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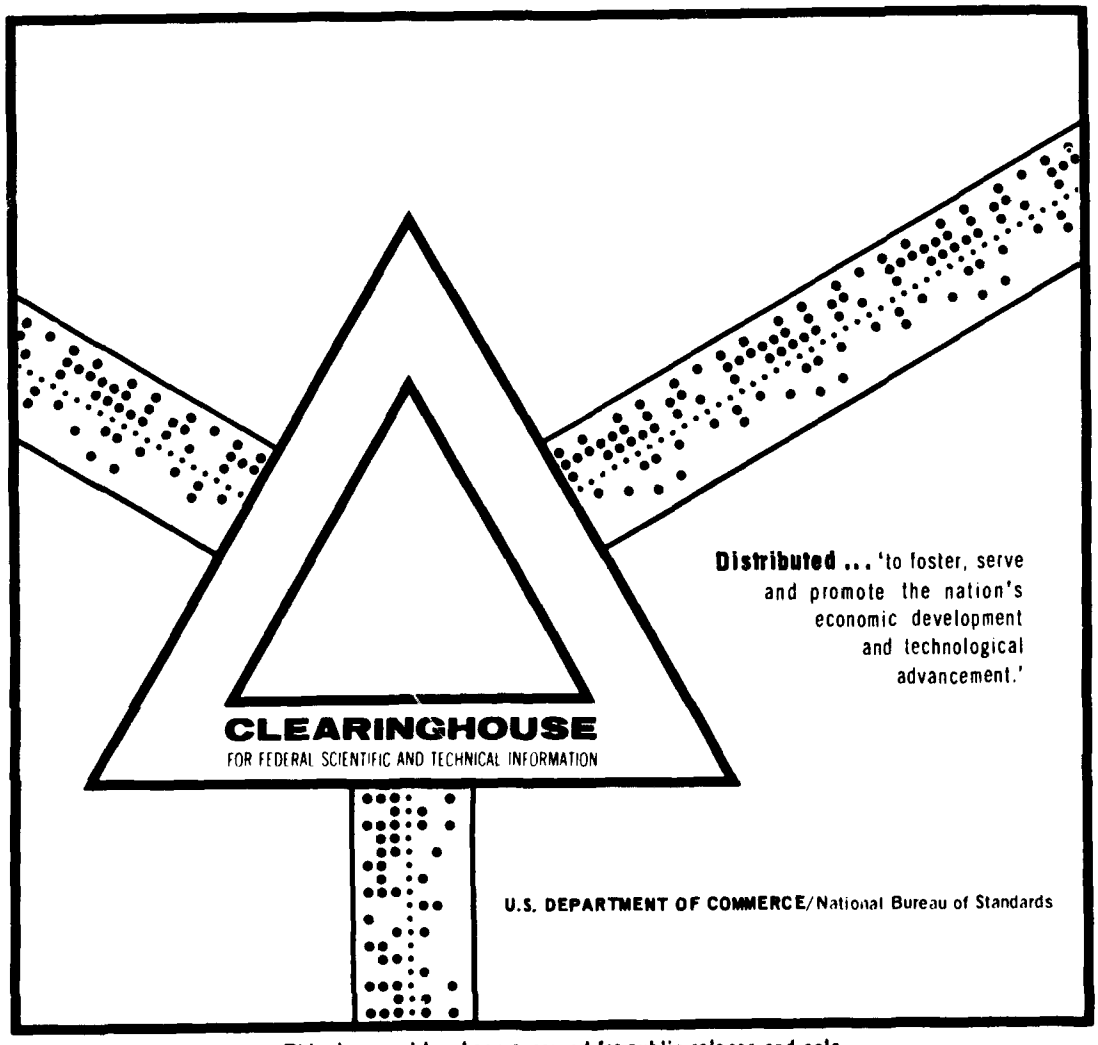
SECONDARY EVALUATION OF ANTIMALARIAL AGENTS

Maurice E. King, et al

IIT Research Institute
Chicago, Illinois

January 1970



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Report No. IITRI-L6038-15

SECONDARY EVALUATION OF ANTIMALARIAL AGENTS

Annual Progress Report

Maurice E. King
Alan M. Shefner

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Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
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ABSTRACT

The objective of this research program is to screen potential antimalarial agents against Plasmodium berghei infections in mice. In addition to the use of blood induced normal and drug resistant infections, procedures were established for the use of sporozoite-induced infections of P. berghei yoelii in testing for causal prophylactic as well as blood schizontocidal activity.

