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IMMUNOLOGICAL PROFILES OF PATIENTS FROM ENDEMIC AREAS INFECTED WITH *SCHISTOSOMA MANSONI*

GIOVANNI GAZZINELLI; IRAMAYA R. C. VIANA; LILIAN M. G. BAHIA-OLIVEIRA; ALDA MARIA S. SILVEIRA; CLAUDIA CARVALHO QUEIROZ; OMAR DOS SANTOS CARVALHO; CRISTIANO L. MASSARA; LUCIA A. O. FRAGA; DANIEL G. COLLEY* & RODRIGO CORREA-OLIVEIRA

Centro de Pesquisas René Rachou – FIOCRUZ, Caixa Postal 1743, 30161-970 Belo Horizonte, MG, Brasil
*Veterans Administration Medical Center and Vanderbilt University School of Medicine, Nashville, Tennessee 37203, USA

Crude extracts of eggs (SEA) adult worms (SWAP) or cercariae (Cerc) have been used to stimulate Peripheral Blood Mononuclear cells (PBMC) and have provided rather distinct profiles of responses in different types of patients. In general it is clear that patients with early infections respond strongly to SEA while response to SWAP are develop more slowly. As infection progresses into the more chronic phases, a general pattern is seen which leads to lower anti-SEA proliferative responses in the face of higher responses to SWAP and variable anti-cerc responsiveness. Cured not re-exposed patients express very high levels of anti-SEA proliferation. It has recently been seen that those individuals who live in endemic areas and have continued water contact, but are reapeatedly stool-negative (who are presumed to have self-cured or be putatively resistant; endemic normals) are strongly responsive to antigenic extracts, particularly to SEA. Furthermore, our results show that endemic normal individuals have significantly higher IFN gamma production upon PBMC stimulation with schistosome antigens than infected individuals.

With the emergence of more studies it is becoming apparent that both the intensity and the prevalence of a given area may influence or shape the general responsiveness of the population under study.

Key words: schistosomiasis mansoni – clinical immunology

Infection with the helminth *Schistosoma mansoni* induces humoral and T cell mediated responses and leads to: (a) a delayed hypersensitivity that results in granulomatous inflammatory disease around the parasite eggs; (b) regulation of these responses resulting in a reduction in this anti-egg inflammatory disease and a relative control of the progression of the severity of the disease; (c) the gradual development of a resistance to reinfection, which protects the host against subsequent infestation by the parasite.

The immunological profile of each individual living in an endemic area is the result of the intensity of each one of these responses which is apparently determined by the genetic background and idiotypic repertoires of the patient, and is associated with multiple external factors such as age, water contact, worm load, duration of the infection, multiple infections with other helminths, and previous treatment. As a consequence the infected population in endemic areas is heterogeneous and consists of several distinct clinical groups (Table). Most of the patients develop only chronic, relatively asymptomatic infections and are included in the intestinal (INT) group. About 15% of the infected population progress to the hepatointestinal (HI) form and fewer than 5% to the more severe form of the disease, hepatosplenism (HS). This most severe HS form is characterized by portal hypertension, collateral circulation, esophageal varices, ascites and hematemesis. A fourth group of individuals (Normal endemics – NE) who live

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TABLE

Distinct clinical groups of patients living in endemic areas for schistosomiasis mansoni

Clinical groups	Description
Intestinal (INT)	Infected patients with/without mild symptoms
Hepatointestinal (HI)	Infected patients with palpable liver
Hepatosplenic (HS)	Infected patients with hepato-splenomegaly
Normal endemics (NE)	Non-infected patients exposed to water contaminated with cercariae
Susceptible (SC)	Reinfected after treatment
Resistant (RS)	non-reinfected after treatment

in endemic areas and have reasonable levels of exposure to water contaminated with cercariae, yet remain persistently stool negative, are considered putatively resistant. After treatment of the infected population, two further groups may be identified: one is composed of patients who are promptly reinfected after treatment and are considered to be susceptible (SC); the other, a putative resistant group (RS), is composed of individuals who live in the same conditions, and have comparable water contact as the SC group, but who remain stool negative for at least two years after treatment.

Many reports have been published concerning the morbidity and resistance to reinfection based on the study of INT, HI, HS, SC and RS clinical groups (Colley, 1987; Butterworth et al., 1989).

