

Death but one unintended consequence of gene-therapy trial

Jesse Gelsinger wanted to help others overcome the same metabolic disorder he had, so he agreed to enter a gene-therapy trial. A short time later, the 18-year-old American became the first person to die because of participation in gene-therapy research.

His death would be but one of several unintended consequences: it also resulted in a lawsuit, a government investigation, the delay of some other clinical trials and the creation of a new regulatory process for gene-therapy trials in the US.

Gelsinger had ornithine transcarbamoylase (OTC) deficiency, a metabolic disorder that affects 1 in 40 000 newborns by impeding the elimination of ammonia. Most of these babies become comatose within 72 hours of birth and experience severe brain damage. Half die within a month of birth, and half of the survivors die by age 5.

Gelsinger's outcome was different because he had only partial OTC deficiency, which he kept in check with a low-protein diet and drugs. He was considered an ideal candidate for the trial, led by Dr. James Wilson, director of the Institute for Human Gene Therapy at the University of Pennsylvania.

On Sept. 13, 1999, Gelsinger was given an infusion of corrective OTC gene encased in a dose of attenuated cold virus, a recombinant adenoviral vector; it was injected into his hepatic artery. Gelsinger experienced a severe immune reaction to the vector — the gene's delivery vehicle — and died 4 days after receiving the injection.

The major question surrounding his death involves informed consent. A lawyer retained by his family says Gelsinger was not told that several other patients had experienced serious side effects from the therapy, or that 3 monkeys had died of a clotting disorder and severe liver inflammation after being injected. (No one realized that the vector itself might pose a risk. In nearly 400

clinical gene-therapy trials involving more than 4000 patients, Gelsinger's was the only death attributable to the vector [*Molecular Therapy* 2000;2:415-6]).

When he died, the US Food and Drug Administration (FDA) suspended the Pennsylvania trial, citing a failure to train staff adequately, develop basic operating procedures and obtain informed consent.

In January 2000, the FDA halted the rest of the University of Pennsylvania's human trials involving gene therapy and began investigating 69 other gene-therapy trials under way in the US. Eventually, 28 trials were reviewed, with 13 requiring remedial action.

Early in 2000, the FDA and the National Institutes of Health decided to enhance patient protection through 2 new programs: the Gene Therapy Clinical Trial Monitoring Plan and the Gene Transfer Safety Symposia.

Monitoring lies "at the heart of the matter," says Dr. Philip Noguchi, the FDA's director of the Division of Cellular and Gene Therapies. "And that's not something the FDA can do alone."

For example, FDA monitoring — which it now admits was sometimes "less than adequate" — used to require sponsors to disclose financial undertakings that might constitute a conflict of interest when they applied for approval or licensure of their products. That meant disclosure didn't take place until after the trial was finished.

Wilson, director of the Penn institute where Gelsinger was treated, owned stock in a company, Genovo, that provided financing for the institute.

The new Gene Therapy Clinical Trial Monitoring Plan requires disclosure and clinical monitoring before a trial begins and clarifies what events need to be reported. The FDA also recently adopted a policy forbidding investigators and team members who are directly involved in patient selection, the informed-

consent process or clinical management of a trial from holding equity, stock options or comparable arrangements in companies sponsoring the trial.

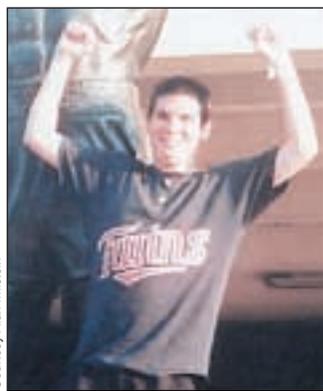
The Gene Transfer Safety Symposia are supposed to allow researchers to share data and clinical experience, particularly regarding adverse events. So far, 3 symposia have been held, but Noguchi already says that a more efficient way to share data is needed.

Alan Milstein, the Gelsinger family's lawyer, says inefficiency isn't the only problem. He says researchers are often reluctant to share information because of the potential loss of future patent rights if a clinical trial produces a marketable product. (In gene-therapy trials in the US, an adverse event can be considered proprietary information. A 1995 proposal to form a common repository of information was rejected.) Milstein says the FDA's new measures are "inadequate" protection for gene-therapy subjects. Milstein and Jesse Gelsinger's father, Paul, want a more extensive approval process, including an impartial oversight committee that will seek out and eliminate conflicts of interest.

In this country, researchers receiving Canadian Institutes of Health Research (CIHR) funding must adhere to guidelines in the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans. Those conducting research outside of CIHR can use the statement as a guideline but don't have to do so.

Paul Gelsinger is determined to bring about change in the US. He does speaking tours with Milstein, and in October 2000 they launched a lawsuit against the Penn State researchers and others. It was settled out of court in November for an undisclosed amount and for the university's promise to move forward with "aggressive efforts to improve its oversight and monitoring of human-subject research."

"We are at the crossroads," says Milstein. "It remains to be seen whether there will be a terrific change or another death. My prediction is another death, because to date there have been no changes that would have prevented Jesse's death." — *Barbara Sibbald, CMAJ*



Courtesy Alan Milstein

Jesse Gelsinger: altruistic trial participant