL ADMINISTRATION TO MOSQUITOES ON SUCROSE FEED FOR 7 DAYS
PARASITE : Plasmodium yoelii nigeriensis
VERTEBRATE HOST : 3 FEM MICE INVERTEBRATE HOST : Anopheles stephensi
TOXICITY : ~~XXXXXXXXXXXXXXXXXX~~ : NO TOXIC EFFECTS SEEN
EXPERIMENT NUMBER : 2776 DATE : 6.6.84

PRELIMINARY TEST

CONCENTRATION (M)	OOCYST COUNTS D + 7										MEAN	CONTROL
2	6	16	25	20	15	24	13	12	22	17	20.7	100
	58											
0.05	4	9	6	12	16	2	15	12	1		8.6	41.6 ± 6.1

~~VERY ACTIVE / ACTIVE / XKBKXKXKXKXKXKXKXKX~~ AT 0.05 M

EXTENDED TEST

CONCENTRATION (M)	OOCYST COUNTS D + 7										MEAN	CONTROL
2												100

2	
0.05	
	1 2 3 4 5 6 7 8 9 10
	3 suppression

Pre-Nitrogen (p.p.m.)

0.01

0.02

Principal Investigator : Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

Summary of Antimalarial Tests
Sporontocidal Activity

Compound: LIN 1726 WR 235485 BH 35770
Formulation: Dissolved / Suspended in 5% Aqueous Sucrose Solution
Route: Oral Administration to Mosquitoes in Sucrose Feed for 7 Days
Parasite: *Plasmodium yoelii nigeriensis*
Vertebrate Host: 3 Fw Mice Invertebrate Host: *Anopheles stephensi*
Toxicity: ~~TOXIC TO MOSQUITOES~~ NO TOXIC EFFECTS SEEN
Experiment Number: 2776 Date: 6.6.84

Preliminary Test

Concentration (%)	Oocyst Counts D + 7										Mean	Control
2	6	16	25	20	15	24	13	12	22	17	20.7	0
	58											
0.05	5	13	3	3	9	17	15	19	11	7	13.7	51.7 ± 7.7

~~XXXXXXXXXX~~ ACTIVE / ~~XXXXXXXXXX~~ AT Dose 2

Extended Test

Concentration (%)	Oocyst Counts D + 7										Mean	Control
2												0

2	
0.05	
Suppression	

Sporontocidal Dose: 0.05

REC

REC

Principal Investigator: Professor W. Petens
Department of Medical Parasitology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS
SPRONTOXICAL ACTIVITY

COMPOUND: LA 1727 WR 232605 SH 69990
 FORMULATION: DISCOURD / SUSPENDED IN 5% AQUEOUS SUCROSE SOLUTION
 ROUTE: ORAL ADMINISTRATION TO MOUTHPIECES IN SUCROSE FEED FOR 7 DAYS
 PARASITE: Plasmodium yoelii subparvius
 VERTEBRATE HOST: ♂ FWA MICE INVERTEBRATE HOST: Aedes albopictus
 TOXICITY: ~~XXXXXXXXXXXXXXXXXXXX~~ NO TOXIC EFFECTS SEEN
 EXPERIMENT NUMBER: 2776 DATE: 6.6.84

PRELIMINARY TEST

CONCENTRATION %	DOCKING COUNTS (0-7)										MEAN	STDEV.
2	6	16	25	20	15	24	13	12	22	17	20.7	4
	58											
0.05	33	7	21	10	11	16	6	15	6	4	16.8	23.7 ± 3.7
	19	16										

~~XXXXXXXXXXXXXXXXXXXX~~ INACTIVE AT 0.05%

EXTENDED TEST

CONCENTRATION %	DOCKING COUNTS (0-7)										MEAN	STDEV.
2												4

2												
0.05												
S. praecox												

AS MOUTHPIECES

10%

10%

Principal Investigator: Professor W. Peters
 Department of Medical Entomology
 School of Veterinary & Tropical Medicine

— 2002

[illegible][illegible]

1. *Journal of the American Medical Association*, 1997; 277: 1001-1005.

[illegible]

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0.05

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— 1 —

EXPERIMENT 1: EFFECT OF PULSE RATE ON THE RATE OF METABOLISM

SOURCE: U.S. DEPARTMENT OF COMMERCE, BUREAU OF ECONOMIC ANALYSIS.

[illegible]

1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2150, 2151, 2152, 2153, 2154, 2155, 2156, 2157, 2158, 2159, 2160, 2161, 2162, 2163, 2164, 2165, 2166, 2167, 2168, 2169, 2170, 2171, 2172, 2173, 2174, 2175, 2176, 2177, 2178, 2179, 2180, 2181, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2190, 2191, 2192, 2193, 2194, 2195, 2196, 2197, 2198, 2199, 2200, 2201, 2202, 2203, 2204, 2205, 2206, 2207, 2208, 2209, 2210, 2211, 2212, 2213, 2214, 2215, 2216, 2217, 2218, 2219, 2220, 2221, 2222, 2223, 2224, 2225, 2226, 2227, 2228, 2229, 2230, 2231, 2232, 2233, 2234, 2235, 2236, 2237, 2238, 2239, 2240, 2241, 2242, 2243, 2244, 2245, 2246, 2247, 2248, 2249, 2250, 2251, 2252, 2253, 2254, 2255, 2256, 2257, 2258, 2259, 2260, 2261, 2262, 2263, 2264, 2265, 2266, 2267, 2268, 2269, 2270, 2271, 2272, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2284, 2285, 2286, 2287, 2288, 2289, 2290, 2291, 2292, 2293, 2294, 2295, 2296, 2297, 2298, 2299, 2300, 2301, 2302, 2303, 2304, 2305, 2306, 2307, 2308, 2309, 2310, 2311, 2312, 2313, 2314, 2315, 2316, 2317, 2318, 2319, 2320, 2321, 2322, 2323, 2324, 2325, 2326, 2327, 2328, 2329, 2330, 2331, 2332, 2333, 2334, 2335, 2336, 2337, 2338, 2339, 2340, 2341, 2342, 2343, 2344, 2345, 2346, 2347, 2348, 2349, 2350, 2351, 2352, 2353, 2354, 2355, 2356, 2357, 2358, 2359, 2360, 2361, 2362, 2363, 2364, 2365, 2366, 2367, 2368, 2369, 2370, 2371, 2372, 2373, 2374, 2375, 2376, 2377, 2378, 2379, 2380, 2381, 2382, 2383, 2384, 2385, 2386, 2387, 2388, 2389, 2390, 2391, 2392, 2393, 2394, 2395, 2396, 2397, 2398, 2399, 2400, 2401, 2402, 2403, 2404, 2405, 2406, 2407, 2408, 2409, 2410, 2411, 2412, 2413, 2414, 2415, 2416, 2417, 2418, 2419, 2420, 2421, 2422, 2423, 2424, 2425, 2426, 2427, 2428, 2429, 2430, 2431, 2432, 2433, 2434, 2435, 2436, 2437, 2438, 2439, 2440, 2441, 2442, 2443, 2444, 2445, 2446, 2447, 2448, 2449, 2450, 2451, 2452, 2453, 2454, 2455, 2456, 2457, 2458, 2459, 2460, 2461, 2462, 2463, 2464, 2465, 2466, 2467, 2468, 2469, 2470, 2471, 2472, 2473, 2474, 2475, 2476, 2477, 2478, 2479, 2480, 2481, 2482, 2483, 2484, 2485, 2486, 2487, 2488, 2489, 2490, 2491, 2492, 2493, 2494, 2495, 2496, 2497, 2498, 2499, 2500, 2501, 2502, 2503, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2513, 2514, 2515, 2516, 2517, 2518, 2519, 2520, 2521, 2522, 2523, 2524, 2525, 2526, 2527, 2528, 2529, 2530, 2531, 2532, 2533, 2534, 2535, 2536, 2537, 2538, 2539, 2540, 2541, 2542, 2543, 2544, 2545, 2546, 2547, 2548, 2549, 2550, 2551, 2552, 2553, 2554, 2555, 2556, 2557, 2558, 2559, 2560, 2561, 2562, 2563, 2564, 2565, 2566, 2567, 2568, 2569, 2570, 2571, 2572, 2573, 2574, 2575, 2576, 2577, 2578, 2579, 2580, 2581, 2582, 2583, 2584, 2585, 2586, 2587, 2588, 2589, 2590, 2591, 2592, 2593, 2594, 2595, 2596, 2597, 2598, 2599, 2600, 2601, 2602, 2603, 2604, 2605, 2606, 2607, 2608, 2609, 2610, 2611, 2612, 2613, 2614, 2615, 2616, 2617, 2618, 2619, 2620, 2621, 2622, 2623, 2624, 2625, 2626, 2627, 2628, 2629, 2630, 2631, 2632, 2633, 2634, 2635, 2636, 2637, 2638, 2639, 2640, 2641, 2642, 2643, 2644, 2645, 2646, 2647, 2648, 2649, 2650, 2651, 2652, 2653, 2654, 2655, 2656, 2657, 2658, 2659, 2660, 2661, 2662, 2663, 2664, 2665, 2666, 2667, 2668, 2669, 2670, 2671, 2672, 2673, 2674, 2675, 2676, 2677, 2678, 26

~~UNCLASSIFIED//FOR OFFICIAL USE ONLY~~

EXPERIMENT NUMBER 2776 DATE 3.6.64

JOE MURPHY TEST

CONCENTRATION	TREATMENT										TIME	DATE
1	0	10	20	30	40	50	60	70	80	90	100	
2	0	10	20	30	40	50	60	70	80	90	100	

REMARKS: AT THE WITHDRAWAL OF THE

1. *Journal of the American Medical Association*, 1997; 277: 1033-1037.

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the β phase of the polymer. The β phase is the more ordered phase and is characterized by a higher density and a higher melting point than the α phase. The β phase is the more stable phase and is the one that is most commonly observed in nature. The α phase is the less stable phase and is the one that is most commonly observed in the laboratory. The β phase is the more ordered phase and is characterized by a higher density and a higher melting point than the α phase. The β phase is the more stable phase and is the one that is most commonly observed in nature. The α phase is the less stable phase and is the one that is most commonly observed in the laboratory.

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Australia, Perth, Australia
E-mail: g.c.1980@uwa.edu.au

PRIMARY ANTIPARASITIC TESTS

FILE # 10

(SPOROZOICIDAL ACTIVITY)

UNWANT: 1000000000 WR 247705 BU 51779

HUMILIATION: 1000000000 SUSPENDED IN 5% AQUEOUS SUCROSE SOLUTION

NOTE: ORAL ADMINISTRATION TO HOSTS IN SUCROSE FEED FOR 7 DAYS

PARASITE: Platyhelminths

INVERTEBRATE HOST: TEA MOLE

INVERTEBRATE HOST: Amphipods

TOXICITY: ~~XXXXXXXXXX~~ NO TOXIC EFFECTS SEEN

EXPERIMENT NUMBER: 2776

DATE: 6.6.84

PRELIMINARY TEST

CONCENTRATION (%)	OOCYST COUNTS D + 7										MEAN	ST. DEV.
2	6	16	25	20	15	24	13	12	22	17	20.7	
	58											
0.05	7	2	8	10	7	11	7	2	11	3	6.8	20.8 + 8.1

XXXXXX ACTIVE / XXXXXXXX ACTIVE AT D+7

EXTENDED TEST

CONCENTRATION (%)	OOCYST COUNTS D + 7										MEAN	ST. DEV.
2												

2
0.05

ANALYSIS OF VARIANCE (ANOVA) TESTS
 REPRODUCIBILITY TESTS
 CORRELATION COEFFICIENTS

AD-A185 118

CHEMOTHERAPY OF RODENT MALARIA(U) LONDON SCHOOL OF
HYGIENE AND TROPICAL MEDICINE (ENGLAND) DEPT OF MEDICAL
PROTOZOOLOGY W PETERS JUL 85 DAMD17-84-C-4018

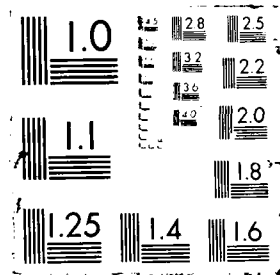
2/3

UNCLASSIFIED

F/G 6/15

NL





76

PRELIMINARY TEST

FXBLX XASTX X XASTX X XSKKNTLX XASTX X INACTIVE AT 0.35

[illegible]

Number of expressions	Frequency
0	10
1	8
2	6
3	4
4	2
5	1
6	1
7	0

96

• 2 •

PRELIMINARY TEST

$$FNUXX \times GUXIX \times GUXIX \times GXIXIX \times GUXIX \times \dots$$

REF ID: A66557

[illegible]

97

SUMMARY OF ANTIMALARIAL TEST

SPOROZOIDAL ACTIVITY

COMPOUND NO. 1733 WR 228708 BG 66798
 FORMULATION DISSOLVED SUSPENDED IN 1% AQUEOUS SUCROSE SOLUTION
 ROUTE OF ADMINISTRATION TO HOSTS IN SUCROSE FEED FOR 1 DAY
 PARASITE Plasmodium falciparum
 VERTEBRATE HOST 2 PM MICE INVERTEBRATE HOST Anopheles stephensi
 TOXICITY ~~XXXXXXXXXXXXXXXXXXXX~~ NO TOXIC EFFECTS SEEN
 EXPERIMENT NUMBER 2796 DATE 10.6.84

PRELIMINARY TEST

CONCENTRATION %	DAYS POST INFECTION											MEAN	ST. DEV.
2	41	16	12	40	14	12	19	42	20	24	20.1	1.1	
	31	15											
4	4	10	20	14	15	21	24	15	13	20	14.0	2.1	

FULLY AROMATISED AROMATISED AROMATISED AROMATISED

DEFINITIVE TEST

CONCENTRATION %	DAYS POST INFECTION											MEAN	ST. DEV.
2													

1. Name of compound
 2. Name of sponsor
 3. Name of investigator

SUMMARY OF ANTIMALARIAL TESTS

4-17-64

SPOROZOICIDAL ACTIVITY

PHONE NO. 1734 WR 242511 AA BH 89438

FORMULATION DISCLOSED: SUSPENDED IN 1% AQUEOUS DEXTRE SOLUTION

ROUTE OF ORAL ADMINISTRATION TO MOSQUITOES IN COURSE OF TEST: 1 DAY

PARASITE: Plasmodium vivax (GIBBER) (SUSCEPTIBLE)

VERTEBRATE HOST: PEROMYSCUS

INVERTEBRATE HOST: ANOPHELES

TEST SITE: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

EXPERIMENT NUMBER: 2796

DATE: 10-16-64

PRELIMINARY TEST

CONCENTRATION	DAYS POST-EXPOSURE												1	2
1	11	16	22	27	34	40	47	54	61	68	75	82		
	31	36												
2	13	17	24	31	38	45	52	59	66	73	80	87		
	15	19												

FULLY ACTIVE: 11-16-64; 11-22-64; 11-27-64; 11-34-64; 11-40-64; 11-47-64; 11-54-64; 11-61-64; 11-68-64; 11-75-64; 11-82-64; 11-89-64

DEFINITIVE TEST

CONCENTRATION	DAYS POST-EXPOSURE												1	2
1														
2														
3														
4														
5														
6														
7														
8														
9														
10														

1. Name of Investigator: _____
 2. Name of Institution: _____
 3. Address: _____

5. 911

QUESTIONS

[illegible][illegible]

11. 11. 1957. 10. 11. 1957. 10. 11. 1957. 10. 11. 1957. 10. 11. 1957.

SUMMARY OF ANTIMALARIAL TESTS
SPORONTICIDAL ACTIVITY

TABLE 51

COMPOUND: WLN 1751 WR 194343 ZN 41968
 FORMULATION: DISSOLVED & SUSPENDED IN 5% AQUEOUS SUCROSE SOLUTION
 ROUTE: ORAL ADMINISTRATION TO MOSQUITOES ON SUCROSE FEED FOR 7 DAYS
 PARASITE: Plasmodium falciparum
 VERTEBRATE HOST: 3 WEEK MICE INVERTEBRATE HOST: Aedes triseriatus
 TOXICITY: TOXIC TO A. triseriatus, 40.0% ~~TOXIC TO A. triseriatus~~ 50% mortality
 EXPERIMENT NUMBER: 2796 DATE: 13.6.84

PRELIMINARY TEST

| CONCENTRATION % | DOSE CONTROL | | | | | | | | | | | MEAN | ST. DEV. |
|-----------------|--------------|----|----|----|----|----|----|----|----|----|------|------|----------|
| 2 | 41 | 16 | 12 | 40 | 14 | 12 | 19 | 42 | 20 | 24 | 20.3 | | |
| | 31 | 15 | | | | | | | | | | | |
| 0.6 | 37 | 13 | 18 | 12 | 15 | 18 | | | | | 17.0 | 70.1 | 1.0 |
| | | | | | | | | | | | | | |

~~EXPERIMENTAL DATA~~ ~~EXPERIMENTAL DATA~~ ~~EXPERIMENTAL DATA~~ ~~EXPERIMENTAL DATA~~ ~~EXPERIMENTAL DATA~~

INTERPRETATION

| CONCENTRATION % | DOSE CONTROL | | | | | | | | | | | MEAN | ST. DEV. |
|-----------------|--------------|--|--|--|--|--|--|--|--|--|--|------|----------|
| 2 | | | | | | | | | | | | | |
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| 2 | |
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| 0.05 | |
| EXPERIMENTAL DATA | |

1. The results of the preliminary test indicate that the compound is active against the parasite.

2. The results of the preliminary test indicate that the compound is active against the parasite.

3. The results of the preliminary test indicate that the compound is active against the parasite.

SUMMARY OF ANTIMALARIAL TESTS

TABLE 8.2

SPOROZOICIDAL ACTIVITY

COMPOUND: LON 1877 WR 199508 AD BK 56500

FORMULATION: DISSOLVED + SUSPENDED IN 5% AQUEOUS SUCROSE SOLUTION

ROUTE: ORAL ADMINISTRATION TO MOSQUITOES ON SUCROSE FEED FOR 7 DAYS

PARASITE: Plasmodium yoelii nederlandsi

INVERTEBRATE HOST: 3 FEMALE MICE

INVERTEBRATE HOST: Anopheles stephensi

TOXICITY: FORMER 49 4-stepheni 4F --- NO TOXIC EFFECTS SEEN

EXPERIMENT NUMBER: 2876

DATE: 20.6.84

PRELIMINARY TEST

| CONCENTRATION (%) | OOCYST COUNTS (D + 7) | | | | | | | | | | MEAN | CONTROL |
|-------------------|-----------------------|----|----|----|----|----|----|----|----|----|------|------------|
| 2 | 15 | 56 | 19 | 16 | 16 | 15 | 14 | 18 | 19 | 26 | 21.4 | 19 |
| 1.5 | 10 | 45 | 17 | 9 | 6 | 9 | 17 | 12 | 18 | 9 | 15.2 | 71.0 ± 7.2 |

FULLY ACTIVE --- ACTIVE --- SLIGHTLY ACTIVE --- INACTIVE AT DOSE 1

EXTENDED TEST

| CONCENTRATION (%) | OOCYST COUNTS (D + 7) | | | | | | | | | | MEAN | CONTROL |
|-------------------|-----------------------|--|--|--|--|--|--|--|--|--|------|---------|
| 2 | | | | | | | | | | | | 19 |
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MEAN OOCYST COUNT

19

15.2

SUMMARY OF ANTIMALARIAL TESTS
SPOROZONICIDAL ACTIVITY

TABLE 8.3

COMPOUND : LON 1940 WR 199508 ZP 43350
FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION
ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS
PARASITE : Plasmodium yoelii nigeriensis
VERTEBRATE HOST : ♂ FFW MICE INVERTEBRATE HOST : Anopheles stephensi
TOXICITY : ~~XXXXXXXXXXXX~~ NO TOXIC EFFECTS SEEN
EXPERIMENT NUMBER : 2830 DATE : 27.6.84

PRELIMINARY TEST

| CONCENTRATION(%) | DOOYST COUNTS 0 + 7 | | | | | | | | | | | MEAN | % CONTROL |
|------------------|---------------------|----|----|----|----|----|----|----|----|----|------|------------|-----------|
| 2 | 30 | 19 | 32 | 25 | 41 | 21 | 10 | 13 | 9 | 28 | 24.9 | 100 | |
| | 46 | | | | | | | | | | | | |
| 0.05 | 4 | 14 | 12 | 6 | 4 | 3 | 60 | 33 | 19 | 33 | 17.3 | 69.3 ± 8.8 | |
| | 16 | 3 | | | | | | | | | | | |

~~XXXXXXXXXXXX~~ SLIGHTLY ACTIVE ~~XXXXXXXXXX~~ AT 0.05 %

EXTENDED TEST

| CONCENTRATION(%) | DOOYST COUNTS 0 + 7 | | | | | | | | | | | MEAN | % CONTROL |
|------------------|---------------------|--|--|--|--|--|--|--|--|--|--|------|-----------|
| 2 | | | | | | | | | | | | | 100 |
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| 2 |
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| 0.05 |
| |

SPOROZONICIDAL ACTIVITY

40%

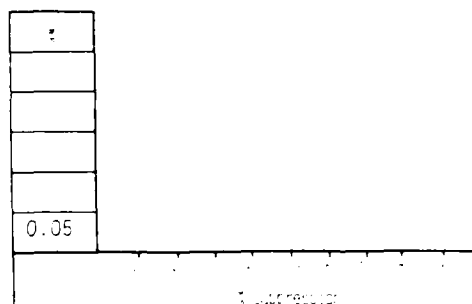
40%

Principal Investigator : Professor A. Peters
Department of Medical Entomology
London School of Hygiene & Tropical Medicine

- 81

PRELIMINARY TEST

~~FBI~~X~~NY~~X~~ACTIVE~~ /X~~SOLICIT~~X~~NY~~X~~INACT~~X AT 0.05 %

[illegible]

141

104

SUMMARY OF ANTIMALARIAL TESTS
SPOROZOIDAL ACTIVITY

TABLE 85

COMPOUND : JCN 1932 WR 251855 AA BK 71178
FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION
ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS
PARASITE : Plasmodium yoelii nigeriensis
VERTEBRATE HOST : ♂ TFW MICE INVERTEBRATE HOST : Anopheles stephensi
TOXICITY : TOXIC TO A. stephensi AT .05% : ~~92% mortality~~ 92 % mortality
EXPERIMENT NUMBER : 2830 DATE : 27.6.84

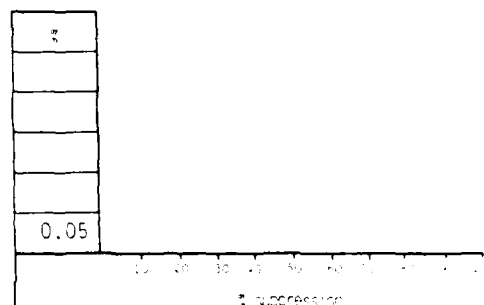
PRELIMINARY TEST

| CONCENTRATION(%) | OOCYST COUNTS D + 7 | | | | | | | | | | MEAN | % CONTROL |
|------------------|---------------------|----|----|----|----|----|----|----|---|----|------|-----------|
| J | 30 | 19 | 32 | 25 | 41 | 21 | 10 | 13 | 9 | 28 | 24.9 | 100 |
| | 46 | | | | | | | | | | | |
| 0.05 | 18 | 12 | | | | | | | | | 15.0 | 60.2 |
| | | | | | | | | | | | | |

~~SPOROZOIDAL ACTIVITY~~ / ACTIVE / ~~SPOROZOIDAL ACTIVITY~~ AT 0.05 %

EXTENDED TEST

| CONCENTRATION(%) | OOCYST COUNTS D + 7 | | | | | | | | | | MEAN | % CONTROL |
|------------------|---------------------|--|--|--|--|--|--|--|--|--|------|-----------|
| J | | | | | | | | | | | | 100 |
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SPOROZOIDAL ACTIVITY

100%

100%

Principal Investigator : Professor A. Peters
Department of Medical Entomology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

TABLE 86

SPORONTICIDAL ACTIVITY

COMPOUND : LON 1884 Ph 4007 BK 64306
 FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION
 ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS
 PARASITE : Plasmodium yoelli nigeriensis
 VERTEBRATE HOST : ♂ TFW MICE INVERTEBRATE HOST : Anopheles stephensi
 TOXICITY : TOXIC TO A. stephensi AT .05% ; ~~NO TOXIC EFFECTS SEEN~~ 100 % mortality
 EXPERIMENT NUMBER : 2816 DATE : 20.6.84

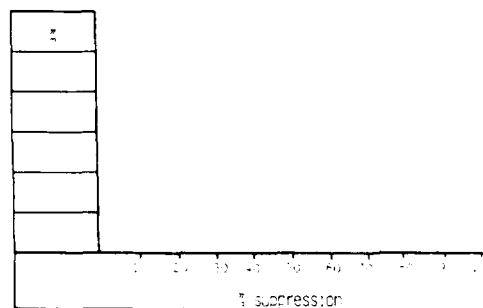
PRELIMINARY TEST

| CONCENTRATION(%) | OOCYST COUNTS D + 7 | | | | | | | | | | MEAN | % CONTROL |
|------------------|---------------------|----|----|----|----|----|----|----|----|----|------|-----------|
| 0 | 15 | 56 | 19 | 16 | 16 | 15 | 14 | 18 | 19 | 26 | 21.4 | 100 |
| 0.05 | | | | | | | | | | | | TOXIC |

FULLY ACTIVE / ACTIVE / SLIGHTLY ACTIVE / INACTIVE AT 0.05 %

EXTENDED TEST

| CONCENTRATION(%) | OOCYST COUNTS D + 7 | | | | | | | | | | MEAN | % CONTROL |
|------------------|---------------------|--|--|--|--|--|--|--|--|--|------|-----------|
| 0 | | | | | | | | | | | | 100 |
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SPORONTICIDAL DOSE (SD)

SD₅₀ :

SD₉₀ :

Principal Investigator : Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS
SPOROZONTICIDAL ACTIVITY

TABLE 87

COMPOUND : LON 1885 Ph 4017 BK 64315
FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION
ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS
PARASITE : Plasmodium yoelii nigeriensis
VERTEBRATE HOST : ♂ FFW MICE INVERTEBRATE HOST : Anopheles stephensi
TOXICITY : TOXIC TO A. stephensi AT 0.05 % : ~~NO TOXIC EFFECTS SEEN~~ 80 % mortality
EXPERIMENT NUMBER : 2816 DATE : 20.6.84

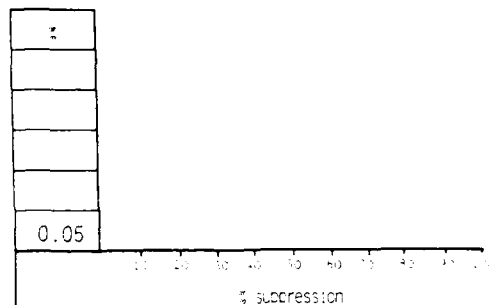
PRELIMINARY TEST

| CONCENTRATION (%) | OOCYST COUNTS D + 7 | | | | | | | | | | MEAN | % CONTROL |
|-------------------|---------------------|----|----|----|----|----|----|----|----|----|------|------------|
| 3 | 15 | 56 | 19 | 16 | 16 | 15 | 14 | 18 | 19 | 26 | 21.4 | 100 |
| 0.05 | 45 | 79 | 6 | 3 | 64 | 31 | | | | | 38.0 | 100 ± 13.1 |

~~ROXXK ROXXK ROXXK ROXXK ROXXK ROXXK ROXXK ROXXK ROXXK ROXXK~~ INACTIVE AT 0.05 %

EXTENDED TEST

| CONCENTRATION (%) | OOCYST COUNTS D + 7 | | | | | | | | | | MEAN | % CONTROL |
|-------------------|---------------------|--|--|--|--|--|--|--|--|--|------|-----------|
| 3 | | | | | | | | | | | | 100 |
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SPOROZONTICIDAL DOSE : 100

LD50 :

LD90 :

Principal Investigator : Professor W. Peters
Department of Medical Parasitology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS
SPOROZOICIDAL ACTIVITY

W: S S

COMPOUND : LON 1886 Ph 4900 BK 64324

FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION

ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS

PARASITE : Plasmodium yoelii nigeriensis

VERTEBRATE HOST : ♂ TFH MICE

INVERTEBRATE HOST : Anopheles stephensi

TOXICITY : TOXIC TO A. stephensi AT .05% : ~~NO TOXIC EFFECTS~~ 72 % mortality

EXPERIMENT NUMBER : 2816

DATE : 20.6.84

PRELIMINARY TEST

| CONCENTRATION (%) | OOCYST COUNTS D + 7 | | | | | | | | | | MEAN | % CONTROL |
|-------------------|---------------------|----|----|----|----|----|----|----|----|----|------|------------|
| 0 | 15 | 56 | 19 | 16 | 16 | 15 | 14 | 18 | 19 | 26 | 21.4 | 100 |
| 0.05 | 12 | 17 | 18 | 14 | 12 | 10 | 8 | | | | 13.0 | 60.7 ± 4.7 |

~~NO TOXIC EFFECTS~~ ACTIVE / ~~NO TOXIC EFFECTS~~ / INACTIVE AT 0.05 %

EXTENDED TEST

| CONCENTRATION (%) | OOCYST COUNTS D + 7 | | | | | | | | | | MEAN | % CONTROL |
|-------------------|---------------------|--|--|--|--|--|--|--|--|--|------|-----------|
| 0 | | | | | | | | | | | | 100 |
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SPOROZOICIDAL INDEX (S.I.)

