BIOMEDICINE

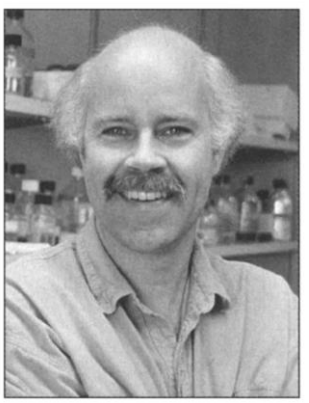
Gene Therapy on Trial

A flurry of reports and congressional hearings, sparked by the death of a volunteer in a study at Penn, are due in the next few weeks. The Penn episode points up a central problem: The field still lacks an ideal vector

Dusty Miller, a veteran gene therapy researcher, wants to test a new idea for treating cystic fibrosis. He has engineered a strain of virus to create a new "vector" to inject useful genes into cells. He has tested it in his lab at the Fred Hutchinson Cancer Research Center in Seattle, getting "wonderful" results in mice. Although he can't guarantee that it's safe for human use, he's confident that it is. Yet he's hesitating about testing it in patients, stretching out preliminary research while using an established but, he thinks, less efficient vector in volunteers. He's being supercautious, he says, because the "climate for gene therapy" has turned cold.

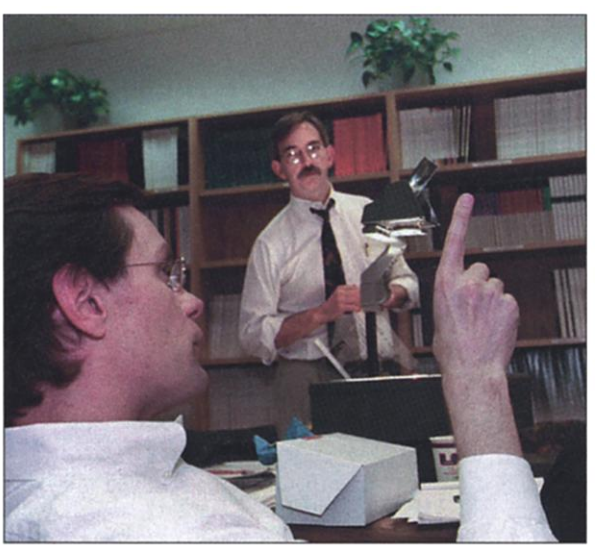
The chill set in on 17 September 1999. That's when Jesse Gelsinger, a young volunteer, died in a gene therapy trial at the University of Pennsylvania in Philadelphia, triggering a blitz of media and government attention. The Food and Drug Administration (FDA) has issued Penn a warning letter and shut down all clinical trials at Penn's Institute for Human Gene Therapy while it investigates what happened. The chill intensified last week when FDA made public a warning letter to cardiac specialist Jeffrey Isner of St. Elizabeth's Medical Center in Boston, alleging infractions of FDA rules in a gene therapy trial for heart disease in which one patient's cancer could have been exacerbated by the treatment and, FDA contends, a death was not properly reported. Isner's studies are now on hold. FDA also halted several other gene therapy trials around the country last winter while investigating vector toxicity.

And the climate is likely to become even more inhospitable over the next few weeks, when a blizzard of reports and hearings are expected. The Senate Health committee is planning a public hearing, its second on the Penn case. The House Commerce subcommittee on oversight and investigations has a probe under way; Penn, according to an official, has sent the committee "truckloads" of files, many of them demanded by Representative John Dingell (D–MI), the committee's fearsome inquisitor. The National Institutes of Health (NIH) has two groups looking into what happened. Penn is conducting two inquiries of its own: one led by its provost and another by an outside panel, due this week. In addition, Penn is concerned that Gelsinger's family may sue. Meanwhile, FDA and other agencies are scrutinizing gene therapy programs around the country. Miller, for example, says FDA inspectors have paid two surprise visits to his lab this year, demanding to see colleagues' lab notes.



Caution. Dusty Miller is delaying testing a new vector in today's chilly climate for gene therapy.

Public attention in this round of reports and investigations is likely to focus on who's to blame for errors, whether patients were adequately informed of the risks, and whether the tangle of relationships among companies, investigators, and institutions has created unacceptable conflicts of interest in the field (see sidebar, p. 954). Many clinicians fear that support for gene therapy will buckle under the onslaught.



In the spotlight. James Wilson (seated) and principal investigator in the OTC trial, Steven Raper.

At the scientific level, what happened at Penn holds two important lessons that are likely to get swamped in the publicity over the next few weeks. The first is the story of the vector James Wilson, director of Penn's gene therapy institute, and his team used: a patented version of a common respiratory tract virus—adenovirus—that had been stripped of certain genes to make it more innocuous. Researchers had once pinned their hopes on adenovirus vectors, believing they would overcome a basic problem that has dogged gene therapy since its inception: the difficulty of getting genes into target cells and, once there, getting the genes to express their proteins. Now some investigators think that, because of their inherent problems, adenovirus vectors may be limited to narrow uses. The problem is, every vector that has been investigated also has limitations (see sidebar, p. 953).

