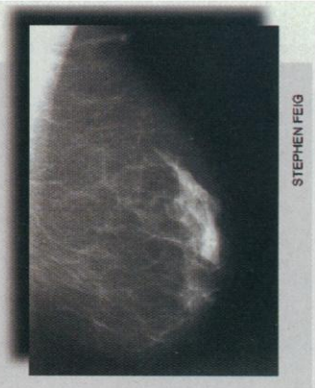
LETTERS

Cautious approach

Last week's discussion continues about whether regular mammograms (right) should be recommended to women in their forties. Two writers advocate the Chilean "Presidential Chairs in Science" program. A "rare bilateral gynandromorph" butterfly is called by its right name. And a growing proportion of elderly persons in a population does not necessarily mean that social services will be "crushed"—in Russia or in the United States.



STEPHEN FEIG

Breast-Screening Brawl

I am grateful for the News & Comment section, which gives the details of scientific news stories. I read the article "The breast screening brawl" by Gary Taubes (21 Feb., p. 1056; see also Letters, 14 Mar., p. 1549) with great interest, as this topic had made headlines in preceding weeks.

I was appalled at the level of the debate. Many of the participants' statements displayed a lack of understanding of what the statistical uncertainties in the various studies mean; most egregious was the demand for an explanation of why screening killed more people in the Canadian National Breast-Screening Study. This study showed no such thing; the results were statistically consistent with a conclusion of "no effect" or even a "benefit from screening" (as well as that of a detrimental effect). Until the level of understanding of mathematics and statistics is raised in this community, such "brawls" will continue to embarrass science as a whole.

James Sowinski
Department of Physics,
Indiana University,
Bloomington, IN 47405, USA

The heart of Taubes' article seems to be the statement that (p. 1057) "virtually all of the women active in the controversy, with the exception of breast cancer survivors or advocates [believe that] the chance of causing harm 'is greater than the chance of having the disease or dying from it.' "

Women are quite capable of seeking out reasonable medical care, which will be different for different women. We only need to hear the evidence; the decision is ours.

Helen Hansma
Department of Physics,
University of California,
Santa Barbara, CA 93106, USA
E-mail: hhansma@physics.ucsb.edu

Taubes suggests that the scientific arguments concerning the question of benefit from screening women ages 40 to 49 for breast cancer have been overshadowed by emotion. I would agree. However, this is a debate in which lives are at stake. I was disappointed by the portrayal of me in Taubes' sidebar "How one radiologist turns up the heat." It has never been my intent to "turn up the heat." I am not an "intellectual terrorist," and a careful review of what I have written and stated would show that my approach is "aggressive" only in the defense of science.

The screening controversy arose as a result of the unplanned subgroup analysis of women ages 40 to 49. Seven out of eight trials were not intended to be stratified by age, and their data lacked statistical power when women under the age of 50 were, retrospectively, analyzed separately (*1*). Even the data from the Canadian trial (*2*), purported to have been properly designed, lacked statistical power (*3*). Its other problems included nonblinded randomization, the knowing inclusion of women with advanced cancers, a statistically significant asymmetric allocation of advanced cancers to the screened group, poor-quality mammography, and differences in treatment between the screened women and the controls (*3*). Opponents of screening women ages 40 to 49 have not to my knowledge ever justified the use of unplanned subgroup analysis of data lacking statistical power to make medical recommendations.

Opponents of screening have repeatedly grouped women ages 40 to 49 and compared them to *all* women age 50 and over. Because the incidence of breast cancer increases steadily with age, this dichotomous grouping skews the analysis; by using the age of 50 as the point of analysis, that age has been made to appear as a true break point, when in reality it is not. Factors such as the density of the breast (*4*) and the cancer detection rate (*5*) change steadily with increasing age, with no abrupt change at age 50; the mammography recall rates and the rates of recommendations for biopsy are the same, regardless of age. There is no biological significance to the age of 50, yet it has been made to appear significant.

In an analysis (*6*) that was presented to the National Cancer Institute (NCI) Board of Scientific Counselors in 1993 and used by NCI as part of its justification for changing the guidelines, the authors not only grouped women ages 40 to 49, but they also added women ages 30 to 39 to the group and compared them to women ages 50 to 70+. Despite the fact that their data, when viewed by smaller age increments, reveal that the detection rate of breast cancer actually increased steadily with increasing age, reflecting the prior probability of cancer in the population, they concluded that, because the cancer detection rate was only 2 per 1000 for women ages 30 to 49, but 10 per 1000 for women ages 50 to 70+, screening should concentrate on women ages 50 and over. Their data show that there is no abrupt change at age 50. Nevertheless, their conclusion was repeated in the media and in an important review of the subject (*7*).

I had expressed concerns to the National Institutes of Health (NIH) Office of Medical Applications of Research over the organization of the Consensus Development Conference Panel on breast cancer screening and the secret selection of panel members. I was correctly quoted by Taubes as calling the 23 January statement by the panel "fraudulent." I did not, however, state this to the press, but specifically to the conference participants for the meeting record. I made this judgment on the basis of the information that had been provided to the panel over the preceding day and a half and because of the panel's apparent complete disregard of that information and their inclusion of significant information that was factually incorrect.

1) The panel was convened to review the latest data on screening, yet their statement made no mention of the latest results from the randomized, controlled trials of screening (*7*) or the data from the other studies that were presented (*8*).

2) The panel's report suggested there was no evidence of benefit from screening for women ages 40 to 49 before 10 years of follow-up, yet two studies (*8*, *9*) (both using shorter screening intervals than other trials) show that benefit can be detected after 5 to 7 years of follow-up.

