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## Gene Therapy Trials Halted

By ANDREW POLLACK

**T**he Food and Drug Administration yesterday suspended 27 gene therapy trials involving several hundred patients after learning that a second child treated in France had developed a condition resembling leukemia.

The agency said it was not aware that any of the patients treated in the 27 American trials had suffered illnesses similar to that of the infants in France but was nevertheless taking precautions.

"We see no evidence that the subjects in these 27 trials are actually at risk," said Dr. Philip Noguchi, acting director of the agency's office of cellular, tissue and gene therapies.

The temporary halt, the largest such action involving gene therapy trials, is yet another setback to the fledgling field, which usually involves introducing healthy genes into patients to treat diseases caused by defective ones. The field is still shaken from the death of a teenager undergoing gene therapy in 1999 at the University of Pennsylvania and from the first case of leukemia in an infant in France last year.

The treatments in France had been considered the only unequivocal success for gene therapy after a decade of failures. Nine of 11 young boys treated for a fatal immune deficiency widely known as bubble-boy disease were able to leave the hospital and take up nearly normal lives. But now two of them have developed the condition resembling leukemia.

"The exciting thing was that it was working," said Dr. Joseph C. Glorioso, president of the American Society of Gene Therapy and chairman of molecular genetics and biochemistry at the University of Pittsburgh. "The horrible thing is that a shadow has been cast over that success."

In September, after the first of the children in France was found to have the leukemia-like disease, the F.D.A. halted three clinical trials that involved a similar treatment for immune deficiencies. Yesterday it decided to halt all trials involving the technique used in the French trial, regardless of the disease being treated. That technique uses a type of virus known as a retrovirus to ferry genes into blood-producing stem cells.

The 30 trials halted represent about 15 percent of the 200 gene therapy trials under way and half of the 60 trials involving retroviruses. The other trials using retroviruses insert the genes into cells other than blood stem cells. The trials involving stem cells are considered more risky because those cells proliferate, and leukemia is a disease in which blood cells proliferate out of control.

Some of the trials being halted are intended to treat AIDS and cancer, Dr. Noguchi said. The agency will consider lifting the suspensions in individual cases for these life-threatening diseases if doctors fully inform the patients of the risk and then monitor them carefully, he said.

Retroviruses are only one of several types of viruses used to deliver genes into cells. But they are considered both particularly promising and risky because the genes they carry become a permanent part of the target cell's DNA. That means that when the cells divide, the inserted genes remain in the daughter cells. Without that permanent insertion, scientists said, gene therapy might have to be performed over and over.

But scientists also knew there was a theoretical risk that a retrovirus would lodge near a cancer-causing gene and turn it on. Scientists say that is what happened in the first leukemia case in France. The cause in the second case has not been announced but some scientists say they have heard the cause is similar.

But until the second case, scientists believed that the risk was low. There have been perhaps 40 or 50 trials involving more than 100 patients in the United States that involved using retroviruses to insert genes into stem cells, said Dr. Donald B. Kohn, professor of pediatrics at the University of Southern California and a gene therapy expert at Children's Hospital in Los Angeles. Most had limited or no success, but none had caused a cancer-like complication.

"The big question is why are we seeing this all of a sudden in two patients in this trial but not all these previous patients?" said Dr. Kohn, who was conducting two trials affected by the F.D.A.'s suspension. He said one explanation could be that gene transfer has become more efficient. Another is that there could be something specific to the disease treated or to the gene used in the French experiment.

The American Society of Gene Therapy, which endorsed the F.D.A.'s precautionary measure, said yesterday that it would set up a committee to study the situation. The gene therapy advisory committee of the National Institutes of Health will meet on Friday to consider the situation, and an F.D.A. advisory committee will meet on Feb. 28.

Scientists said the new problems would not derail gene therapy because the risks had to be balanced against the benefits. In this case, they said, nine infants were virtually cured of a terrible disease. Indeed, after the first three trials were suspended in September, an F.D.A. advisory panel recommended resuming those trials on the ground that the benefits outweighed the risks. The trials had not yet restarted.

Dr. Noguchi said the F.D.A. learned of the second French leukemia case a month ago but did not act until yesterday because it wanted to study the situation.

"We know the impact of F.D.A. taking an action like this," he said. "We didn't want to do this without doing a very thorough evaluation of all the risks and benefits."

Dr. Daniel R. Salomon, associate professor at the Scripps Research Institute and chairman of the F.D.A. advisory panel for gene therapy, said the F.D.A. was right to be cautious. "This definitely is not the way we would have written it out had we had our fantasyland going," he said. "But this is dealing with reality."

Dr. Salomon and Dr. Glorioso said there were techniques that could make gene therapy safer.

Dr. Glorioso described the setback as "bumps in the road that happen when you develop new therapies." He added: "I don't think it will kill the field. I think it will cause us to work harder and engineer our way out of the problem."