The second lesson involves the nature of clinical research itself. Although it's a shock when a patient dies in a toxicity test, says a clinician who has supervised many such trials, it is not unusual. "If you were to look in [a big company's] files for testing small-molecule drugs," he insists, "you'd find hundreds of deaths." Often, warning signs become clear only in retrospect, and many clinicians believe that's what happened in the Penn trial. Hints of toxicity had cropped up in previous experiments done by Wilson and others, but the Penn team may have been misled in one crucial respect by animal data that did not translate to humans.

But others suggest that clinicians at Penn should have been more sensitive to the risks, especially because they were injecting a potentially toxic vector into relatively healthy volunteers. "There were many places where this should have been stopped," says Huntington Willard, a molecular geneticist at Case Western Reserve University in Cleveland and a member of the American Society of Human Genetics board. Several leaders in the field have said that they knew that directly injecting the livers of volunteers with huge quantities of immunogenic viral particles (38 trillion at the highest dose) was risky. But they did not intervene, and the trial was given a green light by several local and federal agencies. Today, Willard sees "a very strong parallel" between a rush to the clinic in gene therapy and the space shuttle Challenger explosion. "It takes an event like that," he says, to let people see "just

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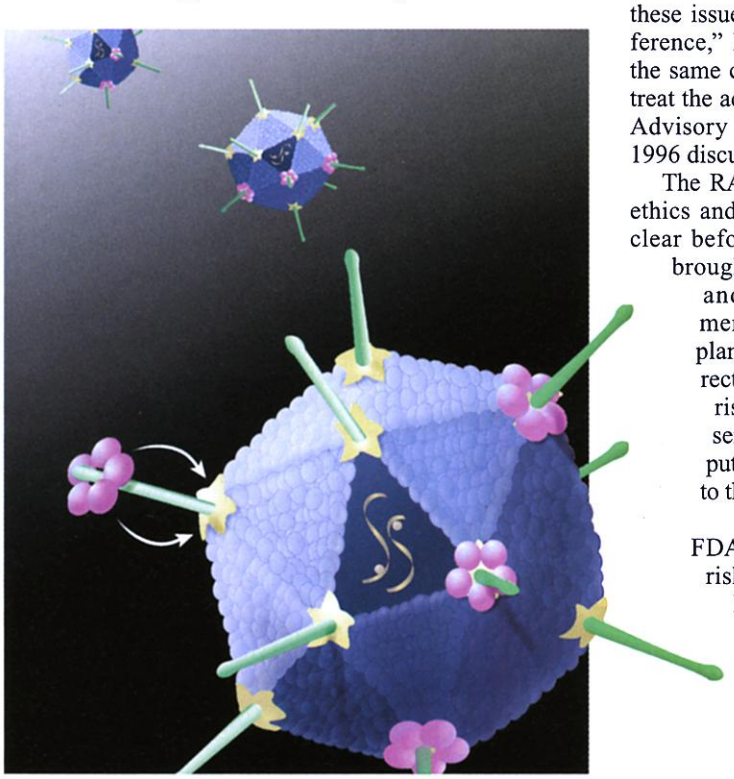
how dangerous some of this stuff really was." Willard concludes that "we need to take a much more sober view of where this field is going."

Design by committee

Regardless of what the critics think, says Arthur Caplan, director of Penn's Institute for Bioethics, people designed this gene therapy trial with the best intentions. He recalls how Mark Batshaw, a pediatrician at Penn in the early 1990s, now at Children's National Medical Center in Washington, D.C., wanted to save children born with a deadly liver problem. The disease occurs when a gene on the X chromosome is missing or defective, producing too little of a liver enzyme, ornithine transcarbamylase (OTC), that's needed to remove ammonia from the blood. Many infants become comatose at birth and die. Some with mild deficiencies—like Jesse Gelsinger—can survive if they keep to a strict diet and take compounds that help eliminate ammonia. But there's no substitute for natural OTC. And even mild deficiencies can be deadly. Gelsinger, for example, neglected his OTC regimen and nearly died in 1998. Caplan says Batshaw "was the pivotal guy" in Penn's OTC gene research: "He was tired of burying babies."



"Cannonball with spikes." The adenovirus capsid protein, which encases the genome, may trigger a powerful immune reaction at high doses, many researchers believe. It is essential for transporting genes into target cells.

Batshaw, Wilson, and a surgeon at Penn named Steven Raper, the principal investigator, devised a plan in 1994–95 to transfer healthy OTC genes into people who lack them. (Through a Penn spokesperson, Raper and Wilson declined to comment.) The objective, according to the protocol, was to develop "a safe recombinant adenovirus" that could infect the livers of patients and release OTC. Wilson's institute at Penn and the private company he founded had additional goals: to develop vectors for treating liver diseases and other illnesses.

