Letter to the Editor

Specificity and Cross-Reactivity of *Plasmodium falciparum* Variant Surface Antigen-Specific Antibody Responses

In their recent study, Chattopadhyay et al. (5) reported the acquisition of agglutinating antibodies that cross-react with variant surface antigens (VSA) expressed by genotypically distinct parasite isolates following single episodes of monoclonal *Plasmodium falciparum* malaria in adults living in an area of low transmission intensity in India. This is in contrast to previous studies from areas of intense parasite transmission in Africa showing that VSA antibodies have a high degree of specificity for the VSA expressed by the infecting isolate (4, 9, 12) and that VSA-specific antibodies predominantly recognize variant-specific rather than cross-reactive epitopes (10). However, the study agrees well with data from Sudan, where it was found that individuals acquired antibodies to VSA expressed by heterologous parasite isolates after a single disease episode (7, 8). As in the study from India, the effect was quite marked, since a single or a few monoclonal malaria attacks can induce production of immunoglobulin G (IgG) that is reactive with VSA expressed by 15 to 20% of heterologous parasite isolates (T. G. Theander et al., unpublished data).

What then is the basis of the relative cross-reactivity of VSA-specific IgG in India and Sudan compared to the variant-specific responses observed in the Gambia, Ghana, and Kenya? David Roberts (13) suggests that the PfEMP1 repertoire of Indian parasites may be more restricted than in tropical Africa, but the above-mentioned data from Sudan are at variance with such a hypothesis. Furthermore, VSA-specific plasma antibodies are generally able to recognize parasites from distant geographical regions well (1, 6; M. A. Nielsen et al., unpublished data).

Instead, we propose that the specificity-cross-reactivity balance is determined by transmission intensity through its impact on acquisition of protective immunity. We and others have shown that antibody recognition of VSA varies markedly between different parasite isolates (2, 3, 11). Thus, some VSA are recognized at high titers by most parasite-exposed individuals, whereas other VSA are only poorly recognized by a minority of people. Importantly, the former type of VSA tend to be expressed by parasites infecting young children with little protective immunity and tend to cause severe disease, whereas the opposite is true for parasites expressing the latter type (2, 3, 11). It thus appears that parasites expressing common VSA are at a selective advantage in nonimmune patients but that the balance is gradually tipping in favor of rare VSA with the acquisition of protective immunity. This hypothesis would explain the long-standing but unresolved observation that immunity to severe disease develops much more rapidly than immunity to parasitemia per se. If—as seems likely—the common VSA are more conserved (and cross-reactive) among isolates than are rare VSA, the differences between the above-mentioned data from India and Sudan on the one hand and the Gambia, Ghana, and Kenya on the other probably reflect differences in seasonality and intensity of malaria transmission—and hence the immune status of patients—more than anything else. Studies such as those by Chattopadhyay et al. (5) emphasize the continued need for field-based immunology studies in a wide variety of epidemiological settings.

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Ed. Note: The authors of the published article declined to respond.