Special studies were also made to differentiate the action of drugs that apparently exhibit both types of activity as well as to determine the period of infectivity of various tissues following sporozoite infection.

FOREWORD

The work described in this report was authorized under Contract No. DA-49-193-MD-3027 entitled, "Secondary Evaluation of Antimalarial Agents". The work reported here was started in January 1969 and completed in December 1969. Data from screening and special studies are recorded in Logbooks C18825, C18827, C18828, C18896, C18897, C19169, C19347, C19418, C19419 and C18033. All test results were incorporated in suitable format on punch cards and magnetic tapes of the card images sent to Walter Reed Army Institute of Research for processing.

Mr. Alan M. Shefner, as responsible investigator has been in overall charge of the program and has coordinated the efforts of the various phases of the program. Dr. Maurice E. King has directed all screening operations and special studies. Dr. Morris D. Schneider developed the tissue differentiation test and Mr. Lionel Richard conducted all experiments concerned with mosquito infection. Other personnel who have contributed to the program include: T. Cason, W. Clark, M. Dickens, W. Jeter, D. Jordan, S. Palfyn, N. Seal and F. Silverstein.

In conducting the research described in this report the investigators adhered to the "Guide for Laboratory Animal Facilities and Care" promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council.

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SECONDARY EVALUATION OF ANTIMALARIAL AGENTS

I. INTRODUCTION

This report summarizes the results obtained during the past year on a program entitled, "Secondary Evaluation of Antimalarial Agents". The work was primarily concerned with the development and use of a protocol for screening drugs against sporozoite induced P. berghei yoelii infection. Special studies have also been made using sporozoite induced infections as well as the continuation of screening in normal and drug resistant P. berghei.

II. SCREENING OPERATIONS

A. Secondary Screening

In this test system single treatments of drugs are given at three dose levels and the effects on parasitemia as well as mortality of infected mice are determined. The mice are infected by intraperitoneal injection of diluted heart's blood from donor mice. Three days after the infection smears of the blood from each mouse are made and the appropriate treatment is given to groups of 5 mice each.

Drugs are administered subcutaneously or orally at dose levels of 640, 160 and 40 mg/kg. Drugs for subcutaneous injection are suspended in peanut oil and those for oral administration are suspended in a mixture of 0.2% methyl cellulose and 0.4% Tween 80 in physiological saline. Blood smears for parasite counts are made again on the sixth day after infection and on the 30th day immediately before surviving mice are sacrificed. Mortality is observed and recorded daily with deaths on days 3, 4 and 5 considered due to drug toxicity. Six runs including a total of 62 compounds were carried out during this report period.

B. Drug Resistant P. berghei

The protocol for screening in the drug resistant system differs from the one described for the regular secondary in that drugs are administered on 4 consecutive days. Mice are infected by intraperitoneal injection of diluted blood from the appropriate donors. Four days following the infection, initial slides for parasitemia determination are made and

groups of 5 mice are given the first of 4 consecutive daily drug treatments of a total of 640, 160 and 40 mg/kg. Slides are again made on day 8 which is one day after the drug treatments are completed. Twelve-day slides are made in the case of TRZ-1 and 15-day slides for CHL-1 and DDS-1. Final slides are made for all surviving mice on day 28 immediately before sacrifice.

Activity of a drug is based on (a) a decrease in mean parasitemia of the treatment group between days 4 and 8; (b) a 12 or 15-day mean parasitemia less than 50% of that of the untreated controls on the same day; and (c) an increase in the number of survivors of the drug test group in comparison with that of the untreated controls. During the past year, 76 compounds were tested in the TRZ-1 system, 69 in the CHL-1 system and 20 in the DDS-1 system.

