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Fisher Unable To Answer Key Questions, Blames NCI, At Second Hearing On NSABP

NCI officials are hopeful that a hearing last week marked the end of Congressional involvement in the controversy over mismanagement of the National Surgical Adjuvant Breast & Bowel Project.

Sources on Capitol Hill and at NCI said the subcommittee on oversight and investigations of the House Energy and Commerce Committee is not planning further hearings on NSABP.

The hearing June 15 was tragic for Bernard Fisher, the cooperative group's ousted principal investigator. Testifying before the subcommittee last Wednesday, Fisher was unable to answer key questions about the

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In Brief

General Motors Cancer Prizes Awarded; Thomas Promoted; HIV Research Funding

GENERAL MOTORS Cancer Research Prizes were awarded last week to five scientists. **Mario Capecchi**, Howard Hughes Medical Institute; and **Oliver Smithies**, Univ. of North Carolina-Chapel Hill; share the Alfred Sloan Prize for basic science. **Tony Hunter**, Salk Institute, received the Charles Mott Prize for understanding the causes of cancer. **Laurent Degos**, Hospital Saint Louis in Paris; and **Wang Zhen-Yi**, Shanghai Second Medical Univ., win the Charles Kettering Prize for advances in cancer treatment. . . . **ANNE THOMAS** has been appointed associate director for communications in the office of the NIH director. Thomas has been acting director since the retirement of Storm Whaley in 1992. She has served since 1991 has director of the NIH Div. of Public Information. She joined NIH in 1967. . . . **HIV RESEARCH** funding will be the topic of a Minority Investigator Workshop sponsored by the Div. of AIDS, National Institute of Allergy and Infectious Diseases and the NIH Office of Research on Minority Health, Sept. 28, from 8:30 am to 8 pm in Bethesda. Inquiries: Maggie Robinson, Div. of AIDS, NIAID, Tel: 301/402-0756, FAX: 301/480-5703. . . . **CORRECTION:** NCI funding for the clinical trials cooperative groups has experienced a 57.2 percent cumulative growth since 1991, not 1981, as reported in **The Cancer Letter** June 10, in the story on NCI Director Samuel Broder's remarks to the National Cancer Advisory Board. During the same period, from FY91 to the President's budget request for FY95, NCI funding as a whole has had 28 percent cumulative growth. The Institute spent $144.5 million on the groups in FY94, compared to $80 million in FY91.

NCI Shares Responsibility, Fisher Says; Broder Disagrees

(Continued from page 1)
controversy and made repeated attempts to shift the blame on NCI and his subordinates.

The examination of Fisher marked the first public questioning of the legendary clinical trialist since the controversy over scientific fraud and other irregularities erupted last spring.

Following Fisher's testimony, the subcommittee called on NCI Director Samuel Broder, who delivered a rebuttal of Fisher's claims.

"Anyone who knows NSABP will know that Dr. Fisher is the person who runs NSABP," said Broder, bouncing the blame back to Fisher.

If the hearing indeed marked the end of the controversy, the winners will be NCI and the Univ. of Pittsburgh.

The Institute emerged looking like it had done its duty to safeguard public investment in research.

The university, though lightly pummeled by Dingell and other subcommittee members, did little more than apologize for failure to detect problems at NSABP and promise to consider reimbursing the government for substandard data the cooperative group may have collected.

Fisher and biostatistician Carol Redmond are under investigation mandated by the NIH Office of Research Integrity.

The inquiry, conducted by the Univ. of Pittsburgh, will determine whether Fisher and Redmond had committed scientific fraud by continuing to publish papers based on data they knew to be tainted by fraud.

Another misconduct allegation stems from a delay by NSABP to disclose the endometrial cancer risk associated with the use of the drug tamoxifen.

THE CANCER LETTER

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The Fisher Version

In his testimony before the subcommittee last week, Fisher made the following claims:

- NCI was "intimately involved in the decision-making business of NSABP," Fisher said in his prepared testimony. "This was a cooperative agreement in name and in fact. Consequently, NCI must share with the NSABP responsibility for deficiencies in our project."
- Fisher said the growth of the cooperative group got ahead of his capacity to administer. "In retrospect, the administrative infrastructure of the NSABP did not keep pace with the tremendous growth," Fisher said.

"I could have been more aggressive in seeking funding for additional administrative personnel," Fisher said. "In retrospect, I believe I should have brought on an executive director to help manage the program."

