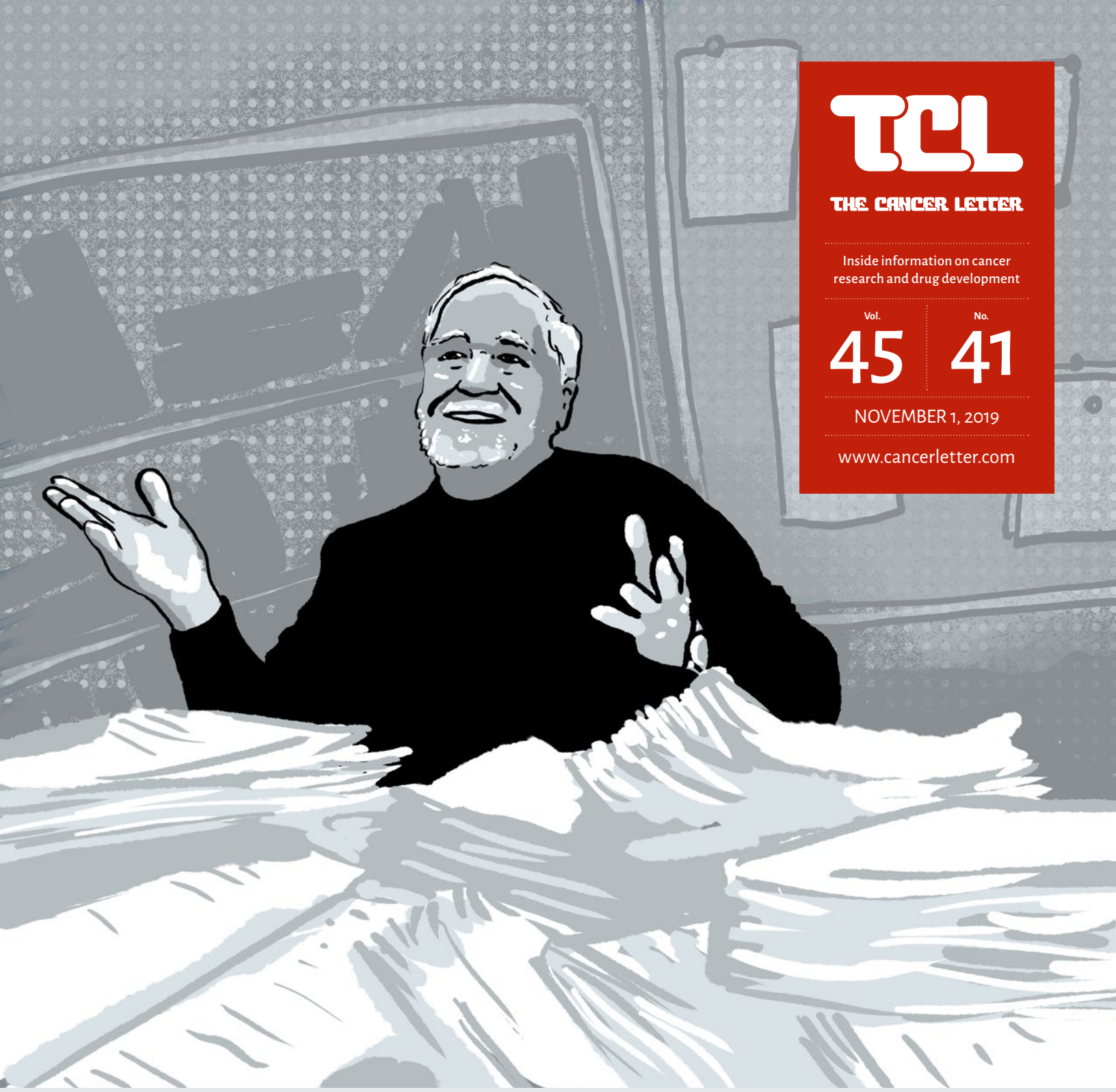


TCL
THE CANCER LETTER

Inside information on cancer research and drug development

Vol. 45 No. 41

NOVEMBER 1, 2019

www.cancerletter.com

WHEN BERNIE FISHER REFUSED TO GROVEL

Bernard Fisher had been in many a fight. He was, after all, an iconoclastic surgeon who had famously infuriated his colleagues by demonstrating that heroic surgeries in breast cancer do more harm than good.

→ PAGE 5

University of New Mexico Comprehensive Cancer Center

Join Our Clinical &

The University of New Mexico Comprehensive Cancer Center (UNMCCC) is the Official Cancer Center of New Mexico and the only National Cancer Institute (NCI) designated comprehensive cancer center in a 500-mile radius. Our 134 oncology physicians, 122 cancer research scientists, and staff focus on discovering the causes and cures for cancers disproportionately affecting the people of the American Southwest — primarily Hispanic, American Indian, and Non-Hispanic White — with strikingly different patterns of cancer incidence, mortality and disparity. In the past year, our center cared for 12,000 patients; 12 percent participated in therapeutic interventional studies and 35 percent in interventional studies. UNMCCC has outstanding programs in Cancer Control and Population Sciences, Cellular and Molecular Oncology, and Cancer Therapeutics. Our research houses national centers: The Molecular Discovery and High Throughput Target Screening Center (nmmlsc.health.unm.edu), one of six Chemical Biology Consortium Centers of Excellence in The NCI NExT Program; Spatiotemporal Modeling of Cell Signaling (stmc.unm.edu), one of 13 NIH National Centers for Systems Biology; and a NIH Clinical and Translational Sciences Center. We enrich our endeavors by collaborating with Sandia and Los Alamos National Labs and Lovelace Respiratory Research Institute. Our members benefit from our Shared Resources: biospecimen collection and tissue analysis, genomics, biostatistics, bioinformatics, cancer population science and behavioral interventions, and the conduct of clinical interventions. UNMCCC is the center of our statewide cancer clinical trials and health delivery research network — partly funded by a NCI NCORP Grant — and is an Oncology Research Information Exchange Network (ORIENcancer.org) member. Our center has conducted 60+ statewide community-based cancer education, prevention, screening, and behavioral intervention studies involving more than 10,000 New Mexicans. Learn more at cancer.unm.edu.

Endowed Chairs and Professorships, significant resources, start-up packages, and rich opportunities for collaboration with multidisciplinary research and clinical teams are available.

Join our Clinical Faculty and Leadership Teams

Medical Director of Cancer Clinical Trials Office

Seeking mid-career/senior clinical trialist to serve as the medical director of the Cancer Clinical Trials Office. The role will work closely with the administrative director of the Cancer Clinical Trials Office to set priorities, allocate resources, drive trial enrollment and ensure that high quality clinical research will be supported throughout UNMCCC. Applicant will have a clinical research program within hematology/oncology.

Gastrointestinal & Hepatobiliary Cancer Program Leader

Seeking mid-career, senior physician or physician-scientist to provide leadership to the UNMCCC Gastrointestinal Cancer Clinical Working Group. Looking for expertise in translational and/or clinical research focused on GI malignancies, and leadership skills to develop a nationally recognized clinical/translational research program in GI malignancies and may serve as the UNMCCC Clinical Trials Office Medical Director.

Phase 1/Experimental Therapeutics

Seeking mid-to-senior level career physicians or physician scientists with expertise in experimental therapeutics, the development and/or testing of novel targeted cancer therapeutics, and the design and conduct of early phase human cancer clinical trials. The role will lead UNMCCC efforts focused on the rapid translation from bench-to-bedside-and-back by working with the basic and translational scientists of UNMCCC. Applicant may serve as the UNMCCC Clinical Trials Office Medical Director.

Gastrointestinal Malignancies

Seeking junior level physicians/physician scientists with expertise in medical oncology and a focus in clinical care and clinical research in GI and hepatobiliary malignancies. The role will be a GI and Hepatobiliary Clinical Working Group member and will contribute to the academic mission of the division of hematology/oncology and the UNMCCC.

Neuro-Oncologist

Seeking physicians or physician scientists with training and expertise in neurology or oncology and a focused interest in clinical care and clinical/translational research in patients with cancers of the brain and spinal cord. The role will participate and/or lead the Neuro-Oncology Clinical Working Group. Leadership opportunities exist for outstanding candidates with a strong track-record of accomplishments, program-building experience and a history of collaboration across multiple departments.

For details and to apply, visit cancer.unm.edu/JoinTheBest

Research Teams

Photo: Bill Tondreau, "River Edge", panoramic photographic, courtesy of sumnerdene.com

Head & Neck and/or Thoracic Oncologist
Seeking junior level physicians or physician scientists with expertise in medical oncology and a focus in the clinical care and clinical research in Head & Neck and/or thoracic malignancies. The position will be a Head and Neck Cancer Clinical Working Group and/or the Thoracic Oncology Clinical Working Group member and will contribute to the academic mission of the division of hematology/oncology and UNMCCC.

Melanoma/Sarcoma Medical Oncologist
Seeking junior level physicians or physician scientists with expertise in medical oncology and a focused interest in clinical care and clinical research in melanoma and/or sarcoma. The role will be a Melanoma and/or Sarcoma Clinical Working Group member and will contribute to the academic mission of the division of hematology/oncology and UNMCCC.

Hematologic Malignancies and Stem Cell Transplantation
Seeking junior level physicians or physician scientists with expertise in hematology and a focus in clinical care and research in malignant hematology and stem cell transplantation to be a member of the Malignant Hematology Clinical Working Group and contribute to the academic mission of the division of hematology/oncology and UNMCCC.

Radiation Oncologist
Seeking physicians or physician scientists with expertise in radiation oncology and an interest in clinical care and clinical and translational research. Applicants will participate in the multidisciplinary clinical care of cancer patients and in the design and conduct of cancer clinical trials as a member of one or more UNMCCC multidisciplinary clinical working groups.

Research Positions at the UNM Comprehensive Cancer Center

Associate Director for Cancer Population Sciences
Endowed Chair and Senior Leadership Role
The UNM Comprehensive Cancer Center is searching for a national leader in cancer population sciences. Seeking candidates with a track record of outstanding scholarly achievement reflected in peer-reviewed funding (preferably NCI and NIH), high quality publications, and collaborative interdisciplinary research with a scientific focus in either cancer epidemiology, cancer prevention and control, health services research, behavioral intervention, or cancer health disparities.

Cancer Molecular & Genetic Epidemiology
Endowed Chair and Senior Leadership Role
Seeking cancer population scientists with expertise in population-based molecular and/or genetic epidemiology. Looking for epidemiologists engaged in biomarkers of risk and prognosis, genomics, epigenetics, gene-environment interactions, genetic ancestry, and genetic risk assessment.

Cancer Control, Health Services & Behavioral Intervention
Endowed Faculty and Leadership Role
Seeking established population scientists focused on cancer control, health services research, and behavioral intervention research to lead programmatic efforts. Looking for mid-career to senior faculty with outstanding scholarly achievement, including peer-reviewed funding (preferably NCI and NIH) and impactful publications.

Biostatisticians
Seeking PhD biostatisticians to join an outstanding team engaged in statistical methodology relevant to cancer and in biostatistical applications integrated with basic, translational, clinical, and population science research. Search chairs:

Cancer Immunology & Tumor Microenvironment
Two Positions: Basic or Translational Scientist
Seeking established mid-career or senior scientists focused on analysis and modeling of pathways that mediate response or resistance to immune therapies, and on signaling perturbations in the context of the tumor microenvironment that enhance or inhibit the immune response to cancer cells.

Cancer Cell Signaling
Seeking cancer cell biology, signaling, and systems biology experts with interests in dissecting mechanisms of perturbed signaling in cancer cells, on analysis and modeling of pathways mediating response or resistance to targeted therapies.

RNA Biologist
Seeking highly interactive basic and translational scientists focused on gene expression, transcriptional regulatory and alternative splicing mechanisms relevant to cancer; the biology and role of noncoding RNAs in cancer development and/or progression; and functional genomics (including investigators employing CRISPR/CAS or other functional genomic screening technologies).

Apply online at cancer.unm.edu/JoinTheBest

Questions? Contact Search Coordinators, Denise Osborne at DOsborne@salud.unm.edu, (505) 925-0415 or Amanda Leigh at ALeigh@salud.unm.edu, (505) 272-2201.

UNM COMPREHENSIVE CANCER CENTER

In this issue

Editor & Publisher
Paul Goldberg

Associate Editor
Matthew Bin Han Ong

Reporter
Alex Carolan

Designer
Jacqueline Ong

Illustrator & Operations Manager
Katie Goldberg

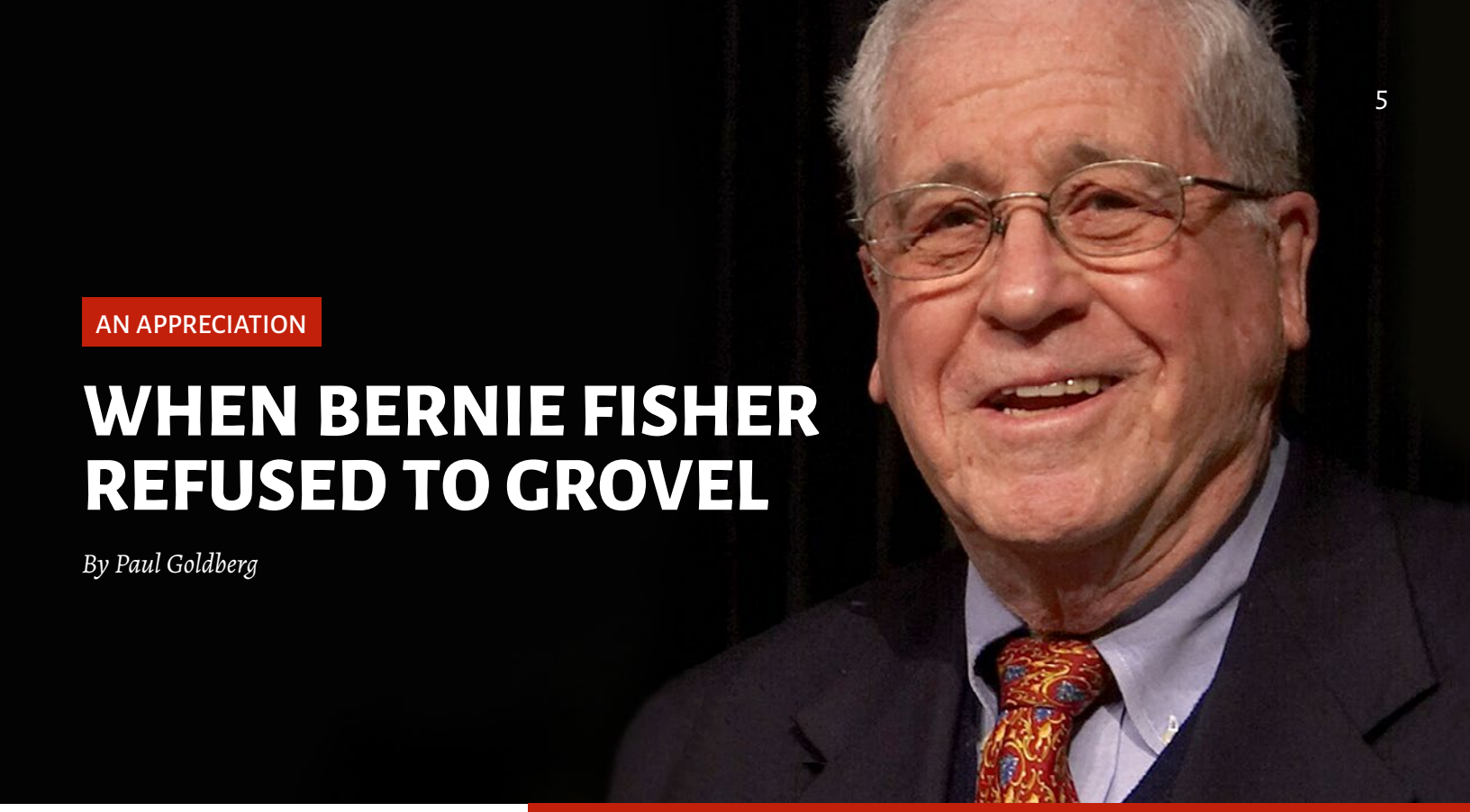
Web Developer
David Koh

Editorial, Subscriptions and Customer Service
PO Box 9905 -
Washington, DC 20016

T 202-362-1809
F 202-379-1787
W www.cancerletter.com

Individual subscriptions $555 per year worldwide. Group subscriptions required for institutional distribution. To subscribe, click here.

ISSN 0096-3917. Published 46 times a year by The Cancer Letter Inc.



AN APPRECIATION

WHEN BERNIE FISHER REFUSED TO GROVEL

By Paul Goldberg

Bernard Fisher had been in many a fight. He was, after all, an iconoclastic surgeon who had famously infuriated his colleagues by demonstrating that heroic surgeries in breast cancer do more harm than good.

However, nothing in his life prepared him for the ordeal that befell him in March 1994.

In a matter of days, everything Fisher had accomplished vanished in the midst of a political brawl sparked by Rep. John Dingell (D-MI) and his squad of investigators. Dingell *et al.* had learned about scientific fraud in a small number of cases in massive clinical trials Fisher directed.

Fisher knew about that, too, but didn't think it was a big problem, and didn't move fast to reanalyze the data. In fact, The Cancer Letter's first story about this brewing scandal appeared on page 6 (*The Cancer Letter*, March 18, 1994).

Initial appearance notwithstanding, the story rapidly acquired hurricane force, and feeling the pressure from the intensely feared Dingell committee, NCI Director Samuel Broder fired Fisher from his position as chairman of the National Surgical Adjuvant Breast & Bowel Project, the cooperative group the surgeon co-founded and ran. The University of Pittsburgh, too, threw Fisher under the bus. Ultimately, the databases run by NCI and the National Library of Medicine—including all NSABP publications and Fisher's Karnofski Lecture at ASCO—were libelously labeled "SCIENTIFIC MISCONDUCT." The surgeon, who was 75 at the time, was never accused of scientific fraud.

The NSABP scandal became the single biggest story in oncology in 1994. People Fisher contemptuously called BAPs—bureaucrats, administrators and politicians—were on the attack, media coverage was intensive and not always correct, academic warlords were contemplating carving up NSABP, and patients were terrified about having relied on NSABP data in their treatment decisions.

As a scientist, Fisher, who died Oct. 16 at age 101, had revolutionized the understanding and treatment of breast cancer (*The Cancer Letter*, Oct. 25). As a scientist and a citizen, he showed what it means to remain faithful to the principles of academic freedom and due process of law at a time when people around him urged him to cave, compromise, apologize. "Grovel" was the technical term communicated to Fisher by his attorney before one of Dingell's hearings.

As the backbones of people around him were losing rigidity, Fisher stood upright, stiffly, explaining over and over that NSABP's scientific findings were solid and the accusations against

him Kafkaesque. Dingell wanted a *mea culpa,* but in a standoff that made network news and the front pages of major newspapers, Fisher insisted that no *mea culpa* was warranted and none would be forthcoming.

Fisher took every kick, every indignity that came his way, shelling out six-figure legal fees in suits against NCI, Pitt, and the law firm of Hogan & Hartson, which represented Pitt.

The NSABP scandal raged through a very different America and a very different U.S. Congress. Different because at that time, newspapers and television networks covered hearings of Congressional committees. Photographers crouched or prostrated themselves in the bullpen between the dais and the witness table, training precision optics on the nasal hairs of Chairman Dingell as he fumed at scoundrels and honest men alike.

> “As the backbones of people around him were losing rigidity, Fisher stood upright, stiffly, explaining over and over that NSABP’s scientific findings were solid and the accusations against him Kafkaesque.”

I was at a press table, watching this astounding Shakespearean tragedy unfold in hearings or tracing it through documents obtained from NCI or the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce. The players in this drama have since changed costumes, but the story line has become a constant. Ethical lapses, fraudulent data, the rigor of audits, and political overreach haven’t gone away.

For me, this was the time and place where I realized that *The Cancer Letter* needs to provide exhaustive coverage of such scandals, instead of dipping in and out of stories like everyone else. *The Cancer Letter* published 57 stories on the NSABP scandal between March and December 1994.

Sometime in the summer of 1994, I got a call from Mackenzie Carpenter, a special projects reporter from the *Pittsburgh Post-Gazette.* She started to get into the NSABP drama as its first, most explosive phase was winding down on Capitol Hill.

Early in the conversation, I started selling Mackenzie on the idea of describing this story for a general audience, doing a recap of history, showing where the story stood at that time. Sometimes to make a story understandable, you need to go to “In the beginning..,” I argued.

Mackenzie and colleague Steve Twedt spent months reconstructing the history on NSABP, going back to Fisher’s hypotheses, pinpointing the relatively small-scale irregularities in the data that caused the scandal, and analyzing events that were still raging in Washington.

Meanwhile, I was committed to writing for a specialized audience in real time, following its implications as they unfolded day after day. By contrast, Mackenzie and Steve were writing for a general audience after many of the key events had occurred. I didn’t have the capacity to tell the story with the luxuries of character development, delineation of plot points, and narrative thrust.

Luckily, Mackenzie and Steve were able to do just that. And they were getting cooperation from the University of Pittsburgh, NCI, the Dingell crew, sundry lawyers, Fisher, his colleagues, and yours truly. Even Roger Poisson, the fraudster in this story, spoke with the *Post-Gazette* team.

The series—**Anatomy of a Scandal**—appeared in the *Post-Gazette* in December 1994. It’s unlikely that you saw it in print unless you were interested in oncology and lived in Pittsburgh at the time. Even today, a quarter-century later, the series allows us to observe Fisher and the people around him as they try to orient themselves in the midst of a cataclysmic disturbance.