50000

50000

Principal Investigator : Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS

189

SPOROZOICIDAL ACTIVITY

COMPOUND : LON 1887 Ph 4901 BK 64333

FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION

ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS

PARASITE : *Plasmodium yoelii nigeriensis*

VERTEBRATE HOST : 3 FWH MICE

INVERTEBRATE HOST : *Anopheles stephensi*

TOXICITY : TOXIC TO *A. stephensi* AT 0.05% ; ~~XXXXXXXXXXXX~~ 92 % mortality

EXPERIMENT NUMBER : 2816

DATE : 20.6.84

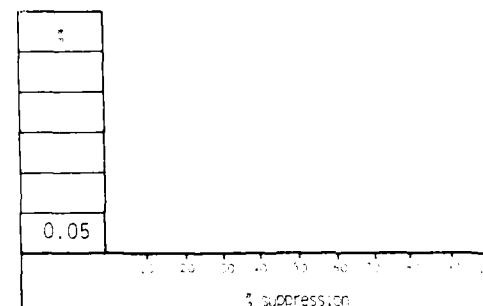
PRELIMINARY TEST

| CONCENTRATION(%) | OOCYST COUNTS 3 + 7 | | | | | | | | | | MEAN | % SUPPRESSION |
|------------------|---------------------|----|----|----|----|----|----|----|----|----|------|---------------|
| 2 | 15 | 56 | 19 | 16 | 16 | 15 | 14 | 18 | 19 | 26 | 21.4 | 0 |
| 0.05 | 100 | 58 | | | | | | | | | 79.0 | 100 |

~~XXXXXXXXXXXX~~ INACTIVE AT 0.05 %

EXTENDED TEST

| CONCENTRATION(%) | OOCYST COUNTS 3 + 7 | | | | | | | | | | MEAN | % SUPPRESSION |
|------------------|---------------------|--|--|--|--|--|--|--|--|--|------|---------------|
| 2 | | | | | | | | | | | | 0 |
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SPOROZOICIDAL INDEX

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Principal Investigator : Professor W. Peters

Department of Medical Protozoology

London School of Hygiene & Tropical Medicine

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| | 26 | 27 |
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 3. DO NOT RECOGNIZE THE GOVERNMENT OF THE PEOPLES REPUBLIC OF CHINA
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1 1 1

1. *Pharmaceutical industry* – The pharmaceutical industry is the largest of the three industries, with sales of \$10.5 billion in 1997. It is the only industry that has not experienced a decline in sales since 1990. The industry is dominated by a few large firms, with the top five firms accounting for 40% of sales. The industry is highly competitive, with many firms competing for market share.

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Figure 1 shows a schematic diagram of a multi-layered structure. It consists of five horizontal layers, labeled A, B, C, D, and E from top to bottom. Each layer contains a series of dots arranged in a regular grid pattern. The layers are separated by horizontal lines. The dots are arranged in a regular grid pattern across the layers.

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REPORT OF INVESTIGATION (Form No. 1)

DATE OF INVESTIGATION: 10/14/47 BY: SA [redacted]
 TITLE: RECEIPT FOR CASH ON HAND
 NAME OF SUBJECT: [redacted] ADDRESS: [redacted]
 OCCASION FOR INVESTIGATION: ROUTINE
 NAME OF WITNESS: [redacted] ADDRESS: [redacted]
 NAME OF OFFICIAL: [redacted] ADDRESS: [redacted]
 NAME OF OFFICIAL: [redacted] ADDRESS: [redacted]

| DATE | TIME | PLACE | PERSONS | OBJECTS | REMARKS | INITIALS | REMARKS |
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REMARKS: RECEIVED CASH ON HAND

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REPORT OF INVESTIGATION: RECEIVED CASH ON HAND
 REPORTED BY: [redacted]
 DATE OF REPORT: 10/14/47

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- 9 -

1. *Chlorophyll a* and *Chlorophyll b* were determined by the method of Arar and Collins (1971).

DATE: 10/10/78

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SECRET

ONLY GOVERNMENT PRINTING OFFICE: 1967

1992-1993

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THE UNIVERSITY OF CHICAGO

SUMMARY OF ANTIMALARIAL TESTS
SPOROZOIDAL ACTIVITY

WELL 9.9

COMPOUND: LON 1716 WR 9792 AU 63248
FORMULATION: DISSOLVED / SUSPENDED IN 5% AQUEOUS SUCROSE SOLUTION
ROUTE: ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS
PARASITE: *Plasmodium yoelii* *oberloensis*
VERTEBRATE HOST: 2 FEMALE
INVERTEBRATE HOST: *Anopheles stephensi*
TOXICITY: ~~XXXXXXXXXXXXXXXXXXXX~~ NO TOXIC EFFECTS SEEN
EXPERIMENT NUMBER: 2760 DATE: 30.5.84

PRELIMINARY TEST

| CONCENTRATION % | DOCT COUNT 0 + 7 | | | | | | | | | | MEAN | CONTROL |
|-----------------|------------------|----|----|----|----|----|----|----|----|----|------|------------|
| 2 | 15 | 26 | 14 | 73 | 82 | 37 | 17 | 22 | 34 | 38 | 35.8 | 4.1 |
| 0.5 | 30 | 27 | 40 | 13 | 36 | 18 | 35 | 22 | 64 | 16 | 30.7 | 35.8 ± 5.0 |

~~XXXXXXXXXXXXXXXXXXXX~~ INACTIVE AT DOSE 2

EXTENDED TEST

| CONCENTRATION % | DOCT COUNT 0 + 7 | | | | | | | | | | MEAN | CONTROL |
|-----------------|------------------|--|--|--|--|--|--|--|--|--|------|---------|
| 2 | | | | | | | | | | | | 4.1 |
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SPOROZOIDAL ACTIVITY

40%

10%

XXXXXXXXXXXXXXXXXXXX
To suppress

Includes investigation of resistance to malarial
Department of Medical Microbiology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS
SPOROZOICIDAL ACTIVITY

100

COMPOUND : LON 1718 WR 158124 BD 22997
FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION
ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS
PARASITE : Plasmodium yoelii nigeriensis
VERTEBRATE HOST : ♂ TFW MICE (INVERTEBRATE HOST : Anopheles stephensi)
TOXICITY : ~~TOXIC TO EXPERIMENTAL MICE~~; NO TOXIC EFFECTS SEEN
EXPERIMENT NUMBER : 2760 DATE : 30.5.84

PRELIMINARY TEST

| CONCENTRATION(%) | OOCYST COUNTS D + 7 | | | | | | | | | | MEAN | % CONTROL |
|------------------|---------------------|----|----|----|----|----|----|----|----|----|------|------------|
| 0 | 15 | 26 | 14 | 73 | 82 | 37 | 17 | 22 | 34 | 38 | 35.8 | 100 |
| 0.05 | 18 | 16 | 17 | 26 | 20 | 33 | 24 | 16 | | | 21.3 | 59.4 ± 4.7 |

~~POORLY ACTIVE~~ / ~~SLIGHTLY~~ ACTIVE / ~~ACTIVE~~ AT 0.05 %

EXTENDED TEST

| CONCENTRATION(%) | OOCYST COUNTS D + 7 | | | | | | | | | | MEAN | % CONTROL |
|------------------|---------------------|--|--|--|--|--|--|--|--|--|------|-----------|
| 0 | | | | | | | | | | | | 100 |
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| 0.05 |

SPOROZOICIDAL ACTIVITY

20%

20%

| | | | | | | | | | | | |
|---------------|------|-----|-----|-----|---|---|---|----|----|----|-----|
| 0 | 0.05 | 0.1 | 0.2 | 0.5 | 1 | 2 | 5 | 10 | 20 | 50 | 100 |
| % suppression | | | | | | | | | | | |

Principal Investigator : Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL TESTS
SPOROZOICIDAL ACTIVITY

TABLE 101

COMPOUND : LON 1909 WR 203659 ZN 39913
FORMULATION : DISSOLVED / SUSPENDED IN 5 % AQUEOUS SUCROSE SOLUTION
ROUTE : ORAL ADMINISTRATION TO MOSQUITOES IN SUCROSE FEED FOR 7 DAYS
PARASITE : Plasmodium yoelii nigeriensis
VERTEBRATE HOST : ♂ TFH MICE INVERTEBRATE HOST : Anopheles stephensi
TOXICITY : ~~XXXXXX~~ ~~XXXXXXXXXX~~ ; NO TOXIC EFFECTS SEEN
EXPERIMENT NUMBER : 2830 DATE : 27.6.84

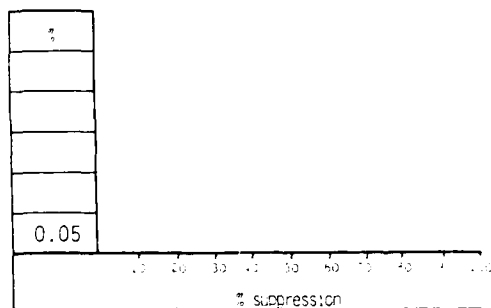
PRELIMINARY TEST

| CONCENTRATION(%) | OOCYST COUNTS D + 7 | | | | | | | | | | | MEAN | % CONTROL |
|------------------|---------------------|----|----|-----|----|----|----|----|---|----|------|-----------|-----------|
| 2 | 30 | 19 | 32 | 25 | 41 | 21 | 10 | 13 | 9 | 28 | 24.9 | 100 | |
| | 46 | | | | | | | | | | | | |
| 0.05 | 47 | 10 | 60 | 101 | 72 | 37 | 23 | 22 | 6 | 13 | 37.4 | 100 ± 7.6 | |
| | | | | | | | | | | | | | |

~~XXXXXXXXXX~~ ~~XXXXXXXXXX~~ ~~XXXXXXXXXX~~ / INACTIVE AT 0.05 %

EXTENDED TEST

| CONCENTRATION(%) | OOCYST COUNTS D + 7 | | | | | | | | | | | MEAN | % CONTROL |
|------------------|---------------------|--|--|--|--|--|--|--|--|--|--|------|-----------|
| 2 | | | | | | | | | | | | | 100 |
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SPOROZOICIDAL ACTIVITY

2000

1000

Principal Investigator : Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

5.5 DRUG INTERACTION TEST DATA

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 102

COMPOUND NAME Mefloquine (M) +
OR NUMBER Spiramycin (SP)..... PARASITE (SUB)SPECIES P. berghei....
FORMULATION Tween 80 / H₂O. ROUTE OF ADMINISTRATION : SC/TP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% x 100 |
|--|----------------------------|----------------|-----------------------|---------------------------------|----------------------------------|
| | M 0.5 + SP 3.0 | 5 | | - | 80.0 ± 11.7 |
| | M 1.0 + SP 3.0 | 5 | | - | 75.7 ± 9.7 |
| N | M 2.0 + SP 3.0 | 5 | 1 | - | 46.2 ± 7.9 |
| | M 3.0 + SP 3.0 | 5 | | - | 2.7 ± 0.9 |
| | Ø | 10 | | 14.9 | |
| ED ₅₀ (range) 1.1 (0.6 - 2.1) | | | | | |
| ED ₉₀ (range) 2.7 (1.7 - 5.3) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | M 0.5 + SP 10.0 | 5 | | - | 22.7 ± 4.3 |
| | M 1.0 + SP 10.0 | 5 | | - | 20.1 ± 7.0 |
| N | M 3.0 + SP 10.0 | 5 | 1 | - | 16.4 ± 1.0 |
| | M 10.0 + SP 10.0 | 5 | | - | 2.7 ± 0.6 |
| | Ø | 10 | | 14.9 | |
| ED ₅₀ (range) 0.4 (0.2 - 0.7) | | | | | |
| ED ₉₀ (range) 1.4 (0.7 - 2.7) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 100

COMPOUND NAME Mefloquine (M) +
OR NUMBER Spiramycin (SP)..... PARASITE (SUB)SPECIES P. berghei.....
FORMULATION Tween 80 / H₂O.. ROUTE OF ADMINISTRATION : SC/TP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% x 100 |
|-----------------------------------|----------------------------|----------------|-----------------------|---------------------------------|----------------------------------|
| | M 0.5 + SP 30.0 | 5 | | - | 4.0 ± 0.7 |
| | M 1.0 + SP 30.0 | 5 | | - | 4.0 ± 1.9 |
| N | M 2.0 + SP 30.0 | 5 | 1 | - | 2.7 ± 0.9 |
| | M 3.0 + SP 30.0 | 5 | | - | 2.0 ± 1.0 |
| | Ø | 10 | | 14.9 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) < 0.5 | | | | | |
| ED ₉₀ (range) < 0.5 | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | M 0.5 + SP 60 | 5 | | - | 0.6 ± 0.3 |
| | M 1.0 + SP 60 | 5 | | - | 1.3 ± 0.7 |
| N | M 2.0 + SP 60 | 5 | 1 | - | 1.0 ± 0.2 |
| | M 3.0 + SP 60 | 5 | | - | 1.3 ± 0.7 |
| | Ø | 10 | | 14.9 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) < 0.5 | | | | | |
| ED ₉₀ (range) < 0.5 | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL RESULTS
 SECOND SUBMITTAL

10

COMPOUND NAME Spiramycin (SP) +
 DR NUMBER Mefloquine PARASITE P. berghei
 FORMULATION Tween 80 / H₂O ROUTE OF ADMINISTRATION sc + ~~oral~~
 MAXIMUM TOLERATED DOSE MTD MG/KG

| Strain | Daily dose
mg/kg DO-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Tested test
control % |
|---|----------------------------|----------------|-----------------------|---------------------------------|--------------------------|
| | SP 3.0 + M 0.5 | 5 | | - | 80.0 ± 11.7 |
| | SP 10.0 + M 0.5 | 5 | | - | 22.7 ± 4.3 |
| N | SP 30.0 + M 0.5 | 5 | 1 | - | 4.0 ± 0.7 |
| | SP 60.0 + M 0.5 | 5 | | - | 0.6 ± 0.3 |
| | Ø | 10 | | 14.9 | |
| ED ₅₀ (range) 5.3 (4.0 - 12.0) | | | | | |
| ED ₉₀ (range) 19.8 (12.5 - 36.5) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | SP 3.0 + M 1.0 | 5 | | - | 75.7 ± 9.7 |
| | SP 10.0 + M 1.0 | 5 | | - | 20.1 ± 7.0 |
| N | SP 30.0 + M 1.0 | 5 | 1 | - | 4.0 ± 1.2 |
| | SP 60.0 + M 1.0 | 5 | | - | 1.3 ± 0.7 |
| | Ø | 10 | | 14.9 | |
| ED ₅₀ (range) 5.0 (2.5 - 10.5) | | | | | |
| ED ₉₀ (range) 22.5 (11.5 - 47) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
BLOOD LIMITING DOSE

TABLE 105

COMPOUND NAME Spiramycin (SP) +
Mefloquine (M) PARASITE SUB SPECIES P. berghei
 FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION SC
 MAXIMUM TOLERATED DOSE (MTD) MG/KG

| Strain | Daily dose
mg/kg 00-0+0 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Tested
control |
|--------|----------------------------|----------------|-----------------------|---------------------------------|-------------------|
| | SP 3.0 + M 2.0 | 5 | | - | 46.2 ± 7.9 |
| | SP 10.0 + M 2.0 | 5 | | - | 16.4 ± 1.0 |
| N | SP 30.0 + M 2.0 | 5 | 1 | - | 2.7 ± 0.9 |
| | SP 60.0 + M 2.0 | 5 | | - | 1.0 ± 0.2 |
| | Ø | 10 | | 14.9 | |

ED₅₀ range 2.4 (1.4-3.5)

ED₉₀ range 15.0 (9.0-22.5)

Resistance factor 1.1

| | | | | | |
|---|-----------------|----|---|------|-----------|
| | SP 3.0 + M 3.0 | 5 | | - | 2.7 ± 0.9 |
| | SP 10.0 + M 3.0 | 5 | | - | 2.7 ± 0.6 |
| N | SP 30.0 + M 3.0 | 5 | 1 | - | 2.0 ± 1.0 |
| | SP 60.0 + M 3.0 | 5 | | - | 1.3 ± 0.7 |
| | Ø | 10 | | 14.9 | |

ED₅₀ range < 3.0

ED₉₀ range < 3.0

Resistance factor 1.1

Principal Investigator: Professor W. Miller
 Department of Medical Entomology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD CONCENTRATIONS)

TABLE 106

COMPOUND NAME

DR NUMBER Halofantrine PARASITE (SUB) SPECIES P. berghei

FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION sc

MAXIMUM TOLERATED DOSE (MTD) MG/KG (X)

| Strain | Daily dose
mg/kg SC-SC | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated
control |
|--------|---------------------------|----------------|-----------------------|---------------------------------|--------------------|
| | 0.03 | 5 | | - | 90.6 ± 3.1 |
| | 0.1 | 5 | | - | 70.6 ± 2.9 |
| N | 0.3 | 5 | 1 | - | 61.0 ± 5.0 |
| | 1.0 | 5 | | - | 9.2 ± 6.9 |
| | 3.0 | 5 | | - | 0.6 ± 0.5 |
| | Ø | 10 | | 23.1 | |

LD₅₀ 0.2 (0.1 - 0.5)

LD₅₀ 0.8 (0.3 - 1.6)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

LD₅₀ 1.0 (0.5 - 2.0)

Principal Investigator: Professor W. J. J. van der
Department of Medical Parasitology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL RESULTS
 80001-80010 (1000)

1000

COMPOUND NAME

DR. NUMBER Spiramycin PARASITE P. berghe

FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION per os

MAXIMUM TOLERATED DOSE (MTD) 1000 MG/KG (X)

| Strain | Daily dose
mg/kg 00-0+3 | No. of
mice | No. of
experiments | Mean (S.D.)
parasite rate % | Mean (S.D.)
parasite rate % |
|--------|----------------------------|----------------|-----------------------|--------------------------------|--------------------------------|
| | 10 | 5 | | - | 87.0 ± 4.9 |
| | 30 | 5 | | - | 84.8 ± 7.1 |
| N | 100 | 5 | 1 | - | 52.9 ± 5.9 |
| | 300 | 5 | | - | 83 ± 3.3 |
| | 1000 | 5 | | - | 17 ± 0.6 |
| | Ø | 10 | | 23.1 | |

ED₅₀ (range) 6.2 (2.7-18.8)

ED₃₀ (range) 26.0 (11.3-78.0)

Resistance factor 130

ED₅₀ (range)

ED₃₀ (range)

Resistance factor 130

Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

Spiramycin (SP) +
 Halofantrine (H)
 Tween 80 / H₂O

| N | SP10 + H0.03 | 5 | - | - | 94.5 ± 3.4 |
|---|----------------|----|---|------|------------|
| | SP30 + H0.03 | 5 | - | - | 82.5 ± 4.9 |
| | SP100 + H0.03 | 5 | - | - | 45.8 ± 4.9 |
| | SP300 + H0.03 | 5 | - | - | 4.9 ± 2.2 |
| | SP1000 + H0.03 | 5 | - | - | 3.4 ± 0.7 |
| | Ø | 10 | - | 23.1 | |

60 (25-128)

300 (130-640)

| | | | | | |
|---|---------------|----|---|------|------------|
| N | SP10 + H0.1 | 5 | - | - | 90.0 ± 6.0 |
| | SP30 + H0.1 | 5 | - | - | 70.1 ± 7.7 |
| | SP100 + H0.1 | 5 | - | - | 37.5 ± 7.9 |
| | SP300 + H0.1 | 5 | - | - | 9.1 ± 3.7 |
| | SP1000 + H0.1 | 5 | - | - | 2.2 ± 0.9 |
| | Ø | 10 | - | 23.1 | |

ED₅₀ range 58 (3.4 - 90)

ED₉₀ range 29.0 (17.0 - 45.0)

Resistance factor I₉₀

Principal Investigator: Professor W. J. J. J.
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

1.0 M, 0.1 M, 0.01 M Spiramycin (SP) +
 Halofantrine (H)

P. berghe

2.0 M, 0.2 M, 0.02 M Tween 80 / H₂O

Resistance factor I₅₀

| Conc. | SP | H | I ₅₀ | Resistance factor I ₅₀ |
|-------|--------|--------|-----------------|-----------------------------------|
| 1.0 M | 0.1 M | 0.01 M | 5 | 84.8 ± 3 |
| 1.0 M | 0.01 M | 0.01 M | 5 | 65.0 ± 8 |
| N | 0.1 M | 0.01 M | 5 | 46 ± 3.9 |
| | 0.01 M | 0.01 M | 5 | 8.7 ± 3.2 |
| | 0.01 M | 0.01 M | 5 | 0.9 ± 0.8 |
| | 0.01 M | 0.01 M | 5 | |
| | 0.01 M | 0.01 M | 10 | 23.1 |

1.0 M, 0.1 M, 0.01 M 52(21-100)

1.0 M, 0.1 M, 0.01 M 25.5(10.0-47.0)

Resistance factor I₅₀

| Conc. | SP | H | I ₅₀ | Resistance factor I ₅₀ |
|-------|--------|--------|-----------------|-----------------------------------|
| 1.0 M | 0.1 M | 0.01 M | 5 | 52 ± 3.5 |
| 1.0 M | 0.01 M | 0.01 M | 5 | 22 ± 1.7 |
| N | 0.1 M | 0.01 M | 5 | 0 |
| | 0.01 M | 0.01 M | 5 | 0 |
| | 0.01 M | 0.01 M | 5 | 0 |
| | 0.01 M | 0.01 M | 10 | 23.1 |

1.0 M, 0.1 M, 0.01 M 0.2(0.1-0.5)

1.0 M, 0.1 M, 0.01 M 0.8(0.4-1.8)

Resistance factor I₅₀

Principal Investigator: Professor Wintner
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

Halofantrine (HA) +
 Spiramycin (SP)
 Tween 80/H₂O

P. berghei

| HA | SP | N | Mean | SD |
|------|------|---|------|------|
| H003 | SP10 | 5 | 945 | ± 34 |
| H01 | SP10 | 5 | 900 | ± 60 |
| H03 | SP10 | 5 | 848 | ± 13 |
| H10 | SP10 | 5 | 52 | ± 35 |
| H30 | SP10 | 5 | 0 | |
| Ø | 10 | | 231 | |

02(0.07-0.6)

06(0.2-1.5)

0.1

| | | | | |
|------|------|---|-----|------|
| H003 | SP30 | 5 | 825 | ± 49 |
| H01 | SP30 | 5 | 701 | ± 77 |
| H03 | SP30 | 5 | 650 | ± 81 |
| H10 | SP30 | 5 | 22 | ± 17 |
| H30 | SP30 | 5 | 0 | |
| Ø | 10 | | | |

01(0.05-0.5)

04(0.1-1.3)

0.1

Principal Investigator: Professor A. Peter
 Department of Medical Parasitology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
BLOOD CONCENTRATIONS

TABLE 111

COMPOUND NAME Halofantrine (H) +
DR NUMBER Spiramycin (SP) PARASITE SUBSPECIES *P. berghei*
FORMULATION Tween 80 / H₂O ROUTE OF ADMINISTRATION : SC ~~IP-0077~~
MAXIMUM TOLERATED DOSE MTD MG/KG X ...

| Strain | Daily dose
mg/kg DC-0+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated $\frac{PM}{Control} \times 100$ |
|--------|----------------------------|----------------|-----------------------|---------------------------------|---|
| | H 0.03 + SP 10.0 | 5 | | - | 45.8 $\pm$ 4.9 |
| | H 0.1 + SP 10.0 | 5 | | - | 37.5 $\pm$ 7.9 |
| N | H 0.3 + SP 10.0 | 5 | 1 | - | 46.1 $\pm$ 3.9 |
| | H 1.0 + SP 10.0 | 5 | | - | 0 |
| | H 3.0 + SP 10.0 | 5 | | - | 0 |
| | $\emptyset$ | 10 | | 23.1 | |

ED₅₀ (range) 0.07 (0.03-0.3)

ED₉₀ (range) 0.2 (0.06-0.6)

Resistance factor i₉₀

| | | | | | |
|---|------------------|----|---|------|---------------|
| | H 0.03 + SP 30.0 | 5 | | - | 4.9 $\pm$ 2.2 |
| | H 0.1 + SP 30.0 | 5 | | - | 9.1 $\pm$ 3.7 |
| N | H 0.3 + SP 30.0 | 5 | 1 | - | 8.7 $\pm$ 3.2 |
| | H 1.0 + SP 30.0 | 5 | | - | 0 |
| | H 3.0 + SP 30.0 | 5 | | - | 0 |
| | $\emptyset$ | 10 | | 23.1 | |

ED₅₀ (range) 0.015 (0.004-0.03)

ED₉₀ (range) 0.09 (0.02-0.1)

Resistance factor i₉₀

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 112

COMPOUND NAME

OR NUMBER ..HALOFANTRINE..... PARASITE (SUB)SPECIES ...P. berghei...

