absent in *Plasmodium vivax* infection—a similar disease in their view—or in other disease states in which endothelial activation is prominent.

Cunnington et al suggest that acidosis might cause the observed microvascular changes in severe falciparum malaria, but this is very unlikely. Acidosis is a ubiquitous clinical occurrence, whereas the pathological finding of sequestration in falciparum malaria is unique. Patients with severe sepsis have lactic acidosis, but they have empty capillaries and increased red blood cell velocity when assessed with orthogonal polarizing spectroscopy (OPS), in complete contrast to the blocked capillaries and reduced erythrocyte velocity observed in the patients in this study [2–4].

Sequestration in falciparum malaria has been assessed in detail with electron microscopy and histopathology, and its molecular mechanisms have been characterized [5–7]. The degree of sequestration correlates with outcome, time to death, and the 3 independent predictors of outcome: cerebral malaria, metabolic acidosis, and acute kidney injury [3–5, 8]. The tissue ischemia that results from sequestration explains the high ratios of lactate to pyruvate seen in patients with falciparum malaria, which is, again, quite different from the pattern of acidosis in patients with sepsis. Cunnington et al correctly note that with the resolution afforded by OPS imaging we cannot see individual parasitized erythrocytes adhering to endothelial cells. However, when the OPS finding of blocked capillaries is identical to the findings described histologically, and when the correlation with disease severity and outcome is the same, we believe that the inference is reasonable.

Combining severe falciparum malaria and severe vivax malaria to create a single disease entity—"severe malaria"—is misleading. The 2 infections are vastly different, both clinically and pathologically. Multiple organ failure and death are much more prominent in falciparum malaria than in vivax malaria, in which coma incidence has been estimated as 1 in 29 000 cases [9–11]. Some complications such as acute lung injury could share pathological processes, but this cannot be generalized.

Sequestration is not the only pathological abnormality seen in falciparum malaria, but it is the primary one. Microvascular pathophysiology is undeniably multifactorial: endothelial dysfunction and changes in the adhesive and elastic properties of erythrocytes contribute significantly to disease manifestations [6], a point that we make quite clearly in the discussion of our article.

The belief that malaria is caused by "bad air" was disproven by assessing the available data rationally and objectively. Sequestration provides a simple, plausible, and obvious explanation for the unique pathology of severe falciparum malaria, which is supported by in vivo and post mortem studies involving adults and children in Asia and in Africa [3, 5, 6]. It is now time to accept that it is far more than a historical assumption.

**Notes**

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