Third Strike for NCI Breast Cancer Study

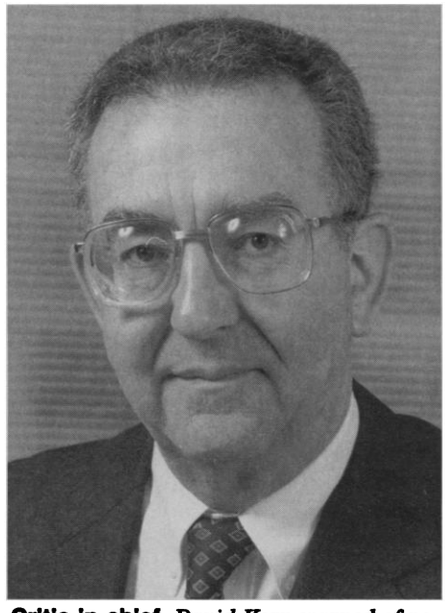
A $107-million "Women's Health Trial" has been sidetracked by the cancer board, arousing congressional ire

WHEN THE NATIONAL CANCER INSTITUTE (NCI) shelved a major study of diet and breast cancer last week, it aroused the ire of Representative Patricia Schroeder (D–CO) and other advocates of women's health issues. Schroeder blasted the agency and its scientific advisers for reneging on a commitment, warning that they're inviting "a declaration of war." Schroeder said that several leaders of the National Institutes of Health had promised her and other members of Congress that the "Women's Health Trial"—as the breast cancer study is known—would get off the ground in 1991. Instead, NCI has postponed the launch date in response to technical and ethical criticism from NCI's scientific advisers.

If it ever gets off the ground, the Women's Health Trial would be the biggest research experiment undertaken by NCI and the largest clinical trial ever to focus on women. It would attempt to answer a long-standing question: Can women reduce the risk of breast cancer by reducing the amount of fat they eat? The evidence so far is ambiguous. Japanese women living in their homeland have about half the incidence of breast cancer as those who migrate to Hawaii. And those who move to North America have still higher rates of breast cancer. The difference can be explained most plausibly by changes in diet. But according to Walter Willett of the Harvard School of Public Health, it's not clear exactly what in the diet one should suspect. The data support two hypotheses: that cancer risk goes up with increasing fat consumption, or that it goes up with increasing total caloric intake. Sorting this out would be expensive—the trial would cost $107 million, take 15 years to complete, and involve some 24,000 women.

To some, the study has become a test of the National Institutes of Health's newfound commitment to women's health issues. Recently, NIH was accused of focusing almost exclusively on men in large health studies (*Science*, 29 June, p. 1601). Indeed, the National Women's Health Network has been lobbying for years to get the Women's Health Trial going, and this cause was also taken up by members of Congress, whose lobbying prompted NIH to establish an Office of Research on Women's Health earlier this year. In September, says Schroeder, "Three of us—myself and [Senator] Barbara Mikulski (D–MD) and [Representative] Connie Morella (D–MD)—spent half a day" talking to directors at the National Institutes of Health, and "they said this study would be undertaken; they were emphatic about that." NCI's decision to go back on that assurance is "unbelievable...just outrageous," said Schroeder.

The institute may have had little choice, though. The project ran into a solid wall of opposition when it came before NCI's National Cancer Advisory Board on 3 December. The board voted to delay the experiment, even though the official presenting it—Peter Greenwald, chief of NCI's division of cancer prevention and control—had brought it before the board merely as a courtesy, not to seek approval. Board chairman David Korn, chief of Stanford University's Medical School, claimed the right to review this project like any other NCI expenditure. The members then rejected it (with one abstention), asking for more research on its design. Greenwald will follow this advice, but hopes to "initiate the first part of the study" within 3 years and scale up slowly to the original plan.



