Study details misconduct in drug research

An orthopedic surgeon under investigation for scientific misconduct by the Food and Drug Administration broke into his own office, setting fire to a file room and throwing medical records into a whirlpool bath. The doctor's shenanigans did him no good: FDA barred him from running clinical drug trials after an audit revealed purported study patients who had never participated in the trial.

Although FDA penalized the surgeon in this case, some drug investigators who flagrantly violate scientific standards escape punishment, according to a report in the May 5 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION. FDA must take stronger action to weed out incompetent or dishonest researchers, say Martin F. Shapiro of the University of California, Los Angeles, and Robert P. Charrow, formerly with the Department of Health and Human Services in Washington, D.C.

FDA regularly sends investigators to examine laboratory records and other data kept by researchers hired by drug firms to study experimental drugs. Shapiro and Charrow analyzed data collected from 1,955 such audits conducted by FDA from June 1977 to April 1988. Auditors found "serious" deficiencies — such as failure to obtain informed patient consent — in 12 percent of audits prior to 1985 but in only 7 percent since that date, the researchers report. "It's nice to see that the rate of serious deficiency has fallen," Shapiro says. "But I think most people would agree that 7 percent is too much."

The overall decline suggests FDA's audit program may deter some drug researchers from conducting sloppy or fraudulent research, Shapiro says. But high rates of deficiencies remain in certain areas, he adds. FDA found serious study-protocol violations — in which physicians failed to follow a detailed scientific method — in 25 percent of audits performed before October 1985 and in 27 percent of audits performed since then. Researchers who disregard protocol can skew or invalidate study results, Charrow notes.

Even when investigators were found guilty of scientific misconduct, some escaped censure, the authors found. Shapiro and Charrow examined 395 "for cause" audits, which are more thorough investigations triggered when a routine audit reveals irregularities. FDA disqualified or placed restrictions on researchers in 16 percent of these cases. However, the vast majority — 84 percent — did not result in any disciplinary action. In a small number of cases, FDA allowed researchers who had more than once deliberately violated regulations to continue their studies after they promised they wouldn't repeat past mistakes.

Researchers guilty of misconduct fall into several categories, Charrow says. Some deliberately fabricate data to advance their careers. Others cut corners in order to boost their research output and their earning capacity. Still others make mistakes through incompetence or inexperience.

FDA must get tough with researchers who repeatedly flaunt scientific standards, the authors argue. They propose suspending researchers immediately after an audit reveals substantial misconduct. Under the current system, such scientists may continue their studies pending a hearing. To weed out incompetent researchers, Shapiro and Charrow suggest that FDA give would-be investigators an examination, certifying those who pass to conduct clinical drug trials.

The authors stop short of recommending that the National Institutes of Health adopt a similar audit program — an idea that has received a great deal of attention in the wake of several highly publicized cases of alleged fraud involving NIH-supported research (see box). Charrow points out that basic biomedical scientists must pass a rigorous peer review before getting NIH grant money, a process that helps eliminate shoddy researchers from the start. In contrast, investigators evaluating drugs for FDA approval contract directly with pharmaceutical companies. FDA can veto a firm's choice but does not put scientists through a peer review, Charrow says. —*K.A. Fackelmann*

Baltimore case reopened

The National Institutes of Health last week reopened its investigation of Nobel laureate David Baltimore and several colleagues amid speculation that potentially damaging evidence would be revealed at a congressional hearing late this week. Baltimore, who directs the Whitehead Institute for Biomedical Research in Cambridge, Mass., and colleague Thereza Imanishi-Kari, formerly at the Massachusetts Institute of Technology and now at Tufts University School of Medicine in Boston, have been unable to shake off fraud allegations prompted by their surprising results pertaining to the mouse immune system in the April 25, 1986 CELL.

The new evidence comes from Secret Service agents who reportedly examined Imanishi-Kari's laboratory notebooks, finding clues that some dates had been changed. The forensic experts were scheduled to testify at a May 4 hearing of the House Energy and Commerce Subcommittee on Oversight and Investigation.

In February, NIH released a report prepared by three outside scientists brought in to investigate the allegations of scientific misconduct (SN: 2/11/89,p.85). Their review found no evidence of fraud but did identify serious inaccuracies and clerical errors in the CELL paper.

Now NIH officials are questioning the conclusion of the investigative report. They say the new probe results from further questions raised by Margot O'Toole, the postdoctoral student who triggered the initial investigation after working in Imanishi-Kari's laboratory.

Some scientists speculate that renewed congressional involvement in the case may lead to a federally imposed system to identify and penalize government-funded scientists engaging in fraud or misconduct. □

Selective abortion of twin

In the latest twist on the abortion dilemma, researchers are refining methods that allow selective termination of a defective fetus in fraternal-twin pregnancies. The controversial procedure allows parents to terminate an affected fetus, yet carry the healthy twin to term.

Usha Chitkara, Richard L. Berkowitz and their colleagues at the Mount Sinai Medical Center in New York City studied 17 twin pregnancies in which one twin had a disorder, such as Down's syndrome, that would cause lifelong mental or physical handicap. The team carefully identified the affected fetuses and used a variety of methods to terminate it during the second trimester of pregnancy. They report in the May OBSTETRICS & GYNECOLOGY that a cardiac injection of potassium chloride was effective in stopping the affected fetus' heart. The dead fetus remains in the womb but shrinks in size and is expelled during delivery.

Chitkara performs the procedure only in fraternal-twin pregnancies, where the fetuses have separate circulatory systems. Identical twins often have connected circulatory systems, and a lethal injection given to one twin may harm the other, she says.

She and her colleagues dramatically improved their method during the course of the experiment. In the first six cases, four women lost the entire pregnancy. Then the researchers refined their technique and began using potassium chloride. The last 11 mothers, they report, delivered a healthy child.

The ethics of the procedure remain the toughest issue, Chitkara admits. In her experience, most of the couples with a severely defective fetus ultimately decided to undergo the experimental procedure rather than abort both fetuses or carry them both to term. But "they really go through a lot of emotional turmoil before deciding to go ahead with it," Chitkara notes. □