Elsewhere in his testimony Fisher said he was more scientist than administrator. "I was on top of the development of the scientific program, the implementation of the scientific program, the pooling together of the information and the publication of the science," he said. "These were the chief efforts that I conducted."

- Fisher said he was not certain whether all reports from audits conducted by the cooperative group had been routinely given to him by the staff. "I received audit reports," Fisher said under questioning by the subcommittee chairman John Dingell (D-MI). "I cannot say with certainty whether these were routine or all audit reports."
- Under questioning by Dingell, Fisher said he was unaware of specific problems with the cooperative group's audits.

"We've not had a chance to review the subcommittee's investigations, or reports, or any other recent analyses, and we would certainly like to have the opportunity to do so, and provide the information to you," Fisher said.

- Fisher said he was unable to reconstruct the date when he learned of the endometrial cancer deaths due to tamoxifen. Asked by Dingell whether he knew of the deaths on Aug. 31, 1993, when the data report on the tamoxifen treatment trial revealed the deaths, Fisher said. "To the best of my knowledge, I was not aware of it."

As Dingell continued to press him on the issue, Fisher said, "I can't be sure... And I apologize for this... I wish the biostatisticians who were responsible for this kind of thing were here. But they are not, and I cannot answer this question."

The deaths were disclosed at an NSABP meeting Oct. 31, 1993.

●It was NCI that suggested that the informed consent form for the Breast Cancer Prevention Trial include the statement that no endometrial cancer deaths had occurred due to tamoxifen, Fisher said.

●Fisher said he was deluged with work at the time NCI directed him to reanalyze the data tainted by fraud at St. Luc Hospital in Montreal. "A lot of other things interfered with going ahead with this paper," Fisher said.

"At that particular time we were talking about some of the consent form changes, the problems with the prevention trial. There were people who were concerned about the prevention trial. [There were] recruitment problems, and there was always something which was coming in which seemed to take precedence over presenting this," Fisher said.

●"There are honest differences of opinion among statisticians regarding the handling of falsified data in large clinical trials," Fisher said, defending his decision to continue to include fraudulent data from St. Luc in NSABP publications.

"There are significant scientific reasons not to exclude all such data. Our statisticians considered that it was not appropriate to exclude all data from these patients who had a diagnosis of breast cancer and who had been randomized, treated and followed appropriately. Excluding all patients would prevent identification of toxicities and other adverse events."

●NCI had not been giving NSABP adequate funds for its audit program, Fisher said.

Asked whether he had approached the Institute with requests for additional funds for administration, Fisher said, "I believe so."

This contradicted the claim by the subcommittee that the annual budget for the auditing program requested by NSABP during recompetition in 1992 was $84,495, about 27 percent below the $115,280 level recommended by the peer review committee.

"Now who was it that cut the peer review committee's recommendations?" Dingell asked. "Did you do that? Or did someone else do that?"

FISHER: I'll have to let you know sir, I can't...

DINGELL: Does this appear to be a wise cut?

FISHER: No.

Broder Invokes Grantee's Responsibility

As the subcommittee gave him the final word, Broder declined to accept the blame Fisher assigned to the Institute.

"It is difficult for me to understand [Fisher's claim] that the trials grew too fast," Broder said. "There was a grant put in. The grant was put in by NSABP to perform a trial. Presumably the grantee knows what the grantee is asking in the trial."

Similarly, Broder said he could not accept the blame for the cuts in NSABP's budget for the auditing program.

"I certainly do not accept the principle that we at NCI inappropriately cut a deserving audit function," Broder said. "The exact proportionality that one chooses to commit for budgeting is in the hands of the grantee.

"I don't believe that most of these issues are focused on resources," Broder said. "Many of the issues that were identified earlier had to do with not acting on information as it came in, information that auditors had picked up."

Responding to Fisher's claim that it was NCI that altered the informed consent form for the Breast Cancer Prevention Trial to include a statement that no endometrial cancer deaths had occurred as a result of administration of tamoxifen, Broder said the statement was based on information provided by Fisher.

It was FDA that requested that the informed consent form specifically address the question of mortality from endometrial cancer, Broder said. "[NSABP officials] were asked, 'Were there any endometrial cancer deaths?' And we were told, 'No,'" Broder said. "Had we known then what we know now, that statement would not have been there, and I submit to you that a grantee has a duty to inform us."