Critic-in-chief. *David Korn warned of potential ethical problems with the study.*

Many of the board members were worried about the study's feasibility and about the ethics of including thousands of women as untreated "controls" without giving them the best available dietary counseling. They concluded that there's a good chance that—even after spending more than $100 million—the NCI would get no conclusive results. "There are still too many loose ends on the table," said board member Samuel Wells of Washington University in St. Louis. Funding it now, without more information, Wells said, would be "like buying the Stealth bomber; we're going to buy this thing and get in trouble with it later."

The board's concerns are not new: The proposal had been shot down twice before by science advisers at NCI, once in 1988, as a contract research project, and a second time in 1989, when it surfaced as an investigator-initiated grant. In a December 1989 letter to NCI chief Samuel Broder, Korn urged the second of these denials in these words: "In the face of serious constraints on resources and the many important scientific opportunities in cancer research, it is not appropriate to fund a trial of this magnitude as an [investigator-initiated] grant...."

In a new approach this year, Greenwald planned to finance the Women's Health Trial as contract research. The plan he presented in December called for NCI to offer contracts next year to 12 clinics and two data centers. At least 24,000 women aged 50 to 69 would be recruited into the study. Of these, 9600 would be taught to keep a strict diet containing only 20% fat, and the other 14,400 would serve as untreated controls. Although they would get a pamphlet recommending they cut fat intake to 30% (NCI's recommended safe diet), they would not get counseling. And, based on experience, NCI officials would expect that their diet would be 38% fat. Clinicians would monitor the two groups for 15 years, noting differences in breast cancer, colon cancer, and heart disease.

This project would follow in the footsteps of an all-male heart disease study known as the Multiple Risk Factor Intervention Trials, or MRFIT. Epidemiologists still argue about the MRFIT results, and the Women's Health Trial would have some of the same problems, perhaps to a greater degree. The objections fall into several categories:

■ **Compliance.** Several board members, including Helene Brown of the Jonsson Comprehensive Cancer Center in Los Angeles, were concerned that the women would not stick to the two contrasting regimes—that the high-fat group might eat less fat and the low-fat group might eat more, blurring the distinction. Greenwald replied that, on the contrary, women in a

pilot study had followed the diet for more than 3 years. He added that the Women's Health Trial is designed with some flexibility: Even if the difference in fat consumption narrowed by as much as 50%, it would still be enough to provide a valid answer.

■ **Credibility.** Even assuming the women are eager to follow instructions, some board members said, it won't be possible to monitor them objectively. Their behavior will be checked by "self-reporting." Greenwald conceded that NCI has not yet found a biomarker that can tell whether a person has adhered to a prescribed diet, but Maureen Henderson, principal investigator for a pilot version of the trial at the Fred Hutchinson Cancer Research Center in Seattle, says that average cholesterol data can be used to keep track of group behavior.

■ **Educating the poor.** It is difficult enough to get middle-class people to change habits. This trial would face an additional challenge: It would have to motivate poor black and Hispanic women as well. By law, public health studies must include a "representative number" of minority and poor participants, and NCI's plan calls for one clinical center to focus on blacks and another on Hispanics. But board members, including Erwin Bettinghaus of Michigan State University, predicted that if the success of the study depends on getting poor people to follow the protocol, it will fail. Others suggested it would be hard to get the oldest participants, some of them over 80, to keep good records. These issues prompted a call for additional research.

■ **Ethics.** Some board members pointed out that the NCI has already declared that everyone should reduce fat intake to 30% of total calories to lower the risk of cancer. Given that this is federal policy, would it be right to allow women in a clinical trial to adhere to a less rigorous diet? Korn said it would be "unfortunate if people in 2003 were to look back at this in terms of a 1990s Tuskegee trial"—a reference to the syphilis study in which researchers withheld medication to enhance the quality of data. Criticism of this kind is unfair, says Henderson. She argues that in preventive studies like this, the control group always gets the usual and customary treatment—which in this case would be a pamphlet describing good dietary habits. The fact that some women would get extra help does not mean that the controls would be getting substandard therapy.