The program used for processing data obtained in the screening tests was written for the IBM 7094 computer and is not compatable with the IBM 360 system currently in use at IITRI. Because of the availability of 7094 time to WRAIR, magnetic tapes containing images of the puched data cards are now being sent there for processing.

C. Sporozoite-Induced Infections

A protocol based on the results of numerous preliminary studies was adopted for the sporozoite mouse test system and used in carrying out 19 runs.

The mosquito colony used for this system is maintained in an insectary at 26°C and 80% relative humidity. Adults for colony maintenance are fed for the first 2 days following emergence on 10% sucrose and then given 4 blood meals from anesthetized male rabbits at 48 hour intervals. Eggs are collected after the 2nd and 4th blood meals.

Cages containing mosquitoes for infection are transferred to a 24°C incubator on the day after emergence. The following day 4 donor mice are placed inside the cage for the infective blood meal. The mice are not anesthetized but are restrained on their back by taping to boards. The average donor parasitemia is 15% with 10% of the parasitized cells containing gametocytes. The donor mice are in the 4th day of the second of two blood passages from mice originally infected with sporozoites. The blood passages are 6 days following sporozoite infection and 4 days following the first blood passage. Therefore a 14 day interval exists between the time of sporozoite infection and recycling through the insect vector. At the end of 4 hours for mosquito feeding the mice are removed and the cage returned to the 24°C incubator. The mosquitoes are

kept in the dark except during daily changes of cotton pads soaked in 10% sucrose.

On the 13th day following infection, mosquitoes in lots of 60 are transferred with an aspirator to pint cardboard cartons and then returned to the incubator. The following day the mosquitoes are anesthetized with chloroform and placed in glass mortars chilled in ice. Each lot of mosquitoes is triturated in 4 ml saline and centrifuged for 5 min at 1000 RPM. Mice are then intraperitoneally injected with 0.2 ml of the supernatant containing the equivalent of 3 mosquitoes.

Each drug is evaluated in infected mice under two treatment schedules. Treatment is carried out for three consecutive days, with drug dosage starting on the day prior to sporozoite infection for evaluation of causal prophylactic activity, and on the 3rd day post infection for evaluation of blood schizontocidal activity. Slides for parasitemia determination are made on days 6, 10, 14 and immediately before sacrifice on day 21.

The effect of selected antimalarials on the parasitemia of sporozoite infected mice is shown in Table 1. Chloroquine which is classed as a blood schizontocide, has no effect when treatments are started on the day before infection. However suppression is obtained if treatment starts on day 3 when blood stages are present. Quinacrine also a blood schizontocide, is quite effective when given on the late treatment schedule but also caused some suppression when treatments are initiated prior to infection. This can be explained by the more pronounced affinity of quinacrine than chloroquine for tissues leading to slower degradation and elimination such that the compound could still be effective when blood stages are present. Primaquine which acts against preerythrocytic forms was quite effective on the early treatment schedule but was relatively ineffective against erythrocytic forms when given later. Triazine, DDS, pyrimethamine and trimethoprim were effective on both treatment schedules, indicating both prophylactic and schizontocidal activity.

When test runs were started on this system, primaquine and chloroquine at 90 mg/kg were included as controls. Primaquine is the positive control and chloroquine is the negative control for the early treatment schedule and chloroquine is the positive control with primaquine as the negative control on the late treatment schedule

In lieu of computer output for the sporozoite mouse runs, a summary of 14-day control data is presented in Table 2. The patency and mean parasitemia for untreated as well as positive and negative control groups are given for each run. Except in 3 cases, Runs 391, 396 and 397 the infection rate was at least 75% and the overall rate is 78% for untreated control groups.

