or not they favored the project. Ward Valley, says Dan Hirsch, president of the Los Angeles–based Committee to Bridge the Gap, a leading dump opponent, is fast becoming "the third rail of American science."

But last May, it seemed the long battle was drawing to a close. The National Academy of Sciences (NAS) released a report declaring that even if the waste canisters leaked, radioactive contaminants were "highly unlikely" to migrate from the unlined Ward Valley trenches to either the water table or the nearby Colorado river (*Science*, 21 April 1995, p. 358). The Clinton Administration moved almost immediately to transfer 1000 acres of federal land in Ward Valley to the state for development.

The NAS left opponents an opening, however. Soil tests conducted at the site in 1989 had detected tritium, deposited on the surface by fallout from nuclear tests in the 1950s and 1960s, at depths of some 30 meters. At that rate, liquid radioactive waste could conceivably sink from the dump to the water table, 210 meters down, in about 200 years, said one member of the 17-person NAS panel, June Ann Oberdorfer, a San Jose State University geologist.

The majority of the NAS panelists downplayed the 1989 test, saying that the tritium detected in the bore holes was probably a contaminant carried down from the surface during the drilling. But just to be certain, the panel recommended more tests to see how fast radionuclides really are migrating through the Mojave soil. The tests could and should be conducted while the dump is being built, most panel members concluded.

Almost a year later, the Interior Department, which now owns the Ward Valley site, has decided to act on that recommendation—but not as a routine test during construction. Instead, at the urging of Boxer and other politicians with ties to California, the department postponed the land transfer for a year to allow time for the tests and enlisted LLNL to do the work.

In a study that would last 4 to 6 months and cost between $150,000 and $200,000, the Livermore researchers plan to monitor not only the migration of tritium but also other fallout constituents like chlorine-36 and carbon-14, which may give a clearer picture of waste migration. "We wouldn't have taken the job if it was just a tritium test," says Jay Davis, LLNL's associate director for environmental programs.

But Ward Valley proponents fear that contamination will skew the results against them in spite of LLNL's sophisticated study. Dump opponents, for their part, are worried because the University of California, which manages LLNL for DOE, is already on record supporting Ward Valley's development. They also wonder whether a nuclear weapons laboratory can be trusted to conduct an unbiased test. "We're a nuclear weapons laboratory," Davis says. "If we worked for University of Alaska, they'd say, 'You gave that answer because you're nuclear guys.' "

LLNL might still get a reprieve, because the laboratory can only proceed with the DOE's consent. Last December, Secretary of Energy Hazel O'Leary rebuffed Boxer when she requested a tritium test, saying that under regulatory law, it is up to the state of California to request such an assay. Governor Pete Wilson, a Ward Valley supporter, plans to make no such request. Earlier this month acting Energy Undersecretary Thomas Grumbly reiterated DOE's position, but said he would discuss the matter soon with Deputy Interior Secretary John Garamendi, a test backer.

If the order falls through, LLNL scientists may sigh with relief. "It's not our project, and we're not driving it," Davis says. "That's my bottom-line comment."

–Jonathan Weisman

Jonathan Weisman is a science writer at the Oakland Tribune.

CLINICAL RESEARCH

New Zealand's Leap Into Gene Therapy

On 6 March, Matthew During, an expert in brain disease, announced that he had conducted New Zealand's first gene-therapy experiment. During injected a recombinant DNA molecule, which he designed while on a visiting professorship at Yale University, into the brains of two children with Canavan disease. (This progressive illness destroys the myelin sheathing of nerves in the brain; it figured in the movie *Lorenzo's Oil*.) The two

Hope in a New Treatment For a Fatal Genetic Flaw

By MATTHEW HAY BROWN

ROGER KARLIN and his wife, Helene, have not seen the movie "Lorenzo's Oil," Hollywood's account of the real-life efforts of a Washington, D.C. couple to find treatment for the rare disease that is ravaging their child. They know the 1992 film well enough to discuss its plot, refer to specific scenes, even quote characters. But they have been unable to bring themselves to watch it.

"It's funny," says Dr. Helene Kar-

three girls. "We haven't wanted to see it. I don't think we could handle it — even though we're living it."

The Karlins, of New Fairfield, are too preoccupied working to save their 15-month-old daughter from a rare form of leukodystrophy to spare even the brief emotional investment in a story so similar to their own.

Lindsay Karlin has Canavan's disease, a hereditary disorder named for Dr. Ruth Canavan, who identified it in the 1890's, in which the normal functioning and development of the brain are impaired. Roger Karlin, an internist with practices in Danbury

devoted their time and resources to organize and fund research to develop a cure.

