Cancer Institute's Drug Program Reproved

Legislators charge NCI with mismanagement and foot-dragging in reporting adverse drug reactions

At two recent congressional hearings, legislators and officials from the Food and Drug Administration leveled serious charges against the National Cancer Institute (NCI). They alleged that the institute has failed to ensure that patients are fully informed of toxic side effects of experimental chemotherapy; to report promptly adverse side effects of drugs which were related to several deaths; and to detect unauthorized testing of

Senator Paula Hawkins

anticancer agents. One of the hearings, held jointly by two House subcommittees on 29 October, was prompted by a series of Washington *Post* articles last month that reported charges of gross mismanagement of NCI's drug development program. A week after the House hearing, another set of hearings was convened by a Senate subcommittee which had conducted its own lengthy investigation of NCI's drug program. Senator Paula Hawkins (R–Fla.), who chairs the Senate Labor and Human Resources investigations and oversight subcommittee, declared that the findings demonstrated management deficiencies which have "crippled" the cancer program.

Cancer therapy in general has been the focus of intense reporting by the media in the past month. Cover stories in *Newsweek* and the *New York Times Magazine* reported progress in chemotherapy. A broadcast of ABC's program "20/20," however, blamed the medical establishment for what it called a failure to recognize unorthodox cancer treatments.

Cancer researchers are upset with both the "20/20" program and the *Post* articles, but it is the *Post* series that dismayed them the most. John E. Ultmann, director of the University of Chicago Cancer Center, said at a House hearing that the articles were "a very inaccurate, imbalanced recitation of partially verified stories." NCI director Vincent T. DeVita, Jr., said, "My major concern is that the reporters so distorted the problems of drug toxicity and drug-related death that patients may leave their treatments or refuse to participate in studies to develop better treatments. . . ." There are anecdotal reports from researchers that a few have done so.

The evidence presented at the House and Senate hearings was extremely critical of the cancer institute. Several cases seemed to be clear illustrations of deficiencies in NCI's monitoring of the program. But some of the instances cited do not appear upon closer inspection to be overwhelming examples of negligence or wrongdoing. Institute officials denied that the problems are widespread but conceded that, in some instances, NCI had erred.

Food and Drug Administration (FDA) officials at the Senate hearing said that NCI has been slow to report adverse side effects of at least three experimental drugs. Their strongest case centered on an anticancer agent known as MeCCNU, which caused serious kidney damage in 20 children with cancer. In a few cases the effect was fatal. FDA investigator and physician, Michael Hensley, said he recommended that criminal charges be brought against some NCI officials and MeCCNU manufacturer Bristol-Myers for withholding information about the drug's toxicity. But, because of staff shortages, federal agents dropped the case after interviewing only one person.

Hensley testified that FDA initiated an inquiry of MeCCNU after a parent wrote the FDA in 1978 that his son, stricken with a brain tumor, had suffered kidney damage after treatment with MeCCNU. "We weren't told about the possibility of kidney failure," Paul Agostino, a retired police officer from New Bedford, Massachusetts, told the subcommittee. Hensley said that when he asked NCI for more information about the drug, "no one knew about any kidney toxicity." He said he then discovered that animal studies published in 1971 indicated that the drug caused kidney damage. In addition, he learned that a physician in 1978 notified NCI officials and Bristol-Myers that several children with brain tumors, who had been treated with MeCCNU, developed severe kidney problems. About one month later, NCI alerted Bristol of the report and, on the same day, the company withdrew an application to market the drug. Hensley suggested that Bristol had kept quiet after the physician first reported the kidney toxicity. Bristol spokeswoman Lorna Corbett said that the withdrawal of the application and federal notification "was a coincidence."

Director Vincent DeVita, Jr.

The cancer institute is obligated to inform the FDA immediately of any possible adverse effects of experimental drugs. But under a special agreement with FDA, which allows the institute to oversee its own clinical researchers, institute officials say in self-defense they mistakenly believed they needed more definitive evidence of kidney toxicity before alerting FDA. DeVita said, because of the misunderstanding, it was almost a year later—after the researcher contacted NCI and Bristol withdrew its application for marketing the drug—that the institute notified the FDA and clinical researchers that the drug was associated with kidney toxicity.

DeVita acknowledged at the House hearing that the institute was "tardy in not telling the FDA. We were wrong on that issue." He reiterated the same point before the Senate subcommittee but added that the MeCCNU matter was "not an example of poor management. Our investigators tend to think in a scholarly way, not a regulatory way." They want to be certain of an adverse reaction before reporting it, he said.

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Broad Receives NASW Prize

News and Comment reporter William J. Broad has won the Science-in-Society Journalism Award of the National Association of Science Writers (NASW) for his three-part series "Nuclear Pulse" (*Science*, 29 May, 5 June, and 12 June). In awarding Broad the prize in the magazine category, which was shared with Janet Raloff who wrote on the subject for *Science News*, NASW cited the articles for their comprehensive and knowledgeable analysis of an issue of national importance.

