rine levels and mean arterial blood pressure (r = 0.89), heart rate (r = 0.78), and platelet activation as estimated by β-thromboglobulin (r = 0.82). Our results provide specific information about important aspects of sympathetic and adrenal overactivity in preeclampsia.

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The authors reply:

To the Editor: We certainly value the data provided by Øian et al., who found increased levels of arterial plasma catecholamines in patients with preeclampsia. Nevertheless, even if measurements of arterial plasma catecholamines seem to provide more reliable data than measurements of urinary or venous levels, the arterial values also merely represent the algebraic sum of different organ-specific increases or decreases in sympathetic activity that can occur with different reflexes and in different disease states. Since sympathetic nervous responses are patterned or regionalized, the global biochemical measures of venous, urinary, or arterial catecholamine levels constitute imperfect measures of sympathetic nervous function.

Gans and Dekker suggest that the increase in sympathetic-nerve activity that we found to be characteristic in women with preeclampsia may be explained by insulin resistance or obesity (a state characterized by hyperinsulinemia), or both. This is an interesting concept, but there are two problems with it. First, except for their own data, the study they cite does not offer convincing evidence that preeclampsia is an insulin-resistant state. This study found a significantly higher frequency of glucose intolerance among women in whom transient hypertension developed during pregnancy but not among women in whom preeclampsia developed. Second, although it is now well established that hyperinsulinemia stimulates sympathetic activity, the interaction among insulin resistance, sympathetic activation, and high blood pressure is still far from clear. Thus, most of the available data in the literature do not show any rise in blood pressure during experimentally induced hyperinsulinemia. Furthermore, the cited study by Parazzini et al. does not allow the conclusion that obesity is a "recognized risk factor" for preeclampsia, since this study also included patients with mild or moderate chronic hypertension and did not clearly define the group with preeclampsia.

In our study, the women with preeclampsia and the normotensive pregnant women who were not obese and did not differ with regard to mean (±SE) pregestational body-mass index (23.6 ± 1.2 and 23.9 ± 1.4, respectively). Unfortunately, we do not have any data on insulin sensitivity in our patients. Thus, whether insulin resistance or obesity

or the combination accounts for the sympathetic overactivity and high blood pressure in women with preeclampsia remains an open question and requires further study.

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Mutations of the Hereditary Hemochromatosis Candidate Gene HLA-H in Porphyria Cutanea Tarda

To the Editor: Porphyria cutanea tarda is characterized by reduced activity of uroporphyrinogen decarboxylase, with hepatic accumulation of uroporphyrins, and photosensitive skin lesions. The clinical symptoms are effectively treated by phlebotomy. Excess hepatic iron, together with inappropriately high iron absorption, also occurs in porphyria cutanea tarda. An association between this disorder and HLA-linked hereditary hemochromatosis has been suggested but also contested. Recently, a new major-histocompatibility-complex (MHC) class I-like gene, HLA-H, has been identified, and two missense variants were found in 87 percent of unselected patients with hereditary hemochromatosis. That this gene has a role in hemochromatosis is supported by studies implicating MHC class I-like proteins in iron metabolism.

We assessed the role of HLA-H mutations in porphyria cutanea tarda by an allelic-association study between porphyria cutanea tarda and the two described HLA-H mutations. Fifteen unselected, unrelated patients with porphyria cutanea tarda being treated with regular phlebotomy were studied. The diagnosis was based on the typical symptoms of photosensitive skin and elevated urinary uroporphyrin levels. The controls were 23 anonymous blood donors and 71 patients with hereditary hemochromatosis.

Genomic DNA was extracted from blood leukocytes. Polymerase-chain-reaction (PCR) amplification of exons 2 and 4 (encoding the α1 and α3 domains) was performed with primers 5'CAACCTTCCTGACTACCTTCAT3' and 5'CTTGTAGGTGTTGATTTCCAT3' and primers 5'CCTTCCTTTGTTGAAAGTAGACAT3' and 5'AGACACAAATGAGGGCTGATCCAT3', respectively. The point mutation in the α1 encoding region was identified by the loss of an Mbol site; the point mutation in the α3 encoding region was identified by the gain of an RsaI site. Digest PCR fragments were analyzed by polyacrylamide-gel electrophoresis. We found that 6 of the 15 patients with porphyria cu-
Ataxia and Slurred Speech after Artesunate Treatment for Falciparum Malaria

To the Editor: Artemisinin compounds are used to treat Plasmodium falciparum infections in many countries worldwide.1,2 We describe a patient with acute cerebellar dysfunction that was temporally associated with the ingestion of artesunate.

In July 1996, a 36-year-old American geologist in Ghana had fever and chills without associated neurologic symptoms. His blood smear revealed *P. falciparum*. He proceeded to a local market and purchased a pack of artemunate tablets manufactured in China. He took two tablets on day 1, followed by one tablet daily for the next four days. He became afebrile on day 2. A blood smear on day 5 contained no malaria parasites.

Two days after completing the artemunate treatment, the patient noted that his gait was unsteady. His electroencephalogram was normal. Over the next week, worsening ataxia and slurred speech developed. Three weeks later, he was evacuated to a London hospital. Magnetic resonance imaging of the brain and a lumbar puncture revealed no abnormalities. He then flew home to California with a nursing escort.

In September 1996, the patient was admitted to a southern California hospital with persistent neurologic symptoms. He had slurred speech; a wide-based, ataxic gait; and impaired heel-to-shin and rapid alternating movements. A peripheral smear was again positive for plasmodium species, but the parasites were too scant to speculate. He was re-treated with oral quinine and doxycycline. In October 1996 he began rehabilitation therapy. One month later, his ataxia was moderately improved, and his speech was nearly normal.

Artesunate is an antimalarial agent derived from the Chinese medicinal plant *qinghao* (*Artemisia annua*). Other related agents are arteether, arteether, and artemelin acid.1 These drugs are available primarily in Asia and Africa, where parenteral, oral, and rectal formulations have been used to treat an estimated 1 million patients.2

Although there are no previous clinical reports of artemisinin-related neurotoxic effects, Brewer et al. observed a staggering gait and respiratory arrest in dogs treated with high doses of intramuscular arteether, as well as ataxia and myoclonic activity in rats given intramuscular arteether and arteether.3 In the Gambian children with cerebral malaria described in the Journal by van Hensbroek et al. (July 11 issue),4 intramuscular arteether was associated with more convulsions and more prolonged coma than was intramuscular quinine. In the accompanying editorial, Hoffman expressed concern about the potential neurotoxicity of all artemisinin compounds.5

Our patient had neurologic sequelae over a four-month period immediately after treatment with artemunate for *P. falciparum*. Since cerebellar dysfunction would be a highly unusual complication of malaria, this case serves as a warning of the need for further attentiveness to the neurotoxic side effects of artemisinin compounds.

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