Far from being involved in the business of the group, NCI was being kept in the dark on the issue of endometrial cancer deaths, Broder said. "I think we should have known that there were deaths," Broder said. "And if there [were] difficulties in sorting them out, then we would [have been] happy to participate."

Institute officials learned of the deaths as they listened to a presentation at an NSABP meeting, Broder said. "That puts us in the status of just another participant in the study, and I reject that concept." he said. "We are the grantor."

Fisher's claim that scientists have "honest differences of opinion" on the optimal way to handle scientific fraud misses the point, Broder said. "I really

think this is an ethics issue, not a statistical issue," he said. "We had received assurances that a paper [analyzing the effects of fraud at St. Luc] was being prepared. It was a surprise to us to learn that that did not occur."

Moreover, Broder said NSABP was inconsistent in its decision to keep the fraudulent data in its analyses.

"There was a publication that came out in June of 1993 which excluded the data from St. Luc origin site," Broder said. "The individual patients from St. Luc appeared to have been removed without a disclosure to the reader."

Pitt Distances Itself From Fisher

In their testimony, Pitt officials offered no support for Fisher and said he would play no official role in NSABP.

This is a significant change. After NCI ousted Fisher as the group's principal investigator, the university attempted unsuccessfully to bring him back as the cooperative group's chief scientist. Also, early in the controversy, attorneys hired by the university represented Fisher as well.

However, after the university was ordered to convene a panel to investigate possible scientific misconduct by the scientist, the university has been forced to make a formal separation of its interests from Fisher's.

Thomas Detre, senior vice chancellor for health sciences, concurred that NSABP has been poorly administered and that the flaws in the running of the cooperative group were not noticed by the university.

"Had I been motivated to probe the management of NSABP more deeply, I would certainly have done so," Detre said. "Why did I not?

"The answer, I believe, primarily relates to the culture of deference that has developed at universities over many, many years, if not centuries. The modern research university is primarily a highly decentralized system for research and teaching in which faculty, especially well-established senior faculty, have very considerable autonomy...

"Our expectation is that if there are problems, they will be reported by the senior faculty member to the chairman of the department, and through him, to the dean. But, clearly, this mechanism alone is insufficient... I believe that an external quality assurance and auditing program is absolutely essential," Detre said.

Pitt officials said the university is considering reimbursing the government for whatever substandard work was performed by NSABP. However, under questioning, officials were unable to provide more than a promise.

"Does the Univ. of Pittsburgh plan to reimburse the federal government the costs associated with generating significant amounts of unusable data?" asked Rep. Sherrod Brown (D-OH).

"We haven't come to a conclusion on that yet," said J. Dennis O'Connor, chancellor at the university.

BROWN: What's your thinking as the person in charge?

O'CONNOR: There are multiple costs involved. If there are legitimate costs that we should reimburse, then the university's position is that we will reimburse.

BROWN: What are legitimate costs? Give me some examples of what you would consider legitimate costs that you should reimburse.

O'CONNOR: I don't have any thoughts at the top of my head, Congressman Brown.

BROWN: Give me the costs that you shouldn't reimburse for.

O'CONNOR: That we should not reimburse...

BROWN: The government for. Since you can't seem to come up with any costs that you should reimburse us for, is there anything you shouldn't reimburse us for?

O'CONNOR: There may be costs that the federal government should be reimbursed for. And, as I said, the university will do that. I don't have a compilation of those costs in front of me right now...

Capitol Hill sources said Dingell had planned to ask Fisher whether any harm had come to the patients as a result of mismanagement of the trial, but the question was never posed.

However, earlier in the day, the Univ. of Pittsburgh officials, under questioning by Dingell, said they were looking into potential problems in medical care arising from mismanagement of research protocols.

"In those instances where [thre is] a question of eligibility for a trial or inappropriateness of treatment, NSABP, under a new organization, will [conduct] reexamination of these women to provide them with the best possible advice," Detre said.

"Individuals who for any reason whatsoever may not have received appropriate care while they were enrolled in trials for which they were not eligible have to be examined by experts—and not on site—but independent experts," he said.

Zeneca: Wisdom Of Prevention Trial In Question

"The uterine cancer deaths in [B-14 tamoxifen treatment trial] have brought into question the wisdom of continuing the tamoxifen prevention trial," said John Patterson, international medical director of Zeneca Pharmaceuticals Group.