Anatomy of a Scandal is being printed in its entirety with permission from *Pittsburgh Post-Gazette.*

Anatomy of a Scandal

By Mackenzie Carpenter and Steve Twedt, Post-Gazette staff writers

On a single day in March, Dr. Bernard Fisher of Pittsburgh, the country's pre-eminent breast cancer researcher, saw his own career crumble, and watched helplessly as the research organization he had led through unprecedented advances in the treatment of breast cancer was abruptly shut down.

It was a shattering experience for the scientists who had spent decades on the work. And for women around the country who suffer from this deadly disease, it was a disturbing setback.

These dramatic developments were the result of another doctor's misguided actions, years ago and miles away. A Montreal surgeon — one of about 5,000 doctors to join Fisher's study group — had begun to falsify the paperwork of some of the patients he enrolled in several studies. Mostly, they were small changes in the dates that determined whether women met the deadline for enrolling in the studies. His actions, which involved 99 women out of the nearly 34,000 in North America who participated, did not seem to change any of the important medical conclusions the studies reported.

Fisher's staff discovered the deception in 1991 and reported it to federal cancer officials, who had funded the experiments for several years. Then, this spring, the story burst into public view when it was printed on Page 1 of a Chicago newspaper. Not long after the headlines, Fisher was fired and the study was put in limbo.

The Montreal doctor's actions were clearly scientific misconduct. But some wonder if the punishment exacted on the research effort was too harsh for the crime.

Was the severity of the penalty simply an effort to maintain the credibility of a medical experiment? Or was it the inevitable result of a struggle by three powerful institutions—science, politics and journalism—to decide who should police medical research?

What really happened here? Was it fair? Did it help anyone? This four-part series tells the story behind the headlines...

Discovering fraud in breast cancer research: A gradual process

The young assistant stared at the papers she had just pulled from the file.

"Look! There are two of them!" said Teresa Wright, in bewilderment.

Dr. Ann Brown, a clinical biostatistician at the National Surgical Adjuvant Breast and Bowel Project in Pittsburgh, leaned over to take a look at the papers, which had come from St. Luc's Hospital in Montreal.

Something did seem odd, she thought.

Instead of just one photocopy of a medical report on a breast cancer patient enrolled in one of the NSABP's studies, there were two of them, exactly alike, except for one critical fact:

One record said the patient had undergone breast cancer surgery on June 19, 1987, while the other said the date was June 29, 1987.

Depending on which date was right, the patient would either have been eligible to enroll in the study, or ineligible.

Errors were sometimes found in the hundreds of thousands of pieces of paper that flooded through the NSABP's offices every year. But on this summer day in 1990, instead of a smudged date, or a dictated patient report that didn't match the original hospital chart, here were two copies of the same document, with different dates neatly typed on each one.

What was this? Brown thought, a dart of worry piercing her.

When she showed the documents to her supervisors, they were equally mystified.

But Walter Cronin, the NSABP's deputy director, wasn't hearing alarm bells yet.

"I figured, gee, maybe there was something different about the way the folks at St. Luc's kept records," he would say later. "They were French-speaking, after all."

Disaster in the making

It wasn't a language gap.

The discovery of the unmatched twin records would lead, four years later, to a scandal that would strike fear in thousands of women with breast cancer.

It would lead to the abrupt dismissal and public humiliation of one of the world's pioneers in breast cancer research, Pittsburgh's Dr. Bernard Fisher.

And it would severely cripple one of the world's most prominent, innovative, and productive breast cancer research organizations, an organization Fisher had helped found.

But no one at NSABP had any reason to imagine any of those agonies in June 1990 when first confronted with the discrepancy of one number on a piece of paper from St. Luc's.

St. Luc's Dr. Roger Poisson, one of Montreal's leading breast cancer surgeons, was a major contributor of patients to NSABP's studies, and had been praised repeatedly by Fisher for his efforts.

So, while the Pittsburgh staff was puzzled, they were not alarmed. Surely, they thought, this could be explained.

But their concern deepened in September 1990, when Cronin conducted an

audit of records at St. Luc's and found more data discrepancies, plus irregularities in women's consent forms. Clearly, something wasn't right, but Fisher — the head of the study — still wasn't told.

It wasn't until November, according to Fisher, that Carol Redmond, his chief biostatistician and closest aide, walked into his office and told him there were "irregularities" in Montreal.

Fisher said that Redmond, who declined to be interviewed for this story, was adamant that "one had to be sure before one made any accusations against anybody. To make any accusations without being sure, you were opening yourself up to a suit," he said.

So, on Dec. 7, Fisher and Redmond met with Poisson and his wife, Sandra Legault-Poisson, in Pittsburgh.

In a memo she wrote later, Redmond said that she and Fisher told the Poissons that there were problems with their data and with information on patients' consent to join experimental therapy trials.

They told them a more intensive site visit would be undertaken "as soon as schedules permitted, after which, we would evaluate whether any additional problems that might be uncovered indicated the need for further actions."

Poisson would say later that the meeting "chagrined and saddened" him but he didn't tell Fisher at that point what he had done.

On Dec. 21, NSABP's Cronin sent a memorandum to Redmond, reporting two cases in which St. Luc's had provided followup information on patients who had already died.

Cronin added, though, that "in our judgment, there is no evidence of intentional falsification of data."

That opinion would soon change.

Vrai and faux

When Cronin and two other auditors returned to St. Luc's in January 1991, they found alterations in five more cases out of 120 they reviewed.

On the third day of their visit, Cronin picked up two reports on a breast cancer patient. Like the ones Wright had found in Pittsburgh, they were identical except for one item — there were two different readings on a lab test.

And then he saw something else.

The first report had a yellow label stuck on it that said "vrai." The other report was labeled "faux."

Cronin's heart sank. Poisson had kept two sets of files, labeled with the French words for "true" and "false."

Cronin turned to the other two auditors, Marge McLaughlin and Larry Wickerham. "Look at this," he said quietly.

Without a word to Poisson, the three NSABP auditors left St. Luc's and somberly boarded a plane to Pittsburgh to tell Redmond the bad news.

Fisher said he wasn't notified that his staff had found clear evidence of falsification until February 1991. He was devastated.

"I had no frame of reference relative to this situation, fraud or anything like that," Fisher said. "All of my research life, I've practiced and preached credibility and honesty."

When he went home that evening, Fisher had a strong sense of foreboding. He remembers telling his wife that "some time, it would come back to haunt us."

On Feb. 8, 1991, Poisson sent a letter to Fisher acknowledging the falsifications. Fisher immediately got on the phone and notified National Cancer Institute officials, who funded most of NSABP's research.

A week later, Fisher sent NCI a detailed letter about the St. Luc's falsifications, and eight days after that, he met personally with NCI staff. He also notified the Office of Scientific Integrity (OSI), which investigated scientific misconduct allegations, as well as the U.S. Food and Drug Administration and the Office for Protection from Research Risks, a separate agency that works to ensure that study participants are not endangered.

All these actions met NCI guidelines, Fisher stressed, and afterward, "Dr. Redmond and myself, we felt very good about what we had done."

What took so long?

The subsequent investigation revealed that Poisson had been fudging his records since 1977.

Why did it take 13 years for the NSABP to discover discrepancies in Poisson's records?

In the early years, Poisson only falsified a handful of cases—a date change here, a date change there. The majority of falsifications would come later, and once the problem became "pervasive," NSABP officials said, they caught it during routine auditing procedures.

The other reason Poisson may have escaped detection for so long was that he didn't tamper with records once a woman had been enrolled in a study.

When Poisson altered a woman's file, it was usually to change the date when a woman's biopsy or cancer surgery had occurred to help her get into a study past the official deadline.

Fisher has been exasperated by charges that NSABP should have caught Poisson much earlier.

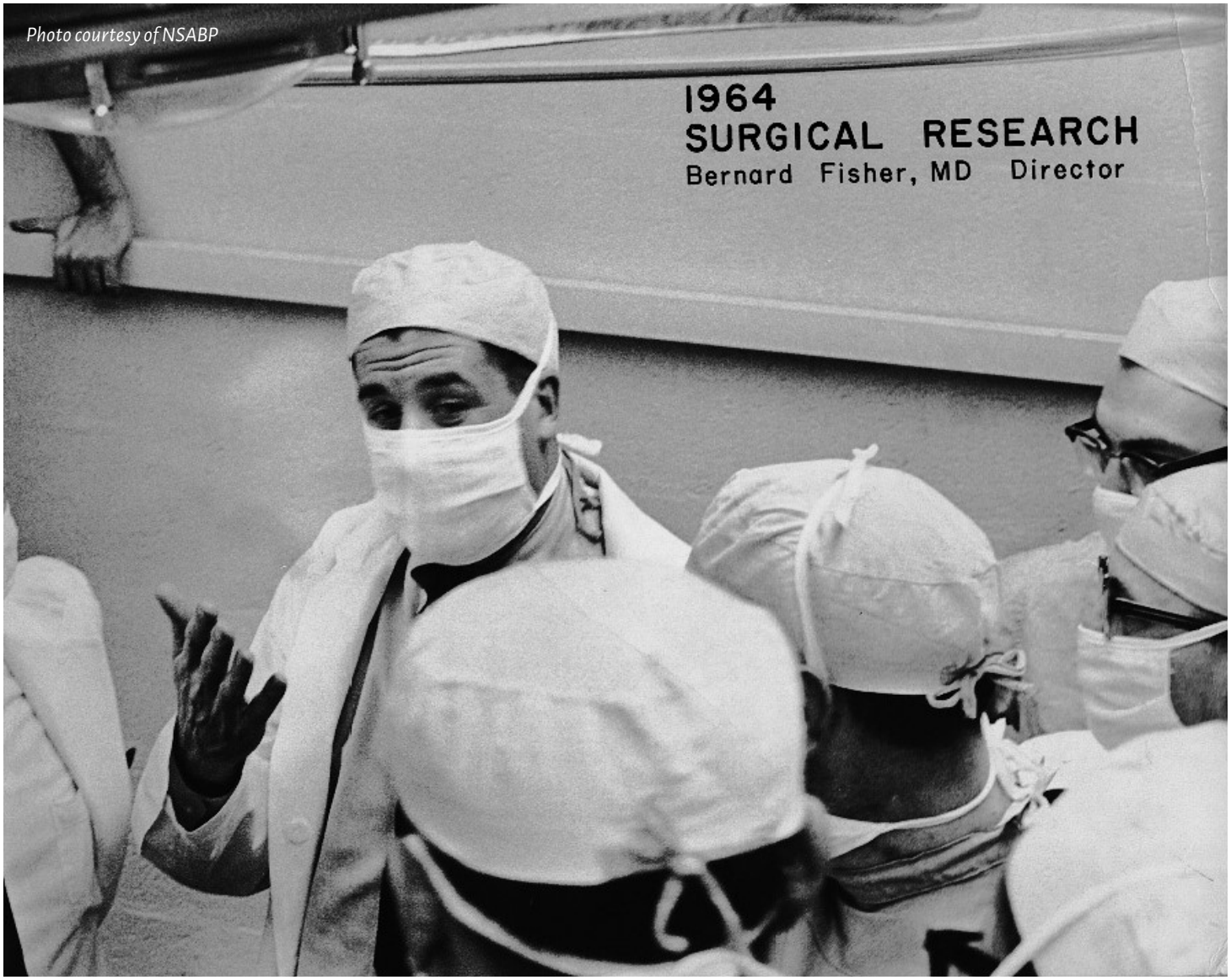


Photo courtesy of NSABP

Being able to detect a small number of eligibility-date changes in the early years would have been "like looking for a needle in a haystack," Fisher said.

Looking back on the problem, however, NCI officials now say that his argument is faulty. NSABP's auditing was insufficient, they said, because it still took several years to catch the falsifications after most of them had occurred, and that was in part because NSABP wasn't looking at enough files.

"It was always eight charts (that were audited), whether the center was big or small," said Dr. Bruce Chabner, director of the Division for Cancer Treatment at NCI.

The eight-chart rule met NCI's guidelines at the time, but the agency was trying to get NSABP to audit more files at each center.

That would have increased the odds that the problem would have been detected more quickly, federal officials said.

But when it was their turn to investigate Poisson, federal investigators moved at a glacial pace.

During the nearly two years it took for them to look into the case, everyone was forbidden to discuss it.

"I don't know why it took so long," said Dr. Jules Hallum, who was OSI director at the time. "We were constantly understaffed and we had other investigations going on, too."

Also, he said, "there was a period of time when we had no travel money."

At one point, OSI investigator Dorothy McFarlane left the NSABP case to work on another project for several months. To add to the confusion, the OSI moved

its offices and some staffers were laid off and then rehired.

Phone calls went back and forth sporadically between McFarlane and the NSABP's Redmond in an effort to reconcile the facts, Fisher remembered, but he never sensed any urgency on the part of federal investigators.

Finally, in December 1992, the newly renamed Office of Research Integrity finished its investigation.

Out of 1,054 cases examined at St. Luc's, the investigators found 115 fabrications or falsifications affecting 99 patients, all but one related to eligibility.

When to tell the public

At that point, the existence of fraud at St. Luc's had been well established for two years, but no one outside the NSABP, the NCI or the Montreal hospital knew about it.

The scandal would stay quiet for another year — in part because Fisher had not yet published a reanalysis of his studies, excluding the bad data.

Fisher and his critics disagree on why it took him so long to do the reanalysis.

In January 1993, two Cancer Institute officials wrote to NSABP and said that the federal report on the fraud would be released in a few weeks, and Fisher's group should be prepared to publish a scientific report on the matter shortly afterward.

The ORI findings were released a month later, but there was no report from Fisher.

Fisher said, however, that he did have a plan to get the word out, one that was developed by Redmond.

First, he would present a technical analysis of the fraudulent data at a May 1994 meeting of the NSABP members in Nashville, and follow it with a commentary on its significance. Then, there would be a written report published in a scientific journal.

It would be a careful, deliberate approach—the way Fisher had always done things.

Fisher said he felt no pressure from NCI. In fact, he said, NCI didn't contact him again in writing about publishing his reanalysis until October 1993.

NCI officials tell a different story.

In an interview in *The Cancer Letter*, a newsletter published in Washington D.C., Samuel Broder, the NCI director, said the agency had received "very strong assurances from Dr. Fisher that he would be writing a reanalysis, and as it turns out, that wasn't the case.

"Don't tell us you're going to publish a paper," Broder said, "and then have us patiently asking you, 'Can you please let us know ... ?' If you say you're going to reanalyze, reanalyze promptly. Do it. Don't give us thousands of reasons why not."

Still, even though Fisher hadn't published his reanalysis, the news did start to seep out—but not exactly on the front page of The New York Times.

The first reference to the fraud investigation came in ORI's own newsletter in the early spring of 1993. Another report appeared in the June 21 U.S. Federal Register, the official federal publication of agency regulations and findings.

A New York science newsletter, Probe, also carried a short story on the matter in September 1993. Its editor, David Zimmerman, had tried to reach Fisher in August, but each time he called, Fisher directed his staff to tell Zimmerman he was out of town or unavailable. Eventually Zimmerman gave up.

Fisher felt no need to go public with the information.

After all, there had been no health crisis. Fisher's staff had already determined that taking out all of Poisson's patients would not change the fundamental outcome of the NSABP studies.

He also didn't feel compelled to call any of the scientific journals in which previous studies had been published, including what was now known to be fraudulent data.

"When you get no change in the results," Fisher said, "you don't call up the New England Journal of Medicine and say, 'Guess what? Nothing happened!'"

Enter Suzanne Hadley

As 1993 came to a close, Poisson's fraud had managed to stay underground for nearly three full years.

That would soon change.

Shortly before Christmas, Suzanne Hadley bumped into a lawyer from the Office of Research Integrity.

Hadley was well known in Washington D.C. as a determined crusader against scientific misconduct. She had spearheaded many of the major investigations into science fraud in recent years, first as deputy director of the Office of Scientific Integrity, ORI's predecessor, and then, working with Michigan Rep. John Dingell, who had made scientific misconduct one of his priorities.

Hadley had been involved in the investigation of Poisson's fraud when it surfaced.

Then she had started working for Dingell, and became deeply involved in the investigation of NCI's Dr. Robert Gallo, who had been accused of falsely claiming credit for discovery of the AIDS virus. The primary journalist working on

that story was the Chicago Tribune's John Crewdson.

On this December day in 1993, her former colleague, the ORI attorney, told her his office had a case "where the investigation was concluded a long time ago and it was clear there was fraud and it was clear that a number of (published scientific) papers contained the fraudulent data," she recalled.

He went on to say that "we can't get the investigator to publish corrections and tell the world about it."

When she asked which case it was, she was told, "Roger Poisson."

Hadley was dumbfounded.

She couldn't believe that the Poisson case was still unresolved.

She told her colleagues on Dingell's Oversight and Investigations Subcommittee, and, in early January 1994, they met with ORI officials.

Hadley discovered at that meeting that nearly a year had passed since ORI had first asked the National Cancer Institute to ask Fisher to publish his reanalysis.

"It was pretty clear that little or nothing had been done" since that time, said Hadley, who is no longer working with the subcommittee. "Should ORI have followed up with NCI? Should NCI have followed up and done something? No question. There's plenty of blame to go around."

Another month-and-a-half went by.

Then, on March 13, the Tribune's Crewdson wrote a front-page story on Poisson's fraud—the first major media attention it had received.

Hadley said she didn't know how Crewdson learned about the Poisson fraud, and Crewdson declined to talk about the matter.

Once the news hit, Hadley wasn't surprised at NCI's reaction.

"This thing didn't happen in a vacuum," she said. "NCI had been on a slow burn with Bernard Fisher for close to two years," she said, because it wanted speedier audits and independent reviews of data quality.

"I think in some ways NCI was just waiting for something."

When the headlines hit, federal officials flew into action.

Fisher's years of achievements crumble overnight

Atlantic City, 35 years ago.

On the same stage in the same auditorium where Miss Americas paraded, preened and wept, a contest of another sort was taking place.

It was a medical conference, the American College of Surgeons' annual meeting. All the great names in breast cancer surgery were on the dais, including Jerome Urban, legendary surgeon from Memorial Sloan-Kettering Hospital in New York City, and Cushman Haagenson of Columbia University, author of a classic text on breast diseases.

Both were staunch defenders of the radical mastectomy—the removal of the entire breast and adjacent pectoral muscles whenever a tumor was malignant.

Before them stood a younger researcher from the University of Pittsburgh named Bernard Fisher, tall, with a rubbery grin like Walter Matthau's, uttering the unspeakable words:

The radical mastectomy, Fisher said to his colleagues on the stage, was unnecessary. Less disfiguring surgery would do the job just as well.

When Fisher finished and came off the stage and began to make his way through the crowd, suddenly, a young medical resident, a disciple of Haagenson's, lunged out of nowhere and grabbed him by the lapels.

"How could you say those things to my teacher . . . !" he hissed at Fisher before the two were separated, while the crowd oohed in horror and delight.

"I thought he was going to punch me," Fisher said, remembering the incident with a certain glee.

Hounding the heretic

Beating up on Bernard Fisher—at least verbally—was a popular sport for members of the American surgical establishment in the 1950s and '60s.

Even though he eventually would be acclaimed for his accomplishments in breast cancer research, in the early days of his career, Fisher was a renegade.

A "dissident surgeon," thundered Haagenson in his writings, warning Fisher's supporters that they risked "ruination of the soul" if they followed him.

"Surgeons were raised to think of Bernard Fisher as the bogeyman," said Craig Henderson, a noted breast cancer oncologist at the University of California at San Francisco, "and these things take a long time to die."

Fisher's sin was to question the radical mastectomy, a procedure introduced in the late 19th Century by William Stewart Halsted. Surgeons knew it was mutilating, but they felt it was necessary if one were to "get it all."

But Fisher believed that cancer cells spread systemically through the body's blood and lymph vessels, instead of by inching through surrounding tissues—a theory that would be incorporated into standard medical practice by the mid 1980s. Because of that, Fisher reasoned, less disfiguring surgery, with radiation, would be just as effective as removing the whole breast.

By 1994, the "Fisher Hypothesis" had revolutionized breast cancer treatment, bringing him worldwide acclaim.

> Surgeons were raised to think of Bernard Fisher as the bogeyman.
>
> *– Craig Henderson*

Bernard Fisher, left, with his brother, Edwin Fisher, a pathologist at the University of Pittsburgh.

In some ways, he was like Pittsburgh's other medical superstar, liver transplant pioneer Thomas Starzl.

Like Starzl, Fisher has won almost all the major prizes in scientific research. And like Starzl, Fisher is a charismatic, larger-than-life personality, a loner with many admirers but few close friends.

The similarities end there, however.

Starzl, who needed to scare up money and military jets for expensive transplant operations, often courted the media.

But Fisher ducked the limelight. He liked to let "the science" speak for him, and didn't particularly trust reporters to translate scientific information correctly.

Had it not been for the fraudulent data controversy that rocked his career in his 76th year, it's entirely possible Bernard Fisher would have lived out his life in peaceful anonymity, lauded in medical circles, but hardly a household name.

The thrill of adventure

As a boy growing up in Squirrel Hill, Fisher showed a natural scientific bent, perhaps influenced by a great uncle who was a physiologist and surgeon at Case Western University at the turn of the century. He also credits Lon Colburn, a chemistry teacher at Taylor Allderdice High School, with inspiring him.

Then, too, there were the tough expectations of his father, Reuben "Ruby" Fisher, a traditional, no-nonsense son of a Jewish immigrant from Lithuania who ran a successful produce business.

The elder Fisher banned his two sons from the premises of the business, determined that Bernard and Edwin would be the first in his family to go to college.

