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EXPERT COMMITTEE ON MALARIA

✓ TRIALS OF CAUSAL PROPHYLAXIS OF MALARIA  
WITH PALUDRINE

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(This article, illustrated with original graphs, will appear in  
the Bulletin of the World Health Organization)

The writings of H. FAIRLEY(1) on the therapeutic value of paludrine have revived the intricate question of causal prophylaxis in malaria which, in former days, had already been extensively tried but with other anti-malaria preparations in different countries, under the auspices of the Malaria Commission of the Health Organization of the League of Nations(2). The research carried out at the Horton Study Centre under the direction of its founder, the late lamented S.P. JAMES, in particular, served to stimulate further attempts at various stations and research centres throughout Europe and India.

In the course of research work carried out at Cairns, nine strains of P. falciparum, tested for their sensitiveness to paludrine, revealed that paludrine (25-100 mgm.) administered daily, 39-131 hours after exposure to infecting bites, acts as a "causal prophylactic".

Our "causal prophylaxis" tests are based upon observation and laboratory control of patients subjected to malaria-therapy and infected with our old strain of P. falciparum 'MT 78'. The infection transmitted for therapeutic purposes was induced by means of bites by experimentally infected anopheles and by intravenous inoculation of a suspension of sporozoites. The subjects were either infected just once, or else twice or three times a week.

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(1) Trans.R. Soc. Trop. Med. Hyg. 38 311-366, 1945.  
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(2) The therapy of Malaria. IIIrd General Report of the Malaria Commission of the League of Nations, 1931/ Quart Bull. of Health Org. II, 199-308.

The treatment of Malaria. IVth General Report of the Malaria Commission of the League of Nations, 1937, Bull Health Org. IV, no. 6 897-1153.

Varying doses of paludrine were administered to our patients by different methods, with a view of determining the effect of that preparation at the various stages of the sporozoite's evolution, particularly the exo-erythrocytic. The varied doses of the medicament and the rate at which it was administered were intended to provide information as to the method possibly to be chosen for prophylactic purposes in the field.

First series. Of four subjects inoculated with one single dose of sporozoites and who received 100 mgms. of paludrine on the day of the exposure to the infection and the three following days, two developed the infection after an incubation period of 28 and 35 days respectively; one developed only parasitaemia (without paroxysm) in the course of 45 days' observation.

Two other patients inoculated and treated in the same circumstances developed no febrile attacks, nor were there parasites in the course of 57 and 66 days' observation respectively.

Of three untreated controls, one developed a slight infection after 11 days' incubation; the second an ordinary infection, while the third showed only parasitaemia after a long period of incubation (34 days).

Briefly: One dose of 100 mgms. of paludrine, administered during the first four days of incubation, appears to be insufficient to achieve in all cases causal prophylaxis. Partial results have, however, been obtained.

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In a second series of tests, the administration of 100 mgms. of paludrine was continued up until the 6th day of the incubation period, the first dose being administered on the day of infection, and the others during the five days following the infection.

Out of four patients inoculated by the same method with at least 280,000 sporozoites and treated as described above: one subject contracted the infection (A P) (1) after a 34-day incubation period; a second only parasitaemia after 35 days' incubation. Two others developed neither febrile attacks nor parasites during an observation period of 23 and 156 days respectively.

Briefly: the results achieved, similar to those in the preceding series, prove that the dosage was insufficient to achieve lasting causal prophylaxis, though partial prophylaxis was obtained.

In a third series of tests, the following technique was applied; a. Infection by inoculation of sporozoites, repeated over a period of 4 weeks; b. Administration of 100 mgms. paludrine once weekly during the period of infection and during the two weeks following the final inoculation with sporozoites.

(1) Editor's Note: A: clinical attack; P: presence of parasites in the blood on microscopic examination. The authors employ the symbols A<sub>0</sub> and P<sub>0</sub> in cases where these are negative, but we have preferred here to use the symbols A<sub>-</sub> P<sub>-</sub>.

The five subjects inoculated and treated by this method reacted as follows:

1. A+ P+ nineteen days after the last inoculation of sporozoites and seven days after the last dose of 100 mgms. of paludrine.

2. A+ P+ 31 days after the final inoculation and 18 days after the final dose of paludrine. This delayed incubation may be due to a concurrent attack of relapsing fever which appeared during the 5th, 6th and 7th weeks of the test and was treated with arsenicals.

3. A+ P+ 17 days after the final inoculation with sporozoites and six days after the final dose of paludrine.

4. A+ P+ 18 days after the final inoculation of sporozoites and six days after the final dose of paludrine.

5. A+ P+ 14 days after the final inoculation with sporozoites and 9 days after the final dose of paludrine.

Two controls were inoculated with sporozoites and not treated. They showed infection A+ P+ after an incubation period of 12 and 14 days respectively.

Briefly: (1) no causal prophylaxis: (2) suppressive effects only during the six weeks' period when paludrine was administered: the disease set in immediately this ceased.

In the graphs which will appear in the printed texts, the relationship between the days of inoculation with sporozoites and those when the medicament was administered can be pursued through the case history of each subject.

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In a fourth series of tests, 5 subjects were repeatedly inoculated with P. falciparum sporozoites over a period of 4 weeks (generally two per week). A prophylactic dose of 300 mgms. of paludrine was administered every week while the inoculations lasted; and continued for a further two weeks after the final inoculations with sporozoites.

None of the five patients developed a febrile attack or parasites during the observation period, as follows:

1. A- P- 23 days after the final inoculation and 10 days after the final dose of paludrine.
2. A- P- 25 days after the final inoculation and 20 days after the final dose of paludrine.
3. A- P- seven days after the final inoculation, followed at a brief interval by the final dose of paludrine.
4. A- P- after a time-lag as above.
5. A- P- after a time-lag as in the two preceding cases. Four

control subjects inoculated with sporozoites and not treated, developed the disease (fever and parasites) after an incubation period of 15, 12, 13 and 14 days respectively.

Briefly: Over the periods noted during our observations, a weekly dose of 300 mgms. of paludrine acts as a causal prophylactic despite repeated inoculations with P. falciparum (1-3 weekly), provided that the administration of paludrine is continued for at least two weeks after the final inoculation with sporozoites.