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PROCEEDING OF THE ROUND-TABLE ON HOST-PARASITE RELATIONSHIP

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The papers in this session dealt with diverse aspects of the malaria parasite-host interaction, ranging from studies on invasion of erythrocytes by merozoites (C. Facer), the structure of a malarial histidine-rich protein which produces knob-protrusions on infected erythrocytes (J. Ravetch), the functional and molecular alterations of the infected cells membrane involved in the cytoadherence property of these cells (R. Howard) and the interaction of human antibodies with the surface of infected cells (J. Kloetzel), to finally, the infectivity and immunogenicity of mature and immature sporozoites to the vertebrate host (A. Krettli). The unifying theme is these papers was the desire to understand the molecular basis for particular biological phenomena of importance in the host-parasite relationship.

Invasion of erythrocytes by merozoites must involve perturbation of the submembrane cytoskeleton of the host erythrocyte. C. Facer described how the oxidant diamide, which increases self-association of spectrin (the major protein constituent comprising the cytoskeleton), reduced erythrocyte invasion. Treatment of erythrocytes with the permeant sulfhydryl reagent, N-ethylmalemide, decreased self-association of spectrin, and also reduced erythrocyte invasion. The importance of an unperturbed cytoskeleton for invasion was further illustrated by the finding that erythrocytes from a patient with hereditary pyropoikilocytosis (wherein the proportion of spectrin dimer is increased over the normal more polymerized state) were resistant to invasion.

Expression of knobs on *P. falciparum*-infected erythrocytes is correlated with expression of an unusual histidine-rich protein (the knob-associated histidine-rich protein). Knobless variants do not express this protein. This protein appears to be involved in some aspect of knob-structure and function other than a direct role in cytoadherence since it is part of the electron dense material under the knobs. J. Ravetch described how the gene encoding this *P. falciparum* protein was cloned using an oligonucleotide probe encoding a sequence of several contiguous histidine residues. The cloned DNA was used as a probe to show by Northern blotting that the homologous mRNA was only expressed by K^+ parasites. Probing of restricted genomic DNA with the same cloned DNA showed that the K^- parasites examined have undergone deletion of genetic material encoding this histidine rich protein. The extent of deletion varied in different K^- parasites. The amino acid sequence of this gene was deduced from the nucleotide sequence and shown to include several stretches of contiguous histidine residues.

The morphological, antigenic and functional alterations at the surface of *P. falciparum*-infected erythrocytes were reviewed by R. Howard. A very large malarial protein has been identified as the most likely cell-surface component responsible for the acquired cytoadherence property of infected erythrocytes. Cytoadherence of infected cells to capillary endothelial cells provides an important mechanism for parasite evasion of localized specific and non-specific immune responses in the spleen. This malarial protein is a potential candidate for vaccination against malaria since it is expressed on the infected cell surface for many hours (hence is accessible to antibody) and probably bears an antigenically conserved domain responsible for the function of cytoadherence. Recent studies on the identification of two host molecules on endothelial cells that are potential ligands for the cytoadherent moeity on infected erythrocytes (the OKM-5 antigen and thrombospondin) were also described by R. Howard and J. Barnwell. Future work on these host ligands may reveal differences in their expression on endothelial cells in 'cerebral' versus 'non-cerebral' malaria and also lead, through affinity purification studies, to identification of the functional portion of the malarial surface antigen responsible for cytoadherence.

The importance of the cytoadherence phenomenon *in vivo* and role of antibody which affects this cell-cell interaction was described by J. Kloetzel, Brazilian strains of *P. falciparum* and plasma from a battery of acutely-infected patients were used in the *in vitro* cytoadherence assay (with C32 melanoma cells) to screen for antibody effects. There was a diversity of antibody effects, ranging from significant inhibition, through no effect to significant enhancement of *in vitro* cytoadherence. Enhancement of cytoadherence by human plasma or sera has not been reported previously. The inhibitory antibodies could block cytoadherence *in vivo* and may work

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to the advantage of the host in that opsonized infected erythrocytes would be phagocytosed in organs such as spleen and liver. Enhancing antibodies may work to the detriment of the host if infected erythrocytes attach more tenaciously, or attach to endothelial cells of tissues where they would otherwise not adhere. The antigenic specificities of these sera are under investigation.

Sporozoites from salivary glands or oocysts were compared for their infectivity and immunogenicity in the vertebrate host by A. Krettli. The model system employed was *Plasmodium gallinaceum* from *Aedes fluviatilis* mosquitoes and chickens for infectivity studies, or, rats and mice for immunogenicity studies. Sporozoites from *both* locations in the mosquito were infective provided they were 10-14 days old. The *in vitro* reactivity of the surface of these sporozoites with antibodies (in the CSP test) was also correlated with their age rather than their origin. These results point to an important difference in the mosquito-tissue-dependent differentiation of an avian malaria and the rodent or simian malarias studied previously. Oocyst derived sporozoites in the latter examples are non-reactive in the CSP test and non-infective. Studies in progress will characterize the CSP proteins of these avian sporozoites at the molecular level to learn if there are other differences between sporozoites of the avian and mammalian malarias.