Sunshine man. Senator Grassley says company payments to doctors should be made public.

ETHICS

Private Money, Public Disclosure

A Senate investigation is forcing federally funded medical institutions to reveal exactly how much money their researchers receive from industry

In the mid-1990s, psychiatrist Alan Schatzberg and colleagues wanted to test a new way of treating psychotic depression. Their aim was to suppress the brain's receptors for the hormone cortisol, which is elevated in patients with this disease. They decided to try a cortisol blocker called mifepristone, also known as RU-486, the abortion drug. Schatzberg, then at Stanford University in Palo Alto, California, won funding from the National Institutes of Health (NIH) for a small clinical study that showed that mifepristone appeared to help some patients overcome psychotic depression.

Stanford then applied for a patent to use mifepristone for treating psychotic depression. When the pharmaceutical industry showed no interest in developing the drug, Schatzberg co-founded a company in 1998, Corcept Therapeutics, to license the technology and test it in larger clinical studies. For nearly 3 decades, federal law has encouraged such interactions so that taxpayer-funded discoveries can make their way into products.

Last summer, the Stanford-Corcept arrangement came under fire. Senator Charles Grassley (R–IA) accused Schatzberg of concealing from his university that he held stock in Corcept worth $6 million. When Stanford informed Grassley it knew the stock's value and argued that Schatzberg was not directly involved with the clinical trial, the senator came back with new questions: Why did Schatzberg head a grant to study mifepristone? And why had he co-authored papers on the clinical results? At that point, Stanford removed Schatzberg from the NIH grant but said no rules were broken.

Schatzberg and Stanford argue that, although their reading of U.S. regulations may surprise the public, it's for a good cause: developing a new drug for severely depressed patients. Grassley is skeptical: He has suggested that medical entrepreneurs at research universities who fail to properly disclose outside income are violating the law and may bias their work in a way that distorts medical care. Grassley's efforts to clean up what he sees as a corrupt enterprise have targeted about a dozen researchers like Schatzberg to date.

As part of his probe, Grassley has homed in on an overlooked trouble spot: federal rules requiring that institutions track and "manage" faculty members' industry ties. NIH is now contemplating the first major overhaul of these rules in nearly 15 years. It has solicited public comments on a variety of issues—the deadline for responses is next week—as a prelude to proposing tighter regulations. The end result is expected to vastly expand the information that faculty—both basic and clinical—must report to their institutions and to NIH. And it will likely ask for more details on how institutions follow up on conflicts. In a related effort, Grassley has introduced a bill that would require drug and device companies to disclose their payments to doctors in an online database. It would inform the public about conflicts and help ensure that researchers report honestly.

Grassley has blamed NIH for not keeping a close enough watch over conflicts; some academic observers agree that the government needs to take a stronger hand. But NIH leaders, echoing the views of the research community, say the primary burden of overseeing conflicts should remain with institutions because rigid rules would stifle innovation. The system has worked well, although it may have been tainted by some bad apples, they say. "A few cases are getting heavily covered in the press. And the implication is that the entire system is corrupt. That is not true. … That's why it's so important for the scientific community to own this, to see what's at stake here," acting NIH Director Raynard Kington said in an interview earlier this year.

When the final rules have been agreed upon, universities will need to show that they can follow through, says Eric Campbell

THE EVOLUTION OF CONFLICTS-OF-INTEREST POLICIES

CREDIT: RYAN KELLY/CONGRESSIONAL QUARTERLY/GETTY IMAGES; ILLUSTRATION: J. NEWFIELD/SCIENCE

Published by AAAS

of Harvard Medical School in Boston, an expert on industry-academic relations. University leaders have "staved off federal intervention for a long time" with the argument that only they can manage the problem, he says. "Over time, public scrutiny wears that argument away"—and right now it seems to have worn thin.

