RESEARCH NOTE

Resistance to Infection/ Reinfection by *Schistosoma mansoni* is not Augmented by Three Treatments with 45 Days Intervals

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Immuno-epidemiologic studies of schistosomiasis report that resistance to reinfection after chemotherapy develops over years of exposure to infection, and thus correlates with age. Responses to schistosome egg antigens may stimulate production of blocking antibodies (AE Butterworth et al. 1987 *Parasitology 94*: 281-300, C Auriault et al. 1990 *J Clin Microbiol 28*: 1918-1924, P Hagan et al. 1991 *Nature 349*: 243-245) that interfere with protective antibody binding, and this may decrease with chronicity of infection and/or continual exposure to schistosome antigens. Also, in murine models, irradiated cercariae induce high levels of resistance to challenge infections with non-attenuated cercariae (SR Smithers 1962, Stimulation of acquired resistance to schistosomiasis and fasciolasis, p. 302-327. In S Cohen & EM Sadun (eds), *Immunology of Parasitic Infections*, Oxford, Blackwell Scientific Publications, England, HF Hsu et al. 1962 *Nature 194*: 98) and resistance is also induced when mice are infected and cured of their nascent infections within 48 hr after exposure (AP Mountford et al. 1989 *J Immunol 143*: 989-995). Therefore, we hypothesized that different treatment regimens for persons with *Schistosoma mansoni* infection living in an area of active transmission might induce different degrees of resistance to naturally occurring reinfection. In Patrimônio Velho (about 400 inhabitants), Minas Gerais, Brazil, volunteers were examined for *S. mansoni* infection by fecal examinations (N Katz et al. 1972 *Rev Inst Med Trop São Paulo 14*: 397-400) and the persons were randomly divided into two groups: group 1, treated once with oxamniquine (15 mg/kg for adults, 20 mg/kg for children <14 years); group 2, treated three times, each time with the same dose of oxamniquine, each treatment dose separated by 45 day intervals (i.e., 90 days between first and third treatments). All persons were then parasitologically followed at three months, one year and two years after the times of their initial (group 2) or only (group 1) treatment to observe reinfection in the groups. Thus the first follow-up stool examinations occurred three months after treatment for group 1 and one week after the last (3rd) treatment given to group 2. Two years and three months after the initial treatments all patients were re-treated if they had a positive stool examination. Our hypothesis was if patients in group 2 were reinfected during the two 45 day periods between treatments, these infections would be aborted (prior to egg production), perhaps boosting their immune responses to schistosomula or young worms, leading to augmentation of acquired immunity to reinfections.

Fecal examination three months after initial treatment (Table) indicated that only 2-3% of all patients remained infected or became reinfected by this time. We did not do water contact studies of these persons. Nevertheless, the data for group 1 (Table) are consistent with previous findings that reinfection rates following single treatment and natural re-exposure are most often related to the age of the patient (Hagan *loc. cit.*) The mean age of those who became reinfected was always less than that of the total participants ($p<0.001$ for group 1 at each time points). Curiously, this difference was not seen for group 2 (Table). Comparable significant decreases in the mean intensities of infection (estimated as eggs per gram of feces) were observed in those reinfected in both groups ($p<0.002$, group 1; $p<0.02$, group 2). The major

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observation of this study is that reinfection rates were comparable in both treatment groups (Table), although these rates were related to age in only group 1 it can be seen that in this study area the rates of reinfection (in both groups) were rather low (19% over 15 months, group 1 *vs* 17% over 12 months, group 2; and 26% over 27 months, group 1 *vs* 29% over 24 months, group 2). It was seen that, the incidence rates for the six months after initial treatment, the time expected to have been most effected by our regimen manipulations, probably could not be expected to be more than 10% for susceptible persons.

Over the time period selected, with the levels of reinfection seen, the regimens adopted did not differentially affect the levels of resistance to reinfection. Either our hypothesis that multiple aborted infections would boost resistance to reinfection is not true, or it was not adequately tested because our patients did not experience sufficient cercarial exposure to achieve this end. We conclude that multiple drug treatment during a brief period of probable exposure to reinfection does not induce differential levels of resistance to reinfection. It is puzzling that the expected age differential in those who are resistant *vs*. susceptible was not observed following the multiple treatment regimen. The Table appears to show that this occurred because treatment three times over 90 days both lowered the mean age of those resistant, and raised the mean age of those susceptible. We have no explanation for why this apparently occurred.

Retrospectively, given the number of persons in this study, a significant difference between treatment groups could have been observed only if the annual rate of reinfection in group 2 was at least 9% (JL Fleiss 1981, *Statistical Methods for Rates and Proportions*, 2nd ed., Wiley, New York, 38 pp.). These observations may prove useful in subsequent study designs to evaluate resistance to reinfection following treatment, exposure to vaccine candidates, and subsequent natural exposure.

TABLE

Effect of chemotherapy on the infection/reinfection rates and egg output of patients from endemic area for schistosomiasis

Treatment groups	Time of fecal exam	Mean age of participants	Mean age of infected/reinfected[a]	Eggs/ gram	Prevalence (%)
1	B.T.	30.1± 20.9 (161)	28.5± 20.3 (95)	170± 290	59
2	B.T.	25.9± 18.9 (124)	24.8± 18.0 (74)	211± 298	60
1	3 mo. A.T.	30.7± 20.5 (126)	23.7± 10.1 (04)	60± 34	03
2	3 mo. and 1 wk.	26.4± 20.1 (105)	30.5± 12.0 (02)	66± 76	02
1	15 mo. A.T.	30.0± 21.2 (108)	17.9± 13.1 (21)	56± 88	19
2	15 mo. A.T.	23.6± 17.4 (88)	19.5± 15.0 (15)	49± 47	17
1	30 mo. A.T.	30.3± 20.6 (108)	17.8± 13.8 (28)	45± 70	26
2	30 mo. A.T.	23.3± 17.7 (86)	18.5± 5.5 (25)	41± 62	29

Groups 1 and 2: 1 and 3 treatments, respectively. B.T.: before treatment; A.T.: after the first treatment; *a*: infected B.T.; reinfected A.T.; ( ) no. of patients.