

and folate may be even more beneficial. Screening patients with Alzheimer's disease for increased homocysteine levels may be particularly important when memantine therapy is established.

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THE AUTHORS REPLY: We thank Dr. Bleich and colleagues for their letter and acknowledge their pioneering work in helping to elucidate the mechanism of action of memantine. We agree that glutamatergic excitotoxicity and its effect on the NMDA receptor is a process relevant to many endogenous and exogenous physiologic conditions. We also agree that the full import of the therapeutic approach described in our article — namely, the use of non-competitive NMDA-receptor antagonism to effect a reduction in glutamate-induced excitotoxicity — requires further study.

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Mammographic Screening for Breast Cancer

TO THE EDITOR: I was troubled by the lack of a cost-benefit analysis in the article by Fletcher and Elmore on the effectiveness of mammography for screening for breast cancer (April 24 issue).¹ In fairness, their recommendations are more fiscally conservative than those of the U.S. Preventive Services Task Force. Still, their omission of any discussion of relative costs and benefits gives the implicit message that cost does not matter.

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1. Fletcher SW, Elmore JG. Mammographic screening for breast cancer. *N Engl J Med* 2003;348:1672-80.

TO THE EDITOR: The article by Fletcher and Elmore on mammographic screening is potentially misleading because it lumps "recalls" together with false positive mammograms (Fig. 1 of their article). A false positive mammogram refers to an interpretation of a screening mammogram as abnormal in a case in which there is no accompanying diagnosis of cancer.¹ A recall occurs when a screening mam-

mogram demonstrates an area of potential concern necessitating additional mammographic views for clarification. An interpretation is not rendered until these additional views are obtained. A recall is therefore distinct from a false positive mammogram.

This point is more than one of simple semantics. If the distinction between recalls and false positive interpretations is blurred, the negative effect of mammography is amplified. Such an analysis creates a subtle bias against mammography, which could be mitigated by careful adherence to these definitions.

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1. Sickles EA, Ominsky SH, Sollitto RA, Galvin HB, Monticciolo DL. Medical audit of a rapid-throughput mammography screening practice: methodology and results of 27,114 examinations. *Radiology* 1990;175:323-7.

TO THE EDITOR: The tone of the article by Fletcher and Elmore suggests that screening women in their 40s is still of questionable value. However, the rate

of death due to breast cancer, as a percentage of the rate of death from any cause, is highest among women in their 40s. A reduction in mortality of 20 percent among women in their 40s is a low estimate. The Gothenberg Breast Cancer Screening Trial,¹ the Malmö Mammographic Screening Program,² and the Swedish trials³ showed statistically significant reductions in mortality of 44 percent, 35 percent, and 29 percent, respectively, among women younger than 50 years of age. Furthermore, because of noncompliance and contamination, the trials underestimate the benefit. Women need to be provided with all the data in order to make informed decisions. The concerns raised by Gøtzsche and Olsen were either unwarranted or of no consequence,⁴ and the trial data remain valid.

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4. Kopans DB. The most recent breast cancer screening controversy about whether mammographic screening benefits women at any age: nonsense and nonscience. AJR Am J Roentgenol 2003;180:21-6.

TO THE EDITOR: Figure 2 in the article by Fletcher and Elmore misleads the reader by exaggerating the number of lives saved by mammography by a factor of 5 to 10. First, the authors assume a 30 percent reduction in mortality among women 50 to 69 years of age. The latest meta-analysis estimates that the reduction is 16 percent.¹ Second, the authors apply this 30 percent reduction in relative risk to the rate of death due to breast cancer calculated on the basis of a screened population rather than a control population, thus compounding the error. They estimate that four lives are saved by screening 1000 women 50 to 60 years of age for 10 years and that six lives are saved by similar screening among women 60 to 70 years of age. In reality, the number needed to screen is 1224 to save 1 life over a 14-year period¹

(approximately 1713, over a 10-year period); in other words, 5.8 lives will be saved per 10,000 women screened, not 4 or 6 per 1000 screened — almost a case of the missing zero. Among women younger than 50 years of age, the number needed to screen is approximately 2508 — that is, over a 10-year period, 4 lives will be saved per 10,000 women screened, not 20 per 10,000, as estimated by the authors.

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1. Humphrey LL, Helfand M, Chan BKS, Woolf SH. Breast cancer screening: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2002;137:347-60.

