Gene Transfer Test Back on Track

After a temporary setback, the first gene transfer experiment in humans now seems headed for certain approval, perhaps as early as this month. On 9 December the human gene therapy subcommittee of the National Institutes of Health (NIH) approved the experiment by a unanimous vote of 13 to 0.

The experiment was all but approved a couple of months ago, having passed the parent recombinant DNA advisory committee, or RAC, by a vote of 16 to 5 (*Science*, 11 November, p. 856). But NIH director James B. Wyngaarden, unhappy with the review process and concerned about the divisive debate over the experiment, refused to sign off on it, instead sending it back to the subcommittee, which had earlier deferred a decision on the experiment because of insufficient information.

The proposal, by W. French Anderson, Steven A. Rosenberg, and R. Michael Blaese of NIH, is controversial because it would be the first introduction of a foreign gene into humans and thus paves the way for long-awaited attempts at gene therapy. This experiment, however, does not really constitute gene therapy, as the introduced gene will confer no therapeutic benefit on the patients. Rather, the foreign gene will serve as a marker to track the progress of an experimental cancer therapy now being tried on terminally ill patients at NIH.

If it proves successful in these patients, however, the same technique could later be used to introduce therapeutic genes, such as genes to fight cancer or perhaps AIDS. Anderson and his colleagues expect to propose such experiments as early as next year.

Although the NIH reviewers maintain that this gene transfer experiment is not a precedent for gene therapy, they know full well it will be viewed as such. Hence the careful scrutiny and Wyngaarden's insistence on exemplary procedures. Last week's was the ninth formal review of the experiment.

Throughout the review process, the issue has been safety; namely, whether the virus vector used to ferry in the gene may cause cancer. The vector has been modified so that it is not infectious, but the reviewers want to be sure that if a few infectious particles slip in anyway, they can be detected before being inserted into the patients.

What should have been a scientific discussion over safety erupted into a bitter personal fight at the October RAC meeting, when the investigators admitted that they had withheld key data from both committees, they said out of fear that it might jeopardize publication. Although the RAC, which shares many of its members with the gene therapy subcommittee, approved the experiment anyway, some members were outraged—at least one threatened to quit—as, reportedly, was Wyngaarden.

By last week's meeting, all the data had been submitted and apologies were offered. After reviewing the new data, the subcommittee decided that the safeguards were adequate and the experiment could proceed, with the same strict limitations that the RAC had imposed: it will be tried on only ten cancer patients who are expected to live no more than 90 days.

Discussion then shifted to fine-tuning the protocol to ensure that maximum scientific information is obtained. The consensus among the group was the scale had been tipped too much on the side of minimizing the already minuscule risk, to the detriment of the science. Indeed, several members were concerned that the experiment might yield no useful information at all.

The subcommittee suggested that by increasing the number of marker cells inserted into the patients, the investigators could design a far more useful experiment with only a slight increase in risk. Anderson, who admitted to being gun-shy by this time, was clearly relieved and will take that course.

The proposal now moves on to a mail vote by the RAC. If the committee approves it as expected in the next few weeks, the proposal will go back to Wyngaarden for the second time. Food and Drug Administration approval is also expected soon, and the investigators hope to begin the experiment in early 1989. ■ LESLIE ROBERTS

AIDS Mice Die in NIH Accident

A laboratory accident at the National Institutes of Health has killed all but 3 of 130 mice that had been produced in an effort to develop an animal model for studying AIDS. The lack of such a model has been hindering AIDS research, especially on drug and vaccine development.

Malcolm Martin of the National Institute of Allergy and Infectious Diseases and his colleagues had created the mice by gene transfer. The researchers had injected newly fertilized mouse eggs with the cloned genome of the AIDS virus, known as human immunodeficiency virus (HIV), and then implanted the injected eggs into foster mothers to develop. Mice are not naturally susceptible to HIV infection, but the researchers hoped that once the AIDS virus genes were in the mouse cells they would produce pathological changes similar to those seen in human AIDS.

The Martin group succeeded in producing mice carrying HIV genes, and one line of the animals spontaneously produced symptoms that resemble those of AIDS in at least some aspects. (These results plus reports on mouse AIDS models from two additional groups will appear in the 23 December issue of *Science*.)

Now, all but three of the mice in the Martin experiment are dead, apparently as the result of an accident that occurred on Saturday, 3 December. "We checked the animals on Friday night, and everything was all right," Martin says. "On Sunday we found a massacre." Two of the three survivors carry HIV genes, although neither belongs to the line that develops spontaneous symptoms.

Although the experiments have been controversial, there was no indication of sabotage, Martin says. On the Saturday in question, the electricity in the building where the animals are kept had been turned off for several hours so that the NIH engineering department could perform preventive maintenance on the alarm system for the building's ventilation system. Because of fears that mice carrying the AIDS virus might escape and allow the virus to spread, the animals had been kept in special containment cabinets, surrounded by moats of bleach.

With the ventilation system shut down, the mice may have died of heat exhaustion, Martin suggests. Temperatures of 85° F are sufficient to begin killing mice.

Martin says he did not know that the electricity was going to be shut off that Saturday. He should have received a notice about it, but for some reason did not. An alarm signal that could have alerted NIH personnel about a possible problem in the building where the animals were kept had flashed at an NIH security monitoring center, but when the workers on duty there checked, they were told that the alarm was the result of the maintenance work and nothing to worry about.

Martin estimates that the accident has set his research back by from 4 to 6 months. He hopes that simpler containment facilities, which are less cumbersome to use than the current ones, can be designed for future work. "It was supposed to be a fail-safe system for protecting people," Martin says of the current setup, "but when it failed the mice were killed." ■ JEAN L. MARX