Patterson reiterated Zeneca's claim that NSABP was tardy in informing the company of uterine cancer deaths in the B-14 trial. "The first of those deaths occurred on June 25, 1991," Patterson said. "Zeneca was informed of that death on Feb.10, 1992, in a routine NSABP report.

"The cause of death was not clearly stated, and several potential causes were stated, including uterine cancer.

"We reported this case to the FDA on April 1, 1992. NSABP reported the remaining three uterine cancer deaths to Zeneca on Dec. 13, 1993. We reported these deaths to the FDA on Jan. 5, 1994.

"According to the subcommittee staff, the NSABP apparently has claimed that it notified Zeneca of these deaths on Feb. 1, 1994. In fact, NSABP provided Zeneca with a data set reflecting that death, but no cause of death was specified.

"It was not until December 1993 that Zeneca learned from NSABP, that this death was due to uterine cancer. Indeed, NSABP's own August 1993 report to its membership failed to identify any uterine cancer death in any patient," Patterson said.

Paul Plourde, senior director of clinical and medical affairs at Zeneca, said that after seeing the first death report in a routine memorandum from NSABP, he obtained additional information from D. Lawrence Wickerham, deputy director, administration, at the cooperative group.

"Upon review of that information, I did discuss the case with Dr. Wickerham, who felt that this patient had actually died of a pulmonary embolism rather than endometrial cancer," Plourde said. "However, given the problems in accurately interpreting the cause of death, I reported to the FDA that it was possible that this woman had died of endometrial cancer, contributed by pulmonary embolism."

Parties v. Auditing?

Throughout the hearing Dingell pointed out that the cost of Zeneca-sponsored banquets at NSABP's semiannual meetings was roughly equal to the cooperative group's data auditing budget.

"Essentially, at the same time the audit program was floundering, Zeneca was providing huge amounts of money—not for audit resources, but for lavish parties and receptions at NSABP's semiannual meetings in splendid places around the US and Canada," Dingell said.

Fisher, Detre and Zeneca executives separately countered that receptions sponsored by drug companies are a common practice in medicine; that it would have been inappropriate to ask Zeneca to finance auditing instead of jumbo shrimp and premium liquor and that, on the balance, physician revelry is the least of the problems of the cooperative group.

Dingell persisted. "It does seem to me that you are more expansive with respect to your parties than you are with your auditing," he said to Fisher.

"I would hate to think that I would be so..." the visibly shaken Fisher replied with a sentence fragment. After a pause, he continued: "After a lifetime of dedication to science, to have thought that... I just find that absolutely devastating.

"I really do."

What Fisher Knew And When Did He Know It: A Transcript

The following are excepts from a hearing June 15 of the subcommittee on oversight and investigations of the House Energy and Commerce Committee.

Rep. John Dingell (D-MI), chairman of the subcommittee: Doctor, the subcommittee staff has been reviewing the audit reports. In addition to the St. Luc [scientific fraud] problems, the auditors uncovered similar problems at sites throughout the [National Surgical Adjuvant Breast & Bowel Project] . For example, a number of locations were found to be violating the eligibility criteria. At one site three-quarters of the patients enrolled did not meet the eligibility criteria. Can you tell us about what you knew about these matters, regarding the depth and the breadth of eligibility problems identified by your auditors?

Bernard Fisher, the ousted principal investigator of NSABP: Mr. Chairman, we recognize that there were administrative deficiencies in the audit program. But with respect to any particular institution, we've not had a chance to review the subcommittee's investigations or reports or any other recent analyses, and we would certainly like to have the opportunity to do so and provide the information

to you.

DINGELL: These were [NSABP] audits which were performed into the 1980's. That was at the time when you were in charge of the program. Didn't that give you some awareness that there were problems with regard to either fraud or slovenly work?

FISHER: Well, it was the audit process which did uncover the St. Luc falsification. We found the falsification through our efforts. And reported it. And that's the only falsification that has been.

DINGELL: And there were some fairly significant eligibility questions. For example, one site had three quarters of the participants ineligible.

FISHER: I am certainly not aware of that, sir. I really am not aware of it.

DINGELL: But it was in the audit reports that came to you, though.

FISHER: I really don't remember seeing that report at all.

