

Nitric Oxide in Tanzanian Children with Malaria: Inverse Relationship between Malaria Severity and Nitric Oxide Production/Nitric Oxide Synthase Type 2 Expression

*Nicholas M. Anstey,*** J. Brice Weinberg,~ Mushtaq Y. Hassanali,** Esther D. Mwaikambo,** Denis Manyenga,** Mary A. Misukonis,~ Derrick R. Arnelleft Donna Hollis,II Malcolm I. McDonald,*** and Donald L. Granger**

From the Divisions of*Infectious Diseases & International Health, *Hematology-Oncology, and ~ Pulmonary Medicine, and IIComprehensive Cancer Center Biostatistics, Duke University Medical Center, Durham, North Carolina 27710; 82 Service, VA Medical Center, Durham, North Carolina 27705; and **Department of Paediatrics and Child Health, and **Duke-Muhimbili Clinical Research Laboratory, Muhimbili Medical Centre, Dares Salaam, Tanzania

Summary

Nitric oxide (NO)-related activity has been shown to be protective against *Plasmodium falciparum* in vitro. It has been hypothesized, however, that excess NO production contributes to the pathogenesis of cerebral malaria. The purpose of this study was to compare markers of NO production [urinary and plasma nitrate + nitrite (NO_x)], leukocyte-inducible nitric oxide synthase type 2 (NOS2), and plasma TNF- α and IL-10 levels with disease severity in 191 Tanzanian children with and without malaria. Urine NO $\cdot$ excretion and plasma NO_x levels (corrected for renal impairment) were inversely related to disease severity, with levels highest in subclinical infection and lowest in fatal cerebral malaria. Results could not be explained by differences in dietary nitrate ingestion among the groups. Plasma levels of IL-10, a cytokine known to suppress NO synthesis, increased with disease severity. Leukocyte NOS2 antigen was detectable in all control children tested and in all those with subclinical infection, but was undetectable in all but one subject with cerebral malaria. This suppression of NO synthesis in cerebral malaria may contribute to pathogenesis. In contrast, high fasting NO_x levels and leukocyte NOS2 in healthy controls and asymptomatic infection suggest that increased NO synthesis might protect against clinical disease. NO appears to have a protective rather than pathological role in African children with malaria.