The Dangerous Promise of Gene Therapy

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Gene therapy has not yet proven successful in curing disease. In the mid-1980's scientists began to extol the promises of gene-therapy. Conceptually (and if you consider the world only at the sub-microscopic level), gene therapy is a logical, straightforward solution to genetic disease: if a gene seems to be causing a disease, then to cure the disease scientists must remove the "bad" gene, and substitute or add a "good" gene. The reality is much more complex. Though more than three hundred gene therapy protocols, involving more than four thousand patients, have been approved for human trials in the United States, gene therapy has yet to fulfill its promise of curing any genetic disease.

Jesse died because of a gene therapy experiment.

Jesse: gene therapy gone wrong

On September 17th, 1999, eighteen-year-old Jesse Gelsinger died as a result of his voluntary participation in a gene-therapy experiment, becoming the first known human victim of this technology. Jesse's experience illuminates important elements in gene therapy that should make government agencies, scientists, and the public take the need to regulate and oversee this technology very seriously.

Jesse had a rare genetic disease, known as ornithine transcarbamylase (OTC) deficiency, which affected his ability to rid his body of ammonia, a usual, but toxic, breakdown product of protein. Half of children with OTC die in their first month of life, and half die before their fifth birthday. Jesse had a mild form of the disease because some of his enzymes were functioning normally. He was therefore able to control the disease with diet and drugs, though he needed to take 32 pills a day. Ironically, Jesse would not have benefited from the experiment.

The therapy was intended to help babies with a rare genetic disease.

The experimental protocol for which Jesse volunteered had no chance of providing him, or any of the other volunteers, with any benefit.

* It was designed only to test the safety of a treatment that would be used on babies with the fatal form of OTC.
* The scientists who designed the protocol at the University of Pennsylvania's Institute for Gene Therapy, Dr. James Wilson and Dr. Mark Batshaw, believed that OTC could be surmounted with gene therapy.
* They hoped to infuse babies who had OTC with genes that would help them produce the missing enzymes.
* In order to get these genes into the patient's cells, Dr. Wilson developed a weakened cold virus (known as adenovirus) which was designed to enter the cells as any virus would, but, instead of delivering disease, it was supposed to deliver the corrective OTC gene.
* Wilson and Batshaw hoped that the infusion of adenovirus and corrective genes could be used to
reduce infant fatalities by controlling the high levels of ammonia in babies with OTC immediately after birth.

Doctors did not foresee serious side effects or fatality. Wilson and Batshaw worked together to develop the OTC protocol and, in 1995, they submitted it to the National Institute of Health's (NIH) Recombinant DNA Advisory Committee (RAC) and the Food and Drug Administration (FDA) for review and approval, as is required for all human experiments involving gene therapy.

Jesse was deemed eligible for the study and assigned to the final test subject group--the group that would receive the highest dose of adenovirus. At the time, the researchers believed that in the worst case, the trial might result in an inflamed liver. On September 13, 1999 Dr. Raper injected 30 milliliters of the adenovirus with the corrective OTC gene into Jesse's bloodstream. According to the physicians, Jesse's severe immune system reaction led to multiple-organ-system failure and he died on September 17th, 1999, four days after the gene-therapy injection.

Some test animals died before human trials.

Some reviewers were concerned but the FDA approved the trials.

The safety of gene therapy

Human gene therapy trials raise the questions:

* How safe must an experiment be before it is ethical to try it on humans? Prior to the human protocol, Batshaw and Wilson had done animal studies to help prove that OTC gene therapy was ready for human trial. They cited more than 20 experiments on mice to prove the efficacy of the treatment, and 12 safety studies in mice, Rhesus monkeys and baboons [several Rhesus monkeys died after intense immune system reactions like Jesse's to high doses of adenovirus].
* Is the review process efficient? The mandatory review of human gene therapy experiments by the FDA and RAC is supposed to add another level of precaution. However, critics of this process have often stated that the current regulatory framework -- review by the NIH's RAC and approval by the FDA -- creates an ineffectual review process. When Wilson and Batshaw first presented their protocol for review by the RAC, both of the RAC scientists reviewing the protocol had reservations about approving it. However, continued negotiations between the federal reviewers (including RAC and FDA officials) and the University of Pennsylvania scientists resulted in approval of the protocol.

After Jesse's death, problems were found with the trial process. Following the report of Jesse Gelsinger's death, and subsequent revelations of six other deaths in gene therapy experiments in New York and Massachusetts, the National Institute of Health (NIH) RAC convened a three-day public inquiry into Jesse's death, the conduct of gene therapy research, and the safety of using adenovirus. The FDA argued that

* Jesse's liver was not functioning well enough at the time of the infusion of adenovirus, and he should not have been eligible for the study.
* Pennsylvania scientists had violated FDA regulations by failing to report information about patients who had experienced serious side effects that could have ended the trial.
* The informed consent document that Jesse signed deviated from the one approved by the agency when it reviewed the protocol (the new consent form had made no mention of the severe immune system responses to adenovirus that led to the deaths of the monkeys).

