Microvascular Dysfunction in Severe Plasmodium falciparum Malaria

To the Editor—Hanson and colleagues present a commendable attempt to determine the relative contribution of macrovascular and microvascular dysfunction in severe Plasmodium falciparum malaria [1]. The number of capillaries with impaired flow correlated with the severity of illness and central venous lactate, whereas most indices of macrovascular function did not [1]. Thus, this study demonstrates that microvascular dysfunction is prominent in patients with severe falciparum malaria. However, the conclusion that “vital organ dysfunction in severe malaria results primarily from sequestration of parasitized erythrocytes in the microvasculature” (Page 571) is not substantiated by the data presented. The authors claim that they “directly visualized and quantitated microvascular sequestration,” (Page 571) using orthogonal polarized spectroscopy of the rectal mucosal microvasculature. This technique allows measurement of red blood cell flow within capillaries but, as the same authors have stated previously [2], cannot determine whether obstruction to flow is caused by sequestered parasitized red blood cells. Considering that acidosis, which showed the strongest association with disease outcome, is known to alter endothelial function and vascular tone [3], it is surprising the authors do not discuss acidosis as an alternative cause of the observed microvascular dysfunction.

It is remarkable that since Marchiafava and Bignami [4] proposed in 1894 that sequestered parasites may cause severe malaria, this hypothesis has become accepted as dogma without ever being rigorously tested. Numerous studies have confirmed the association of parasite sequestration with fatal malaria [5–7], but causality has not been demonstrated. An alternative hypothesis—that extensive sequestration is simply a consequence of endothelial activation and microvascular dysfunction (due to inflammatory mediators and reduced nitric oxide bioavailability [8])—is entirely consistent with the observations presented by Hanson and colleagues. Moreover, endothelial activation and microvascular dysfunction could account for severe malaria caused by different Plasmodium species, such as Plasmodium vivax [9–10], independent of sequestration.

Without challenging historical assumptions, we would still be left with the concept that malaria is caused by “bad air.” The unsubstantiated conclusions drawn by Hanson and colleagues from this study must be challenged to further our understanding of the pathogenesis of severe malaria.

Note

Potential conflicts of interest. All authors: No reported conflicts.
All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Aubrey J. Cunnington,1 Eleanor M. Riley,1 and Michael Walther2
1Department of Immunology and Infection, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, United Kingdom; and 2Immune Regulation Section, Laboratory of Malaria Immunology and Vaccinology, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, Maryland

References

3. Crimi E, Taccone FS, Infante T, Scioletta S, Crudele V, Napoli C. Effects of intracellular

Received 24 June 2012; accepted 23 August 2012; electronically published 6 November 2012.
Correspondence: Aubrey Cunnington, BMBCh, Department of Immunology and Infection, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel St, London WC1E 7HT, United Kingdom (aubrey.cunnington@lshtm.ac.uk).

The Journal of Infectious Diseases 2013;207:369–70
© The Author 2012. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.
DOI: 10.1093/infdis/jis881