DINGELL: Here they are: South Nassau Hospital, Rush Presbyterian Hospital [of Chicago], St. Joseph Hospital in Lancaster, and in the Univ. of Pittsburgh. And the Univ. of California at Davis, had three quarters of participants in the study ineligible. There were your audits in your project. [Editor's note: three quarters of the patients audited at UC-Davis in 1991 were found to be ineligible, sources said to **The Cancer Letter**.]

FISHER: May I make a comment about eligibility? The term eligibility has been used here and elsewhere. Eligibility is not falsification.

DINGELL: I am not making an allegation that eligibility is fraud. It is, however, a matter that goes to the very scientific adequacy of the test because if you are testing people or reporting on people who don't meet your eligibility requirements, it tends to skew your results. All of these matters were essentially found in audits, but we are unable to address them here today because of your lack of familiarity with them.

FISHER: I certainly am not aware of any institution where there were three-quarters of the patients ineligible. I would like to have more information about that.

DINGELL: We will give it to you. It is, however, in your audit reports. Here are other examples. Auditors turned up instances where patients were randomized twice. What is the result of randomizing a patient twice in a study of this kind? What does it do to the statistical validity of the study?

FISHER: I can't answer that question.

DINGELL: Do you know how much double randomization was occurring and what the practical effect of it was?

FISHER: I don't know the number of double randomization that was occurring, and I must think they were extremely few and far between. This has not been brought to my attention as being a problem.

DINGELL: Well, your auditors also identified a number of informed consent problems throughout the sites. For example, no documentation of informed consent obtained after two years post-randomization. First of all, does this constitute a problem in terms of lack of adequate informed consent by the participants, and if so what was done?

FISHER: Let me say emphatically that informed consent is a very important part of what we are doing. It always has been. There is no question about that. And as far as I am concerned, that is something that there should be no excuses for. There are certain situations where informed consent may have been obtained after an operation was done. That is in a particular study of lumpectomy, where prerandomization was used. But in reference to your comments about informed consent, I have seen in some of the audit reports that there was this kind of situation, but I have not been familiar with it as any kind of a serious problem.

DINGELL: Well, your auditors found that a number of sites were not maintaining drug logs. Can you tell us the importance of the drug logs and what happened at the locations that were not properly maintaining these logs?

FISHER: Drug logs are also something that is looked for at the site routinely, to make sure that the drugs that are given to the investigators are used for the patients that they are supposed to be used on.

DINGELL: Well, there were a number of instances where the drug logs were not maintained. Is that important, or is that not important?

FISHER: As far as I am concerned, it's important.

DINGELL: Now, a number of other locations had serious problems with missing data. Were you aware of this?

FISHER: I've heard about that, particularly in certain institutions. And it depends on how long ago the data was collected. For example, in New Orleans, where data was collected in the seventies at a large city hospital, some of that data now, in 1994, may

be hard to obtain. I cannot know more than that about it, however.

DINGELL: If the failure to maintain proper logs and to have data properly assembled is recent, is that a more serious problem?

FISHER: These things are all problems. There are no questions about that. And I will certainly like to address them after I knew more about them. The degree of these problems. For example, I indicated to you that the NSABP had conducted 587 audits since 1982. And of those 587 audits there were major problems identified at 5.8 percent, and some of those problems reveal the things that you are talking about.

DINGELL: You mean problems were identified in 5.8 percent of the audits?

FISHER: Which were serious enough to suspend these investigators and suspend accrual.

DINGELL: These involved some 30 institutions. Are you able to tell me that these were trivial matters?

FISHER: We do the audits to determine these things. Otherwise there would be no point in doing the audit program.

DINGELL: You raised an important question. What did you do with the audits? The audits come in, they say there is a problem with informed consent. They say that a number of suites have not maintained any drug logs. They say that there is a serious problem with missing data. Did you inquire into these problems?

FISHER: The usual process would be that when this happens, the medical auditor, medical reviewer, would write a report, and that report will indicate to the investigator what the problems are, and we would expect them to implement a plan of action to tell us what they are going to do to correct these problems, and then this report also goes to the quality assurance committee which we have. We have a standing committee where all of these reports go for their review and their suggestion as to what punitive actions should be taken.

The investigator is notified about these, and is supposed to provide the NSABP with a plan of action that will be acceptable, and if it is acceptable, then the decision is made to give them a chance to show that they have corrected themselves and resume accrual. If it is not acceptable, accrual continues to be suspended.

DINGELL: Were you ever made aware of the fact that there were problems with informed consent? Were you made aware of the fact that there were problems with the sites not keeping any drug logs? Were you made aware of the fact that a number of locations had problems with missing data?