The improved adenovirus vector developed at Penn seemed like a "wonder vector" back in 1995, Miller recalls. It was easy to grow, versatile, capable of infecting both dividing and nondividing cells, targeted the liver (as everyone assumed), and was quick to express genes in tissue. This vector was the right tool, Batshaw still argues: "Adenovirus is the only one that works rapidly enough, even now." He explains that whereas most other vectors take 3 to 6 weeks to begin working, adenovirus vector starts to express genes within 24 hours. This could be crucial for treating newborns with severe cases of the disease. You need quick action, he says, "if you're trying to get kids out of hyperammonemic coma" and prevent death or mental retardation. "Our plan was to use the adenovirus to get them out of coma; that would last for a few months," then go to second-stage gene therapy with a different vector—one problem with this vector is that gene expression is of limited duration—or possibly to liver transplantation.

But the plan changed when ethicists looked at it. Caplan, who was recruited to Penn shortly after Wilson, argued that it would be preferable to begin with adult volunteers because the trial was designed only to test toxicity. Later, infants could be enrolled. The initial subjects would have no chance of benefiting, in part because adenovirus vector can be given only once. It sets up an immune response that usually causes the body to eliminate the vector if it is used again. This meant that no one who took part in this trial could hope to benefit from adenovirus gene therapy at a later time. Even in ordinary circumstances, Caplan says, obtaining parental consent for experiments on children is "a problem." But it's especially tough "if you're trying to explain to parents in the middle of a crisis that you're only doing a safety study" that would not help a critically ill child. Caplan argued that it was "wrong to do nontherapeutic research on someone who cannot consent."

Batshaw and other OTC experts then took part in a meeting of the National Urea Cycle Disorders Foundation, run by parents of OTC children, to talk about these issues. "At the end of a 2-hour conference," Batshaw recalls, "they came to the same conclusion: It would be better to treat the adults." NIH's Recombinant DNA Advisory Committee (RAC) agreed in a 1996 discussion.

The RAC review was just one of many ethics and safety reviews the trial had to clear before it could begin. The process brought about several small changes and one double reversal. Some members of the RAC thought the plan to inject adenovirus vector directly into a hepatic artery was too risky. But the majority gave consent, provided that the vector was put in a peripheral vein. Penn agreed to this change.

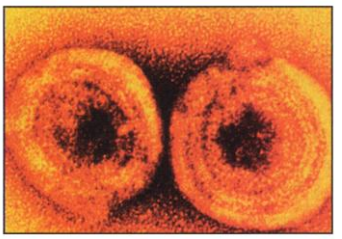
In 1997, safety reviewers at the FDA argued that it would be *less* risky to go directly into the liver. FDA at that time was worried that gene therapy experiments might alter human germ cells and pass risky genes to future generations. FDA's experts felt that by channeling the virus vector into the hepatic artery, it would be concentrated in one lobe of the liver, limiting overall exposure. Everyone assumed that adenovirus had a strong affinity for human liver cells and would be quickly concentrated in them. The Penn team agreed to go back to its original plan of inserting the vector directly into the hepatic artery. But Wilson neglected to inform RAC that it was taking FDA's advice. Wilson apologized to the RAC in December 1999.

Routine toxicology studies in mice, rhesus monkeys, and baboons were reassuring, Penn concluded, although they indicated toxicity at high doses. For example, early versions of the adenovirus vector plus OTC gene damaged the liver of rhesus monkeys, and monkeys given the highest doses died. The improved vector to be used in the clinical trial—from which a different viral gene was removed—appeared to be less toxic, although baboons still showed liver inflammation at high doses. The Penn team proposed using a maximum dose in humans that would be about 5% of the dose that produced maximal toxicity in nonhuman pri-

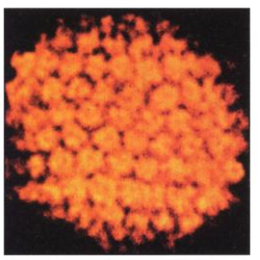
ILLUSTRATION: C. CAIN

Improving Gene Therapy's Tool Kit

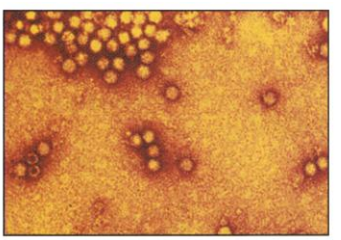
More than 4000 patients have been enrolled in gene transfer experiments over the last decade, but until now the research has produced few unambiguous results. Last month, a French research team announced the first clear success. Marina Cavazzana-Calvo and Alain Fischer of the Necker Hospital for Children in Paris reported that they had put a healthy gene into the bone marrow of two children with a rare, lethal immune disorder (SCID-X1), enabling the children to leave a protective bubble for the first time (*Science*, 28 April, p. 669). It was welcome news, adding substance to the promise that gene therapy will be used to cure genetic diseases. At the same time, however, it was a reminder of how difficult it has been to find ways of transferring genes into patients. The method used by the French team is one of the oldest in the tool kit, a "vector" based on a mouse virus. It is just one of many being developed, each with its own risks and advantages:



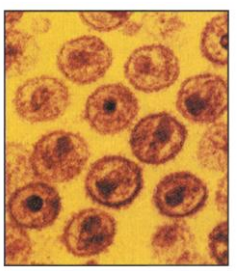
Retroviruses. The vector used to treat the SCID children in France was derived from the Moloney retrovirus (right), an RNA virus that infects mice. Because it inserts its genes into the host's genome, any genes artificially added to the vector are expressed for a long period. It is efficient and seems to produce no strong immune response, but it only works in cells that are actively dividing. Its other main disadvantage is that it integrates into DNA randomly. Gene therapists say there is a remote but real chance that if a retrovirus landed in the wrong location, it might promote cancer.



Adenovirus. Many vectors based on this "cannonball with spikes," as one expert calls it, are being developed for gene therapy. A common DNA virus that infects the human respiratory tract and eyes, it was the basis for the vector used to treat a liver enzyme deficiency at the University of Pennsylvania. Adenovirus is easy to grow in the lab, and it readily infects both dividing and nondividing cells, expressing genes without inserting itself into the host cell's genome or posing a risk of cancer. But adenovirus proteins stimulate strong immune reactions that clear the vector from the body, making it ineffective for long-term therapy. High doses may be required to transfer enough genes to produce a health benefit. But high doses also can produce powerful toxic reactions when given intravenously, as Penn's researchers discovered.



Adeno-associated virus (AAV). This parvovirus is nearly invisible to the human immune system and readily infects human dividing and nondividing cells. It requires a "helper," adenovirus, to replicate, and when it integrates into host DNA it does so at a known and apparently safe location. It has some disadvantages: It's more difficult to grow to high concentrations than adenovirus, and it has a small genome, restricting the amount of therapeutic DNA it can carry. Researchers Mark Kay of Stanford University and Katherine High of the Children's Hospital of Philadelphia recently used this vector to transfer genes for a blood clotting protein (factor IX) into patients with hemophilia B. Two patients in the first cohort of a safety trial appeared to improve, and dogs lacking factor IX have shown benefits for as long as 2 years. In addition, Kay has developed a technique that may double AAV's gene-carrying capacity.



Lentiviruses. These slow-growing retroviruses are promising candidates for vectors, according to one champion, gene therapy researcher Inder Verma of the Salk Institute in La Jolla, California. He likes their "unique advantage of introducing genes into dividing and nondividing cells" and their ability to survive without producing a strong immune reaction in the host. The AIDS virus belongs to this family. And despite its fearful origins, Verma is convinced that HIV (right) can be tamed to create a useful vector for gene therapy, although clinical trials may be a long way off. Herpes simplex virus is another candidate in this family, prized because it can infect nervous system cells, which are resistant to other vectors.

–E.M.

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mates. And they proposed climbing toward that level in five threefold increases, with each step involving three patients.

Satisfied with Penn's plan and responses to queries, FDA gave the trial a green light in 1997. The first of 18 volunteers, a woman, was given a 2-hour infusion of vector with OTC genes on 7 April 1997. Most patients experienced fever and other moderate symptoms. The 10th and 12th patients exhibited signs of liver stress, with liver enzymes in serum higher than the normal upper limit (8 and 5.3 times higher, respectively). FDA later reprimanded Wilson's team for failing to pause and consult FDA by phone at this point. The trial proceeded "like a train," says one outside clinician, until it was halted abruptly on 17 September 1999 when Gelsinger, the 18th patient, died.

Surprising toxicity

After Gelsinger's death, Wilson led scores of researchers in a months-long search for a cause. As possibilities were eliminated, the Penn clinicians were left with one conclusion: Gelsinger died from a massive immune response to the adenovirus vector itself.

The "most unexpected finding" in the postmortem, Raper said at a RAC meeting in December 1999, was that precursors for red blood cells in the boy's bone marrow had been wiped out. The Penn team concluded that this probably did not happen in the short 4-day period of gene therapy. Raper and Wilson speculated at the RAC meeting that a preexisting parvovirus infection might have done the damage. In addition, Batshaw notes, it's possible Gelsinger had inherited a mutation that caused an exaggerated response to adenovirus. But no evidence for either theory has been found. The blood cell problem remains unexplained but appears not to have been the cause of death.

Wilson and Raper also noted that Gelsinger's blood contained high and sustained levels of interleukin-6 (IL-6), a cell signaling protein (cytokine). Even now, researchers don't understand why it was so high, but they do know that IL-6 often surges after an insult to the body, contributing to inflammation. Raper called it "an immune revolt." A systemic inflammation flooded Gelsinger's lungs with fluid, causing acute respiratory failure and death.