FORMULATION Tween 80/H₂O.. ROUTE OF ADMINISTRATION : SC/~~IP~~/PO/IV

MAXIMUM TOLERATED DOSE (MTD) >1.0.. MG/KG X 4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% X100 |
|--|----------------------------|----------------|-----------------------|---------------------------------|---------------------------------|
| | 0.1 | 5 | | - | 91.7 ± 2.9 |
| | 0.3 | 5 | | - | 75.3 ± 6.3 |
| N | 0.5 | 5 | 1 | - | 66.0 ± 9.4 |
| | 1.0 | 5 | | - | 26.2 ± 7.6 |
| | Ø | 10 | | 23.6 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.5 (0.3 - 1.2) | | | | | |
| ED ₉₀ (range) 1.2 (1.0 - 3.5) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | | | | | |
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| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 113

COMPOUND NAME

OR NUMBER ..SPIRAMYCIN..... PARASITE (SUB)SPECIES ..P. berghei.....

FORMULATION ..Tween 80/H₂O.. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) >20... MG/KG X 4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% 100 |
|---|----------------------------|----------------|-----------------------|---------------------------------|--------------------------------|
| | 5.0 | 5 | | — | 83.3 ± 1.8 |
| | 10.0 | 5 | | — | 61.2 ± 8.4 |
| N | 15.0 | 5 | 1 | — | 45.3 ± 11.4 |
| | 20.0 | 5 | | — | 39.4 ± 3.9 |
| | Ø | 10 | | 23.6 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 13.5 (9.0 - 18.0) | | | | | |
| ED ₉₀ (range) 15.0 (13.0 - 17.0) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 111

COMPOUND NAME HALOFANTRINE +

OR NUMBER ..SPIRAMYCIN..... PARASITE (SUB)SPECIES ...P. berghei....

FORMULATION ..Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|---|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.1 + 5.0 | 5 | | - | 68.6 ± 9.7 |
| | 0.3 + 5.0 | 5 | | - | 41.5 ± 2.8 |
| N | 0.5 + 5.0 | 5 | 1 | - | 40.6 ± 3.0 |
| | 1.0 + 5.0 | 5 | | - | 13.0 ± 7.9 |
| | Ø | 10 | | 23.6 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.27 (0.12 - 0.5) | | 0.64 / 0.17 | | | |
| ED ₉₀ (range) 1.1 (0.5 - 2.1) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.1 + 10.0 | 5 | | - | 47.2 ± 5.6 |
| | 0.3 + 10.0 | 5 | | - | 47.9 ± 5.6 |
| N | 0.5 + 10.0 | 5 | 1 | - | 42.2 ± 3.6 |
| | 1.0 + 10.0 | 5 | | - | 1.9 ± 0.2 |
| | Ø | 10 | | 23.6 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.35 (0.26 - 0.48) | | 0.38 / 0.12 | | | |
| ED ₉₀ (range) 0.65 (0.5 - 0.92) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 115

COMPOUND NAME HALOFANTRINE +

OR NUMBER SP. RAMMSEN..... PARASITE (SUB)SPECIES P. berghei.....

FORMULATION Tween 80 / H₂O.. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% $\times 100$ |
|---|----------------------------|----------------|-----------------------|---------------------------------|---|
| | 0.1 + 15.0 | 5 | | - | 84.1 $\pm$ 2.4 |
| | 0.3 + 15.0 | 5 | | - | 67.4 $\pm$ 9.5 |
| N | 0.5 + 15.0 | 5 | 1 | - | 42.0 $\pm$ 11.0 |
| | 1.0 + 15.0 | 5 | | - | 11.0 $\pm$ 3.7 |
| | $\emptyset$ | 10 | | 23.6 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.3(0.18 - 0.52) | | 0.47 / 0.25 | | | |
| ED ₉₀ (range) 0.8(0.5 - 1.4) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.1 + 20.0 | 5 | | - | 73.7 $\pm$ 8.8 |
| | 0.3 + 20.0 | 5 | | - | 38.1 $\pm$ 4.6 |
| N | 0.5 + 20.0 | 5 | 1 | - | 34.8 $\pm$ 4.5 |
| | 1.0 + 20.0 | 5 | | - | 2.1 $\pm$ 1.0 |
| | $\emptyset$ | 10 | | 23.6 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.22(0.13 - 0.4) | | 0.32 / 0.5 | | | |
| ED ₉₀ (range) 0.54(0.32 - 1.0) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 116

COMPOUND NAME SPIRAMYCIN +
OR NUMBER .HALOFANTHRINE..... PARASITE (SUB)SPECIES *P. berghei*.....
FORMULATION ...Tween 80/H₂O. ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|-----------------------------------|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 5.0 + 0.1 | 5 | | - | 68.6 ± 9.7 |
| | 10.0 + 0.1 | 5 | | - | 47.2 ± 5.6 |
| N | 15.0 + 0.1 | 5 | 1 | - | 84.1 ± 2.4 |
| | 20.0 + 0.1 | 5 | | - | 73.7 ± 8.5 |
| | Ø | 10 | | 23.6 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | > 0.33 0.16 | | | |
| ED ₉₀ (range) > 20 | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 5.0 + 0.3 | 5 | | - | 41.5 ± 2.8 |
| | 10.0 + 0.3 | 5 | | - | 47.9 ± 5.6 |
| N | 15.0 + 0.3 | 5 | 1 | - | 67.4 ± 9.5 |
| | 20.0 + 0.3 | 5 | | - | 38.1 ± 4.6 |
| | Ø | 10 | | 23.6 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | > 0.33 0.16 | | | |
| ED ₉₀ (range) > 20 | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 117

COMPOUND NAME SPIRAMYCIN +
OR NUMBER HALOFANTHINE..... PARASITE (SUB)SPECIES *P. falciparum*.....
FORMULATION Tween 80/H₂O. ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|-----------------------------------|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 5.0 + 0.5 | 5 | | - | 40.6 ± 3.0 |
| | 10.0 + 0.5 | 5 | | - | 42.2 ± 3.6 |
| N | 15.0 + 0.5 | 5 | 1 | - | 42.0 ± 11.0 |
| | 20.0 + 0.5 | 5 | | - | 34.8 ± 4.5 |
| | Ø | 10 | | 23.6 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | > 0.73 0.01 | | | |
| ED ₉₀ (range) > 20 | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 5.0 + 1.0 | 5 | | - | 13.0 ± 7.9 |
| | 10.0 + 1.0 | 5 | | - | 1.9 ± 0.2 |
| N | 15.0 + 1.0 | 5 | 1 | - | 11.0 ± 3.7 |
| | 20.0 + 1.0 | 5 | | - | 2.1 ± 1.0 |
| | Ø | 10 | | 23.6 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) ~ 1.0 | | 0.10 10.0 | | | |
| ED ₉₀ (range) ~ 6.2 | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 11-5

COMPOUND NAME

OR NUMBER Halofantrine PARASITE SUB SPECIES P. berghei

FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION PO

MAXIMUM TOLERATED DOSE (MTD) MG/KG X

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Mean test
parasite rate % |
|--------|----------------------------|----------------|-----------------------|---------------------------------|------------------------------|
| | 0.1 | 5 | | - | 94.8 ± 5.2 |
| | 0.3 | 5 | | - | 91.4 ± 2.0 |
| N | 1.0 | 5 | 1 | - | 51.6 ± 4.1 |
| | 3.0 | 5 | | - | 0.1 ± 0.1 |
| | Ø | 10 | | 20.9 | |

ED₅₀(range) 0.5(0.1 - 1.3)

ED₉₀(range) 1.3(0.4 - 3.5)

Resistance factor I₉₀

| | | | | | |
|--|--|--|--|--|--|
| | | | | | |
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| | | | | | |

ED₅₀(range)

ED₉₀(range)

Resistance factor I₉₀

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

Compound Name

IP Number Chloroquine Parasite Sub Species P. berghei

Formulation Tween 80/H₂O Route of Administration PO ~~IP~~

Maximum Tolerated Dose (MTD) 1000 mg/kg

| Strain | Daily dose
mg/kg DD-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | reated ~~DD~~
control % |
|--------|----------------------------|----------------|-----------------------|---------------------------------|-----------------------------------|
| | 0.1 | 5 | | - | 82.8 ± 4.1 |
| | 0.3 | 5 | | - | 80.1 ± 5.7 |
| N | 1.0 | 5 | 1 | - | 52.1 ± 7.6 |
| | 3.0 | 5 | | - | 24.3 ± 8.5 |
| | Ø | 10 | | 20.9 | |
| | | | | | |
| | | | | | |

ED₅₀ range 0.8 (0.2 - 2.1)

ED₉₀ range 3.1 (0.9 - 8.5)

Resistance factor 1₉₀

| | | | | | |
|--|--|--|--|--|--|
| | | | | | |
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ED₅₀ (range)

ED₉₀ (range)

Resistance factor 1₉₀

Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DATA

100 110

BLOOD SCHIZONTICIDIC

COMPOUND NAME Halofantrine (H) +

OR NUMBER- Chloroquine (CQ) PARASITE SUB SPECIES P. berghei

FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION: i.p.

MAXIMUM TOLERATED DOSE (MTD) MG/KG

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated MTD
control % |
|--------|----------------------------|----------------|-----------------------|---------------------------------|--------------------------|
| | H 0.1 + CQ 0.1 | 5 | | - | 100 ± 2.5 |
| | H 0.3 + CQ 0.1 | 5 | | - | 88.8 ± 1.3 |
| N | H 1.0 + CQ 0.1 | 5 | 1 | - | 50.2 ± 16.1 |
| | H 3.0 + CQ 0.1 | 5 | | - | 0.05 ± 0.05 |
| | Ø | 10 | | 20.9 | |

ED₅₀ (range) 0.7 (0.4-1.2)ED₉₀ (range) 1.3 (0.8-2.3)Resistance factor I₉₀

| | | | | | |
|---|----------------|----|---|------|-------------|
| | H 0.1 + CQ 0.3 | 5 | | - | 98.6 ± 2.8 |
| | H 0.3 + CQ 0.3 | 5 | | - | 86.6 ± 4.8 |
| N | H 1.0 + CQ 0.3 | 5 | 1 | - | 44.8 ± 13.6 |
| | H 3.0 + CQ 0.3 | 5 | | - | 0.3 ± 0.2 |
| | Ø | 10 | | 20.9 | |

ED₅₀ (range) 0.6 (0.3-1.2)ED₉₀ (range) 1.3 (0.5-2.6)Resistance factor I₉₀

Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

Summary of Antimalarial Drug Tests
Blood Schizonticide

Table 121

Compound Name Halofantrine (H) +
 Drug Number Chloroquine (CQ) PARASITE SUB SPECIES P. berghei
 Formulation Tween 80/H₂O ROUTE OF ADMINISTRATION i.p. ~~per os~~
 Maximum Tolerated Dose (MTD) MG/KG X DAY

| Strain | Daily dose
mg/kg 00-0+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated vs.
Control, % |
|--------|----------------------------|----------------|-----------------------|---------------------------------|---------------------------|
| | H 0.1 + CQ 1.0 | 5 | | - | 89.0 ± 4.1 |
| | H 0.3 + CQ 1.0 | 5 | | - | 75.3 ± 3.1 |
| N | H 1.0 + CQ 1.0 | 5 | 1 | - | 49.3 ± 11.3 |
| | H 3.0 + CQ 1.0 | 5 | | - | 0 |
| | Ø | 10 | | 20.9 | |

ED₅₀ range 0.6 (0.2 - 1.1)

ED₉₀ range 1.1 (0.3 - 1.9)

Resistance factor I₉₀

| | | | | | |
|---|----------------|----|---|------|------------|
| | H 0.1 + CQ 3.0 | 5 | | - | 81.1 ± 2.7 |
| | H 0.3 + CQ 3.0 | 5 | | - | 74.0 ± 4.0 |
| N | H 1.0 + CQ 3.0 | 5 | 1 | - | 26.5 ± 6.4 |
| | H 3.0 + CQ 3.0 | 5 | | - | 0 |
| | Ø | 10 | | 20.9 | |

ED₅₀ (range) 0.3 (0.1 - 0.8)

ED₉₀ (range) 0.6 (0.3 - 1.9)

Resistance factor I₉₀

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 122

COMPOUND NAME Chloroquine (CQ) +
OR NUMBER Halofantaine (H) PARASITE (SUB)SPECIES P. berghei
FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION : SC/1P/P0/1P
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR %
Control PR % |
|--|----------------------------|----------------|-----------------------|---------------------------------|------------------------------|
| | CQ 0.1 + H 0.1 | | | | 100 ± 2.5 |
| | CQ 0.3 + H 0.1 | | | | 98.6 ± 2.8 |
| N | CQ 1.0 + H 0.1 | | | | 89.0 ± 4.1 |
| | CQ 3.0 + H 0.1 | | | | 81.1 ± 2.7 |
| | Ø | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 8.5(6.6 - 11.0) | | | | | |
| ED ₉₀ (range) 37.0(30.0 - 48.0) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | CQ 0.1 + H 0.3 | | | | 88.8 ± 1.3 |
| | CQ 0.3 + H 0.3 | | | | 86.6 ± 4.8 |
| N | CQ 1.0 + H 0.3 | | | | 75.3 ± 3.1 |
| | CQ 3.0 + H 0.3 | | | | 74.0 ± 4.0 |
| | Ø | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 7.8(1.5 - 27.0) | | | | | |
| ED ₉₀ (range) > 100 | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
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London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 123

COMPOUND NAME Chloroquine (CQ) +
OR NUMBER Halofantrine (H)..... PARASITE (SUB)SPECIES *P. berghei*.....
FORMULATION Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated
Control |
|--|----------------------------|----------------|-----------------------|---------------------------------|--------------------|
| | CQ 0.1 + H 1.0 | | | | 50.2 ± 16.1 |
| | CQ 0.3 + H 1.0 | | | | 44.8 ± 13.6 |
| N | CQ 1.0 + H 1.0 | | | | 49.3 ± 11.3 |
| | CQ 3.0 + H 1.0 | | | | 26.5 ± 6.4 |
| | Ø | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.2(<0.1 - 0.6) | | | | | |
| ED ₉₀ (range) 23.3(3.3 - 80) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | CQ 0.1 + H 3.0 | | | | 0.05 ± 0.05 |
| | CQ 0.3 + H 3.0 | | | | 0.3 ± 0.2 |
| N | CQ 1.0 + H 3.0 | | | | 0 |
| | CQ 3.0 + H 3.0 | | | | 0 |
| | Ø | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) < 0.1 | | | | | |
| ED ₉₀ (range) < 0.1 | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
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London School of Hygiene & Tropical Medicine

NAME: Primaquine PARASITE: P. berghei
 FORMULATION: Tween 80/H₂O ROUTE OF ADMINISTRATION: SC
 MAXIMUM TOLERATED DOSE (mg/kg): 10

| Strain | Dose
(mg/kg BW) | No. of
mice | No. of
experiments | Mean control
parasite rate % | Mean test
parasite rate % |
|--------|--------------------|----------------|-----------------------|---------------------------------|------------------------------|
| | 0.1 | 5 | | - | 92.5 ± 3.6 |
| | 0.3 | 5 | | - | 93.1 ± 2.4 |
| N | 1.0 | 5 | 1 | - | 63.0 ± 5.1 |
| | 3.0 | 5 | | - | 34.4 ± 4.0 |
| | ∅ | 10 | | 20.8 | |

ED₅₀ range: 1.5 (1.1 - 2.2)
 ED₅₀ range: 5.8 (4.1 - 8.4)
 Resistance factor: 1

ED₅₀ range
 ED₅₀ range
 Resistance factor: 1

Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 125

COMPOUND NAME Halofantrine (H) +
DR NUMBER Primaquine (PQ)..... PARASITE (SUB)SPECIES ...P. berghei....
FORMULATION ...Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/TP/PQ/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg 00-0+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | reated PR%
Control PR% |
|--------|----------------------------|----------------|-----------------------|---------------------------------|---------------------------|
| | H 0.1 + PQ 0.1 | 5 | | - | 98.1 ± 2.6 |
| | H 0.3 + PQ 0.1 | 5 | | - | 92.2 ± 0.9 |
| N | H 1.0 + PQ 0.1 | 5 | 1 | - | 70.2 ± 5.6 |
| | H 3.0 + PQ 0.1 | 5 | | - | 0 |
| | Ø | 10 | | 20.8 | |
| | | | | | |
| | | | | | |

ED₅₀(range) 0.7(0.2-1.3)

ED₉₀(range) 1.1(0.3-2.0)

Resistance factor I₉₀

| | | | | | |
|---|----------------|----|---|------|-------------|
| | H 0.1 + PQ 0.3 | 5 | | - | 96.6 ± 2.3 |
| | H 0.3 + PQ 0.3 | 5 | | - | 82.1 ± 3.5 |
| N | H 1.0 + PQ 0.3 | 5 | 1 | - | 66.3 ± 8.0 |
| | H 3.0 + PQ 0.3 | 5 | | - | 0.01 ± 0.01 |
| | Ø | 10 | | 20.8 | |
| | | | | | |
| | | | | | |

ED₅₀(range) 0.7(0.2-1.3)

ED₉₀(range) 1.2(0.3-2.1)

Resistance factor I₉₀

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 126

COMPOUND NAME Halofantrine (H) +
OR NUMBER Primaquine (PQ)..... PARASITE (SUB)SPECIES *P. berghei*....
FORMULATION ...Tween 80/H₂O. ROUTE OF ADMINISTRATION : SC/~~IP~~/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg DO-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% x 100 |
|---|----------------------------|----------------|-----------------------|---------------------------------|----------------------------------|
| | H 0.1 + PQ 1.0 | 5 | | - | 100 ± 1.7 |
| | H 0.3 + PQ 1.0 | 5 | | - | 98.5 ± 2.6 |
| N | H 1.0 + PQ 1.0 | 5 | 1 | - | 66.3 ± 5.4 |
| | H 3.0 + PQ 1.0 | 5 | | - | 0.1 ± 0.1 |
| | ∅ | 10 | | 20.8 | |
| ED ₅₀ (range) 0.9(0.6 - 1.3) | | | | | |
| ED ₉₀ (range) 1.5(1.0 - 2.2) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | H 0.1 + PQ 3.0 | 5 | | - | 94.9 ± 2.1 |
| | H 0.3 + PQ 3.0 | 5 | | - | 96.3 ± 1.8 |
| N | H 1.0 + PQ 3.0 | 5 | 1 | - | 70.5 ± 9.0 |
| | H 3.0 + PQ 3.0 | 5 | | - | 0.4 ± 0.4 |
| | ∅ | 10 | | 20.8 | |
| ED ₅₀ (range) 1.0(0.6 - 1.5) | | | | | |
| ED ₉₀ (range) 1.9(1.2 - 2.9) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 127

COMPOUND NAME Primaquine (PQ) +
OR NUMBER Halofantrine (H)..... PARASITE (SUB)SPECIES P. berghei.....
FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION : SC/IP/PQ/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% |
|-----------------------------------|----------------------------|----------------|-----------------------|---------------------------------|----------------------------|
| | PQ 0.1 + H 0.1 | 5 | | - | 98.1 ± 2.6 |
| | PQ 0.3 + H 0.1 | 5 | | - | 96.6 ± 2.3 |
| N | PQ 1.0 + H 0.1 | 5 | 1 | - | 100 ± 1.7 |
| | PQ 3.0 + H 0.1 | 5 | | - | 94.9 ± 2.1 |
| | Ø | 10 | | 20.8 | |
| ED ₅₀ (range) > 3.0 | | | | | |
| ED ₉₀ (range) > 3.0 | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | PQ 0.1 + H 0.3 | 5 | | - | 92.2 ± 0.9 |
| | PQ 0.3 + H 0.3 | 5 | | - | 82.1 ± 3.5 |
| N | PQ 1.0 + H 0.3 | 5 | 1 | - | 98.5 ± 2.6 |
| | PQ 3.0 + H 0.3 | 5 | | - | 96.3 ± 1.8 |
| | Ø | 10 | | 20.8 | |
| ED ₅₀ (range) > 3.0 | | | | | |
| ED ₉₀ (range) > 3.0 | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 128

COMPOUND NAME Primaquine (PQ) +
OR NUMBER Halofantrine (H) PARASITE (SUB)SPECIES P. berghei
FORMULATION Tween 80/H₂O ... ROUTE OF ADMINISTRATION : SC/IP/PQ/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg DO-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated parasites
Control parasites |
|-----------------------------------|----------------------------|----------------|-----------------------|---------------------------------|--|
| | PQ 0.1 + H 1.0 | 5 | | - | 70.2 ± 5.6 |
| | PQ 0.3 + H 1.0 | 5 | | - | 66.3 ± 8.0 |
| N | PQ 1.0 + H 1.0 | 5 | 1 | - | 66.3 ± 5.4 |
| | PQ 3.0 + H 1.0 | 5 | | - | 70.5 ± 9.0 |
| | Ø | 10 | | 20.8 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) > 3.0 | | | | | |
| ED ₉₀ (range) > 3.0 | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | PQ 0.1 + H 3.0 | 5 | | - | 0 |
| | PQ 0.3 + H 3.0 | 5 | | - | 0.01 ± 0.01 |
| N | PQ 1.0 + H 3.0 | 5 | 1 | - | 0.1 ± 0.1 |
| | PQ 3.0 + H 3.0 | 5 | | - | 0.4 ± 0.4 |
| | Ø | 10 | | 20.8 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) < 0.1 | | | | | |
| ED ₉₀ (range) < 0.1 | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZANTOCIDE)

TABLE 129

COMPOUND NAME

OR NUMBER HALOFANTHINE PARASITE (SUB)SPECIES P. falciparum

FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) > 3.0 MG/KG X 4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PRE
Control PRE |
|--|----------------------------|----------------|-----------------------|---------------------------------|----------------------------|
| | 0.1 | 5 | | - | 80.1 ± 2.3 |
| | 0.3 | 5 | | - | 85.4 ± 2.9 |
| N | 1.0 | 5 | 1 | - | 74.9 ± 7.2 |
| | 3.0 | 5 | | - | 0 |
| | 5 | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.7 (0.4 - 1.4) | | | | | |
| ED ₉₀ (range) 1.2 (0.7 - 2.2) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 130

COMPOUND NAME

OR NUMBER SULFADIAZINE..... PARASITE (SUB)SPECIES P. berghei.....

FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION : SC/IV/PO/IV

MAXIMUM TOLERATED DOSE (MTD) 2.30 MG/KG X 4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|--|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.1 | 5 | | - | 98.2 ± 2.3 |
| | 0.3 | 5 | | - | 13.0 ± 11.5 |
| <u>r</u> | 1.0 | 5 | 1 | - | 25.1 ± 12.8 |
| | 3.0 | 5 | | - | 0.4 ± 0.2 |
| | 0 | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.47(0.3 - 0.8) | | | | | |
| ED ₉₀ (range) 1.1(0.7 - 1.9) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZANTOCIDES)

TABLE 131

COMPOUND NAME HALOFANTRINE +
OR NUMBER SULFADIAZINE..... PARASITE (SUB)SPECIES *P. falciparum*.....
FORMULATION $\text{Twon. 80. H}_2\text{O}$... ROUTE OF ADMINISTRATION : SC/HP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% $\times 100$ |
|--|----------------------------|----------------|-----------------------|---------------------------------|---|
| | 0.1 + 0.1 | 5 | | - | 91.6 $\pm$ 3.4 |
| | 0.3 + 0.1 | 5 | | - | 85.1 $\pm$ 5.5 |
| N | 1.0 + 0.1 | 5 | 1 | - | 41.8 $\pm$ 10.0 |
| | 3.0 + 0.1 | 5 | | - | 0 |
| | Ø | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.5 (0.1 - 1.1) | | | | | |
| ED ₉₀ (range) 0.9 (0.5 - 2.0) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.1 + 0.3 | 5 | | - | 92.8 $\pm$ 4.8 |
| | 0.3 + 0.3 | 5 | | - | 56.0 $\pm$ 17.1 |
| N | 1.0 + 0.3 | 5 | 1 | - | 12.4 $\pm$ 7.0 |
| | 3.0 + 0.3 | 5 | | - | 0 |
| | Ø | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.3 (0.2 - 0.6) | | | | | |
| ED ₉₀ (range) 0.7 (0.3 - 1.2) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZANTOCIDES)

TABLE 132

COMPOUND NAME HALOFANTHINE +
OR NUMBER Sulfadiazine..... PARASITE (SUB)SPECIES P. berghei.....
FORMULATION 1.7% w/v / H₂O... ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR
Control PR x 100 |
|---|----------------------------|----------------|-----------------------|---------------------------------|--------------------------------|
| | 0.1 + 1.0 | 5 | | - | 30.6 ± 8.5 |
| | 0.3 + 1.0 | 5 | | - | 10.7 ± 4.2 |
| N | 1.0 + 1.0 | 5 | 1 | - | 1.3 ± 1.3 |
| | 3.0 + 1.0 | 5 | | - | 0 |
| | $\bar{x}$ | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.05 (0.02 - 0.1) | | | | | |
| ED ₉₀ (range) 0.2 (0.05 - 0.5) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.1 + 3.0 | 5 | | - | 1.0 ± 1.0 |
| | 0.3 + 3.0 | 5 | | - | 0 |
| N | 1.0 + 3.0 | 5 | 1 | - | 0 |
| | 3.0 + 3.0 | 5 | | - | 0 |
| | $\bar{x}$ | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.02 (0.01 - 0.02) | | | | | |
| ED ₉₀ (range) 0.04 (0.03 - 0.06) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. J. E. J.
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| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR ₁₀₀
Control PR ₁₀₀ |
|--------|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.1 + 0 | 5 | | - | 31.6 ± 3.4 |
| | 0.2 + 0 | 5 | | - | 81.2 ± 4.9 |
| 7 | 1.0 + 0 | 5 | 1 | - | 30.6 ± 8.9 |
| | 3.0 + 0 | 5 | | - | 1.2 ± 1.0 |
| | Σ | 10 | | 22.5 | |
| | | | | | |
| | | | | | |

| | | | | | |
|---|-------------|----|---|-----|----------------|
| | $0.1 + 0.3$ | 5 | | | 80.0 ± 1.5 |
| | $0.3 + 0.3$ | 5 | | | 80.6 ± 1.1 |
| 2 | $1.0 + 0.3$ | 5 | 1 | | 1.7 ± 1.1 |
| | $3.0 + 0.3$ | 5 | | | 0 |
| | 0 | 10 | | 2.5 | |
| | | | | | |

Principal Investigator: Stephen A. Weinstein
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTICIDES)

TABLE 131

COMPOUND NAME SULFADIAZINE

OR NUMBER HALOFANTHINE PARASITE (SUB)SPECIES Plasmodium

FORMULATION Two: 80/H₂O ROUTE OF ADMINISTRATION : SC/IV/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|--------|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.1 + 1.0 | 5 | | - | 41.8 ± 16.0 |
| | 0.3 + 1.0 | 5 | | - | 12.4 ± 7.0 |
| N | 1.0 + 1.0 | 5 | 1 | - | 1.3 ± 1.3 |
| | 1.0 + 1.0 | 5 | | - | 0 |
| | 0 | 10 | | 22.5 | |
| | | | | | |
| | | | | | |

ED₅₀(range) 0.1 (0.05 - 0.3)

ED₉₀(range) 0.3 (0.17 - 0.5)

Resistance factor I₉₀

| | | | | | |
|---|-----------|----|--|------|---|
| | 0.1 + 3.0 | 5 | | - | 0 |
| | 0.3 + 3.0 | 5 | | - | 0 |
| N | 1.0 + 3.0 | 5 | | - | 0 |
| | 3.0 + 3.0 | 5 | | - | 0 |
| | 0 | 10 | | 22.5 | |
| | | | | | |
| | | | | | |

ED₅₀(range) < 0.1

ED₉₀(range) < 0.1

Resistance factor I₉₀

Chemical Development and Production
Department of Medicine, University of
Michigan, Ann Arbor, Michigan

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 135

COMPOUND NAME

OR NUMBER .HALOFANTRINE..... PARASITE (SUB)SPECIES .P. berghei.....

