

**Science File / An exploration of issues and trends affecting science, medicine and the environment**  
*A Sense of Control*  
*Technique for Rare Disorder Offers Hope for Others Who Lose Brain Functions Because of Various Diseases*  
*[Home Edition]*

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Hannah Geisinger, only 22 months old, is a happy child, but not a healthy one.

Unlike most children her age, Hannah cannot see, speak, sit, crawl, hold up her head or even hold a rattle in her hands. Developmentally, she is 18 months old. She suffers from Canavan disease, a devastating genetic disorder of the brain that usually leaves its victims dead by the age of 5.

Later this month, however, Hannah and her mother, Sandra, will travel to the Yale University Medical Center, where the infant will undergo an experimental gene therapy that her parents hope may delay, or even reverse, the course of her disease.

"It won't hurt her," said Sandra Geisinger, "and it offers her a chance. In some way, we might be offering her up to science, but as it doesn't hurt her."

If the trial is successful, it could have profound implications that go far beyond Canavan disease, said Dr. Andrew Freese of Thomas Jefferson University in Philadelphia. "If this technique works, we can replace function lost in the brain due to a variety of diseases," he said, including epilepsy and stroke.

Only a few years ago, gene therapy was viewed as the most promising way to treat otherwise intractable genetic diseases. But it has been dramatically dimmed by a long series of, in essence, failures. No one seems to have been hurt by any of the early attempts, but

In part, the problem has involved finding an appropriate "vector," a system for getting the healthy gene into cells. That has been the case with genetic diseases like muscular dystrophy, where the affected tissue is dispersed throughout the body.

The Canavan treatment appears to be a propitious situation in which a safe and potentially effective vector can be used to treat a relatively small area.

Canavan disease, also known as Canavan's leukodystrophy, is a relatively rare disorder, affecting about one in 6,000 births. Like Tay-Sachs, it is common among Ashkenazi Jews, who trace their ancestry to Eastern Europe.

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It is estimated that about one in every 35 members of this population carries the gene. A genetic test is available to identify carriers, but experts said.

The disease has remained largely ignored, perhaps because it is rarely diagnosed correctly. Dr. Michel Philippart, a pediatric geneticist who diagnosed Hannah's condition, said he has seen only about six cases in his 30 years at that institution.

"There must be many more cases," Philippart said. "The question is, where do they go? They may die with no diagnosis having been made. Problems may be blamed on obstetricians. Who knows?"

Canavan is caused by a defect in the gene for an enzyme called aspartoacylase, which is necessary to break down a compound called N-acetylaspartic acid. Accumulation of N-acetylaspartic acid in the brain causes the central nervous system to deteriorate.

Although researchers do not know precisely how that accumulation brings about its effects, the results are dramatic. White matter, which protects the cells that carry neural impulses from the brain to the rest of the body--deteriorates, in effect short-circuiting the brain.

spongy appearance and becomes saturated with fluid, swelling the head and further damaging nerve cells.

Canavan victims have little control of their arms and legs or their heads, and are often blind. Other than supportive measures, the disease.

The current impetus toward gene therapy was provided by Dr. Roger Karlin and his wife, Helene, of New Fairfield Conn. When diagnosed with Canavan in 1995, Karlin began searching for a treatment and found there was none.

But he also discovered that Dr. Matthew During, then at Yale, had developed a new system for getting genes into the brain. Karlin and the system for the treatment of Canavan and he and other Canavan families raised the initial \$200,000 required for the study. They raised more than \$3 million to keep the research going.

During's approach was to encapsulate the healthy gene in small fat globules called liposomes, which could then be infused into the brain. The liposomes merge with fats in the membrane of brain cells, allowing the genes to be released inside the cell, said Dr. Margretta Seay, the principal investigator of the project.

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Two years ago, Lindsay Karlin and Alyssa Mushin of Derby, Conn., received the new therapy at the University of Auckland in New Zealand where they had moved.

According to Lindsay's mother, she has shown some improvement since the therapy. She is now able to touch things, kick her legs, and make movements. A basic communications system allows her to push buttons and watch things happen.

Alyssa also showed some initial improvement after the treatment, but then had a regression. Her condition now is about the same as when she was first treated.

Both girls received a second treatment this year.

The team has some evidence that the gene is causing the missing enzyme to be produced in the treated children's brains, but they do not want to draw any conclusions about its efficacy.

If the tests with Canavan prove successful, the technique could be adapted for treatment of other genetic disorders. Parkinson's disease is deficient in a brain chemical called dopamine, and it should be possible to insert a gene that would produce the neurotransmitter. The blueprint for various nerve growth factors, which stimulate development of brain cells, might be used for the treatment of Parkinson's diseases.

Sandra Geisinger, meanwhile, is trying to restrain her hopes for the procedure. She and her husband have brought in eating therapists and other experts to treat Hannah and, apart from her disease, the infant is quite healthy.

She has gone public with Hannah's treatment to try to alert other parents to the potential danger of Canavan.

"I had an amniocentesis. But nobody thought to look for Canavan disease. I want public awareness of this disease."

If the word gets out, she says, then Hannah's travails may have been worthwhile.

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### Gene Therapy

Yale researchers are experimenting with gene therapy to treat children with Canavan disease, a devastating disorder of the brain. The goal is to insert a healthy form of the gene into the brain so that it can produce a needed enzyme.

1. The healthy gene is attached to short genetic sequences that will help it produce protein in the brain. That stretch of DNA is in a microscopic globule of fat called a liposome.
2. Surgeons pull back a flap of skin on the top of the head and drill a burrhole through the skull.
3. A small, flexible egg-shaped reservoir is inserted under the skin, attached to a catheter that passes through the burrhole and

the brain.

4. Liposomes are injected into the reservoir, which can be pumped by hand to force them into the brain.

5. The reservoir remains in place in case the treatment needs to be repeated.

Researched by Times medical writer THOMAS H. MAUGH II

GRAPHIC-DRAWING: (No Caption), REBECCA PERRY / Los Angeles Times; PHOTO: Sandra Geisinger holds her daughter for experimental gene therapy at Yale University Medical Center, as outlined below.; PHOTOGRAPHER: AL SEIB / Los Angeles T

Credit: TIMES MEDICAL WRITER

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