However, the group of NE, or exposed uninfected individuals who are identified after repeated negative stool examinations, has been over-looked or excluded from these studies.

In our present work special emphasis is given to the cellular and humoral responses of NE individuals in comparison with patients of the INT group from three endemic areas where we are currently carrying on studies: (a) Divino das Traíras, a small community with 800 people located 380 km northeast of Belo Horizonte, district of Engenheiro Caldas, state of Minas Gerais ; (b) Córrego do Bernardo, a community with about 2.000 people, located in the district of Governador Valadares, 350 km from Belo Horizonte, state of Minas Gerais; and, (c) Siqueira, with 250 people located only 25 km from the metropolitan area of Belo Horizonte.

The prevalence and intensity of infection (epg) of the volunteers of these three areas are presented in Figs 1, 2.

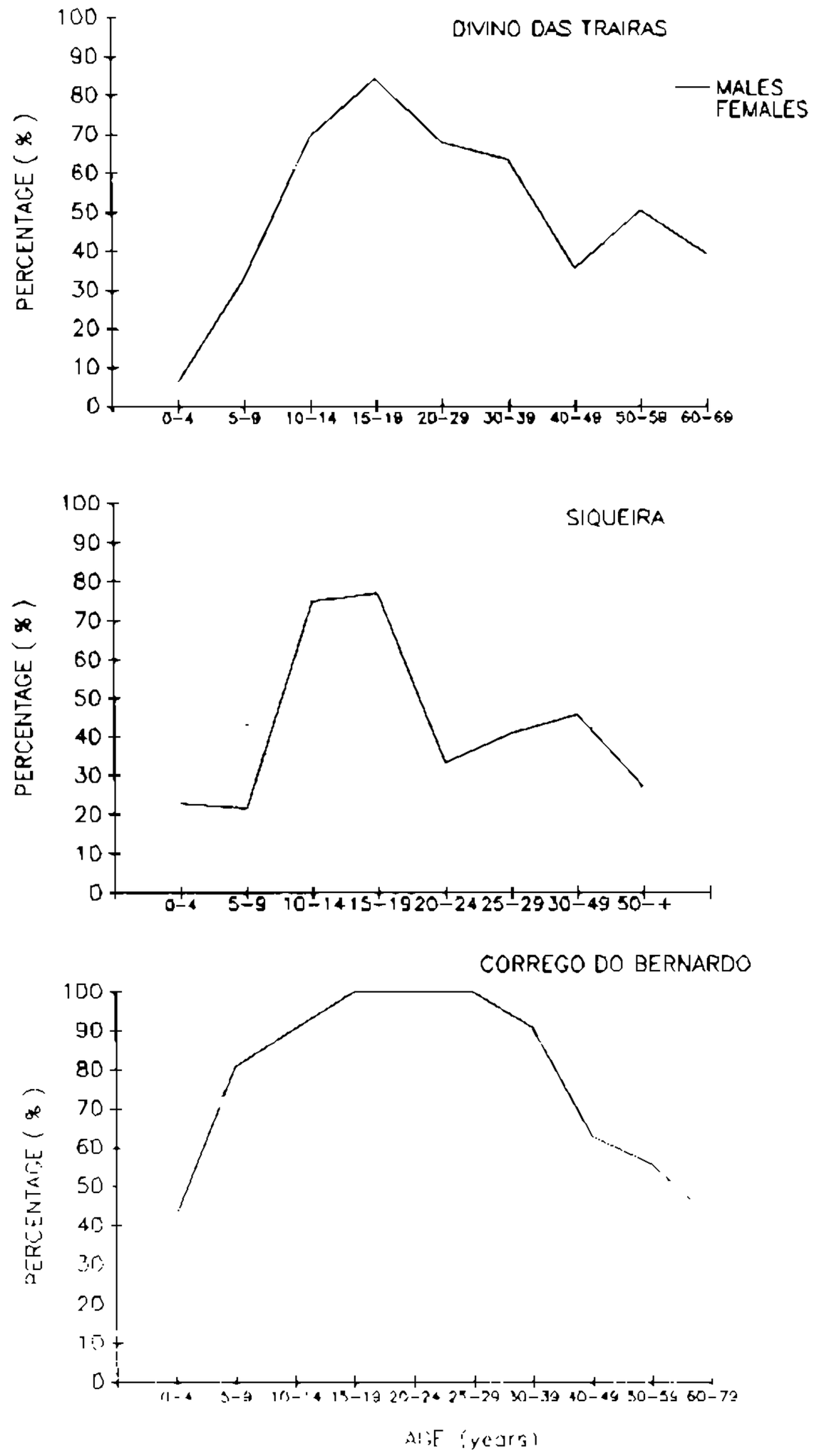

Fig. 1: prevalence of *Schistosoma mansoni* infection according to age and sex.

CELLULAR RESPONSE OF INT AND NE GROUPS TO SCHISTOSOME ANTIGENS

A typical Peripheral Blood Mononuclear Cell (PBMN) response of chronic intestinal patients is characterized by a lower anti-SEA response in contrast to higher anti-SWAP and a variable anti-CERC responsiveness (Colley et al., 1977). This general pattern of responsiveness was presented by the patients of Siqueira where the intensity of infection was very low. In Divino das Traíras and Córrego do Bernardo, however, a significantly higher level of PBMC response to SEA was observed, suggesting that both the intensity and prevalence of a given area may influence or shape the general responsiveness of the population under study.