Their efforts have led to new hope for their daughter. A team of gene therapists at Yale University now is working to develop a treatment to be attempted on Lindsay and 16-month-old Alyssa Muhlin, the daughter of Mark and Eileen Muhlin of Derby. If this attempt, to deliver healthy genes directly to the brain, is successful, it will revolutionize the treatment [illegible] only of Canavan's, but also of Alzheimer's disease, Parkinson's disease and other genetic [illegible] disorders.

Informal notification. *New York Times* story alerted federal regulators to the experiment.

patients, both girls under 2 years old and residents of Connecticut, flew to New Zealand earlier this year to receive the therapy at the Auckland Medical School. In a press release issued after the surgery, During and his colleagues announced that the therapy "could help delay the progression of a fatal neurological disease."

The experiment racked up several firsts, aside from being the first gene-therapy trial in New Zealand. It was the first use of recombinant DNA in humans to attack a disease of the nervous system (other than brain cancer), and it marked the first use in humans of a novel gene-transfer system. But for some regulators in the United States and New Zealand, it is noteworthy for another reason: It illustrates the pressures of regulating gene therapy across national borders when families are desperate for help.

The project began about a year ago, During says, when Roger Karlin, a Connecticut physician who is the father of one of the two patients, approached him at Yale seeking help for his daughter. During declined, he says, because he considered it unlikely any therapy would help. But Karlin persisted. During then "decided this was really quite a reasonable disease to use as a prototype to move the field forward."

Karlin and another Connecticut family raised funds to finance a gene-therapy experiment while During and Leaf Huang of the University of Pittsburgh worked on a vector. Their vector has three main elements: a human gene expressing aspartoacylase (which Canavan patients lack), an adeno-associated virus plasmid to insert the gene into human DNA and express it stably, and a low-risk artificial structure (including liposome and polymer).

During says he made a personal commitment to see the families through a clinical trial. The parents knew "from day one," he says, that they would have to go to New Zealand for therapy because he was due to move there in January. "I felt it appropriate to perform the procedure at the institution where I had jurisdiction," he told *Science*.

Until last summer, however, regulatory bodies were unaware of the impending therapy. During says he didn't notify U.S. authorities because the trial was to be in New Zealand, and in 1995, that country had no gene-therapy review committee. Robert Levine, who chairs a human subjects review panel at Yale, says he first learned of the project from a local paper, which ran a story on the Canavan families in June. Abbey Meyers, a patient advocate and member of the U.S. Recombinant DNA Advisory Committee (RAC), which monitors gene therapy funded by the National Institutes of Health (NIH), learned of During's project through a *New York Times* story in October. Meyers wrote on 16 October to RAC's executive director, Nelson Wivel, claiming that During planned to "ignore the rules that all American and European scientists are obeying." She argued that RAC has jurisdiction because NIH had funded the development of the vector. If RAC failed to intervene, she said, other researchers might also move clinical trials overseas.

In December, as During was preparing to leave Yale, RAC consulted with the university about his project. But Wivel decided that RAC need not intervene for several reasons: Levine was conducting a local ethics review, During is a citizen of New Zealand, and RAC permits U.S.-supported gene therapy to take place overseas if the host country runs a review that's "reasonably consistent" with RAC's methods.

Officials at Yale scrambled to complete their human subjects review in November. During was insisting that time was of the essence because there was a "limited window of opportunity" to intervene in the disease process. New Zealand's Health Research Council created a panel in January to review During's project on a rush basis. It rejected an initial protocol in February, but when During submitted new primate data, the authorities gave the nod for a simple safety test on 1 March. Meanwhile, the U.S. Food and Drug Administration—which had to clear an export permit for the vector—reviewed During's material and gave the OK, just days before the trial was to begin.

During told *Science* that "both children are doing extremely well and are essentially back to their presurgical state at 5 days postsurgery," having experienced a mild fever for 48 hours. Even During says therapeutic benefits are highly unlikely, but he hopes the test will demonstrate the safety of the technique and perhaps yield data on the persistence of the transplanted gene.

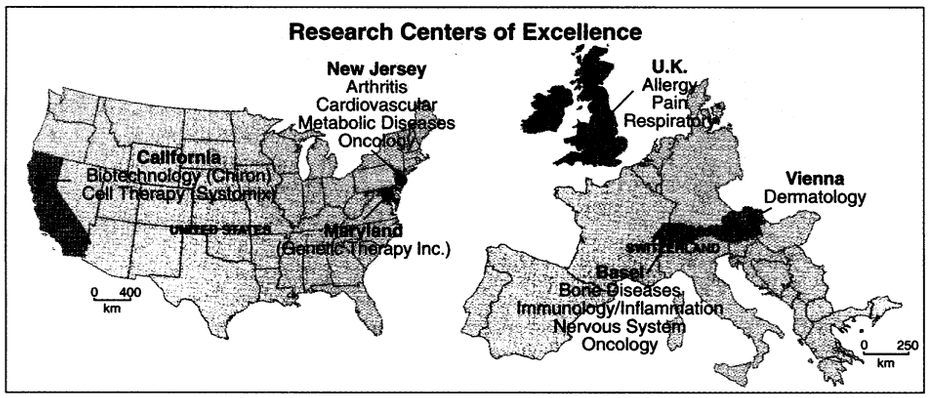
During and his colleagues are pleased with the outcome, because, as their press release says, they packed "5 years' research into 6 months." As for the paperwork, During now claims, "We ended up going through as much scrutiny as if we had just stayed within the U.S."