Conflicting signals

Relatively few academic researchers had ties to companies before 1980, when Congress passed the Bayh-Dole Act. That change in the law encouraged universities to patent and commercialize discoveries made by faculty members who received federal funds. It also led universities to create technology transfer offices and spurred hundreds of start-up companies, industry-endowed chairs, private funding for clinical studies, and consulting deals.

These changes also raised the potential for industry money to bias studies. To deal with that risk, the Public Health Service (which includes NIH), issued its first conflicts-of-interest regulation for PHS-funded investigators in 1995, after 6 years of debate. It requires grantees to report to their institution financial conflicts "related to the research" that are "significant"—defined as more than $10,000 per year from a given company, or 5% equity in a company. These cutoff points, says Susan Ehringhaus, an attorney at the Association of American Medical Colleges (AAMC), were arbitrary. Institutions must review the information, reduce or manage any conflicts, and tell NIH if a grant involves a significant conflict.

Concerns about gaps in this oversight system have been mounting ever since. After a volunteer died in 1999 in a gene therapy trial in which the lead investigator and university had a financial interest, two strong research lobbies—AAMC and the Association of American Universities (AAU)—came forward with plans for reform. Among other recommendations, in 2001 they urged members to adopt a policy barring clinical researchers from having significant conflicts except in compelling circumstances. But when AAMC surveyed members 2 years later, it found many were still lagging behind on the recommendations.

In 2004, a congressional investigation of conflicts within NIH set off alarm bells again. It led NIH to ban industry consulting by in-house scientists, making the rules for NIH researchers far more draconian than those covering their colleagues in academia. The spotlight, university officials realized, could soon swing back to extramural researchers and their industry ties. Last year, it did: The Inspector General of the Department of Health and Human Services slammed NIH for lax oversight of conflicts at grantee institutions.

The issue exploded in the media a year ago thanks to Grassley, the ranking member of the Senate Finance Committee. The 75-year-old Midwesterner, a longtime fraud buster, started out investigating defense contracts. In recent years, Grassley, citing his committee's oversight of Medicare and Medicaid, began probing conflicts of interest involving the approval of drugs such as Paxil and Vioxx.

In 2007, these probes led Grassley's investigators to conflicts of interest at biomedical research institutions. Using a strategy that had worked well in an inquiry by the House of Representatives, they asked both companies and institutions about payments to a faculty member and looked for discrepancies. Grassley says they got leads from media reports and "whistleblowers" such as critical faculty members.

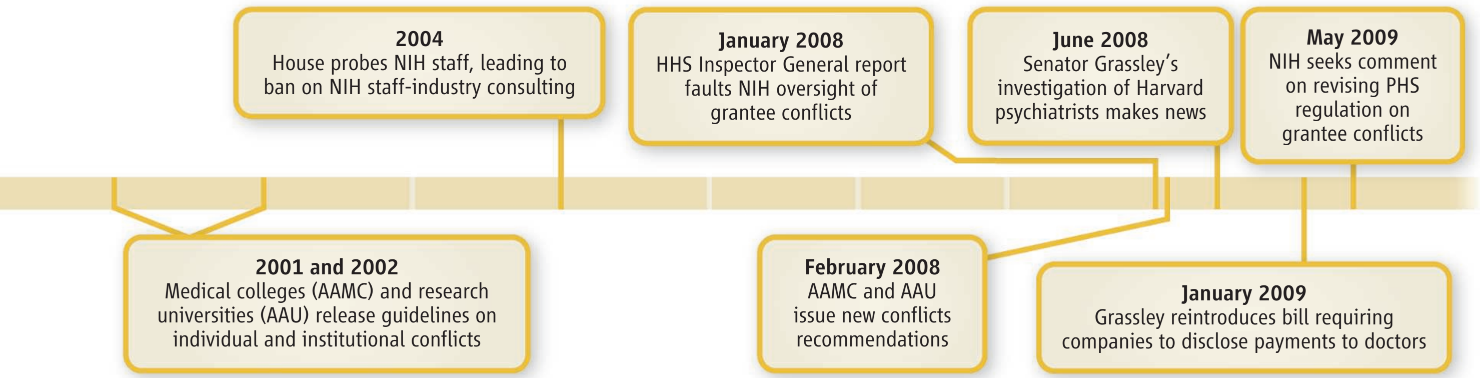
Grassley's team made its first big splash with a front-page story in *The New York Times* last June. They alleged that three Harvard child psychiatrists had failed to report hundreds of thousands of dollars in income they received over several years from drug companies. Other psychiatrists and surgeons have since been accused of hiding similar payments, and some have been disciplined (see table, p. 30).

