# The biological suppression of malaria: an ecological and nutritional interrelationship of a host and two parasites[1]

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ABSTRACT The interrelationship of malaria and severe ascariasis was studied in Anjouan children with a previously described syndrome of enlarged parotids, localized forehead edema, heavy infestation with *Ascaris lumbricoides*, and unusual freedom from malaria. After treatment of 37 such children with the ascaricide piperazine, 35 had resolution of parotid enlargement and forehead edema, but 19 developed attacks of malaria. Children treated with placebo had neither resolution of clinical findings nor attacks of malaria. We propose that suppression of the malaria in these children is a nutritional consequence of severe ascariasis and may represent an ecological balance for optimum co-survival of the host and the two parasites. *Am. J. Clin. Nutr.* 31: 1363–1366, 1978.

The suppression of one infection by another may be more than fortuitous and may represent an ecological balance for optimum co-survival of the host and the two pathogenic organisms. This assumes the basic tenet that an invading organism gains little advantage from killing the host and ideally prefers to live in as near a symbiotic relationship with it as possible. *Plasmodium falciparum,* for example, which invades red cells of all ages would be expected to cause greater mortality than it does in endemic areas were it not for mitigating circumstances such as sickle cell disease, glucose 6-phosphate dehydrogenase deficiency or famine (1). A factor not previously considered as mitigating this disease is the co-existent infection or infestation with another organism. An opportunity to explore the interrelationships of malaria and ascariasis in single hosts arose on the island of Anjouan, situated in the Comorro archipelago between Madagascar and Mozambique. There, we observed and subsequently reported (2) that children heavily infested with *Ascaris lumbricoides* and exhibiting bilateral painless enlargement of the parotid glands with localized edema of the forehead were remarkably free of attacks of malaria despite the high attack rate on the island. Children without these findings and with minimal ascariasis appeared to be ordinarily susceptible to plasmodial infections (2). This type of parotid enlargement which has been generally attributed to an unidentified nutritional deficiency (3) has been observed to have a high association with intestinal helminthiasis in rural East African children (4). We argued, therefore, that severe ascariasis might either deprive the plasmodium of a nutrient necessay for its growth or might stimulate host defense against the plasmodium or the infected red cells. To follow up these hypotheses, we decided to observe the effects of treatment of ascariasis on the attack rate of malaria in these children and compare the results with the effects of a placebo.

## Methods

In our previous study, we observed parotid enlargement and forehead edema in 42% of 632 children examined in four Anjouan villages. Their ages ranged from 2 to 14 and their male to female ration was 3.6:1 (2). For the present study, four groups of children with similar age and sex distribution were chosen from two closely

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neighboring hill villages. Group I consisted of 27 boys and 10 girls, ages 2 to 14, who had no recent history of malarial attacks, no splenomegaly and no malarial parasites visible in thick and thin smears of blood stained with Giemsa by the method of Shute and Maryon (5) but who had severe ascariasis. Evidence for the latter included enlarged abdomens, a history of visible worms in the stool and more than 50,000 ova per gram of feces as determined by the method of Stoll and Hausheer (5). This density of ova was arbitrarily selected as indicative of severe infestation and seemed to relate well to the weight of worms expelled after treatment with piperazine. The peripheral blood smears of members of this and the following groups were also examined for the presence and degree of eosinophilia at the initial examination and during any attacks of fever or clinical malaria. The children were then treated with the ascaricide anhydrous piperazine phosphate, 75 mg per kilogram daily for 2 days.

Group II consisted of 26 boys and nine girls of ages 2 to 13 with similar findings who were treated with placebo tablets composed of aluminum hydroxide and magnesium trisilicate. Group III children were 17 boys and six girls ages 3 to 13 without parotid enlargement and forehead edema, without enlarged abdomens, without a history of visible worms in the stool and less than 5000 ova per gram of feces. Three had splenomegaly, but no plasmodia could be found in their blood smears. They were treated with piperazine phosphate in the same dosage as group I. Group IV had 13 boys and four girls, ages 2 to 12, with findings similar to group III. Two had splenomegaly but none had evidence of parasitization of red cells. They were treated with placebo tablets. The number of children treated with piperazine was limited by the available supplies of the drug.

After dosing, each child was examined at intervals of 48 hr for 20 days. Stools were collected in plastic basins daily for a week after dosing and the worms separated by washing the fecal material through a sieve. The worms were weighed wet and the mean weight expelled per child was calculated for each group. In the event of an episode of fever or the development of splenomegaly, thick and thin blood smears were taken as described and examined for malarial parasites and the degree of peripheral eosinophilia by an independent observer without knowledge of the clinical course. Clinical attacks of malaria were assumed only when an episode of fever was accompanied by a smear that was positive for malaria. All malarial attacks were treated promptly with antimalarials.

