of *Plasmodium malariae* infection seven days after neurosurgery. Their conclusion is that the infection was reactivated "after decades of latency," given that malaria was officially eradicated in Trinidad in 1965 and that the patient denied having traveled to a country where malaria was endemic.

Yet a recent report by the same lead author of reemergence of *P. malariae* infection in Trinidad suggests a more logical explanation for this case.[2] From 1994 to 1996, 22 people from 12 different areas of Trinidad had blood smears that were positive for *P. malariae*. Seven of these 22 people were less than 25 years old and thus had been born after the official eradication of malaria in 1965. All of them denied having traveled outside Trinidad. In addition, a number of other people, half of whom had been born after 1965, were found to have negative blood smears and high-titer seropositivity for *P. malariae*. Mosquito vectors of the parasite were abundant in the geographic areas associated with the detected cases.

Given all these facts, the current patient may very well have been infected with the parasite during the recent outbreak and thus have had a latent infection for only a few years, and not for decades. Only with the great stress and the high level of immunosuppression associated with a major operation did the infection become reactivated. Even though the possibility that the patient became infected before 1965 cannot be ruled out entirely, there is no evidence to reach a conclusion about when and how long this patient had the disease.

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To the Editor: Chadee et al. report a case of *P. malariae* infection that was diagnosed long after the exposure to malaria. The authors state that their patient was treated with "the standard regimen of chloroquine phosphate and primaquine phosphate." However, primaquine phosphate is inappropriate for the treatment of *P. malariae* infection. This drug is used to eradicate dormant hypnozoites in the liver and thus prevent relapses of malaria caused by *P. vivax* or *P. ovale*. Since *P. malariae* has no hypnozoite stage, the appropriate therapy is chloroquine phosphate alone. Primaquine phosphate is often given inappropriately for *P. malariae* or *P. falciparum* infection. Although this drug is usually well tolerated, it can cause serious complications, including fatal hemolysis in persons with a deficiency of glucose-6-phosphate dehydrogenase.[1] The use of primaquine phosphate should be reserved for the treatment, in conjunction with chloroquine phosphate, of *P. vivax* and *P. ovale* infections.

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Dr. Chadee replies:

To the Editor: Our recent report on the reactivation of *P. malariae* in a Trinidadian man after neurosurgery has generated some debate on the exact time the patient contracted the infection and on the drug regimen used for treatment. Kulwichit points out that the patient could have become infected during the small outbreak of malaria that occurred during the period from 1994 to 1996, when infection with *P. malariae* was diagnosed and treated in 22 people in Trinidad. However, our patient denied having traveled to the area where the outbreak had occurred, and no *Anopheles bellator* or *A. homunculus* mosquitoes were found through extensive collections within his home and the surrounding areas. These anopheline mosquitoes have been reported to have a limited flight range within the forest and the outer fringes of the forest.[1] Therefore, the available data do not support the argument that the infection was acquired during the outbreak of *P. malariae* infection from 1994 to 1996.

Kulwichit agrees that the patient could have been infected before 1965 (the year malaria was eradicated in Trinidad). As with most diseases with a long latency period, determination of the exact date of infection is impossible. Consequently, we stated that our patient could have had this infection for "more than 30 years and perhaps, given his clinical history, about 65 years." Similar cases of *P. malariae* infection with long latency periods have been reported elsewhere.[2,3]

Rosenthal suggests that the treatment of *P. malariae* infection with primaquine phosphate was inappropriate. I agree that primaquine phosphate is not recommended for the treatment of quartan malaria, but in Trinidad the use of chloroquine phosphate and primaquine phosphate is the standard treatment for malaria caused by *P. vivax, P. malariae*, or *P. ovale*. The rationale for the use of primaquine phosphate is the frequency of malaria with mixed infections in persons coming from outside the country (especially since *P. vivax* is submicroscopical) and the presence of efficient vectors that are potential risk factors for renewed transmission from persons with relapse. Primaquine phosphate is administered in Trinidad and Tobago only after the appropriate tests for glucose-6-phosphate dehydrogenase have been conducted. This test was conducted in our patient before treatment, and thus there was no risk of complications (such as hemolysis) as a result of the treatment.