FISHER: As I said, I have seen these reports sent to me. At this moment, I don't know what was in the reports. How many of these were related to informed consent? How many of them were related to drug log problem? I am unable to answer that, sir.

DINGELL: So you are able to tell us what was good about these matters. What was there about the informed consent question? What was there about the questions on the number of sites that weren't maintaining drug logs? What was there about the sites that had problems with missing data? What action did you take?

FISHER: We sent the reports back. One of the purposes of the audit program is that it is supposed to be an interactive program where investigators are informed about their deficiencies and are educated against repeating this.

DINGELL: What did you do? What did you do about these matters to correct the situation? Either in general or in any particular case? Did you do anything? Can you tell us one thing you did on any one of these audits that came to your attention?

FISHER: I certainly... My main issue here had been to order the personnel who were responsible for this program to carry out what they were supposed to do.

DINGELL: What were you doing while all those people who were supposed to do those things didn't?

FISHER: I think what we were doing, sir, is that the NSABP did have continuing ongoing workshops at meetings for data managers, for all kinds of people, to educate them and try to get them to prevent this kind of practice. This was what was being done.

DINGELL: What was your job at NSABP?

FISHER: My main role at NSABP—and let me emphasize that I take full share, full responsibility for the administrative errors that took place under my term—but, as I mentioned in my introductory statement...

DINGELL: What were your jobs at the NSABP?

FISHER: As I say...

DINGELL: You were the head of the whole operation. Were you not?

FISHER: Yes, sir. I take responsibility for the operation. I wasn't the head of all of the pieces. They were under me. The biostatistical center. The data center is a major part of the NSABP. It actually

received more of the funding than the operations center...

DINGELL: Now, [NSABP auditors reported] highly problematic sites, such as Tulane and [Louisiana State Univ]. Were there any special efforts taken to try to deal with these sites? That seemed to come up year after year to exhibit an inability to follow protocols of the study.

FISHER: Yes, sir. I have talked to principal investigators on many occasions by myself and by our staff. There was a Catch 22 in that situation. The institutions that put on the larger numbers of patients, if they had problems, and if those institutions were to be eliminated from the NSABP, the backlog of large numbers of patients that needed to be followed up still remained there to be followed up. So we did keep those people. When we suspended them, we kept them on for at least follow-up...

Fisher Questioned On Endometrial Cancer Deaths

FISHER: At the time when the prevention trial started, we had no evidence —as far as we can determine—that there were patients who died specifically because of endometrial cancer.

DINGELL: The NSABP has provided the subcommittee with a number of documents in the last couple of months. One of those documents is a slide dated August, 1993. In these slides, at least at least two patients are known to NSABP to die of endometrial cancer. The information on endometrial cancer deaths was not reported by you to any NSABP meetings until late October of 1993. It was not reported to the drug manufacturer until December. Now, given the fact that the prevention trial was actively recruiting at this time, why was this information not immediately conveyed in August or earlier so the informed consent forms could be changed?

FISHER: Sir, to the best of my ability, I will try to explain that. The date on the slide was the date on which the biostatistical center closes the summary file. The summary file is the cutoff point that they use for preparing their information. I myself did not get that information until the slides were being prepared for the meeting in October. So that is a discrepancy. It wasn't that I made that slide in August. The slide was not made in August. The slide was made in October.

DINGELL: Are you telling us that the NSABP did not tell you about these events? Were you aware...

FISHER: To the best of my knowledge, I was not aware of it.

DINGELL: You were not aware of it. So, then NSABP didn't tell you about these two deaths from endometrial cancer? Shouldn't they have told you?

FISHER: Well, again, the question about the two deaths from endometrial cancer... They should have told me... but... it was a question as to whether these were deaths from—or with—endometrial cancer.

DINGELL: Oh! You didn't know. So you didn't say, Okay, let's find out whether these are deaths caused by endometrial cancer or something else. Is that right?

FISHER: I would have hoped we would know sooner that there were deaths...

DINGELL: But they didn't tell you. And they didn't tell the manufacturer. And the manufacturer's got the possibility of lawsuits. Because of the fact that people have died of cancer from taking this particular substance as part of a test. The NSABP has the possibility of lawsuits against them. The Univ. of Pittsburgh has the possibility of lawsuits against them. Nobody is notified about the fact that we have these cancer deaths... from the use of tamoxifen. Is this good administration?