Vector designers have long known that adenovirus triggers an immune response, but for gene therapy trials, they have taken out some of its genes in an attempt to reduce its immuno-

genicity. Wilson and Ronald Crystal at the New York Hospital–Cornell Medical School in New York City, among others, have patented forms of adenovirus with bits of the genome removed. For the OTC trial, Wilson used a 1996 version of the vector with two key genes deleted.

Some researchers—such as Art Beaudet of Baylor College of Medicine in Houston and Inder Verma of the Salk Institute in La Jolla, California—say there were warning signs that vectors containing any active adenovirus genes were risky and could cause inflammation. The most dramatic early sign came in a 1993 gene therapy trial conducted by Crystal. He was using an early adenovirus vector to inject healthy genes into the lungs of cystic fibrosis patients. During the experiment, a subject known as "patient number three" developed a severe inflammatory reaction, including a rapid increase in IL-6. Crystal reported later that he saw patients' IL-6 levels rise in serum "within 2 to 4 hours after vector administration," and that the peak IL-6 "correlated well" with vector dose. Crystal felt that the inflammation had not been caused by adenovirus itself but by the large volume of fluid used to deliver it. Animal studies had not warned of this possibility, he wrote: It "was a surprise."

Some see a parallel with Gelsinger's reaction: "The patient had high IL-6 levels in plasma, the whole syndrome, including a single-lobe ARDS [adult respiratory distress syndrome]," the proximate cause of Gelsinger's death, says one clinician. The patterns, he says, are "similar." Beaudet, who saw a baboon die of adenovirus toxicity in a preclinical study, also sees a similarity.

But Crystal does not think the 1993 and 1999 cases are comparable. In a RAC meeting last December, he said the inflammation in 1993 was the only serious adverse event attributable to adenovirus in his team's "140 administrations of vector." It occurred "when we were using a larger volume to administer the vector to the bronchi" and a primitive vector containing more viral genes.

Crystal wasn't the only one, however, to report an inflammatory response. Among others, Richard Boucher of the University of North Carolina, Chapel Hill, also ran into the problem in 1994–95 while treating cystic fibrosis patients. He abruptly stopped the trial. "We had two concerns," Boucher recalls. One was that adenovirus "just didn't work," because "it didn't get in" to the targeted cells. And second, "if you pushed [the dose] you got into troubles from flat-out protein load." The North Carolina group followed up with animal studies and concluded that adenovirus vector was stimulating nerve fibers in the epithelium and triggering an inflammatory response. Boucher concluded in 1995 that "it was a capsid protein problem"—a reaction caused by the virus's outer shell—and sent his findings to FDA and published them.

An expert who followed these results, speaking on background, says: "In retrospect, we really should have learned more" from Crystal's experience. "We knew this stuff was toxic back in 1993" for use in the lung. "Why did we think that a damaged liver would be any different?" But, although cytokine release may seem important now, this expert still doesn't think it points to a "clear answer." It only suggests that, "in some people, you get a whopping cytokine response." Robert Warren, an oncologist at the University of California, San Francisco, pointed out at the December RAC meeting that he gave 25 cancer patients adenovirus vector doses nearly as large as the one given to Gelsinger, "and we have not seen anything close to this problem." However, several patients did have other serious adverse reactions, including loss of blood pressure.

The Penn team was taken aback by the lung inflammation, but in view of that reaction, it was astonished to see little liver damage. Relying on mouse studies, they had expected to see adenovirus concentrated in the liver. Instead, as a postmortem revealed, the vector was everywhere. To figure out what happened, Wilson gave the vector intravenously to mice. Tagged adenovirus vector

Gene Therapy's Web of Corporate Connections

Mark Kay, a researcher at Stanford University who has chalked up several recent triumphs in gene therapy, says there was a time when he advised patients directly about enrolling in his studies of hemophilia B. But not any more. Because he is on the scientific board of a company backing this research—Avigen of Alameda, California—he says he keeps an arm's length from clinical work. He lets others who have no stake in the business handle patients. "I still give talks," he says, "but I always mention that I am on Avigen's board and that I get remuneration for this."

Welcome to the new world of genetic medicine. Researchers in gene therapy have become extremely sensitive about perceived conflicts between their financial and scientific portfolios, following the death last year of a volunteer in a clinical trial at the University of Pennsylvania's Institute for Human Gene Therapy (see main text). The trial used a technique for inserting genes into cells that was developed and patented by the institute's head, James Wilson. Wilson and Penn itself have a financial stake in a company Wilson founded to develop the technology.

Wilson's business connections are not unusual. Company sponsorship is pervasive in gene therapy—and for good reason, according to Ronald Crystal, another pioneer in the field, now at the New York Hospital–Cornell Medical School in New York City. Crystal, who developed early cystic fibrosis treatments, says that scientists had to turn to private investors because the clinical tools they need are "very expensive" to develop and were not likely to be funded by National Institutes of Health (NIH) grants.