"You damn well went to school and you damn well performed," recalled Edwin Fisher, a noted Shadyside Hospital pathologist who's a tougher-talking version of his older brother.

In the early 1900s, Ruby Fisher, "King of Potatoes," was successful enough to move out of the North Side to what was then suburbia—Squirrel Hill, where the Fisher boys were born.

For the Fisher brothers, it meant stickball on the streets, the Pittsburgh Pirates at Forbes Field, and a bird's-eye view of the Ringling Brothers Circus tent from the third-floor window of their house.

Occasionally confined to his bed during outbreaks of scarlet fever or whooping cough, Bernard Fisher pored through books about adventurers like Richard Halliburton—"spitting off the Matterhorn, the longest spit in the world!"—or Admiral Byrd's trek to the North Pole, or best of all, "The Microbe Hunters," a classic book about early microbiologists and their discoveries.

In 1936, Fisher entered the University of Pittsburgh, and three years later, its medical school, graduating in 1943.

An ulcer precluded him from serving in the war, so he began his career as an intern at Mercy Hospital.

By the time he had married Shirley Kruman, a bacteriologist at West Penn Hospital, he knew what he wanted to do with his life.

Research.

Learning about cancer

It was a logical choice for a man who had spent his youth devouring books about adventurers, because scientific research seemed to be another way to conquer the unknown.

For the next 20 years, in the 1950s and 1960s, Fisher spent most of his days in a laboratory, often joined by his brother Edwin.

The 1950s were his "Promethean period," he liked to say. Just as the ancients were riveted by the myth of Prometheus, whose liver was devoured by an eagle at night but grew back during the day, Fisher wondered: How could it be that a damaged liver could grow back to normal size and then stop?

Eventually, that would lead him down another path—into the biology of tumor growth. After all, it was the other side of the coin. A liver stops growing at a certain point, but a tumor never stops.

One day in 1957, Fisher's work was interrupted by a telephone call from his mentor, I.S. Ravdin, chairman of the department of surgery at Penn, who asked his former student to drop everything and come to Washington, D.C., for a meeting.

Fisher went reluctantly, hating the distraction.

It was at that meeting at the National Institutes of Health that Ravdin announced his intention to form something called the National Surgical Adjuvant Breast Project.

Unwieldy as the title was, it meant what it said.

Ravdin and his colleagues at the NIH wanted to launch a federally funded program to evaluate the effectiveness of "adjuvant" therapy, or anti-cancer drugs, after surgery for early breast cancers, unlike the prevailing practice of using the drugs only on seriously ill patients.

The proposal interested Fisher only slightly.

"I said, 'Oh, what the hell, OK,'" he would go home and do the study.

Well-behaved disease?

Once he joined NSABP, Fisher's reluctance evaporated in light of a startling discovery: next to nothing was known about how cancer cells grew and spread.

Until that time, it had been assumed that the cancer spread in an orderly fashion, that it was "a well-behaved disease that spread centrifugally, or locally, before it metastasized anywhere else in the body," said Fisher's colleague, Dr. Janet Wolter, a Chicago breast cancer surgeon.

But results in the operating room didn't seem to confirm the local-spread theory.

No matter how much of the tumor and surrounding tissue doctors removed, survival rates remained the same, Wolter said. So "Fisher finally said, cancer is not a well-behaved disease." After much experimentation, he concluded that it spread through the blood and lymph vessels, and if it did, it might be just as effective to do conservative, limited breast surgery combined with radiation to stop the disease.

The only way to test this thesis was through clinical trials, where one group of women would get a mastectomy, and the others would get more conservative surgery.

Fisher soon became a "clinical trials zealot," as he put it.

When he was made chairman of the National Surgical Adjuvant Breast Project in 1967, the first thing he did was move the project's headquarters to his home town of Pittsburgh.

Then, he began setting up trials that would test his theories.

It was tough going at first, because many of the most prestigious research institutions wanted nothing to do with Fisher's experiments.

So Fisher became a traveling salesman, making his pitch at smaller clinics and community doctors' meetings around the nation, from Johnstown and Oil City to Saginaw, Mich., and Wichita Falls, Texas.

Gradually, the gravelly voiced Pittsburgher with a knack for persuasion made converts, enrolling enough patients to begin the first comparative surgery study in July 1971.

One group of patients would receive standard treatment, which at the time was the radical mastectomy. The other group would receive a "simple" mastectomy, where only the breast was removed but not the pectoral muscles, a slightly less mutilating procedure.

Acclaim, then the end

That first study was successful, and Fisher still considers it his personal landmark, even more than the later lumpectomy trial.

But it didn't win him quick respect.

In 1974, when Fisher reported the early results at a National Cancer Institute conference, showing the effectiveness of the simple mastectomy, "we were flushed with success—for about 12 hours."

The next day, the press ignored his claims and his colleagues trashed him.

"He was treated abominably," recalled Samuel Hellman, a prominent radiation oncologist at the University of Chicago, and one of those who still opposes Fisher's theory that cancer spreads systemically.

Slowly but surely, though, the NSABP and Fisher began to gain broader credibility.

As one successful study followed another, more and more doctors joined the NSABP, and Fisher and his staff began attracting awards, fellowships, grants and invitations to speak.

Yet even by 1985, more than 15 years after he took over at NSABP, Fisher still wasn't accepted by some in the establishment.

He and his supporters still fume at what they say was the *New England Journal of Medicine*'s one-year delay in publishing his landmark lumpectomy study that year.

"It was held up by people in the surgical establishment who were opposed to the idea of a lumpectomy," said Canadian surgeon Richard Margolese. "But they couldn't find anything wrong with the manuscript, so they finally had to publish it."

But *New England Journal* Editor-in-Chief Jerome Kassirer disputes that account. "I've heard that story many times before and it's nonsense. It's just not true. We asked them to get more followup data and it took them that time to get it."

By the early 1990s, the NSABP included about 500 institutions and about 5,000 doctors.

Its expansion dovetailed with the growing strength of the women's rights movement.

At first, Fisher's work was lauded by breast cancer activists for pushing the American medical establishment toward lumpectomies.

But the relationship started deteriorating in 1992 when Fisher began what he called his legacy—a huge 16,000-woman study that would test whether the drug tamoxifen could prevent the onset of breast cancer.

Some activists openly challenged him, worried about giving a drug with toxic side effects to health women. They disliked his reaction.

"The moment he found out we had criticisms of his trial, he would never talk to us again," said Cynthia Pearson, director of the National Women's Health Network in Washington D.C., recalling a hearing on the prevention trial held by the Food and Drug Administration.

After one woman in the audience stood up and asked that Fisher's tamoxifen study be delayed until scientists had 10-year results on the safety of the drug, Pearson said, Fisher snapped at her.

"He got just livid and ended up shouting at this woman, 'How long do you want to wait?'" Pearson said.

At around the same time, some of Fisher's colleagues began to wonder when he would turn over the reins at NSABP.

In 1991, a "pink sheet" published by a National Cancer Institute peer review group auditing the NSABP praised Fisher, but asked if he shouldn't start thinking about the "next generation" of leaders.

Fisher, 73 at the time, told the panel that his plan was to leave once his breast cancer prevention trial got under way sometime in the mid-1990s.

"I guess the problem with me is that despite my age, my enthusiasm never ran down, and I've never been told by others that I'm mentally incompetent," he said later.

"But I'm no imbecile. I knew I wasn't going to live forever or be here forever."

Still, he felt he was at the top of his game.

But the rules of the game had changed. There was more and more government oversight, more pressure not to make mistakes. Fisher also watched with distaste as other medical institutions got research grants by catering to the media, something he would not do.

In an oddly prescient speech before the American Society of Clinical Oncologists in 1993, Fisher warned that "politics, personalities, process, publicity, media coverage, fiscal concerns and other secondary considerations must not be permitted to take on a life of their own, and like a cancer, destroy our true mission."

It was a warning that would soon turn into devastating reality for Fisher and the NSABP.

Fisher describes ordeal as "reign of terror"

As spring approached this year, Dr. Bernard Fisher was at the height of a brilliant career. At the age of 75, he had spent more than half a century building his reputation and accumulating nearly every major medical award for his work with breast cancer.

Revered for his achievements and his integrity, he held an unchallenged spot in the medical pantheon.

Until March 13.

On that day, a story in the Chicago Tribune revealed that a Montreal surgeon at St. Luc's Hospital had supplied fraudulent data for more than a decade to breast cancer studies done by Fisher's National Surgical Adjuvant Breast and Bowel Project.

The speed and the vehemence of the negative reaction to the story stunned Fisher. He was in a fog, trying to adjust, trying to focus.

A planned 70th birthday party for his wife Shirley was canceled. His daughter Beth, a Charlottesville, Va., doctor, was home for a visit. Faced with the chaos, she decided to stay on and help her father.

For the next two weeks, Fisher would undergo what he called "a reign of terror" by officials from the National Cancer Institute, people with whom he had been friendly for years.

It started on March 18, at 5:30 on a Friday afternoon, when Fisher got a frantic call from Richard Ungerleider, chief of the clinical investigations branch at the NCI.

Your paperwork shows there are problems with patient records at Louisiana State University and Tulane University, Ungerleider told him. Send your top people down there to do audits by Monday morning and suspend the universities from the study, he told Fisher.

Fisher dispatched his most knowledgeable staffers.

Two days later, Fisher, accompanied by his daughter, met with officials at the University of Pittsburgh, where Fisher's research project was based. The NSABP was an independent organization, but its research money was funneled through Pitt.

Pitt officials had just learned about the Montreal fraud through the Chicago Tribune article because Fisher, who had known about it for three years, had not told them.

Dr. Thomas Detre, Pitt's senior vice chancellor for health sciences, didn't seem overly concerned, Fisher recalled. "It was just a discussion of what could this be about? How could this thing take place?"

A decision was made to do nothing publicly and to wait and see what happened next.

The next day, Monday, March 21, "all hell broke loose," Fisher said.

The fax machine started spewing paper and never let up, he said. The requests came primarily from NCI and the office of Michigan Congressman John Dingell, who was planning to hold hearings on the fraud.

"They'd give you 10 demands—all information about this and that—and we want this by close of business, and all the staff was running like crazy, and it was like something out of Charlie Chaplin," Fisher said.

NCI was feeling the heat, too.

Staff members of Dingell's committee, known for their investigations of scientific misconduct, "were all over us," remembered Dr. Bruce Chabner, director of the Division of Cancer Treatment at NCI. After the Tribune story broke, he said, "there were a series of interviews in which every aspect of this trial was called into question, both the supervision by NCI and the execution by NSABP."

As chief of the division overseeing the NSABP grant, Chabner said he was "very distressed and embarrassed" about the whole episode.

Peoples' jobs were on the line, and not just Fisher's.

"The stakes were very high, scientifically and personally," added another NCI official. "Everybody was concerned for their own scientific careers, for greater or for more narrow reasons."

A humiliating visit

More faxes to Fisher followed, and then came a phone call, alerting Fisher that he would be visited by Chabner and Ungerleider.

When the NCI contingent showed up in Pittsburgh, Fisher felt helpless. The two people who could answer most of NCI's questions, Larry Wickerham and Walter

Cronin, were in Louisiana auditing LSU and Tulane, at NCI's insistence.

The NCI "wanted files on this, wanted files on that," and Fisher, without his two top aides, couldn't accommodate them. A recent move from another part of the building had complicated matters.

As a result of the disastrous visit, NSABP was put on probation.

just derelict in this and derelict in that. I wanted to get up and shriek and say, 'No we weren't!'

"But the university policy was, 'Keep quiet, it'll go away.' "

Why the strategy of silence?

The primary goal, Fisher said, "was not to provoke John Dingell."

> They'd give you 10 demands—all information about this and that—and we want this by close of business, and all the staff was running like crazy, and it was like something out of Charlie Chaplin.
>
> *– Bernard Fisher*

And the demands continued to pour in.

"We were working 18 hours a day, and nothing was going on. We were trying to fulfill these orders, and it was just chaos," Fisher said.

Pitt's specially hired lawyer on the matter, Martin Michaelson, tried to soothe Fisher, suggesting at one point that he read poetry. Michaelson also emphasized his strategy—keep quiet, don't say anything, and it will all blow over.

But it didn't. It was a big story—in fact, it would be listed as one of the top 10 stories of the year, according to the Associated Press.

To Fisher, though, the media coverage seemed unfairly negative. One Pittsburgh television newscaster solemnly reported that Fisher himself had been accused of falsifying data—something that was never true.

They "were making these accusations that were blatantly false, that we were

By now, the powerful Michigan congressman's presence loomed like an ominous thundercloud.

Dingell was known for his rough treatment of witnesses who came before his subcommittee. No one was immune: Nobel Prize-winning scientists, CEOs of major corporations, Navy admirals. A small cottage industry had sprung up in Washington—lawyers specializing in counseling witnesses ordered to appear before Dingell's committee. They even had an informal name: the Dingell bar.

'I've never heard of him'

All of this was new to Fisher.

"I'd never heard of John Dingell, didn't know anything about him," Fisher said. But after he was told about what happened at Dingell hearings, Fisher began to feel real fear.

The fateful moment for Fisher came on March 25.

Looking through the NSABP files, an NCI official found a Sept. 22, 1993, report on a visit to another Montreal hospital, St. Mary's.

The report said the NSABP auditing team had found a major problem with one chart, in which a mammogram date for one woman apparently had been changed. The finding, according to the auditors, "presents a serious problem."

But the audit report had never been forwarded to NCI. It remained in a file cabinet in Pittsburgh.

Chabner said later that this single file was what prompted NCI's insistence that Fisher be replaced as principal investigator for NSABP. After the fraud committed at St. Luc's by Dr. Roger Poisson, after reports of missing files in Louisiana, after learning that no audits had been done by NSABP for months, it was just too much.

"There was a sense that the NSABP was clearly in danger of collapse," said Dr. Michael Friedman, the director of NCI's cancer therapy evaluation program.

"It was clear that Dr. Fisher was being overwhelmed by the workload."

And yet, with the exception of the St. Mary's file, NCI officials had been aware for years of all the problems they later cited when they fired Fisher.

But in the frantic climate following the Tribune story, amid all the telephone calls from Dingell's office, those previous problems looked much more serious to NCI.

It was Friedman who made the decisive call to Fisher on Monday, March 28. The two already knew each other well.

They had worked closely when Fisher was president of the American Society for Clinical Oncologists the year before.

Fisher took the call in his office. Also present were his daughter Beth; Al Ciocca, a Pitt lawyer; and NSABP's chief biostatistician, Carol Redmond.

Friedman was on his speaker phone, joined by Chabner and several other NCI officials. NCI Director Samuel Broder was also in the room at NCI headquarters in Bethesda, Md., but he did not speak.

Fisher remembered that Friedman sounded agitated.

We've found out you knew about the St. Mary's audit, and didn't do anything, Friedman told Fisher angrily.

Fisher said his staff had never told him about the St. Mary's audit until it was discovered by the NCI official. That didn't placate Friedman.

This will tear down research all across the country, Friedman said, over Fisher's protests that he didn't know what Friedman was talking about.

Fisher still remembers the words that ended his distinguished 35-year tenure at the NSABP.

"You're finished, Bernie!" Friedman yelled. "You got (screwed) by your staff. You're out!"

Pitt jumps in

On March 29, NCI, in a letter, officially ordered Pitt to remove Fisher as principal investigator and appoint an interim replacement, citing "a litany of NSABP failures."

Besides the fraudulent data, NCI cited NSABP's decision to halt audits at member hospitals, delays in establishing independent boards to monitor patient records, and Fisher's slowness in publishing a reanalysis of his studies excluding the tainted information.

The NSABP office was formally placed on probation until corrections were made. As part of that, it was ordered to immediately adopt a "rigorous" schedule of audits of patient data, and to suspend enrollment of new patients in various studies.

Fisher was given no opportunity to defend himself in a hearing, and Pitt officials were presented with only two choices: Comply with NCI requirements, or give up NCI grants to NSABP, which totaled about $22 million per year, about $10 million of which went to Pitt.

Pittsburgh Cancer Institute Director Dr. Ronald Herberman—a laboratory scientist who specialized in immunology and knew little of breast cancer clinical trials—was appointed by Pitt to head the NSABP.

It was a shotgun marriage, and it was shaky from the start.

The NSABP might be headquartered in Pittsburgh, but it was actually an international network of about 5,000 surgeons and researchers. They had always prided themselves on their accomplishments and independence. Now, they believed, Pitt's Herberman was co-opting their studies and treating them like errant children.

On the evening of March 30, a grim NSABP executive committee met in Pittsburgh.

Fisher, their leader and inspiration for more than 20 years, spoke first. He simply told his colleagues that he was no longer chairman. Then he left.

Herberman took over the meeting. One of the committee's first acts was to vote unanimously for Fisher's reinstatement—hardly a warm welcome for the new acting chairman.

It would be one of many volleys fired between NSABP committee members and Pitt in the succeeding months, culminating in an acrimonious lawsuit.

"It was not inevitable to lose, irrevocably and forever, the goodwill of leaders of the NSABP, who very naturally had a loyalty to and respect and admiration for Dr. Bernard Fisher," said Dr. Yosef Pilch, a longtime NSABP member.

But Pitt did lose that goodwill, he said, because its officials "overreacted in a very paranoid fashion to pressure from NCI," particularly on auditing patient records.

The employees at NSABP headquarters felt the same way. After years of working with Fisher, whose style, if occasionally overbearing, was also inclusive and open, they found themselves abruptly put under the yoke of Pitt's new management, which was a more top-down, hierarchical structure.

A problem with numbers

NSABP's new management was immediately under the gun, as Dingell's staff pushed it and the NCI to get ready for the congressman's first scheduled hearing on the fraud, less than two weeks away.

And even though Fisher had been ousted, he was still being ordered to produce documents for NCI or the Dingell committee.

The queries were neither tactful nor sympathetic.

On March 30, the day after his firing, a shell-shocked Fisher went to his office at Pitt's Scaife Hall, where he received a fax from NCI demanding to know the number of St. Luc's patients in each paper that NSABP had published or was planning to publish.

"Please fax this information by tomorrow afternoon," it said.

Fisher had just sent one list of papers with the St. Luc's data the day before. By the end of March 30, he had added seven more to the list.

One of the stickiest problems arose over a paper Fisher had submitted to the NCI's own Journal of the National Cancer Institute. That paper, scheduled for publication in April, had included the St. Luc's data, but Fisher hadn't mentioned that fact until NCI officials ordered him to detail it in a footnote.

The dispute over that paper symbolized a larger problem that continues to this day.

What is the proper way to deal with the St. Luc's data in published studies? Poisson was found guilty of altering records on 99 patients out of 1,511 he had enrolled in various NSABP studies.

In scientific papers including St. Luc's patients, should only the falsified cases be excluded, or should all of them go? Should all NSABP papers be published with two sets of statistical tables, one with and one without the St. Luc data?

NCI officials wanted to throw out all the St. Luc's patient data, but NSABP staff in Pittsburgh resisted, citing support from prominent statisticians.

They saw no reason to discard patients whose records were in order. Such a move would void the contributions of hundreds of Montreal-area women who had volunteered to participate in the studies, they said.

Another bone of contention was the "rigorous" audit schedule demanded by NCI.

It was more complex than it sounded, requiring not just "standard" audits, involving a sampling of files—but "for cause" audits that required scrutiny of each patient's record, in Louisiana, New York and other sites where there seemed to be problems.

The NCI wanted every NSABP study with a potential for fraud to be re-examined.

But its first priority was the landmark 1985 lumpectomy study, which showed that conservative breast surgery, combined with radiation, was just as effective in treating early breast cancers as the more disfiguring radical mastectomy.

NCI wanted an intensive audit of the major institutions involved in the study to be done before the April 13 Dingell hearing.

To meet that deadline, the NCI sent teams of eight to ten people to each of 40 institutions in the U.S. and Canada. The teams had been culled from the ranks of pharmacists, Ph.D.'s, oncologists, nurses and others who did not necessarily have experience with either clinical trials or breast cancer research.

A Passover debacle

For some, the audits bordered on the absurd.

Dr. Richard Margolese, principal investigator at Jewish General Hospital in Montreal, said an NCI auditing team showed up unannounced at his hospital on the first Monday of Passover, asking to see records dating back to the 1970s.

The auditors were pleasant, even apologetic, Margolese said. "But, I must tell you, the auditing process was a shambles."

Charts and records of patients—some of whom had moved or had died—had to be retrieved from community doctors' offices, brought to Jewish General, and stacked on the floor. At one point, Margolese said, a stack fell over and records got mixed together.

The auditors stayed all week, then told Margolese his records were in good order.

"The word used was 'pristine.' "

Five days later, though, the auditors were back to look at what they described as "missing data," Margolese said. They wanted to review all 135 charts from the lumpectomy study.

The second visit lasted one day, and Margolese—who had been out of town—met the auditors as they were preparing to leave. "They said they had six ineligible charts," Margolese recalled, but then assured him they considered that a low number.

"I told them, 'I don't think six is a low number.' " Margolese insisted they go over the charts together. He was able to immediately show that all but one of the women was eligible.

Still, for reasons he doesn't know, Jewish General was barred a few weeks later from enrolling patients who had signed consent forms before April.

Margolese was never formally notified, and only learned of the suspension when the center tried to enroll a patient two months later and was told it couldn't.

Finally, after NSABP intervened, the enrollment ban was lifted.

While the auditors were scattering around the countryside, the man who started it all held a news conference in Montreal.

Roger Poisson was not apologetic.

He derided "those people in their ivory towers" who had criticized him for fudging dates on eligibility criteria. "It's all very well to compare clinical experiments carried out in the laboratory," he said. "I was on the battlefront with patients who were dying."