Table 1

ACTIVITY OF ANTIMALARIAL DRUGS IN SPOROZOITE-MOUSE TEST SYSTEM

Group	Daily Dose mg/kg	Parasitemia %: Day on which treatment was initiated -1: Parasitemia, day 6	10	14	21	28	Day on which treatment was initiated 3: Parasitemia, day 6	10	14	21	28
Controls		7.1	12.6	25.7	0.8	0					
Chloroquine	30	3.9	13.5	38.9	13.3	0	0	3.8	6.1	8.1	0
	15	1.6	10.1	32.8	3.5	0	0	5.5	10.8	12.4	0
Quinacrine	30	0.1	4.8	11.3	5.6	0	0.5	1.7	6.9	0	0
	15	0.8	5.5	17.9	0.2	0	0.1	1.9	5.6	0.1	0
Primaquine	30	0.5	0	0.4	0	0	0	4.2	12.2	21.9	0
	15	1.5	9.7	14.8	13.1	0	1.4	8.4	21.2	30.5	0
Triazine	30	0	0	0	0.1	0	0	0	0	0	0
	15	0	0	0	0	0	0	0	0.1	0.1	0
DDS	30	0	0	0	0.9	0	0	0	0	0	0
	15	0	0	0	0.6	0	0	0	0	3.1	0
Pyrimethamine	30	0	0	0	0.2	0	0	0	0	0.1	0
	15	0	0	0	0.1	0	0	0	0	0	0
Trimethoprim	30	0	0	0.1	0	0	0	0	0	0.4	0
	15	0	0	0.1	0	0	0	0	0	0.4	0

Table 2

14 DAY CONTROL DATA FOR SPOROZOITE-MOUSE TESTS

Run No.	Untreated Controls		Primaquine (90 mg/kg)				Chloroquine (90 mg/kg)			
			Prophylactic		Therapeutic		Prophylactic		Therapeutic	
	Patency	Parasitemia %	Patency	Parasitemia %	Patency	Parasitemia %	Patency	Parasitemia %	Patency	Parasitemia %
375	16/18	42.33	7/8	30.04	7/9	5.31	9/9	39.58	8/10	11.28
377	19/19	40.29	7/8	52.01	6/9	13.05	7/9	36.74	7/8	13.72
381	18/18	32.89	8/8	47.01	8/9	8.23	5/10	23.59	10/10	6.95
383	15/20	27.07	10/10	41.96	8/10	17.10	9/9	48.59	10/10	9.73
384	18/20	12.60	8/9	18.99	8/9	2.67	7/10	12.64	10/10	9.60
388	14/18	29.47	8/10	16.56	8/10	8.63	8/10	30.94	7/10	2.76
390	15/20	13.10	9/10	15.55	7/9	5.50	8/10	18.84	7/10	10.08
391	10/20	8.14	2/10	1.00	3/10	3.07	3/10	3.83	3/10	2.07
395	15/20	7.26	10/10	25.30	9/10	8.41	9/9	20.77	0/9	0
396	11/19	7.74	1/10	2.95	8/10	8.55	7/10	19.74	7/10	4.52
397	9/20	11.72	6/10	16.09	8/10	7.05	5/10	8.92	8/9	11.00
399	18/20	23.99	7/10	28.74	8/10	14.54	8/10	22.68	6/9	7.44
403	12/15	25.13	8/9	22.03	7/10	16.99	7/9	20.16	8/9	5.95
406	18/20	33.67	10/10	24.28	8/10	15.51	8/10	23.65	8/10	3.30
408	15/20	17.82	0/10	0	8/10	4.97	5/8	7.09	10/10	6.47

If these 3 runs are eliminated, the infection rate is 85%. The low infection rate for these runs might be due to a change in technique. Prior to Run 390, the whole ground mosquito was injected into mice. However after one particular infection, a large number of mouse deaths occurred which could not be attributed to malaria and was eventually traced to the use of whole mosquitoes. The toxic principle was not identified but the problem did not return when use of the supernatant containing only sporozoites was initiated.

During the preliminary studies, primaquine was quite effective as a causal prophylactic and was ineffective when used on the late therapeutic schedule. Table 2 however, shows that this situation was reversed when primaquine was used in the test runs. Other studies to be described later, indicate that the inconsistency may be related to an undefined change that occurs in the drug as it ages in the bottle. The results shown for Run 396 in which a new sample from WRAIR was used, and for Run 408 in which a commercial sample in tablet form was used support this conclusion. Generally the results with chloroquine were as expected.