–Eliot Marshall

PHARMACEUTICALS INDUSTRY

Giant Merger Creates Biotech Power

BERLIN—Last week's announcement that Swiss pharmaceutical giants Ciba-Geigy and Sandoz are planning to join forces is the latest in a string of mergers that is changing the face of the world's pharmaceutical industry. If shareholders and regulators approve the deal, the new joint company, to be called Novartis, will be the world's second-largest pharmaceutical company, ranking behind the recently merged Glaxo-Wellcome. Novartis will also be a research powerhouse: Last year alone, the two parent companies spent well over $2 billion on R&D efforts in a global network of research centers, academic labs, and affiliated biotechnology companies.



Global research. Novartis plans to maintain at least three research centers of excellence in the United States and Europe currently run by the parent companies, Ciba-Geigy and Sandoz.

Just how the planned merger will affect this far-flung research empire will not become clear until the two companies begin to integrate their operations. In news conferences last week, however, company executives were upbeat about the prospects for R&D in the joint company. Noting that Novartis will be born with assets of $12.5 billion in cash and marketable securities, company officials said this huge sum will ensure that "even greater financial resources will be available for research and development."

Hundreds of research and related administrative positions are likely to be eliminated, however, as Ciba and Sandoz—both of which have headquarters in Basel and U.S. centers in New Jersey—trim overlapping operations. In all, Novartis managers plan to cut about 10% of the companies' 134,000-strong work force over the next 3 years. Some 28,000 of those employees work in the United States and 43,000 in Europe. Daniel Vasella, the Sandoz chief executive who will become Novartis's president, says he expects the fewest job cuts in the R&D sector. Indeed, he said in a statement that the merger "unlocks resources for further expansion."

Eric S. Lander, director of the Whitehead Institute–Massachusetts Institute of Technology Center for Genome Research—which will be participating in a new $1 million gene-mapping venture announced by Sandoz earlier last week—says "I don't think basic science is the issue" in the wave of drug-company mergers. Compared to the development and marketing of new pharmaceuticals, he says, the research is relatively inexpensive. "The 'R' is extremely cheap in comparison to the 'D,' " Lander says. "So if they are merging, they are merging for their 'D.' They'd be crazy to merge for their 'R.' "

Historically, most of the two companies' profits have come from traditional pharmaceuticals. Ciba is a leader in drugs for arthritis and high blood pressure, and owns the second-largest supplier of generic drugs in the United States; Sandoz leads the market in immunosuppressants, as well as drugs to treat schizophrenia and fungal infections. But in recent years, both Ciba and Sandoz have taken over smaller companies to strengthen their research efforts in biotechnology. In 1994, Ciba paid $2 billion for a 50% stake in Chiron Corp., a leading U.S. biotech company, and Sandoz followed suit last July by paying $295 million for gene-therapy pioneer Genetic Therapy Inc.

Novartis is expected to expand research efforts in biotechnology—where Sandoz and Ciba officials already claim to lead all competitors "in gene, cell, and organ-based therapies"—while maintaining an interest in combinatorial chemistry and more traditional areas of research. Once Ciba's specialty chemicals division is spun off as a separate firm, health care will account for 59% of Novartis's business, followed by agrochemicals (27%) and nutrition (14%).

According to a company document, Novartis's pharmaceuticals branch plans to maintain "research centers of excellence" in at least three U.S. and three European sites. These centers will concentrate on research in five main areas: cardiovascular and metabolic diseases, such as renal failure, osteoporosis, and type II diabetes; central nervous system diseases, including schizophrenia, Alzheimer's, and epilepsy; dermatology; immunology, inflammatory and respiratory diseases, such as asthma, arthritis, and transplant rejection; and oncology. Meanwhile, to help ease the impact of expected job losses, Novartis plans to establish a foundation, with an $80 million endowment, "dedicated to job retraining and to fund start-up entrepreneurial activities specifically in biotechnology and emerging technologies."

–Robert Koenig

Robert Koenig is a writer in Berlin.