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.

ban on all organochlorine compounds—the class of chemicals that includes DDT and many other compounds that are still in widespread use. Already alarmed by laboratory evidence that these substances could mimic the female hormone estrogen, which is thought to promote breast cancer, activists viewed the New York study as the smoking gun.

But that part of the case against organochlorines has now weakened significantly with the Kaiser study, which was based on blood samples drawn and frozen during routine physical exams of thousands of women at Kaiser during the late 1960s. From this archive, the researchers chose samples from 150 women (50 black, 50 white, 50 Asian) who had gone on to develop breast cancer an average of 14 years later; 150 matched controls completed the study sample. Comparison of all cases with the controls, says Krieger, showed no association between serum levels of DDE and the risk of breast cancer. For black women alone, there was "a hint of a positive association," says Krieger—but no more than a hint. The study also looked for an association between breast cancer and PCBs, a group of organochlorines once widely used in industry, and again found nothing.

The Kaiser study, says MacMahon, has "a number of features that favor its conclusions over the New York report." For one, the number of breast-cancer cases was nearly three times as large (150 versus 58). What's more, the Kaiser study covered a period before the 1972 DDT ban, when women in the United States were exposed to far higher levels than they are today. The blood samples in the study contained DDE levels four to five times as high as those in the samples in the New York study, which were drawn between 1985 and 1991.

To MacMahon, such swings in the pendulum are inevitable. He calls the New York study "perfectly respectable" but adds that "the spectrum of man's diseases is complex and his environment labyrinthine," and researchers looking for patterns can easily be misled. "We must expect many tentative positive findings not to be confirmed," he writes.

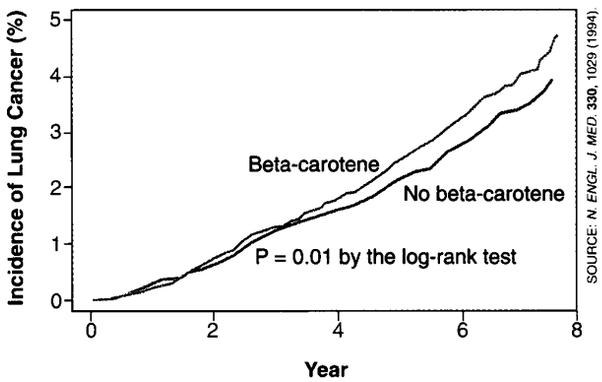
But neither he nor the researchers think the current study offers the last word on a possible pesticide–breast cancer link. "There are a lot of questions about why this result differs from the previous study," says Krieger. "I think the proper scientific response is to pursue the question by doing more research, not by dismissing the hypothesis." Epidemiologist Paolo Toniolo of New York University, who took part in the earlier study, agrees and says his group is now expanding its sample of breast-cancer cases to 400. When the results from that study are in, the anxiety pendulum may swing again. The trick is not to get caught up in its oscillations until it finally comes to rest.

–Gary Taubes

CANCER PREVENTION

Beta-Carotene: Helpful or Harmful?

Over the past decade, it's become a tenet of cancer prevention theory that taking high doses of antioxidant vitamins—like vitamin E or A—will likely protect against cancer. So in light of that popular hypothesis, cancer prevention experts are having to struggle to make sense of the startling finding, published in the 14 April *New England Journal of Medicine*, that supplements of the antioxidant beta-carotene markedly *increased* the incidence of lung cancer among heavy smokers in Finland.



Up and up. By the trial's end, smokers who took beta-carotene had 18% more lung cancers than those who didn't.

The result is particularly worrying because it comes from a large, randomized clinical trial—the gold standard test of a medical intervention. And as well as dumbfounding the experts, the Finnish study has triggered calls for a moratorium on health claims about antioxidant vitamins (beta-carotene is converted into vitamin A in the body), and prompted close scrutiny of several other large beta-carotene trials that are currently under way. "The results [of the Finnish trial] are strong enough that one has to take them seriously; they're worrisome," says statistician David DeMets of the University of Wisconsin, who was a member of the safety monitoring committee of the Finnish study.

What mystifies the experts is that the Finnish trial goes against all the previously available evidence. Beta-carotene's biological activity suggests that it should protect against cancer. It's an antioxidant that can sop up chemicals called free radicals that may trigger cancer. And over a hundred epidemiologic surveys indicate that people who have high levels of beta-carotene in their diet and in their blood have lower risks of cancer, particularly lung cancer. Finally, the idea that beta-carotene would have only beneficial effects on cancer is buttressed by the results of the only other large-scale clinical trial completed thus far. It found that a combination of beta-carotene, vitamin E, and selenium reduced the number of deaths from stomach cancer by 21% among 15,000 people living in Linxian County in China, compared with trial participants who didn't take the supplements.

But about 6 years into the Finnish trial, which was a combined effort from the National Cancer Insitute (NCI) and the Finnish National Public Health Institute, members of the safety monitoring board began to pick up indications that it wasn't going as expected. Participants taking beta-carotene seemed to be getting more lung cancers than those not taking the drug. "We began to see a hint of a trend [towards an increased incidence of cancer] a couple of years ago," says DeMets. The trial was allowed to continue until its scheduled end last year because until then, data analysis had not revealed the size of the difference. Nonetheless, DeMets says, "we did agonize. We did worry." When all the data were in and analyzed at the end of the trial, it became apparent that the incidence of lung cancer was 18% higher among the 14,500 smokers who took beta-carotene than among the 14,500 who didn't. The probability that the increase was due to chance is less than one in one hundred. In clinical trials, a difference is taken seriously when there is less than a one-in-twenty probability that it happened by chance.

The trial organizers were so baffled by the results that they even wondered whether the beta-carotene pills used in the study had become contaminated with some known carcinogen during the manufacturing process. Tests have ruled out that possibility, said Olli Heinonen of the University of Helsinki, Finland, at the press conference NCI called to present the results.

A more frightening explanation is that beta-carotene itself is carcinogenic, and that in the epidemiologic studies it merely acts as a "marker" for other substances in beta-carotene–rich foods—oranges and dark green vegetables such as carrots and broccoli—that do protect against cancer. "The benefits that have been seen in the [epidemiologic] studies may have been overestimated, and the dangers may have been underestimated, or even unsuspected," says Harvard's Julie Buring, who is principal investigator on one beta-carotene clinical trial—the Women's Health Study—and a member of the safety monitoring committee for another—the Carotene and Retinoid Efficacy Trial (CARET) study.