Gene therapy trials shut down at University of Pennsylvania following patient death

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The promising field of gene therapy was rocked by the September 17, 1999 death of 18-year-old patient Jesse Gelsinger. Gelsinger had volunteered to participate in a gene therapy trial for the rare genetic disease ornithine transcarbamylase deficiency (OTC) at the Institute for Human Gene Therapy at the University of Pennsylvania in Philadelphia (Penn). On January 21 the federal Food and Drug Administration (FDA) shut down all gene therapy trials at the institute.

OTC occurs because the patient is born with a liver unable to rid the body of the ammonia created during metabolism. Untreated, the condition can rapidly lead to coma and death. The current treatment is a special diet and medication. At the time, Gelsinger's death was believed to be the first of a patient in a gene therapy trial.

Gene therapy is a 10-year-old field which holds the promise of finding cures for many types of disease. It is part of the biological revolution going on in all of the life sciences where scientists are on the verge of gaining control of the very mechanism by which all life forms reproduce. The origins of this revolution date to the early 1950s when James Watson and Francis Crick uncovered the structure of DNA. The next advances were the cracking of the genetic code in the 1960s and the discovery of restriction enzymes in the 1970s, which enabled researchers to isolate specific genes from DNA and begin to develop gene-splicing technology. In the 1980s, research began in gene transfer systems to find ways to deliver the altered genes into organisms.

In addition to genetic disorders, gene therapy holds promise for making advances against many forms of cancer, AIDS, and blood and heart disorders. This would be done by supplying the patient with cells that have healthy copies of missing or flawed genes. Instead of the patient taking drugs to control or treat symptoms of a disorder, scientists would attempt to alter the gene makeup of the patient's defective cells to correct a genetic or other deficiency.

One method takes cells from the blood or bone marrow of the patient which are then grown in the laboratory under conditions which cause them to multiply. The desired gene is then inserted into the nucleus of cells with the help of a disabled virus. The altered cells are selected out, encouraged to multiply, and then returned to the patient's body. In some cases, disabled viruses are used to deliver the gene directly to nuclei of cells in the patient's body.

In the case of Jesse Gelsinger, the gene therapy trial was an ongoing two-year trial. He began the trial on his eighteenth birthday, the day he became eligible to participate. His liver was infused with trillions of genetically disabled cold viruses containing the corrected OTC genes. The viruses, which were to be the delivery vehicle for the needed gene, caused "an immune system revolt," leading Gelsinger's immune system to go into overdrive and begin attacking his lungs and vital organs. He died four days after the trial began. The exact cause of his death is not understood.

On January 21, after a three-month study, the FDA shut down all gene therapy trials at the Institute for Human Gene Therapy. The institute is one of the largest academic gene therapy centers in the world, with an annual budget of $25 million, a staff of 180, and links to many private biotechnology companies. The FDA said they found numerous violations of federal research regulations and shortcomings in the protection of human subjects at the Institute.

In closing down eight active or pending gene therapy studies at the institute, the FDA found 18 specific violations of FDA rules and regulations in the OTC trial. It found the institute had admitted 18 patients into the study of which Gelsinger was a part without documenting that any fit the eligibility requirements for the study. It found some should not have participated because they were too sick. The FDA suspension affects studies involving cystic fibrosis, lung cancer, melanoma, breast cancer, muscular dystrophy and brain cancer.

The FDA also found that patients in the OTC study had not been properly informed of the risks involved in the trial. These procedures for patient consent have developed as a result of the ethical questions raised by such experiences as the Nazis' medical experiments during World War II and the Tuskegee experiment in which African-American men were purposely denied medical treatment for syphilis for decades.

The FDA found that the Institute consent form had been altered to eliminate mention that monkeys had died in similar tests and the FDA had not been immediately informed of this development. The forms for half the patients were not properly signed and did not disclose that four previous volunteers had suffered serious side effects. Nor had the Institute properly monitored the health of volunteers after the experiment began, and it lost track of several lots of the experimental genes that had been infused into patients' livers.

The FDA raised questions about the institute's, and its key researcher James Wilson's, ties to the biotechnology industry. Wilson is considered one of the world's leading gene therapy researchers and was involved in all eight gene therapy trials. A former president of the American Society for Gene Therapy, Wilson founded Genovo Inc., a suburban Philadelphia company, and both he and the university own stock in the company.

The company and its corporate sponsor, Biogen, contributed one-fifth of the institute's annual budget, and in return have exclusive rights to develop the institute's discoveries into commercial products. Trials funded by private companies do not have to obey federal guidelines if the patient does not use facilities receiving federal funds. As a result, companies can tailor information released to the public not only to hide information from corporate competitors but to publicize good news, while keeping bad news as a "trade secret", in order to encourage stock holder investment in the company.

When gene therapy trials began in the early 1990s, they were under stricter federal regulation than those for pharmaceutical research because of the risks involved. Since the first trial, about 4,000 patients have taken part in some 400 gene therapy trials, most treating patients with terminal cancer. Unlike basic drug research which the FDA supervises in private to protect "company secrets" from other pharmaceutical companies, federally funded gene therapy is overseen by a committee at the National Institutes

of Health whose activities were open to public scrutiny. Three years ago, in a controversial move, the NIH cut back its oversight due to pleas by desperate victims for a speed-up in research and complaints about restrictions from the biotechnology industry. Until Gelsinger's death, the industry had been agitating for even less scrutiny. Increasingly, the agency had relied on scientists themselves to follow the rules they had agreed to.