FISHER: We reported this to the group in October 31.

DINGELL: The slide was made in August.

FISHER: No, the slide wasn't made in August. The slide was made in October.

DINGELL: The day that this data was available was in August. When was the slide made?

FISHER: The slide was made for the meeting in October.

DINGELL: The day the data was available was August, sir.

FISHER: The day that was... I don't know, I can't answer that.

DINGELL: It was significantly before the slide was prepared...

FISHER: In preparing for this meeting... The Aug. 30 date was the cutoff that they used. Now, whether that was known or not known, I don't know.

DINGELL: Here is what the fly sheet on the slide says: endometrial cancer (EC) in B-14. As of Aug. 31, 1993... That means on or prior to Aug. 31, there was awareness that this was a problem.

FISHER: I can't really... I can't be sure. All I can say is, that was when the summary file was closed in the data center. And I apologize for this, and I wish Dr... The biostatisticians who were responsible for this kind of thing were here. But they are not here, and I cannot answer the question.

Fisher's Control Of NSABP Had Downside, Review Found

Peer reviewers scrutinizing the National Surgical Adjuvant Breast & Bowel Project in 1991 found that the centralized control by then-chairman Bernard Fisher was both a "major strength" and a "potential weakness" of the cooperative group.

The NCI Clinical Investigation Review Committee warned the NSABP that Fisher's control over the years had resulted in decreasing participation by group investigators in study design and administration.

As a result, the pool of investigators from which the next generation of NSABP leaders could be chosen was "severely restricted," the committee said in the summary statement of the NSABP's most recent grant review.

A copy of the summary statement, dated Aug. 29, 1991, was obtained by **The Cancer Letter**.

The summary statement, an overview of a review committee's main findings, is commonly called a "pink sheet" because NIH until recently printed the statements on pink paper.

"An Energetic Leader"

The review committee gave NSABP a priority score of 151 and recommended approval at a budget of $8.3 million in fiscal 1992, rising to $9.5 million over five years.

In a section of the summary statement titled "Overall Critique," the review committee described NSABP's two main strengths: its leader and its ability to accrue patients.

"The first and most important strength of the NSABP is its leader, Dr. Bernard Fisher, who has served continuously as chairman for 24 years," the statement said. "Dr. Fisher is an energetic leader who has devoted all his efforts to the evolution of a mechanism for the accrual of large numbers of patients rapidly to answer critical clinical questions about breast cancer.

"The effectiveness of the NSABP in the clinical trials area is directly attributable to the centralized control which the membership has been willing to yield to Dr. Fisher and the excellent use to which Dr. Fisher has been able to put that control," the statement said. "Dr. Fisher's leadership is best characterized by his understanding of breast cancer, his innovative and daring approach to the study of the disease, and his willingness to take risks in study design which have resulted in major changes in the medical community's management of patients with this disease.

"A second major strength of the NSABP is the large number of patients to which the group's investigators have access; no other clinical trials cooperative group is able to accrue patients with breast cancer so rapidly to adjuvant therapy trials as is the NSABP," the statement said.

The group's other strengths were "its willingness to take on innovative, even controversial issues" through large scale phase III trials, and an increasing ability to accrue patients to trials of adjuvant therapy for colorectal cancer, according to the statement.

"Areas of Potential Weakness"

The committee wrote that its "enthusiasm" for the NSABP is "slightly tempered by the significant areas of potential weakness which the group needs to address." The reviewers warned that, "Some of these areas have been mentioned in former reviews, and thus there is some degree of urgency in their having to be considered."

The first concern listed was Fisher's control of the group. "The centralized control of the group chairman and headquarters, although doubtless contributing to organization and productivity, has decreased the participation of the membership in such scientific activities as study development, setting of future directions of the group, and participation in the process of analysis and publication of studies.

"In addition, there has been, as a result of the central control, little development of the talents of the group membership in the area of leadership within the NSABP," the statement said. "The combined effect of these two situations is that the group is deprived of another source of potentially excellent study ideas and that the pool from which the next generation of NSABP leadership will be chosen is severely restricted."

The committee's second concern was study monitoring. "Under the current system, study monitoring depends on the activities of modality-oriented committees and data management personnel at NSABP headquarters in conjunction with a series of computer checks," the statement said. "There is no provision within the current system for a 'study chairman' or equivalent, an individual responsible for the overall clinical review of each case to insure that all of the parts which are reviewed by the committees fit together to make a complete and evaluable case....

