Mem. Inst. Oswaldo Cruz, Rio de Janeiro, Vol. *87*, Suppl. III, 295-296, 1992

ROUNT TABLE 8 - SUMMARY

PATHOPHYSIOLOGY

Chairman: *Masamich Aikawa**
Co-Chairman: *Mats Wahlgreen***

The session "pathophysiology" included four papers which dealt with cytoadherence of *Plasmodium falciparum* – infected erythrocytes (PRBC) and one paper which discussed the roles of cytokines in human malaria. Aikawa et al. found that PRBC sequestration in microvessels of internal organs occurred more frequently in cerebral malaria patients than in non-cerebral falciparum malaria patients. This indicates that the PRBC sequestration in microvessels is related to the severity of falciparum malaria. A pathological study of the brain of cattle that died from *Babesia bovis* also revealed PRBC sequestration in cerebral microvessels by the attachment of protrusions on PRBC to the endothelial cells and to other PRBC. This finding indicates that the pathogenesis of cerebral *Babesia bovis* is similar to human cerebral malaria. A search for cytoadherence proteins in the endothelial cells of cattle may lead to a better understanding of the pathogenesis of cerebral babesiosis.

Crandall et al. studied the effects of pH, the concentration of Ca^{2+} and the various types of buffers used for PRBC cytoadherence assays in the amelanotic melanoma cell system. They found that the optimum pH for adherence was 6.6 to 6.8, that high concentrations of Ca^{2+} (50 mM) resulted in increased levels of binding and that the type of buffer used influenced adherence. In addition, they demonstrated that antibodies against PRBC which recognized parasite modified forms of human band 3 proteins inhibited the adherence of PRBC to melanoma cells.

Goldring and Hommel concluded that the correlation between *in vitro* PRBC cytoadherence and *in vivo* PRBC sequestration was poor based on experimental results from studies performed with material collected in a study of cerebral malaria in African children. They found that the diversity of cytoadherence from one isolate to another is considerable probably due to the existence of different malarial "adhesions" on PRBC and to the existence of different cytoadherence receptors on host cells. They suggested the development of evaluation techniques which take into account not only the diversity in the intrinsic cytoaherence characteristics of parasite hand host cells, but also their ability to respond to regulatory mechanisms which may enhance or reduce cytoadherence.

Whalgren et al. discussed rosetting, a way by which erythrocytes block microvessels. Rosetting and endothelial cell cytoadherence were suggested to hinder the blood flow which lead to severe falciparum malaria. The presence of anti-rosetting antibodies seems important for efficient interaction of rosetting infected RBC and leukocytes. They indicated that parasite derived or induced molecules on the surface of the infected erythrocytes which mediate rosetting may be important candiates to be included in a future malaria vaccine. They also suggested that treatment of patients with anti-rosetting antibodies in combination with other anti-rosetting substances might be an effective adjunct in the treatment of severe malaria.

Tosta discussed the role of cytokines and dyseregulation of the immune response in human malaria. To assess whether a possible deficiency of IL-1 could interfere with T-lymphocyte responses, blood mononuclear cells from patients infected with *P. falciparum*, or healthy subjects were cultured with phytohemagglutinin and lymphocyte proliferation was measured 72 hours later by 3H-thymidine

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incorporation. They found that T-lymphocyte responses are depressed both in *P. falciparum* and *P. vivax*. Addition of recombinant human IL-1 alpha completely reverted the depression of proliferation. In addition, they incubated mononuclear cells from *Plasmodium*-infected individuals with mitogen and showed an inhibition of PGE2 synthesis. They found poor proliferative response of lymphocytes indicating a deficiency of PGE2 production by monocytes. Therefore, they suggested that two defects occurred in the regulation of the immune response in malaria, namely a deficit production of IL-1 alpha by macrophages and a resistance of T lymphocytes to the antiproliferatial effect of PGE2.