In another case, FDA scientist Robert S. K. Young said that the institute did not tell the agency of ten deaths that may have been associated with Deoxycofomycin (DCF). Young said that in January 1980, researchers from three comprehensive cancer centers reported to NCI that several patients had died after treatment with the drug. The cancer institute sent the information to FDA 6 months later, but the data were so buried in a voluminous report about the drug that FDA officials missed it, he said. Young said he requested a detailed analysis of DCF last January but did not receive a report until this month. He said the institute stopped DCF clinical trials in February.

DeVita defended the delay in responding to FDA's request, saying that the institute was about to hold a seminar to discuss DCF. "We were trying to collect more data," he said.

The FDA also discovered that the cancer institute allowed an unnamed individual to manufacture a preparation called "Jim's Juice" for cancer patients. The person was allowed to produce the compound under what is known as a "compassionate IND," which permits the distribution of unapproved drugs when, in the opinion of a doctor, it may benefit the patient. The person halted production after an inspection found that he was making the substance in his kitchen and on his back porch, said Linda S. Little, a special agent in the office of the inspector general of the Health and Human Services Department.

According to Hensley, the institute also failed to alert the FDA about 16 patients who suffered congestive heart failure after treatment with Mitoxantrone, which is also known as DHAD. NCI's decision not to report the cardiac complications was not unreasonable, DeVita said, because the cause and effect of the drug on the patients was not clear.

Hensley claimed that the results of animal studies should have signaled the institute to monitor for heart problems. In one study, all the dogs given high doses of the drug died within 12 hours. Tests with rabbits showed similar results.

NCI researcher Michael Lowe said later that the possibility of heart failure was not apparent from the animal studies. In the dog experiment, the animals died from shock because of a dramatic drop in blood pressure related to the drug. At the Senate hearing, NCI official David Hoth said that the results of the rabbit tests were not available until after the clinical trials were begun. He conceded, however, that the findings were not brought to his attention until June "because of an administrative lapse." Hoth and DeVita both said that it is still not certain whether Mitoxantrone is related to heart failure because 14 of 16 patients cited were previously treated with adriamycin, a drug which is known to cause heart failure after extended use.

At both the House and Senate hearings, legislators criticized the institute for failing to prevent unapproved use of experimental drugs. Hawkins disclosed an internal memorandum written in April 1980 by a former top NCI official who was worried about the misuse of experimental drugs—including Mitoxantrone—at two unnamed comprehensive cancer centers. "None of these studies has been sent to NCI before they were begun. There are many others like this," wrote Vincent H. Bono, Jr., former chief of the investigational drug branch, in a memo to a superior.

DeVita denied that patient safety was compromised. "The protocols were not bad protocols but they were carried in advance of NCI approval." They were conducted by respected researchers, he insisted. "It was not a question of patient safety."

A specific example in which a researcher jumped the gun involved an investigator at M. D. Anderson Medical Center in Houston. Moreover, a bioethicist at the House hearing criticized the researcher for failing to obtain truly informed consent from the six patients in the trial.

In 1980 the scientist Ti Li Loo tested a drug MTHHF (5-methyltetrahydrohomofolate), that had not been approved for clinical trials by the institute. NCI officials became aware of Loo's experiment only after it was published in a medical journal. A site visit by institute authorities ensued last spring. According to their report, a protocol to test the drug was submitted by another M. D. Anderson researcher 2 years prior to Loo's experiment and was approved by the center's institutional review board. The protocol, however, was not approved by NCI. Loo apparently assumed that the protocol had been authorized and did not check with NCI for clearance.

Loo proceeded to test the drug, which was radioactively labeled at levels comparable to the original protocol. The main difference between the two protocols was that Loo administered the drug in trace amounts which were 1/100 and 1/10 of the other protocol. None of the patients showed any adverse side effects, the report said. The drug has since been approved for clinical trials.

After its investigation, NCI barred Loo as a principal investigator and suspended his contracts with the institute. The institute also required the medical center to revise its procedures to store and distribute investigational drugs.

While the incident demonstrates laxity in preventing unapproved use of anticancer drugs, the issue of informed consent is just as troubling to some observers. Alexander M. Capron, executive director of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, charged that the consent forms signed by the patients were misleading and that they "plainly failed to comply with applicable regulations in effect since 1974 [governing informed consent]." Capron quoted from the form that the amount of drug used "will be free of toxic side effects." But he pointed out that possible hazards from the drug were not listed. Among the side effects associated with the drug, based on animal studies, are loss of appetite, diarrhea, rectal bleeding, convulsions, and lethargy. Capron said the consent form "left you with the impression that you are talking about a treatment, not about something for which any prospect of benefit is remote at the very best." Although the cancer institute chastised Loo, it did not go far enough, Capron asserted. "The NCI response was inadequate. It didn't look to see if the problem was isolated or endemic."

Chairman of the House Science and Technology investigations and oversight subcommittee, Albert Gore (D–Tenn.) was particularly angered over the alleged

violation of patient rights. Gore said to M. D. Anderson professor Emil J. Freireich, "What bothers me is that you don't seem to recognize . . . that this grand motivation [to pursue science] can obscure the approach to the individual patient."

