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Trials Are Halted on a Gene Therapy

By SHERYL GAY STOLBERG

WASHINGTON, Oct. 3 Ñ Officials in the United States and France said today that they had suspended four gene therapy experiments because the treatment, which cured a 3-year-old boy of a fatal immune deficiency, may have given him an illness similar to leukemia.

Scientists conducting the research said it was not clear whether the boy, who was treated as an infant in France, was made sick by the therapy. But officials at the Food and Drug Administration said they suspected that the experiment, which until now had been hailed as the only unequivocal gene therapy success, was responsible.

"It is not absolutely a definitive thing, but the preliminary data that we have leads us to suspect that it surely isn't a coincidence," said Dr. Philip Noguchi, the agency official who oversees gene therapy research. "It's a sobering experience, but we are doing what should be done."

The experiments Ñ one in France, three in the United States Ñ were suspended in early September. But the news was not made public until today, authorities said, to give the researchers time to notify the families of 14 children enrolled in the trials.

The move is yet another major setback for the fledgling field of gene therapy, which involves using viruses to introduce healthy genes into cells. The field is still reeling from the death of Jesse Gelsinger, 18, who lost his life three years ago while undergoing gene therapy at the University of Pennsylvania.

Scientists have long theorized that retroviruses, which were used in the suspended experiments, could trigger cancer. The risk was that the virus, which integrates itself into the patient's DNA, would lodge in or near a cancer-causing gene.

But researchers said they had never seen this before, either in animals or humans, even though hundreds of people have received retroviruses in gene therapy experiments for a number of diseases. Experts said it was too soon to tell whether other children treated for immune deficiency were at risk.

"This has been a spectacularly successful endeavor up to this point," said Dr. Savio Woo, former president of the American Society of Gene Therapy. "This is a new enemy that we have discovered. We know that there is a theoretical possibility, but it has never been seen before."

The suspended trials sought to cure severe combined immune deficiency, a disorder that leaves infants without working immune systems. Abbreviated as SCID, but commonly called "bubble boy disease," it is extremely rare and is fatal in the first year of life if left untreated.

In the most severe form, the disease affects boys who have faulty X-chromosomes. The only treatment is bone marrow transplant. But the transplants fail in as many as 40 percent of all children who lack a perfect donor match, so scientists looked to gene therapy as an alternative.

In April 2000, Dr. Alain Fischer and his colleagues at the Necker children's hospital in Paris announced that they had used gene therapy to successfully insert corrective genes into the bone marrow stem cells of three babies with X-linked SCID. Coming on the heels of Mr. Gelsinger's death, Dr. Fischer's study was hailed as long-sought proof that gene therapy could work.

Dr. Fischer went on to treat six more babies and a teenager, who survived because he had a partial immune deficiency. "Up until now, all these patients, more than three and a half years after treatment, are doing well," he said. All had "close to normal immune functions," he said.

But last spring, Dr. Fischer said, one of the boys showed elevated levels of a particular type of white blood cell, known as a T-lymphocyte, though he had no symptoms. Subsequently, though, the boy developed chickenpox. By August, Dr. Fischer said, he had a "significant increase" in the white cell counts, as well as an enlarged spleen, anemia and a drop in platelets.

When scientists examined the child's cells, Dr. Fischer said, they could see that the genetic material of the retrovirus had inserted into a particular gene on the 11th chromosome that controls the proliferation of cells. But he said he was not yet convinced the gene therapy was entirely to blame.

Other factors, including the chickenpox infection and a family history of cancer, could also be at work, Dr. Fischer said. But Dr.

W. French Anderson, a professor at the University of Southern California who was among the first scientists to use gene therapy to treat SCID, said the gene therapy was likely responsible.

"We knew it would happen sooner or later," he said. But even if it turns out that gene therapy causes the disease, Dr. Anderson and other experts said gene therapy might still be used to treat SCID because the illness was so devastating.

The child does not have leukemia per se, Dr. Fischer said. There is no name for his proliferation of cells because scientists have never seen it before, so Dr. Fischer is calling it "lymphoproliferation."

The boy is being treated with chemotherapy and is responding, Dr. Fischer said. But the abnormal cells have not disappeared, he said.

Dr. Fischer said he notified French authorities, as well as the F.D.A. and his colleagues in the field, right after Labor Day, as soon as he knew the problem was serious.

The food and drug agency immediately put what it calls "a clinical hold" on three trials in the United States, two at Children's Hospital in Los Angeles and one at the National Institutes of Health in Bethesda, Md. The N.I.H. study, and one of the Los Angeles studies, have yet to enroll any patients, he said.

The other Los Angeles study is being run by Dr. Donald Kohn, president-elect of the American Society of Gene Therapy. The four children Dr. Kohn and his collaborators have treated all have a form of SCID that is not the X-linked type. But Dr. Kohn said the F.D.A. was correct in suspending his research. "The clinical hold, I think, is the only ethical and responsible course of action until we have more answers," he said.

The F.D.A. will convene a meeting of outside experts next week to discuss the trials, Dr. Noguchi said. He added that other SCID trials had been going on in England and Germany. The German studies have been suspended, but the British research is continuing, he said.

At Cincinnati Children's Hospital Medical Center, researchers said they were collaborating with Dr. Fischer to try to determine what, if anything, went wrong in the study.

But Dr. Christof von Kalle, who is leading the effort, said it could take months, if not years, for a definitive determination.

Today's announcement came as a panel of independent experts released a study of the safety of clinical trials that was prompted by Mr. Gelsinger's death. The panel, at the Institute of Medicine, called for major reforms, including a federal law that would require all research organizations to develop patient protection programs.

Dr. Daniel Federman, a professor of medicine at Harvard Medical School who was chairman of the panel, said the panel was especially concerned about financial conflicts of interest in research. He spoke of a "hodgepodge of protections" that was so haphazard it was impossible to catalog how many Americans were enrolled in research experiments, and how many had been harmed by them.

"At the present time, a lot of people are trying to do a good job, and almost certainly are," Dr. Federman said. "What we are trying to do is raise the level of the system as a whole."

Mr. Gelsinger's father, Paul, who has become an advocate for patient protection and reviewed the study in advance of its publication, applauded the work.

"I have always felt like what happened to Jesse blew the lid off the can of worms of medical research," Mr. Gelsinger said. "The system needs to be looked at, it needs to be unraveled. This study goes a long way toward doing that."