

Money Is Putting

By Lori B. Andrews

WHEN the Food and Drug Administration halted research into human-gene therapy at the University of Pennsylvania in January, after the death of a research subject, Jesse Gelsinger, administrators at universities across the United States took notice. If a research program at an Ivy League institution, run by a scientist as prominent as James M. Wilson, was being accused of serious breaches of law and ethical standards, what problems lurked in the growing number of studies at their own institutions? The Universities of Alabama, Colorado, and Illinois, as well as Duke and Virginia Commonwealth Universities, also have recently faced embarrassing public disclosures about their research programs. For example, federal regulators charged scientists at the University of Illinois at Chicago with failing to obtain subjects' informed consent in a study of an antipsychotic drug, and charged Duke's institutional review board with not monitoring continuing research.

Can other institutions stay out of trouble by giving researchers more education about their ethical and legal obligations? Or do we need radical new laws to remedy the situation?

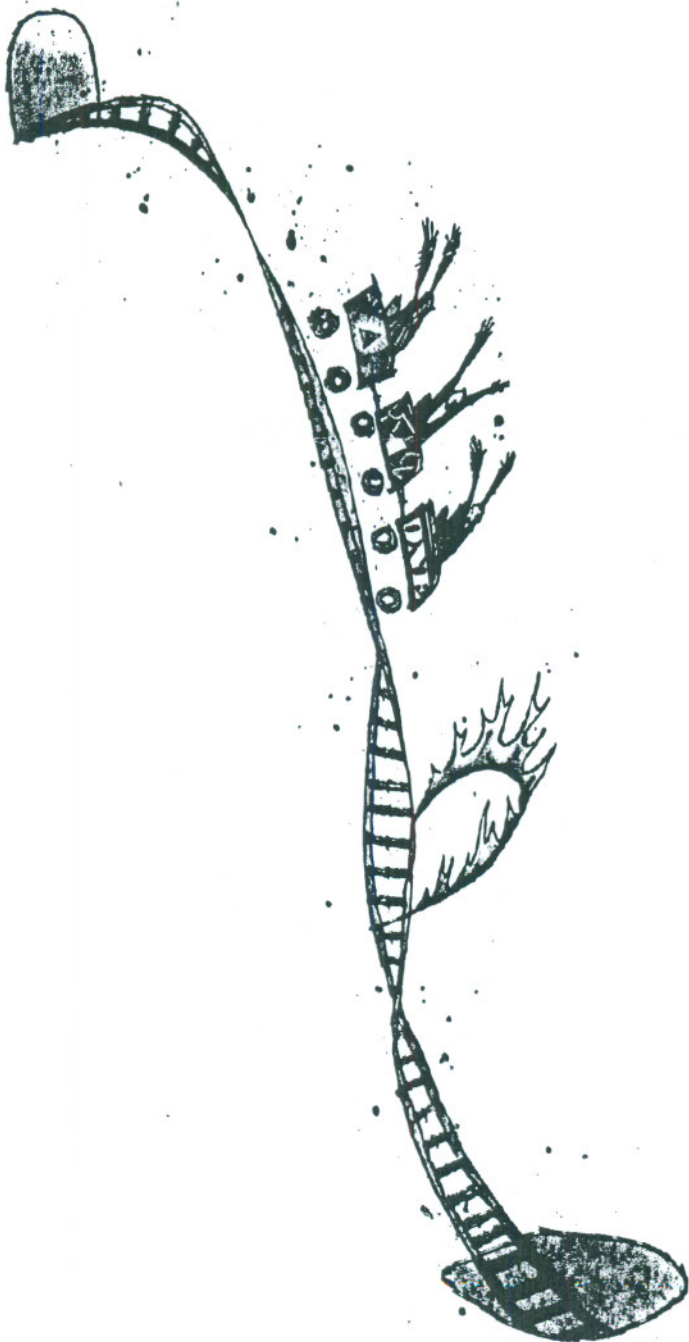
The number of research studies on campuses is soaring, and the potential risks for subjects are increasing. In the 1970's, as an undergraduate majoring in psychology, I earned either course credit or a few dollars by participating in studies in which the major risk was inconvenience or boredom. Now, healthy college students can earn upwards of \$2,000 for taking part in medical studies—but may face permanent harm.