Poisson's defense—that his falsifications were minor and in the best inter-

ests of the patients—was almost universally rejected.

But he was rapidly becoming irrelevant, a quaint sideshow to the real issue at hand: the upcoming Dingell hearing.

On April 5, Donna Shalala, the Secretary of Health and Human Services, weighed in with a point-by-point 12-page response to a list of questions from Dingell's staff.

Shalala offered her assurance that the NSABP study conclusions would hold up, but added that "neither my office, the NCI, nor (federal science fraud investigators) is satisfied with the handling of this matter."

She promised changes.

She was deferential to the congressman. Most Washington bureaucrats were,-because of Dingell's power to make or break them. During the testimony to come, not one of them would stand up for the man who is, arguably, the world's greatest breast cancer researcher.

His "nonobservance" turned into a major fraud case

Roger Poisson can still remember the first time he fudged a a breast cancer patient's medical record, on a day long ago in 1977, so she could be enrolled in a study even though she had missed the deadline by several days.

It was just a small deceit, really. A quick change of dates, so that the woman could meet the study's requirement to be enrolled within 30 days of her diagnosis. It was all "in the best interests of the patient," as the Montreal researcher described it in a recent interview.

Even after he was blackballed from American-funded research for eight years, Poisson was not fired from St. Luc's, because, officials said, they found no proof that he had harmed patients.

> "In my mind, I was thinking that the good I was doing was by far more important than the small irregularities."
>
> *– Roger Poisson*

That little deception, of course, was followed by another. And another. Until all the little deceptions had snowballed into one giant case of scientific fraud, causing the near destruction of the National Surgical Adjuvant Breast and Bowel Project, the world's largest breast cancer research organization.

But even today, Roger Poisson still doesn't quite understand what the fuss was all about.

After all, what he did wasn't really fraud, Poisson said, just "a nonobservance of strict criteria that had no oncological value."

Three years after his falsifications caused his removal from the NSABP, and nine months after the scandal became public, Roger Poisson, 63, appears to be a man at peace with himself and with his actions.

Despite losing his access to U.S. grant money, to his professorships at the University of Montreal and his position as chief of oncology at St. Luc's Hospital, Poisson still has a thriving breast cancer surgery practice—"thousands of patients," he says, a touch of defiance in his soft, reedy, French-accented voice.

And despite the worldwide disapproval that rained down upon him last spring in the wake of the scandal, Poisson says—and other Montreal colleagues confirm—that he has become a hero to many in the French-Canadian community because of a belief that he was scapegoated by U.S. bureaucrats.

The stories about his falsifications seemed suspiciously timed, he thought, appearing simultaneously everywhere from South America to Eastern Europe last March.

"How do you explain something so well-orchestrated?" Poisson said. "It's clear that some people wanted my skin."

Another explanation is that news services are able to move a story around the globe within minutes.

Whatever the world thinks of Roger Poisson, he believes he did the right thing by breaking the rules.

"In my mind, I was thinking that the good I was doing was by far more important than the small irregularities" he committed.

In all, investigators from the U.S. Office of Research Integrity found that Poisson

had been responsible for 115 separate instances of data falsification involving 99 patients in 14 breast cancer studies from 1977 to 1990.

Most were minor, such as changing the date of an operation to make a woman eligible for the study; a few, however, were more serious, including one in which the nature of a breast tumor was deliberately misrepresented as less advanced than it actually was. Another involved a woman with cancer in both breasts who had been classified as having cancer in one breast.

Poisson had a ready explanation for each infraction:

- Of the requirement Poisson most frequently flouted, that a patient be enrolled within 30 days of diagnosis, Poisson said it was an artificial, arbitrary deadline that was later changed to 56 days during the course of the study.
- Of the NSABP staffers' discovery of documents labeled true and false in his files, "one data coordinator did that for about four or five patients," Poisson said, a trace of impatience in his voice. "Why? I can't say. As the principal investigator, do you think I was supposed to supervise everything? They blew that out of proportion."
- Of the incident in which he described one woman's breast cancer as less advanced than it actually was in order to get her into the study, he said the patient actually had "a slight edema," or swelling, in one breast, but years of experience told him that she would still benefit from being in the study.
- Of the patient classified as having cancer in one breast, resulting in her having radiation of that breast, while she was actually afflicted with cancer in both breasts, Poisson pointed out that she also had chemotherapy, which treated both breasts' tumors.

"Roger Poisson would not have changed serious things, like (enrolling) a patient without a cancer, or (enrolling) fictional patients," Poisson said of himself. "None of that has been found in my files."

He said changing dates to make some women eligible was like "crossing against a red light at 2 o'clock in the morning."

Others disagreed.

The federal Office of Research Integrity barred him from performing any U.S.-funded research for eight years, the stiffest penalty ever imposed in a scientific misconduct case, and the U.S. Food and Drug Administration barred Poisson for life from access to experimental drugs.

Later, he said the worst pain was losing the confidence of NSABP Chairman Bernard Fisher, a man he considered almost a father figure.

"It came to me like a death," he said, of Fisher's dismissal of him. "I had no warning."

For his part, Fisher remembered Poisson as "a pleasant enough guy, who was devoted to what was going on, a disciple of what it was we were trying to do."

Fisher never thought there was anything suspicious about Poisson's behavior. Under NSABP's funding system, Poisson enrolled so many patients that he wasn't paid on a per-case basis, but received a flat amount of grant moneyfrom the National Cancer Institute—so money wasn't an incentive, Fisher believed.

Unbeknownst to Fisher, though, Poisson was extremely frustrated whenever he couldn't enroll a woman in a study because of what he considered a technicality.

It often takes a long time to convince a woman to enter an experimental trial, Poisson said.

"You talk to her, she goes home, talks to her husband, she calls you and says, 'I don't know,' and then finally, three weeks later, she agrees to participate.

"And then you look at her medical history and realize that she is two days past the deadline—within 30 days of diagnosis—for enrolling.

"So what am I supposed to do? Tell the woman, I'm sorry, forget it, after all the pep talks? I'm sorry, I did not have the courage to say that to a woman."

Poisson actually thinks his fraud may have helped, in the end, because it led to publicity about the value of lumpectomies.

Fisher's outlook about Poisson's role is less positive.

"The guy did what he did, and as far as I'm concerned, that's his problem," he said. "The hell with him."

Fisher feared Dingell inquiry

On Wednesday, April 13, Rep. John Dingell, one of the most powerful congressmen on Capitol Hill at the time, began another of his dramatic scientific misconduct hearings.

In the past, the Michigan Democrat had put such famous scientists as AIDS researcher Robert Gallo and Nobel laureate David Baltimore in the heat of his spotlight.

This day, the target would be Pittsburgh's Bernard Fisher and his breast cancer research group, the National Surgical Adjuvant Breast and Bowel Project.

But Fisher would not be present for the first hearing.

The day before, there had been an announcement that Fisher was ill, and had decided not to testify.

But Fisher wasn't sick.

That was a cover story devised by a University of Pittsburgh lawyer, who thought it was not the right time yet for Fisher to go public.

The strange turn of events had begun when Fisher met for four hours the week before in Washington with Dingell's staff to go over his testimony.

At the meeting, Fisher "seemed shellshocked," one Dingell staffer remembered.

"Everybody was trying to help him put the pieces together, of what he had done, what he hadn't done. We were trying to help," the staffer said.

Fisher went back to Pittsburgh and spent the weekend in seclusion, preparing his testimony.

"He wanted to tell his story. It was written from his soul," his daughter Beth recalled.

But when a draft of Fisher's testimony was faxed to Pitt's lawyer, Martin Michaelson, the day before the hearing, word came back to Fisher that Michaelson didn't like anything about it. Michaelson didn't think it had come close to accepting enough blame for what had happened.

Thus began a debate between Fisher and the Pitt lawyers. Should he testify, or should he not? Maybe it was best to keep quiet.

Michaelson decided that Fisher should not attend, and that he would cite ill health.

Joseph Onek, whom Fisher had hired as his personal lawyer, remembered concurring with the decision.

"We just didn't know enough" about the allegations against the NSABP, he said. "It didn't seem like a good time to do this."

A charismatic witness

Even without Fisher, the hearing received national media coverage.

Two hours after it was over, Dingell's staff crowded around a television to watch the network coverage of the hearing.

What they saw was the earnest face of Jill Lea Sigal, a 32-year-old Virginia woman who told the world of her own breast cancer diagnosis six months before.

An environmental consultant, Sigal had worked extensively on Capitol Hill for the previous 11 years. So when she first saw the news that a Canadian surgeon had falsified data in some of NSABP's studies, she knew what to do. Sigal immediately called a congressman whom she knew who put her in touch with Dingell's staff.

Sigal told a Dingell staffer that she was furious with Fisher and the agency that funded the studies, the National Cancer Institute, for its lax oversight.

The staffer said, "Well, if we have a victim's panel, maybe we'll want to use you."

Later, another staff member called, asked her more questions and then said, ''You'd be the perfect witness."

And she was.

Sigal's angry words rang through the hushed committee room and on televisions across America.

Although she hadn't participated in the lumpectomy study, she had relied on its findings, she told the House Oversight and Investigations Subcommittee. After consulting with her physicians, she decided to have only the lump and a small amount of surrounding tissue removed from her breast.

Now, she was outraged—outraged at the falsification of records, and outraged that the information about it was not available when she was making life-or-death decisions about her own treatment.

"How many women must now wonder, as I do every day, if they will diebecause they may have made the wrong decision?" Sigal asked.

Afterward, Sigal was approached by Bruce Chabner, a top NCI official, who complained that she had needlessly frightened women into thinking they had opted for the wrong surgery. Furious, Sigal told Dingell about Chabner's remarks, prompting NCI Director Samuel Broder to send her a letter of apology.

Yet for all Sigal's righteous indignation over Chabner, he was simply relying on the best information scientists had—that the basic findings of Fisher's original lumpectomy study were correct.

Two days after the hearing, in fact, Edward Sondik, acting deputy director of NCI, sent out a "Dear Colleague" letter describing a reanalysis that had been done by a government-hired contractor of the lumpectomy study and two other NSABP breast cancer studies.

His conclusion: Discarding the falsified data from the one Montreal hospital "has no substantive effect on the main study findings."

The message was confusing. Television images of angry breast cancer patients were juxtaposed against repeated scientific assurances that the studies were valid.

A sense of proportion

Indeed, for every Jill Sigal, there was a Diane Walsted.

"It seems like it got blown out of proportion," said Walsted, a 52-year-old breast cancer survivor who volunteers on a hotline for breast cancer patients in Chicago.

"I don't mean to say there weren't any problems that shouldn't be corrected. But a lot was made out of it, and it had the effect of not only frightening women, but making it harder for women to participate if they have this image in their mind about fraud."

"I don't mean to say there weren't any problems that shouldn't be corrected. But a lot was made out of it, and it had the effect of not only frightening women, but making it harder for women to participate if they have this image in their mind about fraud."

– Diane Walsted

Another scare for some women was the news that a few patients who took the anti-cancer drug tamoxifen as part of an NSABP study had died after contracting uterine cancer, and that Fisher had delayed putting that information on patient consent forms.

Dingell and some patients were angry at the delay. But that feeling wasn't universal.

Dr. Peter Eisenberg, of Marin Oncology Associates in Greenbrae, Calif., said women at his center weren't shocked by the new information about uterine cancer deaths.

The existing consent forms already listed uterine cancer as a possible side effect of tamoxifen, he said. To say some of those women eventually died was not surprising.

"In fact," he said of his patients, "they couldn't understand what the hubbub was all about."

To Sharon Green of Y-ME, a national breast cancer support organization based in Chicago, one could look at the controversy in terms of "A-problems, B-problems and C-problems.

"A-problems are just messiness," she said. "A-problems are not going to affect outcomes and are not going to hurt anyone's life. B-problems are a little more serious. And C-problems are the serious ethical and scientific problems."

Her assessment of the NSABP controversy: "My guess is, we have more of the A- and B-problems."

Certainly, the falsified data, the poor record-keeping, the unclear documentation on getting informed consent, the delays in telling the public—all these concerned Green.

But she wondered: "In reality, did it really matter?"

Troubles for Pitt

When Fisher had been summarily fired from his post as chairman of NSABP in late March, Pitt officials had stepped in to take over the vast research organization, which involved about 5,000 doctors and 34,000 patients.

By late April, Pitt was having its own problems with the federal government.

NCI officials were pushing for a quick "recompetition" of the NSABP grant so that other medical centers could make proposals to take over its cancer research.

That would cost Pitt more than $20 million a year in federal funding, and would take away control over the massive, 16,000-woman breast cancer prevention trial that NSABP had begun.

Then Pitt got a little breathing room when the NCI's Board of Scientific Counselors balked at the idea and urged that Pitt be given time to fix the NSABP's problems.

In the meantime, NCI had thrown Pitt another curve.

The agency wanted the university to investigate Fisher and Carol Redmond, his chief biostatistician and closest aide, on whether they had been guilty of improper behavior by knowingly submitting research papers containing some of the falsified Canadian data.

Up to that moment, Fisher and Redmond had not been accused of doing anything that was scientifically unethical themselves. Now, they, too, were being tarred with the damning phrase "scientific misconduct."

One of the papers involved a tamoxifen study and included some women whose records had been altered by Montreal surgeon Roger Poisson.

Fisher made an intriguing argument on why it was proper to leave those cases in the study. Two of the Montreal women later contracted uterine cancer and died. If he had excluded the cases where data had been falsified, Fisher said, he would also be throwing out important information on the side effects of the drug.

A top federal cancer official took a different view.

"To include systematically fraudulent cases ... there's no other field of research where you would do that," said Dr. Bruce Chabner, director of the Division of Cancer Treatment at NCI.

Chabner said it was important for Fisher to acknowledge the falsified data, so he directed Fisher to contact several medical and research journals, including the New England Journal of Medicine, which had published NSABP's landmark 1985 lumpectomy study.

But the New England Journal balked at publishing Fisher's reanalysis of the lumpectomy study, saying it wanted to wait until NCI was finished auditing the NSABP records.

NCI had asked Fisher for a year to publish the reanalysis. Now that he was finally ready, he couldn't get it into print.

Eventually, the federal Office of Research Integrity took over the investigation of whether Fisher and Redmond had engaged in misconduct. Today, eight months later, no decision has been made.

On the outs

By now, Pitt's relationship with Fisher had grown muddled and tense.

One of the lawyers who would help Pitt investigate Fisher was Martin Michaelson, the same man whom Fisher had taken into his confidence after the scandal broke, who had perused Fisher's files and who had suggested that he read Kipling and Tennyson to calm his spirits.

Fisher was stunned that a lawyer who knew so much about him would now be investigating him.

Pitt's treatment of Fisher didn't sit well with some at the university.

"A lot of people look at this and say, 'If you can go after people of the quality of Bernie Fisher, you can go after anyone,'" said Dr. Lewis Kuller, a longtime colleague and head of the Graduate School of Public Health's Department of Epidemiology.

Still, Pitt said it was trying to find a way to retain some role for Fisher in NSABP's studies without further angering federal officials.

University officials had initially proposed that Fisher be kept away from any administrative duties, but be allowed to serve as scientific director of the project.

That would recognize his brilliant contributions as a researcher and appease the hundeds of doctors in the United States and Canada who regarded Fisher as the heart and soul of NSABP.

But Dingell's staff, which was getting ready for a second hearing on the breast cancer fraud, was adamant that Fisher no longer be part of NSABP's administrative hierarchy.

That message was relayed to Pitt officials by NCI, and the university announced that the new NSABP would have no formal role for Fisher.

Pitt made one last show of public support for Fisher and Redmond.

It came after U.S. Sen. Arlen Specter appeared at a news conference at Pitt on May 16.

The Philadelphia Republican promised to push to get NSABP's suspended studies restarted.

Afterward, Jeffrey Romoff, president of Pitt's medical center, said the university had asked NCI to consider allowing Fisher and Redmond to have a role in the project.

His comments were printed the following day at the top of a front-page *Post-Gazette* story headlined, "Pitt Fights Back."

Nine days later, NCI officials sent a letter to Dr. Ronald Herberman, a Pitt official serving as interim chairman of NSABP, asking whether Pitt's statements were true.

"Because we have not yet received the formal request referred to in Dr. Romoff's statement, please inform us as soon as possible of the University of Pittsburgh's position on this matter," it read.

Chabner said he later received a call from Pitt in reply.

"Someone said 'I'm sorry. We didn't mean to say that. It was a mistake,' " he said.

'Not enough groveling'

If any question remained that Pitt was backing away from Fisher, it seemed settled when Pitt officials asked to testify separately from Fisher at the second Dingell hearing on June 15.

By then, many of the initial scientific controversies that had erupted in March had diminished.

Nevertheless, the hearing did deliver high drama—the long-awaited

face-to-face meeting between Dingell and Fisher.

For Fisher, it was a total, unmitigated disaster, the low point of his life.

One detail in particular sticks in his mind.

The night before the hearing, he was in his hotel room at the Willard in Washington, D.C., with his wife Shirley,and eldest daughter, Beth, a University of Virginia doctor who had taken a leave of absence to assist her father.

The telephone rang.

It was Joseph Onek, the Washington lawyer whom Fisher had retained.

As was the custom, Fisher's testimony had been forwarded to the Dingell committee, and the committee staffers had indicated that there was a problem, Onek said.

"They said there isn't enough groveling," Onek told him.

While Onek later confirmed that account, a Dingell staffer who declined to be identified strongly disagreed with Onek's interpretation.

The real problem with Fisher's testimony, the staffer said, was that "they really couldn't come to grips with admitting the warts and wrinkles of the project."

In either case, it was clear that Dingell's staff wanted some acknowledgment of mistakes from Fisher.

They certainly got that admission from Pitt officials.

Dr. Thomas Detre, the university's senior vice chancellor for health sciences, preceded Fisher at the hearing and talked about how major universities historically had treated senior researchers like Fisher gingerly, a "culture of deference" that he believed should change.

Fisher was up next.

For the following two hours, he endured withering questioning from Dingell and other subcommittee members.

Reading from his prepared statement, Fisher emphasized that "there was never any intent to hide information regarding the discovery of falsified data at St. Luc Hospital."

He apologized for not having published a reanalysis of the studies yet.

"We did not realize that the failure to publish our findings immediately would be misinterpreted by the public as an indication that we were concealing information," Fisher said.

Of the controversy over the uterine cancer deaths, he said, "it might have been possible to collect and report information about these deaths sooner, but there was never any intent to withhold information."

Then, in a statement that he added after the "not enough groveling" remark by Onek, Fisher conceded that "perhaps my passionate attention to the science overshadowed my administrative insight, and this was a mistake. I should have been firmer with the personnel responsible for the audit program" that checked patient data.

Although he said NCI officials "have been involved in every aspect of our efforts," Fisher did not read a subsequent sentence from his prepared statement:

"Consequently, NCI must share with the NSABP responsibility for deficiencies in our project."

Mary Otto, a writer for Knight-Ridder newspapers, later described Fisher as "tired, abstracted and ill-prepared" during the hearing.

Widespread problem?

Much of Dingell's unrelenting inquisition centered on whether patient data problems existed at other hospitals, beyond St. Luc's, where Poisson had worked.

The congressman said they did.

At one site, he said, "three-quarters of the patients enrolled did not meet the eligibility criteria."

Fisher answered that there "may be some misunderstandings regarding clarification of ineligibility."

Later, as Fisher was explaining the NSABP audit process, Dingell cut him off, and repeated: "One site had three-quarters of the participants ineligible."

"I am certainly unaware of that, sir," Fisher replied, his voice cracking. "I really am not aware of it."

Dingell then listed the centers with "problems with either fraud or slovenly work"—South Nassau Communities Hospital in Oceanside on New York's Long Island, Rush Presbyterian Hospital in Chicago, St. Joseph Hospital in Lancaster, Pa., and Pitt.

At the University of California-Davis, Dingell said for the third time, three-quarters of the patients were ineligible.

It was a dramatic drilling. But it wasn't true.

Dr. James Goodnight, director of the UC-Davis Cancer Center, said later that a sample audit of eight charts had found possible problems with six of the patients' records.

But there was never evidence that three-quarters of all 184 patients at UC-Davis had errors in their records.

A closer look at the other centers cited by Dingell also reveals less than meets the eye.

Pitt's Herberman said he was unclear what problems Dingell was talking about at Pitt, other than some records that had come in late.

At South Nassau, two of 207 patients had been found to be ineligible. The error had been caught by an NSABP audit in 1992 and the women were removed from any studies. Since then, South Nassau had enrolled only one more patient.

A spokeswoman at Rush Presbyterian said there were irregularities on a single audit in 1991, but she could give no further details.

Joan Hess, of St. Joseph Hospital in Lancaster, said its inclusion in the list "was all in error."

"We checked this out and what we ended up getting was a written apology-from ... the University of Pittsburgh," she said. "Our files were up to date. We had no idea how we were named."

Dingell also cited "serious and chronic problems" with data at Tulane and Louisiana State universities at the June hearing.

Eventually, though, those problems turned out to be much less serious.

The first reports intimated that large numbers of ineligible patients might be at both sites.

Dr. Roy Weiner of Tulane said there were "very real problems," but they weren't ethical—they were administrative. Over the 17 years that the Tulane-LSU group had been in NSABP, Weiner said, the office staff remained at two people, even as the number of patients in studies soared to 450.

The staff simply couldn't keep up the records on all those women, and so auditors had to search files in doctors' offices and clinics to find the information verifying that women were eligible.

While not all patient data was found, Weiner said, "some of the deficiencies were truly trivial, and in many instances, the data that was missing was never even required" for the study. Since then, he said, Tulane has beefed up its staff to eight people.

