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.