FORMULATION ..Tween 80/H₂O.. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) >1.0.. MG/KG X 4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% X100 |
|--------------------------------------|----------------------------|----------------|-----------------------|---------------------------------|---------------------------------|
| | 0.1 | 5 | | - | 97.4 ± 4.0 |
| | 0.3 | 5 | | - | 96.8 ± 3.7 |
| N | 0.5 | 5 | 1 | - | 92.2 ± 4.4 |
| | 1.0 | 5 | | - | 24.5 ± 6.2 |
| | Ø | 10 | | 23.3 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.8 (5-12) | | | | | |
| ED ₉₀ (range) 1.5 (11-22) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 136

COMPOUND NAME

OR NUMBER PRIMETHANINE..... PARASITE (SUB)SPECIES P. berghei.....

FORMULATION Two 80% H₂O... ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) >0.3.. MG/KG X 4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|--|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.01 | 5 | | - | 86.5 ± 3.6 |
| | 0.03 | 5 | | - | 79.8 ± 4.1 |
| N | 0.1 | 5 | 1 | - | 45.1 ± 4.4 |
| | 0.3 | 5 | | - | 36.3 ± 10.1 |
| | Ø | 10 | | 23.3 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.1 (0.06 - 0.28) | | | | | |
| ED ₉₀ (range) 1.2 (0.6 - 2.8) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 137

COMPOUND NAME HALOFANTRINE +
OR NUMBER PYRIMETHAMINE..... PARASITE (SUB)SPECIES *P. falciparum*.....
FORMULATION Twice 80./H₂O. ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|---|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.1 + 0.01 | 5 | | - | 89.4 ± 1.5 |
| | 0.3 + 0.01 | 5 | | - | 86.7 ± 4.9 |
| N | 0.5 + 0.01 | 5 | 1 | - | 35.5 ± 9.5 |
| | 1.0 + 0.01 | 5 | | - | 17.9 ± 6.6 |
| | Ø | 10 | | 23.3 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.46 (0.35 - 0.65) | | | | | |
| ED ₉₀ (range) 0.95 (0.7 - 1.4) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.1 + 0.03 | 5 | | - | 90.0 ± 7.6 |
| | 0.3 + 0.03 | 5 | | - | 81.0 ± 5.2 |
| N, | 0.5 + 0.03 | 5 | 1 | - | 73.4 ± 9.1 |
| | 1.0 + 0.03 | 5 | | - | 29.8 ± 8.2 |
| | Ø | 10 | | 23.3 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.58 (0.23 - 1.7) | | | | | |
| ED ₉₀ (range) 1.8 (0.73 - 3.5) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 135

COMPOUND NAME HALOFANTRINE +
OR NUMBER PYRIMETHAMINE..... PARASITE (SUB)SPECIES *P. falciparum*.....
FORMULATION Tween 80 / H₂O.. ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|--|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.1 + 0.1 | 5 | | - | 69.8 ± 6.3 |
| | 0.3 + 0.1 | 5 | | - | 63.0 ± 3.3 |
| N | 0.5 + 0.1 | 5 | 1 | - | 41.5 ± 11.6 |
| | 1.0 + 0.1 | 5 | | - | 29.5 ± 12.3 |
| | Ø | 10 | | 23.3 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.4 (0.25 - 0.72) | | | | | |
| ED ₉₀ (range) 2.6 (1.5 - 5.0) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.1 + 0.3 | 5 | | - | 47.4 ± 11.9 |
| | 0.3 + 0.3 | 5 | | - | 18.0 ± 4.4 |
| N | 0.5 + 0.3 | 5 | 1 | - | 4.1 ± 2.5 |
| | 1.0 + 0.3 | 5 | | - | 1.1 ± 0.4 |
| | Ø | 10 | | 23.3 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.4 (0.14 - 0.72) | | | | | |
| ED ₉₀ (range) 0.4 (0.15 - 0.72) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 139

COMPOUND NAME PYRIMETHAMINE +
OR NUMBER HALOFANTHINE..... PARASITE (SUB)SPECIES *P. berghei*.....
FORMULATION Tween 80 / H₂O... ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% x 100 |
|---|----------------------------|----------------|-----------------------|---------------------------------|----------------------------------|
| | 0.01 + 0.1 | 5 | | - | 89.4 ± 1.5 |
| | 0.03 + 0.1 | 5 | | - | 90.0 ± 7.6 |
| N | 0.1 + 0.1 | 5 | 1 | - | 69.8 ± 6.3 |
| | 0.3 + 0.1 | 5 | | - | 47.7 ± 1.5 |
| | Ø | 10 | | 23.3 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.25 (0.16 - 0.4) | | | | | |
| ED ₉₀ (range) 2 ± 1.5 - 4 | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.01 + 0.3 | 5 | | - | 86.7 ± 4.9 |
| | 0.03 + 0.3 | 5 | | - | 81.0 ± 5.2 |
| N | 0.1 + 0.3 | 5 | 1 | - | 63.0 ± 3.2 |
| | 0.3 + 0.3 | 5 | | - | 18.9 ± 7.7 |
| | Ø | 10 | | 23.3 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.11 (0.05 - 0.16) | | | | | |
| ED ₉₀ (range) 0.42 (0.3 - 0.6) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 140

COMPOUND NAME PYRIMETHAMINE +
OR NUMBER HALOFANTHINE..... PARASITE (SUB)SPECIES ...*P. berghei*.....
FORMULATION $\text{Twinn 80, H}_2\text{O}$... ROUTE OF ADMINISTRATION : SC/~~IP~~/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|---|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.01 + 0.5 | 5 | | - | 35.5 ± 9.5 |
| | 0.03 + 0.5 | 5 | | - | 73.4 ± 9.1 |
| N | 0.1 + 0.5 | 5 | 1 | - | 41.3 ± 10.6 |
| | 0.3 + 0.5 | 5 | | - | 4.3 ± 2.5 |
| | Ø | 10 | | 23.3 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.02 (0.01 - 0.1) | | | | | |
| ED ₉₀ (range) 0.23 (0.14 - 0.36) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.01 + 1.0 | 5 | | - | 17.9 ± 6.6 |
| | 0.03 + 1.0 | 5 | | - | 29.8 ± 8.2 |
| N | 0.1 + 1.0 | 5 | 1 | - | 29.5 ± 12.3 |
| | 0.3 + 1.0 | 5 | | - | 1.9 ± 0.8 |
| | Ø | 10 | | 23.3 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.02 (0.01 - 0.08) | | | | | |
| ED ₉₀ (range) 0.11 (0.05 - 0.35) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 141

COMPOUND NAME

OR NUMBER HALOFANTRINE..... PARASITE (SUB)SPECIES *P. falciparum*.....

FORMULATION 250.0 mg/kg H₂O ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) 250.0 MG/KG X 4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% x 100 |
|--|----------------------------|----------------|-----------------------|---------------------------------|----------------------------------|
| | 0.1 | 5 | | - | 84.8 ± 4.0 |
| | 0.3 | 5 | | - | 72.1 ± 4.7 |
| N | 0.5 | 5 | 1 | - | 63.1 ± 9.0 |
| | 1.0 | 5 | | - | 48.3 ± 5.3 |
| | ∅ | 10 | | 23.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.5 (0.3 - 1.1) | | | | | |
| ED ₉₀ (range) 3.4 (2.1 - 7.4) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 142

COMPOUND NAME

OR NUMBER ..MINOX. YCHINE..... PARASITE (SUB)SPECIES P. berghei.....

FORMULATION Twiss. SC / H₂O... ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) 2.30... MG/KG X 41.

| Strain | Daily dose
mg/kg DO-0+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% X100 |
|---|----------------------------|----------------|-----------------------|---------------------------------|---------------------------------|
| | 1.0 | 5 | | - | 80.0 ± 3.3 |
| | 3.0 | 5 | | - | 66.1 ± 5.0 |
| N | 10.0 | 5 | 1 | - | 40.5 ± 15.0 |
| | 30.0 | 5 | | - | 22.4 ± 7.5 |
| | Ø | 10 | | 23.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 5.4(2.7-12.5) | | | | | |
| ED ₉₀ (range) 70.0(28.0-135) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 143

COMPOUND NAME HALOFANTRINE +
OR NUMBER MINOCYCLINE..... PARASITE (SUB)SPECIES *P. falciparum*.....
FORMULATION *Two 0.5% H₂O* ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR ₂
Control PR ₂ x 100 |
|--|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.1 + 1.0 | 5 | | - | 88.0 ± 4.1 |
| | 0.3 + 1.0 | 5 | | - | 69.5 ± 3.3 |
| N | 0.5 + 1.0 | 5 | 1 | - | 62.4 ± 4.1 |
| | 1.0 + 1.0 | 5 | | - | 43.0 ± 3.3 |
| | 0 | 10 | | 23.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.45 (0.27-1.0) | | | | | |
| ED ₉₀ (range) 2.3 (1.4-5.1) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.1 + 3.0 | 5 | | - | 88.8 ± 4.1 |
| | 0.3 + 3.0 | 5 | | - | 80.4 ± 4.0 |
| N | 0.5 + 3.0 | 5 | 1 | - | 69.8 ± 6.0 |
| | 1.0 + 3.0 | 5 | | - | 37.1 ± 5.1 |
| | 0 | 10 | | 23.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.48 (0.24-1.0) | | | | | |
| ED ₉₀ (range) 1.7 (0.8-3.5) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 1 1 1

COMPOUND NAME HALOFANTRINE +
OR NUMBER MINGSHICHINE..... PARASITE (SUB)SPECIES *P. berghei*.....
FORMULATION Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% x 100 |
|--|----------------------------|----------------|-----------------------|---------------------------------|----------------------------------|
| | 0.1 + 10.0 | 5 | | - | 92.0 ± 2.0 |
| | 0.3 + 10.0 | 5 | | - | 79.5 ± 4.0 |
| N | 0.5 + 10.0 | 5 | 1 | - | 45.0 ± 5.0 |
| | 1.0 + 10.0 | 5 | | - | 35.0 ± 7.0 |
| | Ø | 10 | | 23.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.45(0.26-0.95) | | | | | |
| ED ₉₀ (range) 2.1(1.2-4.2) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.1 + 30.0 | 5 | | - | 27.6 ± 9.4 |
| | 0.3 + 30.0 | 5 | | - | 12.3 ± 5.4 |
| N | 0.5 + 30.0 | 5 | 1 | - | 4.2 ± 1.0 |
| | 1.0 + 30.0 | 5 | | - | 0.7 ± 0.4 |
| | Ø | 10 | | 23.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.05(0.03-0.1) | | | | | |
| ED ₉₀ (range) 0.25(0.15-0.45) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 145

COMPOUND NAME MINOCYCLINE +
OR NUMBER HALOFANTRINE..... PARASITE (SUB)SPECIES *P. berghei*.....
FORMULATION $\text{Twice } 80 / \text{H}_2\text{O}$ ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% $\times 100$ |
|--|----------------------------|----------------|-----------------------|---------------------------------|---|
| | 1.0 + 0.1 | 5 | | - | 80.0 $\pm$ 2.3 |
| | 3.0 + 0.1 | 5 | | - | 85.8 $\pm$ 1.1 |
| N | 10.0 + 0.1 | 5 | 1 | - | 84.0 $\pm$ 2.1 |
| | 30.0 + 0.1 | 5 | | - | 24.5 $\pm$ 1.2 |
| | $\emptyset$ | 10 | | 25.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 13.0 (2.7 - 44) | | | | | |
| ED ₉₀ (range) 64.0 (13.0 - 215) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 1.0 + 0.3 | 5 | | - | 60.5 $\pm$ 1.1 |
| | 3.0 + 0.3 | 5 | | - | 80.4 $\pm$ 1.1 |
| N | 10.0 + 0.3 | 5 | 1 | - | 74.5 $\pm$ 1.1 |
| | 30.0 + 0.3 | 5 | | - | 12.5 $\pm$ 1.4 |
| | $\emptyset$ | 10 | | 25.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 8.3 (1.4 - 27.0) | | | | | |
| ED ₉₀ (range) 33.0 (5.7 - 105) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
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AB 110

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR
Control PR |
|---|----------------------------|----------------|-----------------------|---------------------------------|--------------------------|
| | 100 + 0.5 | 5 | | | 4.5 ± 1.1 |
| | 300 + 0.5 | 5 | | | 5.7 ± 1.5 |
| N | 1000 + 0.5 | 5 | 1 | | 4.5 ± 1.1 |
| | 3000 + 0.5 | 5 | | | 4.5 ± 1.1 |
| | Q | 10 | | 23.4 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 3.8(1.1 - 9.4) | | | | | |
| ED ₉₀ (range) 17.0(5.0 - 41.0) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 100 + 1.0 | 5 | | | 4.5 ± 1.1 |
| | 300 + 1.0 | 5 | | | 5.7 ± 1.5 |
| N | 1000 + 1.0 | 5 | 1 | | 35.6 ± 4.1 |
| | 3000 + 1.0 | 5 | | | 6.4 ± 2.4 |
| | Q | 10 | | 23.4 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 2.0(0.8 - 7.1) | | | | | |
| ED ₉₀ (range) 8.0(3.0 - 28.0) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTAIDES)

TABLE 111

COMPOUND NAME

OR NUMBER

HEC-1, FIDANTHIL, etc.

PARASITE (SUB)SPECIES *P. falciparum*

FORMULATION *Two 80/H₂O* ROUTE OF ADMINISTRATION: SC/*intraperitoneal*

MAY. MUM TOLERATED DOSE (MTD) ≥ 1.0 MG/KG X 5d.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PPE
Control PPE |
|-----------------------------------|----------------------------|----------------|-----------------------|---------------------------------|----------------------------|
| | 0.1 | 5 | | | |
| | 0.3 | 5 | | | |
| N | 0.5 | 5 | 1 | | |
| | 1.0 | 5 | | | |
| | 2 | 10 | | 27.0 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL ACTIVITY
(BIOASSAY METHOD)

115

COMPOUND NAME:

OR NUMBER: 115/116/117/118/119/120/121/122/123/124/125/126/127/128/129/130/131/132/133/134/135/136/137/138/139/140/141/142/143/144/145/146/147/148/149/150/151/152/153/154/155/156/157/158/159/160/161/162/163/164/165/166/167/168/169/170/171/172/173/174/175/176/177/178/179/180/181/182/183/184/185/186/187/188/189/190/191/192/193/194/195/196/197/198/199/200/201/202/203/204/205/206/207/208/209/210/211/212/213/214/215/216/217/218/219/220/221/222/223/224/225/226/227/228/229/230/231/232/233/234/235/236/237/238/239/240/241/242/243/244/245/246/247/248/249/250/251/252/253/254/255/256/257/258/259/260/261/262/263/264/265/266/267/268/269/270/271/272/273/274/275/276/277/278/279/280/281/282/283/284/285/286/287/288/289/290/291/292/293/294/295/296/297/298/299/300/301/302/303/304/305/306/307/308/309/310/311/312/313/314/315/316/317/318/319/320/321/322/323/324/325/326/327/328/329/330/331/332/333/334/335/336/337/338/339/340/341/342/343/344/345/346/347/348/349/350/351/352/353/354/355/356/357/358/359/360/361/362/363/364/365/366/367/368/369/370/371/372/373/374/375/376/377/378/379/380/381/382/383/384/385/386/387/388/389/390/391/392/393/394/395/396/397/398/399/400/401/402/403/404/405/406/407/408/409/410/411/412/413/414/415/416/417/418/419/420/421/422/423/424/425/426/427/428/429/430/431/432/433/434/435/436/437/438/439/440/441/442/443/444/445/446/447/448/449/450/451/452/453/454/455/456/457/458/459/460/461/462/463/464/465/466/467/468/469/470/471/472/473/474/475/476/477/478/479/480/481/482/483/484/485/486/487/488/489/490/491/492/493/494/495/496/497/498/499/500/501/502/503/504/505/506/507/508/509/510/511/512/513/514/515/516/517/518/519/520/521/522/523/524/525/526/527/528/529/530/531/532/533/534/535/536/537/538/539/540/541/542/543/544/545/546/547/548/549/550/551/552/553/554/555/556/557/558/559/560/561/562/563/564/565/566/567/568/569/570/571/572/573/574/575/576/577/578/579/580/581/582/583/584/585/586/587/588/589/590/591/592/593/594/595/596/597/598/599/600/601/602/603/604/605/606/607/608/609/610/611/612/613/614/615/616/617/618/619/620/621/622/623/624/625/626/627/628/629/630/631/632/633/634/635/636/637/638/639/640/641/642/643/644/645/646/647/648/649/650/651/652/653/654/655/656/657/658/659/660/661/662/663/664/665/666/667/668/669/670/671/672/673/674/675/676/677/678/679/680/681/682/683/684/685/686/687/688/689/690/691/692/693/694/695/696/697/698/699/700/701/702/703/704/705/706/707/708/709/710/711/712/713/714/715/716/717/718/719/720/721/722/723/724/725/726/727/728/729/730/731/732/733/734/735/736/737/738/739/740/741/742/743/744/745/746/747/748/749/750/751/752/753/754/755/756/757/758/759/760/761/762/763/764/765/766/767/768/769/770/771/772/773/774/775/776/777/778/779/780/781/782/783/784/785/786/787/788/789/790/791/792/793/794/795/796/797/798/799/800/801/802/803/804/805/806/807/808/809/810/811/812/813/814/815/816/817/818/819/820/821/822/823/824/825/826/827/828/829/830/831/832/833/834/835/836/837/838/839/840/841/842/843/844/845/846/847/848/849/850/851/852/853/854/855/856/857/858/859/860/861/862/863/864/865/866/867/868/869/870/871/872/873/874/875/876/877/878/879/880/881/882/883/884/885/886/887/888/889/890/891/892/893/894/895/896/897/898/899/900/901/902/903/904/905/906/907/908/909/910/911/912/913/914/915/916/917/918/919/920/921/922/923/924/925/926/927/928/929/930/931/932/933/934/935/936/937/938/939/940/941/942/943/944/945/946/947/948/949/950/951/952/953/954/955/956/957/958/959/960/961/962/963/964/965/966/967/968/969/970/971/972/973/974/975/976/977/978/979/980/981/982/983/984/985/986/987/988/989/990/991/992/993/994/995/996/997/998/999/1000/1001/1002/1003/1004/1005/1006/1007/1008/1009/1010/1011/1012/1013/1014/1015/1016/1017/1018/1019/1020/1021/1022/1023/1024/1025/1026/1027/1028/1029/1030/1031/1032/1033/1034/1035/1036/1037/1038/1039/1040/1041/1042/1043/1044/1045/1046/1047/1048/1049/1050/1051/1052/1053/1054/1055/1056/1057/1058/1059/1060/1061/1062/1063/1064/1065/1066/1067/1068/1069/1070/1071/1072/1073/1074/1075/1076/1077/1078/1079/1080/1081/1082/1083/1084/1085/1086/1087/1088/1089/1090/1091/1092/1093/1094/1095/1096/1097/1098/1099/1100/1101/1102/1103/1104/1105/1106/1107/1108/1109/1110/1111/1112/1113/1114/1115/1116/1117/1118/1119/1120/1121/1122/1123/1124/1125/1126/1127/1128/1129/1130/1131/1132/1133/1134/1135/1136/1137/1138/1139/1140/1141/1142/1143/1144/1145/1146/1147/1148/1149/1150/1151/1152/1153/1154/1155/1156/1157/1158/1159/1160/1161/1162/1163/1164/1165/1166/1167/1168/1169/1170/1171/1172/1173/1174/1175/1176/1177/1178/1179/1180/1181/1182/1183/1184/1185/1186/1187/1188/1189/1190/1191/1192/1193/1194/1195/1196/1197/1198/1199/1200/1201/1202/1203/1204/1205/1206/1207/1208/1209/1210/1211/1212/1213/1214/1215/1216/1217/1218/1219/1220/1221/1222/1223/1224/1225/1226/1227/1228/1229/1230/1231/1232/1233/1234/1235/1236/1237/1238/1239/1240/1241/1242/1243/1244/1245/1246/1247/1248/1249/1250/1251/1252/1253/1254/1255/1256/1257/1258/1259/1260/1261/1262/1263/1264/1265/1266/1267/1268/1269/1270/1271/1272/1273/1274/1275/1276/1277/1278/1279/1280/1281/1282/1283/1284/1285/1286/1287/1288/1289/1290/1291/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Figure 11.10

OR NUMBER PARAGRAPH SUBJECT

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTICIDES)

TABLE 10,1

COMPOUND NAME: *Chloroquine*

OR NUMBER: *1000* PARASITE (SUB) SPECIES: *Plasmodium falciparum*

FORMULATION: *0.5% w/v* ROUTE OF ADMINISTRATION: *SCIP/PO/IV*

MAXIMUM TOLERATED DOSE (MTD) *100* MG/KG X *1*

| Strain | Daily dose
mg/kg DO-G+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated DEF
Control DEF |
|-----------------------------------|----------------------------|----------------|-----------------------|---------------------------------|----------------------------|
| <i>100</i> | <i>0.5</i> | <i>5</i> | | | |
| <i>100</i> | <i>1.0</i> | <i>5</i> | | | |
| <i>100</i> | <i>2.0</i> | <i>5</i> | | | |
| <i>100</i> | <i>4.0</i> | <i>5</i> | | | |
| <i>100</i> | <i>8.0</i> | <i>5</i> | | | |
| <i>100</i> | <i>16.0</i> | <i>5</i> | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| <i>100</i> | <i>0.5</i> | <i>5</i> | | | |
| <i>100</i> | <i>1.0</i> | <i>5</i> | | | |
| <i>100</i> | <i>2.0</i> | <i>5</i> | | | |
| <i>100</i> | <i>4.0</i> | <i>5</i> | | | |
| <i>100</i> | <i>8.0</i> | <i>5</i> | | | |
| <i>100</i> | <i>16.0</i> | <i>10</i> | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTICIDES)

Table 151

COMPOUND NAME CLINDAMICIN +

DR NUMBER HALOANTHRIN-95 PARASITE SUB SPECIES P. falciparum

FORMULATION 1.25% SC / H₂O ROUTE OF ADMINISTRATION : SCAP-PO-IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PRE
Control PRE |
|------------------------------------|----------------------------|----------------|-----------------------|---------------------------------|----------------------------|
| | 10 + C1 | 5 | | - | 9.1 ± 1.1 |
| | 30 + C1 | 5 | | - | 1.1 ± 1.1 |
| N | 100 + C1 | 5 | 1 | - | 3.1 ± 1.1 |
| | 300 + C1 | 5 | | - | 1.3 ± 1.1 |
| | Ø | 10 | | 24.0 | |
| ED ₅₀ (range) 1.1 - 1.1 | | | | | |
| ED ₉₀ (range) 1.1 - 1.1 | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 10 + C3 | 5 | | - | 10.0 ± 1.1 |
| | 30 + C3 | 5 | | - | 10.0 ± 1.1 |
| N | 100 + C3 | 5 | 1 | - | 10.0 ± 1.1 |
| | 500 + C3 | 5 | | - | 1.3 ± 1.1 |
| | Ø | 10 | | 27.0 | |
| ED ₅₀ (range) 1.1 - 1.1 | | | | | |
| ED ₉₀ (range) 1.1 - 1.1 | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

Figure 1. The study area.

