Gene Therapy Guidelines Revised

Changes in requirements for an essay on social issues and an easing of demands governing animal experimentation mark revisions in guidelines

A committee of the National Institutes of Health (NIH) has just revised guidelines that will govern human gene therapy when the first experiments in this emerging field of medicine take place sometime within the next year or two. In January, the Working Group on Human Gene Therapy, which is a subcommittee of the NIH Recombinant DNA Advisory Committee (RAC), issued draft regulations in a document called "points to consider" in preparation of an experimental protocol for human studies (*Science,* 1 February, p. 493–496). On the basis of public comment and working group discussion, the revised draft contains some important additions and modifications.

For example, the early draft, which was published in the 22 January *Federal Register*, asked gene researchers to answer complex social and ethical questions as part of their experimental protocol. "Is it likely that somatic cell therapy for human genetic disease will lead to: (a) germ-line therapy, (b) the enhancement of human capabilities by genetic means, or (c) eugenics programs encouraged or even mandated by governments?" was one such question.

In the revised document, these issues are noted as topics for continuing discussion by the Working Group. As one member of the Working Group said in an interview with *Science,* "Philosophers, ethicists, and members of this group have yet to answer those questions.

Another modification—of particular importance to the handful of scientists who are likely to be among the first to attempt gene therapy in patients—is one that introduces flexibility in requirements for animal testing prior to human experimentation. The first "points to consider" draft clearly implied that the Working Group would not approve protocols unless there had been studies in primates. Arguing that research in laboratory mice or dogs or other animals could well be sufficient, opponents of the primate requirement prevailed on the Working Group to modify its position. The revised document asks for information about laboratory studies in "nonhuman primates and/or other animals." Researchers find this change important for a couple of reasons. First, some believe, primate studies, which are particularly costly, would not necessarily produce data that cannot be obtained from other species. Second, the diseases that will be the target of the first human gene therapy trials are so devastating that experimentation in patients can be justified ethically as long as some animal data are in hand.

A cogent argument for moving ahead as quickly as possible was made by a University of Wisconsin (Madison) physician who responded to the Working Group's call for public comment on its initial document. Sheldon Horowitz addressed several important questions in his letter to Working Group chairman LeRoy Walters of the Kennedy Institute of Ethics at Georgetown University. "I am now taking care of a 6-½-year old child with ADA [adenosine deaminase] deficiency and severe combined immune deficiency who I feel should receive gene therapy as soon as possible. Enzyme replacement therapy, thymic factor and thymic transplant have been tried in this child without effect. A bone marrow transplant could be tried in this girl. However, since there is no sibling who is identical, it would be a mismatched transplant. . . . I think it is very likely that the transplant attempt would kill her." With this, Horowitz has spoken to one of the important issues surrounding experimental gene therapy. Namely, "is there any good alternative that should be tried first?" Horowitz, who estimates that his patient has only 12 months to live, also wrote that he believes the risk of the experiment itself producing a new infectious virus is "remote."

With regard to issues about informed consent, Horowitz said, ". . . the parents are very well informed of the issues and very much want to proceed with gene therapy. There is no reasonable alternative. Gene therapy may have only a small chance of success, but its risks are minimal compared with certain death."

ADA deficiency is one of only a handful of genetic diseases that are candidates for early gene therapy trials. Like others on the list, the disease is rare (there are fewer than 50 ADA patients known worldwide), a fact that the Working Group believes is pertinent to consideration of the first experimental protocols. "It is expected that these first cases will involve one or a very few patients, using biological material prepared under the direct personal supervision of the principal investigator," it says. When gene therapy becomes more widespread, not only might the Working Group amend its guidelines but the Food and Drug Administration, as monitor of new drugs and biologicals, would become party to the approval process as well.

Additional modifications in "points to consider" include the following:

- Public review. The group believes that open, public access to information about initial gene therapy experiments is critical. Therefore, in a statement intended to speak to the question of proprietary data, it now says "The [group] would prefer that the first proposals submitted for RAC review contain no proprietary information or trade secrets, enabling all aspects of the review to be open to the public. The public review of these protocols will serve to inform the public not only of the technical aspects of the proposals but also on the meaning and significance of the research."
- Germ line therapy. For the present, only experiments involving somatic cell therapy will be considered. Making a clear distinction between somatic cell therapy, in which genetic changes would not be heritable, and germ line therapy, in which genetic alterations would be passed on to future generations, the group will not even consider germ line therapy protocols until somatic cell therapy has progressed and public discussion of the implications of germ line work has been broadened.
- Patient responsibilities. First, they will be asked to agree to long-term fol-

Smith Wins Foreign Reporting Prize

The Overseas Press Club has awarded a Citation for Excellence to R. Jeffrey Smith for his series of News and Comment articles on European missile deployment that were published last year. Smith's citation was in the category of "best magazine story on foreign affairs," in which V. S. Naipaul took first place for an article in *Harper's* on Grenada.

low-up (at least 3 to 5 years) as a precondition for participation in the study. Second, they will have to agree to an autopsy in the event of death.

