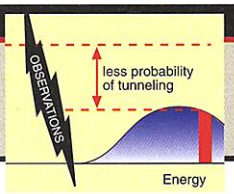

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BIOMEDICAL ETHICS

Penn Report, Agency Heads Home In on Clinical Research

In the 8 months since a teenager died in a gene therapy experiment at the University of Pennsylvania, clinical researchers have been on tenterhooks to learn what the consequences would be for Penn—and for national policy. Last week, they began to find out. Several federal agencies put forward proposals for sharply increasing the surveillance of human trials, especially those involving the use of viral carriers in gene therapy. And Penn, which has been in the hot seat for several investigations, announced a more rigorous system for approving and monitoring the use of human subjects that could add significantly to the cost of some types of academic research.

The most dramatic move was a decision by Penn president Judith Rodin to trim the sails of its Institute for Human Gene Therapy (IHGT). The institute, directed by James Wilson, will no longer conduct any clinical trials, but will focus on basic science and animal studies. IHGT's six active clinical protocols had already been put on hold by the Food and Drug Administration (FDA); their fate is unresolved. However, 12 outside-sponsored gene therapy trials that are still under way elsewhere at Penn will continue. Wilson, who received this news in his office as Rodin delivered it to the press on 24 May, issued a short statement referring to "my continuing role" as director and promising to "refocus our efforts in the preclinical area."

Rodin's comments came partly in response to the findings of an outside panel headed by William Danforth, former chancellor of Washington University in St. Louis. His seven-member group interviewed the IHGT staff and submitted its report on 27 April. The report studiously avoids issuing clear-cut findings of fault. Instead, it hints at its feelings through a series of questions. For example, it asks: "[Does it make] sense to have an entire institute devoted to gene therapy?" And in another section, the report observes that IHGT is a place where young investigators can administer potentially toxic viral vectors to patients almost like a new drug. It asks: "Are the risks well enough understood to promote widespread testing in inexperienced hands?" Without answering, the Danforth panel got across its message that administrative change was needed.

RESEARCH ON HUMAN SUBJECTS AT PENN

Research protocols on file	5600
Active protocols	3900
Full IRB review	2200
Tests of drugs and devices	1200
Sponsored and monitored by NIH/industry	1075
Sponsored and monitored by Penn	125
Monitored by contract	20
Est. cost of outside monitoring, small trial	$150,000
Gene therapy trials	20
By Institute for Human Gene Therapy (on hold)	8

Portfolio review. President Judith Rodin (*inset*) has ordered a stem-to-stern examination of how clinical trials are conducted at the University of Pennsylvania.

The report does make some explicit general recommendations, however. One is that Penn review its policies on conflict of interest, noting that "equity positions by an investigator and/or the university may be ill advised" because of the perception of a conflict, whether or not it is real. (Both Penn and Wilson had an equity stake in a company that supplied reagents for the clinical trial in question.) Most importantly, the report urges Penn to be as meticulous as industry in adhering to federal regulations, even to the point of hiring professional staff to ensure compliance.

Penn plans to follow that advice, Rodin says. Starting this year, it will ask all clinical researchers to submit a detailed safety monitoring plan that must be approved prior to the start of a new clinical trial. Ongoing trials will also get reviewed. Those posing a minimal risk to subjects will be handled by a new in-house office of five to 10 regulatory professionals. Those posing higher risk will be managed by an outside contractor. Penn is also allocating additional resources—including a new computerized data tracking system—to its Institutional Review Board, which clears protocols for ethical and safety concerns. In addition, the university will review its policies on conflicts of interest.

Rodin said the goal is "to meet the highest possible standards for academic excellence and patient safety and care." Provost Robert Barchi added that the extra cost of outside monitoring will in itself be "very significant"—about $100,000 to $200,000 for each small trial. "This is an important issue for clinical research nationally," he noted.

Responding to congressional concern about the same gene therapy trial, several federal agencies have also announced plans to boost surveillance of clinical research (*Science*, 26 May, p. 1315). On 25 May, William Raub, deputy assistant secretary for science policy of the Department of Health and Human Services (HHS), testified before the Senate's public health subcommittee, chaired by Senator William Frist (R–TN), along with officials from FDA and the National Institutes of Health (NIH).

Raub issued a long list of promises. HHS, he said, will soon propose guidelines asking its grantee institutions to audit clinical records and to make sure that research subjects have given proper consent. In a new requirement, clinicians will be asked to inform participants about any serious adverse events relevant to them and have them "reconfirm" their consent. NIH intends to ask clinicians to submit plans for monitoring the safety of smaller phase I and phase II plans, something not required in the past. New reporting requirements are being considered that would require sharing more data from ongoing trials with local review boards.

The witnesses also pledged changes in clinical research standards. This summer, NIH and FDA will sponsor a national dialogue on conflicts of interest. Raub said these discussions will lead to new guidelines on financial disclosure "which will apply to all NIH-funded research."

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The renewed attention to financial conflicts has already had an impact. Last week Harvard Medical School, which was considering a proposal to relax its strict limits on faculty members' involvement in outside commercial ventures, decided to table the proposal. In a 25 May memo to faculty explaining this decision, medical school dean Joseph Martin wrote, "I believe that the most important role academic medicine can have in clinical research today is to try to bolster the public's faith in the veracity and ethical underpinnings of this noble endeavor."

