TABLE I.
The Pressures Required to Produce Intradermal Wheals.

No. of determinations	Characteristics of subjects		Bevel of Needle	Solution	Pressures—mm Hg		
	No.	Sex			Range	Mean pressure	Mean deviation
16	2	M	Up	Saline	1600-2800	2170	318
62	5*	M	Down	"	1000-3200	1970	454
14	3	F	Up	"	1900-3080	2240	128
24	5	F	Down	"	1280-2840	2160	400
44	4	M	"	Histamine acid phosphate 1-100,000 in saline	1260-3200	2460	405

* One Negro and one Japanese.

male and female skins, or among the skins of the Whites, Negroes, and Japanese studied. No attempt has been made in this preliminary study to determine the physiological variations in wheal-pressure which might occur with marked changes in environmental temperature or in the normal phases of the menstrual cycle. As shown in the table, the wheal-producing action of histamine is apparently too slow to lower the pressure required to produce wheals in this fashion. In fact the figures would rather indicate that histamine increased the pressure required.

Conclusion. The pressures required to produce intradermal wheals in normal individuals varied from 1,000 to 3,200 mm Hg with a mean pressure of about 2,000 mm Hg. No consistent differences in wheal pressures were found between males and females, or among Whites, Negroes and Japanese.

15487

Curative Action of Drugs in Lophurae Malaria of the Duck.*

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Scanty data have been published on the curative action of drugs in avian malarias, either in sporozoite or blood-induced infections.† No data has been published on the curative effect of drugs on lophurae malaria in the duck. For this reason, it appears advisable to record the following observations, despite the fact that the experiments are not perfectly controlled due to a large number of "accidental" deaths among our birds.‡

Infection was produced in ducks about 10 to 14 days of age by intravenous injection of 50×10^6 parasitized erythrocytes. The drug-diet method[1] of treatment was used. Administration of the diet was started 18 hours before infection and was continued for various lengths of time after infection. All drugs except SN 11,437, SN 187 and SN 475 were administered in the form of a salt.

* This investigation was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and The Johns Hopkins University.

† A considerable amount of data has been accumulated for various avian infections in the cooperative program of malarial research sponsored during the past five years by the Committee for Medical Research of the OSRD.

‡ These "accidental" deaths appear to be due to a filtrable agent. A preliminary study of this agent is reported elsewhere.[4]

[4] Dearborn, E. H., PROC. SOC. EXP. BIOL. AND MED., 1946, **63**, 48.

[1] Marshall, Litchfield, and White, *J. Pharm. and Exp. Therap.*, 1942, **75**, 89.

TABLE I.
Curative Action of Drugs in Lophuræ Malaria in the Duck.

Survey No.*		Duration of treatment days	Dose mg/kg/day	No. of ducks Used	Not Cured	"Cured"	Died†
359	Quinine (base)	6	180	10	9	0	1
		10	225	9	3	1	5
390	Quinacrine, dihydrochloride	6	280-310	12	6	0	6
		13	115	9	3	0	6
971	Pamaquine (base)	6	3.5	19	6	5	8
		6	9	44	16	17	11
		10	4	10	3	1	6
7618	Chloroquine, diphosphate	6	303	5	3	0	2
		6	183	8	5	0	3
11437	N¹-(5-chloro-2-pyrimidyl)-metanilamide	6	785	8	4	0	4
		26	225	7	5	0	2

* This number (SN) is used to designate a drug in the Monograph referred to above.[3]
† Figures in this column represent ducks which exhibited no evidence of infection but which died before "cure" could be established.

Subinoculations were done by intravenous injection of 2 cc of blood from the treated bird into a normal duck of about 150 g weight. Blood smears of the treated birds were made at the end of treatment, at the time of each subinoculation and as frequently as possible during the intervening periods. It was found that the injection of one to 10 parasitized erythrocytes into ducks of about 150 g weight produced an infection with the appearance of parasites in smear on the 10th-13th day. In some cases reinfection was attempted by injection of 20-30 $\times$ 10^8 parasitized erythrocytes into the treated ducks which at this time weighed about 800-1000 g. This dose in a normal duck of corresponding size would give a parasitemia of 40-50% erythrocytes parasitized on the 3rd day. The reinfected ducks were examined on the 3rd day. Those having 40% or more of erythrocytes parasitized were considered to be successfully reinoculated while those with less than 20% erythrocytes parasitized were considered to exhibit some degree of immunity.

