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# PROCEEDINGS, OF THE ROUND-TABLE ON IMMUNOLOGY AND IMMUNOPATHOLOGY

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Although several other sections of the International Symposium on Malaria included papers which dealt in some way with immunological aspects of malaria, this round-table focused on the presentations concerning the "host's side" of the immune response against malaria parasites. Special emphasis was given to the analysis of the anti-parasite immune response, their mechanisms and genetic control, as well as some of its immuno pathological aspects. Talks were given by Dr. Carlos Eduardo Tosta from the Malaria Laboratory-Section of Tropical Medicine and Nutrition of the Universidade de Brasília; Dr. Paul-Henri Lambert from the Department of Pathology of the University of Geneva; Dr. Masamichi Aikawa from the Institute of Pathology at the Case Western Reserve University and Dr. Claudio Tadeu Daniel Ribeiro from the Department of Immunology of the Fundação Oswaldo Cruz. The presentations by Dr. Pierre Druilhe from the Department of Parasitology and Tropical Medicine of the Hôpital Salpétrière, who unfortunately did not send the papers concerning his communications for publication in this issue, will also be analyzed here.

The paper by Tosta & Saboia Moura reported a sero epidemiological survey performed in northwestern Brazil to study the prevalence of two types of anti-plasmodial antibodies involved in protection. The first one is directed against the tetrapeptide $R_{32}$ tet $R_{32}$ which concentrates most of the immunogenicity of the circumsporozoite protein of *P. falciparum* and is considered a possible candidate for a malaria vaccine. This peptide has been used to evaluate the level of anti-sporozoite immunity in endemic areas. The other anti-malarial antibody studied was assessed by a functional test of inhibition of *in vitro* growth of erythrocytic forms of *P. falciparum* that have been employed to study anti-blood stages protective immunity. Although the prevalence and dynamics of acquisition of anti-sporozoite and of anti-blood stages *P. falciparum* antibodies were different, it was apparent that the development of protective immunity by non immune individuals migrating to an endemic area may require several years.

In view of the perspectives of the availability of a malaria vaccine in a not too remote future, the importance of gathering baseline data on the degree of anti-sporozoite and anti-blood stage immunities cannot be underscored. Moreover, in populations like those of the northwestern Brazil, constituted mainly by migrant people from non endemic areas, this kind of study will also help in the definition of the priorities in terms of target groups for application of a future vaccine.

One mechanism of cooperation between cells and antibodies against *P. falciparum* erythrocytic stages was described by Druilhe, Funel & Khusmith. They showed that merozoite specific cytophilic IgG could increase the uptake of merozoites (but not of infected erythrocytes) by normal human monocytes. The levels of antibodies promoting merozoite phagocytosis (APMP) increase slowly and gradually with exposure to malaria (production of high levels requiring at least 15 years) but if exposure is descontinued APMP levels decrease abruptly. The effect of cells and antibodies on the *in vitro P. falciparum* growth was evaluated. A non specific inhibitory effect (i.e. in absence of Ab) was observed using polymorphonuclears (PMN), monocytes (MN), lymphocytes, platelets and adherent spleen and liver cells from healthy subjects when these cells were present at high concentration (cell/RBC ratios of 1/5 to 1/20). However, only the monocyte – IgG cooperation was found to be able to induce, at low ratios of cell/RBC (1/50-1/200), a specific reduction of *in vitro* parasite growth.

The paper by Daniel Ribeiro and coworkers demonstrated at a cellular level in human malaria the existence of the phenomenon of Polyclonal B lymphocyte activation (PBA) proposed in 1974 by Greenwood to explain the diversity of the immune response in malaria and well documented in rodent since 1978 by different groups of authors. In this paper, the correlation between the PBA and the RBC sensitization by immunoglobulins (G & M) and complement, as well as the relevance of these two phenomena in the development of malaria associated anaemia were analyzed. The conclusion of their study is that, although the sensitization of erythrocytes by IgG can be involved in the pathogenesis of the malaria anaemia it does not seem to be a direct consequence of the malaria associated PBA phenomenon reflected by an important increase in the number of cells spontaneously secreting IgG and IgM.