The financial incentives for researchers are escalating, too. Last year, *The New York Times* reported that pharmaceutical companies often pay doctors handsomely—in some cases, \$1-million per year—for enrolling patients in studies. The results: Doctors from one field enroll their patients in drug trials in another field. For example, asthma specialists run studies on psychiatric medications. Patients who are not appropriate candidates for a study have received drugs for conditions they did not have, sometimes without even being told that the drugs were experimental. That not only subjected them to unnecessary risks, which is malpractice, but also compromised the study results.

Even \$1-million a year is small potatoes, though, in light of the incentives created for university researchers in the 1980's by the federal laws governing technology transfer. Before that time, research conducted at universities and supported by public funds belonged to the public. But the new laws give academic researchers intellectual-property rights; now they can, for example, patent a gene they discover or an invention they make, even if the entire enterprise has been financed by taxpayers through the National Institutes of Health or another federal agency.

Academic researchers can form biotech companies or enter into joint ventures with them. Penn's James Wilson, for example, founded a gene-therapy company. Many university biologists have become millionaires, with stock options and fees as directors of corporations far exceeding their university salaries.

Is it any wonder, then, that federal investigators from the Food and Drug Administration and the N.I.H.'s Office for Protection from Research Risks find that, even



COURTESY GRAMMER FOR THE CHRONICLE

People at Risk in Biomedical Research

though federal regulations require scientists to disclose the risks of participating in research to potential subjects, the researchers often underplay the risks and enroll inappropriate candidates? At Penn, the informed-consent form that Jesse Gelsinger signed did not disclose the fact that two monkeys had died after receiving the gene-therapy vector that he, too, was given. And researchers had accepted Gelsinger as a subject despite the fact that, according to the government, his liver function was not good enough to meet the study's criteria.

Other universities have covered up the risks of gene therapy in studies conducted on their campuses. Disregarding federal rules, researchers reported promptly to the N.I.H. only 39 of the 691 deaths and illnesses suffered by participants in gene-therapy research who had received the same vector as Gelsinger.

AT CONGRESSIONAL HEARINGS in February, sponsored by Sen. Bill Frist, a Republican from Tennessee, the testimony by federal regulators was disappointing. It sounded almost exactly like that of the biotech companies. Jay Siegel, of the F.D.A., pointed to the "potential for tremendous patient benefit" of gene therapy. He reported that "since the first human gene transfer in the late 1980's, human gene therapy products have become one of the fastest growing areas of product development."

Referring to "products" makes it seem as if valid gene therapies are being marketed already. In reality, gene therapy has been a dud—not one successful experiment has been reported in a peer-reviewed journal. Yet, thanks to hype by companies and regulators alike, 36 percent of the public, according to a survey conducted by the National Center for Genome Resources, thinks that gene-therapy treatments have already succeeded in curing human diseases. Research volunteers thus may not realize the preliminary nature of the experiments they have agreed to participate in.

The business perspective among researchers is even more obvious. As far back as September 1995, at a meeting at Stanford University on genetics research, faculty members and graduate students filled the auditorium when George Poste, of SmithKline Beecham, was speaking. But when Nancy Wexler, then chair of the N.I.H.-D.O.E. Working Group on the Ethical, Legal, and Social Implications of the Human Genome Project, took to the stage to discuss the risks to participants in genetic research, many members of the audience left. I overheard researchers in the hall discussing how to handle psychological risks—not to their subjects, but to the researchers themselves when there was a dip in the value of their biotech stock.

Whether the corporate mentality of many researchers is part of the reason for the abuses recently uncovered in research with human subjects, or whether investigators have simply become more aggressive, is an interesting question. It is clear, however, that the violations of the federal regulations protecting human subjects are serious.

According to the American Bar Association's Coordinating Group on Bioethics and the Law, between January 1997 and June 1999 the F.D.A. issued 36 warning letters to investigators undertaking research with

drugs, medical devices, and biological products. The reported violations are similar to those found by the Office for Protection from Research Risks for human research in general. They include failures to submit studies to an institutional review board, obtain informed consent, report adverse effects of the research, and determine the suitability of research subjects, as well as inappropriate promotion to solicit subjects' participation, and inadequate record-keeping.

