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EDITORIAL
DYNAMIC DETERMINANTS OF THE CYTOADHERENCE OF *PLASMODIUM FALCIPARUM*–INFECTED ERYTHROCYTES

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Since Marchiafava and Bignami noted in their pathologic studies of falciparum malaria that "malignancy coincides with an exceptionally abundant quantity of parasitic forms, a quantity much more abundant—where the cases terminate fatally—in the blood of the viscera than in the blood of the finger," sequestration has been considered central to the pathology of this potentially lethal infection.[1] The Roman pathologists also observed that the process was not uniform among the vital organs, noting particularly the "accumulation in the cerebral vessels of red blood corpuscles loaded with amoebae." The result of this pathologic process was described as "mechanical alterations in the circulation"; or, in other words, a traffic jam. With the development of methods for *ex vivo* culture of *Plasmodium falciparum,* malariologists have studied this process of cytoadherence of parasitized erythrocytes to endothelial cells (or the purified immobilized cell surface "receptors") in the laboratory and have progressively tried to recreate the same conditions that occur *in vivo*. This is not easy, as blood is a thick and complex soup of deformable cells suspended in a variable consommé of plasma proteins, electrolytes, and a variety of small organic molecules. Its effective viscosity changes nonlinearly under the different shear rates encountered in the circulation (non-Newtonian behavior). Malaria is associated with fever, progressive anemia, thrombocytopenia, an increase in acute phase proteins, reduction in serum albumin, and, in severe infections, reduced uninfected red cell deformability.[2]

The original laboratory assessments of cytoadherence took place under static conditions, with melanoma cells as surrogates for the vascular endothelium, at unphysiologically low hematocrits, in largely crystalloid solutions, and at normal (i.e., not febrile) temperatures. At hematocrits less than 12%, red blood cell suspensions exhibit Newtonian behavior. Recreating the *in vivo* conditions of the circulation, we have learned that the mechanical processes that lead to cytoadherence under flow conditions are similar to those with which leukocytes adhere to vascular endothelium.[3,4] Tethering (the initial contact) is followed by rolling and then adherence (stasis)—and once adherent, the parasitized cell remains stuck until schizogony—and even afterwards the residual membranes remain adherent to the vascular endothelium. Rolling is probably the rate-limiting step in cytoadherence.[5] The main, but not the only glue that sticks the parasitized cells to the endothelial surface is a high-molecular-weight antigenically variant protein, PfEMP1, which is expressed on the surface of the infected red cells after approximately 12–15 hours of growth.[6,7] The process is accelerated by febrile temperatures.[8] A variety of endothelial surface proteins and glycoproteins mediate attachment, of which the most important are probably CD36, ICAM1, and in the placenta, chondroitin sulfate A.[7,9] Infected red cells also stick to uninfected red cells (rosetting) and each other (agglutination).

