

# First Human Gene-Therapy Test Begun

Culminating years of laboratory studies, legal wrangling, and scientific and ethical debate, researchers at the National Institutes of Health last week performed the first federally approved infusion of therapeutic, genetically engineered cells into a patient.

A billion or so gene-altered immune-system cells, suspended in about 2 ounces of sterile saline solution, made medical history as they dripped down a plastic tube into the vein of a 4-year-old girl with an inherited, life-threatening immune deficiency.

Scientists and physicians involved in the case say that because of the experimental treatment's conservative design, they expect to detect few if any benefits for the young patient within the next year or more. Nonetheless, by providing the girl's circulatory system with a small army of cells bearing the critical gene she has lacked since conception, medical practitioners took their first tentative steps into the world of gene therapy.

That world's landscape stands in sharp contrast to the familiar scenery of current medical practice. Its landmarks are not the body's organs and cells or the microorganisms infecting them, but the basic molecular and genetic elements from which all inherited traits arise. Scientists expect gene therapy to prove valuable against a range of medical problems, including inherited diseases, cancer, cardiovascular diseases and possibly

AIDS.

"Gene therapy is potentially a major, new therapeutic option that should have significant clinical effects in the next century," says NIH researcher W. French Anderson. "This should provide cures for what today are incurable diseases."

Anderson and co-workers R. Michael Blaese and Kenneth W. Culver directed the infusion, nearly 3½ years after first submitting to NIH officials their unprecedented proposal to correct genetic errors in the cells of patients with an inherited disease. That highly technical, several-inches-thick document — dubbed "The Phone Book" because of its size — went through seemingly endless major revisions over the years. The changes reflected requests by various federal agencies and scientific advisory boards for additional information relating to the procedure's risks, potential benefits and ethical implications.

Final FDA approval arrived at 8:59 a.m. on Sept. 14. Within hours, the young patient — whose identity remains unpublicized at the family's request — was wheeled into the pediatric intensive care unit at the NIH clinical center in Bethesda, Md. There, over a period lasting about 30 minutes, her left arm received the nation's first infusion of gene-altered, therapeutic cells.

In an experiment last year, NIH researchers had inserted a foreign, non-therapeutic gene into some immune-

system cells to trace their movement and survival in a small group of cancer patients (SN: 9/23/89, p.197).

The cells infused Sept. 14 were lymphocytes culled from the girl's own blood a week earlier. In the laboratory, researchers had inserted into those cells copies of a missing gene that directs production of the toxin-destroying enzyme adenosine deaminase (ADA). Without the enzyme, toxic metabolic by-products were accumulating in the patient's lymphocytes and destroying her immune system. About 20 other children worldwide suffer from ADA deficiency; most of those who inherit the abnormality die within the first few years of life from infections usually inconsequential to kids.

Although bone marrow transplants can cure the disease, most of those affected can't find compatible donors. A new drug called PEG-ADA — an injectable, chemically altered form of the missing enzyme — seems to help. But researchers say that at least some children receiving the drug still appear at grave risk of acquiring lethal infections — a risk they say may be lessened by providing living cells that have been genetically engineered to produce the enzyme.

The girl who received the gene-altered cells has taken PEG-ADA for several years and currently appears in good health, according to her family physician. But in the past year, she has required four hospitalizations and has failed to gain weight. Plans call for her to remain on PEG-ADA while the NIH team administers monthly infusions of engineered cells and monitors her immune status.

Because the girl shows no outward signs of disease and because the current protocol involves relatively small doses of cells, improvement may be difficult to document, Anderson says. Thus, this first experiment may serve more to prove the treatment's safety than to establish its effectiveness.

Ultimately, Blaese says, the researchers want to insert copies of the ADA gene into patients' bone marrow cells to provide a constant, lifelong supply of the enzyme. Technical problems preclude doing that now. Meanwhile, Blaese says, other young ADA-deficient patients are in line for the current protocol, which may eventually undergo revision to allow the researchers to infuse more cells and take patients off PEG-ADA.

The NIH team has federal permission to infuse ADA-engineered cells into 10 patients. Says Blaese: "Our hope is that with this treatment we'll be able to give them long-term, long-lasting immune reconstitution."  
— R. Weiss

## NIH addresses women's ills

To ensure "appropriate" and adequate participation of women in study populations, especially in therapeutic trials, the National Institutes of Health last week established an Office of Research on Women's Health.

Though NIH officials say they have planned this office for months, its creation coincided with a visit to NIH by prominent female members of Congress who have criticized the federal agency for funding male-only studies of many diseases and treatments that affect both sexes. One of those lawmakers, Sen. Barbara A. Mikulski (D-Md.), amended NIH's budget authorization bill last month to require creation of the new office as soon as the bill passes.

Since October 1986, NIH has maintained a policy to "encourage the inclusion of women" in studies it funds. However, a report issued this summer by the General Accounting Office (GAO) concluded that "NIH has made little progress in implementing its policy." GAO found that the policy on women,

which affects outside researchers only, "has not been well communicated or understood within NIH or in the research community," has been applied inconsistently by NIH's various institutes, and receives no mention in the grant application booklet used by most researchers seeking NIH funding.

Acting NIH Director William F. Raub pledges to add a special insert to NIH grant application forms, describing its policy on women; to see that all NIH program managers and staff with review responsibilities attend training sessions this month and next on the policy; and to discuss the policy at initial meetings of peer-review panels assessing clinical research proposals.

Raub appointed physician Ruth L. Kirschstein to head the newly established office, which he says will "have the authority and responsibility to act with and on behalf of the NIH director" to rectify deficiencies and monitor research on women's health. Kirschstein already heads the National Institute of General Medical Sciences. □