ty and efficacy of the most commonly used dose while paying particular attention to the methodologic weaknesses of previous studies. Therefore, we tested a large population over a long period and used a standard measure of symptoms of benign prostatic hyperplasia, a well-matched placebo capsule, and an assessment of the adequacy of blinding. Given the contrast between our negative results and the positive findings of many previous studies, we believe it is important to conduct validation studies that could include a dose-ranging protocol and an active control (alpha-blockade).

We agree with Dr. Dimitrakov that LUTS may be caused by a number of different types of obstruction of the urethra or bladder outlet and that patients with certain forms of obstruction may not be expected to benefit from medications or herbs that reduce the size of the prostate or promote smooth-muscle relaxation. However, most previous clinical trials of saw palmetto and other medical therapies for patients with LUTS probably caused by benign prostatic hyperplasia simply enrolled patients who reported some threshold of severity of urinary symptoms, with other causes of LUTS excluded through history, physical examination, and directed laboratory testing, without an evaluation of the specific pathophysiological cause of those symptoms.

The patients who were enrolled in our study had characteristics (including the size of the prostate and transitional zone) that were similar to those of patients in earlier studies of pharmaceutical drugs for the treatment of LUTS caused by benign prostatic hyperplasia.[2,3] It is probably correct to say that our study found that saw palmetto was not effective for LUTS caused by benign prostatic hyperplasia,[4] but we chose to follow the precedent in previous studies of saw palmetto and used the term benign prostatic hyperplasia.

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Racial Differences in Lung Cancer

TO THE EDITOR: The study of ethnic and racial differences in the smoking-related risk of lung cancer by Haiman et al. (Jan. 26 issue)[1] omits an analysis of important potential confounders: a family history of cancer and parental exposure to relevant harmful substances (e.g., cigarettes, radon, inhaled particulates associated with mining, and pesticides). Paternal smoking can select for epimutations in sperm[2] and inhibit the production of DNA-repair enzymes such as O^6-methylguanine-DNA methyltransferase and MLH1,[3] causing heritable but nonfamilial susceptibility to cancer that is detectable in nonsmoking progeny as microsatellite instability, reduced DNA repair, early-onset cancer, or specific mutation patterns within tumors.[4] The association of achondroplastic germ-line mutations in the gene encoding fibroblast growth factor receptor 3 (*FGFR3*) — somatic homologues of which characterize bladder tumors in nonsmokers — with excess ancestral cancer[5] mirrors this epistatic model of transgenerational carcinogenesis.

Since each racial or ethnic group has its own family-smoking dynamic,[6] uncontrolled epigenetic–environmental interactions could contribute to apparent variations in cancer susceptibility. It may be timely to hypothesize about polymorphisms affecting carcinogen metabolism, yet it is also pertinent to note that lung cancer was extremely rare in all ethnic groups just two centuries ago. The elimination of noxious exposures through legislation and education may thus remain a surer

strategy than genomic research for reducing lung cancer in racial and ethnic minorities.

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TO THE EDITOR: Haiman and colleagues highlight metabolic differences as potential explanatory factors for the increased susceptibility to lung cancer of African-American and Native Hawaiian cigarette smokers in California and Hawaii. Differing cigarette preferences may also be a factor. The proportions of African-American and Native Hawaiian smokers who prefer mentholated cigarettes (74 percent and 55 to 83 percent, respectively) is markedly higher than the proportions of whites and Latinos (16 percent and 19 percent, respectively).[1,2] A previous California study found an increased risk of lung cancer among male smokers of mentholated cigarettes, as compared with the risk among male smokers of nonmentholated cigarettes (odd ratio, 1.45).[3] African Americans (primarily smokers of mentholated cigarettes) have also been found to take in 30 percent more nicotine per cigarette than do whites.[4] During the 1990s, California increased cigarette taxes and implemented bans on smoking in public places, resulting in marked reductions in cigarette consumption. Smokers of mentholated cigarettes may find it easier to maintain their usual nicotine intake by inhaling more deeply per cigarette without excessive irritation of the throat. The effects of menthol on the addictiveness and health effects of cigarettes warrant further attention.

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Dr. Foulds reports having received payment as an expert witness for plaintiffs in litigation against tobacco companies.