TO THE EDITOR: Fletcher and Elmore's account of the issues is not balanced. They describe a number of criticisms of our work that have been raised and — conversely — contend that all the criticisms of the mammography trials we raised have been answered, apart from those of one trial (in Edinburgh, Scotland) that was excluded from our meta-analysis.

First, the criticisms Fletcher and Elmore mention concern our first article in the *Lancet*, which were answered in our Cochrane Review and in our second *Lancet* article.¹ Second, the most important criticisms we raised against the trials remain unanswered^{2,3}: the biased misclassification of the cause of death, discrepancies in numbers in the analyses of the Swedish trials, and differential exclusions from analysis of women with breast cancer before randomization. For example, Fletcher and Elmore indicate that there was no problem with exclusions in the New York trial, but the trial's lead investigator admitted that even in 1985, more than 20 years after the study started, the investigators were unaware of some previous cases of breast cancer in controls, who should have been excluded.⁴

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THE AUTHORS REPLY: We strongly agree with Dr. Hensel regarding the importance of cost effectiveness. However, as we point out in our article, information about cost effectiveness is especially important for policymakers and payers when they are making decisions about the allocation of finite resources. The key issues for clinical practice are the underlying risk of the condition being screened for, the effectiveness of screening in the prevention of major untoward outcomes such as death, and the hazards associated with the screening procedure, such as false positive results.

Dr. Fishbein's concern about differentiating between recalls and false positive mammograms is understandable. The recall rate (which we defined as the percentage of mammograms that result in recommendations for further testing) includes both false positive and true positive mammograms, but because most positive mammograms are false positives, lowering the recall rate would most likely reduce the risk of false positive mammograms; this is important, because many studies have shown that false positive mammograms make women anxious.¹ Mammographers have a difficult task: they must not miss cancers, but they must also not recall too many women.

Dr. Kopans is concerned that the 20 percent reduction in the rate of death due to breast cancer that we used to calculate the number of women in their 40s whose lives would be saved by regular mammographic screening is too low, and Drs. Vaidya and Baum think our estimates are too high. Estimates differ mainly according to which trials are included in a given analysis. Whatever the estimate, Figure 2 of our article makes it possible to translate the relative effect into absolute numbers. For example, we estimated that 2 of 1000 women who regularly un-

derwent mammography during their 40s might owe their lives to mammography. If mortality due to breast cancer is reduced by 40 percent, the number would be about four.

In addition, Vaidya and Baum are concerned that we missed a zero in our calculations. They are mistaken, since the numbers in the figure are based on 10,000 mammograms. Because mammography is recommended repeatedly, we chose to demonstrate the effect of 10,000 mammograms in 1000 women tested annually for 10 years, rather than that of 10,000 mammograms in 10,000 women tested once each. We also included many other effects of a program of regular screening mammography.

We made a list of Dr. Göttsche's concerns about the randomized trials, along with responses we found, and presented them in a table in a supplementary appendix on the *Journal's* Web site (available with the full text of our article at <http://www.nejm.org>). Interested readers can review the list there.

Finally, we wish to point out an error in our article. The statement (beginning on the last line of page 1674) that "obtaining mammograms during the luteal phase of the menstrual cycle may decrease mammographic density" should have read "obtaining mammograms during the luteal phase of the menstrual cycle may decrease mammographic sensitivity."

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Skin Cancers after Organ Transplantation

TO THE EDITOR: Euvrard et al. (April 24 issue)¹ note that adjuvant radiotherapy may be useful in the management of squamous-cell carcinoma. Primary irradiation is not mentioned as a therapeutic option. Although surgery may be preferable, radiotherapy should also be given consideration. Candidates for radiotherapy include patients who cannot undergo surgery for medical reasons, patients with large lesions for whom surgery may be functionally or cosmetically disfiguring, and patients who wish to consider a noninvasive therapeutic option.

Regarding the management of cutaneous T-cell lymphomas, the authors state that current treatment is "unsatisfactory." Rituximab, bexarotene, and denileukin diftitox are described by the authors as promising therapeutic possibilities that are emerging. Radiotherapy is not presented as an option for management, although in the case of localized cutaneous T-cell lymphoma, it would be the first-choice therapy. The therapeutic options suggested by the authors are associated with response rates inferior to those achieved with localized irradiation