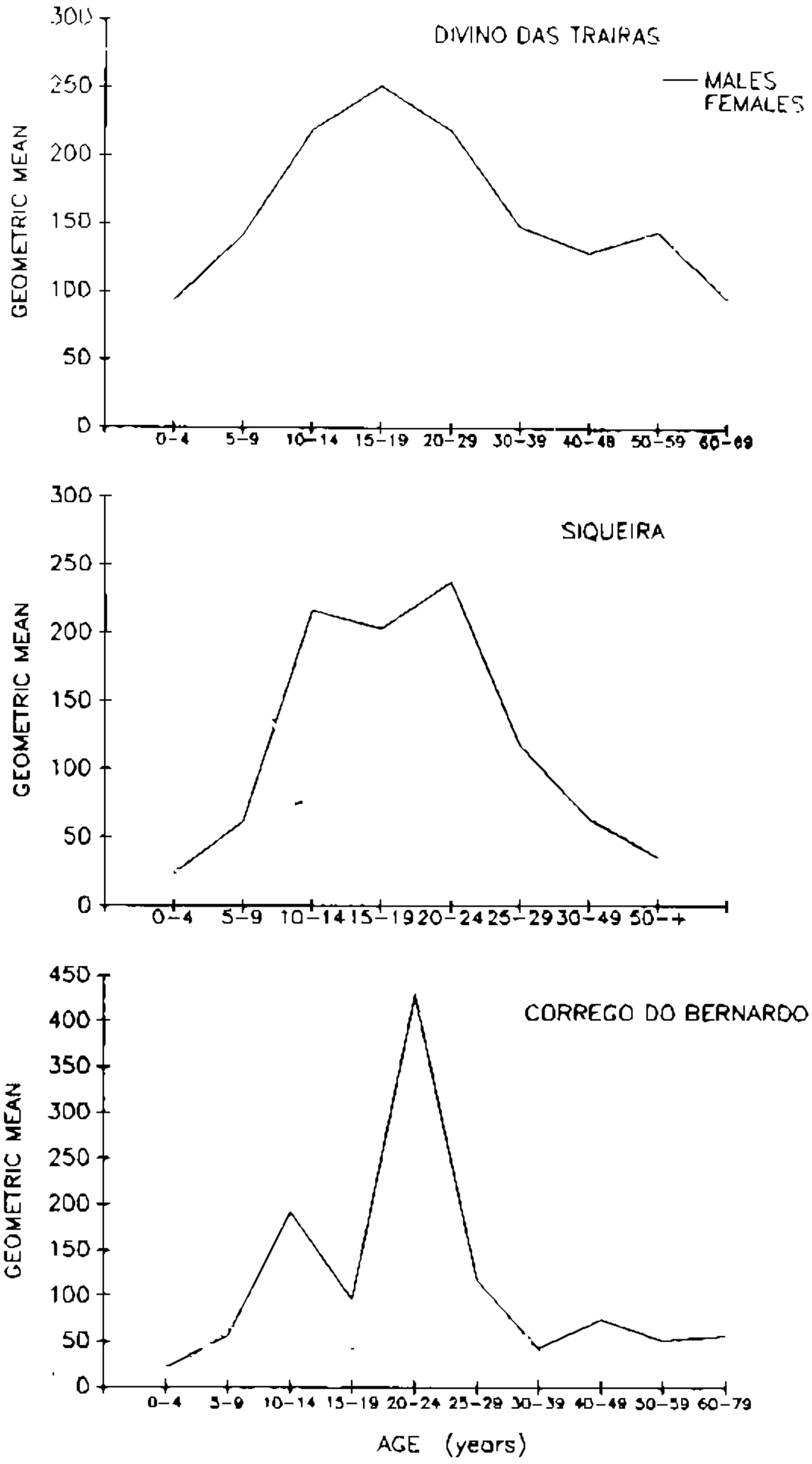

Fig. 2: intensity of *Schistosoma mansoni* infection according to age and sex (eggs/g).

On the other hand, PBMC of NE individuals from all three areas under study showed very high proliferative responses, particularly to SEA antigens. In this respect their patterns of responsiveness resemble those shown by former patients e.g. patients who had been treated at least five years ago and was not re-exposed to the threat of schistosome infection (Colley et al., 1986; Gazzinelli et al., 1987).

The PBMC response of INT and NE was also compared by measuring the Interferon (IFN) gamma production in supernatant fluids of antigen-stimulated cultures. Confirming the data of Zwingenberger et al. (1989) and Bahia-Oliveira et al. (1991) no significant IFN gamma was detected in antigen-stimulated PBMC cultures of infected patients. In contrast, high levels of IFN gamma were produced by PBMC of most of NE patients (Viana et al., manuscript in preparation).

COMPARISON OF SPECIFIC ANTIBODIES PRODUCTION BETWEEN INT AND NE CLINICAL GROUPS

The antigenic complexity of *S. mansoni* stages in human host elicit multiple antibody responses during the course of chronic schistosomiasis (Ottesen et al., 1981; Khalife et al., 1986). In general INT patients exhibit higher levels of IgM and IgG anti-SEA, anti-SWAP and anti-CERC antibodies than NE individuals (Vianna et al.; Bahia-Oliveira et al., works in progress). On the other hand, the NE group, while indistinguishable from infected subjects in both anti-SWAP and anti-Glutathione-S-transferase (GST) responses, had significantly elevated antibody levels to paramyosin (Correa-Oliveira et al., 1989).

