Mental Health and the Global Agenda

TO THE EDITOR: Becker and Kleinman (July 4 issue) highlight the burden of mental diseases worldwide. Major concerns are for people living in less-developed countries (because of the low level of resources devoted to neuropsychiatric illnesses) and for young people (because of the difficulty accessing mental care).

We would like to emphasize the enormous suffering associated with mental disorders in older people. The prevalence of mental diseases in older people has increased dramatically in the past decades, not only because of aging itself (e.g., Alzheimer's disease), but also because of new emotional and sociodemographic situations to which the elderly are exposed. Moreover, disorders such as depression and dysthymia often become chronic, and the link between mental and physical health (ultimately leading to disability) is extremely strong. Finally, the use of psychotropic medications without fair evidence of safety, efficacy, and effectiveness in persons who are already receiving many other medications is fraught with danger. Training primary care clinicians in the care of elderly patients with mental illness should be a priority.

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THE AUTHORS REPLY: Marengoni and Pecorelli raise an important point about the large and growing mental health burden in older persons. Indeed, the formidable burden imposed by Alz-
Primaquine Failure and Cytochrome P-450 2D6
in Plasmodium vivax Malaria

TO THE EDITOR: Primaquine is the only medication approved by the Food and Drug Administration to eradicate the hypnozoites of Plasmodium vivax, but relapses of P. vivax malaria due to drug failure occur. Human cytochrome P-450 isozyme 2D6 (CYP2D6) may be a key enzyme involved in metabolizing primaquine into redox-active metabolites against hypnozoites in the liver.

As part of a phase 1 clinical trial of a vaccine against P. vivax (Study of VMP001 and AS01B in Healthy Malaria-Naïve Adults; ClinicalTrials.gov number, NCT01157897), 33 participants were exposed to P. vivax sporozoites from the bites of infected mosquitoes. Parasitemia developed in all participants by day 13 after the challenge, and parasitemia rapidly cleared on initiation of the directly observed administration of a combination of chloroquine (at a dose of 1500 mg base by mouth over a period of 48 hours) and primaquine (at a dose of 30 mg by mouth daily for 14 days). Two participants (6%) had multiple relapses of malaria (see Fig. 1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). After each relapse, parasitemia was rapidly cleared in these participants with chloroquine (at a standard dose of 1500 mg base by mouth over a period of 48 hours) and a weight-based dose of primaquine (at a total dose of 6 mg per kilogram of body weight). To our knowledge, true resistance to primaquine in P. vivax hypnozoites has not been described; this suggests a role for host factors in drug failure.

We sought to identify an association between CYP2D6 activity and primaquine drug failure. CYP2D6 phenotypes were ascertained in 25 available participants. The institutional review boards of the Walter Reed Army Institute of Research, the Naval Medical Research Center, and the Walter Reed Army Medical Center, as well as the Western Institutional Review Board approved the study, and all participants provided written informed consent. CYP2D6 phenotyping was performed; 21 participants had an extensive-