SCIENTIFIC MISCONDUCT

NIH Tightens Clinical Trials Monitoring

In the aftermath of a firestorm that sprang up after revelations that some of the data in a landmark breast-cancer trial were fraudulent (*Science*, 25 March, p. 1679), officials of the National Institutes of Health (NIH) have tightened procedures for ensuring the integrity of clinical trials. In one big change, a new Clinical Trials Monitoring Branch has been set up at the National Cancer Institute (NCI) to make sure that principal investigators follow all the rules. The officials, including NIH director Harold Varmus and NCI director Samuel Broder, spelled out the new procedures at a 13 April hearing of the Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce, which is chaired by Congressman John Dingell (D–MI).

Dingell called the hearing after details of the fraud in the National Surgical Adjuvant Breast and Bowel Project (NSABP), a cooperative study group consisting of several thousand doctors at over 400 sites, started hitting the headlines in mid-March. The fraud, which involved a researcher at the St. Luc Hospital in Montreal who falsified the records of at least 100 patients, put into question a major NSABP finding: that lumpectomy followed by radiation is just as effective as mastectomy for treating early stage breast cancer.

Compounding the problem was the fact that while the Office of Research Integrity issued a final report on the fraud a year ago, the highly regarded NSABP principal investigator, Bernard Fisher of the University of Pittsburgh, had not published a reanalysis without the fraudulent data—despite repeated urgings from NCI officials to do so. Additionally, during his testimony, Broder confirmed Dingell's assertion that Fisher delayed reporting deaths from endometrial cancers associated with the chemotherapeutic agent, tamoxifen—a drug being tested on healthy women for the prevention of breast cancer. NCI officials last month relieved Fisher of his job as head of the NSABP and performed their own reanalysis of the lumpectomy data, which supports the initial conclusion.

But at the committee hearing both Varmus and Broder accepted a share of the blame. Both made profuse *mea culpas* for failing to move forcefully enough to get the NSABP data reanalyzed and have the problems with the study made public. As Broder testified to the committee, "we as government workers were not arrogant enough" in reporting fraud and fabrication to the public. But no more. Broder repeatedly assured the committee that regardless of a researcher's preeminence, he or she would have to answer to the NCI.

As the principal means of asserting its control, the NCI established a Clinical Trials Monitoring Branch to manage the oversight of all clinical trials including those run by cooperative groups like the NSABP. All prospective grantees will have to accept NCI's terms for that oversight or simply not get their money, Broder says. The new branch will be headed by medical oncologist Michaele Christian.

Christian's branch will enforce a mandatory data auditing program requiring cooperative groups to review each study once every 3 years to identify any data problems. All audits will be done on site and include at least one person who is not a member of the cooperative group. A report of pass or fail must be made to NCI in 24 hours, and a written report must be filed within 6 weeks. If a site isn't audited during a 3-year cycle, patients cannot be accrued until the requirement is satisfied. In addition, all cooperative sites will be subject to random audits by the NCI on short notice.

And if fraud is found, NCI itself will notify the journals and other cooperative group members and demand the retraction of all papers submitted using fraudulent data. The grantee will be required to submit a reanalysis to the journals in 90 days or NCI will seize the data and publish its own reanalysis. Broder states that NCI has the right to the data and will not "tolerate explanations that the data belong to the grantee."

In order to assure that NCI is "the very first in line to receive" notice of investigational drug toxicities, the institute plans to hold the Investigational New Drug Application (INDA). The holders of the INDA are responsible for reporting all adverse drug effects to the Food and Drug Administration. Broder testified that because NCI did not hold the INDA for tamoxifen, they were not necessarily the first to know about increased endometrial cancers in women taking the drug in the NSABP.

Finally, NCI plans to recoup any money awarded to institutions where fraud is found. "We don't pay for fraud," Broder says flatly.

A big question still remains, however. Will the Dingell committee be satisfied with the changes NCI is instituting? According to a Dingell aide, the committee is pleased that NCI has an active plan for dealing with fraud, but remains skeptical that NCI officials will enforce these regulations when they couldn't enforce their previous ones. But the committee is encouraged, he says, by the "attitude" of NCI officials.

–Lisa Seachrist

PUBLIC HEALTH

Pesticides and Breast Cancer: No Link?

It's getting harder and harder to know what to worry about these days. Every week brings another epidemiologic study—and with it, another swing of the anxiety pendulum. Just one year ago, Mary Wolff of Mount Sinai Hospital in New York City and her colleagues reported in the *Journal of the National Cancer Institute* that breast cancer was four times more common among women with the highest blood levels of a pesticide residue than among women with the lowest levels. The culprit was a chemical known as DDE, a breakdown product of DDT. Although DDT has been banned in the United States for more than 20 years, it seemed that residues in the environment and in women's bodies might be taking a delayed toll.

This week, the same journal revisits the subject and comes to the opposite conclusion. A new study of the breast cancer–pesticide link—the largest yet—from a group led by Nancy Krieger of the Kaiser Foundation Research Institute in Oakland, California (a group that includes Wolff herself) finds no connection between the pesticide and cancer. The lesson? "As if we needed it, another reminder of the caution with which the results of a single epidemiologic study, or even a handful of them, should be regarded," writes Brian MacMahon, professor emeritus of epidemiology at the Harvard School of Public Health, in an accompanying editorial.

When it comes to a deadly disease, though, it can be difficult to maintain the detachment MacMahon recommends. After last year's New York study, breast-cancer activists and environmentalists were quick to widen a call for a

MARILYN HUMPHRIES/IMPACT VISUALS

Toxic anxiety. New results exonerate DDT for now, but other suspects are still at large in the environment.