The F.D.A. and the risk-protection office also found that some universities did not seem to be taking seriously the review of human-subjects research. Their I.R.B.'s had too few members for the volume of studies they were expected to review, and their researchers had inappropriately claimed that studies fell within regulatory exceptions and so did not need to be approved by the institution's I.R.B.

Administrators and researchers at many colleges and universities seem to think that they should be exempt from regulation because they work at nonprofit institutions. Yet human research subjects deserve protection no matter who is conducting the study. That is particularly true in an era when universities are acting more and more like businesses, even to the point of forming for-profit companies to commercialize their professors' research.

The University of Minnesota developed, manufactured, and sold an antirejection drug for use in transplants, making more than \$85-million. It was forced to stop marketing the drug when federal investigators found that the university had failed to get F.D.A. approval for the drug, and had not properly reported serious adverse reactions, including deaths. The government sued the university for allegedly selling an unlicensed drug, fraudulently billing Medicare for the drug, and submitting false grant applications—claiming that Minnesota was distributing the drug at cost rather than making a profit—to the N.I.H. The university settled the suit in 1998 for \$32-million.

The academics involved in the affair seemed to feel that they were above the law. An internal university report suggested that "cost recovery in any form is strictly illegal, but . . . when it is done on behalf of the University, the FDA probably will not take action."

WHAT CAN BE DONE to better protect the subjects of academic research? Individual colleges and universities need to put more resources—both people and money—into their institutional review boards. They need to do a better job of educating their employees about the federal regulations and state laws that govern human research.

Academe as a whole should also devote more effort to the question of I.R.B.'s. We need research on how well the system is working, mechanisms to evaluate the performance of individual boards, and new ways to reward faculty members who serve on I.R.B.'s—such as offering them release time from other duties, and counting I.R.B. service in promotion and tenure decisions.

Universities must also guard against conflicts of interest among members of I.R.B.'s. The risk-protection office found that some review-board members do not recuse themselves from voting when they have such conflicts. At Duke, both the director and the assistant

director of the medical center's Office of Grants and Contracts, which is responsible for bringing in grants had improperly served as voting members of the medical center's I.R.B.

The government needs to do a better job of monitoring research—including periodic reviews of I.R.B. files—and making available information about the risks involved. Serious side effects uncovered in studies paid for by industry are sometimes labeled proprietary information and—though they are reported to the F.D.A.—are not disclosed to the public. Such censorship should not be allowed.

The Department of Health and Human Services has not provided sufficient personnel or resources—in their Office of Biotechnology Activities, for example—to complete important public databases about research risks. Such data are crucial both to people's decisions about whether to participate in research, and to investigators' determinations about when research is too dangerous to continue.

More generally, Congress needs to reconsider the laws governing technology transfer. By trying to ensure that products are brought to market quickly, lawmakers have so commercialized academe that there are now few neutral scientists who can provide credible assessments of the risks and benefits of new medical developments. We should revise the laws so that academics and universities cannot profit from the sale of treatments created through research that the taxpayers have paid for.

The federal regulations developed in the mid-1970's for use by a kinder, gentler generation of researchers may be outdated now. Last August, the bar association's Coordinating Group on Bioethics and the Law initiated a major project to analyze the research abuses of the past three years. The group is assessing what proportion of abuses violate existing regulations, and what proportion could have been prevented only by new regulations. Many things have changed since the current federal regulations were adopted, including greater financial incentives for researchers, more and larger conflicts of interest, more research on tissue samples collected for other purposes, and greater risks to people's privacy when genetic information about them is obtained.

"When lives are at stake, and my son's life was at stake," Paul Gelsinger told Senator Frist and his colleagues in February, "money and fame should take a back seat. The concern should not be on getting to the finish line first, but on making sure no unnecessary risks are taken, no lives filled with potential and promise are lost forever, no more fathers lose their sons."

Academic researchers seem to be focusing on their new role as business people. Universities and regulators need to remind them of their obligations to their subjects and society.

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