Of the 77 drugs tested in the runs for which 14 day parasitemia data is complete, 37 were conpletely inactive, 18 exhibited both prophylactic and schizontocidal activity, 8 exhibited only prophylactic and 7 exhibited only schizontocidal. Several additional drugs show borderline activity and will be retested.

III. SPECIAL STUDIES

A. Differentiation of Drug Activity

When a drug exhibits both prophylactic and schizontocidal activity, it must be determined whether the results are real or apparent. A drug which acts only on blood stages may appear to have causal prophylactic activity as indicated earlier for quinacrine. In reality, the drug may be slowly metabolized or eliminated and thus an effective dose may still be present when blood stages appear. As a means of solving this problem, studies were conducted to determine the relative infectivity of blood and tissue from control and drug treated sporozoite infected mice. Mice were infected with sporozoites and sacrificed in groups of 5 at the end of 48 and 72 hr. The blood from each group was pooled and centrifuged and the red cells resuspended in preservative solution. Groups of 5 fresh mice were then intraperitoneally injected with graded doses of pooled donor RBC, and with homogenates of liver, spleen and kidneys. Slides for parasitemia determination were made of the 48 and 72 hr donor mice and of the recipient mice after 6, 10 and 13 days.

Slides from the 48 hr donor mice showed no patent infection in any of the 5 mice. However fluorescence microscopic examination of the pooled RBC and the homogenates that had been virtually stained with acridine orange revealed multinucleate forms which resembled EE forms in structure and size. Three of the five 72-hr donor mice showed patent infections in addition to the fluorescing forms in the blood and homogenates.

Results from the recipient mice are summarized in Tables 3 and 4. Malaria infections were induced by the blood and all tissues from 72 hr donors and all except for the kidney at 48 hr. The relatively high infectivity of the 48 hr donor blood was surprising since examination of Giemsa stained slides revealed no evidence of circulating malarial stages.

Having established the infectivity of liver at 48 hr and 72 hr, presumably containing preerythrocytic stages, additional studies were made on drug-treated mice. Primaquine and DDS at 30 mg/kg/day were used in treating groups of 10 sporozoite-infected mice on the early prophylactic schedule. The treated groups and an untreated control group were sacrificed at 72 hr after infection. Graded doses of pooled RBC and homogenized tissue were injected into groups of 5 mice in order to calculate the relative potency of each preparation. The results are shown for 2 such experiments in Table 5. In both cases, DDS completely eliminated the infectivity of the liver and very drastically reduced that of the other tissues. Primaquine on the other hand had very little effect on tissue infectivity as compared to that of the untreated controls. On this basis, DDS would be classed as a causal prophylactic but not primaquine.

Earlier the inconsistent results with primaquine in the test protocol were described. Similar problems were observed with WR 40070A which exhibited only prophylactic activity when originally tested but on a blind retest as AS 58265 showed no activity. As a means of checking these inconsistencies 2 samples of these drugs and of DDS were tested using the protocol that will be used in actual differentiation tests

Groups of 5 sporozoite infected mice were treated with 30 mg/kg of each sample on days -1, 0 and +1 after infection. Three days after infection the mice were sacrificed and the tissue pooled. Instead of graduated doses of RBC and tissues, 20 μl of RBC or 20 μg homogenized tissue were injected into each of 10 mice per drug per test group. Slides were made on day 6 and on day 10 prior to sacrifice. Results for the 2 part experiment are shown in Table 6. Blood and liver from donor mice treated with the two DDS samples did not produce infections in recipient mice as was found in the earlier studies. Differences were found in the samples of the other drugs. Both blood and liver from donor mice treated with primaquine sample WR 02975A produced infections in recipient mice while that from

