Cerebral malaria is one of the most common neurologic diseases in the world. According to WHO estimates, in 2010 alone there were over 216 million cases of malaria, and over 650,000 deaths, with 90% of deaths occurring in children. Among survivors of cerebral malaria, neurologic sequelae are common, with almost a third of patients developing epilepsy or other neurodevelopmental disabilities. Despite this, we know surprisingly little about the pathophysiology of cerebral malaria. Presumably sequestration of the parasite in the central circulation, with parasitized red blood cells interrupting normal cerebral blood flow, plays an important role. However, recent evidence suggests that the pathophysiology may be modulated by downstream effectors including nitric oxide, immune activation, excitotoxicity, and disruption of the blood–brain barrier leading to increased intracranial pressure. Complicating any discussion of pathophysiology, however, is the difficulty in describing exactly what we mean when we talk about cerebral malaria.

Cerebral malaria is defined by the WHO as unexplained coma in the presence of circulating *P. falciparum* parasitemia. This definition is problematic in much of Sub-Saharan Africa, where rates of asymptomatic parasitemia may be as high as 30%–50%. Thus, many patients diagnosed with cerebral malaria may actually have coma of a completely different etiology with an incidental and unrelated parasitemia. In this setting, the description of a characteristic malaria retinopathy that accurately identifies cerebral malaria has important implications. Retinal findings in malaria were first described in 1878, but it was not until the 1990s that a characteristic malaria retinopathy was identified, consisting of patchy retinal whitening and changes in vessel color, with or without retinal hemorrhages and papilledema. Interest in malaria retinopathy was heightened by an autopsy study in 2004 that confirmed that patients with malaria retinopathy had high rates of central parasite sequestration, whereas those patients without retinopathy often had unrelated causes of coma including meningitis, Reye syndrome, and toxic ingestion.

In this issue of *Neurology*, Postels et al. examine outcomes in retinopathy-negative cerebral malaria compared both to retinopathy-positive patients and to uninfected controls. The authors prospectively enrolled and followed survivors of cerebral malaria and concurrently hospitalized controls in Malawi for approximately 18 months and evaluated them for the development of epilepsy, behavior disorders, and other neurodevelopmental disabilities. This is the first study to look at relatively long-term outcomes in this population, and combined with the earlier article on outcomes in retinopathy-positive patients, the current work provides valuable insight into prognosis in cerebral malaria survivors. Surprisingly, retinopathy-negative patients had strikingly similar rates of adverse neurologic outcomes compared with retinopathy-positive patients, with both groups having much higher rates of epilepsy, new neurodisabilities, and behavior problems than controls.

The study results raise the following question: If malaria retinopathy accurately distinguishes between “true” cerebral malaria and coma with incidental parasitemia, then why are the outcomes in retinopathy-positive and -negative patients so similar? There are several possibilities. The first possibility is that identification of malaria retinopathy is not as good as we think it is in distinguishing “true” cerebral malaria from coma with incidental parasitemia. This may be due to inherent difficulties with fundoscopy in this setting, variability in examiners, use of direct fundoscopy instead of a slit lamp, or other factors, but if a portion of patients are being misclassified this could make the groups appear more similar than they really are. A second possibility is that malaria retinopathy accurately distinguishes central parasitic sequestration from peripheral parasitemia, but that central parasitemia is unnecessary for the development of cerebral malaria which may arise due to other factors such as immune activation or increased permeability.
of the blood–brain barrier. A third possibility is that retinopathy-positive and -negative patients are indeed pathophysiologically distinct, but happen to converge upon similar outcomes.

An important contribution of this study is that it suggests that both retinopathy-positive and -negative patients are at high risk for neurodevelopmental issues. But where do we go from here? It seems clear that patients with retinopathy-positive cerebral malaria represent a much more homogenous group, which might be the most appropriate population for clinical trials that target parasite sequestration. However, given similar poor outcomes, retinopathy-negative patients should not be ignored. Future studies of pathophysiology and prognosis should incorporate patients with and without malaria retinopathy. Studies that incorporate MRI to investigate differences between these groups (for example, using perfusion or arterial spin label sequences) could be key to unraveling these pathophysiologic differences, since presumably perfusion abnormalities detectable on MRI could accurately distinguish the microvascular congestion that is the hallmark of true parasitic sequestration. Finally, it is important to emphasize that given the various potential causes of coma in patients with retinopathy-negative cerebral malaria, a thorough evaluation for other causes of coma in these patients should always be pursued.

Improving outcomes in cerebral malaria is one of the most important tasks facing neurologists working in the developing world, but the pathophysiologic puzzles surrounding cerebral malaria have made the search for targeted therapies challenging. With this article, Postels et al. have taken an important step in elucidating this topic. While this article answers key questions regarding prognosis, it brings up even more questions on the subject of basic pathophysiology. What are we talking about when we talk about cerebral malaria? Hopefully, we are getting closer to an answer.

DISCLOSURE
The author reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES