

area of Mozambique: a double blind randomised controlled phase I/IIb trial. *Lancet* 2007;370:1543-51.

10. Snow RW, Guerra CA, Mutheu JJ, Hay SI. International funding for malaria control in relation to populations at risk of stable *Plasmodium falciparum* transmission. *PLoS Med* 2008;5(7):e142.

11. Ceesay SJ, Casals-Pascual C, Erskine J, et al. Changes in ma-

laria indices between 1999 and 2007 in The Gambia: a retrospective analysis. *Lancet* 2008;372:1545-54.

12. O'Meara WP, Bejon P, Mwangi TW, et al. Effect of a fall in malaria transmission on morbidity and mortality in Kilifi, Kenya. *Lancet* 2008;372:1555-62.

Copyright © 2008 Massachusetts Medical Society.

## Real-World Therapies and the Problem of Vivax Malaria

J. Kevin Baird, Ph.D.

Wellems and Miller<sup>1</sup> wrote of two worlds of malaria: one, of the residents of rural tropical areas in which the disease is endemic, and the other, of travelers to those areas, who typically have greater resources. The distinction is sharp, valid, and important in considering the development of tools to combat the global burden of malaria. Drugs considered safe and effective in one world may not be so in the other.<sup>2</sup> The majority of the hundreds of millions of people in whom malaria will develop over the next year will obtain and consume antimalarial medication without medical supervision. Although the licensing of complex or poorly tolerated therapeutic regimens requiring clinical screening for contraindications may be perfectly suitable for populations with access to close clinical supervision, distributing the same regimen in the rural tropics is reckless.

Two other worlds of malaria are those with and without endemic *Plasmodium vivax*. Vivax malaria was known as "benign tertian malaria" for more than a century and is still viewed as rarely dangerous; evidence suggests a historical underestimation of both the burden of disease and the potential for death with *P. vivax* infection.<sup>3-7</sup> Endemic vivax malaria occurs throughout the tropics, except where there is a natural absence of anopheline mosquitoes (east of Vanuatu in the South Pacific) or among populations lacking the Duffy receptor on red cells (in much of Africa). Vivax malaria stands alone among the plasmodia infecting humans in its capacity to reach well into the temperate latitudes, as it does today — up to the Korean peninsula and across the southern temperate latitudes of Asia to the Mediterranean Sea. Approximately 2.6 billion people are at risk, and estimates of annual infections range from 70 to 390 million,<sup>3,4</sup> with about 80% occurring in South and Southeast Asia. Vivax malaria accounts for at least 70% of the malaria burden in the Americas.

Objective examination of the clinical evidence underpinning available therapies for *P. vivax* infection reveals a conspicuous neglect of this parasite.<sup>5</sup> More importantly, the analytical tools for critically assessing experimental or standard therapies may be considered insufficient, at best, for the task of identifying the treatments that are safe and effective and capable of reducing the disease burden of vivax malaria.

The distinction between the worlds of malaria with and without *P. vivax* finds expression in the study by Karunajeewa et al.<sup>8</sup> (Australian New Zealand Clinical Trials Registry number, ACTRN12605000550606) reported in this issue of the *Journal*. This state-of-the-art clinical trial evaluates the safety, tolerability, and efficacy of therapeutic options among young children exposed to endemic falciparum and vivax malaria in Papua New Guinea. By virtue of the analytical tools applied, the findings with regard to *P. falciparum* provide useful insights. The estimated 88% efficacy of dihydroartemisinin-piperaquine falls well below other estimates of efficacy for this combination against this parasite. The authors point to both suboptimal absorption of piperaquine and to cross-resistance between chloroquine and piperaquine by local parasites *in vitro* as a possible basis for the relatively poor performance of the drug combination. Their carefully assembled evidence makes a compelling case for the selection of artemether-lumefantrine for treatment of uncomplicated falciparum malaria in northwestern Papua New Guinea.

The authors have much less analytical leverage with regard to the data on *P. vivax*, however. The liver stage of *P. vivax* responsible for relapse (the hypnozoite) casts a nearly opaque shadow of ambiguity across the data. The curve showing occurrences of recrudescence provides almost no useful information for discerning the advantage of one therapeutic option over another:

all appear highly effective in the week after treatment and uniformly poor thereafter. Dihydroartemisinin–piperaquine appears to be the least inadequate of the four, but this may be an illusion created by successfully suppressed relapse. The authors did not correct the data for post-therapy reinfection or relapse using a polymerase-chain-reaction (PCR) assay, because no existing assay can achieve such a correction. Nor did they examine parasite responses to these drugs in vitro, because no standardized protocol for doing so exists, and experimental protocols yield findings that are notoriously difficult to interpret.<sup>9,10</sup> The authors cannot assign an attributable risk of reinfection as compared with relapse among their subjects, because there are no baseline data for doing so. Even if the authors had applied primaquine against hypnozoites, the only drug currently approved and available for this use, they could not have assumed its good efficacy, because there are no data to support that contention.

