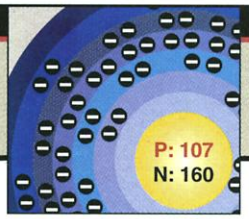

PAGE 1270
Happily boring bohrium

1271
California food fight

BIOETHICS

Financial Conflicts Get More Scrutiny in Clinical Trials

With concern growing that some research universities are getting too cozy with drug companies, it's perhaps fitting that the debate over reducing conflicts of interest in clinical research sounds a lot like an argument about premarital sex. While some insist that abstinence is the only solution, others believe that education is enough to keep the problem under control. Last week, at a national conference,* the "abstainers" gained an important ally—Greg Koski, the incoming head of the federal government's new Office for Human Research Protections. And his support for the idea that scientists should have no financial ties to companies whose products they are testing hints at an upcoming shift in government rules that govern the relationship between scientists and the pharmaceutical industry.

Koski, after noting that some critics contend that "there are certain financial conflicts of interest that can be avoided," said, "I believe that's true." He added, "I believe that they probably should be avoided in most instances." His comments came at a meeting convened by Health and Human Services (HHS) Secretary Donna Shalala as part of a reevaluation of federal protections for clinical research patients following the death last year of 18-year-old Jesse Gelsinger in a University of Pennsylvania gene therapy trial.

To the roughly 700 attendees—including university officials, Institutional Review Board (IRB) members, and industry research sponsors—it signaled that the government may soon go beyond its current policy of counting on universities to "manage or reduce" conflicts. That 5-year-old policy, itself a reaction to suggestions that drug trials were affected by researchers' ties to companies, is generally seen as having had little effect. Indeed, Koski said that in recent years, industry-academia ties "have gotten entirely out of control." And most participants said they felt some action was needed, even if they were uncertain what it should be.

"These are very significant issues, and they simply have to be addressed," says Nils Hasselmo, president of the Association of American Universities (AAU). Wendy Baldwin, deputy director for extramural research at the National Institutes of Health (NIH), predicted that the exercise would take time. "This is actually the beginning of the process," she said. But there was consensus that the problem, aggravated by the burgeoning biotechnology industry, won't correct itself.

SPONSOR INFORMATION
Please be aware that the University of Pennsylvania, Dr. James M. Wilson (the Director of the Institute for Human Gene Therapy), and Genovo, Inc., (a gene therapy company in which Dr. Wilson holds an interest) have a financial interest in a successful outcome from the research involved in this study.

VOLUNTARY CONSENT
I have read this consent form, or it has been read to me. Any questions I have concerning this study have been answered. I understand that if I wi
information regarding my rights as a research subject, I may contac
Office of Research Administration at the University of Pennsylvania
7293, and I may contact the Vice President for Research Administra
Children's Hospital of Philadelphia by calling 215-590-2854.

My signature below means that I am freely giving my permission to study and that I have received a copy of this informed consent.

Case in point. Concern about researchers' financial stakes in clinical research—of the type cited in this consent form used in a trial at the Institute for Human Gene Therapy at Penn, directed by James Wilson (*right*)—prompted a review of U.S. policies.

"Let's be realistic," said Jane Henney, commissioner of the Food and Drug Administration. "Profits do drive this business. As a result, financial conflicts of interest are now an inherent part of the process, and we must deal with them."

A decade ago, when NIH began considering a conflict-of-interest rule for all federally funded researchers, many individuals and some universities contended that such conflicts didn't exist or didn't matter. In 1995, after a long review, NIH's parent agency, the Public Health Service, issued a rule that requires federally funded researchers to disclose to university committees any "significant" interests—defined as $10,000 in income, a $10,000 equity stake, or 5% ownership in a company that might be affected by a scientist's research. The committees are supposed to "manage, reduce, or eliminate" the conflicts.

NIH officials say they believe that universities "in general" are complying, but they don't really know. They acknowledge that they began monitoring compliance only this year. Acting NIH Director Ruth Kirschstein told the conference that some universities have adopted a "culture of compliance"—while others have not.

Gene therapy leader Savio Woo of Mount Sinai School of Medicine in New York City suggested that the best solution may be a simple one. In an April policy statement, Woo noted, the American Society of Gene Therapy's board of directors declared that clinical researchers should have no "equity, stock options, or similar arrangements" with companies sponsoring trials. Not a single member has complained, he said. Koski challenged other professional societies to adopt the same policy: "Just say no."

But most of the discussion at the conference revolved around questions of how to "manage" conflicts rather than do away with them. Breakout panels debated whether IRBs—which must approve consent forms and patient protections in all clinical trials at federally funded institutions—should try to resolve conflict-of-interest issues. The consensus answer seemed to be "no," because IRBs are already overloaded and understaffed. Should IRBs take account of possible conflicts of interest? The answer to that one seemed to be "yes"—although NIH officials say only about 25% of IRBs look into the question now. Conference attendees also appeared to agree that clinical-trial patients deserve to be told, in an informed consent form, if researchers might have a financial stake in the outcome, as was done in the Penn trial (see graphic). But how much detail should be disclosed will be hard to decide.