Dingell smiles on Pitt

Between his first and second hearings, Dingell underwent a noticeable change in attitude toward Pitt.

At the first hearing, Dingell had hinted he might want to look into other scientific misconduct cases that had occurred at the university in the past.

By the second hearing, though, Dingell was solicitous toward Pitt officials who testified, including Chancellor J. Dennis O'Connor, Detre and Herberman. Dingell praised Pitt as "a great institution, one of which you are justifiably proud."

In the weeks leading up to the hearing, Dingell's staff had wanted a pledge that Pitt would live up to its "institutional responsibility" to take care of problems at NSABP, Herberman said.

He said O'Connor, Pitt's top administrator, wrote to NCI Director Samuel Broder, "providing very strong and unequivocal assurances" that Pitt recognized the problems and was committed to fixing them.

Fisher was becoming more and more isolated.

After his fumbling performance at the second Dingell hearing, Fisher went home with his family, numb with grief.

"We were sitting shiva," his daughter Beth said, evoking the Jewish tradition of mourning, as she described the black mood in the Fisher household as friends dropped by to try to lend support.

Still dazed from Dingell's harsh treatment, Bernard Fisher faced the prospect of building a defense against Pitt's investigation of him.

He figured it was time to get new lawyers. He hired John Bingler, a member of Thorp, Reed & Armstrong, and James Lieber, a member of the law firm Lieber & Hammer in Shadyside.

Bingler and Lieber wrote to Pitt, complaining about how Pitt's special lawyer, Michaelson, had unfairly started out as Fisher's attorney and then became involved in the investigation of Fisher over misconduct allegations.

They got no response.

So, on a humid day in early July, Fisher called a news conference in his lawyers' office and announced he was suing the university, a place he had called home for most of his adult life.

"Now is the time when this whole thing has got to stop," Fisher said.

He wanted his job back and he wanted the university to halt its investigation.

One month later, he was joined in the federal lawsuit by members of his executive committee. They thought their action would force a quick responsefrom Pitt.

Instead, it led to protracted, unfruitful settlement negotiations between lawyers for Fisher and Pitt officials.

At one point, a settlement agreement was drafted by Fisher's attorneys that would have made Fisher scientific director for NSABP. It remained unsigned.

The ongoing talks became an albatross for the NSABP.

The project had selected Dr. Norman Wolmark, a respected breast cancer surgeon from Allegheny General Hospital, to become the new leader of NSABP.

As NCI director, Broder had to approve Wolmark's appointment before he could begin. But Broder wouldn't do that as long as the suit was pending.

Eventually, committee members realized they had to get back "on line" with NCI or face possible extinction.

Nothing showed the change in attitude more clearly than a meeting of the executive committee in Bethesda, Md., headquarters city of NCI, in November.

Present were Fisher and his brother Edwin, a longtime research associate. Some committee members then asked: Did it serve NSABP's interest to continue in the Fisher lawsuit?

The question was rhetorical, but its implications, coming from a group of Fisher's most loyal supporters, were far-reaching: NSABP was ready to move forward, with or without Bernard Fisher.

Fisher affair clouds future study

As the new year draws closer, Bernard Fisher waits.

He waits for the completion of a federal investigation into studies he published. He waits for the resolution of his lawsuit against the University of Pittsburgh. He waits, most of all, for vindication.

At 76 years old, with his spirits flagging and his legal bills mounting, he feels precious time slipping away.

The pre-eminent breast cancer researcher is cut off from the important work that has consumed his life.

Each day, he still goes to work at his old offices in the University of Pittsburgh's Scaife Hall. But instead of analyzing data that might lead to medical advances, Fisher confers with lawyers, writes defenses of his actions and takes calls from colleagues expressing sympathy.

The breast cancer studies he once directed six days a week for a quarter of a century are being run elsewhere on the campus. It's a short walk away—but it might as well be another galaxy.

This is what Fisher has come to in the nine months since the world learned that a Canadian doctor had falsified data used in several of Fisher's studies.

His eldest daughter, Beth, is always by his side. A Virginia doctor, she took a leave of absence to help restore her father's reputation. During his interviews with reporters, she takes notes furiously, quick to jump in with corrections if her father stumbles or a reporter makes the wrong assumption.

Recently, Fisher ran into an old friend.

"The guy said to me, 'What do you do? What are you doing now? You go to work every day, but you don't have access to this, or that? What are you doing?'" Fisher said, mimicking the man's nagging voice.

"Well," Fisher said quietly, "that's a good question."

With no meaningful scientific work to do, he is a king without a court.

Epilogue: Other scientists

The humiliation that Fisher has undergone, and the failure of Pitt and the National Cancer Institute to stand by him, have sent shock waves through the scientific community.

If it could happen to him, many believe, it might happen to any scientist who is ambitious enough to tackle large and complex research projects, but might be a little too arrogant, or stubborn, or slow to respond to demands by federal agencies.

As a result of Fisher's ordeal, scientists once again are debating who should police science and how to do it fairly.

The federal Office of Research Integrity, a little-known department working out of the Department of Health and Human

Services, is responsible for investigating reports of serious misconduct.

But because the office is understaffed and underfunded, investigations often drag on for more than a year. Scientists are forbidden from discussing the case publicly until a conclusion is reached.

Despite the gag order, the biggest cases often are played out in front of a national audience long before the formal probe is completed. That occurs when the staff of the House oversight and investigations subcommittee decides it, too, will investigate.

In the past, the subcommittee's involvement often has led to dramatic public showdowns between scientists and the panel's chairman, Rep. John Dingell, a Michigan Democrat.

But these public hearings did not provide the same safeguards as court proceedings. At the Dingell hearings, the accused scientists could not confront

their accusers and cross-examine them, or call their own witnesses. They had to submit their testimony ahead of time, and if Dingell or his staff didn't like it, they could insist on changes—or the witness would suffer the consequences.

Dr. Bernadine Healy, the former director of the National Institutes of Health, said that when scientists come under Dingell's scrutiny, they often are victimized by the subcommittee's staff leaking damaging information about their cases to the media.

Some believe the investigative process is more harmful than the scientific misconduct it's meant to correct. Science, by its nature, is self-correcting, they say.

"The notion of massive misconduct in science is really fairly ludicrousbecause of the inherent nature of science," said Edward Richards, a University of Missouri law professor who has examined scientific misconduct. ''If your experiments don't work, someone will find you out. There have been incidents of misconduct by scientists but, by and large, compared to any other part of the public sector, science is exemplary."

Epilogue: Clinical trials

The fraud committed by Montreal surgeon Roger Poisson that triggered the Fisher investigation has done its greatest damage to clinical trials, a research tool that was largely pioneered by Fisher.

Clinical trials use the power of numbers—the statistical potency of comparing hundreds or thousands of patients—to determine whether a certain diagnostic test or diet or drug or surgical procedure is safe and effective.

Organizations around the country that conduct clinical trials have been deeply shaken by what happened to Fisher's research group, the NationalSurgical Adjuvant Breast and Bowel Project. Some fear that federal officials' efforts to deal with the scandal may end up causing more harm than good.

Last spring, shortly after the public revelation of the fraud at Poisson's St. Luc's Hospital in Montreal, National Cancer Institute officials moved quickly to establish tighter control over the clinical trials they funded.

> "No other nation in the world has been so committed to clinical trials, and the American taxpayers have a right to ask that we monitor and successfully administer such trials."
>
> *– Mace Rothenberg*

Among the changes are a new department that will be a watchdog over clinical trials; surprise audits; more frequent routine audits; and a requirement that NCI be immediately notified of any evidence—no matter how small—of scientific misconduct.

Dr. Samuel Broder, the outgoing NCI director, told an NSABP conference in June that the tighter rules are the price scientists must pay for getting public money.

"No other nation in the world has been so committed to clinical trials, and the American taxpayers have a right to ask that we monitor and successfully administer such trials," he told the group.

Dr. Bruce Chabner, director of NCI's cancer treatment division, said the agency probably will double its budget for auditing patient records in clinical trials. Of course, he said, that means "you can do less research." Every dollar spent on checking records is one that can't be spent on recruiting patients.

Richard Peto, an internationally acclaimed statistician and co-director of the Oxford University Clinical Trial Service Unit in England, said the new NCI rules will make clinical trials harder to do.

"Because they make (studies) complicated, they make it impractical to make them large, and therefore they will be less reliable. You've got to get serious numbers into the trial. Otherwise the data will not be good, no matter how proper it is."

Peto said the NSABP controversy has a "Kafka-esque" quality. "People who actually know about trials know that (Poisson's falsifications) could not in principle have any material effect" on the studies' outcomes, because he did not contribute enough patients to the trials to make a difference in the results.

NSABP "is being destroyed, all in the name of morality. The whole thing is completely hypocritical. They've destroyed research in the name of saving research."

George Canellos, a former NCI official who is chief of medical oncology at the Dana-Farber Cancer Institute in Boston, also is worried about the new regulations.

Scientists will resist being second-guessed on each of their actions, he said.

"You have to basically trust that the vast majority of people do things honestly," Canellos said. "The freedom of inquiry, the freedom to do your science is a very important part of scientific pursuit, and if you feel Big Daddy is watching you for everything, and if you are painted with the same brush as some of the cleverer cheaters, the demoralization to science will be awful."

But Mace Rothenberg, a top official at the Southwest Oncological Group, which has conducted several clinical trials on cancer, took a different view.

"We've sustained a great trauma for clinical research that has shaken its foundations," Rothenberg said. "You just can't dismiss that in offhand fashion. Unfortunately, a bad thing happened and we're going to pay a price. That means more cumbersome government regulations and a slight decrease in the number of centers, but I don't see any other alternative."

> You just can't dismiss that in offhand fashion. Unfortunately, a bad thing happened and we're going to pay a price. That means more cumbersome government regulations and a slight decrease in the number of centers, but I don't see any other alternative.
>
> *– Mace Rothenberg*

There is one new rule that troubled Rothenberg, though.

He didn't like the requirement that study groups report the first sign of scientific misconduct.

"What does that mean?" Rothenberg said. "If you can't locate a consent form, or if there's an error in a date, must we notify the NCI immediately? I don't think we can operate that way."

Epilogue: NSABP

While other clinical trial groups fret, the atmosphere at the 500 member institutions of the NSABP is fearful.

With Fisher sidelined, they are uncertain about who will lead them into the future.

They also worry about the NSABP's landmark breast cancer prevention trial, which was designed to test the anti-cancer drug tamoxifen on 16,000 healthy women to see whether it can prevent the disease.

That trial was put on hold after Fisher was fired, and only last month began accepting women again. Without the interruption, the study by now would have enrolled the total number needed to assess whether the drug works.

If the study shows tamoxifen is an effective deterrent of breast cancer, that delay could end up costing some women their lives.

Even if the breast cancer prevention trial gets back on track, it's not clear whether NSABP will end up supervising it.

In fact, the organization's future is uncertain.

In June, NCI Director Samuel Broder told NSABP members, "We must be sure that the NSABP succeeds and is restored to its proud reputation. We need to have the NSABP strong; we have other surgically oriented groups, but there are very few groups that have the tradition of the NSABP, so we want to work with you."

Dr. Ronald Herberman, who was appointed by Pitt as NSABP's interim chairman, also is upbeat. There's a good possibility the organization will return to its previous strength, he said this month.

But in an interview last month with *The Cancer Letter*, a Washington, D.C.-based publication, Broder sent a different signal.

Asked whether the NSABP could survive "in its present form," Broder said parts of it could, such as the prevention trial. But then he said the prevention trial could do very well without NSABP overseeing it.

Contributing to Broder's ambivalence, perhaps, was NSABP's selection of a successor to Fisher as chairman. Broder's choice for the position was Dr. Janet Osuch, an outspoken breast cancer surgeon from Michigan State University who had roundly criticized Fisher for how he handled the Poisson scandal.

Instead, the NSABP executive committee chose Dr. Norman Wolmark, a respected breast cancer surgeon now at Allegheny General Hospital.

Broder, who last week announced he will leave the NCI in April, has not yet approved Wolmark's selection.

The NCI director was clearly unhappy with the NSABP's participation in Fisher's lawsuit against Pitt, and said he would not approve Wolmark as long as the organization stayed in the lawsuit.

The NSABP's executive committee still is suing Pitt, but has softened its demands.

While still insisting that the courts recognize their right to hire and fire their own chairman—which they believed was taken away from them when Fisher was deposed—the committee members decided this month to drop their demand that he be fully reinstated as head of the group.

If the leadership of the organization still is in question, so are many of its future studies.

One such trial wanted to test whether it was possible to eliminate surgery for some women suffering early breast cancers by giving women enough chemotherapy to shrink their breast tumors out of existence.

Fisher said another new study would have tested using the drug Taxol after surgery to determine if overall survival rates for breast cancer could be improved.

It's uncertain if the NCI will ever approve them, he said.

Epilogue: St. Luc's

At St. Luc's Hospital, nearly three years after Poisson admitted falsifying patient records, about 300 women still come to be treated in a breast cancer study.

They subject themselves to mammograms twice a year, they take a placebo or tamoxifen and they allow information on their medical histories to be collected and kept.

What the women don't know is that their participation may never be used to find better treatment for breast cancers.

Because of Poisson's falsifications, NCI officials say data from all St. Luc's patients should be thrown out of any past or future studies.

But NSABP officials argue that only the 99 past cases with proven falsifications by Poisson should be deleted.

Dr. Pierre-Michel Huet, St. Luc's director of clinical research, is bothered that no one has told the women their contribution to science could be for naught.

"We are in a very bad position for that," he said, but because he is getting conflicting signals from officials in Pittsburgh and Washington on whether the data will be used, he has chosen not to say anything to the women.

That is only one of the problems facing Huet, who took over as principal investigator for the St. Luc study after Poisson was ousted from it in 1991.

Because the hospital was suspended from the project after Poisson was removed, Huet inherited a study with hundreds of patients and no U.S. research money.

Another problem, he said, is Poisson, who refuses to give up his post at St. Luc's.

"Once a doctor is affiliated with a hospital, it's almost impossible under (Canadian) law to have him resign from the hospital unless there is very severe medical fault," Huet explained.

Poisson, meanwhile, continues to be a passionate adherent of lumpectomies and the latest non-surgical treatments. His passion, after all, is what motivated him to fake the records in the first place, he said.

He believed the lumpectomy, which removes only the tumor and a small amount of tissue surrounding it, was the right treatment for most patients and that NSABP's landmark 1985 study would prove it and persuade more doctors to use it. If getting to that point meant subjecting some women in the trial to mastectomies in order to have a comparison group, it was worth it.

Later on, he said, he changed records so women would be eligible for tamoxifen and other experimental drugs, which they would not have been able to obtain otherwise.

Huet said he thinks Poisson genuinely believes he acted in his patients' best interests, but he does not defend him.

"You are not allowed to put in danger all the study because you think you're right. It's gambling, and you are not allowed to gamble when thousands of women are enrolled and millions of dollars are involved."

Dr. Richard Margolese of Montreal's Jewish General Hospital, who is a member of NSABP's executive committee and has known Poisson for years, is equally critical.

"We all had the problems (Poisson) had. We all wanted to include more cases than we did. But none of us did what he did."

Epilogue: The activists

In recent years, the number of groups advocating better breast cancer treatment has proliferated.

As the Fisher controversy drags on, these activists are unified in their criticism of Poisson's fraud.

But they are sharply divided on another issue—the ethics of Fisher's breast

cancer prevention trial, which gives healthy women tamoxifen. While Fisher believes tamoxifen may prevent breast cancer, it also increases the risk of uterine cancer.

Those already opposed to the idea of such an experiment were outraged when they learned from news stories in February that Fisher had delayed divulging that several patients in an earlier tamoxifen study had died after developing uterine cancer.

To opponents of the study, Fisher's actions were a scandal far worse than the falsified records in Montreal.

"As far as I'm concerned, they fired the right guy for the wrong reason," said Nancy Evans of San Francisco's Breast Cancer Action.

Fisher said he resisted releasing the information because he believed the deaths needed to be investigated more fully.

To this day, he thinks people like Evans have overreacted to the news of uterine cancer deaths.

Of the six women in the previous study who died after getting uterine cancer, records show, only five had taken tamoxifen, and only one of the five had died from a malignancy that was clearly linked to uterine cancer.

"The important issue here is whether a woman who had breast cancer and received tamoxifen died with uterine cancer or from uterine cancer," Fisher said. "This is a very difficult call for physicians, pathologists and oncologists to make … and such medical detective work takes a long time."

Some other breast cancer advocates side with Fisher. Amy Langer at the National Association of Breast Cancer Organizations said the tamoxifen trial is worthwhile because "we currently have no prevention methods."

As the tamoxifen study resumed last month, though, activists such as Evans were working to alert women to the drug's dangers in hopes they would not participate.

Epilogue: Lumpectomies

From the moment the Montreal fraud was discovered, the most critical question was: Did the falsifications undermine the 1985 study showing that lumpectomies were as effective as more disfiguring mastectomies?

The most definitive answer came in mid-November when the NCI announced the results of an intensive re-examination of the study.

It found that Fisher was right all along—Poisson's falsifications hadn't made any difference in the study's conclusions.

It also is improbable that Poisson's fraud affected any other NSABP studies.

Poisson had tampered with 99 patients' records, spread among 14 studies that looked at everything from alternative methods of surgery to different combinations of chemotherapy.

The lumpectomy study included only six falsified records, representing three-tenths of a percent of the 2,163 women who participated.

Of Poisson's 93 other patients with falsified records, the largest number—35—were in a study looking at the effectiveness of tamoxifen in preventing a recurrence of breast cancer. They represented 1 percent of the 2,892 women in the project.

Fisher said that the NCI's audit, bolstered by a study of lumpectomies released last month by the General Accounting Office, amounted to "a 100 percent vindication" of his stewardship of NSABP.

But NCI Director Broder, whose agency spent about $2 million on its investigation of Fisher's group, disagreed. The fact that the study results remained the same did not absolve NSABP of its weaknesses in checking patient records or its slowness in publishing a scientific article explaining the effects of fraudulent data.

"That's like saying it's OK to go 100 miles an hour through a residential neighborhood as long as you don't hit anybody."

Epilogue: The players

Since March, when Fisher was fired, the political landscape in Washington and Pittsburgh has shifted dramatically.

Rep. Dingell has lost much of the power he had to police scientific misconduct. The Republican sweep last month stripped him of his chairmanship and sent his investigative staff looking for new jobs.

Broder plans to leave the NCI in April and join a Florida pharmaceutical company. Although Broder took plenty of heat from all sides for his actions during the Fisher episode, he is unapologetic, and says it did not play a direct role in his decision to leave.

Broder's top deputy, Bruce Chabner, the man who oversees NCI's cancer treatment programs, also will leave the agency next spring for a position at Massachusetts General Hospital.

Michael Friedman, the NCI official who made the phone call to fire Fisher at the request of his supervisors, said he also is considering leaving the institute, after a 22-year career there.

He said he still believes that the NSABP's administrative problems were "of unprecedented scope and seriousness."

But does Friedman think that Fisher should have been fired?

"There certainly could have been better ways that some aspects of this could have been handled," he said slowly, then added, "I have not yet had the opportunity for dispassionate reflection on that matter."

Neither Friedman nor any other NCI official has talked with Fisher since he was fired.

Perhaps most galling for Fisher has been his shunning by the NCI's Broder.

After his wife contracted breast cancer, Broder called Fisher last December for advice. They had long, friendly telephone conversations before the scandal became public, Fisher said.

Fisher tried to call Broder to set up a meeting in the weeks after the news broke in March, but said he never got through to him and never received a call back.

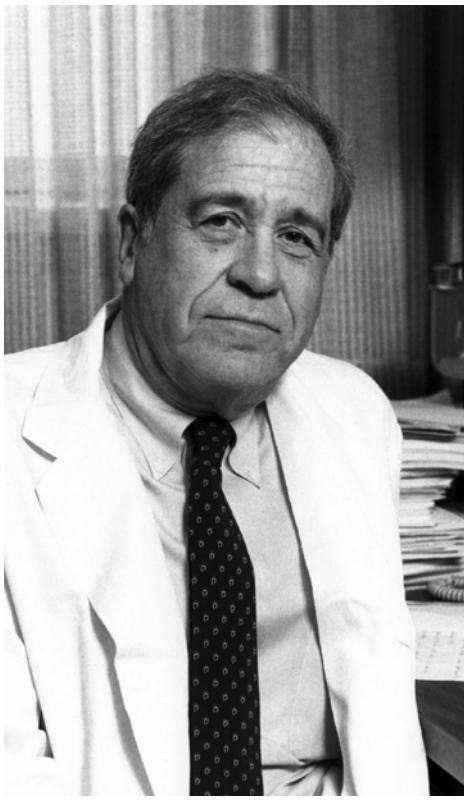
Epilogue: Bernard Fisher

In the case of Dr. Bernard Fisher, the facts are these:

- He never was accused of falsifying information about patients himself.
- The fraud committed by Poisson on 99 patients' records has not changed the basic outcome of the studies he directed at NSABP.
- There is no evidence of systematic fraud in the other medical centers Fisher oversaw.

Yet, in the end, Fisher lost his career, and what may have been lifesaving research has been derailed or at least delayed.

Fisher clearly had his faults. He had little patience for what he derisively called "BAPs"—bureaucrats, administrators and politicians—the very people he had to answer to in order to continue his federally funded research.



Also, he was slow to reveal bad news, believing that he knew best when the public should find out about such issues as the falsifications and the uterine cancer cases.

It is part of his basic personality, said one longtime friend.