TABLE 15-3

OR NUMBER HUC6709 PARASITE (SUB)SPECIES A. A. 1

FORMULATION : Two 50/1/1, C... ROUTE OF ADMINISTRATION : SC ~~10/10/10~~

MAXIMUM TOLERATED DOSE (MTD) 2100 MG/KG X 4

[illegible]

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

- TABLE 1.5.1

COMPOUND NAME

OR NUMBER TETRAHYDRO-4-CHLORO-1-METHYLPYRIMIDIN-2(1H)-ONE PARASITE (SUB)SPECIES P. falciparum

FORMULATION Tetrahydro-4-chloro-1-methylpyrimidin-2(1H)-one ROUTE OF ADMINISTRATION : SC/ID/PO/IV

MAXIMUM TOLERATED DOSE (MTD) > 3.6 MG/KG x 4 d.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR ₁₀₀
Control PR ₁₀₀ |
|-----------------------------------|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 1.0 | 5 | | - | 76.0 ± 3.0 |
| | 3.0 | 5 | | - | 54.0 ± 3.0 |
| N | 10.0 | 5 | 1 | - | 43.0 ± 3.0 |
| | 30.0 | 5 | | - | 31.0 ± 3.0 |
| | 2 | 5 | | 20.0 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 155

COMPOUND NAME HALOFANTHRINE +

OR NUMBER TELITHIOCYANIDE..... PARASITE (SUB)SPECIES P. falciparum.....

FORMULATION 100% S.C. / H₂O. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% x 100 |
|------------------------------------|----------------------------|----------------|-----------------------|---------------------------------|----------------------------------|
| | 0.1 + 1.0 | 5 | | - | 50.7 ± 4.2 |
| | 0.3 + 1.0 | 5 | | - | 51.1 ± 4.5 |
| N | 0.5 + 1.0 | 5 | 1 | - | 39.2 ± 4.0 |
| | 1.0 + 1.0 | 5 | | - | 34.3 ± 3.0 |
| | ✓ | 10 | | 26.6 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.1 - 1.0 | | | | | |
| ED ₉₀ (range) 0.3 - 1.0 | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.1 + 3.0 | 5 | | - | 75.3 ± 2.1 |
| | 0.3 + 3.0 | 5 | | - | 69.5 ± 4.1 |
| N | 0.5 + 3.0 | 5 | 1 | - | 52.9 ± 5.4 |
| | 1.0 + 3.0 | 5 | | - | 48.0 ± 2.5 |
| | ✓ | 10 | | 26.6 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.1 - 3.0 | | | | | |
| ED ₉₀ (range) 0.3 - 3.0 | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 156

COMPOUND NAME HALOFANTRINE +

OR NUMBER TETRACYCLINE..... PARASITE (SUB)SPECIES P. falciparum.....

FORMULATION T. 1000.80 / H₂O ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg DO-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% x 100 |
|---|----------------------------|----------------|-----------------------|---------------------------------|----------------------------------|
| | 0.1 + 10.0 | 5 | | - | 73.6 ± 2.0 |
| | 0.3 + 10.0 | 5 | | - | 44.7 ± 1.0 |
| N | 0.5 + 10.0 | 5 | 1 | - | 42.5 ± 2.4 |
| | 1.0 + 10.0 | 5 | | - | 31.7 ± 3.4 |
| | Ø | 10 | | 26.6 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.5 (0.1 - 1.2) | | | | | |
| ED ₉₀ (range) 1.35 (1.0 - 3.2) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.1 + 30.0 | 5 | | - | 75.1 ± 2.3 |
| | 0.3 + 30.0 | 5 | | - | 56.0 ± 5.3 |
| N | 0.5 + 30.0 | 5 | 1 | - | 40.2 ± 4.4 |
| | 1.0 + 30.0 | 5 | | - | 35.2 ± 3.0 |
| | Ø | 10 | | 26.6 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.6 (0.3 - 1.5) | | | | | |
| ED ₉₀ (range) 1.35 (1.0 - 3.2) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
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London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 157

COMPOUND NAME TETRACYCLINE +

OR NUMBER ..HALOFANTHINE..... PARASITE (SUB)SPECIES ..P. M. ...

FORMULATION $T_{max} 80/H_2O$. ROUTE OF ADMINISTRATION : SC/1P/P0/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|--|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 1.0 + 0.1 | 5 | | - | 80.7 ± 4.2 |
| | 3.0 + 0.1 | 5 | | - | 75.3 ± 2.1 |
| N | 10.0 + 0.1 | 5 | 1 | - | 73.6 ± 2.0 |
| | 30.0 + 0.1 | 5 | | - | 75.1 ± 2.3 |
| | 0 | 10 | | 26.6 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) > 30 | | | | | |
| ED ₉₀ (range) > 30 | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 1.0 + 0.3 | 5 | | - | 51.1 ± 4.5 |
| | 3.0 + 0.3 | 5 | | - | 69.5 ± 4.1 |
| N | 10.0 + 0.3 | 5 | 1 | - | 44.9 ± 3.0 |
| | 30.0 + 0.3 | 5 | | - | 56.0 ± 5.3 |
| | 0 | 10 | | 26.6 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 18.0 (5.2 - 47.0) | | | | | |
| ED ₉₀ (range) 15.5 (4.0 - 40.0) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 158

COMPOUND NAME TETRACYCLINE +
OR NUMBER HALOFANTINE..... PARASITE (SUB)SPECIES *P. berghei*.....
FORMULATION Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|-----------------------------------|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 1.0 + 0.5 | 5 | | - | 39.2 ± 4.9 |
| | 3.0 + 0.5 | 5 | | - | 52.9 ± 5.9 |
| N | 10.0 + 0.5 | 5 | 1 | - | 40.5 ± 3.4 |
| | 30.0 + 0.5 | 5 | | - | 40.2 ± 4.4 |
| | ∅ | 10 | | 26.6 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) > 30 | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 1.0 + 1.0 | 5 | | - | 34.3 ± 3.0 |
| | 3.0 + 1.0 | 5 | | - | 48.0 ± 2.5 |
| N | 10.0 + 1.0 | 5 | 1 | - | 31.7 ± 3.7 |
| | 30.0 + 1.0 | 5 | | - | 35.2 ± 3.0 |
| | ∅ | 10 | | 26.6 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) > 30 | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

3. J. C. SUTHERLAND, *ibid.* 1961, 109.

TABLE 159

COMPOUND NAME

OR NUMBER FLOPPING PARASITE (SUB)SPECIES F. floppae

FORMULATION : $\text{TiSO}_4/\text{H}_2\text{O}$ ROUTE OF ADMINISTRATION : SC/IV/PO/IV

MAXIMUM TOLERATED DOSE (MTD) 2.5.0. MG/KG X 4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR
Control PR $\times 100$ |
|---------------------------------------|----------------------------|----------------|-----------------------|---------------------------------|---------------------------------------|
| | 0.1 | 5 | | - | 83.4 ± 4.9 |
| | 0.2 | 5 | | - | 70.4 ± 5.1 |
| N | 0.2 | 5 | | - | 46.6 ± 7.8 |
| | 1.0 | 5 | | - | 4.2 ± 3.9 |
| | 3.0 | 5 | | - | 0.02 ± 0.01 |
| | 7 | 10 | | 25.3 | |
| | | | | | |
| ED ₅₀ (range) 0.3(0.2-0.5) | | | | | |
| ED ₉₀ (range) 0.4(0.4-1.2) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W.Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

- Page 160

OR NUMBER QUININE HYDROCHLORIDE PARASITE (SUB)SPECIES Plasmodium

MAXIMUM TOLERATED DOSE (MTD) ~ 600 MG/KG X 4.

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

• TABLE 61

OR NUMBER Quinine..... PARASITE (SUB)SPECIES T. trachy.....

FORMULATION Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/~~IP~~^F/~~PO~~^Q

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

S. 100-101-102

COMPOUND NAME: FLOXAPYRONE

GR. NUMBER: 100-101-102 PARASITE: SUBMITED TO: (100-101-102)

FORMULATION: 100-101-102 ROUTE OF ADMINISTRATION: F + G

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated mean
control parasite rate % |
|--------|----------------------------|----------------|-----------------------|---------------------------------|---|
| | 0.1 + 30.0 | 5 | | - | 80.0 ± 2.2 |
| | 0.3 + 30.0 | 5 | | - | 54.4 ± 13.9 |
| N | 0.5 + 30.0 | 5 | 1 | - | 27.1 ± 15.9 |
| | 1.0 + 30.0 | 5 | | - | 0.4 ± 0.0 |
| | 3.0 + 30.0 | 5 | | - | 0 |
| | ✓ | 10 | | 25.3 | |

ED₅₀(range) 0.2 (0.1 - 0.4)ED₉₀(range) 0.5 (0.3 - 1.0)Resistance factor I₉₀

| | | | | | |
|---|-------------|----|---|------|-----------|
| | 0.1 + 100.0 | 5 | | - | 82 ± 3.0 |
| | 0.3 + 100.0 | 5 | | - | 5.8 ± 1.4 |
| N | 0.5 + 100.0 | 5 | 1 | - | 4.1 ± 1.5 |
| | 1.0 + 100.0 | 5 | | - | 0 |
| | 3.0 + 100.0 | 5 | | - | 0 |
| | 0 | 10 | | 25.3 | |

ED₅₀(range) 0.05 (0.03 - 0.1)ED₉₀(range) 0.1 (0.04 - 0.4)Resistance factor I₉₀

Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOCK SUBSTITUTED)

TABLE 163

COMPOUND NAME QUININE +
OR NUMBER FLXABRUSE PARASITE (SUB)SPECIES P. berghei
FORMULATION 100.0% H₂O ROUTE OF ADMINISTRATION : SC/TP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PPS
Control PPS |
|--|----------------------------|----------------|-----------------------|---------------------------------|----------------------------|
| | 3.0 + 0.1 | 5 | | - | 88.0 ± 4.4 |
| | 10.0 + 0.1 | 5 | | - | 81.3 ± 2.9 |
| N | 30.0 + 0.1 | 5 | 1 | - | 80.0 ± 2.2 |
| | 100.0 + 0.1 | 5 | | - | 82 ± 3.0 |
| | ∅ | 10 | | 25.3 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 35.0(25.0 - 60.0) | | | | | |
| ED ₉₀ (range) 90.0(61.0 - 150) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 3.0 + 0.3 | 5 | | - | 82.7 ± 2.3 |
| | 10.0 + 0.3 | 5 | | - | 73.8 ± 7.7 |
| N | 30.0 + 0.3 | 5 | 1 | - | 84.4 ± 13.1 |
| | 100.0 + 0.3 | 5 | | - | 85 ± 1.4 |
| | ∅ | 10 | | 25.3 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 17.0(7.1 - 50.0) | | | | | |
| ED ₉₀ (range) 70.0(30.0 - 200) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL TESTS

- TABLE 16.1

(BY ROUTE OF ADMINISTRATION)

COMPOUND NAME QUININE +OR NUMBER EXPERIMENTAL PARASITE (SUBCULTURED) F. longiFORMULATION Twice 800 mg H₂O ROUTE OF ADMINISTRATION SC 4000 H

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated / Control
parasite rate % |
|--|----------------------------|----------------|-----------------------|---------------------------------|--------------------------------------|
| | 3.0 + 0.5 | 5 | | - | 51.8 ± 15.3 |
| | 10.0 + 0.5 | 5 | | - | 50.2 ± 16.2 |
| N | 30.0 + 0.5 | 5 | 1 | - | 25.0 ± 15.8 |
| | 100.0 + 0.5 | 5 | | - | 4.1 ± 1.8 |
| | 0 | 5 | | 25.3 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 11.5 (7.5 - 20.0) | | | | | |
| ED ₉₀ (range) 50.0 (40.0 - 100) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 3.0 + 0.5 | 5 | | - | 0.7 ± 0.2 |
| | 10.0 + 0.5 | 5 | | - | 0.05 ± 0.03 |
| N | 30.0 + 0.5 | 5 | 1 | - | 0.4 ± 0.2 |
| | 100.0 + 0.5 | 5 | | - | 0 |
| | 0 | 10 | | 25.3 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0 (0.0 - 0.4) | | | | | |
| ED ₉₀ (range) 1.5 (0.0 - 3.2) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor A. Peters
 Department of Medical Protozoology,
 London School of Hygiene & Tropical Medicine

Date: 10/10/1964

COMPOUND NAME

OR NUMBER FLOXALONE PARA 101 - 10/10/64FORMULATION TWINS 80/H₂O ROUTE OF ADMINISTRATION PO ~~PO~~MAXIMUM TOLERATED DOSE (MTD) 2.3.0 MG/KG X 4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated %
control % |
|--------|----------------------------|----------------|-----------------------|---------------------------------|------------------------|
| | 0.1 | 5 | | - | 8.6 ± 4.0 |
| | 0.3 | 5 | | - | 7.9 ± 5.0 |
| N | 0.5 | 5 | 1 | - | 4.2 ± 2.5 |
| | 1.0 | 5 | | - | 4.2 ± 3.9 |
| | 3.0 | 5 | | - | 0.2 ± 0.5 |
| | Ø | 10 | | 25.3 | |

ED₅₀(range) 0.3 (0.2 - 0.5)ED₉₀(range) 0.5 (0.5 - 1.4)Resistance factor I₉₀

| | | | | |
|--|--|--|--|--|
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

ED₅₀(range)ED₉₀(range)Resistance factor I₉₀

Contract Laboratory, Department of Health

Department of Medicine, University of

Glasgow, Scotland, U.K. (Telephone & Telex)

Chemical Name

Chemical Name

OR NUMBER ... C.N.S. 400000000 ...

Formulation ... $\text{C}_6\text{H}_5\text{O}_2\text{S}_2\text{N}_2\text{H}_2\text{O}$ Route of Administration ...

Maximum Tolerated Dose (MTD) ≥ 10 mg/kg x 4

| Strain | Daily dose mg/kg D0-D+3 | No. of mice | No. of experiments | Mean control parasite rate $\pm$ S.E. | Treat. group parasite rate $\pm$ S.E. |
|--------|-------------------------|-------------|--------------------|---------------------------------------|---------------------------------------|
| | 0.3 | 5 | | 7 | 5.0 $\pm$ 1.0 |
| | 1.0 | 5 | | 7 | 4.0 $\pm$ 1.0 |
| IN | 3.0 | 5 | 1 | 7 | 3.0 $\pm$ 1.0 |
| | 5.0 | 5 | | 7 | 2.0 $\pm$ 1.0 |
| | 10.0 | 5 | | 7 | 1.0 $\pm$ 1.0 |
| | 20 | 10 | | 20 | |

ED₅₀ (range) ...

ED₉₀ (range) ...

Resistance factor 10_5

ED₅₀ (range)

ED₉₀ (range)

Resistance factor 10_5

... of ...

... of ...

... of ...

10

1. *Chrysomelids* 2. *Cyberus*

MAXIMUM TOLERATED DOSE (MTD) (mg/kg/day)

6000 range)

range: {

distance factor i_q

1. *Chlorophyll a* (Chl *a*)

1. *Chlorophyll a* (Chl *a*)

... ..

where $\mathbf{A} = \mathbf{A}(\mathbf{y})$ is the matrix of the linearized system, $\mathbf{B} = \mathbf{B}(\mathbf{y})$ is the matrix of the linearized forcing, and $\mathbf{C} = \mathbf{C}(\mathbf{y})$ is the matrix of the linearized boundary conditions. The matrices $\mathbf{A}$, $\mathbf{B}$, and $\mathbf{C}$ are functions of the state vector $\mathbf{y}$. The matrices $\mathbf{A}$, $\mathbf{B}$, and $\mathbf{C}$ are functions of the state vector $\mathbf{y}$. The matrices $\mathbf{A}$, $\mathbf{B}$, and $\mathbf{C}$ are functions of the state vector $\mathbf{y}$.

NAME OF NAME: FLEKXOLINE +

NAME OF NAME: S.M.S. EXAMINER: ... PARASITE SUBSTRATE: *Plasmodium*

FORMULATION: Triclosan, H_2O . ROUTE OF ADMINISTRATION: SC/IT

MAXIMUM TOLERATED DOSE (MTD) ... MG/KG X DAY

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PPT
Control PPT |
|---|----------------------------|----------------|-----------------------|---------------------------------|----------------------------|
| | 0.1 + 3.0 | 5 | | - | 25.5 ± 4.5 |
| | 0.3 + 3.0 | 5 | | - | 24.5 ± 2.4 |
| N | 0.5 + 3.0 | 5 | 1 | - | 3.4 ± 2.0 |
| | 1.0 + 3.0 | 5 | | - | 0.02 ± 0.01 |
| | 3.0 + 3.0 | 5 | | - | 0 |
| | 0 | 10 | | 25.3 | |
| ED ₅₀ (range) 0.03(0.01-0.2) | | | | | |
| ED ₉₀ (range) 0.2(0.1-0.5) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.1 + 5.0 | 5 | | - | 25.3 ± 4.5 |
| | 0.3 + 5.0 | 5 | | - | 19.0 ± 0.4 |
| N | 0.5 + 5.0 | 5 | 1 | - | 1.2 ± 0.5 |
| | 1.0 + 5.0 | 5 | | - | 0.02 ± 0.01 |
| | 3.0 + 5.0 | 5 | | - | 0 |
| | 0 | 10 | | 25.3 | |
| ED ₅₀ (range) 0.1(0.06-0.2) | | | | | |
| ED ₉₀ (range) 0.2(0.1-0.4) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Paton
Department of Medical Parasitology
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SUMMARY OF ANTIMALARIAL DRUG TESTS

- Jan 1969

TABLE 1. CHLOROQUINE

COMPOUND NAME CHLOROQUINE +

DR NUMBER ~~FL-100-101~~ PARASITE (SUB)SPECIES *P. berghei*FORMULATION ~~Tween 80~~ / H₂O ROUTE OF ADMINISTRATION : SC/IV/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|---|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.3 + 0.1 | 5 | | - | 52.6 ± 1.5 |
| | 1.0 + 0.1 | 5 | | - | 35.8 ± 3.1 |
| N | 3.0 + 0.1 | 5 | 1 | - | 25.5 ± 4.5 |
| | 5.0 + 0.1 | 5 | | - | 25.3 ± 4.8 |
| | Ø | 10 | | 25.3 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.3 (0.2 - 0.5) | | | | | |
| ED ₉₀ (range) 21.0 (11.0 - 48.0) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.3 + 0.3 | 5 | | - | 45.8 ± 3.7 |
| | 1.0 + 0.3 | 5 | | - | 30.8 ± 3.3 |
| N | 3.0 + 0.3 | 5 | 1 | - | 24.0 ± 2.4 |
| | 5.0 + 0.3 | 5 | | - | 18.0 ± 4.4 |
| | Ø | 10 | | 25.3 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.3 (0.2 - 0.5) | | | | | |
| ED ₉₀ (range) 0.3 - 1.4 | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. J. L. ...
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

OR NUMBER 100-100000000 100-100000000 100-100000000 100-100000000 100-100000000

FORMULATION ... Tween 80 + 4% ...

MAXIMUM TOLERATED DOSE (MTD) mg/kg/day

Department of Internal Medicine
University of Michigan
Ann Arbor, Michigan 48106

AD-A185 118

CHEMOTHERAPY OF RODENT MALARIA(U) LONDON SCHOOL OF
HYGIENE AND TROPICAL MEDICINE (ENGLAND) DEPT OF MEDICAL
PROTOZOOLOGY W PETERS JUL 85 DAND17-84-C-4018

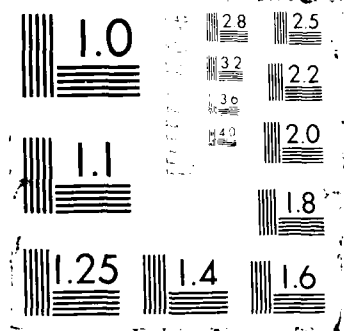
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 171

COMPOUND NAME FLOXACRINE

OR NUMBER ..4.V.1528..... PARASITE (SUB)SPECIES ..P. berghei.....

FORMULATION ..Tween 80./H₂O.. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) ..1.0... MG/KG X 4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|---|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.1 | 5 | | - | 95.5 ± 5.7 |
| | 0.3 | 5 | | - | 90.0 ± 2.9 |
| N | 0.5 | 5 | 1 | - | 43.6 ± 14.3 |
| | 1.0 | 5 | | - | 0.3 ± 0.3 |
| | ∅ | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.44 (0.31 - 0.52) | | Isobolar Unit | | | |
| ED ₉₀ (range) 0.64 (0.46 - 0.8) | | | | | |
| Resistance factor I ₉₀ 1.0 | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 17.2

COMPOUND NAME

OR NUMBER TETRACYCLINE..... PARASITE (SUB SPECIES) P. falciparum

FORMULATION Tween 30/H₂O... ROUTE OF ADMINISTRATION : SC/12-14

MAXIMUM TOLERATED DOSE (MTD) >100.0 MG/KG X 4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% $\times 100$ |
|---|----------------------------|----------------|-----------------------|---------------------------------|---|
| | 3.0 | 5 | | - | 95.4 $\pm$ 2.3 |
| | 10.0 | 5 | | - | 78.4 $\pm$ 8.7 |
| N | 30.0 | 5 | 1 | - | 53.7 $\pm$ 10.9 |
| | 100.0 | 5 | | - | 4.3 $\pm$ 2.0 |
| | $\emptyset$ | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 20.0 (12.0 - 42.0) | | Isobolar Unit | | | |
| ED ₉₀ (range) 67.0 (41.0 - 140) | | | | | |
| Resistance factor I ₉₀ 1.0 | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 173

COMPOUND NAME FLOXAURINE +

OR NUMBER TETRALYCHNE..... PARASITE (SUB)SPECIES P. berghei.....

FORMULATION Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg DO-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|--|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.1 + 3.0 | 5 | | - | 95.6 ± 3.1 |
| | 0.3 + 3.0 | 5 | | - | 57.6 ± 10.0 |
| N | 0.5 + 3.0 | 5 | 1 | - | 15.6 ± 6.7 |
| | 1.0 + 3.0 | 5 | | - | 0 |
| | Ø | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.23(0.17 - 0.37) | | Isobolar Units | | | |
| ED ₉₀ (range) 0.38(0.27 - 0.6) | | | | | |
| Resistance factor I ₉₀ 0.59 | | | | | |
| | 0.1 + 10.0 | 5 | | - | 88.4 ± 3.2 |
| | 0.3 + 10.0 | 5 | | - | 60.2 ± 4.4 |
| N | 0.5 + 10.0 | 5 | 1 | - | 1.9 ± 1.9 |
| | 1.0 + 10.0 | 5 | | - | 0 |
| | Ø | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.22(0.14 - 0.35) | | Isobolar Units | | | |
| ED ₉₀ (range) 0.36(0.24 - 0.58) | | | | | |
| Resistance factor I ₉₀ 0.56 | | | | | |

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 171

COMPOUND NAME FLOXACRINE +
OR NUMBER TETRACYCLINE..... PARASITE (SUB)SPECIES ...*P. berghei*....
FORMULATION ...Tween 80 / H₂O.. ROUTE OF ADMINISTRATION : SC/IP/PO/IV
MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|---|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.1 + 30.0 | 5 | | - | 51.6 ± 10.4 |
| | 0.3 + 30.0 | 5 | | - | 28.2 ± 7.0 |
| N | 0.5 + 30.0 | 5 | 1 | - | 2.6 ± 1.7 |
| | 1.0 + 30.0 | 5 | | - | 0 |
| | Ø | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.17 (<0.1 - 0.26) | | Isobolar Units | | | |
| ED ₉₀ (range) 0.3 (0.16 - 0.46) | | | | | |
| Resistance factor I ₉₀ 0.46 | | | | | |
| | 0.1 + 100.0 | 5 | | - | 4.3 ± 1.6 |
| | 0.3 + 100.0 | 5 | | - | 3.5 ± 0.6 |
| N | 0.5 + 100.0 | 5 | 1 | - | 0.3 ± 0.3 |
| | 1.0 + 100.0 | 5 | | - | 0 |
| | Ø | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.03 (0.02 - 0.05) | | Isobolar Units | | | |
| ED ₉₀ (range) 0.1 (0.05 - 0.19) | | | | | |
| Resistance factor I ₉₀ 0.16 | | | | | |

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 175

COMPOUND NAME TETRACYCLINE +

OR NUMBER FLOXALINE..... PARASITE (SUB)SPECIES P. berghei.....

FORMULATION Tween 80 / H₂O. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|--|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 3.0 + 0.1 | 5 | | - | 95.6 ± 3.1 |
| | 10.0 + 0.1 | 5 | | - | 88.4 ± 3.2 |
| N | 30.0 + 0.1 | 5 | 1 | - | 51.6 ± 10.4 |
| | 100.0 + 0.1 | 5 | | - | 4.3 ± 1.6 |
| | Ø | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 22.0(12.0 - 40.0) | | Isobolar Units | | | |
| ED ₉₀ (range) 80.0(44.0 - 140) | | | | | |
| Resistance factor I ₉₀ 1.2 | | | | | |
| | 3.0 + 0.3 | 5 | | - | 57.6 ± 10.0 |
| | 10.0 + 0.3 | 5 | | - | 60.2 ± 4.4 |
| N | 30.0 + 0.3 | 5 | 1 | - | 28.2 ± 7.0 |
| | 100.0 + 0.3 | 5 | | - | 3.5 ± 0.6 |
| | Ø | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 7.5(2.7 - 18.0) | | Isobolar Units | | | |
| ED ₉₀ (range) 39.0(14.0 - 95.0) | | | | | |
| Resistance factor I ₉₀ 0.58 | | | | | |

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 176

COMPOUND NAME TETRACYCLINE +

OR NUMBER FLUXALURINE..... PARASITE (SUB)SPECIES *P. berghei*.....

FORMULATION Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/TP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg DO-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|---|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 3.0 + 0.5 | 5 | | - | 15.6 ± 6.7 |
| | 10.0 + 0.5 | 5 | | - | 11.9 ± 1.9 |
| N | 30.0 + 0.5 | 5 | 1 | - | 2.6 ± 1.7 |
| | 100.0 + 0.5 | 5 | | - | 0.3 ± 0.3 |
| | ∅ | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.95 (0.3 - 2.0) | | Isobolar Units | | | |
| ED ₉₀ (range) 0.9 (2.2 - 14.0) | | | | | |
| Resistance factor I ₉₀ 0.1 | | | | | |
| | 3.0 + 1.0 | 5 | | - | 0 |
| | 10.0 + 1.0 | 5 | | - | 0 |
| N | 30.0 + 1.0 | 5 | 1 | - | 0 |
| | 100.0 + 1.0 | 5 | | - | 0 |
| | ∅ | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) < 3.0 | | Isobolar Units | | | |
| ED ₉₀ (range) < 3.0 | | | | | |
| Resistance factor I ₉₀ < 0.04 | | | | | |

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 177

COMPOUND NAME

OR NUMBER ..FLOXARINE..... PARASITE (SUB)SPECIES ..P. berghei.....