At the present time, the NIH has received no gene therapy protocols. However, it is gearing up the necessary administrative apparatus in expectation that one or more will be coming before long. There are five laboratories in the United States that, at present, are pursuing research that will lead to human gene trials. When they are ready to go, their research protocols will undergo one of the most extensive reviews any research has been subjected to.

Approval from the investigators' local Institutional Review Board and Institutional Biosafety Committee must precede submission to the NIH Working Group. Its review will be followed by a review by the full Recombinant DNA Advisory Committee, which then will forward its opinion to the director of NIH for his final review.

At all federal stages, this process will take place in the open. Not only will NIH committee meetings be open, a précis of the protocol itself will be published in the *Federal Register* for public comment.

Some Working Group members have been struck, in the process of revising their "points to consider," by the fact that public comment has been minimal. Only 14 letters were received, some of them from federal agencies providing an official response. One group member reports that there has been consideration of setting aside an additional period for public comment to preclude allegations that the draft document was somehow rushed through. Conspicuous by their silence were signers of a petition that activist Jeremy Rifkin wrote nearly 2 years ago, protesting the extension of recombinant DNA technology to medical genetic intervention (*Science*, 24 June 1983, p. 1360). Each signer of that petition was sent a copy of the points to consider document. None, except Rifkin himself, replied. He criticized the present Working Group as "not broad-based enough in its professional composition," saying, for instance, "There are no anthropologists, sociologists, psychologists, or theologians. . . ." The Working Group may decide to create special subgroups to deal with special issues as needed when it feels the need for greater expertise in certain areas.

The next stage in the policy process will be a review of the revised guidelines when the Recombinant DNA Advisory Committee meets at NIH on the third of May.—**BARBARA J. CULLITON**

Shuttle Encounters Landing Trouble

As the shuttle Discovery returned on 19 April from its fourth visit to space, it encountered unusually serious, but not entirely unexpected, landing trouble. The touchdown itself went smoothly, but as the shuttle braked to a stop, first one of its main wheel sets locked and then another, causing a blowout of one tire and the shredding of another. Had the lockups occurred earlier, when the shuttle was rolling more quickly, all four main tires might have failed, and disaster would have ensued.

No one was immediately certain what caused the mishap, but suspicion centered on the shuttle's brakes and landing gear, components that have long been plagued with problems. National Aeronautics and Space Administration (NASA) officials claim that the brakes and landing gear have worked relatively well during the first 16 flights, suffering only a few broken parts. "No flight safety issue exists with the current design," the agency concluded after a special review last summer.

A different picture emerges from the annual reports of the program's independent auditors, a group known as the Aerospace Safety Advisory Panel. As long ago as January 1982, the panel—composed of nine experienced aeronautical engineers—concluded that the margin of safety for the landing gear was low, and noted that the "design is such that should a tire fail, its mate (almost certainly) would also fail—a potential hazard." As predicted, both of the Discovery's right main tires experienced serious damage at roughly the same time.

In January 1983, the panel again noted that "the landing gear tires and brakes have proven to be marginal and constitute a possible hazard to the shuttle." It recommended three major modifications, each of which has been resisted by cost- and schedule-conscious shuttle program managers. First, it recommended that the brakes, which are manufactured by the B. F. Goodrich Company, be replaced or significantly upgraded. "There have been actual or incipient brake failures on almost every landing even though landing weights have not yet approached the design maximum," the panel said. The risks have increased over time because shuttle pilots have steadily demanded more braking power. During the Discovery's latest landing, for example, the braking force on one tire set reached 41 million foot pounds, well beyond the average for previous flights.

Second, the panel recommended that program managers install a mechanism for automatic braking, relieving the pilot of a fairly arduous task during "a period of high strain." Such mechanisms are already installed on 747, DC-10, DC-9, and other jetliners, the panel noted. "Adaptation for use on the shuttle should be a simple process and would relieve crew workload and result in shorter, consistent stopping distances."

Third, the panel recommended that steps be taken to reduce the shuttle's landing speed and to relieve stress on the rear wheels. Specifically, a small wing, known as a canard, should be attached near the nose, the forward landing gear should be lengthened, and the number of rear tires should be doubled, the panel said.

Although the agency has expressed a willingness to study the problems further, it is notably unenthusiastic about the suggested reforms. Doubling the number of rear wheels would require a larger wheel compartment, the agency concluded last August, which in turn would require wing modifications. Lengthening the nose gear would cost $50 million and take 3 years. Adding a canard would require redesign of the fuselage, and various flight controls, resulting in significant schedule delays. "Future generation vehicles will include consideration of canards," the agency said.

In January, the advisory panel said that it accepts the impracticality of adding a canard, but urged NASA "to continue to seek other, more readily adaptable solutions." For the moment, the agency has decided only to install additional brake and landing-gear sensors, to modify a few brake parts, and to make it somewhat easier for the pilot to depress the brake pedal. Additional reforms may result from study of the Discovery's mishap.—**R. JEFFREY SMITH**