

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.

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### 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.

TABLE I.  
Effect of Aureomycin on 4 Primary Attacks of Chesson Strain Vivax Malaria in Volunteers Bitten by 10 Infected Mosquitoes on 30 August, 1949.

| Date,<br>Sept. | Volunteer No. 248         |                      |                        |                           | 252                  |                        |                           |                      | 253                       |                      |                        |                           | 254                  |                           |                      |                        |
|----------------|---------------------------|----------------------|------------------------|---------------------------|----------------------|------------------------|---------------------------|----------------------|---------------------------|----------------------|------------------------|---------------------------|----------------------|---------------------------|----------------------|------------------------|
|                | Parasites,<br>5000<br>WBC | Peak<br>fever,<br>°F | Aureo-<br>mycin<br>(g) | Parasites,<br>5000<br>WBC | Peak<br>fever,<br>°F | Aureo-<br>mycin<br>(g) | Parasites,<br>5000<br>WBC | Peak<br>fever,<br>°F | Parasites,<br>5000<br>WBC | Peak<br>fever,<br>°F | Aureo-<br>mycin<br>(g) | Parasites,<br>5000<br>WBC | Peak<br>fever,<br>°F | Parasites,<br>5000<br>WBC | Peak<br>fever,<br>°F | Aureo-<br>mycin<br>(g) |
| 11             | <10                       | —                    | —                      | 0                         | —                    | —                      | <10                       | —                    | 0                         | —                    | —                      | 0                         | 100.2                | 0                         | —                    | —                      |
| 12             | <10                       | 102.4                | —                      | <10                       | —                    | —                      | 0                         | —                    | 0                         | —                    | —                      | 0                         | 105.2                | 0                         | —                    | —                      |
| 13             | 200                       | 99.4                 | —                      | 100                       | 98.4                 | —                      | 230                       | 104.0                | 190                       | 105.0                | —                      | 190                       | 100.6                | 190                       | 100.6                | —                      |
| 14             | 140                       | 104.2                | 8.0                    | 130                       | 103.6                | —                      | 190                       | 105.4                | 140                       | 105.4                | 4                      | 140                       | 105.2                | 140                       | 105.2                | 4                      |
| 15             | 3010                      | 99.2                 | 8.0                    | 2310                      | 99.2                 | 8.0                    | 4420                      | 105.0                | 420                       | 105.0                | 4                      | 940                       | 102.8                | 810                       | 106.2                | 4                      |
| 16             | 1890                      | 104.0                | 7.3                    | 780                       | 104.4                | 8.0                    | 2350                      | 105.6                | 2350                      | 105.6                | 4                      | 810                       | 106.2                | 810                       | 106.2                | 4                      |
| 17             | 5430                      | 99.6                 | 6.6                    | 6520                      | 99.6                 | 6.6                    | 10,120                    | 103.0                | 10,120                    | 103.0                | 4                      | 2380                      | 103.2                | 700                       | 103.2                | 4                      |
| 18             | 4480                      | 103.2                | 0.3                    | 3350                      | 104.6                | 2.3                    | 4100                      | 105.4                | 4100                      | 105.4                | 4                      | 700                       | 106.4                | 700                       | 106.4                | 4                      |
| 19             | 400                       | 99.2                 | 1.5*                   | 890                       | 98.8                 | 1.5*                   | 50                        | 99.2                 | 50                        | 99.2                 | 1.5*                   | 40                        | 99.6                 | 40                        | 99.6                 | 1.5*                   |

\* Aureomycin was discontinued and quinine therapy instituted after the blood smears of September 19th had been made but before their examination.

bitten by the same mosquitoes had patent infections beginning 12 to 14 days after exposure. In 92 similarly infected controls of previous tests positive blood smears appeared 10 to 16 days after exposure (mean  $12.0 \pm 0.15$ ). The delay in the aureomycin-treated subjects is interpreted as indicative of antiparasmodial action although complete prophylaxis was not attained.

*Therapeutic action.* The 4 controls from the foregoing experiment were treated with aureomycin. The original plan was to give 2 patients 8 g per day for 7 days and 2 patients 4 g per day for 14 days. The higher dosage caused nausea and vomiting in patients with active malaria, so that at times administration by vein was necessary. As shown in Table I, parasite densities in the blood increased and fever continued unabated until the 5th to 6th day of treatment, when the parasite counts in all subjects dropped precipitously. Unfortunately, because of the apparent lack of response, quinine sulfate therapy was begun on September 19, after the drop in parasite counts had occurred, but before the slides had been examined. This prevents knowledge of how soon aureomycin alone might have resulted in negative blood smears. The point is academic, however, because the action against erythrocytic parasites, although significant in primary attacks, is far too slow for practical usefulness. Relapses occurred in all of the 4 subjects within 10 to 14 days after the completion of quinine therapy (2 g per day for 7 days). Aureomycin, therefore, does not eradicate the fixed-tissue stage of *P. vivax*.

*Summary.* Aureomycin, although not a causative prophylactic against the Chesson strain of *P. vivax*, delayed the appearance of malaria in volunteers for at least 2 weeks as compared with controls. When given therapeutically in high dosage, the antibiotic had a delayed action against erythrocytic parasites, too slow to be of practical value. Infections were not cured.

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