Frist was not impressed with HHS's efforts, however. He took the government officials to task for not moving more rapidly to increase surveillance and enforcement of clinical research rules. "I am very disappointed" with HHS's progress to date, Frist said, adding that "your response absolutely must be more comprehensive."

Even so, one intrepid witness—Savio Woo, president of the American Society of Human Gene Therapy in Milwaukee—offered a contrary view. He suggested that it would be unwise to rush forward with some new regulations and warned that doing so could have damaging consequences. By requiring even small clinical trials to be managed by someone other than the principal investigator, Woo said, the government could impose "excessive costs that will stifle academic clinical research." Innovative studies of rare diseases would be hit hardest, he added.

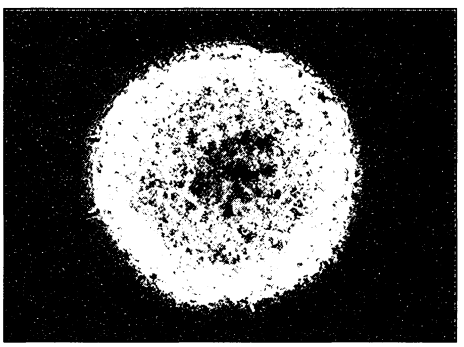
–ELIOT MARSHALL

DEVELOPMENT

Brain Cells Reveal Surprising Versatility

When a team of scientists reported last year that stem cells from the brains of adult mice could become functional blood cells, many scientists were intrigued, if a bit skeptical. Now, these versatile cells have shown even more surprising abilities: When injected into embryos, it seems, they can develop into nearly every type of tissue in the body. The work, described on page 1660, leaves a number of questions open. Even so, the cells' apparent flexibility is "amazing; it's really quite spectacular," says developmental biologist Janet Rossant of Mount Sinai Hospital in Toronto.

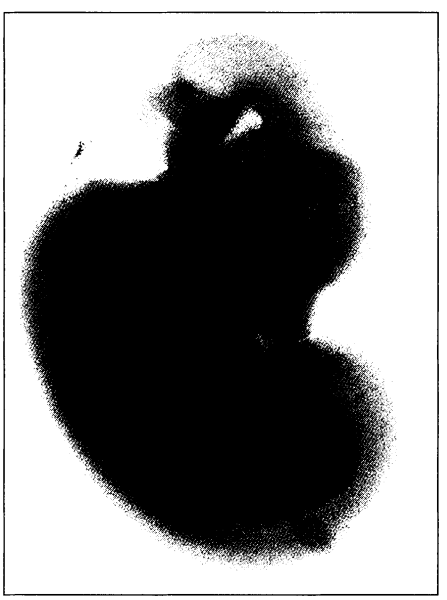
Scientists are amazed because decades of study had suggested that as development proceeds, cells become more and more specialized, and more restricted, in what they can do. According to widely accepted dogma, only embryonic stem (ES) cells, which are isolated before key differentiation steps occur, can become any tissue in the body. The latest results are another blow to that idea, showing that cells from adult animals are "able to revert into essentially ES cells" when they receive certain signals from the environment, says developmental neuroscientist Derek Van Der Kooy at the University of Toronto.



The findings may also have political implications. Because of the broad developmental potential of ES cells, researchers want to explore whether they can be used to provide replacement tissues for treating conditions such as spinal cord injuries, Parkinson's disease, and diabetes. But because human ES cells have to be taken from embryos, the U.S. Congress currently prohibits using federal funds to produce them. If certain molecular signals can indeed induce adult stem cells to develop into many different kinds of tissue, the work may fuel the arguments of the opponents of ES cell research who have testified that federal funding of human ES cell research is unnecessary, because cells from adults are equally promising. However, most scientists caution that the research on both adult and embryonic stem cells is too premature to compare the potential of the two.

Clues that adult stem cells might have wider abilities than expected began to accumulate last year, as researchers reported that mouse brain cells could become blood and cells taken from bone marrow could become muscle (*Science*, 25 February, p. 1418). Scientists have had trouble replicating some of these findings, and developmental neuroscientist Jonas Frisén and his colleagues at the Karolinska Institute in Stockholm decided to put adult stem cells to an even more rigorous test: to see if they could duplicate the characteristic feat of mouse ES cells, which can incorporate into another embryo and contribute to all the tissues of the resulting chimeric mouse.

Postdoctoral researcher Diana Clarke began by removing cells from the brains of adult mice and culturing them for about a week, to separate stem cells from fully differentiated cells, which die in culture. She and her colleagues then injected early mouse embryos either with neurospheres, aggregates of neural stem cells that form in culture from single cells, or with a group of dissociated cells, and allowed the embryos to develop until embryonic day 11. Because the researchers had derived the stem cells from mice that express a bacterial enzyme



Multitalented. When scientists inject stem cells *(left)* from the brains of adult mice into an early mouse embryo, their progeny (stained blue) contribute to nearly every tissue in the body.

called β-galactosidase, they were able to follow their fates by applying a sugar derivative that releases a blue dye when cut by the enzyme. The team found blue-stained descendents of the stem cells in various organs—including the heart, liver, intestine, and nervous system—in six of the 600 embryos injected with dissociated cells, and 11 of the 94 embryos injected with neurospheres.

They had even better success with a different model. Mouse ES cells can incorporate themselves into developing chicks, and when Clarke injected neurospheres into the

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