Good science demands a knowledgeable medical review of each case to insure that the case makes sense and can properly be evaluated as a part of the study data set."

A third concern was "the group's propensity to collect a huge volume of data on each study with no obvious plans of how each piece of data would be analyzed or how the results of such analyses would be used."

For example, the committee questioned the group's practice of followup beyond 10 years for long-term survivors. "A more selective approach... seems warranted," the committee said.

Finally, the committee was concerned about the quality of the group's colorectal cancer research, which did not seem "as well conceived or as bold as the trials in breast cancer," the statement said. "To some extent, this may reflect the limited treatment options available in colorectal cancer."

However, the committee said, funding for colorectal cancer research "is predicated on the group's ability to come up with innovative ideas worthy of study" in large phase III trials.

"It is hoped that the next five years will see a broadening of participation of the group membership in the leadership and scientific activities of the NSABP, a greater attention to the clinical review of all cases with respect to each case as a whole, a more selective and well conceived approach to the selection of data to be collected on each study, and a major effort to improve the quality of the trials in the colorectal area," the summary statement's critique concluded. "Despite the concerns, however, the NSABP remains a unique and valuable resource led by a dynamic and charismatic individual."

RFP Available

RFP NCI-CM-57218-28

Title: Primary rodent production centers

Deadline: Approximately Aug. 12

NCI's Developmental Therapeutics Program is seeking organizations with the capability and facilities to produce large numbers of inbred rodents whcih are genetically sound and free of pathogenic organisms. To be considered for contract award, offerors should meet the following criteria: 1) the principal investigator and other key personnel must have experience and expertise in the production of the highest quality rodents free from pathogenic organisms, 2) the facility must be available at the time of award, capable of producing highest quality rodents at tasks specified levels, 3) organizational experience in pertinent areas of quality rodent production including pedigreeing procedures, isolator production etc, at a scale commensurate with tasks performance, and 4) willingness to participate in grantee reimbursement collections. It is anticipated that three awards will be made for a three-year incrementally funded period.

Contract specialist: Carolyn Barker, Treatment Contracts Section, RCB Executive Plaza South Rm 603, Tel: 301/496-8620.

RFAs Available

RFA CA-94-009

Title: **Collaborative Cancer Prevention Research Units**

Letter of Intent Receipt Date: Aug. 11

Application Receipt Date: Oct. 13

The Cancer Control Science Program in NCI's Div. of Cancer Prevention and Control seeks to stimulate the establishment of programs in primary and secondary cancer prevention, health promotion and prevention services research through the award of grants involving project-specific collaborations. Applications may be submitted by domestic and foreign, non-profit and for-profit organizations. This RFA will use the NIH R01, and the FIRST Award grant mechanism (R29).

The CCPRU must consist of a minimum of two independent applications. A CCPRU package can consist of a combination of R01s and R29s, or R01s only, but may not consist of solely R29 applications. Total project period for R01 applications may not exceed 4 years. R29 awards must be for 5 years. Approximately $3 million per year in total costs for 4 years will be committed. Up to five (a combination of approximately 10 individual R01 and R29 projects) CCPRU awards will be made.

Inquiries: Sherry Mills, DCPC, NCI Executive Plaza North Rm 320, Bethesda, MD 20892, Tel: 301/496-8520.

RFA CA-94-018

Title: **Program Projects In Nutrition And Basic Biology Research For Cancer Prevention**

Letter of Intent Receipt Date: July 25

Application Receipt Date: Nov. 18

The NCI Div. of Cancer Prevention and Control and the Div. of Cancer Etiology invite Program Project Grants for multidisciplinary nutrition and basic biology research relevant to the prevention of cancer. They seek to encourage application of the techniques of molecular biology and molecular genetics to address questions about the fundamental role of nutrition in the initiation, promotion, progression, and prevention of cancer and the use of that knowledge to develop dietary interventions for the prevention of cancer, with a special emphasis on breast cancer, prostate cancer, and cancer in women and minorities. Up to $4 million in total costs per year for up to four years will fund three to four awards.

Inquiries: Susan Pilch, DCPC, NCI, Executive Plaza North Suite 212, Bethesda, MD 20892, Tel: 301/496-8573, FAX: 301/402-0553.