In the last 20 years the genetic revolution has brought ever closer ties between medical schools and biotech corporations. Academic scientists who do not have ties to the industry are now very rare. The trend began in 1980 with the passage of the Bayh-Dole Act by Congress. This law was designed to speed up commercialization of academic discoveries by encouraging universities to patent inventions and then reassign those patents to private companies that could develop them as products. Many scientists raised their own venture capital and started their own companies and now have a financial stake in the companies testing their discoveries. Some doctors even enroll and treat patients in clinical studies that are paid for by companies they own.

The FDA report prompted the National Institutes of Health to begin its own investigation at Penn since it had awarded the Institute seven federal grants making up nearly half of the institute's budget. The NIH has suspended biomedical research on a number of campuses in the last year, including Duke University, the University of Illinois at Chicago, and the University of Colorado Health Sciences Center, after finding they did not have adequate systems for monitoring patient safety. The Muscular Dystrophy Association and Cystic Fibrosis foundation have also recently suspended gene therapy trials at Penn and other medical centers. MDA had given $1.6 million to Wilson and other researchers at Penn for their research.

As a result of Gelsinger's death, the NIH last fall requested agencies to send information on "adverse events" in gene therapy trials. At the end of January, the Washington Post received the reports through a Freedom of Information Act request and reported that the NIH has been swamped with reports of previously unreported serious adverse events during gene therapy trials. Since 1993, 652 of 691 reports had never been filed. Many patients suffered fevers, clotting abnormalities and serious drops in blood pressure. They included several unexplained deaths raising the possibility that Gelsinger was not the first to die during a gene therapy trial.

These deaths were usually attributed to underlying illnesses or other causes, but autopsies were rarely done.

On February 2, the Senate Health, Education, Labor and Pensions subcommittee held hearings to investigate the crisis. It found that in addition to scientists not reporting problems in a timely way, the NIH and FDA were not coordinating efforts and lacked adequate staff to monitor experiments, forcing them to rely on written reports from scientists rather than on-site inspections. Amy Patterson, head of the NIH office overseeing gene therapy, said the situation may be far worse because the 691 "adverse events" involved only the 25 to 30 percent of gene therapy experiments that rely on the gene-altered cold virus used in the Gelsinger experiment. Forty other adverse events in other areas of gene therapy had already been reported.

On February 14, Penn officials issued a 34-page response to the FDA report. The report said the FDA requirements were ambiguous, allowing differing interpretations of requirements. It said they did not believe any of the lapses detailed by the FDA led to Gelsinger's death. On March 3, the FDA rejected this attempt to lift the freeze on clinical trials at the institute and test programs have been shut down in other parts of the country since January. The strongly worded letter all but accused Wilson of lying to the FDA.

However, on March 7 the FDA and NIH issued new guidelines for gene therapy experiments which fell short of what critics say is needed. The new guidelines require researchers to appoint someone not involved with the experiments to monitor safety, such as another research group or scientists from another hospital or university. The FDA would also make surprise inspections at the more than 350 gene therapy experiments under way. The monitors, however, would be hired by the researchers doing the experiment.

Alan Milsten, the attorney representing Gelsinger's father, said it was "too little, too late." He added, "The FDA and the NIH have yet to address their own mistakes with respect to Jesse's death--particularly and most glaringly their approval of Penn's study, which had the prospect of very little benefit and tremendous risk for patients."

On February 16, the University of Pennsylvania fired William Kelly from his $1.2 million job as chief executive officer of the Health System and dean of the Medical School, which he held for 11 years. Officials claimed the gene therapy crisis had no bearing on their decision.

The Medical School, which ranks second in NIH funding, has lost $300 million in the past two years due to medical reimbursement cutbacks from Medicare, Medicaid and private health insurers. It laid off 2,800 employees last year, 20 percent of its workforce. The University of Pennsylvania is considering joining other universities in establishing its medical practice as a separate nonprofit or profit corporation. This would be done to cut medical costs and would have a major impact on medical research. Kelly is expected to take a position at Merck Pharmaceutical and Health Care, where he sits on the Board of Directors.

At the Congressional hearings on February 2, Jesse's father, Paul Gelsinger, a handyman from Tucson, Arizona, testified that he now believed he had been "misled" by the Penn scientists. Until the FDA report he had been a strong supporter of the Penn team. Gelsinger said, "It looked safe. It was presented as being safe. Since it would benefit everybody, I encouraged my son to do this. I was misled, that's what hurt the most." He told the committee that Penn researchers told him that a previous volunteer in the study experienced a 50 percent improvement in liver function, when in fact no such improvement had been documented.

Gelsinger criticized the FDA for conducting its business in secret and being unduly influenced by "business interests," the NIH for failing to investigate adverse events in gene therapy trials, and scientists in the field for putting money and fame ahead of patient safety. "Guys want to own this [technology] ... they want to have the patents on it," Gelsinger said. "I thought this was all about people. I'm very disappointed to find that it is not all about people."

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