Changes Ahead for Gene Therapy Review Process?

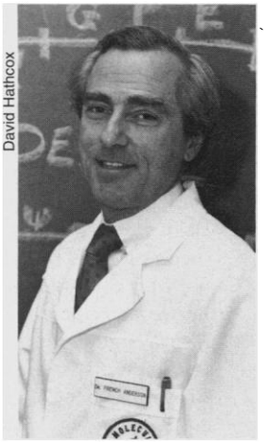
While they were approving new experiments, federal reviewers were questioning their own existence

IN WASHINGTON THE SAYING GOES THAT people who like legislation and sausage shouldn't see how either of them is made. After last week's marathon, 2-day meeting of the National Institutes of Health (NIH) Human Gene Therapy Subcommittee, squeamish scientists might want to steer clear of the gene therapy approval process as well.

Showing unprecedented largess, the subcommittee that reports to the NIH Recombinant DNA Advisory Committee (RAC) granted provisional approval to four of five new gene therapy experiments involving human subjects. Carrying away their precious seals of approval were three new cancer therapies and a treatment for a genetic disease that brings its victims extremely high levels of serum cholesterol (see box). Only two gene therapy experiments have been approved so far. But even the "lucky winners" would say that the approval process is unnecessarily time consuming and repetitious.

Indeed, that concern may soon change the route by which gene therapy projects go from the lab bench into human subjects. For one thing, the RAC itself seems to be acknowledging that its approval process is redundant and slow, and NIH is at least considering doing away with its own gene therapy subcommittee in an effort to cut out duplication. In addition, research teams in the private sector who don't need NIH approval may choose to circumvent the RAC altogether and go straight to the Food and Drug Administration (FDA) for approval—raising concern among some researchers, who fear the loss of public scrutiny that the RAC's process provides.

There's no question the process as currently constituted can take time: A researcher can spend years racking up the necessary approvals. First they must obtain the blessing of the human subjects review and biosafety committees of their home institutions. Then, they need an OK from the RAC as well as the RAC's gene therapy subcommittee that was so generous with its approvals last week. But even at this stage there's one more major hurdle: a grilling from the final arbiter of all human therapies, the FDA.



David Hathcox

Anderson: *How much scrutiny is enough?*

Few have had more direct, personal experience with the process than National Heart, Lung and Blood Institute researcher W. French Anderson. He, along with National Cancer Institute researchers Steven A. Rosenberg and R. Michael Blaese in 1988 presented the first protocol to the gene therapy subcommittee. That experiment was an attempt to put a genetic marker on white blood cells to show that foreign genes could be safely introduced into humans. Since then, Anderson has also received approval for an experiment to use gene therapy to treat a rare immunological disorder in children. He's also involved in several other protocols that have either received or are nearing RAC approval.

But Anderson argues that now that the RAC and the gene therapy subcommittee have gained experience with such protocols and learned where the pitfalls lie, they should look for ways to streamline the review process. "People are starting to think about getting around the review," warns Anderson.

Four Thumbs Up—One Thumb Down

Although getting grilled by the Human Gene Therapy Subcommittee may not be pleasant for researchers, it does tend to keep them on their toes, and helps make certain that no potential problems with an experiment fall through the cracks. That function was most evident when the panel discussed the protocol from molecular biologist Gary J. Nabel of the University of Michigan Medical Center. Nabel and his colleagues want to put proteins called histocompatability antigens into tumor cells to provoke immune responses. Experiments in mice suggested that such an approach could lead to tumor regression. But during the discussion of the protocol, Dusty A. Miller of the Fred Hutchinson Cancer Research Center, a panel member who developed some of the techniques now being used in gene therapy experiments, pointed out that a manipulation proposed by Nabel could inadvertently inject a cancer-causing gene into a human subject. The subcommittee promptly sent Nabel back to the lab to demonstrate this would not happen before they would approve his experiment.

But Nabel was the only principal investigator shot down by the subcommittee. After much discussion, the panel voted to approve an experiment proposed by James M. Wilson, a Howard Hughes investigator at the University of Michigan Medical Center, to treat patients with familial hypercholesterolemia, an inherited disorder that causes extremely high levels of cholesterol in the blood. Wilson's experiment involves removing a portion of a subject's liver, inserting a gene that helps remove cholesterol from the blood into progenitor liver cells, and then injecting the modified cells back into the patient.

The subcommittee also approved two protocols from Steven A. Rosenberg of the National Cancer Institute. In one, Rosenberg will incorporate the gene for the naturally occurring anticancer substance called tumor necrosis factor into a patient's own tumor cells. He then plans to inject the tumor cells expressing the new gene back into the patient. The idea is that the modified tumor cells will stimulate a more powerful immune response. In the other the tumor cells will be modified with an immune modifier known as IL-2.

Although few members of the subcommittee gave it much chance of working, the subcommittee nevertheless approved a protocol submitted by Scott M. Freeman of the University of Rochester Medical Center that would put a protein on the surface of killed ovarian cancer cells that makes them sensitive to the drug gancyclovir. Based on observations in mice, Freeman predicts that both the modified cells and those growing in the cancer patient will be rendered susceptible to gancyclovir by the experiment.

All these protocols must still be approved by the full RAC, which meets next in October. ■ J.P.

And indeed, if a research team can live without NIH support, there's no reason for it to come to the gene therapy subcommittee at all. Take a company like Viagene, Inc., in San Diego. Using recombinant DNA techniques, researchers there are developing a way of inserting certain proteins from the AIDS virus into an AIDS patient's cells in the laboratory, and then injecting those cells back into the patient to stimulate an immune response to the virus. All this is being done with private financing. So although Douglas Jolly, scientific director of Viagene, says that the gene therapy subcommittee might provide useful advice, he concedes that it's not certain the team will seek RAC approval since it's the FDA that will determine whether Viagene has a marketable process.