Table 3

RELATIVE INFECTIVITY OF RED BLOOD CELLS AND TISSUE HOMOGENATES OF MOUSE DONORS 48 HOURS AFTER SPOROZOITE INFECTION

Malaria source and intraperitoneal dose, µl or mg		No. of infections per no. of mice	Mean parasitemia,% Day of infection 6	10	13	Measurements taken before and after test mice survivors were killed on 13th day Temperature, °C Range	Mean	Average wt. Body, gm	Spleen, mg	Splenic index[b]
RBC	40	5/5	13	16	27[a]	32.2-34.9	33.6	18.8	906	48.2
	5	5/5	7	13	12	35.5-37.0	36.2	22.6	1096	48.4
Liver	20	5/5	7	12	22	34.7-36.4	34.5	21.2	1092	51.5
	10	4/5	2	12	12	35.8-37.0	36.4	22.0	780	35.5
	5	0/5	0	0	0	37.5-37.8	37.7	23.0	140	6.1
	1	1/5	1	5	11	35.2-37.8	37.1	23.4	303	12.9
Spleen	20	3/5	2	9	13	34.1-37.8	35.9	19.4	582	30.0
	5	5/5	3	9	18	34.7-37.4	36.0	23.0	878	38.2
	1	0/5	0	0	0	36.4-37.8	37.2	23.2	120	5.2
Kidneys	20	0/5	0	0	0	36.1-37.0	36.3	22.8	117	5.1
Noninoculated controls	0	0/5	-	-	-	35.2-37.0	36.0	21.4	110	5.2

[a] One mouse died of malaria (day 13).

[b] This value is the numerical expression of wet spleen weight in milligrams per gram of mouse weight.

Table 4

RELATIVE INFECTIVITY OF RED BLOOD CELLS AND TISSUE HOMOGENATES OF MOUSE DONORS 72 HOURS AFTER SPOROZOITE INFECTION

Malaria source and intraperitoneal dose, l or mg		No. of infections per no. of mice	Mean parasitemia,% Day of infection 6	10	13	Measurements taken before and after test mice survivors were killed on 13th day: Temperature, °C Range	Mean	Average wt. Body, gm	Spleen, mg	Splenic index[b]
RBC	40	5/5	11	22	25(2)[a]	34.5-37.2	36.2	22.0	894	40.6
	5	5/5	14	24	31(1)	33.8-36.6	35.6	19.4	1118	60.8
Liver	20	5/5	21	36	50	32.2-37.2	35.1	20.2	1175	58.1
	20	4/5	14	28	32	35.2-37.8	36.2	21.6	1053	49.8
	5	5/5	9	15	16	32.2-37.0	35.2	20.4	835	40.9
	1	4/5	3	10	17	34.7-36.6	35.7	22.6	943	41.7
Spleen	20	5/5	13	38	33	33.4-37.2	35.4	22.2	1303	58.6
	10	5/5	16	23	18	33.8-37.2	35.9	19.4	1126	58.0
	5	5/5	29	50	42	32.8-36.2	33.8	19.2	939	48.8
	1	5/5	16	30	40	32.8-37.2	35.4	20.4	1044	51.2
Kidneys	20	4/5	14	28	45	33.4-36.6	35.1	22.0	998	45.4
Noninoculated controls	0	0/5	-	-	-	36.2-37.2	36.8	23.8	124	5.2

[a] Number in parenthesis is number of survivors with no detectable parasitemia by Giemsa-method. These animals are recovering from the induced malaria in the absence of any therapy.

[b] This value is the numerical expression of wet spleen weight in milligrams per gram of mouse weight.

Table 5

EFFECT OF DRUGS ON POTENCY OF RED CELLS AND TISSUES OF MICE 72 HOURS AFTER SPOROZOITE INFECTION

Drug Treatment[a]	Potency Value[b]			
	RBC	Liver	Spleen	Kidneys
None	$>1.65 \times 10^5$	7.05×10^4	7.85×10^1	1.45×10^2
	1.29×10^4	1.91×10^4	2.77×10^2	2.86×10^2
Primaquine	$>1.75 \times 10^2$	$>2.14 \times 10^4$	$>3.04 \times 10^2$	1.05×10^2
	8.35×10^2	$>1.97 \times 10^3$	$>3.51 \times 10^2$	3.94×10^1
DDS	1.00×10^1	0	1.85×10^0	0
	9.45×10^1	0	9.10×10^{-1}	1.56×10^0

[a] 30 mg/kg/day on days -1, 0, and +1

[b] Calculated number of infectious malarial units per tissue per donor mouse.