FORMULATION ..Tween 80/H₂O.. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) ≥1:0... MG/KG X 4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^x 100 |
|--|----------------------------|----------------|-----------------------|---------------------------------|---|
| | 0.1 | 5 | | - | 95.5 ± 5.7 |
| | 0.3 | 5 | | - | 90.0 ± 2.9 |
| N | 0.5 | 5 | 1 | - | 43.6 ± 14.3 |
| | 1.0 | 5 | | - | 0.3 ± 0.3 |
| | 0 | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.44(0.31 - 0.52) | | Isobolar Unit | | | |
| ED ₉₀ (range) 0.64(0.46 - 0.8) | | | | | |
| Resistance factor I ₉₀ 1.0 | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 178

COMPOUND NAME

OR NUMBER ERYTHROMYCIN..... PARASITE (SUB)SPECIES P. berghei.....

FORMULATION Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/HP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) > 600.0 MG/KG X 4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|--|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 30.0 | 5 | | - | 91.6 ± 1.5 |
| | 100.0 | 5 | | - | 70.4 ± 14.7 |
| N | 300.0 | 5 | 1 | - | 49.2 ± 9.6 |
| | 600.0 | 5 | | - | 14.8 ± 8.2 |
| | Ø | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 190(113 - 370) | | Isobolar Unit | | | |
| ED ₉₀ (range) 950(560 - 1850) | | | | | |
| Resistance factor I ₉₀ 1.0 | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 170

COMPOUND NAME FLOXALINE +

OR NUMBER ERYTHROMYCIN PARASITE (SUB)SPECIES P. berghei

FORMULATION Tween 80 / H₂O ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% x 100 |
|---|----------------------------|----------------|-----------------------|---------------------------------|----------------------------------|
| | 0.1 + 30.0 | 5 | | - | 82.4 ± 6.7 |
| | 0.3 + 30.0 | 5 | | - | 77.4 ± 7.9 |
| N | 0.5 + 30.0 | 5 | 1 | - | 22.1 ± 14.2 |
| | 1.0 + 30.0 | 5 | | - | 0 |
| | Ø | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.23(0.13 - 0.43) | | | | | |
| ED ₉₀ (range) 0.38(0.21 - 0.7) | | | | | |
| Resistance factor I ₉₀ 0.59 Isobolar Units | | | | | |
| | 0.1 + 100.0 | 5 | | - | 79.1 ± 6.3 |
| | 0.3 + 100.0 | 5 | | - | 69.2 ± 4.4 |
| N | 0.5 + 100.0 | 5 | 1 | - | 4.5 ± 1.6 |
| | 1.0 + 100.0 | 5 | | - | 0 |
| | Ø | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.22(0.13 - 0.32) | | | | | |
| ED ₉₀ (range) 0.36(0.21 - 0.53) | | | | | |
| Resistance factor I ₉₀ 0.56 Isobolar Units | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 180

COMPOUND NAME FLOXACRINE +

OR NUMBER .ERYTHROMYCIN..... PARASITE (SUB)SPECIES ...P. berghei.....

FORMULATION ..Tween 80./H₂O.. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{X100} |
|--|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.1 + 300.0 | 5 | | - | 48.8 ± 14.2 |
| | 0.3 + 300.0 | 5 | | - | 24.7 ± 9.1 |
| N | 0.5 + 300.0 | 5 | 1 | - | 2.0 ± 0.9 |
| | 1.0 + 300.0 | 5 | | - | 0 |
| | ∅ | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.12(0.08 - 0.23) | | Isobolar Units | | | |
| ED ₉₀ (range) 0.24(0.16 - 0.46) | | | | | |
| Resistance factor I ₉₀ 0.38 | | | | | |
| | 0.1 + 600.0 | 5 | | - | 18.4 ± 6.1 |
| | 0.3 + 600.0 | 5 | | - | 3.3 ± 2.2 |
| N | 0.5 + 600.0 | 5 | 1 | - | 1.3 ± 1.2 |
| | 1.0 + 600.0 | 5 | | - | 0 |
| | ∅ | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.06(0.04 - 0.12) | | Isobolar Units | | | |
| ED ₉₀ (range) 0.16(0.11 - 0.3) | | | | | |
| Resistance factor I ₉₀ 0.25 | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

- TABLE 181

COMPOUND NAME ERYTHROMYCIN +

OR NUMBER FLOXALURINE..... PARASITE (SUB)SPECIES *P. berghei*.....

FORMULATION ...Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/~~IP~~/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg DO-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|---|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 30.0 + 0.1 | 5 | | - | 82.4 ± 6.7 |
| | 100.0 + 0.1 | 5 | | - | 79.1 ± 6.3 |
| N | 300.0 + 0.1 | 5 | 1 | - | 48.8 ± 14.2 |
| | 600.0 + 0.1 | 5 | | - | 18.4 ± 6.1 |
| | ∅ | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 155(76.0 - 460) | | Isobolar Units | | | |
| ED ₉₀ (range) 930(450 - 2700) | | | | | |
| Resistance factor I ₉₀ 0.98 | | | | | |
| | 30.0 + 0.3 | 5 | | - | 77.4 ± 7.9 |
| | 100.0 + 0.3 | 5 | | - | 69.2 ± 4.4 |
| N | 300.0 + 0.3 | 5 | 1 | - | 24.7 ± 9.1 |
| | 600.0 + 0.3 | 5 | | - | 3.3 ± 2.2 |
| | ∅ | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 95.0(50.0 - 195) | | Isobolar Units | | | |
| ED ₉₀ (range) 400(205 - 800) | | | | | |
| Resistance factor I ₉₀ 0.42 | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

- TABLE 192

COMPOUND NAME ERYTHROMYCIN +

OR NUMBER FLOXACINE..... PARASITE (SUB)SPECIES *P. berghei*.....

FORMULATION Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg DO-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|---|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 30.0 + 0.5 | 5 | | - | 22.1 ± 14.2 |
| | 100.0 + 0.5 | 5 | | - | 4.5 ± 1.6 |
| N | 300.0 + 0.5 | 5 | 1 | - | 2.0 ± 0.9 |
| | 600.0 + 0.5 | 5 | | - | 1.3 ± 1.2 |
| | ∅ | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 7.5(3.5 - 19.0) | | Isobolar Units | | | |
| ED ₉₀ (range) 70.0(33.0 - 130) | | | | | |
| Resistance factor I ₉₀ 0.07 | | | | | |
| | 30.0 + 1.0 | 5 | | - | 0 |
| | 100.0 + 1.0 | 5 | | - | 0 |
| N | 300.0 + 1.0 | 5 | 1 | - | 0 |
| | 600.0 + 1.0 | 5 | | - | 0 |
| | ∅ | 10 | | 22.5 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) < 30 | | Isobolar Units | | | |
| ED ₉₀ (range) < 30 | | | | | |
| Resistance factor I ₉₀ <0.03 | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 183

COMPOUND NAME

OR NUMBER ... FLOXACRINE ... PARASITE (SUB)SPECIES ... *P. berghei* ...

FORMULATION ... Tween 80.1.H₂O ... ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) ... 1.0 ... MG/KG X 4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% × 100 |
|--|----------------------------|----------------|-----------------------|---------------------------------|----------------------------------|
| | 0.1 | 5 | | - | 80.4 ± 2.3 |
| | 0.3 | 5 | | - | 64.5 ± 5.1 |
| N | 0.5 | 5 | 1 | - | 28.3 ± 8.7 |
| | 1.0 | 5 | | - | 1.0 ± 0.5 |
| | Ø | 10 | | 35.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.25(0.16 - 0.42) | | | | | |
| ED ₉₀ (range) 0.6(0.36 - 0.97) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
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| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 181

COMPOUND NAME

OR NUMBER ...PRIMAQUINE..... PARASITE (SUB)SPECIES ...*P. berghei*.....

FORMULATION ...Tween 80/H₂O.. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) >.5:0. MG/KG X .4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|--|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.3 | 5 | | - | 87.5 ± 3.8 |
| | 1.0 | 5 | | - | 83.6 ± 2.5 |
| N | 3.0 | 5 | 1 | - | 53.0 ± 11.2 |
| | 5.0 | 5 | | - | 8.1 ± 4.2 |
| | Ø | 10 | | 35.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 1.6(0.8 - 4.3) | | | | | |
| ED ₉₀ (range) 6.0(3.0 - 16.0) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 185

COMPOUND NAME FLOXACRINE +

DR NUMBER PRIMAQUINE..... PARASITE (SUB)SPECIES *P. berghei*.....

FORMULATION Tween 80./H₂O... ROUTE OF ADMINISTRATION : SC/HP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% x 100 |
|--|----------------------------|----------------|-----------------------|---------------------------------|----------------------------------|
| | 0.1 + 0.3 | 5 | | - | 86.2 ± 1.8 |
| | 0.3 + 0.3 | 5 | | - | 74.9 ± 2.5 |
| N | 0.5 + 0.3 | 5 | 1 | - | 43.8 ± 6.0 |
| | 1.0 + 0.3 | 5 | | - | 0.01 ± 0.01 |
| | Ø | 10 | | 35.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.25(0.14 - 0.5) | | | | | |
| ED ₉₀ (range) 0.4(0.22 - 0.8) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.1 + 1.0 | 5 | | - | 81.7 ± 4.7 |
| | 0.3 + 1.0 | 5 | | - | 54.1 ± 5.4 |
| N | 0.5 + 1.0 | 5 | 1 | - | 20.6 ± 9.0 |
| | 1.0 + 1.0 | 5 | | - | 0.3 ± 0.1 |
| | Ø | 10 | | 35.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.2(0.15 - 0.36) | | | | | |
| ED ₉₀ (range) 0.45(0.31 - 0.75) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 185

COMPOUND NAME FLOXACRINE +

OR NUMBER PRIMAQUINE..... PARASITE (SUB)SPECIES *P. berghei*.....

FORMULATION *Tween 80/H₂O*. ROUTE OF ADMINISTRATION : SC/~~IP~~/~~PO~~/~~IV~~

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|--|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.1 + 3.0 | 5 | | - | 47.6 ± 10.1 |
| | 0.3 + 3.0 | 5 | | - | 8.8 ± 8.2 |
| N | 0.5 + 3.0 | 5 | 1 | - | 0 |
| | 1.0 + 3.0 | 5 | | - | 0 |
| | Ø | 10 | | 35.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.13(0.08 - 0.21) | | | | | |
| ED ₉₀ (range) 0.2(0.13 - 0.33) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.1 + 10.0 | 5 | | - | 10.8 ± 7.2 |
| | 0.3 + 10.0 | 5 | | - | 0.01 ± 0.01 |
| N | 0.5 + 10.0 | 5 | 1 | - | 0 |
| | 1.0 + 10.0 | 5 | | - | 0 |
| | Ø | 10 | | 35.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.06(0.04 - 0.07) | | | | | |
| ED ₉₀ (range) 0.1(0.07 - 0.12) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTICIDES)

TABLE 187

COMPOUND NAME PRIMAQUINE +

OR NUMBER FLOXACRINE PARASITE (SUB)SPECIES P. berghei

FORMULATION Tween 80/H₂O ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|--|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.3 + 0.1 | 5 | | - | 86.2 ± 1.8 |
| | 1.0 + 0.1 | 5 | | - | 81.7 ± 4.7 |
| N | 3.0 + 0.1 | 5 | 1 | - | 47.6 ± 10.1 |
| | 10.0 + 0.1 | 5 | | - | 10.8 ± 7.2 |
| | Ø | 10 | | 35.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 1.6 (0.9 - 3.1) | | | | | |
| ED ₉₀ (range) 7.2 (4.2 - 14.0) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.3 + 0.3 | 5 | | - | 74.9 ± 2.5 |
| | 1.0 + 0.3 | 5 | | - | 54.1 ± 5.4 |
| N | 3.0 + 0.3 | 5 | 1 | - | 8.8 ± 8.2 |
| | 10.0 + 0.3 | 5 | | - | 0.01 ± 0.0 |
| | Ø | 10 | | 35.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.65 (0.44 - 1.2) | | | | | |
| ED ₉₀ (range) 1.3 (1.2 - 3.3) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 183

COMPOUND NAME PRIMAQUINE +

OR NUMBER FLOXACRINE..... PARASITE (SUB)SPECIES P. berghei.....

FORMULATION Tween 80/H₂O. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|--|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.3 + 0.5 | 5 | | - | 43.8 ± 6.0 |
| | 1.0 + 0.5 | 5 | | - | 20.6 ± 9.0 |
| N | 3.0 + 0.5 | 5 | 1 | - | 0 |
| | 10.0 + 0.5 | 5 | | - | 0 |
| | Ø | 10 | | 35.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.4 (0.24 - 0.73) | | | | | |
| ED ₉₀ (range) 0.78 (0.47 - 1.4) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.3 + 1.0 | 5 | | - | 0.01 ± 0.01 |
| | 1.0 + 1.0 | 5 | | - | 0.3 ± 0.1 |
| N | 3.0 + 1.0 | 5 | 1 | - | 0 |
| | 10.0 + 1.0 | 5 | | - | 0 |
| | Ø | 10 | | 35.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) < 0.3 | | | | | |
| ED ₉₀ (range) < 0.3 | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 183

COMPOUND NAME

OR NUMBER ..FLOXACRINE..... PARASITE (SUB)SPECIES ..P. berghei.....

FORMULATION ..Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) >100... MG/KG X .4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% x 100 |
|--|----------------------------|----------------|-----------------------|---------------------------------|----------------------------------|
| | 0.1 | 5 | | - | 80.4 ± 2.3 |
| | 0.3 | 5 | | - | 64.5 ± 5.1 |
| N | 0.5 | 5 | 1 | - | 28.3 ± 8.7 |
| | 1.0 | 5 | | - | 1.0 ± 0.5 |
| | ∅ | 10 | | 35.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.25(0.16 - 0.42) | | | | | |
| ED ₉₀ (range) 0.6(0.36 - 0.97) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

- TABLE 190

COMPOUND NAME

OR NUMBER ... CHLOROQUINE ... PARASITE (SUB)SPECIES ... *P. berghei* ...

FORMULATION ... Tween 80/H₂O ... ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) ... 10.0 MG/KG X 4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% x 100 |
|--|----------------------------|----------------|-----------------------|---------------------------------|----------------------------------|
| | 0.3 | 5 | | - | 68.7 ± 4.8 |
| | 1.0 | 5 | | - | 66.6 ± 6.3 |
| N | 3.0 | 5 | 1 | - | 23.5 ± 2.7 |
| | 10.0 | 5 | | - | 0.01 ± 0.01 |
| | Ø | 10 | | 35.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 1.4 (1.1 - 2.2) | | | | | |
| ED ₉₀ (range) 2.7 (2.1 - 4.1) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) | | | | | |
| ED ₉₀ (range) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 191

COMPOUND NAME FLOXACRINE +

OR NUMBER CHLOROQUINE..... PARASITE (SUB)SPECIES *P. berghei*.....

FORMULATION Tween 80, H₂O. ROUTE OF ADMINISTRATION : SC/IP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|---|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.1 + 0.3 | 5 | | - | 78.6 ± 8.3 |
| | 0.3 + 0.3 | 5 | | - | 45.7 ± 4.2 |
| N | 0.5 + 0.3 | 5 | 1 | - | 20.6 ± 8.0 |
| | 1.0 + 0.3 | 5 | | - | 4.3 ± 3.5 |
| | Ø | 10 | | 35.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.22 (0.12 - 0.3) | | | | | |
| ED ₉₀ (range) 0.7 (0.4 - 0.95) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.1 + 1.0 | 5 | | - | 75.5 ± 2.2 |
| | 0.3 + 1.0 | 5 | | - | 50.9 ± 4.5 |
| N | 0.5 + 1.0 | 5 | 1 | - | 11.2 ± 4.3 |
| | 1.0 + 1.0 | 5 | | - | 1.1 ± 0.9 |
| | Ø | 10 | | 35.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.22 (0.14 - 0.33) | | | | | |
| ED ₉₀ (range) 0.49 (0.31 - 0.74) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 192

COMPOUND NAME FLOXACRINE +

OR NUMBER .CHLOROQUINE..... PARASITE (SUB)SPECIES *P. berghei*.....

FORMULATION ..Tween 80./H₂O.. ROUTE OF ADMINISTRATION : SC/~~IP~~/~~PO~~/~~IV~~

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|--|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.1 + 3.0 | 5 | | - | 35.7 ± 4.1 |
| | 0.3 + 3.0 | 5 | | - | 26.0 ± 2.4 |
| N | 0.5 + 3.0 | 5 | 1 | - | 1.2 ± 0.6 |
| | 1.0 + 3.0 | 5 | | - | 0.4 ± 0.2 |
| | Ø | 10 | | 35.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.08(0.04-0.17) | | | | | |
| ED ₉₀ (range) 0.26(0.15-0.56) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.1 + 10.0 | 5 | | - | 0.06 ± 0.05 |
| | 0.3 + 10.0 | 5 | | - | 0 |
| N | 0.5 + 10.0 | 5 | 1 | - | 0 |
| | 1.0 + 10.0 | 5 | | - | 0 |
| | Ø | 10 | | 35.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) < 0.1 | | | | | |
| ED ₉₀ (range) < 0.1 | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

TABLE 193

COMPOUND NAME CHLOROQUINE +

OR NUMBER FLOXACRINE..... PARASITE (SUB)SPECIES ...P. berghei.....

FORMULATION ...Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/TP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|--|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.3 + 0.1 | 5 | | - | 78.6 ± 8.3 |
| | 1.0 + 0.1 | 5 | | - | 75.5 ± 2.2 |
| N | 3.0 + 0.1 | 5 | 1 | - | 35.7 ± 4.1 |
| | 10.0 + 0.1 | 5 | | - | 0.06 ± 0.05 |
| | Ø | 10 | | 35.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 1.8 (1.2 - 2.6) | | | | | |
| ED ₉₀ (range) 3.6 (2.5 - 5.2) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.3 + 0.3 | 5 | | - | 45.7 ± 4.2 |
| | 1.0 + 0.3 | 5 | | - | 50.9 ± 4.5 |
| N | 3.0 + 0.3 | 5 | 1 | - | 26.0 ± 2.4 |
| | 10.0 + 0.3 | 5 | | - | 0 |
| | Ø | 10 | | 35.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 1.3 (0.9 - 2.2) | | | | | |
| ED ₉₀ (range) 2.6 (1.8 - 4.3) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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SUMMARY OF ANTIMALARIAL DRUG TESTS
(BLOOD SCHIZONTOCIDES)

-TABLE 191

COMPOUND NAME CHLOROQUINE +

OR NUMBER .FLOXARINE..... PARASITE (SUB)SPECIES *P. berghei*.....

FORMULATION ...Tween 80/H₂O.. ROUTE OF ADMINISTRATION : SC/HP/PO/IV

MAXIMUM TOLERATED DOSE (MTD) MG/KG X ...

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% ^{x100} |
|---|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.3 + 0.5 | 5 | | - | 20.6 ± 8.0 |
| | 1.0 + 0.5 | 5 | | - | 11.2 ± 4.3 |
| N | 3.0 + 0.5 | 5 | 1 | - | 1.2 ± 0.6 |
| | 10.0 + 0.5 | 5 | | - | 0 |
| | Ø | 10 | | 35.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.17 (0.03 - 0.33) | | | | | |
| ED ₉₀ (range) 0.7 (0.33 - 1.3) | | | | | |
| Resistance factor I ₉₀ | | | | | |
| | 0.3 + 1.0 | 5 | | - | 43 ± 3.5 |
| | 1.0 + 1.0 | 5 | | - | 1.1 ± 0.9 |
| N | 3.0 + 1.0 | 5 | 1 | - | 0.4 ± 0.2 |
| | 10.0 + 1.0 | 5 | | - | 0 |
| | Ø | 10 | | 35.7 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.03 (0.01 - 0.06) | | | | | |
| ED ₉₀ (range) 0.2 (0.05 - 0.4) | | | | | |
| Resistance factor I ₉₀ | | | | | |

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5.6 DRUG INTERACTION ISOBOLOGRAMS

