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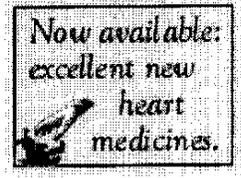
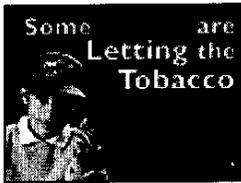
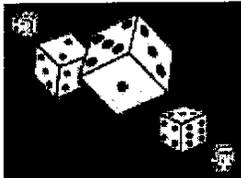
# Teen Dies Undergoing Experimental Gene Therapy

By Rick Weiss and Deborah Nelson  
Washington Post Staff Writers  
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An 18-year-old Arizona man with a rare metabolic disease has died while participating in a controversial gene therapy experiment, marking the first death attributed by doctors to a burgeoning field of research that seeks to cure people by giving them new genes.

The death is the latest in a series of setbacks for a promising approach that has so far failed to deliver its first cure and that has been criticized as moving too quickly from the laboratory bench to the bedside.

Some members of a federal advisory committee that approved the study had expressed concerns about the experiment because they felt it posed unduly serious risks and included people who were already being treated successfully with conventional therapy.

Jesse Gelsinger, a high school graduate who had suffered on and off from a serious genetic disorder that often leads to coma and death in childhood, died Sept. 17 after undergoing an experimental therapy administered at the University of Pennsylvania in Philadelphia, university and federal officials said yesterday.

Scientists and doctors involved in the case said Gelsinger succumbed over a four-day period after doctors infused a batch of genetically engineered viruses into his liver at the highest dose allowed under an experimental protocol approved by the Food and Drug Administration.

The experiment, the first in which such a virus was shot directly into the liver's blood supply, has been halted pending an investigation, and federal officials today will send out letters to the more than 100 researchers in the country conducting human research with similar viruses, asking them to report any evidence of trouble. Seventeen other University of Pennsylvania patients who received various doses of the virus before Gelsinger had no notable problems, and a few improved.

"This was a tragic unexpected event," said James M. Wilson, director of the university's Institute for Human Gene Therapy. "I hope in a month we'll have looked at every angle so we can share with whomever is interested in listening what we've learned from this."

Researchers and officials familiar with the case said they had few clues about what may have triggered the death, so its impact on the field of gene therapy remained uncertain. Thousands of U.S. patients have been treated with various kinds of gene therapy, an experimental technique in which doctors use live viruses and other means to transport potentially therapeutic genes into the body.

The class of virus used in the Philadelphia experiment, a modified version of a cold virus called an adenovirus, is the most common type of gene therapy virus in use today. But the study had raised several novel concerns when the researchers began their long effort to gain federal approval to conduct the work.

Typically gene therapy studies involve desperately ill patients who have failed conventional therapy. But this one included healthy people and people who were already being treated successfully with dietary and drug regimens. The method was controversial because the genetically altered virus, which often causes severe inflammation, risked exacerbating the disease in some patients when it was injected directly into their livers, while promising at best only a transient improvement.

Gelsinger suffered from ornithine transcarbamylase (OTC) deficiency, a genetic disorder that affects mostly boys. The disease blocks the body's ability to break down ammonia, a normal byproduct of metabolism, and often causes death soon after birth.

Gelsinger was born with a mild form of the disease and had it well under control during the past year with drugs and a strict non-protein diet, said his father, Paul Gelsinger, of Tucson. But he volunteered in the hope that it might lead to a cure that would benefit him and children with more deadly forms of the disease.

"I lost a hero," Paul Gelsinger said.

Gelsinger said he is not angry at the researchers. "They're as hurt as I am. They've promised full disclosure."

At the same time, he said, "I've got a ton of questions for them."

Among them, Paul Gelsinger said, was why they accepted his son as a subject when they knew that he had a different form of the disease than most affected individuals.

Mark Batshaw, the study's principal investigator and now chairman of pediatrics at the George Washington University Medical School, yesterday confirmed that Gelsinger did not have the usual inherited form of OTC deficiency. Typically it is caused by a tiny missing piece of genetic material passed along from the mother, but Jesse Gelsinger's form was caused by a much larger deletion that occurred after he was conceived.

Perhaps because of that difference, Gelsinger's liver functioned at an

especially low efficiency level -- lower than anyone else in the clinical test even though he was healthier than many others with the disease.

Batshaw and other doctors involved in the case said they did not know if that difference left Gelsinger more susceptible to fatal liver damage from the therapy. They said when the trial started, they had no reason to believe so, and had some reason to believe he might benefit more than most. That question will be among many it the things they will now investigate.

Whatever the reason, his liver went into a steep decline the day after getting the virus infusion, which was meant to deliver a gene that would help him make the enzyme he lacked. Other organs progressively failed over the next three days, including much of his brain.

"By Friday morning, studies suggested that even if -- and this was a big 'if' -- he were able to come through the multiple organ system failure, the chances that Jesse would be able to be Jesse again were essentially zero," said Steven Raper, a Penn surgeon involved in the clinical trial.

The team recommended to the young man's father that they withdraw life support equipment, and he agreed.

Staff researcher Alice Crites contributed to this report.

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