and Kamiokande, leave open two small ranges of solutions based on the MSW effect.

Finding themselves in an even tighter bind than before, solar neutrino researchers are looking to the next round of results for relief. Both SAGE and GALLEX plan to collect data for several years, improve their statistics, and calibrate their instruments with an artificial neutrino source. It's assumed that the results from the two instruments will converge—but whether at 125 SNU, 83 SNU, or 20 SNU, no one can say. At a neutrino conference this week in Granada, Spain, for example, SAGE reported preliminary data from six month-long runs in 1991, ranging from close to zero all the way to 100 SNU. Says SAGE's Bowles, "It seems likely that our [original] results will come up a bit."

If the figure of 83 SNU ends up holding firm, then the case of the missing neutrinos will have to wait for a retrial in the next generation of experiments, in particular the Sudbury Neutrino Observatory (SNO), to be commissioned in the spring of 1995. SNO, already under construction in a nickel mine in northern Canada, will snare neutrinos in a tank of ultrapure heavy water, making it the first detector sensitive to muon and tau neutrinos as well as electron neutrinos. That will enable it to test whether the neutrinos have been changing their identities, as the MSW theory holds, or whether the sun itself is not behaving by the book. "If the results of the gallium experiments stay in this indefinite area," says the University of Pennsylvania's Gene Beier, a member of the SNO collaboration, "then you can't distinguish neutrino physics from solar physics. SNO can."

–Gary Taubes

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CANCER THERAPY

Molecular 'Surgery' for Brain Tumors

Perhaps nothing frustrates a neurosurgeon—or terrifies a patient—more than an inoperable brain tumor, its murderously dividing cells tucked out of reach of scalpel or laser. To overcome that kind of frustration, a team of National Institutes of Health (NIH) neurosurgeons is planning a remarkable new form of molecular "surgery," based on gene therapy, for attacking some inoperable brain tumors. Last week, the NIH recombinant DNA advisory committee (RAC) voted 19-0 (with 1 abstention) to approve a protocol for transferring a viral gene into brain tumor cells, making them susceptible to destruction by the antiviral drug ganciclovir. The RAC's approval of the trials, which will likely begin in the fall, was based largely on promising animal results reported in this week's *Science* (see page 1550).

The new protocol has provoked considerable enthusiasm in the gene therapy community. "It's like putting bull's eyes in the tumor cells and shooting them," says Nelson Wivel, director of NIH's office of recombinant DNA activities. "It's an exciting protocol." The new method is creating a stir in part because it includes a significant twist on current gene therapy. In standard procedures, researchers extract cells from a patient who lacks normal copies of a particular gene. They then add that gene to the cells via a vector (often a virus) and inject the cells into the patient. In this case, however, the NIH researchers can't reinject human cells. Instead, they plan to modify cells from another species and inject those. "We're going to be putting mouse cells in these patients' brains," explains Edward H. Oldfield, head of the surgical neurology branch of NIH's National Institute of Neurologic Disorders (NIND), who will be carrying out the clinical trials with NIND neurosurgeon Zvi Ram.

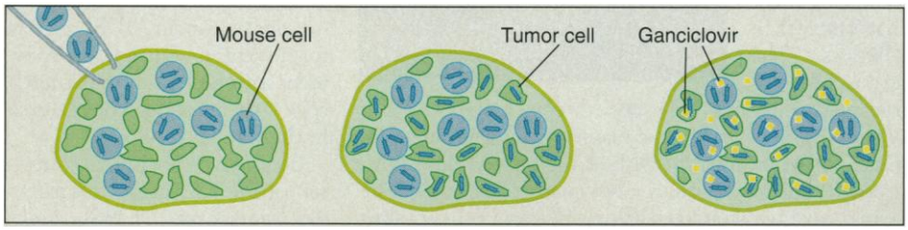
The method was conceived and initially developed 18 months ago by Kenneth Culver, an oncology researcher working in the laboratory of R. Michael Blaese, chief of the National Cancer Institute's cellular immunology section. "When I proposed this idea, people thought it was crazy," says Culver. His "crazy" idea, essentially, was to inject tiny biochemical factories into patients' brains. The method calls for inserting into mouse cells a retroviral vector carrying a gene from another virus—herpes simplex. The herpes gene codes for an enzyme called thymidine kinase, which turns any cell producing it into a target for antiviral drugs. The mouse cells—known as fibroblasts—that carry the retroviral vector are injected very precisely into a brain tumor. There the fibroblasts' molecular machinery starts pumping out copies of the retroviral vector, which infect nearby tumor cells. The infected cells now produce thymidine kinase, laying themselves open to attack by ganciclovir.

In rats this form of gene therapy proved to be surprisingly toxic to cancer cells, says Blaese, whose laboratory collaborated with the NIND neurosurgeons on the animal studies. In addition to killing the tumor cells that were known to have the herpes gene in them, ganciclovir killed other tumor cells in their vicinity. Exactly how the "bystander effect" operates isn't known, but Blaese speculated that it might be due to thymidine kinase and ganciclovir interacting to produce toxic triphosphates that inhibit DNA synthesis in rapidly replicating cells. A similar bystander effect is exploited in a gene therapy protocol being developed by Scott Freeman, a medical researcher at the Tulane University School of Medicine.

Along with the excitement over these results comes a certain amount of nervousness. "The risk is higher," says Gary Nabel, a molecular biologist at the University of Michigan, whose laboratory works with the herpes thymidine kinase gene. "But, then," he adds, "so are the stakes." Nabel warns of a slim possibility that "helper" viruses might contaminate the recombinant retroviral vectors and cause a secondary infection in noncancerous cells. "The key will be to make sure that the quality control of the cell lines is good," he says. Researchers also worry that the retroviral vector might infect proliferating noncancerous cells—such as cells in the bone marrow, thymus, and intestinal epithelium. This didn't seem to happen in rats, nor did toxicity studies in monkeys raise any red flags, says Oldfield.

Whether or not the concerns are justified will become clearer after the protocol clears its final hurdle: approval by the Food and Drug Administration (FDA). If the FDA agrees, Oldfield and Ram will use a surgical procedure called MRI-guided stereotaxis to inject the retrovirus into brain tumors in three patients having life expectancies of less than 3 months. If the retrovirus does not cause significant toxicity in these patients, the researchers will expand the clinical trial to 20 people. Despite the impressive animal results, the NIH researchers are cautious in predicting clinical success. "This is a nice idea, but we're just getting started," says Blaese. "It will take a long time for the method to prove itself." But if the procedure lives up to the promise indicated in the animal trials, the payoff could be large: The NIH researchers plan to conduct a "broader search" of other tumors—including some kinds of liver metastases, Culver says—that might be treated with the same kind of molecular surgery.

–Richard Stone



SOURCE: KENNETH CULVER ILLUSTRATION: D. DEFRANCESCO

Shooting bull's eyes. Mouse cells carrying a herpes virus gene are injected into a brain tumor *(left)*. The herpes genes are inserted into the genomes of nearby tumor cells *(center)*, making them a target for an antiherpes drug called ganciclovir *(right)*.