Table 6

TEST OF DIFFERENT SAMPLES OF DRUGS FOR PROPHYLACTIC ACTIVITY

Drug Treatment[a]	Parasitemia in Recipient Mice[b]			
	Blood		Liver	
	6 day	10 day	6 day	10 day
Controls	13.9	32.7	13.2	19.6
	6.7	24.6	18.2	23.2
DDS (00448G)	0	0	0	0
DDS (00448G)	0	0	0	0
Primaquine (02975A)	9.4	22.3	18.2	22.3
Primaquine (02975D)	0	0	0	0
AS58265	8.5	17.4	11.1	12.1
WR40070A	0	0	0	0

[a] 30 mg/kg/day on days -1, 0, +1 for donor mice.

[b] Donor material from 72 hour mice.

donor mice treated with newly opened WR 02975D did not. The fact that the "A" sample was inactive infers that some type of chemical reaction leading to loss of activity occurs in the bottle that had been opened for some time. Results with the other drug were analogous to those obtained earlier - WR 40070A was active as a causal prophylactic while AS 58265 was not. In this case there was no apparent change with time but an obvious difference in the biological activity of the two samples.

B. Period of Infectivity

A study was also made of the length of the period of infectivity of blood and liver from sporozoite infected mice. For this prupose a group of 22 mice were intraperitoneally infected with sporozoites and then sacrificed in groups of 2 at specific time intervals. Blood and liver from the two mice were pooled and injected into fresh mice as in the differentiation test. Slides were made of the recipient mice on day 6 and day 10 prior to sacrifice.

The results from this study are summarized in Table 7. The mice sacrificed on day 3 post infection did not produce infections in recipients although day 2 mice produced infections and all previous day 3 donors were infective despite the absence of parasites in blood films. Parasitemia of donor mice followed the usual pattern but no quantitative relationship can be seen between donor parasitemia and that of recipient mice receiving either blood or liver. It was expected that infectivity from the blood would continue longer than from liver. However except for day 19, the liver was as infective as blood. This can be interpreted as due either to secondary tissue schizonts in the liver or the presence of infective blood in the liver samples. An experiment is now underway involving chloroquine-treated mice that may help to interpret these findings.

Table 7

INFECTIVITY OF BLOOD AND LIVER FOLLOWING SPOROZOITE INFECTION

Donor Mice		Recipient Mice[a]			
		6-Day Parasitemia		10-Day Parasitemia	
Day after Infection	Parasitemia %	Blood	Liver	Blood	Liver
1	0	0	0	0	0
2	0	14.4	11.9	20.9	17.1
3	0	0	0	0	0
6	3.0	11.1	10.9	31.9	37.4
8	7.0	8.3	5.8	11.5	12.6
10	23.0	21.7	12.7	16.3	12.2
13	43.5	5.2	3.0	9.3	11.5
15	43.5	10.8	6.9	16.9	9.7
17	1.5	17.2	10.5	34.3	26.9
19	0	1.1	0	1.8	0
21	0	0	0	0	0

[a] Recipient mice infected with blood and liver from donor mice sacrificed on day shown.

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13. ABSTRACT

The objective of this research program is to screen potential antimalarial agents against Plasmodium berghei infections in mice. In addition to the use of blood induced normal and drug resistant infections, procedures were established for the use of sporozoite-induced infections of P. berghei yoelii in testing for causal prophylactic as well as blood schizontocidal activity.

Special studies were also made to differentiate the action of drugs that apparently exhibit both types of activity as well as to determine the period of infectivity of various tissues following sporozoite infection.

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Anopheles stephensi						