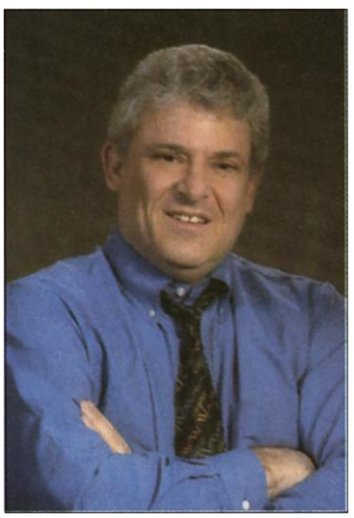
Indeed, W. French Anderson, the former NIH scientist who filed one of the first applications to perform a clinical trial in gene therapy and who also holds one of the first broad patents in the field, left NIH to pursue this research. In 1987 Anderson helped launch one of the first companies in the field, Gene Therapy Inc. of Gaithersburg, Maryland. By seeking private money, researchers "flipped the whole paradigm of drug development on its head," Crystal says: It put academic clinicians in charge of developing their own medical products—not just testing products created by others. "We are playing the role of a pharmaceutical company."

Crystal holds patents on many gene therapy inventions. He, too, founded a company: GenVec of Gaithersburg, Maryland, which exploits his discoveries under license agreements. In return, GenVec helps pay for Crystal's studies at the New York Hospital. Data from Crystal's efforts to grow new blood vessels in patients with heart disease, for example, are featured in GenVec's press releases. But Crystal says that, to avoid conflicts, he does not get directly involved in patient care. Nevertheless, his dual roles as clinician and businessman recently drew press attention, because he asked the government not to disclose a report he filed on deaths that had occurred among his patients. Crystal and outside reviewers had concluded that the deaths were caused by the patients' underlying disease, not gene therapy. Crystal's request, which was not honored, did not violate federal guidelines.

It was the Penn case, however, that brought potential conflicts of interest to the fore. Like other leaders in the field, Wilson holds patents on several gene therapy delivery techniques, one jointly with Francis Collins, director of the National Human Genome Re-

first appeared in macrophage or scavenger cells in the liver, called Kupffer's cells (which secrete IL-6). Later, it reached the intended target, primary liver cells (hepatocytes). This "may not be a good thing," Wilson said at the RAC meeting in December, because low doses of vector might not put enough OTC genes into hepatocytes, and high doses might saturate nontarget organs. This might explain the low gene transfer rate (less than 1%).

Animal data may have given clinicians false hope that adenovirus would work well in the human liver. A key docking site adenovirus uses to enter a cell, known as the Coxsackie adenovirus receptor (CAR), is much more abundant in mouse livers than in human livers. In fact, "rodent models might be misleading" for gene therapy, says Jeffrey Bergelson of the Children's Hospital of Philadelphia. Again, the warning signs were there before Gelsinger entered the Penn experiment but may have become obvious only in retrospect. Bergelson published a paper in 1998, a year after the trial began, reporting that he found "barely detectable" signs of CAR in human liver, while signs of CAR were "off the wall" in mouse liver. One implication, Bergelson notes, is that clinicians relying on the mouse model may find it necessary "to give higher and higher doses" to deliver genes to the human liver.



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A mortal blow for adenovirus?

Expert opinion is divided on whether the tragic events at Penn should spell the end of the once-promising adenovirus vector for treating genetic diseases. The key question is whether the virus can be re-engineered to eliminate the immune response.

Researchers have been trying for more than a decade to create a tamer adenovirus. The virus is shaped like an icosohedral box studded with "penton" bases that support long fibers—described by FDA gene therapy specialist Philip Noguchi as "a cannonball with spikes." The box, or capsid, shields the genome. Modifications such as those used by Wilson and Crystal have focused on editing out key bits of DNA inside the capsid that are expressed early during infection of a cell, genes labeled E1 through E4, which trigger immune reactions. The goal is to make the vector as stealthy as possible. The fewer viral proteins the immune system "sees," the less likely it will attack. And the longer the vector survives, the better its chances of delivering therapeutic genes.

For the OTC trial, Wilson used a version with E1 and E4 genes deleted. In his cystic fibrosis trials, Crystal has used a version with E1 and E3 deleted, which he claims can even be given safely in repeat doses. Since switching to an inhaled spray containing this new vector, Crystal says, "we have had no significant serious toxicities."

Some scientists have also attempted to create fully "gutless" vectors by hollowing out all viral genes and replacing them with substitutes. They include Jeffrey Chamberlain at the University of Michigan, Ann Arbor, Beaudet and Larry Chan at Baylor, and a group at Merck in Whitehouse Station, New Jersey, under former executive Thomas Caskey. Beaudet and Caskey say researchers in their labs have observed virtually no toxicity when their gutless vector is given to mice at high doses. However, it is hard to eliminate contamination by live "helper" virus and to produce high-concentration batches.