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Systemic Absorption of Food Dye in Patients with Sepsis

To the Editor: Critically ill patients who are receiving enteral feeding are susceptible to pulmonary aspiration of gas-

tric contents. Measures to enhance the early detection of aspiration include the tinting of feedings with the food dye FD&C blue no. 1.[1] During sepsis, gastrointestinal permeability increases because of enterocyte death and loss of barrier function at intercellular gaps. Thus, substances that are otherwise nonabsorbable may be absorbed during sepsis.[2] We report two deaths associated with the systemic absorption of blue dye no. 1 from enteral feedings; in both cases, the absorption was heralded by the appearance of blue or green skin and serum.

A 54-year-old woman with chronic renal failure was hospitalized for congestive heart failure and confusion. Hemodialysis and nasogastric feeding were initiated. Later, staphylococcal pneumonia with sepsis was attributed to aspiration, prompting the addition of blue dye no. 1 to her enteral feedings. The patient was febrile but hemodynamically stable until two days later, when her skin and serum turned green. She died of refractory hypotension and acidosis that day.

A 12-month-old boy with trisomy 21 underwent tracheostomy for obstructive apnea. Pseudomonas pneumonia with sepsis developed; aspiration was believed to have occurred. Blue dye no. 1 was added to his enteral feedings. He remained hemodynamically stable, with normal renal function, until the next day, when his skin (Fig. 1), serum, and urine became blue and hyperthermia developed (rectal temperature, 47°C). He died of refractory hypotension and acidosis that day.

Neither patient had bacteremia. Autopsies of both patients revealed green or blue discoloration of the skin and internal organs, without gastrointestinal perforation. Light-spectroscopic analysis of the child's serum and of the stock of blue dye no. 1 revealed identical, single absorption peaks at 629 nm (a peak that was absent in control serum), confirming the systemic absorption of dye. Although the blue tinting of feedings was visually titrated at our institutions, it is unlikely that oral-intake limits established by the Food and Drug Administration (FDA) for blue dye no. 1 (12 mg per kilogram of body weight per day)[3] were exceeded. The adult patient had renal failure, which is notable given that this dye is cleared by the kidneys.

FD&C blue dye no. 1 was approved by the FDA for use in food after experiments showed that the dye was nontoxic and was not absorbable. However, these experiments were performed in healthy animals.[3] Artificial food dyes can inhibit mitochondrial oxidative phosphorylation in vitro by acting as uncouplers (as does 2,4-dinitrophenol), by blocking electron transport (as does cyanide), or by inhibiting energy transformation by blocking the generation of ATP. Blue dye no. 1, a triphenylmethane dye, is a potent inhibitor of mitochondrial respiration in vitro[4] and reduces oxygen consumption by a factor of eight in mitochondrial preparations in vitro.[5] It appears to inhibit energy transformation by blocking the adenine nucleotide translocator (as is the case with atractyloside).[5]

Although both patients had serious underlying illnesses, their condition was improving before they received the dye and turned color. We hypothesize that the refractory hypotension and metabolic acidosis seen in these patients may be explained by the known biochemical effects of this dye, since neither patient had hypotension or severe acidosis immediately before the discoloration. The hyperthermia in the child may represent an uncoupling effect of FD&C blue dye no. 1 that is not apparent in vitro. We encourage judicious use of this food dye in patients with sepsis or other illnesses associated with increased gastrointestinal permeability.

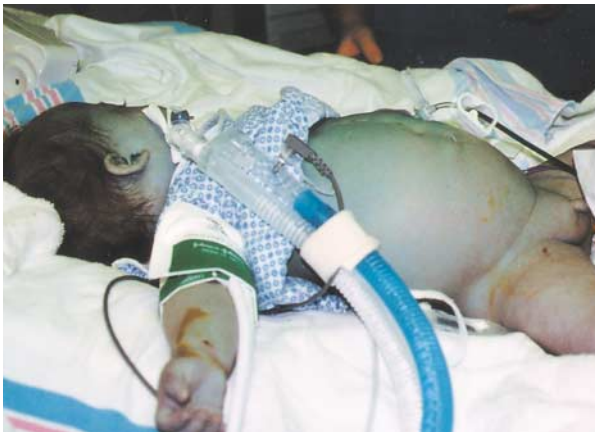

Figure 1. Blue Discoloration of the Skin in a 12-Month-Old Boy Who Had Received Enteral Feedings Tinted with FD&C Blue Dye No. 1.

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