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Aikawa, Maung Oo & Igarashi studied, by light and electron microscope as well as by immunological methods the brain of patients who died of cerebral malaria (CM). They reported the presence of electron dense knobs which protrude from the membrane of infected erythrocytes resulting in the sequestration of RBC and their blockage in capillary lumen. These authors drewn attention to the relevance of works aiming the development of a vaccine to knob proteins that could delay the development of capilary blockage and prevent CM. Immunoperoxidase studies revealed the presence of *P. falciparum* antigens and IgG deposits in the capillary basement membrane and suggested the participation of immune mechanisms in the damage of the cerebral capillary.

The work presented by Druilhe, Camacho & Calvet also concerned the participation of the immune response in the pathogenesis of cerebral malaria (CM). It was shown that serum IgG from patients suffering from CM reacted with Purkinje (PUN) dentrites and could inhibit their *in vitro* development. Sera from individuals with uncomplicated malaria (even when containing high levels of anti-malaria antibodies) or from normal controls did not show the same property. This activity was related to the presence in the sera of CM patients of a IgG class Ab that was found by indirect immunofluorescence to react with apical dentrites of human and animal pyramidal and purkinje cells. The presence of the IgG fraction of CM patient sera induced in cultured kitten PUN cells several effects: a three fold reduction of the size of the dentritic array (without reduction of the spine ratio and of axonal development) and an increased electrical activity consisting of a higher frequency of spike discharges. In contrast, no effect was observed in the presence of the non IgG fraction of the same sera and of IgG from control sera. It was suggested that protection against the major complication of *P. falciparum* malaria may correspond to the repression of an abnormal stimulation of auto-reactive cells (ARC).

Since the "abnormal stimulation" of these ARC, can arise as a consequence of an antigen-sharing between *P. falciparum* itself and purkinje cells this repression can be a very difficult task since it would implicate in the suppression of a specific anti-parasite "normal" immune response. The genetic control of the immune response against this Ag shared by parasite and self has to be considered and could explain the development of cerebral malaria in a proportion of *P. falciparum* infected patients.

The involvement of anti-parasite specific response in the pathogenesis of CM was also considered in the paper by Lambert, Del Giudice & Grau. In a model of *P. berghei* experimental murine malaria, these authors reported several evidences for a role of $L_3T_4$ (helper) T cells in the induction of cerebral malaria. In view of the consistent absence of antibodies directed against mature stages of *Plasmodium* (polysegmented schizonts) in $L_3T_4$ depleted mice (which were protected against cerebral malaria) and its appearance after adoptive transfer of $L_3T_4$ T cells to adult thymectomized irradiated and bone marrow reconstituted mice it was suggested that the absence of these *Plasmodium* specific antibodies might be of importance in the protection of $L_3T_4$ depleted mice against cerebral malaria. These data were consistent with those reported by Finley et al. in 1983 showing that T cell blasts bearing phenotypes of suppressor cells could prevent cerebral malaria upon *in vivo* transfer. These results lead the authors to suggest that indirect mechanisms dependent on the immune response to malaria are involved in the pathogenesis of CM. In view of these data, the risk of immunopathology induction by *Plasmodium* specific immunization procedures aiming immunoprophilatic purposes has to be considered.

Finally, the study by these authors on the specific antibody response to $(NANP)_{40}$ (the synthetic CS repetitive epitope of *P. falciparum*) in mice with different genetic background clearly showed that the effectiveness of the immune response to this candidate to a malaria vaccine is under strict genetic control. The genetical restriction was overcome when different strains of mice were immunized with $(NANP)_{40}$ coupled to keyhole limpet hemocyanin as a carrier protein. These results taken together with the observation of variable frequencies of anti-$(NANP)_{40}$ antibodies in children living in the same endemic villages in spite of the similarities in several parameters (such as spleen rates, parasitaemia, anti-*P. falciparum* blood stage antibodies and exposure to mosquitoes) (see the conference by M. Tanner in the section "Methods in diagnosis and epidemiological studies") lead the authors to suggest a possible role of genetic background in the natural immunization against the CS immunodominant epitope.