## Results

The results are recorded in Tables 1 and 2. Attacks of malaria occurred in 19 children of group I (54%) who passed a mean weight of 274 g of worms per person but experienced no change in eosinophil counts. *Plasmodium vivax* was the cause in seven and *P. falciparum* in 12. The peak incidence of five cases occurred 9 days after dosing, but the first case appeared on the 6th day and the last on the 14th day. Parotid enlargement regressed in

TABLE 1
Clinical characteristics and response to treatment of groups

| Group | N | Clinical findings | Treatment | Malarial attacks | Parotid regression | Edema regression |
|---|---|---|---|---|---|---|
| I | 37 | Parotids enlarged forehead edema. No splenomegaly heavy ascariasis.[a] Malaria smear negative. | Piperazine | 19 (54%) | 35 (97%) | 37 (100%) |
| II | 35 | Parotids enlarged forehead edema. No splenomegaly heavy ascariasis[a] Malaria smear negative. | Placebo | 0 | 0 | 0 |
| III | 23 | Parotids normal no forehead edema. Splenomegaly (3) minimal ascariasis[b] Malaria smear negative. | Piperazine | 1 (4%) | | |
| IV | 17 | Parotids normal no forehead edema. Splenomegaly (2) minimal ascariasis. Malaria smear Negative. | Placebo | 2 (8%) | | |

[a] >50,000 ova per gram of feces. [b] <5,000 ova per gram of feces.

TABLE 2
Effect of treatment with piperazine on worms and eosinophilia

| Group | Mean eosinophil count before treatment | Mean total weight of worms expelled | No. of malarial attacks | Mean eosinophil count with attack of malaria |
|---|---|---|---|---|
| | % | g | | % |
| I | 5.4 | 274 | 19 | 5.7 |
| II | 5.3 | 9 | 0 | |
| III | 4.9 | 20 | 1 | 5.0 |
| IV | 4.7 | 0 | 2 | 4.6 |

97% and forehead edema in all the children in group I during the period of observation. Neither malarial attacks nor regression of parotid enlargement and forehead edema occurred in children of group II who passed a mean weight of 9 g of worms per person. One episode of falciparum malaria occurred 1 day after dosing in group III who passed a mean weight per person of 20 g of worms, confirming their light infestation. Two episodes of vivax malaria occurred in group IV on the 4th and 18th days, respectively.

## Discussion

Treatment of severe ascariasis, while associated with resolution of parotid enlargement and forehead edema was accompanied by a striking occurrence of malarial attacks in children of group I. We believe these attacks represented recrudescences of preexisting quiescent malaria rather than new attacks for the following reasons: a spontaneous attack rate of 54% from new malaria would be unlikely in this group when the attack rate from recrudescence and/or new attacks in untreated controls was only 8%. This difference is significant to a $P$ value of less than 0.001 using the standard error of the differences of two percentages as the statistical method of comparison. Furthermore, the maximum spontaneous attack rate in children from the island of Grande Comore as reported in our previous observation (2) never exceeded 23% in the absence of ascariasis. Even mild ascariasis on Anjouan may have reduced the malarial attack rate below the 23% of their counterparts on Grande Comore. Finally the majority of malarial attacks in group I occurred within 10 days of dosage with piperazine, an unusually short incubation period for newly acquired parasites.

The attack rate of malaria in group III after treatment with piperazine presumably was low because there was no marked suppression of existing malaria to start with. The three cases of clinical malaria occurring in groups III and IV most likely reflected the spontaneous clinical attack rate of children chronically infected with malaria but not suffering from the syndrome of parotid enlargement and forehead edema. If the latter was a nutritional abnormality, then it was reasonable to suspect that it might have been responsible for the apparent suppression of malaria and that its correction by eradication of the ascariasis was responsible for the high incidence of attacks in children of group I.

It is tempting to suggest that the ascaris in large enough numbers, deprives the plasmodium of a nutrient essential for its growth, either through consumption by the worm itself or more probably by interference with host absorption; by doing so it may permit optimal co-survival of the host and the two parasites. Eradication of the worm may correct the defect, allowing a sudden flush of nutrients to stimulate growth and division of the dormant plasmodia and produce clinical attacks of malaria.

Since the ascaris produces antitryptic materials (7) to prevent its own destruction in the host's gut, absorption of specific nutrients by the host might be hindered by the same process or by injury of the mucosal cells (8). For example, prevention by the worm of host absorption of paraaminobenzoic acid, a known requirement of some plasmodia, might interfere with plasmodial division and suppress attacks of malaria (9). Other theories, however, cannot be disregarded. Host defense against the plasmodium might be stimulated by chronic protein insufficiency that in turn may be a consequence of malabsorption induced by severe ascariasis (10). Cooper et al. (11) have shown that chronic protein insufficiency of inbred strains of mice may lead to increased vigor of phagocytosis for *Listeria monocytogenes,* another intracellular organism. Eosinophilia of the host which may result from ascariasis might act in concert with specific antibody to destroy the plasmodium by the vigorous production of superoxide (12). The last theory seems unlikely to account for the phenomenon on Anjouan as the eosinophilia was rarely

marked and changed little with treatment. Excretions or secretions of the Ascaris into the gut might be absorbed and exert an antibiotic effect on the malarial parasite, a possibility we were unable to explore at the time. Whatever the mechanism, the clinical attacks of malaria coincided with the resolution of parotid enlargement and forehead edema.

Our observations on the effect of piperazine support the hypothesis that severe ascariasis, although often debilitating but rarely fatal to the host, may prevent the more serious complications of malaria by nutritional deprivation and in doing so may permit optimal ecological balance for co-survival of the host and the two parasites.

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