

periments suggest that such is the case. Trials in man under proper conditions would seem worth while in connection with military establishments.

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Control of Malaria Infection (*P. lophurae*) in Ducks by Sulfonamides.

H. A. WALKER AND H. B. VAN DYKE.

From the Division of Pharmacology, the Squibb Institute for Medical Research, New Brunswick, N.J.

The effect of a number of sulfonamides has been studied in various species of birds infected with different parasites. The course of infection by *Plasmodium cathemerium*, *P. relictum*, and *P. nucleophilum* in canaries apparently is not significantly altered by sulfonamides.^{1, 2} However, sulfapyridine can prevent patent infection by *P. circumflexum* or cause the rapid disappearance of parasites if administered after the infection is patent.² No beneficial effects of sulfonamides could be demonstrated in *Hemoproteus columbae* infections in the pigeon.³ In the Java sparrow infected by *P. praecox*, prontosil was believed effectively to reduce the number of circulating parasites.⁴ The action of sulfonamides in infections by *P. lophurae* in the chicken¹ or duck⁵ has been reported to be of little or no benefit.

The course of infection by the Coggeshall strain of *P. lophurae* in the duck is particularly suitable for chemotherapeutic study because the number of parasites in the blood usually grows rapidly until death occurs.* In our experiments, Peking ducks 4 or 7 days old were inoculated intravenously with citrated blood from infected

¹ Coggeshall, L. T., *Proc. Soc. Exp. Biol. and Med.*, 1938, **38**, 768.

² Manwell, R. D., Counts, E., and Coulston, F., *Proc. Soc. Exp. Biol. and Med.*, 1941, **46**, 523.

³ Durand, P., and Villain, *Arch. Inst. Pasteur de Tunis*, 1939, **28**, 94.

⁴ Africa, C. M., Dy, F. J., and Soriano, L. J., cited in *Biol. Abstr.*, 1941, **15**, 1455.

⁵ Hegner, R., West, E., and Dobler, M., *Am. J. Hyg.*, 1941, **34**, Sec. C, 132.

* We are indebted to Professor Robert Hegner and Miss Evaline West not only for infected ducks carrying the Coggeshall strain of *P. lophurae* but also for information concerning the transmission and preservation of the parasite in the laboratory.

TABLE I.
Effects of Quinine Hydrochloride, Atabrine Dihydrochloride, or of Two Sulfonamides on Course of Infection by *P. lophurae* in Ducks.

Group	No. of ducks	Drug*	Total daily dose, g	Avg No. of parasites in 10,000 erythrocytes from day following inoculation										
				Day										
				1	2	3	4	5	6	7	9	11	13	
IA	2	—	—	50	585	1265	2970			13900	Dead			
IB	2	Quinine HCl	.015†	46	80	107	67			9	6	4	5	
IC	2	Sulfathiazole	.150‡	40	284	497	390			153	40	23	12	
ID	2	Sulfadiazine	.150‡	55	275	380	297			157	54	24	8	
IIA	2	—	—	198	318		2990		11900		Dead			
IIB	4	Atabrine (HCl) ₂	.020§	191	158		75		4		0	0	0	

*Administered for a six-day period beginning 24 hours after inoculation.

†One dose by stomach tube daily.

‡Estimated from consumption of food containing 0.5% drug.

§Divided into two daily doses by stomach tube.

Average weight of ducks: groups of I, 64 g; groups of II, 114 g.

donors. Ducks of the same age and, as nearly as possible, of the same weight were used. In a given experiment, the doses of infected blood were all obtained from a single donor and after dilution by citrated saline, were injected intravenously in proportion to body weight. Blood for smears was withdrawn at 9 a. m. Tables I and II illustrate some of the variations encountered 24 hours after inoculation. Among 17 control ducks of these and other experiments, in all of which parasitization had been demonstrated, only 3 survived. All the deaths occurred 7-10 days after inoculation.

Knowing that a sulfonamide such as sulfathiazole may have little effect on the course of bacterial infections in mice unless it be administered incorporated in the food by the technic of Bieter and associates⁶ we were led similarly to investigate the action of sulfanilamide, sulfathiazole, and sulfadiazine on *P. lophurae* infections in ducks. Moreover, it seemed that investigators of the chemotherapy of bird malaria had neglected the principle of maintaining an adequate blood level of sulfonamide, so important in the control of bacterial infections. An early experiment is summarized in Table I and demonstrates clearly that if sulfathiazole or sulfadiazine is incorporated in the dry poultry mash[†] fed, ducks will survive with a very low parasite count. However, the two sulfonamides appear to be much less effective than the hydrochlorides of either quinine or atabrine.

⁶ Bieter, R. N., Larson, W. P., Levine, M., and Cranston, E. M., *Proc. Soc. Exp. Biol. and Med.*, 1939, **41**, 202.

† New Jersey Poultry Mash, Coöperative G. L. F. Mills, Buffalo.

TABLE II.
Effects of Three Sulfonamides on the Course of Infection by *P. lophurae* in Ducks.

Group	No. of ducks	Drug*	% fed in dry poultry mash	Mean and S.E. of number of parasites in 10,000 erythrocytes from day following inoculation						
				1	3	5	7	9	14	21
IIIA	2	Sulfanilamide	1.0	83 ± 20	408 ± 89	651 ± 64	156 ± 29	48 ± 12	272 ± 208	1950 ± 1215†
IIVA	3									
IIIB	3	Sulfathiazole	0.65	91 ± 16	379 ± 57	416 ± 31	145 ± 18‡	61 ± 28	37 ± 22	20 ± 13
IIVB	3									
IIIC	3	Sulfadiazine	0.65	71 ± 21	286 ± 48	278 ± 58	92 ± 16	25 ± 5	16 ± 6	90 ± 60§
IIVC	2									
IIID	2	—	—	92 ± 26	691 ± 126	4680 ± 796	12700 ± 507	Dead		
IIVD	2									

* Administered for a six-day period beginning 24 hours after inoculation.