In this issue of the journal, Flatt and her colleagues show how changes in hematocrit over the range commonly encountered in severe malaria (venous hematocrit, 10–30%; capillary values are lower) have major effects on cytoadherence.[10] Rolling increased 5-fold as hematocrit rose from 10% to 20%, and cytoadhesion rose 12-fold between 10% and 30%. Over this range, the viscosity of blood approximately doubles, and so if shear stress is held constant, shear rates fall by approximately half—allowing greater time for contact between cells and endothelium. More cells roll along the endothelial surface, and a higher proportion of these stick. Interestingly, suspending the cells in serum rather than culture medium, and reducing the deformability of the uninfected cells, as happens in severe malaria,[2] both reduced cytoadherence. The relevance of these observations to clinical medicine is that these large alterations in the cytoadherence of parasitized erythrocytes occur in the range of venous hematocrits commonly encountered when children with severe malaria in high-transmission areas are given blood transfusions. Although the conditions in the laboratory experiments are still not the same as those occurring in the partially obstructed microcirculation in severe malaria, the relative changes observed may well hold true. So does severe anemia at the time of infection protect against severe malaria? Could blood transfusions do more harm than good under some circumstances? We know that nearly all parasitized erythrocytes do sequester. Keeping them in the circulation for minutes or hours longer gives additional opportunity for splenic removal—particularly if artemisinin derivatives are given. So transfusion of blood would not be expected to cause any harm if the majority of parasites have already sequestered and might not have any adverse consequences if they are predominantly very young rings still many hours from becoming adhesive. But perhaps if the majority of parasites are about to cytoadhere, sequestration might be enhanced. This would pertain particularly to quinine-treated patients, because, in contrast to the artemisinin derivatives, quinine does not prevent further development to sequestering forms.[11] It would also argue for ensuring dehydration is corrected as swiftly as is safe. These theoretical concerns must be balanced against the known dangers of severe anemia. Once the venous hematocrit falls below 15%, mortality rises as a direct result of reduced oxygen carrying capacity. Blood transfusion is life-saving. Acute resuscitation in childhood malaria is a controversial subject, and these intriguing results add yet another layer of complexity. This really is one of those questions where "more work is needed."

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REFERENCES

1. Marchiafava E, Bignami A, 1894. *On Summer-Autumnal Fever.* London: New Sydenham Society.

2. Dondorp AM, Kager PA, Vreeken J, White NJ, 2000. Abnormal blood flow and red blood cell deformability in severe malaria. *Parasitol Today 16:* 228–232.
3. Cooke BM, Coppel RL, 1995. Cytoadhesion and falciparum malaria: going with the flow. *Parasitol Today 11:* 282–287.
4. Serirom S, Raharjo WH, Chotivanich K, Loareesuwan S, Kubes P, Ho M, 2003. Anti-adhesive effect of nitric oxide on Plasmodium falciparum cytoadherence under flow. *Am J Pathol 162:* 1651–1660.
5. Yipp BG, Anand S, Schollaardt T, Patel KD, Looareesuwan S, Ho M, 2000. Synergism of multiple adhesion molecules in mediating cytoadherence of Plasmodium falciparum-infected erythrocytes to microvascular endothelial cells under flow. *Blood 96:* 2292–2298.
6. Baruch DI, Gormely JA, Ma C, Howard RJ, Pasloske BL, 1996. Plasmodium falciparum erythrocyte membrane protein 1 is a parasitized erythrocyte receptor for adherence to CD36, thrombospondin, and intercellular adhesion molecule. *Proc Natl Acad Sci U S A 93:* 3497–3502.
7. Sherman IW, Eda S, Winograd E, 2003. Cytoadherence and sequestration in Plasmodium falciparum: defining the ties that bind. *Microbes Infect 5:* 897–909.
8. Udomsangpetch R, Pipitaporn B, Silamut K, Pinches R, Kyes S, Looareesuwan S, Newbold C, White NJ, 2002. Febrile temperatures induce cytoadherence of ring-stage Plasmodium falciparum-infected erythrocytes. *Proc Natl Acad Sci U S A 99:* 11825–11829.
9. Newbold C, Craig A, Kyes S, Rowe A, Fernandez-Reyes D, Fagan T, 1999. cytoadherence, pathogenesis and the infected red cell surface in *Plasmodium falciparum. Int J Parasitol 29:* 927–937.
10. Flatt C, Mitchell S, Yipp B, Looaresuwan S, Ho M, 2005. Attenuation of cytoadherence of *Plasmodium falciparum* to microvascular endothelium under flow by hemodilution. *Am J Trop Med Hyg 72:* 660–665.
11. Udomsangpetch R, Pipitaporn B, Krishna S, Angus B, Pukrittayakamee S, Bates I, Suputtamongkol Y, Kyle DE, White NJ, 1996. Antimalarial drugs reduce cytoadherence and rosetting Plasmodium falciparum. *J Infect Dis 173:* 691–698.