FINANCIAL CONFLICT

Universities Puncture Modest Regulatory Trial Balloon

Even the blandest words can be incendiary when they're about money. U.S. officials have learned that lesson the hard way this winter after the chief lobbies for academic medicine kicked up a fuss about suggestions on how to deal with financial conflicts of interest. Their opposition is likely to shoot down a mildly worded "draft interim guidance on financial relationships in clinical research" issued by the Department of Health and Human Services (HHS) in January.

The HHS rule-writing effort was designed to tune up policies that were last examined in 1995. The current push began after a young man died in a university-based gene therapy experiment in 1999. The case drew attention because one of the clinicians in the project, and the academic institution itself—the University of Pennsylvania—had equity in a company that was hoping to benefit from the research (*Science*, 12 May 2000, p. 954). But the cry for clear and consistent new standards regarding money and medicine, led by former HHS Secretary Donna Shalala, so far has failed to win the attention of the new Bush Administration.

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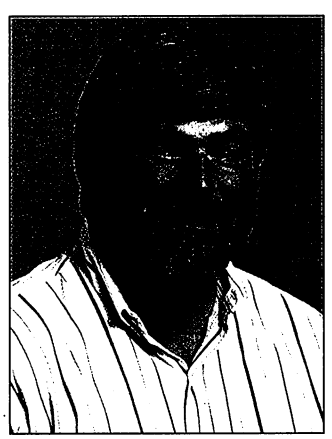
—Greg Koski



The HHS draft guidance (ohrp.osophs.dhhs.gov/nhrpac/mtg12-00/finguid.htm) reflects what officials saw as a consensus on how to deal with the increasing role of industry in academic medicine. Among other things, it suggests that researchers' potential conflicts be disclosed to the same Institutional Review Boards (IRBs) that now monitor other ethical issues, and possibly to patients as well. About a third of the publicly funded IRBs are considering whether to take a look at financial issues, according to HHS. The draft statement also encourages academics to become involved in reviewing "institutional" conflicts—the kind that occur when a university itself has a financial stake in the outcome of a clinical trial. Drawing on public comments from a meeting last August, the guidance sought to harmonize patchy federal and university policies. It was developed by the new Office for Human Research Protections (OHRP), a high-profile version of an outfit previously housed within the National Institutes of Health.

But even that gentle prodding was too much for academic leaders. The draft is "quite premature," says David Korn, a former dean of medicine at Stanford University who now works on government issues at the Association of American Medical Colleges (AAMC) in Washington, D.C. "I think it is necessary to address these issues," says Korn, but "I don't think the government has any great wisdom [to offer]. We don't even know how to define an institutional conflict of interest."

On 2 March, four major education organizations wrote to OHRP director Greg Koski, asking him to "withdraw" the guidance and "reissue portions of it as points for consideration." They argued that some of the HHS ideas—particularly on potential institutional conflicts—were based on anecdote rather than good evidence. On 8 March, the Federation of American Societies for Experimental Biology echoed those views in a separate letter.

It's not that the community is ignoring the issue. The AAMC, which signed the call for withdrawing the draft along with the Association of American Universities, the Council on Government Relations, and the National Association of State Universities and Land Grant Colleges, is setting up a new panel to formulate its own policy. AAMC president Jordan Cohen is hoping that its 125 member institutions will "agree voluntarily to abide by a common set of principles for managing those conflicts." The panel is headed by William Danforth, former president of Washington University in St. Louis, who has yet to set a date for the first of the proposed twice-yearly meetings.

Koski says he was taken aback by the sharp and "misleading" tone of the response from academia. "We haven't issued any guidance yet," he points out, "and you can't withdraw something that hasn't been issued." HHS published the statement "to start a broad discussion," he adds.

The government and the private sector can work in parallel, says Koski, adding that he hopes HHS can learn from the Danforth committee as it undertakes its review. And he doesn't think it will be too hard to clarify the rules and build public confidence in research: "This isn't rocket science."

–ELIOT MARSHALL

PARKINSON'S RESEARCH

Fetal Cell Transplant Trial Draws Fire

In just 1 week, an experimental treatment for Parkinson's disease—fetal cell transplants—went from promising to perilous. At least, that's how much of the general media reported the publication of mixed results from the first double-blind study. But Parkinson's researchers caution that results from a single trial, especially one that was controversial from the start, should not be the final word on the technique.

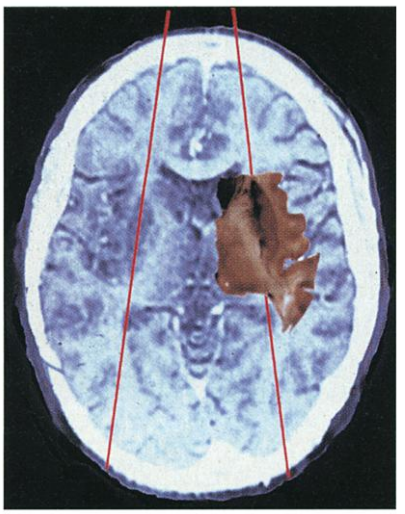
On 8 March, neuroscientist Curt Freed of the University of Colorado School of Medicine in Denver, neurologist Stanley Fahn of Columbia University College of Physicians and Surgeons in New York City, and their colleagues reported in *The New England Journal of Medicine* that injecting fetal cells into the brains of Parkinson's patients resulted in a significant improvement in some recipients. Several patients, however, also experienced troubling side effects.

