Gene Test Begins

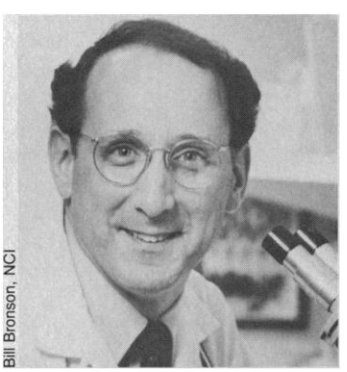
A landmark gene transfer experiment began this week after all the legal hurdles were finally cleared

AT 10:47 MONDAY MORNING, physicians at the National Institutes of Health launched medicine into a new genetic era. A cancer patient with advanced melanoma, who is almost certain to be dead by the end of the summer, made political history when he received an infusion of his own white blood cells containing a foreign gene. Researchers plan to use that gene as a marker to track the lymphocytes as they go on a search-and-destroy mission for tumors throughout the patient's body.

Monday's test, in a patient hospitalized at the NIH Clinical Center, was the first authorized "gene transfer" experiment in the United States—one step away from actual gene therapy. The milestone study is a collaboration among Steven A. Rosenberg of the National Cancer Institute, W. French Anderson of the heart institute, and R. Michael Blaese, a cancer institute pediatrician who is an expert on immunodeficiency diseases. It was Blaese who brought Rosenberg and Anderson together more than a year ago when he realized that Rosenberg's experiments with potent killer lymphocytes, known as TIL cells, would be good system for gene transfer studies. (Anderson and Blaese had been working together on gene therapy protocols for immune system diseases.) Between April and June 1988, the three drew up the protocol that was the basis for this week's clinical tests.

The buildup to this week's test bore a certain resemblance to a space launch. First came a long and frustrating period during which the proposed gene transfer test was subjected to intense scrutiny by the NIH's human gene therapy review committee, as well as other oversight bodies responsible for monitoring the ethics and safety of infusing humans with foreign genes. (There is almost unanimous agreement that the gene transfer experiment is safe.) There were nearly a dozen meetings, all held in public, and mountains of minutes made available to anyone who asked. Chief skeptic was activist Jeremy Rifkin who brought a lawsuit alleging that the review process violated requirements that all decisions be made in public. Rifkin's complaint centered on the fact that, for expediency, NIH director James B. Wyngaarden conducted a single telephone poll of committee members for a final decision after all the i's had been dotted in the final protocol. Then, last week, a federal court in Washington, D.C., dismissed the suit, as part of a settlement in which NIH agreed that in the future all decisions will be entirely open.

With the suit out of the way, the NIH team could begin the final countdown. "It looks like we're going to start the first patient late Monday morning if we have a 'go,'" Rosenberg told *Science* about 48 hours before the test began. A "go" required a special combination of factors—an ideal preparation of cells and a patient in just the right state of readiness. Once before, a countdown had looked good at 36-hours only to be aborted at 24-hours to infusion because the concentration of genetically labeled cells was not up to expectations.



Pioneers. *Steven Rosenberg (left) and W. French Anderson (right) teamed up on a test in which foreign genes were inserted into a patient.*

The last step in Monday's countdown was word from the lab that the bag of TIL cells was clean or infection-free. According to Anderson, when the call came, "Rosenberg gave a big smile and that was it. We were ready."

The first infusion took about 45 minutes, Anderson told *Science*, with two more scheduled for the afternoon. The test is designed to provide research information to physicians studying "adoptive immunotherapy"—a fairly new approach to cancer treatment that involves use of a patient's own cells. The team's first patient and those that follow, if lucky, will respond to the infusion of TIL cells, but the addition of the marker neomycin resistance gene is not expected to offer any medical benefit. Indeed, in this regard, the experiment harks back to the idea that some patients volunteer for the benefit of others who will follow them.

The gene transfer test itself is conceptually quite simple. Since 1986, Rosenberg has had increasing success in treating intractable melanomas with TIL cells (tumor infiltrating lymphocytes) that are surgically removed from a patient's cancer and cultured for 4 to 6 weeks in the laboratory with interleukin-2 (IL-2), a growth factor that stimulates the immune system. Then the cells are reinfused into the dying patient.

Unlike most cancer agents, TIL cells leave normal cells alone; TIL cells have a selective affinity for the particular cancers from which they came. When everything works, the TIL plus IL-2 combination infiltrates and destroys tumors and their metastases. Advanced melanoma, for instance, often spreads to lung, liver, bone, and skin.

In several cases, Rosenberg and his colleagues have seen significant remission of tumors that have resisted all other forms of attack. However, as with many new therapies, TIL–IL-2 only works a fraction of the time. The question is "Why?" The gene transfer experiment is an attempt to answer that.

Using a retrovirus as a delivery system, Anderson and his colleagues succeeded in getting more than 5% of TIL cells to take up the gene for neomycin resistance—a gene that is being used simply because it can be easily traced in the body. Research perfecting the delivery system has taken years. By following the neomycin-labeled TIL cells, the team hopes to find out just where they go, and where they don't go. The team also will examine the possibility that the marker gene itself somehow affects the TIL cells by changing their appearance or function.

This first series of studies, which will be limited to 10 patients, may shed light on the mechanism of the TIL cells' antitumor properties which can be turned to therapeutic advantage down the road.

A second patient may receive gene-labeled TIL cells as early as Friday, 26 May, and others will follow shortly.

The Rosenberg-Anderson-Blaese experiment paves the way for further studies of adoptive immunotherapy for cancer and, eventually, for a host of genetic diseases, such as cystic fibrosis and sickle cell anemia, that result from a defect in a single gene.

■ BARBARA J. CULLITON