tients 2 and 6 collapsed during extreme exercise and fasting for rapid weight loss. In addition, Patient 7 did not have an adverse event; her premature infant died from necrotizing enterocolitis. An autopsy in Patient 9 demonstrated the anomalous origin of the left coronary artery from the pulmonary trunk, a well-known cause of sudden death. With an adequate explanation of the reported adverse events, the implication of ephedrine-type alkaloids in deaths from a wide variety of conditions that occur in the general population is no more than idle speculation.

GROVER M. HUTCHINS, M.D.
1 Stratford Rd.
Baltimore, MD 21218

1. The National Women's Health Information Center. Public Meeting on the Safety of Dietary Supplements Containing Ephedrine Alkaloids, Washington, D.C., August 8 and 9, 2000. (See http://www.4woman.gov/owh/public.)
2. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. N Engl J Med 2000;343:1833-8.

To the Editor: We wish to report on a previously healthy, 19-year-old male bodybuilder who had a myocardial infarction after using ephedra.

The patient reported chest pain of 30 minutes' duration that had begun shortly after the use of Dymetadrine Xtreme. He dissolved the recommended dose (two tablets, each reported to contain 24 mg of ephedra alkaloids and 100 mg of caffeine[1]) in water and drank the solution, as he had done in the past. Severe chest pain, radiating to the left arm, developed 15 minutes later. He had no history of chest pain or cardiac disease and reported that he had no other cardiac risk factors, including cocaine use. Vital signs were as follows: pulse, 116 per minute and regular; blood pressure, 147/84 mm Hg; respirations, 22 per minute; temperature, 37.3°C (99.1°F). The physical examination was otherwise unremarkable except for diaphoresis.

The electrocardiogram showed evidence of an inferolateral myocardial infarction. The patient was given oxygen, aspirin, heparin, and nitroglycerin, and his ST-segment elevation resolved. Five hours later, inferolateral ST-segment elevation recurred. After treatment with phentolamine and labetalol, the electrocardiographic findings again returned to normal. The creatine kinase level was initially 351 U per liter, with an MB fraction of 23 ng per milliliter; it peaked at 1271 U per liter, with an MB fraction of 104 ng per milliliter. The value for troponin I peaked at 256.1 ng per milliliter. A toxicologic test of a urine specimen was negative for cocaine. Echocardiography revealed hypokinesis of the inferior wall. Cardiac catheterization demonstrated only minimal intimal disease of the distal left anterior descending artery. The patient recovered and was doing well at follow-up.

The temporal association between the use of the supplement and the infarction, the absence of clinically significant findings on cardiac catheterization, and the negative test for cocaine led us to conclude that the myocardial infarction was caused by the use of ephedra.

This case highlights the potential dangers of ephedra use by presumably healthy persons. Given the growing numbers of reports of ephedra-related adverse events, both the general public and the medical community should be alerted to the dangers posed by over-the-counter products containing ephedra. Furthermore, we urge greater regulation of these potentially lethal products.

STEPHEN J. TRAUB, M.D.
New York City Poison Control Center
New York, NY 10016

WISSAM HOYEK, M.D.
Staten Island University Hospital
Staten Island, NY 10305

ROBERT S. HOFFMAN, M.D.
New York City Poison Control Center
New York, NY 10016

1. AST sports science Web site. (See http://www.ast-ss.com.)

The authors reply:

To the Editor: Dr. Hutchins argues that because several of the patients who had severe cardiovascular events while taking ephedra-alkaloid–containing dietary supplements had underlying disease, it is idle speculation to implicate the dietary supplements as the cause of these events. Before addressing the individual cases mentioned by Dr. Hutchins, we would like to restate our point that ephedra-related events are uncommon but are most likely to occur in vulnerable populations. Persons with underlying cardiovascular disease are an obviously vulnerable population. The effects of ephedrine and caffeine — constricting blood vessels, increasing blood pressure, and releasing catecholamines — would be most likely to cause injury in persons with underlying cardiovascular disease. In such persons, ischemia, infarction, or arrhythmias, or a combination of these events, could well be precipitated by the sympathomimetic effects of ephedrine and caffeine. Most important, these cases illustrate that people with unrecognized cardiovascular disease are using products that are potentially hazardous to them.

In response to Dr. Hutchins's comments on individual cases, it should be noted that in some cases the information provided to us by the FDA differed from that cited by Dr. Hutchins. In any case, assuming that the information provided by Dr. Hutchins is correct, one should be concerned about a 43-year-old man with chest pain (Patient 4 in Table 4 of our article) or a patient with known hypertension (Patient 5 in Table 4) who is taking a supplement that contains an ephedra alkaloid. These circumstances raise questions about the adequacy of warnings about contraindications. The fact that two patients collapsed and died during extreme exercise and dieting underscores another serious concern about the use of ephedrine-containing dietary supplements, which are recommended for increased energy and weight loss. On the basis of the known pharmacologic characteristics of ephedrine and caffeine, these drugs might be likely to have more injurious effects in the context of intense exercise. Likewise, a person with a congenital anomaly of a coronary artery might be more likely to have ischemia in the presence of a sympathomimetic drug. With respect to Patient 7 in Table 5 of our article, the adverse event was fetal death, which was presumed to be due to premature delivery, which in turn may have been induced by the consumption of ephedrine-containing dietary supplements.

Thus, it is likely that unrecognized cardiovascular disease confers a predisposition to adverse events associated

with the use of ephedrine-containing dietary supplements. The fact that several persons had underlying cardiovascular disease does not mean there were no adverse reactions to these dietary supplements. Even if appropriate warning statements were listed on the product labels, users with unrecognized risk factors could not be expected to respond to such warnings. Until there is a way to identify persons who are at risk for adverse effects, supplements containing ephedra alkaloids should be considered unreasonably dangerous. Perhaps one solution is to perform coronary angiographic screening of all patients before they take these products.

