A-01: Study of factors, which mediate clinical disease in *Plasmodium vivax* malaria

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Malaria is probably the most important parasitic disease in Sri Lanka, from a public health viewpoint. Paroxysms, which are episodes of fever with chills and rigors, are characteristic of uncomplicated malaria. These episodes are known to coincide with the rupture of schizont infected erythrocytes in patients' circulation.

We have previously demonstrated that plasma TNF levels in patients' circulation rise and fall in close parallel to the rise and fall of body temperature observed during a paroxysm. We have also demonstrated that plasma taken during the peak of a paroxysm from malaria non-immune patients have the capacity to abolish the infectivity of gametocytes, and that this phenomenon of gametocyte inactivation is dependant on the following factors - a parasite product released during schizont rupture, plasma TNF-α and IL-2. In the past we used gametocyte inactivation as a marker of the pathological events that occur during a malarial paroxysm.

In searching for more easily measured surrogate markers of this phenomenon than gametocyte inactivation, we have found that in the presence of plasma taken from a non-immune *P.vivax* patient at the peak of a paroxysm, white blood cells (mainly neutrophils) from a healthy donor form cellular aggregates in *in vitro* cultures. These cellular aggregates which can be observed in Giemsa stained thin and thick smears prepared from cultures containing paroxysm plasma are either very low in number or entirely absent in cultures containing normal human plasma or plasma obtained before (pre-paroxysm) or after a paroxysm (post-paroxysm) from the same patients. Neither were they present in significant numbers in plasma from semi-immune *P.vivax* patients in whom a paroxysm is mild and clinically indistinct. To this extent, the cellular aggregation phenomenon appears to mark specific pathological events underlying a malaria paroxysm.

The factors present in paroxysm plasma that mediate this white cell aggregation effect were then elucidated. Depletion and reconstitution experiments revealed that cellular aggregation is dependent on the presence in paroxysm plasma of TNF-α, IL-3, IL-6, and IL-10 and on parasite derived molecules which are represented in schizont extracts. The immunological basis of this cellular aggregation process should be useful in understanding the pathological basis of clinical malaria.