Risky business

Several of the universities targeted by Grassley's investigation are now tightening their conflicts policies, and several broad reform efforts are under way. Even before Grassley's campaign, some major medical schools had begun to restrict faculty participation in industry-funded medical education courses and promotional talks arranged by speakers' bureaus. An Institute of Medicine (IOM) panel this spring urged all schools to curb these activities, which some of Grassley's quarry said they didn't think they needed to report (*Science*, 1 May, p. 579).

NIH also says it is taking action. It has suspended a $9 million grant to one university for failing to handle conflicts properly. This spring, the agency announced that it may strengthen the PHS conflict rule and asked for comment on questions such as whether researchers should be required to provide much more specific financial information. Many universities ask researchers to check a box if outside payments are above a certain threshold. If that threshold is, say, "above $50,000," that means a payment of $57,000 or $2 million would look the same. "That's a huge problem," because it doesn't distinguish between minor and major conflicts, says conflicts researcher Lisa Bero of the University of California, San Francisco, a member of the IOM panel.

That could change if NIH follows the advice of the academic community. Three heavyweight organizations—IOM and, in comments to NIH, AAMC and AAU—all say that investigators should disclose to their institutions specific payments, no matter how small, that are directly or indirectly related to their research. The Federation of American Societies for Experimental Biology (FASEB) recommends reporting income of $200 or more. AAMC and AAU say they'd like to see the "significant" threshold for reporting to NIH lowered to $5000 from the current $10,000, and 0.1% equity rather than 5%.



SENATE PROBE OF RESEARCH PSYCHIATRISTS

Senator Charles Grassley (R–IA) has cast a wide net in search of physicians who failed to fully disclose payments they received from drug and device companies. One of his concerns, he said, is that biased research could be influencing treatment decisions. Starting with psychiatrists in 2007, Grassley's investigators moved on to orthopedic surgeons this year; he has also looked into fees paid to academic cardiologists, professional associations, and a radio show host. About 30 universities have now received queries from Grassley. This table includes cases made public by Grassley involving NIH-funded researchers—all psychiatrists, many of whom allegedly received consulting income from companies whose drugs they were studying. (Some researchers have said they didn't realize that certain types of payments had to be disclosed.) Dollar amounts are based on letters and statements from Grassley. **–J.K.**

Researcher	Industry Income Disclosed	Total Received	Status
Melissa DelBello, University of Cincinnati	about \$100,000 over 2 years	more than \$238,000 from AstraZeneca	UC has increased monitoring of DelBello's industry activities.
Joseph Biederman, Harvard/Mass General Hospital	about \$200,000 over 7 years	about \$1.6 million	MGH and Harvard are still reviewing, but Biederman agreed to suspend his industry-related activities in December 2008. Harvard is reviewing its conflicts policy.
Thomas Spencer, Harvard/Mass General Hospital	about \$200,000 over 7 years	about \$1 million	MGH and Harvard are reviewing.
Timothy Wilens, Harvard/Mass General Hospital	about \$200,000 over 7 years	about \$1.6 million	MGH and Harvard are reviewing.
Alan Schatzberg, Stanford	more than \$100,000	\$6 million in stock	Stanford says it knew the stock's value. Stanford's medical school soon plans to publicly disclose faculty members' industry ties but not dollar amounts.
Charles Nemeroff, Emory	\$1.2 million over 7 years	more than \$2.4 million	NIH suspended a \$9 million grant to Emory. The HHS Inspector General is investigating the case. Last December, Nemeroff stepped down from research and as department chair.
Zachary Stowe, Emory	not available	\$253,700 over 2 years from GSK for about 95 lectures	Emory told Stowe to eliminate his conflicts in April. The school recently banned promotional speaking.
Karen Wagner, University of Texas, Austin	about \$100,000 over 7 years	more than \$236,000	UT is reviewing.
Augustus John Rush, University of Texas, Southwestern	about \$600,000 over 7 years	more than \$600,000	Rush left UT for Singapore last August and is no longer being investigated, according to Grassley's staff.