The data presented by Karunajeewa et al. should nonetheless alert public health and health care providers alike to the substantial health burden imposed by hypnozoites. One third of the children with *P. falciparum* infection in this study had recurrent *P. falciparum* parasitemia within 42 days after the start of treatment. Almost two thirds of those cases proved to be reinfections, suggesting a 6-week cumulative incidence of new infections of about 20%. Incidence-density studies in nearby Western New Guinea consistently found new *P. falciparum* infections to outnumber new *P. vivax* infections by about 2:1.<sup>11,12</sup> The 6-week cumulative incidence of new *P. vivax* infections in the study by Karunajeewa et al. may be thus crudely estimated at less than 10%, whereas the realized cumulative incidence of recurrent *P. vivax* parasitemia was about 65%. During the follow-up period, *P. vivax* parasitemia developed in almost half of the subjects treated for acute falciparum malaria. The hypnozoite appears to be the overwhelmingly dominant source of new parasitemia and the consequent opportunities for disease and further transmission.

For operational malarial control, attacking the hypnozoite may be more effective in relieving disease burdens than measures minimizing human contact with anopheline mosquitoes. What can be said of primaquine, the only drug available for eliminating this source of vivax malaria? Primaquine has been in continuous use for more

than 50 years. Standard therapy is implemented over 14 days. Good tolerability requires that a snack or meal be taken with the drug. Safe administration requires that pregnancy and glucose-6-phosphate dehydrogenase deficiency are ruled out, by means of clinical and laboratory screening. Mechanisms of the drug's toxicity and activity are not known. There is no standardized means of gauging its efficacy against hypnozoites. No body of current clinical data show that it has good efficacy in the field, and it may have no efficacy against hypnozoites unless administered with an appropriate companion drug.<sup>13-15</sup>

The inadequacy of primaquine and its critical importance in attacking vivax malaria symbolizes the technical poverty of the malaria world that includes *P. vivax*. If we are to remove the barriers separating the two worlds of malaria identified by Wellems and Miller, we must deal with the control of vivax malaria, and perhaps its eradication. It seems likely that this will prove unmanageable without a safe, practical, and effective therapy aimed at the hypnozoite.

No potential conflict of interest relevant to this article was reported.

This article (10.1056/NEJMe0808729) was published at www.nejm.org on December 8, 2008.

From the Eijkman–Oxford Clinical Research Unit, Jakarta, Indonesia; and the Center for Tropical Medicine, Nuffield Department of Clinical Medicine, Oxford University, Oxford, United Kingdom.

1. Wellems TE, Miller LH. Two worlds of malaria. *N Engl J Med* 2003;349:1496-8.
2. Baird JK. Effectiveness of antimalarial drugs. *N Engl J Med* 2005;352:1565-77.
3. Hay SI, Guerra CA, Tatem AJ, Noor AM, Snow RW. The global distribution and population at risk of malaria: past, present, and future. *Lancet Infect Dis* 2004;4:327-36.
4. Price RN, Tjitra E, Guerra CA, Yeung S, White NJ, Anstey NM. Vivax malaria: neglected and not benign. *Am J Trop Med Hyg* 2007;77:79-87.
5. Baird JK. Neglect of Plasmodium vivax malaria. *Trends Parasitol* 2007;23:533-9.
6. Barcus MJ, Basri H, Picarima H, et al. Demographic risk factors for severe and fatal vivax and falciparum malaria in northeastern Indonesian Papua. *Am J Trop Med Hyg* 2007;77:984-91.
7. Tjitra E, Anstey NM, Sugiarto P, et al. Multidrug-resistant Plasmodium vivax associated with severe and fatal malaria: a prospective study in Papua, Indonesia. *PLoS Med* 2008;5(6):e128.
8. Karunajeewa HA, Mueller I, Senn M, et al. A trial of combination antimalarial therapies in children from Papua New Guinea. *N Engl J Med* 2008;359:2545-57.
9. Russell B, Chalfein F, Prasetyorini B, et al. Determinants of in vitro drug susceptibility testing of Plasmodium vivax. *Antimicrob Agents Chemother* 2008;52:1040-5.
10. Sharrock WW, Suwanarusk R, Lek-Uthai U, et al. Plasmodium vivax trophozoites insensitive to chloroquine. *Malar J* 2008;7:94.