All of these issues will be reexamined as NCI officials try to respond to the questions that arose in the advisory board. But if Congress takes an interest—as Schroeder expects—it may not be able to take 3 years to get the answers. ■ ELIOT MARSHALL

Deficits Trip U.K. Science Funding Agencies

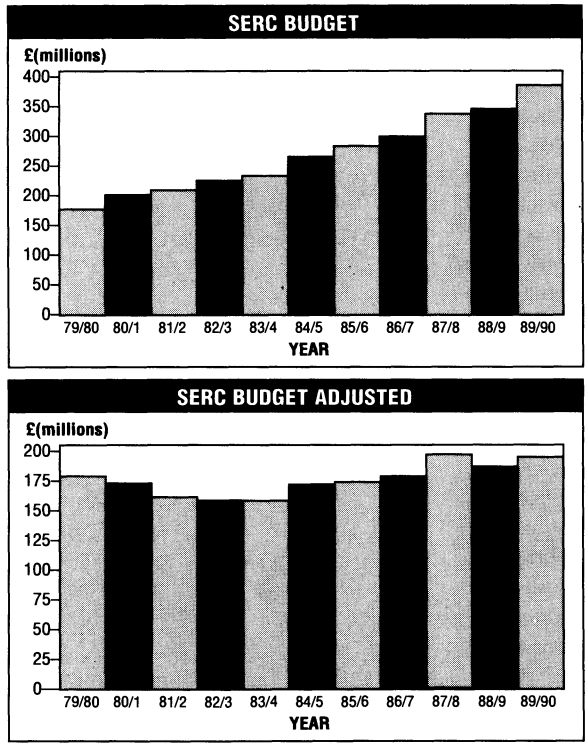
The Science and Engineering Research Council is the latest agency to be hobbled by a financial shortfall

A WAVE OF RED INK IS WASHING OVER BRITish science funding—with dire results for government-supported researchers. The Medical Research Council recently announced a freeze on recruitment and grants to make up for a deficit of £3.5 million. The Agricultural and Food Research Council is preparing to axe 300 jobs because of its deficit. And now the Science and Engineering Research Council (SERC), the largest source of government funds for nonmilitary research in Britain, facing a £40-million deficit, has frozen all new grants and fellowships for science students. In addition, SERC is embarking on a reconsideration of future priorities that may entail pulling out of "big science" projects that involve international collaborations. "There should be no stone unturned," said Sir Mark Richmond, SERC's chairman since October. "We have got to get our spending down by £40 million."

SERC's difficulties stem largely from "underindexation," government inflation forecasts that have consistently turned out to be low. Last year, the treasury figured 5% inflation into its grant to SERC of £407 million. Universities, however, agreed to a pay increase of 11% for researchers, and SERC is obliged to pay many researchers according to university pay-scales—but has no voice in salary negotiations. "Almost half the amount that we will be overspent is [the result of] underindexation," said Geoff Heaford, spokesman for SERC. Much of the other half is due to currency fluctuations that make Britain's contributions to international collaborations such as CERN more expensive than anticipated.

SERC's immediate cheese-paring consists of "natural wastage" of staff, along with halts on new research grants and training for doctoral candidates. Staff vacancies will not be filled, although there will be no layoffs—because SERC cannot afford severance pay. Research grants last year totaled £150 million, 37% of the budget. This year's first round of grants ended last month, and some lucky winners have already received letters notifying them of their awards. Those "will be honored," says Heaford. The rest will miss out: Their applications will go into the second round—next spring. Richmond acknowledges the unfairness of this expedient, adding that "the tragedy is that much excellent work will be jeopardized."

Among the largest awards to be frozen are three for Interdisciplinary Research Centers, large units designed to tackle academic problems that yield technologically exploitable results. One is for work on biomedical materials, one for work on biomechanical engineering, and the other for studies of nervous systems of simple animals. William Bonfield, head of the department of materials at Queen Mary and Westfield College at the University of London, and director designate of the IRC on biomedical materials, says he is "very hopeful" a rescue can be mounted. "It's obviously im-



Not so sterling. *The SERC budget (above) has grown steadily, but adjusted for inflation (below), it has been essentially flat.*