The experiments given in this report are not as satisfactory as might be desired on account of the failure of either all the treated or all the subinoculated ducks to survive the necessary periods of observation. A series of experiments on uninfected untreated birds has shown that these deaths are not attributable to conditions of holding or procedures relevant to obtaining smears or subinoculating blood but to the filtrable contaminant mentioned in the note above. Obviously, the large number of deaths occurring before the observations are complete complicates the interpretation of the data; however, certain conclusions appear to be justified. As a result of deficiencies in our knowledge of the natural history of malaria in the duck, it must be recognized that while the presence of parasites in the blood of treated or subinoculated ducks is definitive evidence of failure to cure, inability to demonstrate either parasites in the blood or lack of immunity to them can only indicate probability of cure.

In Table I is given a very brief summary of the results obtained with the well known drugs, quinine, quinacrine and pamaquine, and also with chloroquine[2] and SN 11,437. This drug (SN 11,437) is rather unique in that it is a complete causal prophylactic in gallinaceum malaria in the chick, lophurae malaria in the turkey and cathemerium malaria in the canary.[3] However, it has no

[2] Board for the Coordination of Malarial Studies, *J. A. M. A.*, 1946, **130**, 1069.

[3] A Survey of Antimalarial Drugs, 1941-45, sponsored by the Committee on Medical Research of the Office of Scientific Research and Development (Ed. F. Y. Wiselogle).

curative effect in a blood-induced infection of lophurae malaria in the duck. Quinine, quinacrine and chloroquine are not curative, while pamaquine appears to cure a fair percentage of ducks. When treatment is started 24 hours after infection, pamaquine is still curative. However, when treatment is started 48 hours after infection a much smaller per cent of cures is produced. In the table the criterion of "cure" is interpreted as 2 negative subinoculations, the last taken at least 26 days after infection. In our experience a small percentage of ducks having 2 negative subinoculations will prove to be infected if further subinoculations are done; however, this percentage is so small that it would not significantly change these data.

In addition to the drugs listed in Table I, we have found that SN 6911, 7-chloro-4-(4-diethylamino-1-methylbutylamino) - 3-methyl quinoline; SN 1796, α-(diamylaminomethyl)-1,2,3,4 - tetrahydro-9-phenanthrene-methanol; SN 187, 3',5'-dibromosulfanilanilide; SN 6520, 2 - (dimethylaminomethyl)-1-naphthol; SN 901, 6-chloro-2-methoxy-9-[3-(6-methoxy-8-quinolylamino)-propylamino] acridine; SN 475, 2,2',3,3'-tetramethyl-1,1'-diphenyl-4,4'-bi-3-pyrazoline-5,5'-dione; SN 11,426, 5-(*p*-chlorophenyl) - 1-isopropyl-1-methylbiguanide, salt with acetic acid; are not curative when given in maximal tolerated dosage for 6 days. However, SN 5241, α-(dinonylaminomethyl)-1,2,3,4-tetrahydro-9-phenanthrene methanol appears to cure a certain per cent of ducks when given in the maximal tolerated dosage. With the exception of SN 5241, pamaquine is the only drug examined which appears to cure lophurae malaria in a moderate percentage of ducks.

Summary. A number of drugs have been examined for their curative action in lophurae malaria in the duck. Pamaquine appears to cure a fair percentage of the birds, while quinine, quinacrine, chloroquine and a number of other drugs do not.

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15488

Filtrable Agents Lethal for Ducks.*

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In studying the curative activity of drugs against lophurae malaria in ducks it was found that approximately half the birds died with no demonstrable malaria before it could be established that they were cured. Extensive studies indicated that the deaths were not due to living conditions or to the various experimental procedures to which the birds were subjected. It appeared that the causative agent was in the blood injected to produce the malarial infection. Injection of blood from normal ducks did not produce deaths.

It seemed unlikely that the lethal agent was a toxin since the deaths were delayed 15 to 30 days after infection and since the causative agent was transferable by blood passage. It also seemed unlikely that it was a form of malaria since the birds which died had no detectable erythrocytic forms of the parasite and since studies in this and other laboratories[1] had failed to reveal any large number of exoerythrocytic forms of *P. lophurae* in the duck. Bacteriologic studies indicated that none of the common bacteria was responsible for the deaths. In view of these data it seemed likely that the lethal agent might be a filtrable organism. Subse-

* This investigation was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and The Johns Hopkins University.

[1] Porter, R. J., personal communication.