1. Fleming GA. The FDA, regulation, and the risk of stroke. N Engl J Med 2000;343:1886-7.
2. Ekins BR, Spoerke DG. An estimation of the toxicity of non-prescription diet aids from seventy exposure cases. Vet Hum Toxicol 1983;25:81-5.
3. Lake CR, Gallant S, Masson E, Miller P. Adverse drug effects attributed to phenylpropanolamine: a review of 142 case reports. Am J Med 1990;89:195-208.

The authors reply:

To the Editor: Drs. Ernst and Hartz write that our study reports an increased risk of hemorrhagic stroke only in association with the use of appetite suppressants containing phenylpropanolamine and not with the use of decongestants that contain this agent. We disagree. Among women who were 18 to 49 years of age, the first use of any product containing phenylpropanolamine was associated with an increased risk of hemorrhagic stroke (odds ratio, 3.13; $P=0.08$). All first uses involved decongestants. Although this odds ratio did not reach conventional criteria for statistical significance ($P<0.05$), this criterion itself may be too stringent for evaluating potentially harmful associations.

Drs. Ernst and Hartz further argue that the main alternative to phenylpropanolamine, pseudoephedrine, is "not without potential problems." We examined the association between pseudoephedrine and the risk of hemorrhagic stroke in our subjects. Among 702 patients, 9 (1.3 percent) were exposed to pseudoephedrine as a first use (defined as use within 24 hours before the stroke and no other use during the preceding two weeks), as compared with 18 of 1376 control subjects (1.3 percent), yielding an adjusted odds ratio of 1.07 (95 percent confidence interval, 0.45 to 2.57; $P=0.87$). This point estimate for the adjusted odds ratio suggests that the use of pseudoephedrine is not associated with an increased risk of hemorrhagic stroke. As indicated by the upper bound of the confidence interval, however, we cannot exclude the possibility that it has a potentially harmful effect.

Drs. Ernst and Hartz and Dr. Wolowich and colleagues all argue that the stronger association between the use of appetite suppressants containing phenylpropanolamine and the risk of stroke than between the use of phenylpropanolamine-containing decongestants and the risk of stroke may be explained by differences in the dose. We believe that the dose may provide a partial explanation. The mean amount of phenylpropanolamine in appetite suppressants consumed over a period of three days was 300 mg (range, 75 to 600), as compared with 203 mg (range, 13 to 890) of phenylpropanolamine in cough or cold remedies. As we reported in our paper, higher doses of phenylpropanolamine were associated with higher odds ratios for stroke.

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The editorialist replies:

To the Editor: I accept the hypothesis of Wolowich et al. that women who abuse phenylpropanolamine in an attempt to lose weight represent a pattern of use that would explain — but only in part — the risk of stroke reported by Kernan et al. Wolowich et al. cite a 1983 report from a poison-control center of the adverse effects of phenylpropanolamine that not surprisingly found that most of the reported cases were in women who took very large doses of phenylpropanolamine.[1] This report helps characterize acute toxicity in the context of the abuse of phenylpropanolamine. More important, Kernan et al. establish that stroke is also associated with the use of phenylpropanolamine in the recommended way. The 1990 report cited by Wolowich et al. in fact establishes, and the study by Kernan et al. in effect confirms, that more than half the cases in that series of toxic reactions to phenylpropanolamine were associated with "non-overdose amounts."[2] No one is surprised when the abuse of a drug leads to adverse effects. The study by Kernan et al. establishes that women who apparently took phenylpropanolamine as directed were much more likely to have a stroke than matched control subjects who had not taken phenylpropanolamine. These findings, without need for further distinctions, are a sufficient basis for the conclusion that the risk–benefit ratios for the use of phenylpropanolamine as an antiobesity treatment and probably as a cough suppressant are unacceptable.

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1. Ekins BR, Spoerke DG. An estimation of the toxicity of non-prescription diet aids from seventy exposure cases. Vet Hum Toxicol 1983;25:81-5.
2. Lake CR, Gallant S, Masson E, Miller P. Adverse drug effects attributed to phenylpropanolamine: a review of 142 case reports. Am J Med 1990;89:195-208.

Dietary Supplements Containing Ephedra Alkaloids

To the Editor: As an anatomical pathologist and paid consultant to the Ephedra Education Council, I reviewed 22 reports of adverse events received by the Food and Drug Administration (FDA) in which death had occurred and assessed the likelihood that death was related to the use of ephedrine-type alkaloids. My review, reported August 8, 2000, at the Department of Health and Human Services's Public Meeting on the Safety of Dietary Supplements Containing Ephedrine Alkaloids, in Washington, D.C., showed no consistent clinical or pathological features of the reported adverse events and showed that ephedrine-type alkaloids were not likely to have been causative or contributing factors in the deaths.[1]

The report by Haller and Benowitz (Dec. 21 issue)[2] included eight of the cases I had reviewed and interpreted these adverse events as related to the use of ephedrine-type alkaloids. Table 4 of the report by Haller and Benowitz lists adverse events that were definitely or probably related to the use of ephedrine-type alkaloids, but in the column labeled "preexisting conditions or concurrent risks," the authors have omitted the following data: Patient 4 had chest pain, Patient 5 hypertension, and Patient 7 severe coronary artery disease. Table 5, which lists events possibly related to the use of ephedrine-type alkaloids, omits the fact that Pa-

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.

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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.

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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