† Two deaths on 18th and 24th days after inoculation owing to malaria.

‡ One death from cardiac puncture 7 days after inoculation.

§ One death 16 days after inoculation, cause unknown as smear on 14th day was negative.

|| Controls died 8, 8, 9 and 10 days after inoculation.

Average weight of ducks of all groups: 105 g.

The combined data[†] of two later experiments are given in Table II and demonstrate how strikingly the parasite count falls to a low level on the 7-9 day although on the ninth day medication had already been stopped for 48 hours and although the severe infection in the controls led to death at about this time (8, 8, 9, and 10 days). In control birds the peak of infection occurred just before death. In birds receiving sulfathiazole or sulfadiazine the peak of infection probably occurred 4-5 days after inoculation or after 3-4 of the 6 days of treatment. In birds eating mash containing 1% sulfanilamide, the course of the infection paralleled that of other treated groups during the first 9 days. However, a marked rise in parasite count appeared later and culminated in the death of 2 of the 5 ducks. In all the birds treated by sulfonamides, the parasites were almost entirely gametocytes on the 7-9 days. This fact suggests that these drugs act principally on schizonts. If the parasite count later rose, as in ducks receiving sulfanilamide, schizonts in a normal proportion could then be found. On the fourteenth and twenty-first days no parasites could be found in 2 of the birds receiving sulfadiazine; one of these ducks died from an unknown cause (day 16). One bird, a member of the sulfathiazole group, died with a low parasite count (108) on the seventh day as a result of cardiac puncture.

Each bird was weighed at the time of inoculation, on the third day of treatment and at the end of treatment. Infected birds, whether untreated or receiving sulfathiazole or sulfadiazine gained weight at about the same rate (100-131% increase over starting weight after 7 days). Ducks treated with sulfanilamide gained 41% of their inoculation weight during the same period.

The feeding habits of growing ducks permit only very crude estimates of the daily consumption of the poultry mash. Ducks weighing 60-120 g at inoculation are believed to consume 25-35 g of mash daily.

Specimens for the determination of blood sulfonamide levels⁷ were removed at either 8 a. m. or 2 p. m. from all the birds of Table II. We wished to secure data on the height and uniformity of the blood levels and on the degree of conjugation; we believed that diurnal variations such as occur in mice⁸ and rats⁹ owing to habits of feeding might be found, although the illumination of the ducks was

† High standard errors are in part the result of combining two experimental groups receiving different infecting doses of parasitized blood.

⁷ Bratton, A. C., and Marshall, E. K., Jr., *J. Biol. Chem.*, 1939, **128**, 537.

⁸ Litchfield, J. T., Jr., White, H. J., and Marshall, E. K., Jr., *J. Pharm. and Exp. Ther.*, 1939, **67**, 437.

⁹ Walker, H. A., and van Dyke, H. B., *J. Pharm. and Exp. Ther.*, 1941, **71**, 138.

TABLE III.
Mean and S.E. of Level of Sulfonamides in Blood of Ducks of Table II.

Drug	% in diet	8 A.M.			2 P.M.		
		No. of detms.	Free	Total	No. of detms.	Free	Total
			mg%	mg%		mg%	mg%
Sulfanilamide	1.0	13	20.9 ± 1.6	31.9 ± 1.5	13	19.0 ± 1.9	29.9 ± 2.0
Sulfathiazole	0.65	15	4.9 ± 0.6	5.6 ± 0.7	15	5.2 ± 0.5	6.0 ± 0.5
Sulfadiazine	0.65	14	25.3 ± 1.2	27.6 ± 1.3	13	20.2 ± 1.4	21.9 ± 1.4

quite uniform because of the presence of heating lamps. The blood levels and the degree of conjugation were surprisingly uniform for a given drug (Table III). The average percentages of total drug conjugated were: sulfanilamide, 35%; sulfathiazole, 13%; and sulfadiazine, 8%. The metabolism of the 3 sulfonamides used, so far as this can be inferred from the blood levels, resembles that in mammals. The experiments suggest that in terms of the blood levels of drugs, sulfathiazole is the most effective and sulfanilamide is the least effective.

Summary. Malarial infection (*P. lophurae*) of the young Peking duck usually progresses with rapid multiplication of the parasites in the blood and death after 5-16 days¹⁰ (7-10 days in our series). If sulfonamides are administered by incorporation in the food, the multiplication of parasites is checked after a few days and the birds survive at least several weeks with relatively few or, occasionally, no parasites in the blood (sulfathiazole or sulfadiazine). Sulfanilamide appears to be less effective.

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Comparison Between Destruction of Angiotonin, Hydroxytyramine and Tyramine by Renal Extracts.

R. J. BING, M. B. ZUCKER AND W. PERKINS. (Introduced by M. I. Gregersen.)

From the Department of Physiology, College of Physicians and Surgeons, Columbia University.

According to Page and Helmer,¹ the arteriolar constriction occurring in experimental renal hypertension is caused by angiotonin,

¹⁰ Hegner, R., West, E., Ray, M., and Dobler, M., *Am. J. Hyg.*, 1941, **33**, Sec. C, 101.

¹ Page, I. H., and Helmer, O. M., *J. Exp. Med.*, 1940, **71**, 29.