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Waking the Sleeping Beauty

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Artemisinin derivatives are essential for the treatment of *Plasmodium falciparum* malaria throughout the world. Given orally, artesunate and artemether—the 2 main compounds—are rapidly absorbed and metabolized to dihydroartemisinin (DHA), the metabolite responsible for the majority of the parasitocidal activity. The precise mechanism of action is still debated, but the main properties of this class of drugs are clear: they are the most active of known antimalarials, providing the highest killing rates and the broadest spectrum of stage activity (from young rings to gametocytes), and they are rapidly eliminated (within hours). The rapid killing of parasites (especially the young rings) is particularly beneficial, because it translates into rapid recovery for patients with uncomplicated infections, reduces gametocytogenesis, and prevents further sequestration in patients with high biomass and more severe infection. It was observed in early Chinese studies that, despite their potency, short courses (<5 days) of these drugs resulted in a high rate of parasitemia recurrence after the usually rapid initial clearance [1]. These episodes of recurrent parasitemia are not caused by the emergence of resistance to the artemisinins but might be explained by parasites that have escaped short drug exposure. However, longer courses of artemisinin treatment also could not achieve 100% cure rates, which demanded other explanations.

In 1996, Kyle et al [2] described the dormancy theory, in which some of the parasites exposed at ring stage in vitro become metabolically inactive and resume growth after removal of the drug. They called them “sleeping beauties.” Others have since confirmed this phenomenon [3], which was previously described for other organisms. In this issue of the *Journal*, Teuscher et al [4] present further evidence for the theory and, using an elegant experimental design, provide new information on the frequency and the timing of recovery of “dormant” parasites and the drug dose-effect relationship. First, the authors report that all 5 laboratory stains of *P. falciparum* tested exhibited the dormancy property—essentially a growth arrest of some parasites at ring stage—although the investigators note that strains with different genetic backgrounds varied in their capacity to recover. This suggested a conserved phenotypic trait in *P. falciparum*, as opposed to a rare event affecting particular parasite strains. Second, the recovery of dormant parasites occurred relatively soon after exposure: 50% of dormant parasites resumed growth during the first 9 days. This may be relevant clinically, because it could explain some of the recurrences observed in patients during the weeks after treatment. Third, the cumulative proportion of parasites recovering over a period of 20 days was relatively high under these experimental conditions—between 0.044% and 1.313% of the initial parasite load. Even if the daily recovery rate is very low, in patients who routinely harbor 1×10^8–1×10^{12} parasites at presentation this would translate into tens of thousands of parasites that are able to resume growth after days or weeks of dormancy, triggering a new parasitemic episode. Finally and perhaps most importantly, the

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proportion of parasites recovering from the dormancy stage is dose dependent: higher exposures to DHA and coexposure to mefloquine resulted in lower proportions of parasites capable of surviving the drug exposures through growth arrest. This underscores the importance of correct dosage of antimalarials when used clinically.

Although the work of Teuscher and colleagues provides important insights into the dormancy theory, many questions remain. The molecular mechanism that allows some malarial parasites to enter this stage of low or no metabolic activity is unknown. More importantly, however, this observation is still limited to laboratory-adapted strains, and we now need to know whether this phenomenon is observed in nature and how it may contribute to recurrences of malaria in patients treated with these drugs. Also of importance are questions of whether different derivatives of artemisinin or other (synthetic) peroxides have different effects on dormancy and whether different partner drugs have different effects on the proportion of parasites recovering from dormant stages. However, the most pressing question is whether this observation can be related to resistance to the artemisinins.

Until recent years, it was reasonable to assume that, with a correct prescription (dosage and administration), the artemisinin derivatives were universally effective against *P. falciparum*. Recurrent cases (some of which may have been explained by dormant parasites) were limited in number by the use of artemisinin combination therapy with a slowly eliminated partner drug and, in some patients, by natural host immunity. The recent description in western Cambodia of *P. falciparum* infections with slow parasite clearance during treatment with artesunate that was not explained by pharmacological or obvious host factors is generating considerable worry. Could this new phenotype be explained by the dormancy theory? Probably not, because the decline in parasitemia levels observed after treatment in Cambodia, although slower than that seen in the past, still roughly follows a first-order decline and does not suggest the recovery of a minority of transiently dormant parasites. Are the 2 observations (the dormancy phenomenon and the slow-clearance phenotype) totally unrelated? We can only speculate at this stage, but we observe that parasites must be exposed to DHA *at ring stage* to enter dormancy in vitro. Is this a random effect, or are some parasites genetically primed to become dormant? Are parasites that recover from dormancy more “tolerant” to DHA? Have they adapted? Could these effects on the ring stage explain the delayed clearance? All these important questions will not be answered easily. The molecular basis of the slow-clearance phenotype and of dormancy will need to be elucidated first. The prime suspects (Pfmdr1, Pf-ATPase-6, 6-kb mitochondrial genome, and ubp-1) do not appear to be involved in the slow-clearance phenotype [5], so the search must be intensified.

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References

1. Li GQ, Arnold K, Guo XB, Jian HX, Fu LC. Randomised comparative study of mefloquine, qinghaosu, and pyrimethamine-sulfadoxine in patients with falciparum malaria. Lancet. 1984; 2:1360–1361. [PubMed: 6150365]
2. Kyle, DE.; Webster, HK. Postantibiotic effect of quinine and dihydroartemisinin derivatives on *Plasmodium falciparum in vitro*: implications for a mechanism of recrudescence. Abstracts of the XIVth International Congress for Tropical Medicine and Malaria; 1996. Abstract 0-22-6
3. Witkowski B, Lelievre J, Barragan MJ, et al. Increased tolerance to artemisinin in *Plasmodium falciparum* is mediated by a quiescence mechanism. Antimicrob Agents Chemother. 2010; 54:1872–1877. [PubMed: 20160056]

4. Teuscher F, Gatton ML, Chen N, Peters J, Kyle DE, Cheng Q. Artemisinin-induced dormancy in *Plasmodium falciparum*: duration, recovery rates, and implications in treatment failure. J Infect Dis. 2010; 202(9):1362–1368. (in this issue). [PubMed: 20863228]

5. Imwong M, Dondorp AM, Nosten F, et al. Exploring the contribution of candidate genes to artemisinin resistance in *Plasmodium falciparum*. Antimicrob Agents Chemother. 2010; 54:2886–2892. [PubMed: 20421395]

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