Parkinson's disease is marked by the mysterious death of brain cells that produce a chemical messenger called dopamine, which helps control motor function. The researchers had hoped to replace the lost cells by injecting dopamine-producing neurons from the brains of aborted fetuses into the affected areas of patients' brains. Several studies of this experimental technique had yielded encouraging results, but none included a control group.

The Colorado-Columbia study was the first one the National Institutes of Health (NIH) supported after President Bill Clinton lifted the ban on federal funding for research involving fetal tissue. From the outset, the 1993 award was controversial. Some researchers worried that the decision to fund a trial that used only one of several transplant techniques could harm the field if the results weren't positive (*Science*, 4 February 1994, p. 600; 11 February 1994, p. 737). Those fears seemed prescient last week as newspapers, magazines, and television news programs called the results disappointing and the technique a failure. "It's a bit of a setback," says neuroscientist John Sladek of the Chicago Medical School, one of the early critics of the NIH decision. "But it should not be the end of research on cell therapy for Parkinson's." Indeed, in 1995 NIH funded a second study using slightly different transplant techniques; results are expected early next year.

Freed's team randomly assigned 40 patients to two groups: Half had four holes drilled in their skulls through which fetal cells were injected, while the other half underwent "imitation" surgery, in which the same holes were drilled but no cells injected. (The design itself raised questions because of the risks to those in the control group.) One year later, the patients were asked to evaluate the overall severity of their disease on a scale of –3 to +3. By that measure, the two groups reported no significant difference.

However, on a standardized test in which physicians evaluated patients' symptoms while they were off their medicine, the data were more encouraging. After 12 months, those who had undergone the imitation surgery experienced no significant change, but transplant recipients improved by an average of 15%. After the evaluations, patients were told whether they had received cells, and those in the control group had a chance to receive transplants.



New growth. Dopamine-producing cells (stained brown) survive in a transplant recipient's brain. (Red indicates needle track.)

Three years after the operation, transplant recipients who were under 60 when they underwent surgery had improved by an average of 38% on the standardized test, and older patients by 14%. But by then, some troubling side effects had also appeared: Five recipients began to show jerky movements typical of Parkinson's patients who become oversensitive to dopaminergic drugs. The condition persisted after the patients reduced or stopped taking the drugs. Freed attributes these effects to a possible overgrowth of the transplanted cells or an oversensitization of dopamine-receiving cells in the region.

"Few in the field anticipated that too much dopamine would be an issue," says neurosurgeon Thomas Freeman of the University of South Florida in Tampa, an investigator in the second NIH trial. Instead, he says, most researchers have concentrated on encouraging enough cells to survive to produce sufficient dopamine.

Patients in other ongoing studies in Europe and the United States have experienced similar side effects, although none as severe as those reported by Freed, says neurologist Olle Lindvall of the University of Lund, Sweden. In these studies, he says, researchers transplant fresh tissue rather than cultured cells and use different doses and surgical techniques. Lindvall does not think an overgrowth of dopamine-producing neurons caused the side effects. He notes that autopsy data from two transplant recipients in the Colorado-Columbia study who later died—one in a car accident, the other of a heart attack—found between 45,000 and 63,000 surviving cells per patient. Other studies have suggested that as many as 100,000 surviving cells are required for a functional graft, he says.

Freeman and his colleagues hope their study will answer some of these questions. That double-blind trial, which also uses imitation surgeries, includes 34 patients and tests different doses of cells. Patients are not told whether they received cells for 2 years. Last week's report "has put a huge burden on our trial," Freeman says. "If our trial using different methodologies is negative as well, [continuing the research] certainly will be a bigger uphill battle." –GRETCHEN VOGEL

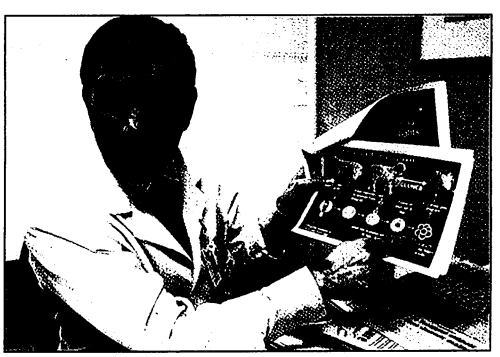
CREDITS: (TOP TO BOTTOM) C. FREED *ET AL.*; *NEW ENGLAND JOURNAL OF MEDICINE* **344** (10), 710 (8 MARCH 2001); JANET WORNE/*LEXINGTON HERALD-LEADER*/AP

HUMAN CLONING

Experts Assail Plan to Help Childless Couples

ROME—A plan to create the first human clone announced here last week is drawing widespread condemnation from the scientific community. Unlike previous such pronouncements, however, experts worry that the three researchers who are intent on treading into this moral and political minefield may have the expertise to carry out their plan—with potentially disastrous consequences for both the mother and her offspring. "They want to use humans as guinea pigs, and this is absolutely preposterous," says Rudolf Jaenisch of the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts.

This is not the first time individuals have threatened to break what has become a taboo in many countries and religions. Three years ago, physicist Richard Seed aired plans to launch a human cloning clinic in Chicago (*Science*, 16 January 1998, p. 315), and has since vowed that he would clone his wife. In addition, a Canadian cult, the Raëlians, laid out its vision of human cloning (*Science*, 25



Cloak of anonymity. Panos Zavos claims his team has animal cloners on board but declined to name names.