To the Editor: Drs. O'Keeffe and Lavie take issue with my position that it is premature to recommend vitamin E supplementation for the prevention of coronary heart disease. They say: "Vitamin E appears to provide substantial protection against coronary heart disease." "Appears" is the operative word. Yes, there is impressive experimental evidence for the hypothesis that oxidation of low-density lipoprotein plays a major part in atherosclerosis and that such oxidation occurs in humans. However, there is also epidemiologic evidence correlating vitamin E intake with an increased risk of coronary heart disease, including two recent papers in the Journal. However, not a single clinical intervention trial demonstrating efficacy has been published in detail. "Appearing" to provide protection just will not do. The analogy with the current widespread use of prophylactic angioplasty is more an argument for appropriate evaluation of that intervention than a justification for a green light on other incompletely tested interventions. Moreover, the analogy is not exact: the benefits of angioplasty have at least been demonstrated in patients with symptomatic coronary heart disease, whereas there is no evidence of clinical benefit from vitamin E supplementation at any stage of this disease.

Drs. O'Keeffe and Lavie make the "It can't hurt" argument. I agree that vitamin E is unlikely to be toxic, which would justify lowering the required level of proof of efficacy. But it certainly does not totally remove the need for such proof. Moreover, once the use of vitamin E is endorsed, even if only in high-risk patients, most patients will conclude that it is beneficial and will probably neglect risk factors that are well established but that make more than pill-popping to change (e.g., smoking and intake of saturated fat).

Finally, Drs. O'Keeffe and Lavie say that many physicians are convinced that vitamin E works, sufficiently so to be taking it themselves, thus implying that this fact alone justifies recommending its use. I cannot agree. We must insist on an objective demonstration of efficacy. Recall that at one time most physicians were convinced of the value of prophylactic tonsillectomy.

I find myself in the somewhat anomalous position of arguing against clinical intervention and medical advice based on a hypothesis that my colleagues and I played a major part in developing. Do I believe that vitamin E supplementation will prove efficacious? I certainly hope so. However, that makes me no less demanding of clinical proof of efficacy than I would be in the case of any other proposed intervention. At the same time, I recognize that proof is not an all-or-nothing matter; there are levels of proof. Even results of clinical trials have P values attached to them. Practitioners (and patients, too, since prescriptions are not required) will decide for themselves what to do about vitamin E. They should be clear, however, that at this time no one can truly state, "This medicine will help you." And there is no rush. Clinical intervention trials are already in progress, and we should have a definitive answer in a few years.

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To the Editor: I suggest that the observations of Taveira da Silva et al. cast further doubt on the role of endotoxin in the sepsis syndrome.

The patient's elevated pulmonary-capillary wedge pressure 12 hours after the endotoxin injection and the rapid therapeutic response, with a decrease in heart rate following the administration of furosemide after 44 hours, suggest that the pulmonary edema was more likely a consequence of the positive fluid balance of 15 liters than of a capillary leak.

The metabolic and coagulation abnormalities were surprisingly mild given the 1-mg dose of endotoxin administered and the levels of tumor necrosis factor (and endotoxin) that were measured. If each Escherichia coli cell is assumed to contain a total of 10^-14 g of endotoxin, the dose of endotoxin administered was equivalent to the total contained in 10^-11 bacterial cells. This is 10 times the 100 percent lethal dose (10^-10 cells) of live E. coli bacteria in baboons — a dose at which the mean time to death is eight hours.

I disagree with the conclusion that the successful outcome may have been due to the limited nature of the insult. The
standard of care for neurosyphilis in the prepenicillin era was the infusion of endotoxin over a period of several days, with dose escalations reaching a level equal to that self-administered by the patient. After a period of adaptation, patients with neurosyphilis were said to tolerate the infusions so well that the treating physicians would administer viable malarial parasites as a second-line agent to produce fever.

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The authors reply:

To the Editor: In response to Dr. Stern we wish to point out that details not germane to the effects of endotoxin were omitted from the case report at the patient’s request. This was the patient’s only instance of self-induced illness, and the patient did receive appropriate inpatient and outpatient care.

We disagree with Dr. Hurley’s statement that this case casts “further doubt on the role of endotoxin in the sepsis syndrome.” Our patient had all the clinical manifestations of septic shock, confirming that endotoxin alone can initiate these events. The positive fluid balance of 15 liters was part of the resuscitation effort. Fluid loading to increase the pulmonary-capillary wedge pressure to 12 to 18 mm Hg and to optimize ventricular performance is standard in the treatment of septic shock.1 The fluid requirement is in itself an indication of increased vascular permeability. Furthermore, as the shock syndrome resolves, the need for a small dose of furosemide after fluid resuscitation is not unusual.

Data on infusions of live bacteria in other species should not be extrapolated to this case. The toxicity of different preparations of endotoxin can vary widely. In addition, the median lethal dosages of different bacterial strains can vary by several logs. We agree, however, that factors other than endotoxin may cause or affect the development of septic shock. Endotoxemia is not a necessary component of septic shock,2 and even in gram-negative infections, bacterial products other than endotoxin may be important contributors to toxicity.3 Furthermore, it is not yet clear that therapies directed at endotoxemia itself will be of benefit in septic shock.4 Once this syndrome has developed, neutralization of circulating endotoxin may not be useful, because tachyphylaxis to endotoxin (tolerance) may develop or ongoing toxicity may be due to tissue- or cell-associated endotoxin.

The treatment we used is not analogous to the treatment of neurosyphilis. That therapy employed killed bacteria preparations (not purified endotoxin), prolonged infusions (not bolus injections), and the gradual acclimation (over a period of several days) of the patients to material containing endotoxin. Tolerance to repeated challenges of endotoxin has been well described.5 Dr. Hurley implies that our patient survived because endotoxin is safe in the dose administered. The patient presented to the hospital with a blood pressure of 42/20 mm Hg and required norepinephrine infusion for two days. It seems reasonable to conclude that without medical intervention, death was imminent.

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PATHOGENETIC MECHANISMS OF SEPTIC SHOCK

To the Editor: Dr. Piarillo (May 20 issue)1 raises an important issue concerning the use of inhibitors of nitric oxide synthase in septic shock in his article “Pathogenetic Mechanisms of Septic Shock.” The view that these inhibitors may be harmful in the treatment of septic shock is based on experiments in animals given 2 to 4 mg of endotoxin per kilogram of body weight. These amounts of endotoxin are 1 million times greater than those that cause cardiovascular changes in humans.2 In contrast, only concentrations of endotoxin measurable in picograms per milliliter have been detected in the serum of patients with septic shock. Although the administration of very high doses of endotoxin to animals results in marked cardiac decompensation that is not influenced by or attributable to nitric oxide synthase inhibitors,3 in animals given lower doses of endotoxin or cytokines that are known to mediate septic shock, these inhibitors are potent and potentially useful pressor agents.4 In preliminary studies of patients with septic shock, the administration of Nω-monomethyl-L-arginine, an inhibitor of nitric oxide synthesis, resulted in a prompt increase in blood pressure.5 Although inhibitors of nitric oxide synthase are a novel class of drugs and specific compounds may have unexpected toxic effects, they may be useful for a condition that is difficult to treat and associated with a high mortality.

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Editor’s note: The authors are among the inventors of a patented method of using arginine derivatives to inhibit systemic hypotension associated with nitric oxide production. M.D. Anderson Cancer Center and Cornell University

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