"Bernie is a bit of a pat-you-on-the-head sort," said Helene Brown, a health educator at UCLA. "And when people ask, 'Why didn't you take steps to tell the whole world?' (about the Canadian fraud), the bottom line is that the study didn't change, and inside, he felt, as long as it didn't change, I'm not going to upset all these women."

He has paid a steep price for that attitude.

He knows that his name might always be associated with "l'affaire Poisson"—the scandal in Montreal.

He desperately wants his reputation restored.

That is why he spends each day writing down "the truth" about what really happened.

He doesn't know when his story will get to be told, but he writes it down anyway, hoping that "someday, somebody, somewhere will hear it."

Mackenzie Carpenter, was a projects writer for the Post-Gazette. The Princeton, N.J., native previously worked for United Press International, and for public television in both Washington D.C. and Harrisburg. She received a B.A. from Trinity College in Hartford, Conn., and a master's degree in legal studies from Yale Law School. She is retired and living in Pittsburgh.

Steve Twedt, was a medical writer for the Post-Gazette. A native of Portland, Ore., Twedt has worked for the newspaper since 1993. Before that, he worked for The Pittsburgh Press and for newspapers in Washington, Oregon and Alaska. Twedt earned a bachelor's degree from the University of Oregon. He covers business, finance, health and national news at the Post-Gazette.

Added indignity: NIH labels Fisher's papers as "SCIENTIFIC MISCONDUCT"

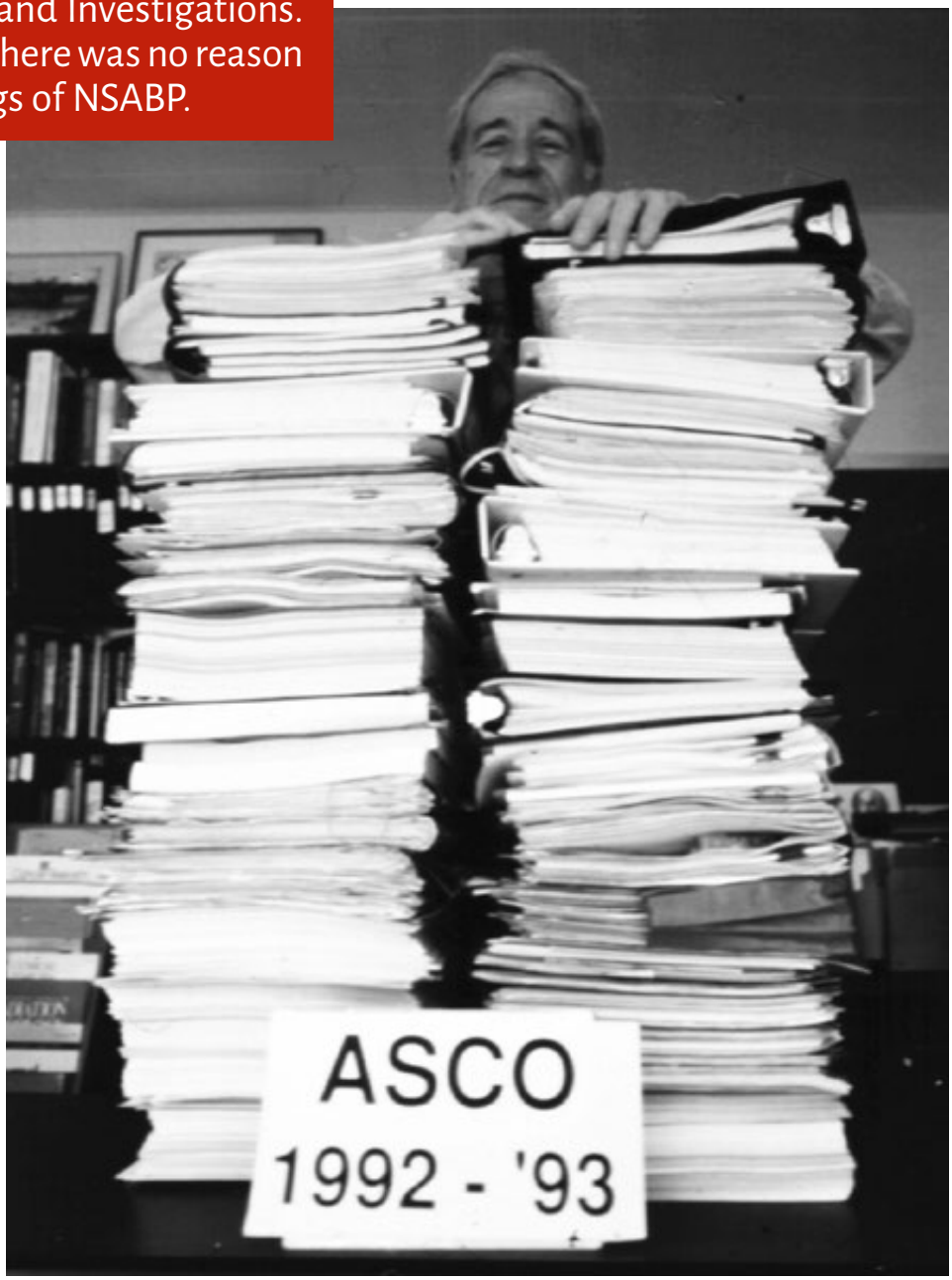
By Paul Goldberg

The midterm elections of 1994 brought on political change that cost Dingell chairmanship of Energy & Commerce and Oversight and Investigations. He lost most of his staff, and there was no reason to continue oversight hearings of NSABP.

Also, at the end of the year, NCI Director Samuel Broder announced that he would go off and join a company making a taxane drug.

Though the players changed, the NSABP scandal continued to chug along, now driven by a volatile mixture of legal procedure, institutional politics, futile investigations, bureaucratic inertia—and, for the lack of a neutral word—idiocy.

Thus, in February 1995, I reported a shocking story about annotations that were placed on Fisher's and NSABP's publications. This story is being reprinted in full:



Fisher with binders of information sent to him during his year as ASCO president. *Photo by © ASCO 2019*

Under ultimatum, NIH databases remove "misconduct" tags from papers by Fisher

Vol. 21 No. 8 | Feb. 24, 1995

Users of medical literature databases run by NCI and the National Library of Medicine have been finding an announcement tagged to papers that list Bernard Fisher as an author:

[SCIENTIFIC MISCONDUCT—DATA TO BE REANALYZED]

Another tag proclaimed:

[SCIENTIFIC MISCONDUCT—REANALYSIS OF NSABP PROTOCOL B-06 AVAILABLE VIA PDQ, CANCERNET, OR CANCERFAX]

Scientific misconduct? By whom?

The HHS Office of Research Integrity has not announced the findings of its investigation of Fisher. The only misconduct related to his case was committed by Roger Poisson, a Montreal surgeon.

Does the Poisson case warrant inserting the "misconduct" tag on at least 88 papers that list Fisher as an author?

Among those papers are primary studies that clearly include Poisson's fraudulent data. However, also tagged were publications in which Fisher expresses his opinions, a review of literature by *The Cancer Letter* confirmed. The review also found that publications are flagged inconsistently in Medline and Cancerlit, two databases operated by NIH. Also, at least one paper was flagged by Cancerlit even though the data was obtained prior to the first documented incident of fraud at Poisson's hospital.

Last week, an attorney for Fisher gave NIH an ultimatum: Remove the tags within 48 hours or face legal action. In response, officials at the HHS Office of Research Integrity ordered that the words "scientific misconduct" be struck from the tags.

The question that remains is what is to be done with the remainder of the tag: DATA TO BE REANALYZED. Should it continue to adorn Fisher's "The Evolution of Paradigms for the Management of Breast Cancer: A Personal Perspective"?

"It's very simple," said Robert Charrow, Fisher's attorney. "They ought to pull the flags off all the papers until they can figure out what to do.

"They likely owe Dr. Fisher some damages,"

Charrow, of the Washington firm Crowell & Moring, said to *The Cancer Letter.*

Charrow contends that NIH officials went beyond warning cancer researchers about fraudulent data from Montreal.

"It appears that NLM and NCI designated articles without regard to the data in those articles, and instead, based their decision solely or largely on whether Dr. Fisher was an author," Charrow wrote in his Feb. 15 letter to NIH Legal Advisor Robert Lanman.

In an interview with *The Cancer Letter,* Lyle Bivens, ORI director, said the wording of the tag was an oversight on his part.

Bivens said the tags were written by the National Library of Medicine. ORI provided the library with a list of papers that were believed to include data from Poisson's institution, St. Luc Hospital, he said.

"We didn't ask for a 'scientific misconduct' flag on it," Bivens said "NLM is used to that when they get a request from my office, because usually it is as a result of a misconduct finding.

"I was not explicit enough in what the statement should have been," he said.

Bivens said that earlier this week he directed that the words "scientific misconduct" be removed. "Today I sent a memo to NLM asking that they take 'scientific misconduct' label off," he said in an interview Feb. 21.

An NLM official contradicted Bivens's statement, saying that the tag was written by ORI.

In an interview with *The Cancer Letter,* Lois Ann Colaianni, NLM associate director for library operations, said ORI had specifically asked the library to use the words "scientific misconduct."

Colaianni said NLM did not select the papers for tagging.

"We had nothing to do with identifying the papers," she said. "It was through a special request that we labelled these.

"Generally we steer away from labeling papers. We have retractions, and errata, and comments. At the time these went in as comments. However, there was concern that it wasn't enough to cause people to read the reanalyzed data," she said.

From documents and interviews *The Cancer Letter* has learned that the ORI staff selected the papers that were ultimately tagged.

Removing the words "scientific misconduct" does not wipe out the damage to Fisher and to scientific literature, Charrow said.

"Had this language been contained in a news report and had Medline and Can-

cerlit been a private publication, their actions would have constituted defamation," Charrow said.

"While the government may believe it is immune from defamation claims, private publishers are not," Charrow said. "We are advising the scientific community that we will take action against anyone who republishes the defamatory statements contained in Medline."

The NIH tags are beginning to filter into medical 1 iterature. Two flags can be found on p. 318 of the Feb. 15 issue of the Journal of the National Cancer Institute.

Fisher case different from the start

ORI's actions in the Fisher case were unprecedented, Bivens said.

"This is the first case we've had where we put out a notification prior to any scientific misconduct finding," he said in an interview.

"We made a commitment to let the clinical community know even prior to an investigation if there is a problem with publications that may inform treatment decisions," he said.

Asked why ORI decided to go beyond flagging publications that involved Poisson data, Bivens said, "As the situation developed, it became a possibility that either bad data or suspect data might be contained in other publications.

"That is the primary question we are asking." A review of publications was an essential part of the Fisher case, Bivens said. ORI had to compile its own list because Fisher's cooperative group, the National Surgical Adjuvant Breast & Bowel Project, failed to provide a complete list of publications to the investigators, he said.

"We never have gotten a complete list of publications from NSABP that we feel we need," Bivens said. "We needed to find out what publications had been submitted from NSABP when it was known that St. Luc data was shown to be falsified."

The anatomy of a tagging

From documents and interviews, *The Cancer Letter* was able to reconstruct the process that resulted in the flagging of Fisher's publications.

On April 25, 1994, NCI Director Samuel Broder wrote a memorandum to Donald Lindberg, NLM director, in which he asked the library to help the Institute ensure that the databases denote serious error, fraud or scientific misconduct in research supported by NCI.

The memorandum, which did not mention Poisson, Fisher or NSABP, sought to set up a mechanism for NCI and NLM to work together.

In a May 4 memo, Lindberg informed Broder that Colaianni was designated to work with NCI on denoting in the literature episodes of misconduct and fraud.

Broder designated Susan Hubbard, head of the NCI International Cancer Information Center, to work on the project. ICIC runs the Cancerlit database.

Initially, ORI officials requested that NCI compile

a list of papers that could have been affected by fraud.

However, documents indicate that NCI officials did not perform the selection of papers that were subject to flagging. Instead, NCI provided to ORI a list of NSABP publications, leaving it to the investigators to decide which publications ought to be flagged.

A memorandum from Bivens dated May 20 and addressed to Colaianni confirms that ORI investigators were working with a list of NSABP publications, crossing out the publications that in their judgment were unrelated to the clinical trials in question.

Attached to the memorandum was a list on which some entries were marked with an "X." The library was instructed to avoid flagging the articles so marked.

However, in the memorandum, Bivens said the list was compiled with the help of NCI. In an interview with *The Cancer Letter*, he repeated that statement.

"NCI gave us a list," Bivens said. "NCI identified the articles as containing data that might need to be reanalyzed."

Sources said that the same scientific papers were to be flagged in both NLM's Medline and NCI's Cancer lit.

However, Charrow's letter includes 88 "unique identifier" numbers for publications authored by Fisher and contained in Cancerlit and 19 identifier numbers for publications cited in Med line. A review of the databases by *The Cancer Letter* indicates that many of the articles flagged in Cancer! it were not flagged in Medline.

"The action that was taken was to try to flag articles that had data from St. Luc," Hubbard said to *The Cancer Letter*. "The purpose was not to make the cancer community feel that Dr. Fisher was responsible for scientific misconduct. The language used did not make that clear.

"If we were to do it again, we would all do it differently."

Hubbard said that once NSABP's reanalysis of the B-06 study is published, the "data to be reanalyzed" flag will be removed from both Medline and Cancerlit. Instead, a comment will refer readers to the publication of the reanalysis.

Can all data from St. Luc be excluded?

The controversy over what is to be flagged is likely to rekindle the question of whether the government has the legal authority to exclude all St. Luc data from the trials, regardless of whether the data were submitted by Poisson or other researchers.

So far, the government has been guided by the ORI recommendations contained in the 1993 report on the investigation of Poisson. "The reliability of the entire data set from St. Luc Hospital remains questionable," Bivens wrote in a memorandum that accompanied that report.

"It would not be unreasonable to exclude all data on patients from this institution from any future analyses," Bivens wrote.

The ORI report on the Poisson investigation listed only five publications affected by scientific misconduct.

The ORI report did not claim to offer the authoritative list of affected publications. However, another list, compiled by NSABP interim leadership following Fisher's firing, claimed to be complete.

That list, contained in an appendix to an action plan for restructuring the cooperative group, listed

18 papers submitted between 1986 and 1994.

In an interview, Fisher's attorney Charrow said he plans to challenge the exclusion of all St. Luc data regardless of whether it was submitted by Poisson.

"The only person they had any proof against was Dr. Poisson," Charrow said to *The Cancer Letter*. "There is no proof against any other physician at St. Luc who was enrolling patients in NSABP clinical trials."

Dangerous data?

A review of literature by *The Cancer Letter* found that at least five papers labelled "scientific misconduct" were expressions of opinion by Fisher.

Two of those publications listed Fisher as the only author:

- "The Evolution of Paradigms for the Management of Breast Cancer: A Personal Perspective," Cancer Research, 52(9):23 71-23 83, 1992. The article appeared under the heading "Perspectives in Cancer Research."
- Fisher's 1992 Steiner Award lecture, published in International Journal of Cancer, 55(2): 179-180, 1993.

Also labelled were:

- "On the Underutilization of Breast-Conserving Surgery for the Treatment of Breast Cancer," an editorial by Fisher and Leora Ore, published in the Annals of Oncology, 4:96-98, 1993.
- "New Perspectives on Cancer of the Contralateral Breast: A Marker for Assessing Tamoxifen as a Preventive Agent," an editorial by Fisher and NSABP biostatistician Carol Redmond, JNCI, Sept. 18, 1991.
- "Adjuvant Therapy in Node-Negative Breast Cancer. A Panel Discussion." The discussion between Fisher, William McGuire, Martin Abeloff, John Glick, I. Craig Henderson and C. Kent Osborne was published in Breast Cancer Research and Treatment, 13(2):97-115, 1989.

The only possible explanation for flagging editorials and panel discussions is their reliance on NSABP studies, Charrow said. However, if that criterion is to be applied to Fisher, it should be applied to other authors who cite NSABP studies, he said.

"Followed to its illogical conclusion, a warning flag should be placed on the conclusions of the final document of the 1990 NIH Consensus Development Conference on the Treatment of Early-Stage Breast Cancer," Charrow said.

Drawing heavily on NSABP data that included patients from St. Luc, that conference concluded that breast preservation is the preferable treatment for women with stage I and II disease.

Differences between databases

In at least one case, a tag was placed on a paper from a study that clearly fell outside the time frame of the Poisson investigation, which, according to ORI documents, found that falsified records at St. Luc existed since 1976.

The study traced long-term mortality among patients who received radiation treatment prior to 1975:

"Cause-Specific Mortality in Long-term Survivors of Breast Cancer Who Participated in Trials of Radiotherapy," John Cuzick, et al., Journal of Clinical Oncology, 12(3):447-453, March 1994. The paper, which lists Fisher among the authors, was flagged both in Medline and Cancerlit.

A review of Medline and Cancerlit shows that publications were not flagged in a coordinated fashion.

Medline did not flag at least three papers that listed Poisson among authors and included fraudulent data. Two of those papers were cited in the ORI report on Poisson.

The papers are:

- Fisher et al., "Eight-Year Results of a Randomized Clinical Trial Comparing Total Mastectomy and Lumpec-

tomy With or Without Irradiation in the Treatment of Breast Cancer," New England Journal of Medicine, 320(13): 822-828, March 30, 1989.

- Fisher et al., "A Randomized Clinical Trial Evaluating Tamoxifen in the Treatment of Patients with Node-Negative Breast Cancer who Have Estrogen-Receptor-Positive Tumors," NEJM, 320(8):479-484, Feb. 23, 1989.

Another paper that escaped the flag in Medline despite the fact that it listed Poisson as an author and contained St. Luc data was:

- Fisher et al., "Two Months of Doxorubicin Cyclophosphomide With and Without Interval Reintroduction Therapy Compared With Six Months of Cyclophosphamide, Methotrexate, and Fluorouracil in Positive-node Breast Cancer Patients With Tamoxifen-Nonresponsive Tumors: Results from the NSABP Project B-15," Journal of Clinical Oncology , 8(9):1483-1496, 1990.

All three papers were flagged in Cancerlit.

In fact, the parameters of Cancerlit appeared to have been altered to allow for tagging of an expanded number of Fisher's articles, Charrow said.

Typically, Cancerlit citations are arranged in reverse chronological order, and at this time, the database runs back from 1994 to 1988. However, in the case of Bernard Fisher, the bottom boundary drops back to 1979, Charrow said.

For those extra nine years, a Cancerlit user sees nothing but flagged papers by Fisher. A literature check for entries on Poisson found three papers written before 1988.

An unpopular action

The flagging of Fisher's papers has met with sharp criticism from clinical cancer researchers nationwide.

- "This is the computer equivalent of the air brush that removes people from the reviewing stand at the May Day parade," said O. Ross McIntyre, former chairman of the Cancer and Leukemia Group B, invoking imagery from the Moscow Trials of the 1930's.

- "I think this is the most unfortunate approach and a disservice to clinical trials," said Norman Wolmark, chairman of NSABP. "I hope NCI will remedy this transgression."

- "It seems unbelievably extreme to me," said Charles Coltman, chairman of the Southwest Oncology Group, who said he was surprised by NCI' s use of the tag line beyond papers that reported primary clinical trials.

"I don't know where you stop when you begin doing that," Coltman said. "I am not surprised that Bernie and his attorneys are outraged by this approach."

- "It's gratuitous, vindictive, inaccurate, and it contributes nothing to our understanding of cancer," Emil J Freireich, professor of oncology and hematology at M.D. Anderson Cancer Center said.

Freireich said he was stunned to find the tag on Fisher's "Evolution of Paradigms" paper.

"That paper is a brilliant, innovative, original formulation of the modern paradigm of breast cancer, and it has been confirmed over and over again," he said. "There is no controversy about the science here. This is personal."

- "This is the blunderbuss approach to government," said James Holland, professor at the Mt. Sinai School of Medicine.

"Bernard Fisher is one of the towering figures in medical science of the last half of the 20th century. To paste him as if he were a villain is a complete disregard of the scientific process.

"I react to this with dismay that the NLM has been dragged in to the fiasco that I believe represents the conduct of NCI in this attempt to sort out the problems that faced NSABP."

- "First of all, I think the data from all NSABP trials has been reanalyzed, both with the fraudulent data included and excluded, and Dr. Fisher eloquently presented this analysis at the May 1994 meeting of the American Society of Clinical Oncology," said John Glick, director of the Univ. of Pennsylvania Cancer Center and ASCO president-elect.

"While those results have not been published, the oral presentation showed that none of the NSABP scientific conclusions were altered by the removal of fraudulent data. Therefore, the NSABP contribution to scientific advancement of breast cancer research remains valid.

"Obviously, we are awaiting the republication of NSABP papers in peer reviewed journals, and I think those papers will convince the public that none of the NSABP results have significantly changed," Glick said.

Asked whether he believes that the publication in which he appears as a coauthor warranted a "scientific misconduct" tag, Glick said:

"That was a panel discussion, and there is nothing in that paper that would warrant any warning about scientific misconduct whatsoever."

LETTER TO THE EDITOR

Two weeks later, Lyle Bivens, then director of the HHS Office of Research Integrity, explained that he didn't mean to say that the "misconduct" annotation and his comments were not intended as presumption of guilt on the part of Fisher.

I still fail to follow the curvature of his clarification, but here it is:

Bivens: No intent to link flags with NSABP inquiry

To the Editor:

In your Feb. 24 issue, I was quoted as saying that, "This is the first case we've had where we put out a notification prior to any scientific misconduct finding." However, I did not mean to connect the issuance of the Medline and Cancerlit notifications to an ongoing ORI investigation of NSABP.