Finally, our report describes a series of cases in which the use of ephedrine-containing dietary supplements was associated with adverse cardiovascular events. Our report does not prove causation, nor does it provide quantitative information with regard to risk. A large-scale case–control study similar to the Hemorrhagic Stroke Project for phenylpropanolamine[1] is needed to determine the risks associated with these dietary supplements.

CHRISTINE A. HALLER, M.D.
NEAL L. BENOWITZ, M.D.
University of California, San Francisco
San Francisco, CA 94143-1220

1. Kernan WN, Viscoli CM, Brass LM, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. N Engl J Med 2000;343:1826-32.

The Diagnosis and Treatment of Cough

To the Editor: We share the concern of Irwin and Madison (Dec. 7 issue)[1] about the unnecessary treatment of acute cough with antibiotics, which recent meta-analyses have shown has no clinically significant benefit.[2-4] However, we disagree with the authors' terminology. Irwin and Madison avoid the diagnosis of bronchitis for patients with cough and production of phlegm, but there are compelling reasons to retain the term. "Acute bronchitis" is common in the medical literature and is familiar to patients and physicians alike. Unfortunately, the diagnosis of acute bronchitis has traditionally been used as justification for the administration of antibiotics and has even been described as "a cough that gets treated with antibiotics." Instead of jettisoning the term, we favor educating both physicians and patients by informing them that antibiotics do not alter the course of acute bronchitis.

Several small studies have demonstrated the efficacy of β-agonists for decreasing the duration of acute cough. In one placebo-controlled trial,[5] 46 patients with acute bronchitis were randomly assigned, in a two-by-two factorial design, to erythromycin or placebo and albuterol or placebo. On day seven, 61 percent of the patients in the albuterol group were still coughing, as compared with 91 percent in the placebo group ($P=0.02$). The result was not influenced by the use of erythromycin.

Confirmatory studies are warranted, but the use of β-agonists makes biologic sense. Patients with acute bronchitis demonstrate obstruction on pulmonary-function testing.[6] Albuterol allows physicians to prescribe effective therapy, satisfy patients, and avoid unnecessary antibiotics.

JEFFREY A. LINDER, M.D.
RANDALL S. STAFFORD, M.D., PH.D.
Massachusetts General Hospital
Boston, MA 02114

1. Irwin RS, Madison JM. The diagnosis and treatment of cough. N Engl J Med 2000;343:1715-21.
2. Bent S, Saint S, Vittinghoff E, Grady D. Antibiotics in acute bronchitis: a meta-analysis. Am J Med 1999;107:62-7.
3. Smucny JJ, Becker LA, Glazier RH, McIsaac W. Are antibiotics effective treatment for acute bronchitis? A meta-analysis. J Fam Pract 1998;47:453-60.
4. Fahey T, Stocks N, Thomas T. Quantitative systematic review of randomised controlled trials comparing antibiotic with placebo for acute cough in adults. BMJ 1998;316:906-10.
5. Hueston WJ. Albuterol delivered by metered-dose inhaler to treat acute bronchitis. J Fam Pract 1994;39:437-40.
6. Williamson HA. Pulmonary function tests in acute bronchitis: evidence for reversible airway obstruction. J Fam Pract 1987;25:251-6.

To the Editor: There is increasing evidence that in many cases of acute cough the cause is not the common cold or acute bronchitis. Two recent studies showed that acute bronchitis is often (in about one third of cases) the first manifestation of asthma, which becomes full-blown in the next several years.[1,2] In nearly half of the patients presenting with a cough of at least two weeks' duration, there were signs of asthma or features of chronic obstructive pulmonary disease such as bronchial hyperresponsiveness (as measured with a methacholine challenge). Most patients could be classified correctly by history taking and physical examination only. Female sex, prolonged expiration, smoking, reports of wheezing and dyspnea, and symptoms elicited by allergens helped to predict the risk of asthma or chronic obstructive pulmonary disease.[3] The physician must decide whether to proceed with further examination, referral to a respiratory specialist, or initiation of treatment with inhaled corticosteroids or bronchodilators.

HENK A. THIADENS, M.D., PH.D.
MACHIEL P. SPRINGER, M.D., PH.D.
Leiden University Medical Center
Leiden 2301 CB, the Netherlands

DIRKJE S. POSTMA, M.D., PH.D.
University Hospital Groningen
Groningen 9700 AD, the Netherlands

1. Jonsson JS, Gislason T, Gislason D, Sigurdsson JA. Acute bronchitis and clinical outcome three years later: prospective cohort study. BMJ 1998;317:1433-4.
2. Thiadens HA, Postma DS, De Bock GH, Huysman DAN, van Houwelingen HC, Springer MP. Asthma in adult patients presenting with symptoms of acute bronchitis in general practice. Scand J Prim Health Care 2000;18:188-92.
3. Thiadens HA, de Bock GH, Dekker FW, et al. Identifying asthma and chronic obstructive pulmonary disease in patients with persistent cough presenting to general practitioners: descriptive study. BMJ 1998;316:1286-90.

To the Editor: Irwin and Madison provide excellent guidelines for the management of cough in primary care but do not address the use of opioid antitussive medications. Among the many opioid preparations, some contain as little as 2.5 mg of codeine phosphate per dose or as much as 1 mg of hydromorphone per dose. At equivalent doses, the analgesic potency of hydromorphone is 130 times that of codeine. Preparations containing up to 5 mg of hydrocodone (which is approximately four times as potent as codeine) per dose are also available. For codeine, cough suppression has been shown to be dose related, and the analgesic po-