And therein lies the rub for gene therapists like Anderson. While they're all for streamlining the process, they worry that even if the FDA has the ability to judge whether a protocol involving cutting-edge science such as gene therapy is safe and effective, the process will go behind closed doors since the FDA typically conducts its reviews in private. If an unsafe proposal should slip through—and the potential always exists for unexpected behavior from an inserted gene or the vector that carries it into a cell—the hard-won public confidence in gene therapy would vanish. At least in NIH's public forum, skeptical scientists can warn their colleagues or the public if they feel something is amiss.

The RAC and its gene therapy subcommittee have begun to look for ways to shorten the approval process. At last week's meeting the subcommittee formed a working group to identify which projects would no longer need close scrutiny. The subcommittee also considered but did not act on a proposal to combine the RAC and its subcommittee into a single entity, since the two committees perform much the same task with many of the same people.

But sometimes it's hard to know just what the subcommittee is doing. After railing for hours at University of Rochester researcher Scott Freeman for his failure to provide detailed answers to the committee's formal "points to consider" in his protocol—warning him and others that such a failure was intolerable—the committee nevertheless approved his protocol 7 to 1 with two abstentions. Even those interviewed by *Science* who voted for the experiment were at a loss to explain why they had abandoned their own rules. One person observing the meeting suggested the approval might have been associated with the fact that the meeting had dragged on for 9 hours, and the dinner hour was beckoning. Perhaps future reviews should be scheduled only for the morning. ■ JOSEPH PALCA

A Trap to Snare a Monopole

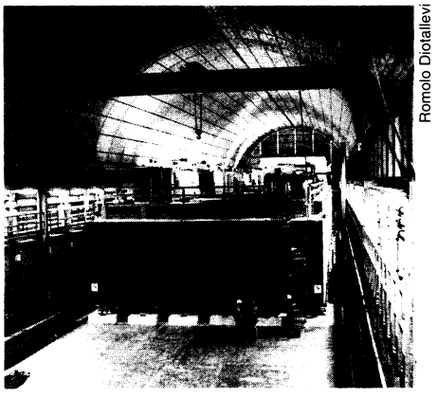
Deep inside Gran Sasso, a peak in Italy's Apennine mountain chain, physicists are waiting for the most massive elementary particle yet theorized to lumber in from outer space and reveal itself. If the search for this elusive particle, the magnetic monopole, is "a gambler's field," as one physicist calls it, then this group of scientists from the United States and Italy is betting big—to the tune of $20 million, the cost of the Monopole, Astrophysics and Cosmic Ray Observatory (MACRO), which has been under construction for 7 years and now stands ready for a monopole sighting.

"It's really a long shot, but a very important long shot," says University of Chicago physicist Henry J. Frisch, adding, "It would be the discovery of the century." More specifically, a monopole detection would be the first unequivocal sighting of a particle conceived as a solitary magnetic pole—a "north" without a "south."

Scientists can't make a monopole by cutting a magnet in half—each half is left with two poles. Nor can they conjure one up in an accelerator—the mass of a monopole is so great (about the same as a paramecium) that cooking one up from scratch would take too much energy. So physicists need to catch the strange beast to prove its existence.

The search amounts to more than a unicorn hunt, for the quest has high theoretical stakes for particle physicists and cosmologists. Grand Unified Theories (GUTs), which mathematically tie together the strong, weak, and electromagnetic forces, predict that the Big Bang created a slew of monopoles. Many of them would have annihilated themselves in the early universe, but GUTs insist that a few monopoles must survive. And if they do, the massive particles could help cosmologists out of their own theoretical bind, posed by the fact that the universe seems to contain a large helping of invisible—and so far inexplicable—mass. According to Caltech physicist Barry Barish, who codirects the joint U.S.-Italy detector, monopoles could account for "anywhere between 3% and 100% of the dark matter in the universe, depending on how many we find and how heavy they are."

Physicists have set off on monopole hunts before, only to be disappointed. In the 1960s and 1970s, they had high hopes that they could squeeze monopoles out of magnetic materials such as iron ore or moon rocks or detect their ancient tracks in flakes of mica. But after fruitlessly combing rocks for monopoles or their traces and making several efforts to create monopoles in accelerators, many physicists were ready to give up the chase. Then, on Valentine's Day 1982, using a coil of superconducting niobium wire, Stanford University physicist Blas Cabrera announced the discovery of what he thought was a magnetic monopole. But that seems to have been a false alarm.



Romolo Diotallevi

The waiting game. *MACRO gets ready.*

Having tried unsuccessfully for 8 years to record another monopole, Cabrera wrote in the 19 February 1990 *Physical Review Letters* that the find "should be discarded."

So the burden of proof falls on MACRO, actually a collection of three kinds of detectors layered in a football field-sized mass of concrete and iron that, in addition to monopoles, will detect neutrinos, muons, and other exotic particles. Last month scientists fired up two of the detector's six sections, and they plan to complete the other four sections in the coming weeks. If a monopole does pass through any one of the detector's sections, which are cloistered underground to limit the background radiation, it should leave three separate marks: a flash of light in the liquid scintillation counters, a burst of ionized helium in the plastic streamer tubes, and a trail of cracks in the plastic track-etch detectors.

Scientists say the redundancy will prevent spurious detections. But the main reason physicists give MACRO better odds than previous efforts is its sheer size, about 1000 times bigger than Cabrera's desktop-sized detector. Says Richard Heinz, an Indiana University physicist working at MACRO, "We'll be the first detector that has a chance." ■ RICHARD STONE