SOURCES: SENATE FINANCE COMMITTEE (MINORITY); UNIVERSITY OF CINCINNATI; HARVARD/MASS GENERAL HOSPITAL; STANFORD UNIVERSITY; EMORY UNIVERSITY; UT SYSTEM

AAMC and AAU also agree that NIH should collect more details from institutions on the conflicts they're managing. Under the current rules, institutions only have to tell NIH whether a conflict was managed, reduced, or eliminated. That's partly where the current problems stem from, suggests Julie Gottlieb, assistant dean for policy coordination at Johns Hopkins University School of Medicine in Baltimore, Maryland. If NIH officials are serious, says Gottlieb, "they need to do more than they've been doing."

However, a prohibition on financial conflicts above a specific level remains unpopular, even for studies involving human subjects. Although AAMC and AAU have recommended to their members that significant conflicts should be prohibited in clinical research, they say institutions need flexibility, and in comments to NIH they oppose an "a priori prohibition." One reason to avoid broad caps, notes Gottlieb, is that a great deal of human subjects research is low-risk—on human tissue samples, for example. AAU and AAMC also argue that it's premature to require policies for institutional-level conflicts. They warn that "imposing overzealous regulations could disrupt productive partnerships to the detriment of science and the public."

Grassley has applauded the AAMC and AAU statements, saying NIH "should consider everything" in the comment letter. At least one expert on academic-industry ties, however, thinks the regulation should prohibit any conflicts in clinical research. "I think there should be a zero threshold, or very small," says Sheldon Krimsky of Tufts University in Medford, Massachusetts, because even a \$100 payment could influence a researcher's objectivity.

No rule is universally obeyed, of course, and scientists could still hide their income. Many of those Grassley has probed allegedly were not following existing rules. The remedy for that, many observers say, is a public database of payments reported by companies—such as one that would be created by the bill introduced by Grassley and Senator Herbert Kohl (D–WI), potentially by October 2011. University officials could use the database to audit their faculty members, say AAMC and AAU, which support the bill.

The disclosure system would work much better, the IOM report says, if the research community developed a standard reporting format. Some major medical centers have begun discussing this with companies so that items they consider irrelevant—such as a research grant or reimbursement for travel expenses—don't get counted as income. AAMC's Ehringhaus says standardization is "a terrific idea," but "I don't know yet" if her organization will move it forward. FASEB has suggested that PHS develop a "universal" form.

Harvard's Campbell thinks institutions are making progress. "It's gone from the Wild West 15 years ago to a system that seems to be much more regulated. Over time, people will pay greater and greater attention," says Campbell, who was also on the IOM panel.

Even with stricter rules and full public disclosure, none of these steps will change the fundamental contradiction spurred by Bayh-Dole, says C. K. Gunsalus, special counsel at the University of Illinois, Urbana-Champaign, a longtime follower of integrity in science: "We tell people with one side of the mouth to be pure as the driven snow and with the other side say, 'Take this money,'" says Gunsalus. Stanford's Schatzberg, for example, was following both commands when he came under fire for receiving compensation related to his NIH-funded research. But with the new reforms at least one thing will be clear: Right from the start, everyone will know about that private money.

–JOCELYN KAISER

Published by AAAS