

Tailoring Genes to Bring Hope

Doctors explore the brain's most fundamental processes to tackle a neurological disorder

By **SIMON ROBINSON** AUCKLAND

TWO-YEAR-OLD ALYSSA MUSHIN LIES propped on a cushion, hand in hand with 19-month-old Lindsay Karlin. The girls cannot sit up or roll over unaided, their motor control robbed by Canavan's disease. This rare neurological disorder kills most sufferers by the time they are about eight, but the stitches on the two girls' skulls are evidence of innovative research that just might halt the disease's destructive progress.

Two weeks ago in Auckland, doctors using synthetic laboratory-manufactured genes performed pioneering operations on the girls, who were brought by their parents from Connecticut in the U.S. for treatment. It was their last desperate hope. "What we are dealing with here is people who are very sick and will die otherwise," says Lindsay's father Roger of gene therapy. "Nobody could be against trying to help them." The results of the operation won't be known for weeks, and doctors insist the girls' chances are extremely slim.



NIGEL MARPLE FOR TIME 2

NEVER SAY NEVER: 'We were meant to go home and wait for our baby to die,' says Helene Karlin of her daughter Lindsay, left, with fellow Canavan's sufferer Alyssa Mushin

Nevertheless, some scientists believe the operations represent a step toward treating more common neurological diseases like Parkinson's, Alzheimer's and epilepsy. It may also mean we are nearing the possibility of genetic intervention to alter the way our minds work. "Clearly, introducing genes into the brain is something that will affect the neurological system, the central nervous system and eventually the thought processes," says Nelson Wivel, director of the Office of Recombinant DNA Activities in America's National Institutes of Health. "It's the first step on a long road, there's no question of that."

Gene therapy uses clones or synthetic copies of healthy genes to reverse the natural course of diseases caused by flawed genes. Experts use the simple analogy of replacing a missing or faulty fuse. Over the past five years the procedure has been tried on a range of conditions from cancers to HIV, with mixed results. And though

gene therapy has already been used to treat inoperable brain cancers, the two Auckland operations were the first to specifically target a neurological disorder.

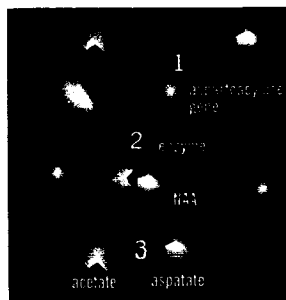
Canavan's disease affects between 200 and 500 children in the U.S. and seems to be most prevalent among Ashkenazy Jews. Canavan's results from a flaw in the gene aspartoacylase, which normally produces an enzyme to break down the naturally occurring compound N-acetylaspartate, or NAA. Broken down, the elements of NAA are thought to aid in building myelin, the brain's white matter. In Canavan's sufferers the gene fails to produce any enzyme and NAA accumulates, stifling the brain's communications networks. "It's like having a wire with no covering," says Karlin, a doctor himself. "A message might originate but it can't transmit properly."

The operation to restore those neural communications networks was relatively straightforward. A tiny hole was drilled in the girls' skulls, and a fine catheter inserted into the ventricular cavity, the fluid core of the brain. About 5 ml of cerebral spinal fluid was tapped off and replaced by 5 ml of liposomes—microscopic fat particles—laced with the synthetic gene. The liposomes will act as a carrier for the genes, which doctors hope will spread through the brain and begin producing the enzyme to break down the NAA.

The doctor behind the research, Wellington-born Professor Matthew During, is quick to point out that the operations were only the first step in attempts to treat neurological diseases with gene therapy. Their main purpose, he says, was to show that synthetic genes could be introduced into the brain. The disease has probably progressed too far in Alyssa and Lindsay for the genes, even if they work as hoped,

THE GENE

In a normal human brain the aspartoacylase gene (1) produces an enzyme (2) that breaks down naturally occurring n-acetylaspartate (NAA) into aspartate and acetate (3)



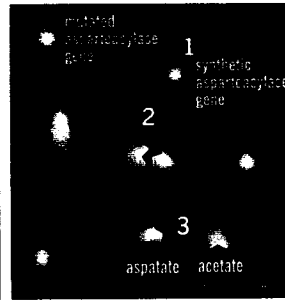
THE PROBLEM

In sufferers of Canavan's disease, the aspartoacylase gene doesn't produce the enzyme required to break down the NAA, which subsequently builds to dangerous levels



THE SOLUTION?

Using gene therapy, a synthetic replica of the aspartoacylase gene (1) produces the enzyme (2) which breaks down the NAA into aspartate and acetate (3), mimicking the normal process



to have any dramatic impact. "We are going into this knowing that we have to win the lottery if something's going to happen," says During.

Still, the girls' parents dream. "I imagine her running up to me when I get home from work, shouting: 'Daddy, Daddy, I missed you,'" says Mark Mushin, who owns an auto-transmission repair shop in Connecticut. "But I'll take whatever we get, because we love her so much."

The two families met last year through During, who was then at Yale University researching gene therapy in another neurological disorder, Parkinson's disease. When he returned to New Zealand in January to become head of molecular medicine at the University of Auckland's medical school, the families followed. They returned to America last week. "The least we are hoping for is a slowing of the progress," says Karlin, who, with the Mushins, plans to set up a fund for other Canavan's sufferers. "The most we are hoping for is a miracle."

Even if theirs doesn't happen, the research may make future miracles more likely. "No other family, no other child, no other mother should have to go through this," says Alyssa's mother Eileen, a science teacher.

Other neurological diseases may prove treatable too. During says Parkinson's offers the most hope of success, while epilep-

tics and Alzheimer's sufferers could also one day be helped by gene therapy. Beyond the treatment of disease, though, lies an ethical minefield. If a gene that causes a disease of the brain can be isolated and effectively replaced, will this give doctors the ability to alter other aspects of people's minds? Will personality surgery become as popular as plastic surgery? "You are altering someone's personality, their intelligence, who they are," says During. He believes that within 10 to 15 years the technology will make some alterations theoretically possible. "I think it's important to realize that we have come to a point where we have to start thinking about that."

Most human behavior, however, relies on the complex interaction of many different genes, and the job of isolating and mapping them has been underway for just a few years. It is a massive scientific challenge. In the end, our ability to alter the brain will depend on our ability to marshal its powers. ■



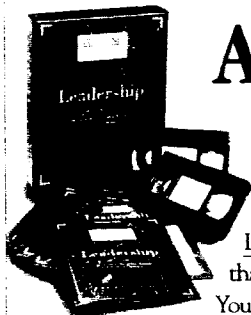
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