11. Jones TR, Baird JK, Bangs MJ, et al. Malaria vaccine study site in Irian Jaya, Indonesia: Plasmodium falciparum incidence measurements and epidemiologic considerations in sample size estimation. *Am J Trop Med Hyg* 1994;50:210-8.
12. Ohrt C, Richie TL, Widjaja H, et al. Mefloquine compared with doxycycline for the prophylaxis of malaria in Indonesian soldiers: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1997;126:963-72.
13. Alving AS, Arnold J, Hockwald RS, et al. Potentiation of the curative action of primaquine in vivax malaria by quinine and chloroquine. *J Lab Clin Med* 1955;46:301-6.
14. Baird JK, Rieckmann K. Can primaquine therapy for vivax malaria be improved? *Trends Parasitol* 2003;19:115-20.
15. Baird JK, Hoffman SL. Primaquine therapy for malaria. *Clin Infect Dis* 2004;39:1336-45.

Copyright © 2008 Massachusetts Medical Society.

## Energy In, Energy Out, and the Effects of Obesity-Related Genes

Rudolph L. Leibel, M.D.

More than 100 genes have been implicated in the determination of body weight. These genes, acting primarily in or through the central nervous system (primarily the hypothalamus and brain stem), affect conscious and unconscious aspects of food intake and energy expenditure. They include genes mediating brain sensing of fat stores, calorie flux in the gut, hedonic responses to specific foods, rates of energy expenditure, and even inclination to physical activity.<sup>1-3</sup> In some populations, mutations in one of these genes — the melanocortin 4 receptor (*MC4R*), which conveys hypothalamic signals suppressing food intake and increasing energy expenditure — can account for 3 to 5% of severe obesity (body-mass index [BMI] >40, with BMI defined as the weight in kilograms divided by the square of the height in meters).<sup>4</sup> Other quantitatively significant single genes have been hard to identify. Possible reasons for this failure may be that obesity is so physiologically complex that no single gene or even handful of genes is likely to have a dispositive role, that examining gene–gene interactions is difficult without large numbers of subjects, and that variations among current candidate genes are not the most important contributors to human adiposity.

Enter the genomewide association study,<sup>5</sup> which uses large numbers of common single-nucleotide polymorphisms (SNPs) in DNA spaced more or less evenly across the human genome to identify genetic variation associated with ordinal or cardinal phenotypes. Unlike the candidate-gene approach, the genomewide association study is genetically agnostic: it looks for genetic intervals associated with the phenotype or phenotypes; the constituent genes are “discovered” after the fact by examining those in the implicated

interval. The fat mass and obesity–associated gene (*FTO*) examined in the article by Cecil et al. in this issue of the *Journal*<sup>6</sup> was previously identified as a new obesity candidate by a genomewide association study.<sup>7</sup>

Frayling et al.<sup>7</sup> found a strong association between SNPs (e.g., rs9939609) and adiposity in the first intron of *FTO*. This association has been replicated in several additional studies, using data on more than 80,000 adults and children. The statistical power of the association ( $P \approx 1.2 \times 10^{-29}$ ) in the aggregate data is much higher than for any previous candidate-gene association study.

Cecil et al. studied the effects of genetic variation in the region around SNP rs9939609 in children. The major effect appears to be on energy intake and preference for foods of high caloric density. The magnitude of the increase in energy intake correlated with the A allele of this SNP is high enough to account for some or all of the differences in adiposity. No effect of genotype at rs9939609 on resting energy expenditure (corrected for body size) was detected, and physical activity was actually estimated to be increased in these children. Given the findings of studies of the molecular physiology of weight regulation, excess intake (rather than reduced basal energy expenditure) is probably the major mechanism for obesity in humans. Conducting studies of the contributions of genetic variation to the risk of obesity during the dynamic process of weight gain is crucial, because once a stable weight is reached, energy intake per unit of metabolic mass does not differ between obese and lean people.<sup>8</sup>

Two known genes lie within the implicated genetic interval. One is *FTO* (a locus associated with fat mass and obesity), which has been implicated in nucleic acid demethylation and is