On January 21, 2000, the FDA indefinitely shut down human gene therapy experiments at the University of Pennsylvania. The trials will remain "on-hold" until the Institute responds formally to the FDA's report, and convinces the FDA that it can properly follow the federal rules designed to ensure the safety of study volunteers.

Since the news of Jesse's death was first brought to the attention of government regulators and the public in September 1999, further evidence of serious risks to patient safety in other gene therapy experiments has come to light.
* The NIH received 691 reports of "serious adverse events" in gene therapy experiments.
* Though the current regulatory structure requires researchers to promptly notify the NIH as problems arise, 652 of these reports had never been presented to the NIH.
* At least two gene therapy experiments reported patient deaths. Though in both cases researchers decided that the deaths were not related to the gene therapy treatment, their reports indicate that, in fact, researchers cannot conclusively say what caused some of the patient deaths.

Concerns about conflict of interest were raised.

Corporate interests in gene therapy

In addition to questions of safety, the massive amount of corporate interest in the development of gene therapy technology raises questions that can only be addressed with diligence. Intense commercial interest in gene therapy may create conflicts between business decisions and medical decisions.

In the case of the gene therapy trial that led to Jesse's death:

* Dr. James Wilson, the head of the Institute for Gene Therapy at the University of Pennsylvania, also owns a private company called Genovo Inc, which he founded in 1992. Genovo has the rights to any discoveries made by Wilson at his University of Pennsylvania lab.
* Through this arrangement, Genovo has access to Wilson's discoveries, at the same time minimizing its business risks as the company can let the lab run the clinical trials prior to deciding to invest.
* The NIH, further reduced Genovo's risk and maximized the company's benefits by funding the OTC trial in which Jesse took part.
* Genovo also has a financial stake in the adenovirus variation Wilson developed and tested on Jesse in the human gene therapy trial, which would have been very marketable if it had been successful.
* In addition, BIOGEN, a Cambridge-based biotechnology company, has paid Genovo thirty-seven million dollars since 1995 for the right to eventually market any liver and lung related therapies developed by Genovo. Genovo shares the money from BIOGEN with Dr. Wilson's Institute at U. Penn, and in fact the Biogen money accounts for twenty percent of the Institute's budget. The Genovo-Biogen deal (which is up for renewal this year) calls for Genovo to make progress in moving gene therapy towards a marketable product.
* In August, 1999, Genovo entered into an agreement with GENZYME (another Cambridge-based biotech company), to develop liver-directed gene therapy for metabolic disorders.

People with genetic disorders are vulnerable to medical scams or promises. Willing and able volunteers

The intense corporate interest in human gene therapy becomes even more disturbing when considered in conjunction with the fact that people are literally lining up to be test subjects for clinical trials. Gene therapy gives promise to people who are desperately searching for hope. It is a technology marketed as a cure for genetic disease -- diseases that often lead to suffering which is entirely unjustifiable. If a friend or a family member had a genetic disease, and you watched him or her suffer without respite or chance of cure, wouldn't you jump at any opportunity to end that? This scenario raises serious concerns since it puts a most vulnerable and well-meaning group of people at serious risk without adequate protections.

Initially, Wilson and Batshaw believed that the protocol should be tried on infants with severe OTC, as the therapy was designed specifically for these babies. But Arthur Caplan, the resident bioethics expert at the University of Pennsylvania disagreed. He stated that it would be unethical to experiment with sick babies because the parents of dying infants are too stressed to be able to give informed consent.

Consequently, Wilson and Batshaw decided to use stable adults for the protocol-men like Jesse who had the disease but were surviving with drugs and diet, and women who carry the gene linked to OTC. This shift from dying infants to stable adults meant that people who were living with their disease and benefiting from conventional treatments were put at risk in situations which would not
produce any benefit for them. Some participants had been coerced into the gene therapy trial. The NIH/RAC hearings after Jesse's death also made public the fact that some of the volunteers for this study were recruited in a coercive manner--using internet sites and newsletters which detailed the promise of the therapy if it worked and which stressed the need for human subjects. This type of information, placed where it would be seen by a population sensitive to the problems of living with a genetic disease, raises further issues about getting truly informed, voluntary subjects for human experimentation.

Conclusion: Gene therapy trial procedures and the review process need to be reevaluated.

Conclusion

Human gene therapy experimentation raises many issues. The promise of the technology is represented as very great and the reality of it is very dangerous. Human gene therapy must be seriously and cautiously evaluated. Without increased and more effective oversight, Jesse's death could be the first of many in gene therapy. Though Jesse's participation in the human trial did not provide him or the infants with OTC with any benefit, it did perhaps lead to something even more important in this field. Jesse's death has forced researchers and government officials

* to reappraise the current framework and structure of gene therapy research,
* to reexamine informed consent procedures,
* and to take public responsibility for their actions.

Actionbioscience.org Editor's Update: In early October 2002, the U.S. Food and Drug Administration (FDA) halted several gene therapy trials in the U.S. after a boy in France developed a leukemia-like disease almost three years after undergoing gene therapy. The boy was one of four who were given the therapy for a rare immune system disorder. The FDA did not cancel another 150 or so gene therapy trials because these trials targeted disorders other than severe combined immunodeficiency. (Source: FDA's Division of Cellular and Gene Therapies and Los Angeles Times)


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