Antimalarial Activity of Aureomycin Against *Plasmodium gallinaceum* in the Chick. (17506)

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During the routine testing of several antibiotics for antimalarial activity, aureomycin was found active against *Plasmodium gallinaceum* in the chick. This is the first demonstration that aureomycin has activity against any malarial parasite.

Action against erythrocytic parasites (A-1 test).(1) This series of experiments was designed to test for action against erythrocytic parasites. Week-old New Hampshire Red chicks were inoculated intravenously with 16×10^6 parasitized erythrocytes. Treatment was begun 4 to 5 hours before inoculation and continued twice daily for 4 days. On the morning of the 4th day (day of inoculation is day 0) blood smears were examined and estimations made of the number of parasitized erythrocytes per 10^4 erythrocytes. In the first test aureomycin,* dissolved in water, was administered by injection into the pectoral muscles at a dose of 80 mg/kg. This regimen resulted in a significant reduction in parasitemia (Experiment 1, Table I). The chicks gained weight normally and there was no evidence of tissue damage at the site of inoculation. In Experiments 2, 3, 4 and 5 the aureomycin was administered orally. As shown in Table I, 75 mg/kg in all instances resulted in a pronounced reduction in parasitemia. Per unit weight the drug is thus approximately one-fourth as effective as quinine.(1)

TABLE I.
Activity of Aureomycin Against Blood-Induced *Plasmodium gallinaceum* in the Chick.

Exp. No.	Dosage of aureomycin mg/kg b.i.d. for 4 days	Parasitized r.b.c. in treated birds as compared with controls (%)
1	80*	12†
2	80	39†
3	75	4†
	150	6†
4	37.5	80
	75	33†
5	18	69
	37.5	63
	75	44†
	150	16†

* Intramuscular; all other dosages oral.
† The probability of this reduction in parasitemia occurring by chance is less than one in one hundred.

Action against early exoerythrocytic parasites (A-2 test).(1) The first test for causal prophylaxis included 30 chicks, New Hampshire Reds, one week old, divided into 3 groups of 10 birds each. Each chick received one mosquito equivalent of sporozoites injected into the pectoral region.(2) Treatment was begun 4 to 5 hours before inoculation and continued twice daily for 4 days. Group A received aureomycin orally at a dosage of 75 mg/kg twice daily, group B received 150 mg/kg twice daily, and group C served as the control. Blood smears were examined daily from the 7th through the 20th day, then every other day through the 35th day after inoculation. All control birds had detectable erythrocytic parasites between the 7th and 9th day after inoculation. Seven of the 10 birds in group A developed infections, the first on the 9th and the last on the 15th day after inoculation; in 50% of the group patency was delayed for 6 days beyond that of the controls. In group B, only 5 of the 10 birds developed patent infections, the first on the 11th day and the last on the 22nd day after inoculation. Whereas 9 of the 10 control birds died of an overwhelming exoerythrocytic infection (days 9 to 15), only 5 of the 20 treated chicks died as a result of either

1. Coatney, G. R., and Sebrell, W. H., in Wiselogle, F. Y., *A Survey of Antimalarial Drugs, 1941-1945*, J. W. Edwards, Ann Arbor, Mich., 1946.

* Aureomycin was kindly supplied through the courtesy of Doctor J. M. Ruegsegger of the Lederle Laboratories Division, American Cyanamid Company.

2. Coatney, G. R., Cooper, W. C., and Trembley, H. L., *Am. J. Hyg.*, 1945, v42, 323.

exo- or endoerythrocytic infection during the 35-day observation period.

The second experiment included 45 week-old New Hampshire Red chicks, divided into 3 groups of 15 birds each. Each chick received 0.01 mosquito equivalent of sporozoites injected into the pectoral region. The treatment schedule, dosage of aureomycin for each of the 3 groups (A, B and C) and blood smear examination was exactly the same as described for the preceding experiment. In the control series, all of the chicks had detectable parasitemia 8 to 10 days after inoculation. Only 4 of the 15 chicks in group A and 2 of the 15 chicks in group B developed malaria. Whereas 11 of the 15 control chicks died of an overwhelming tissue infection, only 1 of the 30 treated chicks died during the observation period of 35 days.

Action against late exoerythrocytic forms. This experiment included 15 New Hampshire Red chicks one week old at the time of inoculation with 0.01 mosquito equivalent of sporozoites of *P. gallinaceum*. Five chicks were given aureomycin orally at 100 mg/kg twice daily for 7 days beginning at the time parasites were first detected in the blood, which in this test was 9 or 10 days after inoculation. The other 10 birds were kept as controls. On the 13th day after infection 9 of the 10 control chicks were dead and autopsies of their brains showed an overwhelming exoerythrocytic infection. (The remaining control chick survived until sacrificed 31 days after infection; no exoerythrocytic parasites were demonstrable). One of the 5 aureomycin-treated chicks died of an exoerythrocytic infection after 2 doses of the drug. The other 4 treated chicks survived until sacrificed 31 days after inoculation and no exoerythrocytic parasites were demonstrable at autopsy.

Although radical cures were not obtained, since erythrocytic parasites were demonstrable beginning 4 to 8 days after cessation of treatment, aureomycin was able to prevent death from exoerythrocytic forms, a property previously exhibited only by certain 8-aminoquinolines (pamaquine and pentaquine), chlorguanide (paludrine) and sulfadiazine.(3)

Summary. Aureomycin acted as a causal prophylactic and was therapeutically active against erythrocytic parasites and late exoerythrocytic forms of *P. gallinaceum* in the chick.

3. Greenberg, J., Trembley, H. L., and Coatney, G. R., *Am. J. Hyg.*, in press.

Received October 25, 1949. P.S.E.B.M., 1949, v72.

Aureomycin in Experimental Chesson Strain Vivax Malaria. (17507)

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Aureomycin has been given a limited trial against sporozoite-induced Chesson strain vivax malaria in white male volunteers, and the results, although still incomplete, warrant a brief progress report. The procedures used were those employed throughout our program of screening speculative antimalarial drugs.(1) Very high dosages of aureomycin were given, approaching the range found by Coatney *et al.*(2) to be effective against *Plasmodium gallinaceum* in the chick.

Protective action. Two volunteers were each given 8 g of aureomycin* per day (1 g every 3 hours) on the day of bites by 10 heavily infected *Anopheles quadrimaculatus* mosquitoes, and for 6 days thereafter. They did not develop patent malaria until 30 and 31 days after exposure, whereas 4 controls

1. Coatney, G. R., Cooper, W. C., and Ruhe, D. S., *Am. J. Hyg.*, 1948, v47, 113.

2. Coatney, G. R., Greenberg, J., Cooper, W. C., and Trembley, H. L., PROC. SOC. EXP. BIOL. AND MED., 1949, v72, 586.

* Aureomycin was furnished by courtesy of Doctor Stanton M. Hardy, Lederle Laboratories Division, American Cyanamid Company.