As stated in my original request to the National Library of Medicine, I asked that a flag be placed in Medline "to indicate that a reanalysis of the [NSABP) study may be needed based on a [June 1993] finding of scientific misconduct on the part of one of the contributors [Dr. Poisson]." The Medline and Cancerlit notifications were predicated solely on the confirmed findings of scientific misconduct by Dr. Poisson, a contributor to the data base underlying anumber of NSABP publications, and were not related to the current NSABP investigation.

Although the current NSABP investigation will examine the data underlying a number of NSABP publications and may therefore generate a fact-base to indicate what publications need reanalysis due to the Poisson misconduct, it is only in this sense that the Poisson and the ongoing NSABP case are related. My comments were not intended to, and should not be construed as, a determination that any authors of NSABP publications, other than Dr. Poisson, have engaged in scientific misconduct.

I did not intend to link the NSABP investigation to the notifications, and to the extent that message was conveyed, it was in error.

Lyle Bivens
Director, Office of Research Integrity

In September 1997, after years of litigation against NCI, the University of Pittsburgh, and the law firm of Hogan & Hartson, Fisher received an apology and a check for $2.75 million.

Here is The Cancer Letter's story about the settlement:

Bernard Fisher settles suit for $2.75M, retains title; University apologizes

Vol. 23 No. 34 | Sept. 5, 1997

Cancer researcher Bernard Fisher last week agreed to drop his suit against NCI, the University of Pittsburgh and the Washington law firm of Hogan & Hartson.

Under an agreement that settles the suit, Fisher will receive $2.75 million and retain his title of Distinguished Service Professor, but would collect no salary or employee benefits, legal documents state.

Pursuant to the agreement, the university issued an apology for "any harm and public embarrassment that Dr. Fisher sustained which was in any manner related to the activities of the University of Pittsburgh and/or its employees."

NCI, also a defendant in the civil action brought by Fisher, issued a statement that enumerated Fisher's contributions to the understanding and treatment of breast cancer.

"Through his role as the scientific leader of the National Surgical Adjuvant Breast and Bowel Project, [Fisher] has not only changed the way breast cancer is treated, but enlightened medical science to view breast cancer as not just a tumor confined to the breast, but as a systemic disease requiring more than surgical intervention," NCI said in a statement.

The Institute contributed $300,000 to the overall settlement, to cover a portion of Fisher's legal expenses, sources said.

The settlement was reached Aug. 27, six days before the case was scheduled to

go to trial at the US District Court for the Western District of Pennsylvania.

Though all parties agreed not to discuss the terms of the settlement agreement, *The Cancer Letter* obtained a copy of the document under the Freedom of Information Act.

Tangled controversy concluded

"I am glad to be alive to see this vindication," Fisher said to *The Cancer Letter.* "I feel that I am still in a position to continue to make contributions, and I want to go forward in the best way I can: to write, and to complete data that needs to be put out."

Fisher declined to describe his plans for the future. "My plans are in the process of being formulated," said Fisher, who is 78. "At this time, I am scientific director of the NSABP, and I would like to continue in that mode, and to make whatever contributions that I can to the organization as it now exists."

The scientific director's post can have a significant impact on generating interest in clinical trials and development of protocols, sources said.

The statements by NCI, the University of Pittsburgh, and Fisher appear on pages 3 and 4.

The settlement is likely to conclude the tangled controversy that began on March 13, 1994, when an article in the Chicago Tribune disclosed that Montreal surgeon Roger Poisson had contributed falsified data to NSABP clinical trials. Soon after the publication of the story, Fisher was removed from leadership of the cooperative group.

The oversight and investigations subcommittee of the House Committee on Commerce conducted hearings on the matter, and the HHS Office of Research Integrity was brought in to investigate possible misconduct by Fisher and two other officials at the cooperative group.

Ultimately, the subcommittee, then headed by Rep. John Dingell (D-MI), accepted the mea culpa from NCI and Pitt and bowed out. Earlier this year, the ORI completed its investigation, finding no misconduct by Fisher and other NSABP officials (*The Cancer Letter,* March 7).

In the just-settled suit, Fisher claimed that NCI officials had "unlawfully terminated" him as principal investigator of NSABP and "crafted multiple false accusations" against him.

"In an effort to keep millions of federal research dollars flowing to the University," Pitt officials assisted NCI in Fisher's firing, Fisher's attorneys stated in the most recent version of the complaint, filed in December 1995.

The suit also named Martin Michaelson, an attorney with Hogan and Hartson, who was hired by the university to handle the matter in its initial stages.

"Defendants Michaelson and Hogan & Hartson obtained Dr. Fisher's confidences by representing that a privileged attorney-client relationship existed between them," but ultimately shared these privileged and confidential communications with the university, NCI, ORI, and the staff of the Subcommittee on Oversight and Investigations of the House Committee on Commerce, the complaint states.

Under the settlement agreement, Fisher is to receive a single check for $2.75 million, documents say. The check would be issued by the University of Pittsburgh "on behalf of all defense interests" within 45 days of the signing of the agreement

While the federal government will contribute$300,000 toward the settlement, it is unspecified how much of the remaining $2.450 million would come from Pitt and how much (if anything) would come from Hogan & Hartson.

Though Fisher will retain his title, he would collect neither a salary nor employee benefits. If he chooses to stay at the university, Fisher would be provided with office space, but no support staff. If he accepts a position elsewhere, he would receive no office space.

Regardless of whether he stays or goes, Fisher would continue to have unrestricted access to NSABP data kept at the university, the agreement states.

In the document, federal defendants stated that all investigations surrounding Fisher have been concluded and that all previously imposed sanctions have been lifted. The text of that section of the memorandum follows:

- "Dr. Fisher is not required to submit his manuscripts to the NCI prior to publication... [Any] requirement to that effect was rescinded April 10, 1995.
- "Dr. Fisher is not precluded from participation in any federally funded cancer research project;
- "A grant applicant, including any applicant for the Operations Center [based at Allegheny General Hospital in Pittsburgh] or Biostatistical Center [based at the University of Pittsburgh] NSABP grants, may list Dr. Fisher as a participant on an application, and any such application will be reviewed through the normal peer review process;
- "NCI will consider Dr. Fisher for a position on a top advisory committee at the NCI, taking into account his achievements and reputation;
- "After a thorough investigation, the Office of Research Integrity did not make a finding of scientific misconduct."

Pitt apologizes to Fisher, expresses pride in his work

The text of the joint statement by Fisher and the University of Pittsburgh:

The University of Pittsburgh and Dr. Bernard Fisher announce the withdrawal of the lawsuit initiated by Dr. Fisher following his removal as principal investigator and chairman of the National Cancer Institute's National Surgical Adjuvant Breast and Bowel Project in the spring of 1994.

The University of Pittsburgh wishes to take this opportunity to apologize to Dr. Fisher and express its sincere regret at any harm or public embarrassment that Dr. Fisher sustained which was in any manner related to the activities of the University of Pittsburgh, and/or its employees.

The University and Dr. Fisher wish to affirm that at no time was Dr. Fisher found to have engaged in any scientific or ethical misconduct concerning any of his work.

The University's acceding to the National Cancer Institute's decision in the spring of 1994 to remove Dr. Fisher as principal investigator of the NSABP and the subsequent developments in the now settled litigation reaffirms the necessity of the university's commitment to fully investigate any allegations against faculty members which leave the potential to impinge upon their First Amendment rights or the essential rights and freedoms of the academic community.

The university wishes to express its pride in the many accomplishments Dr. Fisher has had while associated with the university's Department of Surgery and wishes him success as he continues in the position of Distinguished Service Professor and Scientific Director of the NSABP.

Dr. Fisher will continue his efforts relative to the cause of women's health care, particularly as it relates to breast cancer research through his continuing role as Scientific Director of the NSABP.

NCI: Fisher a dominant force in breast cancer for 40 years

The text of the NCI statement:

Bernard Fisher has been a dominant force in the study of breast cancer for the last 40 years.

Through his role as the scientific leader of NSABP, he has not only changed the way breast cancer is treated, but enlightened medical science to view breast cancer as not just a tumor confined to the breast, but as a systemic disease requiring more than surgical intervention.

Among his contributions were:

- Showing that, for treatment of breast cancer, lumpectomy plus radiation provides the same surgical benefit as the radical, disfiguring Halsted mastectomy or modified radical mastectomy, while permitting conservation of the breast.
- Demonstrating that when used as an adjuvant therapy, tamoxifen, a hormonal treatment, improved survival of women with early stage breast cancer. Combined with his studies of adjuvant chemotherapy, this work led the NCI to state that all women with early stage breast cancer should consider adjuvant therapy (either hormones or chemotherapy) to improve their survival. His research on tamoxifen also showed that five years of tamoxifen therapy is as good as longer courses of treatment.
- Showing that neoadjuvant chemotherapy (chemotherapy before surgery) can safely permit some women with large breast tumors to choose lumpectomy plus radiation instead of mastectomy. He also showed that chemotherapy plus tamoxifen improves survival for early stage, node-positive breast cancer patients when it was compared to tamoxifen alone in both premenopausal and post-menopausal women.
- Initiating the Breast Cancer Prevention Trial, a study of tamoxifen in the prevention of breast cancer, which recently completed accrual of over 13,000 women.
- Convincing his medical colleagues of the importance of clinical research and that clinical studies could be carried out at the community level.

> "The issue of integrity of the research is now completely put to rest. There wasn't anything that would have altered data or would have changed the results."
>
> *– Bernard Fisher*

Fisher: "So many people don't understand clinical trials"

Bernard Fisher's statement to The Cancer Letter:

I'm appreciative of the letter of apology that the university rendered. It's an important thing to recognize one's errors. This goes a long way to inform women that all that I did was correct.

The issue of integrity of the research is now completely put to rest. There wasn't anything that would have altered data or would have changed the results. There was a disruption of science that should never have taken place. That's very harmful.

I pursued this [litigation] to the end, because I honestly believe this was a bigger issue than me. It was about the scientific process. That's why I did this.

The greatest asset of this country is democracy as it is structured. This means you shouldn't be presumed guilty without due process. One has to have the ability to confront one's accusers in an environment that promotes exchange in a non-hostile manner. That's not the way I got it. There was a rushed judgement in my case. I didn't get due process. A [Congressional] hearing that was adversarial and rigged is not the kind of an environment to let this take place.

The other thing I got out of this was a realization of the extent of misunderstanding and misinterpretation of randomized trials. It was so disappointing to me to learn that so many people did not understand—and to this day don't understand—the science, the process, and the mechanisms by which clinical trials are conducted.

Much of what happened was due to this lack of understanding at all levels—government, public, university. If something didn't seem to be logical to them, then it was wrong.

I am glad to be alive to see this vindication. That, to me, is an emotional experience, because so many people have died, and then it was some time later for their vindication to appear. From that standpoint, I am very fortunate.

If I have made any contribution to the betterment of women with breast cancer, to society in general, then I'm happy for that. It's not for me to decide what contributions I made. That is to be decided by others. I'm too close to know what I really did.

I feel that I am still in a position to continue to make contributions, and I want to go forward in the best way I can: to write, and to complete data that needs to be put out.

My plans are in the process of being formulated. I am scientific director of the NSABP, and I would like to continue in that mode: to make whatever contributions I can to the organization as it now exists.

BREAKING NEWS

Sharpless to return to NCI as Hahn gets nominated as FDA commissioner, with Giroir to serve as acting

By Alex Carolan

President Donald Trump has announced his intention to nominate Stephen M. Hahn to the position of FDA commissioner Nov. 1.

HHS Assistant Secretary for Health Brett P. Giroir is expected to serve as FDA acting commissioner while Hahn goes through the confirmation process, multiple Washington sources said.

Hahn is the chief medical executive at MD Anderson Cancer Center and a professor in the Department of Radiation Oncology. Giroir, an admiral, became HHS assistant secretary in February, despite opposition from Democrats because of his conservative approach to reproductive rights.

At this writing, Acting FDA Commissioner Norman "Ned" Sharpless is expected to return to his previous position as director of NCI.

As of Nov. 1, Sharpless has served as acting commissioner for 210 days, reaching the limit of a stint he can legally serve under the Federal Vacancies Reform Act (*The Cancer Letter*, Oct. 11). Sharpless would have been able to remain acting commissioner once Hahn is nominated, but instead, Giroir is expected to take on this role in the interim.

Douglas R. Lowy has served as NCI acting director since Sharpless's move to FDA seven months ago (*The Cancer Letter*, March 8).

Hahn's appearance as an alternative to Sharpless came as a surprise to Washington insiders. In September, 56 cancer groups and four former FDA commissioners urged President Trump and HHS Secretary Alex Azar to nominate Sharpless to the top job at the agency.

The letter from the cancer groups is posted here.

The letter from past FDA commissioners is posted here.

Hahn will need to go through a two-to-three-month clearance process and then Senate confirmation, leaving him with less than a year to serve as commissioner before Trump's presidential term ends (*The Cancer Letter*, Sept. 6). Optimistically, it takes around six months to get a real understanding for the job, past commissioners say.

Hahn would also be taking a pay cut. As acting FDA commissioner, he will earn $155,500, federal disclosures show. His most recently reported compensation at MD Anderson added up to $1.3 million.

As NCI director, Sharpless earned $375,000 a year, which roughly matched his earnings as director of UNC Lineberger Comprehensive Cancer Center.

Neither Sharpless nor Hahn have given extensively to political causes.

Federal Election Commission records show that Sharpless has made campaign contributions to Democrats, including a $250 contribution to the Obama-Biden ticket in 2008 and a $500 contribution to the Obama Victory Fund in 2012.

Sharpless's connection to the White House—and his appointment to the job of NCI director—came through Ronald DePinho, his lab chief at Harvard (*The Cancer Letter*, June 16, 2017).

Most of Hahn's political contributions were made to radiology and radiation oncology societies.

Hahn contributed $250 to Rep. John Murtha, a Pennsylvania Democrat in 2008, $206 to Republican Mitt Romney's campaign in 2012, and in 2017, he gave $1,000 to New Pioneers PAC, a Republican group.

Hahn's connection to the administration isn't publicly known.

Paul Goldberg contributed to this story.

IN BRIEF

Robert Winn named director of VCU Massey Cancer Center

Robert Winn was named director of Virginia Commonwealth University Massey Cancer Center. The lung cancer and community-based health care expert will begin his role at VCU Dec. 2.

Winn comes to VCU from the University of Illinois at Chicago, where he has served as director of the University of Illinois Cancer Center and as associate vice chancellor of health affairs for community-based practice at the University of Illinois Hospital and Health Science System. At UIC, Winn built a community-to-bench integrated health model that brings together both the discovery and implementation sciences into one health delivery and research system, and he oversaw the research and clinical activities of 13 Federally Qualified Health Centers.

Prior to joining UIC, Winn spent 13 years at the University of Colorado Health Sciences Center and School of Medicine in leadership roles and clinical faculty appointments, including associate dean of admissions, vice chair of career development/diversity inclusion and senior medical director of the pulmonary nodule clinic.

"I am incredibly impressed with the cancer center's research, clinical and educational programs as well as the collaboration that Massey fosters across VCU, VCU Health and beyond to discover, develop, deliver and teach effective means to prevent, detect, treat and cure cancer," Winn said in a statement. "Also, Massey's commitment to ensuring equal access to cancer care is deeply important to me."

Winn is a pulmonologist whose scholarship has focused on lung cancer, health disparities and community-based health care. His basic science research, which was supported by NIH and Veterans Affairs Merit awards, focuses on the mechanisms that drive the proliferation of cancer and on the role of cellular senescence in lung cancer. He is a principal investigator on several community-based projects funded by the NIH and NCI, including the All of Us Research Program, a NIH precision medicine initiative. His research aims to develop methods to eliminate health disparities.

Winn replaces Gordon Ginder, who has served as Massey's director for 22 years and announced his desire to step down last summer.

Myles Brown, Celina Kleer to receive awards at San Antonio Breast Cancer Symposium

Myles Brown is the recipient of the 2019 AACR Distinguished Lectureship in Breast Cancer Research award at the San Antonio Breast Cancer Symposium, and Celina Kleer will receive the 2019 American Association for Cancer Research Outstanding Investigator Award for Breast Cancer Research at the symposium.

The Distinguished Lectureship is supported by Aflac Inc. Outstanding Investigator award is
supported by the Breast Cancer Research Foundation.

Brown, the Emil Frei III Professor of Medicine at Dana-Farber Cancer Institute and Harvard Medical School, is being recognized for his research on steroid receptor-coregulators that has put a spotlight on the dynamic ability of these proteins to regulate the genome.

His research has elucidated the epigenetic factors underlying the action of steroid hormones and effectively shaped understanding of the role of nuclear hormone receptors in normal physiology and breast cancer. Brown will deliver a lecture Dec. 12, at 11:30 a.m., "Essential genes and cistromes in breast cancer."

Kleer, the Harold A. Oberman Collegiate Professor of Pathology at the University of Michigan Medical School and Rogel Cancer Center, is being recognized for her work generating key insights into the development of aggressive forms of breast cancer and for advancing the characterization of clinical biomarkers and potential therapeutic targets for these cancer subsets.

Kleer's research led to the initial demonstration of EZH2 overexpression in metastatic hormone receptor negative breast cancer and the elucidation of molecular determinants of metaplastic breast carcinoma. Kleer will present a lecture on Dec. 13 at 11:30 a.m., "Novel non-canonical functions of EZH2 in triple negative breast cancer."

The 2019 SABCS will be held Dec. 10-14 at the Henry B. González Convention Center in San Antonio.

Brian Rini joins Vanderbilt-Ingram as chief of clinical trials

Brian Rini, an expert in genitourinary oncology, kidney cancer and clinical drug development, is joining Vanderbilt-Ingram Cancer Center as the inaugural chief of clinical trials.

Rini was recruited from Cleveland Clinic, where he serves as director of the Genitourinary Cancer Program and professor of medicine at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University. His start date is Jan. 28, 2020.

At Vanderbilt, he will be an Ingram Professor of Medicine and will lead kidney cancer clinical research efforts, in addition to the new role, which will focus on expanding oncology clinical research operations and training opportunities in clinical cancer research across the board.

Rini will join Jordan Berlin, associate director for Clinical Research at VICC and Ingram Professor of Cancer Research, and Vicki Keedy, associate professor of medicine and medical director of the Clinical Trials Office.

Rini served as chair of the FDA Oncologic Drugs Advisory Committee in 2018-2019 and completed a four-year term on that committee. He was a founding member of the Kidney Cancer Programmatic Panel for the Department of Defense Congressionally Directed Medical Research Programs, now the largest source of kidney cancer research support in the nation, directing more than $20 million in grant funding to kidney cancer basic, translational and clinical investigations.

FDA in April approved the combination of the targeted therapy axitinib and the immunotherapy pembrolizumab after results of a clinical trial were published in The New England Journal of Medicine. Rini was the lead author of that study.

NCI awards UCLA prostate cancer SPORE $8.7M

The prostate cancer program at the UCLA Jonsson Comprehensive Cancer Center and UCLA Health was awarded a $8.7 million SPORE grant from NCI.

The grant will support the development of approaches for improving the diagnosis, prognosis and treatment of prostate cancer.

The 2019 designation is the fourth time UCLA has received the five-year cycle of funding. The UCLA program is one of eight programs with this designation and the only one to be awarded the designation in the state of California.

The grant helped support the work of Michael Jung, a UCLA distinguished professor of chemistry and biochemistry, and Charles Sawyers, a former professor of medicine and molecular pharmacology at UCLA. They developed enzalutamide and apalutamide, anti-androgen treatments that can prolong life for men when hormone and chemotherapies did

not work for them. These drugs have been used by thousands of men with castration-resistant prostate cancer.

Developments in imaging for detecting prostate cancer have also been supported through the grant. UCLA was among the first places in the country to employ MRI for detection, diagnosis and management of prostate cancer. MRIs are now regularly used to detect and assess the aggressiveness of malignant prostate tumors.

Over the next five years, the grant will fund three translational research projects to find better ways to treat men with advanced stages of the disease:

- Developing drug inhibitors for men with metastatic castration-resistant prostate cancer.

  Led by Jung and Matthew Rettig, the team will look to develop a drug inhibitor that helps minimize resistance, prolong life expectancy and improve quality of life for men with metastatic castration-resistant prostate cancer. This stage of prostate cancer accounts for virtually all prostate cancer-specific deaths.

- Using CAR T-cell therapy to treat men with advanced prostate cancer.

  Working with researchers at City of Hope, Owen Witte and colleagues will test a new CAR T-cell targeting the prostate stem cell antigen in prostate cancer. The team has engineered and tested the CAR T-cell therapy in laboratory models of prostate cancer and will bring them to a human clinical trial to test its efficiency.

- Targeting a protein to help inhibit lethal prostate cancer.

  The project, led by Isla Garraway from UCLA and Michael Freeman from Cedars Sinai, will test if the protein ONECUT2 is a target in a subset of aggressive prostate cancers where ONECUT2 is highly active. Currently, most drugs in development to treat advanced prostate cancer are focused on targeting the androgen receptor, which many men still do not benefit from.

Johns Hopkins opens proton center at Sibley Memorial Hospital

Johns Hopkins Medicine collaborated with Children's National Hospital to open the Johns Hopkins National Proton Center at Sibley Memorial Hospital, providing proton technology for pediatric and adult cancer patients in the District of Columbia.

The proton center is part of the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center in Baltimore. Sibley houses the only proton center in the greater Washington, D.C. region with a dedicated pediatric team.

The proton collaboration with Children's National Hospital represents an expansion of the earlier collaboration between Children's and Johns Hopkins Medicine that established the pediatric radiation oncology program at Sibley, which treats a broad range of children's cancers.