High doses may still be required to produce a clinical benefit, and, as Boucher suggested in 1995, high doses may run into toxicity from capsid proteins. Wilson suggested as much in the December RAC meeting, and Noguchi and FDA toxicologist Anne Pilaro have raised this possibility in several meetings. So has Salk's Verma.

search Institute. And in 1992, Wilson founded a company—Genovo of Sharon Hill, Pennsylvania—which has R&D agreements with two larger companies, Biogen Inc. and Genzyme, both in Cambridge, Massachusetts. Genovo uses some of the revenue from these deals to help support Penn's gene therapy institute, reportedly providing about $4 million a year. The institute, which has a budget of about $25 million, also receives federal grants and other revenue. Penn's guidelines do not allow faculty members to hold an executive position in an outside business such as this. But Wilson, an unpaid consultant to Genovo, holds equity in the company, as does Penn.

News reports have spotlighted an apparent conflict between Wilson's and Penn's responsibility to give primary attention to the needs of patients and their obligation to provide data to corporate sponsors. The gene therapy trial in which the patient died was not expected to benefit the enrolled patients, but it had a good chance of developing information that could improve the prospects of Genovo. Although Wilson was involved, his connection to Genovo apparently did not violate university or NIH guidelines on conflict of interest because Wilson was not directly involved in the recruitment or care of patients in the clinical trial, nor did Genovo finance the trial. Arthur Caplan, director of Penn's Institute for Bioethics, says Wilson was just "the vector supplier," and it is "irresponsible" to suggest he was influenced by financial interest. (Wilson declined to comment through a Penn spokesperson, who also declined to respond to questions about the university's policies submitted by fax.)

It is "irresponsible" to suggest that Wilson was influenced by financial interest.

—Arthur Caplan

The furor over this case prompted the American Society of Gene Therapy, of which Wilson was president in 1999, to issue a statement on conflicts of interest in April. It essentially echoes the NIH guidelines. It says that members who are "directly responsible for patient selection, the informed consent process and/or clinical management in a trial must not have equity, stock options or comparable arrangements in companies sponsoring the trial." Crystal supports it, saying, "we already had that in place" in his clinic. Anderson, likewise, says he has followed this rule in all 16 clinical trials he's been involved in.

The American Society of Human Genetics (ASHG)—whose membership is less directly involved in gene therapy—also issued a statement in April calling for caution in gene therapy. But it stopped short of ruling on conflicts of interest. ASHG president Ron Worton of Ottawa Hospital Research Institute says: "We debated ... a ban on recruitment of patients by physicians who have a financial interest," but board members didn't want to take that step, arguing that "this is something traditionally policed by the universities." But, as the Penn case illustrates, universities themselves may have potential conflicts to be policed. **–E.M.**

ma, who co-authored a 1998 study of adenovirus vector that called for a "reevaluation" of its use in long-term gene therapy.

Recently, FDA staffers heard from another scientist who concluded 5 years ago that adenovirus capsid protein toxicity was a problem: Prem Seth, senior scientist at the Human Gene Therapy Research Institute in Des Moines, Iowa. Based on studies he did in the mid-1990s, he concluded that "empty capsids appear to be immunogenic, like intact virus," and produce similar effects, like cytokine release. He never published the data, because "there wasn't much interest."

This analysis suggests that even gutless vectors may be dangerous in some circumstances, but the jury is not in. "It's still debatable," says Chamberlain. Beaudet agrees: "Based on our published mouse data," he says, "we think the capsid proteins are not a big problem." But he concedes that there are "not convincing data yet" from nonhuman primates to settle the issue.

As far as Noguchi is concerned, "the most critical issue for the field right now" is determining the risk of these new, "safe" vectors. "Are there two types of toxicity with adenovirus or just one?" he asks. Is the shell itself a problem, in addition to viral gene expression? "What is its inherent toxicity? Is this the dose-limiting thing? We need to rethink these hard questions."

For many people in the field, however, the critical question over the next few months is whether they will be able to continue gene therapy trials while everyone rethinks these questions.

–ELIOT MARSHALL

SCIENTIFIC COMMUNITY

National Academy of Sciences Elects New Members

The National Academy of Sciences last week elected 60 new members and 15 foreign associates. More details are available at national-academies.org/nas

Newly elected members and their affiliations at the time of election are:

Alexei A. Abrikosov, Argonne National Laboratory, Argonne, Illinois; **Peter C. Agre**, Johns Hopkins University; **J. Roger P. Angel**, University of Arizona, Tucson; **Marsha J. Berger**, New York University; **Howard Brenner**, Massachusetts Institute of Technology (MIT), Cambridge; **Steven P. Briggs**, Novartis Agribusiness Discovery Unit, San Diego; **Robert L. Byer**, Stanford University, Stanford, California; **Moses H. W. Chan**, Pennsylvania State University, University Park; **Rita R. Colwell**, National Science Foundation, Arlington, Virginia; **Eric A. Cornell**, National Institute of Standards and Technology and University of Colorado, Boulder; **Robert J. Cousins**, University of Florida, Gainesville; **Francis A. Dahlen Jr.**, Princeton University; **Jack E. Dixon**, University of Michigan Medical School, Ann Arbor; **Kenneth B. Eisenthal**, Columbia University, New York; **Stanley Fields**, Howard Hughes Medical Institute (HHMI) and University of Washington, Seattle; **Jean M. J. Frechet**, University of California (UC), Berkeley; **Lila R. Gleitman**, University of Pennsylvania; **Sen-Itiroh Hakomori**, Pacific Northwest Research Institute and University of Washington, Seattle; **Susan E. Hanson**, Clark University, Worcester, Massachusetts; **Martha P. Haynes**, Cornell University, Ithaca, New York; **Arthur M. Jaffe**, Harvard University; **Charles A. Janeway Jr.**, HHMI and Yale University; **William A. Jury**, UC Riverside; **Jon H. Kaas**, Vanderbilt University; **Thomas Kailath**, Stanford University; **James P. Kennett**, UC Santa Barbara; **Richard D. Kolodner**, UC San Diego; **Robert H. Kraichnan**, Robert H. Kraichnan Inc., Santa Fe, New Mexico; **Simon A. Levin**, Princeton University; **Roderick MacKinnon**, HHMI and Rockefeller University, New York City; **Robert W. Mahley**, UC San Francisco and Gladstone Foundation, San Francisco; **Joan Massague**, HHMI and Memorial Sloan-Kettering Cancer Center; **Barbara J. Meyer**, HHMI and UC Berkeley; **Jacob Mincer**, Columbia University; **Michael E. Moseley**, University of Florida, Gainesville; **William T. Newsome III**, HHMI and Stanford University; **David R. Nygren**, Lawrence Berkeley National Laboratory, Berkeley, California; **Eric N. Olson**, University of Texas Southwestern Medical Center, Dallas; **Peter Palese**, Mount Sinai School of Medicine, New York City; **Jeffrey D. Palmer**, Indiana University, Bloomington; **George C. Papanicolaou**, Stanford University; **Walter C. Pitman III**, Columbia University; **Alejandro Portes**, Princeton University; **Akkihebal R. Ravishankara**, National Oceanic and Atmospheric Administration, Boulder, Colorado; **Douglas C. Rees**, HHMI and California Institute of Technology, Pasadena; **Kenneth A. Ribet**, UC Berkeley; **Richard H. Scheller**, HHMI and Stanford University; **Joseph Schlessinger**, New York University Medical Center; **Eric M. Shooter**, Stanford University; **Robert M. Silverstein**, State University of New York, Syracuse; **Sean C. Solomon**, Carnegie Institution of Washington, Washington, D.C.; **Peter J. Stang**, University of Utah, Salt Lake City; **Leonard Susskind**, Stanford University; **Leslie G. Ungerleider**; National Institute of Mental Health, Bethesda, Maryland; **Grace Wahba**, University of Wisconsin, Madison; **Robert H. Waterston**, Washington University, St. Louis; **Rainer Weiss**, MIT; **Michael J. Welsh**, HHMI and University of Iowa, Iowa City; **Tim D. White**, Cleveland Museum of Natural History and UC Berkeley; **Reed B. Wickner**, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland.

Newly elected foreign associates, their affiliations at the time of election, and their country of citizenship are:

Simon K. Donaldson, Imperial College of Science, Technology, and Medicine, University of London (U.K.); **Reinhard Genzel**, Max Planck Institute for Extraterrestrial Physics, Garching (Germany); **Shirley Jeffrey**, Commonwealth Scientific and Industrial Research Organization, Hobart (Australia); **Yoshito Kaziro**, Tokyo Institute of Technology, Yokohama (Japan); **Willem J. M. Levelt**, Nijmegen University and Max Planck Institute for Psycholinguistics, Nijmegen (Netherlands); **Shigetada Nakanishi**, Kyoto University (Japan); **Roddam Narasimha**, National Institute of Advanced Studies, Indian Institute of Science, and Jawaharlal Nehru Center for Advanced Scientific Research, Bangalore (India); **Eviatar Nevo**, University of Haifa (Israel); **Armando J. Parodi**, University of Buenos Aires (Argentina); **A. M. Celal Sengor**, Istanbul Technical University, Istanbul (Turkey); **Nicholas J. Shackleton**, University of Cambridge and Godwin Institute for Quaternary Research, Cambridge (U.K.); **T. N. Srinivasan**, Yale University (India); **Bruce W. Stillman**, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York (Australia); **Akira Tonomura**, Hitachi Ltd., Saitama (Japan); **Martinus Veltman**, University of Michigan, Ann Arbor (Netherlands).