Based on the study of a community in the Gambia endemic for *S. haematobium*, it was claimed that the gradual development of immunity to schistosome infection may in part depend on pathways involving IgE/IgG4 ratios, with the IgE mediating (or correlating with) resistance, and high levels of IgG4 antibodies blocking these mechanisms in younger patients (Hagan et al., 1991). Preliminar results on anti-schistosome specific antibody assays of these isotypes in several age-groups of INT patients and in NE individuals from Siqueira showed, in both groups, high levels of anti-SEA IgG4 and anti-CERC IgE. The level of IgG4 against SEA was higher in infected children, dropping slightly in the subsequent age-groups reaching its lower value in the NE group. On the other hand the level of anti-CERC IgE was slightly higher in the NE group as compared with the group of infected children. These results, however, were not conclusive and further analysis will be necessary in order to establish if the ration IgG4/IgE is a correlative factor in susceptibility/resistence in *S. mansoni* infections in these populations.

In conclusion, we hypothesize that NE are a group of resistant individuals and therefore may have differences in their immune response which play important roles in the prevention and/or elimination of the infection. Based on the same principle, the immune responses of the group of individuals that do not get reinfected after treatment are being compared with those observed for NE (Viana et al., work in progress). This comparison is fundamental for the understanding of the mechanisms involved in the development of resistance to

infection. So far, analysis of the immune responses of these individuals has shown that while infected patients, as well as NE, show significant proliferative responses to the various antigens, only the group of NE show significant IFN gamma production upon antigenic stimulation of PBMC. Detailed analysis of specific antibody responses to *S. mansoni* antigens is in progress in these groups in order to establish their contribution to the mechanism involved in the development of resistance to infection.

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