Freireich replied that federal regulations were becoming overly burdensome and are hampering scientific progress. "These regulations are in fact harming the very patients they are designed to protect." He argued that patient consent forms are frightening cancer patients by disclosing the "intimidating details" of their treatment.

At the Senate hearing, Charles A. LeMaistre, president of the University of Texas System Cancer Center, further defended M. D. Anderson. "It is clear that the violations were procedural in nature, that there were no ethical violations, no intent to deceive and no harm to patients in this study."

Hawkins declared that the evidence her subcommittee staff gathered "painted a very bleak picture." She said that the drug development program "has been confused and disorganized and painfully slow to react. Either you promptly report life-threatening drug reactions or you don't; either you obtain adequate informed consent from patients who volunteer themselves for experimental use or you don't," she declared.

DeVita pointed out that the matter of reporting adverse reactions quickly enough "will always be a problem." It is difficult to sort out whether health complications stem from drug treatment or the disease itself, he stated. Only with benefit of hindsight does the relationship become clearer, DeVita said. At the House hearings, he said that during the past 18 months, more than 1400 terminal cancer patients have entered experiments that test a new anticancer drug for the first time on humans. Less than 3 percent, or 43, of these patients died of "true drug-related causes," he said. Beneficial response rates frequently exceed this figure, the NCI director noted.

Senator Edward Kennedy (D–Mass.) defended the institute. "The problems are serious and they have to be remedied. We should also understand that NCI is not an agency in crisis. That agency has done more to enhance life than any other agency in government," said Kennedy, whose own son, Teddy, has survived bone cancer.

The cancer institute, however, will continue to be the object of investigation. Hawkins and the Washington *Post* have promised to probe NCI further.

—MARJORIE SUN

Northern Tier Pipeline in Trouble

The United States at present has no major pipeline to carry crude oil from the West Coast to major markets in the middle of the country. If a decision made by a council in the state of Washington this fall is allowed to stand, the only existing proposal to build such a line may be killed.

The pipeline project, financed by a consortium known as the Northern Tier Pipeline Company, received much attention during the Carter Administration. Congress even designated it a high-priority energy project in the national interest. It would relieve the crude oil surplus (about 400,000 barrels a day) now found on the West Coast and provide an efficient new route for transporting oil to the Midwest. The pipeline would run from Port Angeles at the northwest corner of Washington through Washington and four other states, ending in northern Minnesota.

The federal government and four of the states involved have handled applications for construction permits quickly. But state officials in Washington have decided that there is more to be lost than gained by cooperating, and they have voted to deny a construction permit.

On 16 October, the state Energy Facility Site Evaluation Council (EFSEC) voted by a large margin (22 to 4) to turn down the application submitted by Northern Tier. EFSEC Chairman Nicholas Lewis describes this as a preliminary vote and an attempt to get the council's judgment "out on the street for public comment." Since Northern Tier filed its first application in 1976, an EFSEC examiner has collected 45,000 pages of testimony from the company and 29 intervenors.

EFSEC has invited the applicant to respond to its decision before a final vote is taken in mid-November. The chief objections to the proposal, according to Lewis, have to do with the siting of the tanker port and the safety of a submarine segment of the pipeline.

Tankers bringing oil from Alaska would dock at a terminal on a spit of land outside Port Angeles, 7000 feet from the center of town and 8000 feet from the only hospital in the area. If there were an explosion, Lewis says, it might wreck the hospital. He adds that it would take 2 hours to bring emergency help in by helicopter. EFSEC was not satisfied with the company's research on the effects of tidal water scouring on an 18-mile segment of the line which would be placed under Puget Sound. If earth covering the line washed away, the pipe might buckle and break, spilling 20,000 gallons of oil before the leak could be stopped, damaging the state's precious fisheries.

When EFSEC looked into local benefits from the project, Lewis says, "We frankly couldn't find much." There would be some short-term employment for construction and a remote possibility that a spur line would be built to supply oil to a new refinery in eastern Washington. But, without a firm appeal in the name of national security, EFSEC decided that it could not justify the risk to the local environment.

Secretary of Energy James Edwards did write to Washington's Governor John Spellman last August. But the letter made only a mild appeal for accelerated licensing, urging the state to let the free market work its will. Edwards did not base his request on any national imperative.

Jerry Smedes, an environmental scientist employed by Northern Tier, claims that fears about a tanker explosion are unwarranted. A worst-case engineering study, he says, indicates that an explosion would do no significant damage to structures beyond 2500 feet. He also says that concerns about underwater erosion and pipe breakage are exaggerated since the company has promised to carry out regular inspections along the entire submarine route of the pipeline. Erosion would not occur suddenly, he claims. But Smedes does not think it likely that a majority of EFSEC could now be persuaded to reverse the vote of 16 October. Nor does the company have plans at the moment to submit a new application.

The governor must affirm or veto EFSEC's ruling within 60 days after the final vote this month. Spellman has said that he is inclined to listen to his council's recommendation unless he finds that some important evidence has been ignored.—ELIOT MARSHALL

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