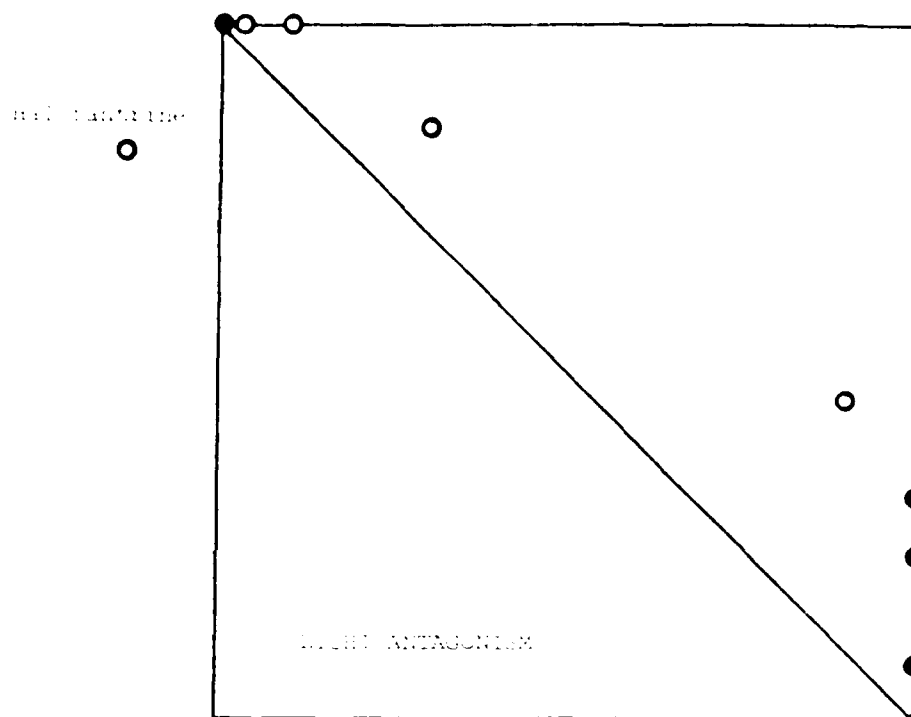


Figure 1

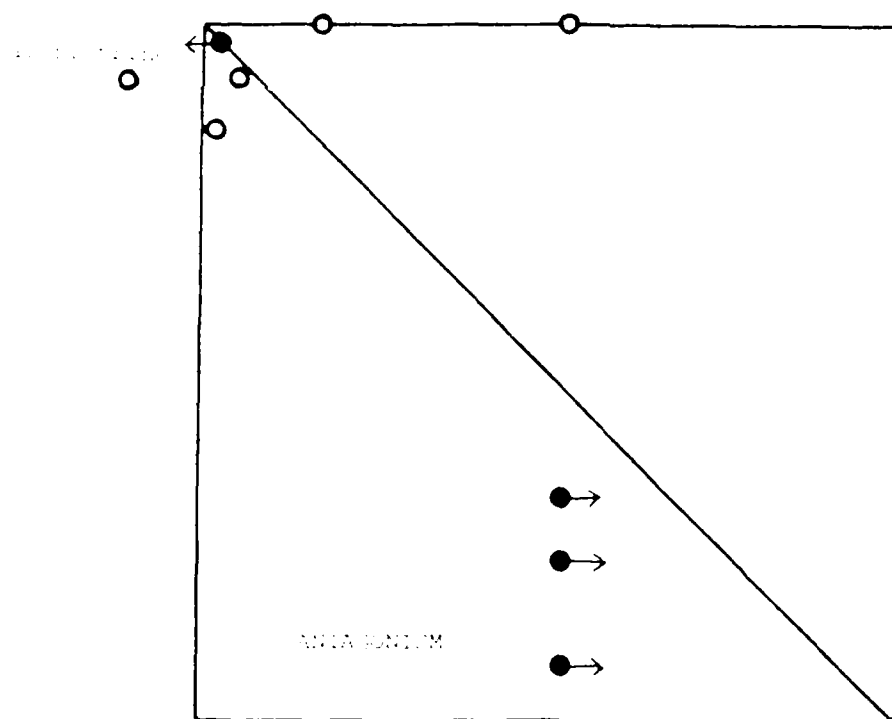


Figure 2

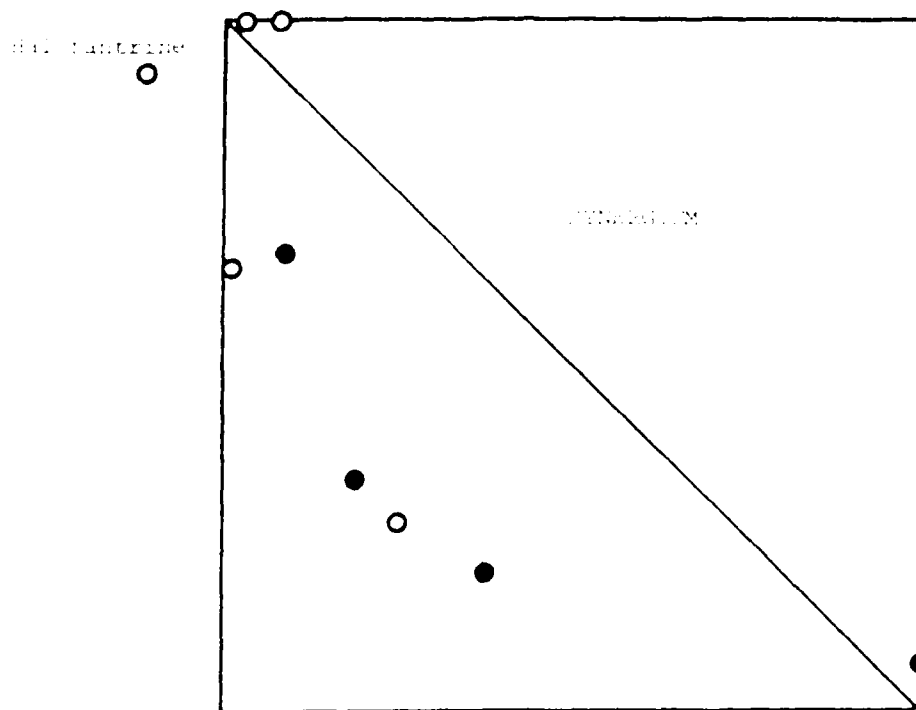


Figure 3

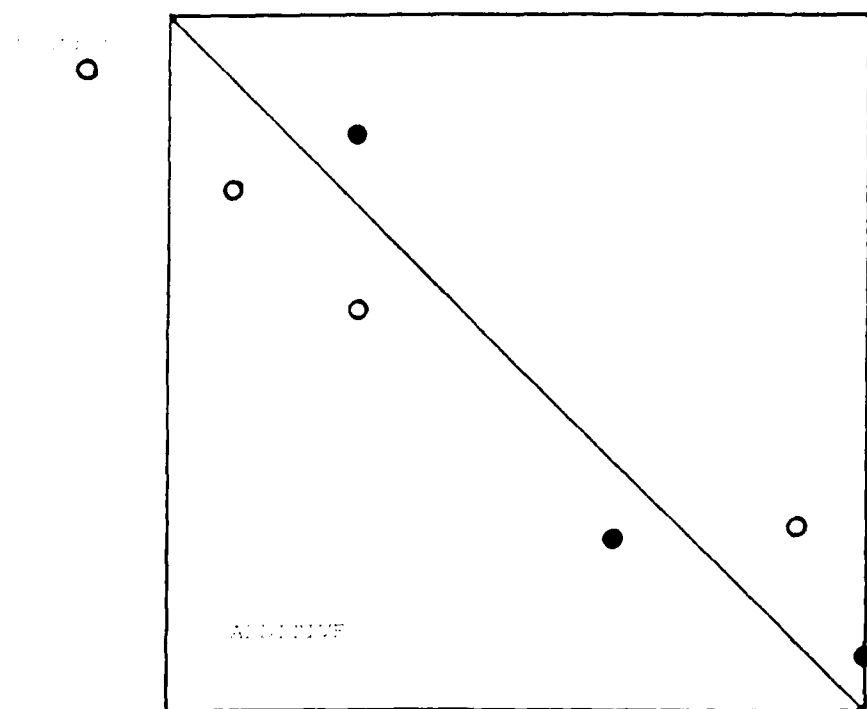


Figure 4

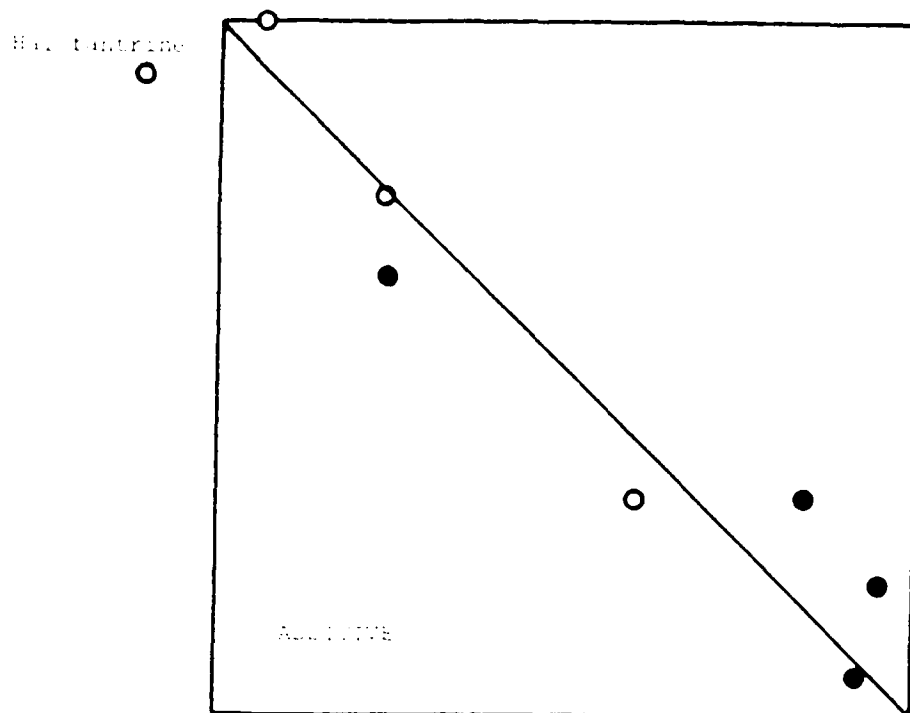


Figure 5

Stimulating

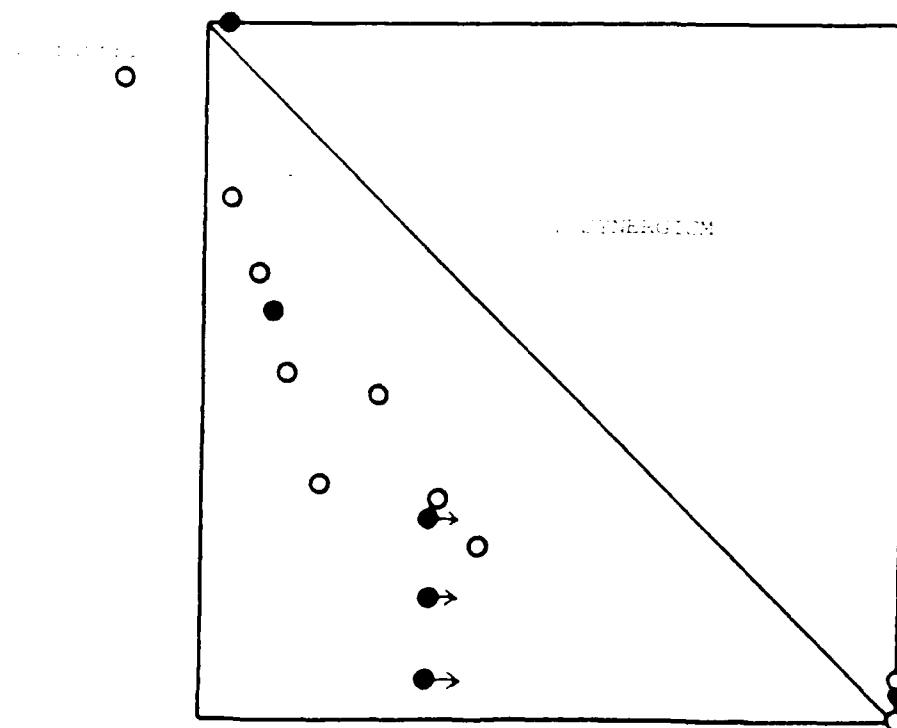


Figure 6

Stimulating

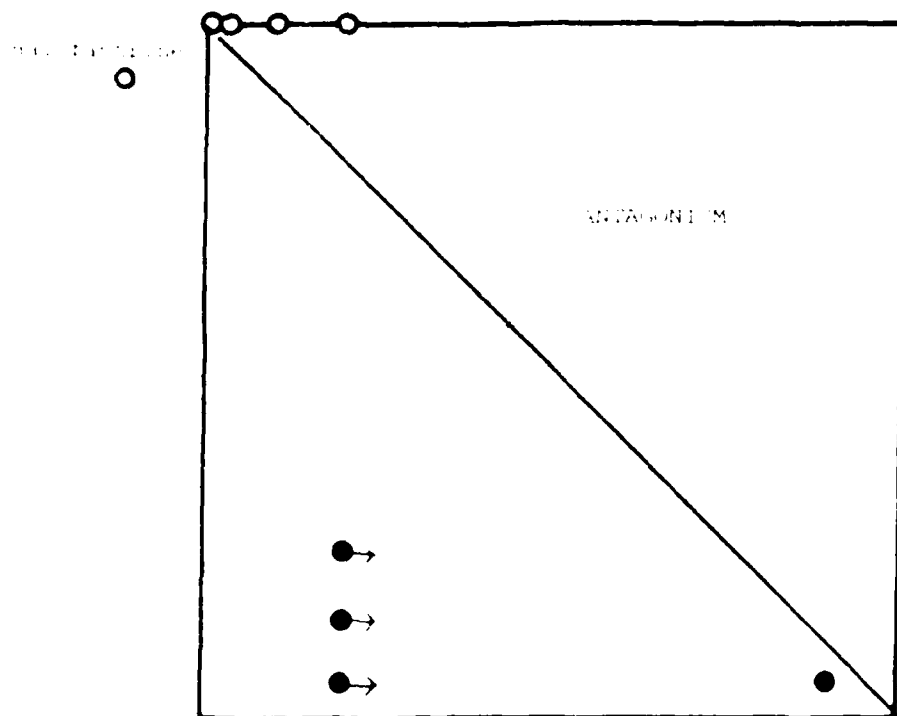


Figure 7

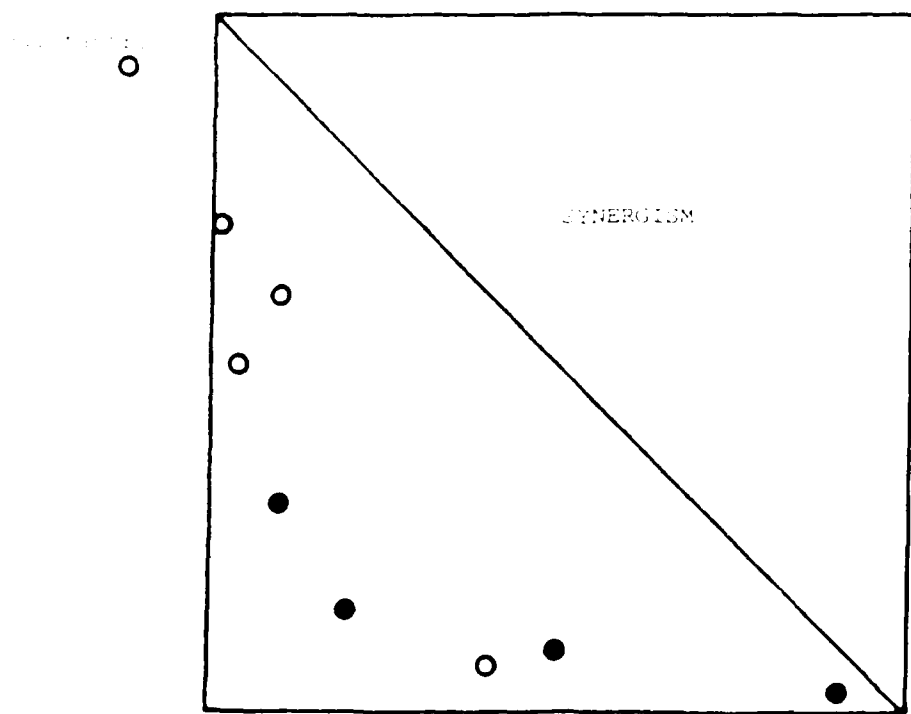


Figure 8

Figure 9

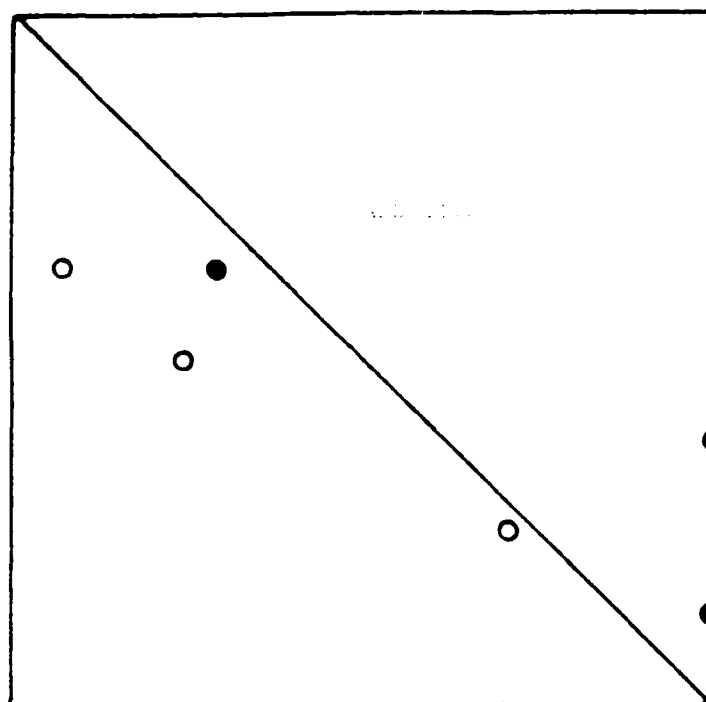


Figure 9

Figure 10

Figure 10

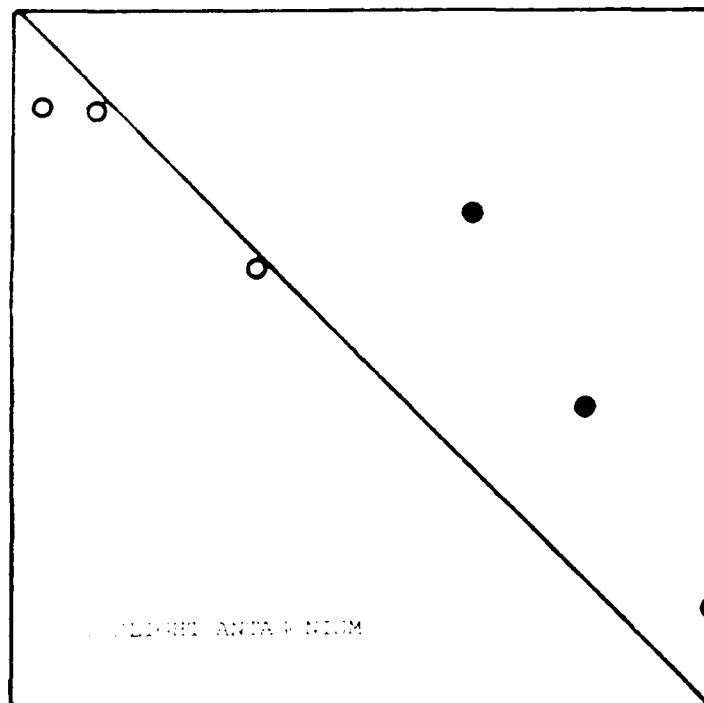


Figure 10

Figure 10

Figure 11

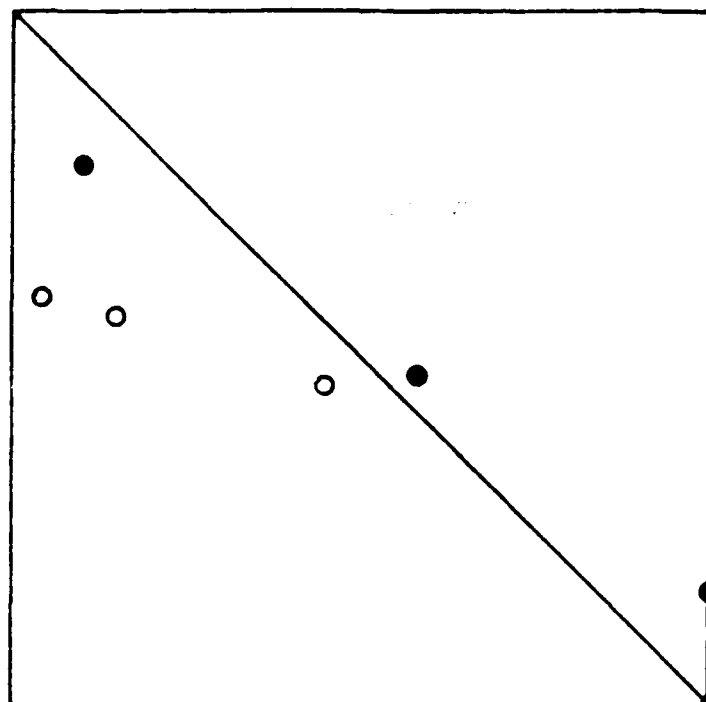


Figure 11

Figure 12

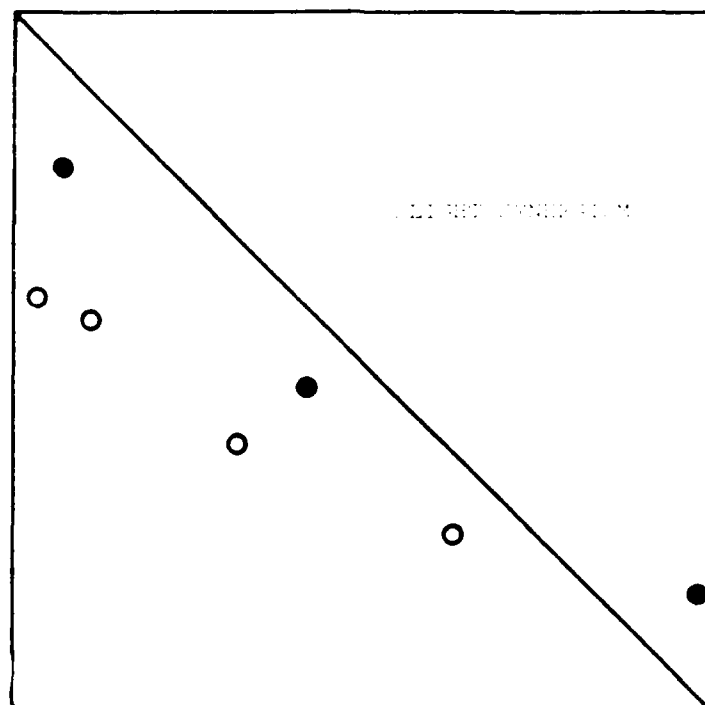


Figure 12

Figure 12

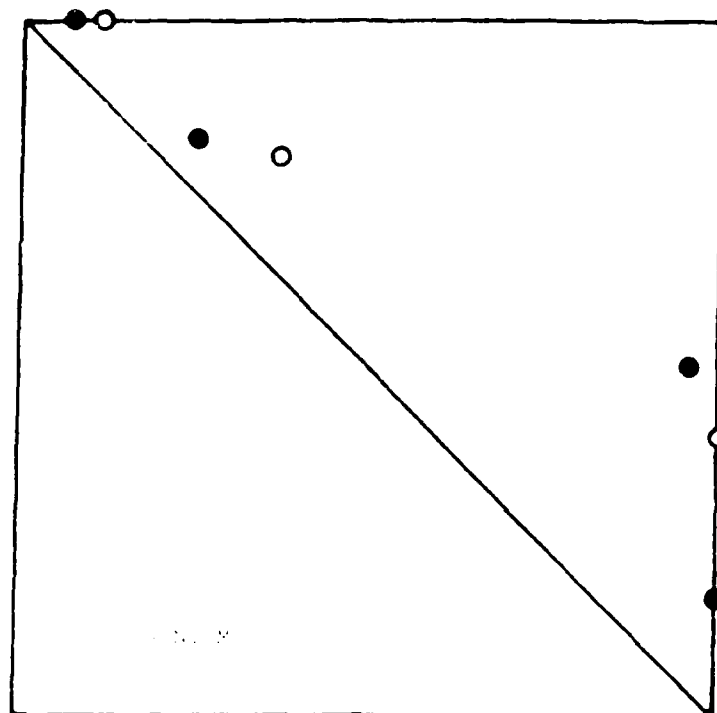


Figure 1b

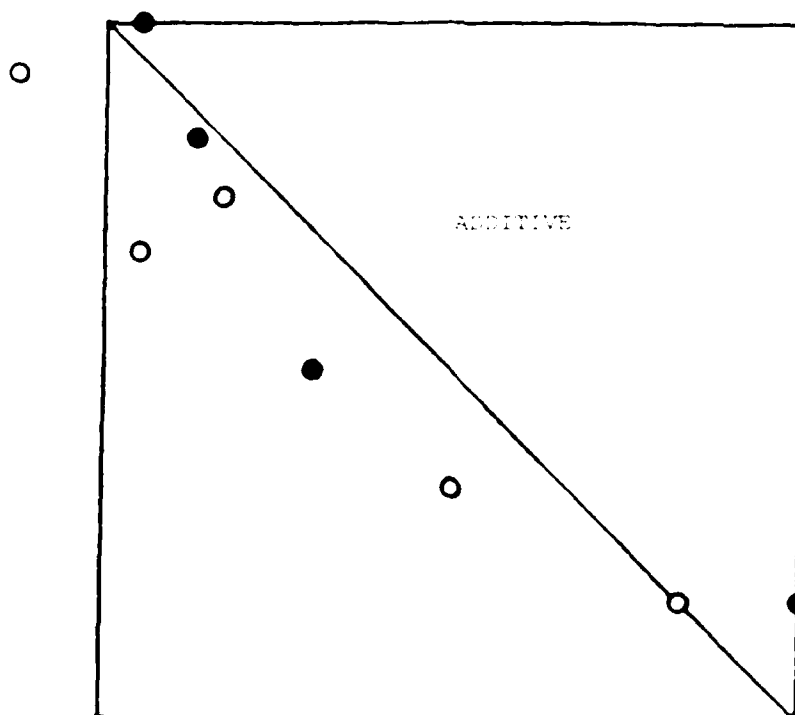
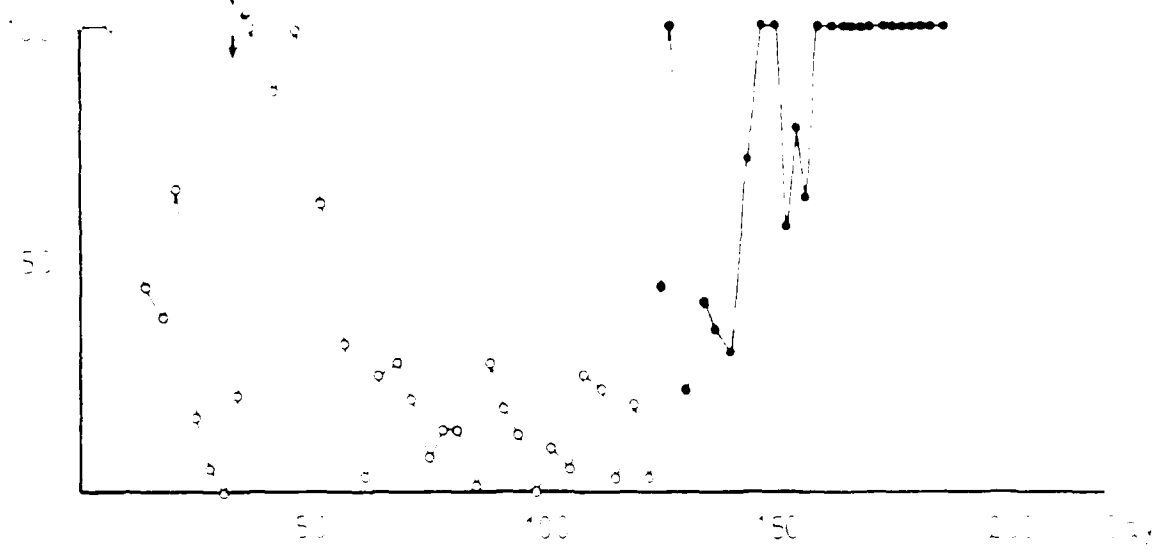


Figure 1c

5.7 ACQUISITION OF RESISTANCE GRAPHS

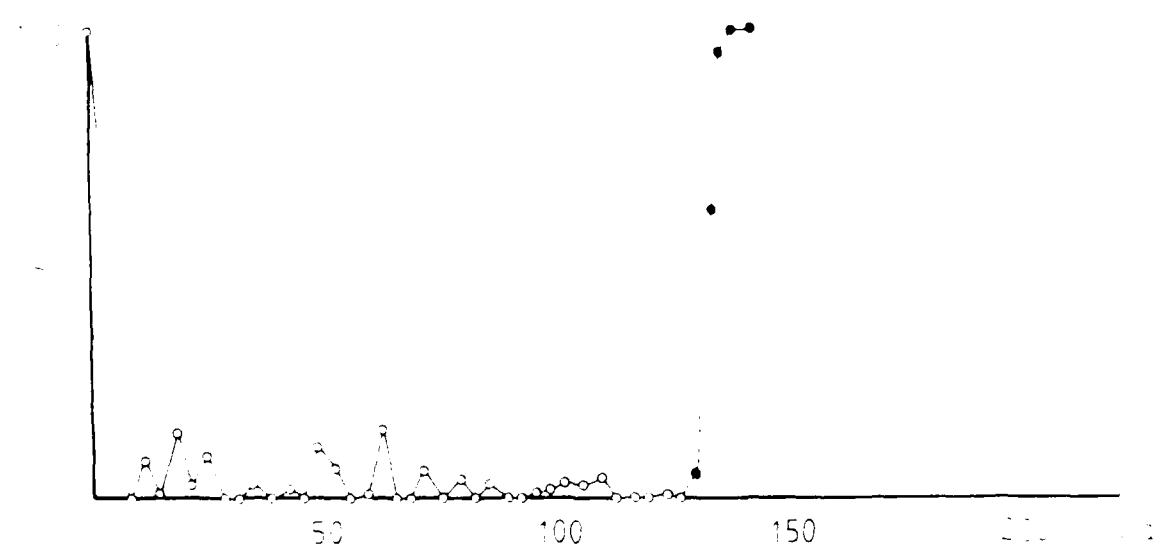
% Passage
Delay

NS-4₁
Halothane 8m₂ 100%



% Passage
Delay

NS-4₁
Halothane 30m₂ 100%

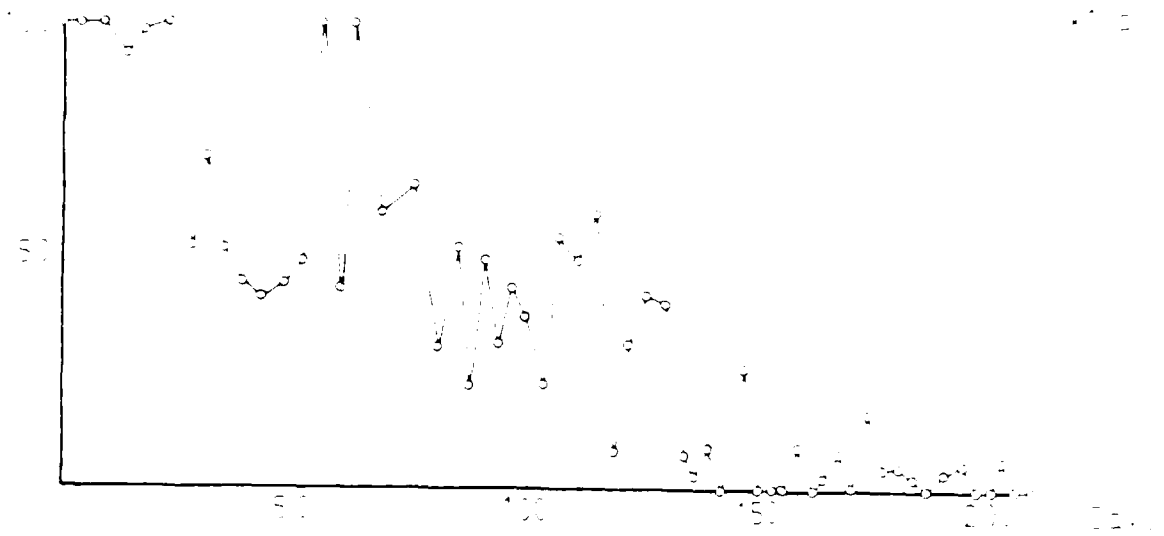


Passage 1

Dea.