"We will be conducting groundbreaking research that will potentially help expand this technology for use in treating other types of cancers while at the same time helping improve the effectiveness of the proton treatments for the cancers currently most amenable to proton therapy," Hasan Zia, interim president and CEO of Sibley Memorial Hospital, said in a statement.

The Johns Hopkins National Proton Center at Sibley will have a fully integrated research room, which will allow clinical, basic science, and medical physics faculty to advance clinical trial research, translational research, and technology development research in proton therapy. There, experts will lead efforts to study proton outcomes for sarcoma, gynecological tumors, pancreatic and liver tumors, lymph node cancers and tumors located near the heart and major blood vessels. In addition, the researchers will examine how the cancer cell-killing proton energy interacts with the cells and tissue surrounding the tumors.

Christina Tsien was appointed proton center medical director and Curtiland Deville will serve as the associate proton director, while maintaining his role as the clinical director for the Radiation Oncology Clinic at Sibley Memorial Hospital.

Through a strategic partnership with Howard University, the proton center will serve as an educational and training site for students enrolled in Howard's medical physics program.

The first treatment room opened in October. The second room is scheduled to open in spring 2020, and the third room and fixed beam research room are scheduled to open in fall 2020.

Allyson Kinzel named senior vice president and chief legal officer at MD Anderson

MD Anderson Cancer Center has named Allyson Hancock Kinzel as senior vice president and chief legal officer, effective Nov. 1.

Kinzel will lead legal and regulatory affairs in her role after serving as chief legal officer since 2018. She will report to the president and will be a member of the institution's executive leadership team.

As senior vice president, Kinzel will oversee three legal and regulatory departments: Legal Services, Internal Audit and the Office of Institutional Compliance. Kinzel will be responsible for identifying and managing risk across

the institution, leading auditing and monitoring efforts and ensuring the institution's compliance with federal and state laws. As chief legal officer, she has guided responses to hospital-wide federal regulatory surveys, established MD Anderson's institutional conflict of interest policy and program structure and led the institution's response to the Office for Civil Rights regarding federal enforcement provisions.

Before serving as chief legal officer, Kinzel worked for 10 years in Institutional Compliance at MD Anderson and was vice president and chief compliance and ethics officer from 2014 to 2018. Prior to coming to MD Anderson, Kinzel represented health care providers as a partner at Baker Hostetler, LLP, and as an attorney at Vinson and Elkins, LLP.

James Kochenderfer receives Foundation for the NIH Awards 2019 Trailblazer Prize

The Foundation for the National Institutes of Health awarded the second annual Trailblazer Prize for Clinician-Scientists to NCI's James Kochenderfer.

Kochenderfer received the Trailblazer Prize and a $10,000 honorarium for developing immunotherapies that leverage chimeric antigen receptor T-cells to treat blood cancers. John I. Gallin and Elaine Gallin fund the prize.

The Trailblazer Prize recognizes contributions of early career clinician-scientists whose work has the potential to or has led to innovations in patient care and seeks to raise awareness of the critical role the clinician-scientist plays in biomedical research and clinical care.

Kochenderfer and prize finalists Ami S. Bhatt, of Stanford University, and Evan Macosko, of Broad Institute, and Giovanni Traverso, of Massachusetts Institute of Technology and Brigham and Women's Hospital, Harvard Medical School, gave presentations at an event on Capitol Hill to inform policymakers about their research and the need to inspire more clinician-scientists to join the field.

The FNIH's Charles A. Sanders Legacy Fund has awarded all finalists $5,000 for their laboratories.

Kochenderfer is an investigator in the surgery branch at the Center for Cancer Research at NCI. He was the first to design and demonstrate the effectiveness of anti-CD19 CAR T cells in humans, leading to the first FDA approval of a CAR T-cell therapy for lymphoma. He also led the first clinical trials focused on the anti-B-cell maturation antigen CAR for the treatment of multiple myeloma.

Kochenderfer has open trials investigating novel CAR T-cell therapies for diseases and is developing new methods to improve the cancer fighting ability of CAR T cells.

Astellas awards $200,000 in cancer grants

Astellas awarded $200,000 in total grants and resources to winners of the fourth annual Changing Cancer Care prize, a challenge that funds ideas beyond medicine to improve cancer care for patients, caregivers and their loved ones.

Audrey Guth, founder of Nanny Angel Network in Toronto, was chosen as the 2019 Grand Prize winner.

Guth, a cancer survivor and mother of four, established the Nanny Angel Network in 2009 after she found a gap in healthcare and social services for mothers with cancer and their children. The program provides stability, normalcy, and support during a challenging time. Nanny Angel Network trains volunteers to care for children whose mothers have cancer.

This year's challenge awarded four prizes totaling $200,000 in funds (one grand prize of $100,000, two $45,000 Innovation prizes, and one Emerging Ideas prize of $10,000). Along with the funding, all winners will have the opportunity to attend TEDMED 2020 as TEDMED Scholars.

The winners will receive a yearlong membership to MATTER, a global healthcare startup incubator.

The 2019 Innovation Prize winners are:

- **Daniella Koren**, founder of Arches Technology, whose idea is to expand a digital patient education and engagement program called MyCare-Compass that provides information and evidence-based education to people impacted by cancer throughout their treatment journey.
- **Leslie Schover**, founder of Will2Love, whose idea is to tailor self-help programs for men and women to meet the needs of special populations including younger survivors and LGBTQ survivors. Will2Love provides online education and guidance to help people impacted by cancer overcome problems with sexual health and fertility, trains oncology professionals to better manage these problems, and consults with hospitals to establish reproductive health programs.

Astellas introduced a new Emerging Ideas prize to recognize ideas that need additional cultivation before implementation. Abby Westerman of b-present Foundation was selected for this prize and also presented at the live pitch event. Westerman plans to use the Emerging Ideas prize to extend the reach of b-there, a web-based patient and supporter connection tool to lower the barrier for young adults with cancer to stay connected with friends, offering a way to control visits, convey status updates, and request needed items.

THE CLINICAL CANCER LETTER

CLINICAL ROUNDUP

Study finds racial disparities in treatment of multiple myeloma patients

African Americans and Hispanic people with multiple myeloma start treatment with a novel therapy significantly later than white patients, according to a study published Oct. 17 in *Blood Advances*.

The study found that on average it took about three months for white patients to start novel therapy after diagnosis, while it took about five months for African Americans and Hispanic patients to start novel therapy after diagnosis.

The time between diagnosis and treatment is crucial to multiple myeloma outcomes. If treatment is delayed, multiple myeloma patients can suffer organ damage, kidney dysfunction, anemia, skeletal fractures, infections and other serious conditions. Best practice is to start patients on immunomodulatory drugs such as lenalidomide and/or proteasome inhibitors such as bortezomib and carfilzomib. The use of these therapies has more than doubled survival of multiple myeloma patients within the past decade.

"We noted that minorities are not getting introduced to treatment early enough to derive adequate clinical gains," lead author Sikander Ailawadhi, of Mayo Clinic Florida, said in a statement. "Since our analysis is based on Medicare patient data, these disparities cannot be attributed to differences in insurance coverage. Patients are not receiving treatment equally even in this ostensibly equal-access setting."

Researchers reviewed data from the SEER–Medicare database from 2007-2013. The study included 3,504 white patients, 858 African Americans and 468 Hispanic patients. Their analysis found that the average length of time between multiple myeloma diagnosis and start of treatment for white patients was 2.7 months, compared to 4.6 months for Hispanics and 5.2 months for African Americans. Rates of autologous stem cell transplant within one year of diagnosis, considered the standard of care for eligible patients, rose among whites and African Americans but not for Hispanics.

This study found that median overall survival was similar across all groups, but comparison to previous studies suggests the survival rate for African Americans in particular has not increased as much as it could have with equal and timely access to treatment. The authors suggest the delay in treatment initiation may have inhibited African Americans' normally better survival outcome, but this would have to be confirmed in another study.

One encouraging observation in the study was the increasing trend of beginning these therapies within the first six months of multiple myeloma diagnosis for all three race/ethnicity cohorts over the duration of the study. However, this increase was more pronounced among white and Hispanic patients compared with African Americans.

The study also found that medical costs were highest among Hispanic patients. The total monthly medical costs for whites averaged $10,143, versus $11,546 for African Americans and $12,657 for Hispanics. Researchers suggest the higher cost could be due in part to higher hospitalization costs, possibly incurred as a result of complications from delayed treatment.

Dana-Farber and UT Southwestern study finds racial disparities in culturally competent cancer care

Many non-white minority cancer survivors place importance on seeing doctors who share or understand their culture, but are less likely than non-Hispanic whites to be able to see such physicians, according to a new study from Dana-Farber Cancer Institute and University of Texas Southwestern.

The study, one of the first nationally-representative studies to examine patient-reported preference for, access to, and quality of provider cultural competency among cancer survivors, was published in *JAMA Oncology*.

Almost half of non-white minorities (49.6%) said it was somewhat or very important to be treated by doctors who understand their culture. However, these patients were less likely than non-Hispanic whites to receive treatment from these providers, by a difference of 65.3% to 79.9%. And 12.6% of the minority patients said they were never able to see physicians who shared or understood their culture, compared with 4% of non-Hispanic whites.

"There are data to show that oncology subspecialties, compared with other specialties in medicine, are comprised of the lowest representation of under-represented minority physicians," co-senior author Brandon A. Mahal, of Dana-Farber, said in a statement. According to Mahal, the oncology workforce is currently made up of only 5.3% black/African American and Hispanic/Latino physicians.

Despite these disparities, minority and non-Hispanic white cancer survivors were equally positive about their encounters. Both groups reported high rates of instances where physicians frequently treat them with respect, provide easily understood health information, and ask them for their opinions or beliefs regarding care.

The researchers based their findings on a national survey that included 2,244 adult cancer survivors, of whom 1,866 were non-Hispanic white, who responded to a set of questions regarding physician cultural competency.

Racial or ethnic cultures may have different forms and norms of communication and varying levels of trust in the healthcare system. Prior research has shown that oncologists' implicit racial bias (among racially discordant oncologist-patient relationships) is associated with poorer measures of patient confidence in treatment, patient recollection of information, length of visit, and provider supportiveness and patient-centeredness.

While the very limited diversity of the oncology workforce is one likely explanation for the mismatch between patients' preferences and their experiences, the researchers said other factors could be involved. These include insufficient training in cultural competency, geographic variations in physician availability, insurance plan coverage networks, and the possibility that some patients may value other physician characteristics than cultural competency.

"Our findings highlight a persistent shortcoming of longitudinal cancer care for minority patients and the critical need for culturally competent providers," first author Santino S. Butler, of Dana-Farber/Brigham and Women's Cancer Center, said in a statement.

Butler said the survey's results reinforce policy initiatives set forth by major cancer organizations, including the American Society of Clinical Oncology, which recently highlighted the association between racial/ethnic disparities in cancer outcomes and a "lack of access to high-quality care that is understanding and representative of diverse traditions and cultures."

The investigators added that "institutions should emphasize the need for, and offer opportunities for their workforce to pursue continuing medical education in cultural competency in order to improve care for their diverse patient populations."

NCCN publishes guidelines on managing complications and improve readiness for stem cell transplants

The National Comprehensive Cancer Network published guidelines that provide step-by-step information on best practices in evaluating patients for hematopoietic cell transplantation and managing complications afterwards.

This type of specialized treatment is increasingly common, occurring approximately 22,000 times a year in the United States in people with various malignancies, most commonly for blood-related cancers.

"The current version of the guidelines addresses both pre-transplant evaluation and the management of a common complication: graft versus host disease," NCCN Guidelines panel chair for HCT, Ayman A. Saad, professor of clinical medicine at The Ohio State University Comprehensive Cancer Center—James Cancer Hospital and Solove Research Institute, said in a statement.

"Given the diversity of practice and expertise, we believe these guidelines will provide a pivotal tool for learning about the continuously updated therapy landscape in HCT. We hope this will help streamline clinical practices and educate new generations of physicians-in-training," Saad said.

The NCCN Clinical Practice Guidelines in Oncology for hematopoietic cell transplantation provide recommendations on how to evaluate a potential transplant recipient to

determine if the patient is an appropriate candidate for the procedure, and how to best manage different manifestations of post-transplant GVHD. They reflect the latest evidence and consensus from foremost experts across the 28 leading academic cancer centers that comprise NCCN, including hematologists/oncologists, transplant-specific practitioners, and infectious disease specialists.

The NCCN Guidelines for Hematopoietic Cell Transplantation are available free-of-charge for non-commercial use at NCCN.org and via the Virtual Library of NCCN Guidelines app. NCCN will continue expanding blood cancer resources through continuous updates to the HCT guidelines, along with upcoming new NCCN Guidelines for Histiocytosis, Myeloid/Lymphoid Neoplasms, Pediatric B-Cell Lymphomas, and Pediatric Hodgkin Lymphoma.

Acute lymphoblastic leukemia relapses reduced by 31%, St. Jude study shows

St. Jude Children's Research Hospital's Total Therapy Study 16 showed a reduced rate of central nervous system relapse in acute lymphoblastic leukemia, according to results published online Oct. 28 in the *Journal of Clinical Oncology*.

Despite modern therapies, 10% of patients with ALL treated in the United States relapse, which dramatically reduces their chance of survival.

The study evaluated interventions aimed at preventing relapse by improving systemic and CNS disease control. Researchers found that adding doses of chemotherapy in the cerebrospinal fluid earlier in care improved CNS control without adding toxicity for high-risk patients.

On the predecessor clinical trial (Total 15), the rate of CNS relapse for high-risk patients was 5.7%. Under Total 16, the rate of CNS relapse for a similar group of patients was reduced to 1.8%, the lowest among reported studies. As in Total 15, no patient received prophylactic cranial radiation. These results further supported the conclusion of Total 15 that all children with acute lymphoblastic leukemia can be safely spared prophylactic cranial radiation.

Total 16 enrolled 598 patients age 18 and younger from 2007-2017. This study included all subtypes of ALL, including B-ALL and T-ALL, those with Philadelphia chromosome rearrangements, and infant leukemia, among others.

The next St. Jude clinical trial for ALL, Total 17, continues to stratify patients based on their risk of relapse and introduces novel molecular targeted and immunotherapies, including CAR T-cells.

The study's authors are Sima Jeha, Ching-Hon Pui, Dequing Pei, John Choi, Chang Cheng, John Sandlund, Hiroto Inaba, Jeffrey Rubnitz, Raul Ribeiro, Tanja Gruber, Susana Raimondi, Raja Khan, Jun J. Yang, Charles Mullighan, James Downing, William Evans, Mary Relling and Ching-Hon Pui. Elaine Coustan-Smith and Dario Campana of the National University of Singapore also contributed to the study.

The research at St. Jude was funded by grants from the National Cancer Institute (CA21765, CA36401, CA176063 and P50 GM115279), and ALSAC, the fundraising and awareness organization of St. Jude.

DRUGS & TARGETS

AACR Project GENIE begins five-year research project with $36M in industry funding

Project GENIE (Genomics Evidence Neoplasia Information Exchange), an initiative by the American Association for Cancer Research, is launching a five-year, $36 million research collaboration with nine biopharmaceutical companies to obtain clinical and genomic data from an estimated 50,000 de-identified patients.

The patients are treated at institutions participating in AACR Project GENIE. The additional clinical data furthers the project goals of advancing precision oncology and powering clinical decision making through open and transparent data sharing.

The nine biopharmaceutical companies participating in the collaborative project are:

- Amgen Inc.
- AstraZeneca
- Bayer HealthCare Pharmaceuticals Inc.
- Boehringer Ingelheim
- Bristol-Myers Squibb Company
- Genentech, member of the Roche Group
- Janssen Research & Development, LLC
- Merck
- Novartis

AACR Project GENIE is a publicly accessible international cancer registry of real-world data assembled through data sharing between 19 cancer centers across the world. Through the efforts of strategic partners Sage Bionetworks and cBioPortal, the registry aggregates, harmonizes, and links clinical-grade, next-generation cancer genomic sequencing data with clinical outcomes obtained during routine medical practice from cancer patients treated at these institutions.

Currently, AACR Project GENIE's registry contains clinical-grade cancer genomic sequencing data from nearly 71,000 patients. These data are linked to a limited set of clinical data, such as age, sex, primary diagnosis, and type of tumor sample analyzed (primary or metastatic).

The new collaboration will greatly expand the scope and accelerate the speed of clinical data collection.

In the first two years, the project will add prior cancer treatments, tumor pathology and clinical outcomes to the clinical data already linked with the genomic profiles of nearly 8,000 bladder, breast, colorectal, lung, pancreatic and prostate cancer patients treated at three of the institutions participating in AACR Project GENIE: Dana-Farber Cancer Institute, Memorial Sloan Kettering Cancer Center and Vanderbilt-Ingram Cancer Center.

In years three through five, this data collection will be expanded to as many cancer types as possible from all active participating institutions.

"Recognizing the importance of the outputs of this project to the broader research and patient communities, and in alignment with the guiding principles of openness, transparency, and inclusion, all data generated will be made publicly available 12 months following data lock," Shawn M. Sweeney, director of the AACR Project GENIE Coordinating Center, said in a statement.

European Commission approves Astellas' Xospata indication for relapsed or refractory AML

The European Commission has approved Astellas' oral once-daily therapy Xospata (gilteritinib) as a monotherapy for the treatment of adult patients with relapsed or refractory (resistant to treatment) acute myeloid leukemia with a FLT3 mutation. Gilteritinib has the potential to improve treatment outcomes for AML patients with two forms of the most common mutation—FLT3 internal tandem duplication and FLT3 tyrosine kinase domain mutation.

This approval is based on results from the phase III ADMIRAL trial, which investigated gilteritinib versus salvage chemotherapy in patients with relapsed or refractory FLT3mut+ AML. Patients treated with gilteritinib had significantly longer overall survival than those who received salvage chemotherapy.

Median OS for patients who received gilteritinib was 9.3 months, compared to 5.6 months for patients who received salvage chemotherapy (Hazard Ratio

= 0.64 [95% CI 0.49, 0.83], P=0.0004). Rates of one-year survival were 37% for patients who received gilteritinib, compared to 17% for patients who received salvage chemotherapy.

The EC marketing authorization for gilteritinib in relapsed or refractory FLT3mut+ AML is applicable to the European Union member countries, and is also valid in Iceland, Norway and Liechtenstein. Gilteritinib was designated an orphan medicinal product and also received accelerated assessment from the European Medicines Agency earlier this year, which reduced the timeframe for approval.

Patients' FLT3mut+ status can change over the course of AML treatment, even after relapse. Due to the poor outcomes associated with FLT3mut+ AML, patients' FLT3 mutation status may be confirmed to help inform the best treatment approach.

FDA grants Cytotron Breakthrough Device Designation for breast, liver and pancreatic cancers

FDA granted Shreis Scalene Sciences Breakthrough Device Designation for the Cytotron, a CE-marked, whole-body therapeutic medical device.

The Center for Devices and Radiological Health granted the designation.

The company's designation request stated that "The Cytotron is intended to be used to cause degeneration of uncontrolled growth of tissues. It is indicated for treating protein-linked, abnormally regenerating disorders such as neoplastic disease, by selectively targeting and enabling tissue apoptosis, allowing extended progression-free survival, with pain relief, palliation, improved quality and dignity of life. It is indicated for the treatment of solid tumors of the breast, liver, and pancreas."

Shreis, while actively pursuing collaborations for clinical trials in the current proposed indications for use, intend to also submit a request for Breakthrough designation in other solid tumors such as adult and pediatric brain tumors, lung cancer, and other life-limiting diseases.

MD Anderson, Ziopharm Oncology to expand TCR-T Program

Ziopharm Oncology Inc. and MD Anderson Cancer Center established a research and development agreement relating to Ziopharm's Sleeping Beauty immunotherapy program to use non-viral gene transfer to stably express and clinically evaluate neoantigen-specific T-cell receptors in T cells.

"This new agreement is a launch point to expand our TCR library and execute two new clinical trials; a trial for utilizing TCRs from the library targeting hotspot mutations in KRAS, TP53 and EGFR, and a second trial for personalized TCRs targeting patient-specific neoantigens," Ziopharm CEO Laurence Cooper said in a statement.

Under the agreement, Ziopharm commits to fund an additional $20 million for this expanded work in the TCR-T program through 2023, as well as certain milestone payments for clinical development or regulatory approval in the U.S., European Union, Japan and the rest of the world. The funding for this new agreement was included within the budget forecast provided by Ziopharm in its second quarter 2019 financial results news release and webcast commentary.

MD Anderson will receive low, single-digit royalties on net sales in the U.S. and international markets, as well as warrants for Ziopharm common stock which vest upon achievement of clinical milestones. According to institutional guidelines, MD Anderson has implemented an Institutional Conflict of Interest Management and Monitoring Plan to manage this research.

This new agreement expands the relationship between Ziopharm and MD Anderson, established under a 2015 research agreement related to CD19-specific CAR T. Earlier this month, FDA cleared an IND application for a phase I clinical trial to evaluate CD19-specific CAR T, manufactured and infused within two days of gene transfer using Ziopharm's rapid personalized manufacture, as an investigational treatment for patients with relapsed CD19+ leukemias and lymphomas. Ziopharm has approximately $20 million of pre-funded R&D at MD Anderson under the prior agreement, which may now be used under the new agreement, for both the CAR T or TCR-T initiatives.

Ziopharm has entered a lease agreement with MD Anderson to access laboratory and office space within the institution's campus. This new facility will serve as home for Ziopharm's expanded Houston office, under the direction of Eleanor de Groot, of GM Cell Therapy, and Drew Deniger, head of Ziopharm's TCR-T cell therapy program.