The conference barely touched on a new

CREDIT: SAM KITTNER

* Conference on Human Subject Protection and Financial Conflict of Interest, held at NIH in Bethesda, Maryland, 15–16 August.

issue introduced by Kirschstein and Baldwin: What should be done when a university owns a piece of a company whose value will be affected by the outcome of a clinical trial? Such situations appear to be growing more numerous, although Kirschstein says no one has much data about the topic, except for "a few anecdotes, I think."

Gene therapist Woo says he knows enough to express his views: "I find it difficult to understand a nonprofit, public university holding equity in a for-profit company," Woo says. Nonprofit universities should be "precluded" from such investments, he says.

Concerned. Koski thinks conflicts are "out of control."

That position is too radical for AAU's Hasselmo. "We shouldn't throw out some valuable babies with the bath water here, because some of these collaborations are very important," he says, noting that an AAU task force is trying to develop principles for managing conflicts. Universities, he adds, see self-policing as preferable to "further rules and regulations" by the government.

Koski noted that the problems facing U.S. clinical research extend beyond federally funded academic medicine. A growing proportion of the work is being performed outside of academic health centers and beyond government oversight, he said. This situation calls for "uniform guidance" at the national level, he added, warning that "if guidance itself is not effective, then it seems to me that rules and regulations and legislation will follow."

Koski, who takes up his new job next month, said that shoring up the protections for human subjects in research involves issues that "go well beyond conflict of interest." Proposals by HHS's Office of Inspector General for redesigning the entire system of protecting clinical research subjects "are very, very much on my mind," Koski said. "Individuals and institutions who fail to truly accept their responsibilities and work to achieve them," Koski said, "simply should not be permitted to engage in" clinical research. "More on that after Labor Day," he promised. But he clearly intends to take a tough line. **–BRUCE AGNEW**

Bruce Agnew lives in Bethesda, Maryland.

GENOMICS

Building a Case for Sequencing the Chimp

First came humans, then mice and, most recently, rats (see next story). And now, a motley queue of other vertebrates—including dogs, chickens, and pufferfish—has formed, each one vying to have its genome sequenced next on the limited budget of the National Human Genome Research Institute (NHGRI).

The most recent entrant is the chimpanzee. In a letter to *Science* on page 1295, an interdisciplinary group—which includes 26 geneticists, anthropologists, and molecular evolutionists—says top priority should be given to a primate. Their first choice is the chimp, whose genome is 98% identical to that of humans.

By finding those few critical genetic differences between humans and chimpanzees, geneticists hope to solve the mystery of what makes humans unique. Specifically, they want to find the genes that underlie the striking differences between humans and chimpanzees in cognition, reproductive biology, and behavior. "Until we understand how we differ genetically from our nearest relatives—the apes—we won't understand the genetic basis for being human," says Edwin McConkey, a molecular biologist at the University of Colorado, Boulder, and one of two co-authors of the letter. "The mouse genome will tell us why we are not mice, but it will never tell us why we are not apes."

The advocates, who include Nobel Prize winners Francis Crick of the Salk Institute and George Palade of the University of California, San Diego, also argue that identifying the differences in the DNA of chimps and humans should explain why humans but not chimps get diseases such as malaria and Alzheimer's, and why chimpanzees rarely get cancer and get a much milder form of HIV. Finally, the group writes that a chimpanzee genome project might raise public awareness of this endangered species.

Those arguments are already well known at NHGRI, where deputy director Elke Jordan says that the chimpanzee is "definitely a strong candidate" to have at least part of its genome sequenced. Jordan even sees a way to reduce the estimated $100 million cost, by focusing not on the entire genome but on areas of suspected differences between humans and chimpanzees. Still, the chimpanzee lobby is up against a host of other organisms. Notes Jordan: "There are all kinds of animals of great interest to somebody."

–ANN GIBBONS

GENOMICS

Rat Genome Off to An Early Start

Assuming that if two mammalian genomes are good, then three would be better, the National Human Genome Research Institute (NHGRI) has jump-started efforts to determine the order of the roughly 3 billion bases in the rat genome. The original plan had been to wait for funding, expected in fiscal year 2001 (*Science*, 26 May, p. 1317). Instead, two of the 10 centers involved in sequencing the mouse genome are now shifting to the rat. If the budget proposal passes, the National Heart, Lung, and Blood Institute (NHLBI) will kick in a total of $58 million, as planned, to be distributed in 2001 and 2002. During that time sequencers will produce a rough draft of the rat genome—in parallel with the rough draft of the mouse.

Having data from two rodent species should speed the discovery of genes and regulatory regions in the human genome and make it easier to determine their functions. Although the mouse is a favorite of geneticists, the rat has captivated physiologists for 150 years and is the animal most often used by pharmaceutical companies for preclinical testing of new drugs. Thus,

NHGRI VERTEBRATE SEQUENCING PROJECTS

Organism	Status
Human	Finished version by 2003
Mouse	Finished version in 3–5 years
Rat	Working draft in 2–3 years
Chicken	Pilot project
Pufferfish	Pilot project
Zebrafish	Pilot project
Primate	Under consideration