1923

June 10, 1923



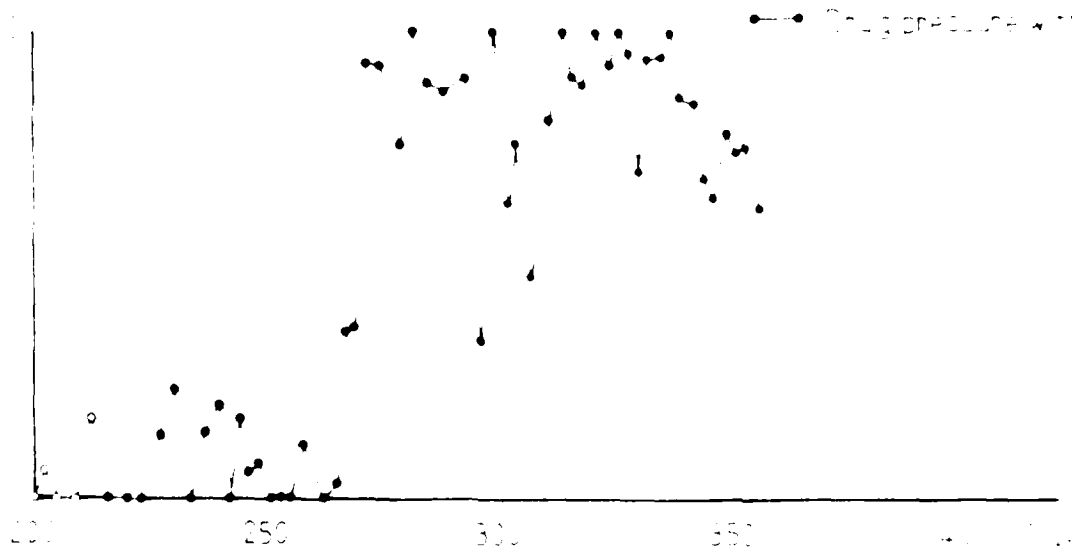
Passage 1

Dea.

1923

Under drug pressure

Drug pressure with work



5. - FIVE DAY TEST DATA NEW RESISTANT LINES

SUMMARY OF ANTIMALARIAL DRUG TESTS

Table 198

SINGLE THERAPEUTIC DOSE

COMPOUND NAME

DR NUMBER

HALOFANTRINE

PARASITE (SUB)SPECIES

P. berghei

FORMULATION

Tween 80 / H₂O

ROUTE OF ADMINISTRATION :

SC/IP/PQ/IV

MAXIMUM TOLERATED DOSE (MTD)

>30 MG/KG X 4

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR ₂₋₁₀
Control PR ₂₋₁₀ |
|--|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 0.1 | 5 | | - | 94.8 ± 5.2 |
| | 0.3 | 5 | | - | 91.4 ± 2.0 |
| N | 1.0 | 5 | 1 | - | 51.6 ± 14.1 |
| | 3.0 | 5 | | - | 0.1 ± 0.1 |
| | Ø | 10 | | 20.9 | |
| ED ₅₀ (range) 0.5 (0.1 - 1.3) | | | | | |
| ED ₉₀ (range) 1.3 (0.4 - 3.5) | | | | | |
| Resistance factor I ₉₀ 1.0 | | | | | |
| | 0.3 | 5 | | - | 84.3 ± 3.9 |
| | 1.0 | 5 | | - | 74.2 ± 9.6 |
| N/HAL | 3.0 | 5 | 1 | - | 44.4 ± 13.1 |
| Pass.31 | 10.0 | 5 | | - | 0.1 ± 0.1 |
| | 30.0 | 5 | | - | 0.02 ± 0.01 |
| | Ø | 10 | | 23.9 | |
| ED ₅₀ (range) 1.1 (0.4 - 2.8) | | | | | |
| ED ₉₀ (range) 3.6 (1.1 - 9.0) | | | | | |
| Resistance factor I ₉₀ 2.8 | | | | | |

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS

-TABLE 197

BUTHE (CHIT) MEDICINE

COMPOUND NAME

DR NUMBER CHLOROQUINE PARASITE (SUB)SPECIES ... *P. berghei* FORMULATION ... Tween 80/H₂O ... ROUTE OF ADMINISTRATION : SC/1P/P0/17MAXIMUM TOLERATED DOSE (MTD) ≥ 100 .. MG/KG X 4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% $\times 100$ |
|--|----------------------------|----------------|-----------------------|---------------------------------|---|
| | 0.1 | 5 | | - | 82.8 $\pm$ 4.1 |
| | 0.3 | 5 | | - | 80.1 $\pm$ 5.7 |
| N | 1.0 | 5 | 1 | - | 52.1 $\pm$ 7.6 |
| | 3.0 | 5 | | - | 24.3 $\pm$ 8.5 |
| | $\emptyset$ | 10 | | 20.9 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 0.8(0.2 - 2.1) | | | | | |
| ED ₉₀ (range) 3.1(0.9 - 8.5) | | | | | |
| Resistance factor I ₉₀ 1.0 | | | | | |
| | 1.0 | 5 | | - | 91.4 $\pm$ 3.9 |
| | 3.0 | 5 | | - | 53.6 $\pm$ 8.9 |
| N/HAL | 10.0 | 5 | 1 | - | 0.8 $\pm$ 0.3 |
| Pass. 31 | 30.0 | 5 | | - | 0.08 $\pm$ 0.08 |
| | $\emptyset$ | 10 | | 23.9 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 2.7(1.4 - 3.9) | | | | | |
| ED ₉₀ (range) 7.0(3.6 - 10.3) | | | | | |
| Resistance factor I ₉₀ 2.3 | | | | | |

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TEST

- LAB : 198

BLOOD FILM AT 72 H

COMPOUND NAME

DR NUMBER ... PRIMAQUINE ... PARASITE (SUB)SPECIES *P. berghei* ...FORMULATION Tween 80/H₂O... ROUTE OF ADMINISTRATION : SC/1P-25-14

MAXIMUM TOLERATED DOSE (MTD) > 60.0 MG/KG X 4

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% (100) |
|--|----------------------------|----------------|-----------------------|---------------------------------|----------------------------------|
| | 0.1 | 5 | | - | 92.5 ± 3.6 |
| | 0.3 | 5 | | - | 93.1 ± 2.4 |
| N | 1.0 | 5 | 1 | - | 63.0 ± 5.1 |
| | 3.0 | 5 | | - | 34.4 ± 4.0 |
| | 10.0 | 5 | | - | 0 |
| | Ø | 10 | | 20.9 | |
| ED ₅₀ (range) 1.5 (1.1 - 2.2) | | | | | |
| ED ₉₀ (range) 5.8 (4.1 - 8.4) | | | | | |
| Resistance factor I ₉₀ 1.0 | | | | | |
| | 1.0 | 5 | | - | 77.6 ± 4.8 |
| | 3.0 | 5 | | - | 68.1 ± 8.0 |
| N/HAL | 10.0 | 5 | 1 | - | 14.7 ± 7.8 |
| Pass 31 | 30.0 | 5 | | - | 0.3 ± 0.07 |
| | 60.0 | 5 | | - | 0.03 ± 0.01 |
| | Ø | 10 | | 23.9 | |
| ED ₅₀ (range) 2.9 (1.6 - 6.0) | | | | | |
| ED ₉₀ (range) 10.5 (5.6 - 23.0) | | | | | |
| Resistance factor I ₉₀ 1.8 | | | | | |

Principal Investigator: Professor W. Peters
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IN VIVO SCHIZONTICIDES

COMPOUND NAME

DR NUMBER

MEFLOQUINE

PARASITE (SUB)SPECIES

*P. berghei*FORMULATION *Tween 80/H₂O* ROUTE OF ADMINISTRATION : SC ~~AD~~ ~~PO~~ ~~IV~~MAXIMUM TOLERATED DOSE (MTD) *>.60*... MG/KG X *4*.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% x 100 |
|--------|----------------------------|----------------|-----------------------|---------------------------------|----------------------------------|
| | 0.3 | 5 | | - | 100 ± 7.1 |
| | 1.0 | 5 | | - | 85.9 ± 2.3 |
| N | 3.0 | 5 | 1 | - | 17.4 ± 5.2 |
| | 10.0 | 5 | | - | 0 |
| | Ø | 10 | | 20.9 | |
| | | | | | |
| | | | | | |

ED₅₀(range) 1.6 (0.5 - 2.2)ED₉₀(range) 2.8 (0.9 - 3.7)Resistance factor I₉₀ 1.0

| | | | | | |
|----------|------|----|---|------|------------|
| | 1.0 | 5 | | - | 87.5 ± 3.8 |
| | 3.0 | 5 | | - | 73.8 ± 6.3 |
| N/HAL | 10.0 | 5 | 1 | - | 25.8 ± 4.8 |
| Pass. 31 | 30.0 | 5 | | - | 0.1 ± 0.08 |
| | 60.0 | 10 | | - | 0 |
| | Ø | 10 | | 23.9 | |
| | | | | | |

ED₅₀(range) 3.4 (2.2 - 6.5)ED₉₀(range) 9.0 (5.8 - 18.0)Resistance factor I₉₀ 3.2

Principal Investigator: Professor W. Peters
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 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS

TABLE 200

BLIND SCHIFF METHOD

COMPOUND NAME

OR NUMBER ... QUININE ... PARASITE (SUB)SPECIES ... *P. berghei* ...FORMULATION ... Tween 80/H₂O ... ROUTE OF ADMINISTRATION : SC-IT-PO-IT

MAXIMUM TOLERATED DOSE (MTD) > 600.0 MG/KG X 4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated F ₁ %
Control F ₁ % |
|--|----------------------------|----------------|-----------------------|---------------------------------|--|
| | 10.0 | 5 | | - | 98.2 ± 2.7 |
| | 30.0 | 5 | | - | 61.3 ± 7.3 |
| N | 100.0 | 5 | 1 | - | 36.1 ± 7.8 |
| | 300.0 | 5 | | - | 0 |
| | Ø | 10 | | 25.3 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 45.0(23.0-90.0) | | | | | |
| ED ₉₀ (range) 85.0(43.0-175) | | | | | |
| Resistance factor I ₉₀ 1.0 | | | | | |
| | 30.0 | 5 | | - | 86.1 ± 3.5 |
| | 100.0 | 5 | | - | 48.9 ± 7.5 |
| N/HAL | 300.0 | 5 | 1 | - | 13.3 ± 9.3 |
| Pass. 31 | 600.0 | 5 | | - | 0.02 ± 0.01 |
| | Ø | 10 | | 23.9 | |
| | | | | | |
| | | | | | |
| ED ₅₀ (range) 90.0(55.0-180) | | | | | |
| ED ₉₀ (range) 210(125-420) | | | | | |
| Resistance factor I ₉₀ 2.5 | | | | | |

Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

SUMMARY OF ANTIMALARIAL DRUG TESTS

- TAB. 201

B.L. 11. 1917. 11. 11. 11. 11.

COMPOUND NAME

OR NUMBER ... HALOFANTRINE ... PARASITE (SUB)SPECIES *P. yoelii* ...FORMULATION *Tween 80* / H_2O ROUTE OF ADMINISTRATION : SC/1P, 80, 11MAXIMUM TOLERATED DOSE (MTD) 2.100 MG/KG X $.4$.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PR%
Control PR% |
|--|----------------------------|----------------|-----------------------|---------------------------------|----------------------------|
| | 0.1 | 5 | | - | 86.1 ± 2.6 |
| | 0.3 | 5 | | - | 67.6 ± 6.1 |
| NS | 1.0 | 5 | 1 | - | 36.5 ± 10.5 |
| | 3.0 | 5 | | - | 1.6 ± 0.6 |
| | 10.0 | 5 | | - | 0.02 ± 0.01 |
| | 30.0 | 5 | | - | 0 |
| | $\emptyset$ | 10 | | 24.4 | |
| ED ₅₀ (range) 0.4 (0.3 - 1.0) | | | | | |
| ED ₉₀ (range) 1.6 (0.9 - 3.5) | | | | | |
| Resistance factor I ₉₀ 1.0 | | | | | |
| | 3.0 | 5 | | - | 98.8 ± 3.0 |
| | 10.0 | 5 | | - | 90.0 ± 4.1 |
| NS/HAL | 30.0 | 5 | 1 | - | 87.3 ± 2.4 |
| Pass.35 | 100.0 | 5 | | - | 46.4 ± 9.8 |
| | $\emptyset$ | 10 | | 10.2 | |
| ED ₅₀ (range) 85.0 (48.0 - 118) | | | | | |
| ED ₉₀ (range) 560 (320 - 780) | | | | | |
| Resistance factor I ₉₀ 350 | | | | | |

Principal Investigator: Professor W. Peters
 Department of Medical Protozoology
 London School of Hygiene & Tropical Medicine

COMPOUND NAME

DR NUMBER ... CHLOROQUINE ... PARASITE (SUB)SPECIES ... *P. yoelii* ...FORMULATION ... Tween 80 / H₂O ... ROUTE OF ADMINISTRATION : SC ~~IP~~ IV

MAXIMUM TOLERATED DOSE (MTD) > 100. MG/KG X 4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated vs.
control % |
|--|----------------------------|----------------|-----------------------|---------------------------------|--------------------------|
| | 1.0 | 5 | | - | 81.1 ± 9.6 |
| | 3.0 | 5 | | - | 54.9 ± 6.7 |
| NS | 10.0 | 5 | 1 | - | 24.9 ± 5.7 |
| | 30.0 | 5 | | - | 18.0 ± 6.5 |
| | 60.0 | 5 | | - | 9.4 ± 1.3 |
| | Ø | 10 | | 24.4 | |
| ED ₅₀ (range) 4.7(2.2-120) | | | | | |
| ED ₉₀ (range) 42.0(19.0-108) | | | | | |
| Resistance factor I ₉₀ 1.0 | | | | | |
| | 10.0 | 5 | | - | 100 |
| | 30.0 | 5 | | - | 100 ± 4.5 |
| NS/HAL | 60.0 | 5 | 1 | - | 86.1 ± 7.7 |
| Pass 35 | 100.0 | 5 | | - | 85.1 ± 2.4 |
| | Ø | 10 | | 10.2 | |
| ED ₅₀ (range) > 100 | | | | | |
| ED ₉₀ (range) >> 100 | | | | | |
| Resistance factor I ₉₀ >> 2.4 | | | | | |

Principal Investigator: Professor W. Peters
 Department of Medical Parasitology
 London School of Hygiene & Tropical Medicine

Date: 1961.11.10

MEDICAL NAME

DRUG NAME: PRIMAQUINE PARASITE (SUB SPECIES): *Pyopelli*FORMULATION: Tween 80/H₂O ROUTE OF ADMINISTRATION: SC ~~1-15-17~~

MAXIMUM TOLERATED DOSE (MTD): >60.0 MG/KG X 4.

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PPR
Control PPR |
|--|----------------------------|----------------|-----------------------|---------------------------------|----------------------------|
| | 1.0 | 5 | | - | 91.0 ± 5.1 |
| | 3.0 | 5 | | - | 78.0 ± 10.3 |
| NS | 10.0 | 5 | 1 | - | 7.0 ± 2.5 |
| | 30.0 | 5 | | - | 0 |
| | Ø | 10 | | 29.2 | |
| ED ₅₀ (range) 3.4 (2.0-6.0) | | | | | |
| ED ₂₀ (range) 7.0 (4.1-12.6) | | | | | |
| Resistance factor I ₉₀ 1.0 | | | | | |
| | 3.0 | 5 | | - | 92.2 ± 8.3 |
| | 10.0 | 5 | | - | 79.3 ± 7.0 |
| NS/HAL | 30.0 | 5 | 1 | - | 0.2 ± 0.2 |
| Pass 35 | 60.0 | 5 | | - | 0.04 ± 0.02 |
| | Ø | 10 | | 10.2 | |
| ED ₅₀ (range) 7.0 (2.7-19.8) | | | | | |
| ED ₂₀ (range) 16.0 (6.0-44.0) | | | | | |
| Resistance factor I ₉₀ 2.3 | | | | | |

Principal Investigator: Professor W. Peters
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SAMPLE NAME

DR. NUMBER: MEFLOQUINE

FORMULATION: Tween 80/H₂O ROUTE OF ADMINISTRATION: ~~PO~~ ~~IV~~

MAXIMUM TOLERATED DOSE MTD: >600.0 MG/KG X 4

| Strain | Daily dose mg/kg D0-D+3 | No. of mice | No. of experiments | Mean control parasite rate % | Control % |
|--|-------------------------|-------------|--------------------|------------------------------|-------------|
| | 3.0 | 5 | | - | 70.8 ± 5.0 |
| | 10.0 | 5 | | - | 14.1 ± 9.5 |
| NS | 30.0 | 5 | 1 | - | 0.07 ± 0.07 |
| | 100.0 | 5 | | - | 0 |
| | Ø | 10 | | 29.2 | |
| ED ₅₀ (range) 4.4 (3.4-6.0) | | | | | |
| ED ₉₀ (range) 10.0 (7.8-14.0) | | | | | |
| Resistance factor I ₉₀ 1.0 | | | | | |
| | 3.0 | 5 | | - | 92.8 ± 9.8 |
| | 10.0 | 5 | | - | 100.0 ± 3.0 |
| NS/HAL | 30.0 | 5 | 1 | - | 100.0 ± 3.0 |
| Pass 35 | 60.0 | 5 | | - | 94.3 ± 3.2 |
| | Ø | 10 | | 10.2 | |
| ED ₅₀ (range) >> 60 | | | | | |
| ED ₉₀ (range) >> 60 | | | | | |
| Resistance factor I ₉₀ >> 10 | | | | | |

Principal Investigator: Professor W. Feter
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QUININE AND METIDIN

MEDICAL NAME

DRUG NAME: QUININE PARASITE (SUB)SPECIES: *P. berghei*FORMULATION: Tween 80/H₂O ROUTE OF ADMINISTRATION: ~~SC~~ IP $\pm$

MAXIMUM TOLERATED DOSE (MTD) >600 MG/KG X 4.

| Strain | Daily dose
mg/kg DO-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Mean %
Control (SE) |
|--------|----------------------------|----------------|-----------------------|---------------------------------|------------------------|
| | 3.0 | 5 | | - | 100 $\pm$ 0.1 |
| | 10.0 | 5 | | - | 77.8 $\pm$ 11.9 |
| NS | 30.0 | 5 | 1 | - | 67.3 $\pm$ 13.0 |
| | 100.0 | 5 | | - | 52.6 $\pm$ 3.8 |
| | 300.0 | 5 | | - | 9.1 $\pm$ 4.6 |
| | 600.0 | 5 | | - | 0.2 $\pm$ 0.2 |
| | $\emptyset$ | 10 | | 19.6 | |

ED₅₀ (range) 46.0 (11.0-95.0)ED₃₀ (range) 190.0 (45.0-390.0)Resistance factor I₉₀ 1.0

| | | | | | |
|---------|-------------|----|--|------|----------------|
| | 100.0 | 5 | | - | 100 $\pm$ 2.3 |
| | 300.0 | 5 | | - | 98.8 $\pm$ 1.3 |
| NS/HA | 600.0 | 5 | | - | 91.7 $\pm$ 5.5 |
| Pass 35 | $\emptyset$ | 10 | | 10.2 | |
| | | | | | |
| | | | | | |
| | | | | | |

ED₅₀ (range) >600ED₃₀ (range) >>600Resistance factor I₃₀ >>3.2

Principal Investigator: Professor W. Peters
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SUMMARY OF ANTIMALARIAL DRUG TESTS

-1961-208

BLOOD-LEVEL ANTICIDITY

COMPOUND NAME

DR NUMBER

HALOFANTRINE.....

PARASITE (SUB)SPECIES

P. berghei.....

FORMULATION

Tween 80/H₂O

ROUTE OF ADMINISTRATION : SC/IP/PQ/IT

MAXIMUM TOLERATED DOSE (MTD)

>30... MG/KG X .4

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Treated PPE
Control PPE |
|--|----------------------------|----------------|-----------------------|---------------------------------|----------------------------|
| | 0.1 | 5 | | - | 94.8 ± 5.2 |
| | 0.3 | 5 | | - | 91.4 ± 2.0 |
| N | 1.0 | 5 | 1 | - | 51.6 ± 14.1 |
| | 3.0 | 5 | | - | 0.1 ± 0.1 |
| | Ø | 10 | | 20.9 | |
| ED ₅₀ (range) 0.5 (0.1 - 1.3) | | | | | |
| ED ₉₀ (range) 1.3 (0.4 - 3.5) | | | | | |
| Resistance factor I ₉₀ 1.0 | | | | | |
| | 1.0 | 5 | | - | 87.5 ± 6.2 |
| | 3.0 | 5 | | - | 86.8 ± 16.3 |
| N/1923 | 10.0 | 5 | 1 | - | 91.5 ± 3.1 |
| (R ₁₅ , 56) | 30.0 | 5 | | - | 100 ± 2.2 |
| | 100.0 | 5 | | - | 80.3 ± 11.8 |
| | Ø | 10 | | S.C | |
| ED ₅₀ (range) > 100 | | | | | |
| ED ₉₀ (range) > 100 | | | | | |
| Resistance factor I ₉₀ > 77 | | | | | |

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COMPOUND NAME

CP NUMBER CHLOROQUINE

FORMULATION Triclin. SC/H₂O ROUTE OF ADMINISTRATION

MAXIMUM TOLERATED DOSE MTD >1000 mg/kg (A)

| Strain | Daily dose
mg/kg DO-0+3 | No. of
mice | No. of
experiments | Mean (range)
parasite rate ± | Standard error |
|--------|----------------------------|----------------|-----------------------|---------------------------------|----------------|
| | 0.1 | 5 | | - | 8.5 ± 4.1 |
| | 0.3 | 5 | | - | 80.1 ± 5.9 |
| N | 1.0 | 5 | 1 | - | 52.1 ± 7.6 |
| | 3.0 | 5 | | - | 24.3 ± 8.5 |
| | ∅ | 10 | | 20.0 | |
| | | | | | |
| | | | | | |

ED₅₀(range) 0.8 (0.2-2.1)

ED₉₀(range) 3.1 (0.9-8.5)

Resistance factor I₉₀

| | | | | | |
|-----------|------|----|---|------|------------|
| | 3.0 | 5 | | - | 94.5 ± 4.0 |
| | 10.0 | 5 | | - | 91.8 ± 4.1 |
| N/1923 | 30.0 | 5 | 1 | - | 91.8 ± 7.4 |
| (Pass 56) | 60.0 | 5 | | - | 100 ± 5.5 |
| | ∅ | 10 | | S.C. | |
| | | | | | |
| | | | | | |

ED₅₀(range) > 60

ED₉₀(range) > 60

Resistance factor I₉₀ > 19

Principal Investigator: Professor W. Peters
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PRIMAQUENE 100 mg 100 mg Plavix.

MAXIMUM TOLERATED DOSE (MTD) = 600 MG/KG X 4

| | | | | | |
|---|-------|----|---|----|-------------|
| EC ₅₀ range: 1.5 (1.1 - 2.2) | | | | | |
| EC ₃₀ range: 5.8 (4.1 - 8.4) | | | | | |
| Resistance factor I ₉₀ 1.0 | | | | | |
| | 30 °C | 5 | | - | 55.0 ± 14.7 |
| | 10 °C | 5 | | - | 34.0 ± 13.1 |
| N _L 1923 | 30 °C | 5 | 1 | - | 9.5 ± 4.3 |
| (Pass 56) | 10 °C | 5 | | - | 0.3 ± 0.1 |
| | ✓ | 10 | | 50 | |
| | | | | | |
| | | | | | |

Resistance factor 100 3 2

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MEFLORINE

NAME: MEFLORINE PARASITE: P. berghei

FORMULATION: Tween 80/H₂O ROUTE OF ADMINISTRATION: SC

MAXIMUM TOLERATED DOSE (MTD): >600 MG/KG X 5d

| Strain | Daily dose
mg/kg D0-D+3 | No. of
mice | No. of
experiments | Mean control
parasite rate % | Resistance factor
Control |
|--------|----------------------------|----------------|-----------------------|---------------------------------|------------------------------|
| | 0.3 | 5 | | - | 100 ± 7.1 |
| | 1.0 | 5 | | - | 83.0 ± 2.5 |
| N | 3.0 | 5 | 1 | - | 174 ± 3.2 |
| | 10.0 | 5 | | - | C |
| | Ø | 10 | | 20.9 | |

| |
|---------------------------------------|
| ED ₅₀ range: 1.6 (0.5-2.2) |
| ED ₉₀ range: 2.8 (0.3-3.7) |
| Resistance factor I ₉₀ 1 C |

| | | | | | |
|-----------|------|----|---|-----|-------------|
| | 3.0 | 5 | | - | 83.5 ± 7.4 |
| | 10.0 | 5 | | - | 73.5 ± 13.0 |
| N1923 | 30.0 | 5 | 1 | - | 97.5 ± 4.6 |
| (Pass 56) | 60.0 | 5 | | - | 100 |
| | Ø | 10 | | 8.0 | |

| |
|---------------------------------------|
| ED ₅₀ range: >60 |
| ED ₉₀ range: >60 |
| Resistance factor I ₉₀ >21 |

Principal Investigator: Professor W. Peters
Department of Medical Protozoology
London School of Hygiene & Tropical Medicine

MOUSE NAME

QUININE PARASITE SUBSPECIES *P. berghei*

FORMULATION $\text{Tween 80} / \text{H}_2\text{O}$ ROUTE OF ADMINISTRATION ~~SC~~ IP

MAXIMUM TOLERATED DOSE (MTD) > 600 MG/KG (ST)

| Strain | Daily dose mg/kg D0-D+3 | No. of mice | No. of experiments | Mean control parasite rate % | Treated parasite rate % |
|--------|-------------------------|-------------|--------------------|------------------------------|-------------------------|
| | 100 | 5 | | - | 98.2 ± 2.7 |
| | 300 | 5 | | - | 61.3 ± 7.3 |
| N | 100 | 5 | 1 | - | 36.1 ± 7.5 |
| | 300 | 5 | | - | C |
| | 0 | 10 | | 25.3 | |

ED_{50} (range) 45.0 (23.0-90.0)

ED_{90} (range) 85.0 (43.0-175)

Resistance factor I_{90} 1.0

| | | | | | |
|----------------------|-----|----|---|-----|-----------------|
| | 100 | 5 | | - | 55.0 ± 8.2 |
| | 300 | 5 | | - | 70.5 ± 8.4 |
| N10023 | 100 | 5 | 1 | - | 75.4 ± 23.1 |
| (R ₅₀ 56) | 0 | 10 | | 8.0 | |

ED_{50} (range) > 600

ED_{90} (range) > 600

Resistance factor $I_{90} > 7.1$

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