specific antibodies); CD4+, CD8+, and natural killer cells; and functional antibodies to the nonstructural protein NS1. We agree that dissection of immune responses over time, including serotype-specific antibodies, in seronegative and seropositive participants in phase 3 efficacy trials is important to understand the role of specific immune responses in protection against each dengue serotype.

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Drs. Tricou and Dean report being permanent employees of the Takeda Group of companies. Since publication of his article, Dr. Biswal reports no further potential conflict of interest.

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Effects of Intermittent Fasting on Health, Aging, and Disease

TO THE EDITOR: In their review article, de Cabo and Mattson (Dec. 26 issue)[1] suggest potential positive effects of intermittent fasting. We would like to highlight safety concerns regarding intermittent fasting in persons with diabetes mellitus. Furmli et al. reported a considerable reduction in or elimination of the need for oral antihyperglycemic agents and insulin in persons with type 2 diabetes after the onset of fasting.[2] In a prospective trial involving adults with type 2 diabetes who were participating in a 5:2 intermittent fasting regimen (fasting 2 days each week), the mean medication effect score for oral antihyperglycemic agents and insulin was reduced.[3] The investigators anticipated a reduction in the dose of the antihyperglycemic agent and used a medication management protocol[3] that was modified for patients with hypoglycemia. The dose reduction occurred as early as 5 days after the initiation of the fasting protocol,[2] and most changes in medications occurred within 3 months.[3]

When prescribing intermittent fasting for persons with diabetes, a reduction in the dose of the antihyperglycemic agent should be anticipated early in treatment. The risk of hypoglycemia is increased, particularly among patients who are receiving insulin or sulfonylureas, and it is more pronounced on restricted-feeding days.[3] Caution is warranted in persons with a history of hypoglycemic unawareness. Intermittent fasting is probably safe in persons with diabetes that is controlled by dietary changes alone.[3]

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TO THE EDITOR: The article by de Cabo and Mattson promotes intermittent fasting as a dietary pattern that has cardiovascular benefits, including reduced blood pressure, lipid levels, and inflam-

matory markers. Although the authors also report improvement in insulin sensitivity, the results of one study appear to be variable, especially among patients in different weight categories.[1]

Although fasting may affect obese and nonobese patients differently, the particular regimen and how the regimen syncs with one's circadian rhythm may contribute to the success of the diet. Regimens that match the circadian clock may improve insulin sensitivity, lipid production, and blood-pressure control because persons who adhere to such regimens avoid eating late in the day and in doing so may decrease their cardiovascular risk.[2,3]

Finally, given the benefits that the authors mention with respect to recovery of ischemic tissue after trauma and traumatic brain injury, future studies are warranted to determine whether fasting reduces myocardial injury. A study involving mice with myocardial infarction showed that fasting decreased inflammation, adverse remodeling, and mortality.[4] Intermittent fasting appears to be promising in reducing cardiovascular risk factors.

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

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TO THE EDITOR: The review article by de Cabo and Mattson concludes that "intermittent fasting has broad-spectrum benefits for many health conditions," and the authors present "sample prescriptions" to implement intermittent fasting in clinical practice. However, these clinical conclusions and recommendations overstate the evidence presented in the article.

The authors frequently cite results of studies of caloric restriction as evidence of the efficacy of intermittent fasting. Select outcomes are presented from case reports, case series, and small clinical trials to support the idea that "obesity, diabetes, cardiovascular disease, and cancers" are "major indications" for intermittent fasting. The authors present data from three randomized, controlled trials with sample sizes of 100 participants or more that assess intermittent fasting; all three trials compare intermittent fasting with caloric restriction with respect to effects on measures of metabolic health.[1-3] Two randomized, controlled trials showed that weight loss and most metabolic markers were not different between participants assigned to intermittent fasting and those assigned to caloric restriction.[1,2] Although one randomized, controlled trial showed a significantly greater reduction in body fat and insulin resistance with intermittent fasting than with caloric restriction, no significant differences were observed in other metabolic measures, including the glycated hemoglobin level, cholesterol level, weight, and waist circumference.[3]

Further investigation of intermittent fasting is warranted, given its promising results in animal models. However, it is important that clinical conclusions and recommendations accurately convey the limited clinical evidence available.

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TO THE EDITOR: In their review article, de Cabo and Mattson describe the eventually favorable assignment of the benefits of caloric restriction to the inadvertent intermittent fasting that participants underwent during caloric restriction. It would be prudent to consider the benefits of intermittent fasting as a possible further surrogate for restriction of protein and especially restriction of branched-chain amino acids (leucine, isoleucine, and valine). These branched-chain amino acids are commonly found in meat products and are difficult to obtain in predominantly plant-based diets.[1]

Protein restriction provides a novel route to cellular mechanisms involved in intermittent fasting; in Figure 1 of their article, de Cabo and Mattson show how amino acid sensing can activate the mammalian target of rapamycin (mTOR) directly. In particular, leucine restriction has been shown to have a potent effect on cellular signaling, similar to that which occurs in intermittent fasting.[2]

Low dietary protein and a predominantly plant-based diet are a fundamental part of the Okinawan diet discussed by the authors. Similar diets are common in so-called blue zones, regions of the world where people have been found to live longer than average.[3] Further experimental studies that account for the protein content and, ideally, the amino acid composition of the eating period in intermittent fasting diets are warranted to avoid potentially aberrant conclusions.

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

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THE AUTHORS REPLY: The letters prompted by our recent review article provide valuable information for physicians when they consider the effects of intermittent fasting on the health of patients. Lamos et al. rightly point out that the improvement in insulin sensitivity afforded by intermittent fasting could enable patients with type 2 diabetes to reduce or eliminate their dependence on antihyperglycemic drugs. We agree that it is imperative that these patients transition to an intermittent-fasting eating pattern under the supervision of their physicians and with careful monitoring of blood glucose levels while tapering their medication dose. The potential for hypoglycemia during short fasting periods can be reduced by a gradual transition to intermittent fasting, as suggested in Figure 4 of our article.

In the case of daily time-restricted eating, the question posed by Dong et al. of whether and how the timing window for eating and circadian rhythms affect health outcomes remains to be answered. This is important because the notion that breakfast is the "most important meal" is not supported by evidence.[1] To properly answer this question, randomized, controlled trials that are designed to directly compare early with late 6-to-8-hour eating periods should last at least 2 months to enable full adaptation to the new eating pattern.

In response to Kleinman and Kleinman: our review article stated that animals on caloric restriction consume their entire daily allotment of food within a few hours after its provision and, therefore, they fast for approximately 20 hours every day (see Section S1 in the Supplementary Appendix, available with the full text of our article at NEJM.org).[2,3] Regarding studies in humans, we agree that randomized, controlled trials of intermittent fasting should include a control group matched for weekly calorie intake.[4] Our suggestion that intermittent fasting might prove to be beneficial in patients with diabetes, cardiovascular disease, and cancer is based on clear findings from studies in animals and from scores of studies in humans.

Finally, Saad notes that inhibition of the mTOR pathway by dietary protein restriction may elicit beneficial effects on health similar to those of intermittent fasting. This has important implications for health and disease risk because the notion that a high-protein intake is good for health is a myth promulgated by some food and dietary-supplement industries. However, a low-

protein diet alone may not elicit the same organismal response as intermittent fasting, and data from randomized, controlled trials that compare intermittent fasting with low-protein diets are lacking.

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Since publication of their article, the authors report no further potential conflict of interest.

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