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THE AUTHORS REPLY: With regard to the comments of Dr. Foulds and colleagues: there are well-known differences in the type and brand of cigarettes preferred by racial or ethnic groups in the United States. The literature on whether smokers of mentholated cigarettes have a greater risk of lung cancer than do smokers of nonmentholated cigarettes has been equivocal, with two studies finding no association.[1,2] Dr. Foulds and colleagues point to one study that found a modest association among men (risk ratio, 1.45; 95 percent confidence interval, 1.03 to 2.02). In our study, we observed that the risk of lung cancer among African-American and Native Hawaiian smokers is two to three times that of smokers in other populations. Considering that one study[3] showed that 75 percent of African-American smokers favor mentholated cigarettes, as compared with 20 percent of Latino smokers, then we would expect the relative risk of lung cancer among smokers of mentholated cigarettes to be perhaps seven times that of smokers of nonmentholated cigarettes. The upper limit of the confidence interval (2.02) in the study by Sidney et al.[4] rules out an effect of this magnitude.

Drs. Epstein and Zhao present an interesting hypothesis regarding the role of transgenerational epigenetic phenomena in the alteration of racial or ethnic variability in the risk of lung cancer. Unfortunately, we are not able to address this hypothesis in the Multiethnic Cohort Study, since we did not collect information about parental exposures. In addition to parental exposures associated with the risk of lung cancer (e.g., ciga-

rettes, radon, and inhaled particulates associated with mining) that Drs. Epstein and Zhao mention, other exposures, such as dietary factors, may also result in a preprogramming of genes that alters susceptibility to carcinogens in cigarettes. These exposures would need to be widely distributed across racial or ethnic populations and would need to have strong effects in order to account for even a small fraction of the large differences in risk that we observed among racial and ethnic groups. These profound differences in risk need to be explained, and although genomic and epigenomic research has been proposed as a possible avenue of future research, we can all agree that the removal of cigarette smoking in all populations would have the greatest effect on public health.

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Aprotinin in Cardiac Surgery

TO THE EDITOR: Although potent and effective drugs may have undesirable side effects in some patients, we believe that the study by Mangano et al. (Jan. 26 issue)[1] overemphasizes the risk of aprotinin for the prevention of bleeding during cardiac surgery without a demonstration of its substantial benefits. This overemphasis may have occurred because of a flawed study design, imprecision in the definition of variables, selection bias during development of the study model, and a lack of proper weighting of evidence from the literature.

The observational study involved institutions in many countries with no reported uniformity in indications for drug administration. The period in which postoperative mortality was assessed was not stated. The sampling method that was used to identify study patients was peculiar, with more weight given to programs with a low volume of patients. The exclusion criteria that were used need further explanation, since the death rate among patients who were excluded from the study was three times that in the experimental group.[1,2] Furthermore, the rate of renal failure in a previous article from the same database was 7.8 percent,[3] not too different from the rate of 8 percent shown for aprotinin in Figure 2 of the article and substantially different from the control rate of 3 percent.[1]

Many important determinants of outcome were not described. These data included the use of antithrombotic drugs before surgery, the duration of cardiopulmonary bypass or other operative details, the amounts of blood transfused, and important postoperative details, such as use of inotropic drugs and the occurrence of hypotensive episodes, all of which can affect outcome. Moreover, the article minimizes the risk associated with blood transfusion and recommends the use of antifibrinolytic drugs (tranexamic acid and aminocaproic acid) that are either not approved for use in Australia, Japan, and Europe or not approved for this indication.

During the development of guidelines on blood-conservation strategies, the Workforce on Evidence-Based Surgery of the Society of Thoracic Surgeons found several dozen randomized trials, including a meta-analysis, and a Cochrane Collaboration summary that indicated no significant change in mortality, myocardial infarction, or the risk of renal failure associated with the use of aprotinin. Aprotinin was associated with a reduced risk of stroke and a trend toward a reduced rate of postoperative atrial fibrillation.[4,5]

The best evidence suggests that aprotinin has an acceptable risk–benefit profile and is indicated for blood conservation in patients at increased risk for bleeding (e.g., patients undergoing complex or repeated cardiac procedures and patients with either congenital or acquired abnormalities