3) The panel arbitrarily decided that any benefit that was not significant by 7 years was unimportant (*10*). Despite clear explanations as to why the benefit took longer to appear in the trials (too long an interval between screenings), the panel dismissed the benefit of screening for women ages 40 to 49, even though, in some of the trials, the benefit is greater than that shown for women ages 50 and over (*11*), and the curves for younger women continue to diverge, showing increasing benefit.

4) The panel's statement did not mention that, despite a general lack of statistical power because of unplanned subgroup analysis, two of the Swedish trials (Gothenberg and Malmo) have demonstrated statistically significant ($p = 0.05$) mortality reductions of 44% and 35%, respectively, for women in their forties. Compounding this omission, the panel stated (*10*) that "randomized clinical trials have shown clearly that early

detection . . . reduces breast cancer mortality in women ages 50 to 69," but they did not mention that there are only two trials (Health Insurance Plan and Kopparberg) for women ages 50 and over that are by themselves, significant (*11*).

5) The panel did not state that a statistically significant mortality reduction is demonstrated for women ages 40 to 49 when data from all of the trials are combined; this is so even when the markedly different and flawed Canadian trial (*2*) is included in the analysis (*12*).

6) The panel had been cautioned that analyzing trial data by age at diagnosis can introduce significant bias (*13*). They had also been informed that three of the trials had performed such analyses (Health Insurance Plan, Kopparberg, and Gothenberg) and that the majority of the benefit was a result of cancers being diagnosed before the women reached the age of 50. Nevertheless, the panel suggested that the benefit was a result of women in their forties reaching age 50 and of screening beginning to work. The panel did not offer a biological explanation as to how the body and cancers know when age 50 has been attained. Furthermore, two of the trials (Health Insurance Plan and Kopparberg) looked at the benefit by 5-year increments and found that it was actually greatest for women ages 40 to 44 who never reached the age of 50 during the trials. This also is contrary to the panel's statement (*10*) that "any benefit of mammography would be greater for women in their late forties."

7) The five Swedish trials (Ostergotland, Stockholm, Gothenberg, Kopparberg, and Malmo) did not provide clinical breast examination, yet the panel wrote (*10*) that the decrease in breast cancer mortality may be the result of other factors, "including CBE's [clinical breast examinations] given to women in the screening group."

8) The panel stated (*10*) that "false positive examinations are relatively more common in younger women" and that the rate of biopsies was higher, yet they had been provided with the data from three modern screening programs (University of California, San Francisco; Massachusetts General Hospital; and New Mexico Screening Program) which showed that the rates of recall for abnormal mammograms and the rate at which biopsies are recommended are the same regardless of age.

9) The panel stated (*10*) that mammography missed "one fourth of all invasive breast cancers" among women ages 40 to 49, while it missed only "one tenth" of cancers in 50- to 59-year-olds, but data presented at the conference from two modern screening programs (University of California, San Francisco and the New Mexico Screening Program) showed that the sensitivity of modern mammography was the same for women ages 40 to 49 as it was for women ages 50 to 59 (approximately 85%).

The screening controversy is deeply regrettable because it has obscured the underlying effort to reduce the death rate from breast cancer. Nevertheless, I believe that the defense of science is important and that truth should be pursued. "Society" may decide that it does not wish to support screening women ages 40 to 49 for breast cancer, but at least women should be provided with accurate information so that they can make informed decisions for themselves. The Panel correctly pointed out that the mortality reduction, as demonstrated in the screening trials, likely underestimates the potential benefit due to confirmation and noncompliance. No one is suggesting that mammography is the ultimate solution to the problem of breast cancer, but it is available today and can significantly reduce the death rate for women who begin screening by the age of 40.

Daniel B. Kopans
Department of Radiology, Harvard Medical School, and Massachusetts General Hospital, Boston, MA 02114, USA

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Presidential Chairs in Chile

We fully agree with Ivan N. Saavedra (Letters, 7 Feb., p. 738) that there is a need to foster competence of Chilean science in the international arena. However, his criticism of the recently created program of Presidential Chairs in Science is unfair. The competition for these Chairs is open to all senior scientists, and the Chairs have been assigned by an International Scientific Committee that has had among its members three Nobel laureates in science. The International Scientific Committee has decided with full independence to whom to assign the Presidential Chairs.

By good fortune, one can evaluate the procedures of the committee that has assigned these Chairs. The article cited by Saavedra ("Science in Latin America," 10 Feb., 1995, p. 819) highlighted two scientific fields in Chile—astronomy and biophysics. Biophysics was considered "one of the brightest areas of Chilean science." The International Scientific Committee has done nothing but stimulate strong research teams in these two areas. Six Chairs have been granted to biophysics and related fields, and four Chairs in Physics are in the hands of astronomers.

Last year, the Howard Hughes Medical Research Institute opened an international competition for Latin America and Canada in the Biomedical Sciences. Four fellowships have been awarded to Chilean scientists. Two were given to scientists holding Presidential Chairs, and the other two went to more junior scientists. In addition, in the last competition of the Chilean National Fund for Scientific and Technological Development, the research project of a scientist holding a Presidential Chair in Science obtained the highest score.

Pedro Labarca
Ramon Latorre
Department of Biology, Faculty of Sciences, University of Chile, and
Centro de Estudios Cientificos de Santiago, Santiago 9, Chile

I cannot disagree more with Saavedra's suggestion that the Chilean National Commission for Scientific and Technological Research is the only national agency that should distribute funds for science in Chile. On the contrary, the example of the United States suggests that having multiple funding agencies is an advantage. From the receiving end, what could be better than having more than one agency to apply to for funds? With diversity there is competition, and competition ensures that funding agencies with the best track record fare better when the nation's budget is discussed.

Saavedra goes so far as to say the Presidential Chair program is "fail[ing] to reach its objective." No serious scientific institution would return a verdict on a program that is less than 2 years old.