expected, may be initiated without RAC review if approved by another Federal agency.

X. Discussion on Adenoviral Vector Toxicology

On January 19, 1995, Dr. Philip Noguchi, Food and Drug Administration, Rockville, Maryland, requested the Recombinant DNA Advisory Committee discuss adenoviral vector toxicology. In his letter, he states:

'The RAC has correctly identified an emerging issue in terms of preclinical toxicities of adenoviral vectors given parenterally. From the FDA's point of view, the area of biotoxicology is an evolving one that has been one of FDA's main tools for determining dosing in gene therapy clinical trials. For gene therapies, most preclinical toxicology studies to date with retroviral and adenoviral vectors have not revealed toxicities of the magnitude seen recently. While the newest results are indeed significant, from the FDA's point of view, animal toxicity is the primary means of estimating safe starting doses in human trials. Thus, lack of overt or major preclinical toxicity is not comforting, but instead raises the specter of unanticipated adverse events in humans. The unexpected adverse event in a cystic fibrosis patient given an adenoviral vector is a case in point. The FDA would like to have one of its toxicologists present a fifteen minute overview of our current philosophy and testing requirements. This would be followed by a short presentation by a patient who will give a perspective on safety concerns in the real world of cancer therapy.'

XI. Discussion on Adenoviral Vector Toxicology

On January 19, 1995, Dr. Philip Noguchi, Food and Drug Administration, Rockville, Maryland, requested the Recombinant DNA Advisory Committee to discuss transgenic xenotransplantation. In his letter, he states:

"Millions of Americans suffer tissue loss or end-stage organ failure, leading to over eight million surgical procedures annually. Current therapies include organ transplantation, surgical reconstruction using human tissues, and use of mechanical devices such as kidney dialysis machines. These treatments have significantly reduced the morbidity and mortality associated with tissue loss and end-stage organ failure. Transplantation as curative or

live-saving therapy, however, is greatly hampered by a critical donor shortage. For example, over 40,000 patients die from liver failure annually yet only 4,000 donors are available annually to address this need for lifesaving organs. The number of patients who die while on waiting lists for organ transplantation is increasing while the availability of donor organs is decreasing. Novel combination products used as bridging mechanisms may extend patients' lives and increase the number of patients on organ transplant waiting lists. The unmet demand for clinically needed human tissues coupled with the scientific and biotechnological progress during the past decade have also provided the impetus for new therapies involving xenogeneic cells, tissues, and organs.

'The FDA has become aware through the press and personal contacts that some Institutional Review Boards are reviewing proposals for xenotransplantation. Although it appears that most of the current proposed protocols seek to use nonhuman primate donors with conventional patient immunosuppression, a growing number of academic and commercial groups are exploring the use of transgenic animals in which human genes are introduced into the animal in an attempt to lower or mask immunogenicity. This latter category is a form of human gene transfer, since the transplanted transgenic organs contain human genes and/or human gene products. The RAC review process has served society well in the measured public introduction of gene therapies into clinical experimentation. We suggest that this exciting new area, in which genetic engineering is further extended to the manipulation and construction of new therapeutic entities, would likewise benefit from regular scientific, legal and ethical review in a public forum.

"Some issues for public discussion might include: (1) Preclinical: What kind of animal model testing would be needed before initiation of transgenic xenotransplantation? What would be the most appropriate animal model? What degree of scientific rationale is necessary? (2) Recipient issues: Should categories of patients be defined for first experimentation? Those who are acutely dying with no immediate human organ available? Those whose priority is so low that the patient would die before receiving an organ? What kinds of patient screening and follow-up would

be needed? (3) Hazards: What type of donor screening should be conducted? What new hazards might be created with transgenic transplantation, i.e., activation of a latent human virus in the animal organ? How could these concerns be addressed, i.e. specific scientific studies? (4) Informed consent and study results: What new elements of informed consent would be required? How can the field be monitored for success and failure? Should the local IRBs take the lead in primary monitoring of patient safety? Would the data monitoring efforts used for gene therapies be useful in this new field?

"Obviously, we do not expect that definitive answers to these questions and issues would be forthcoming at the meeting, but we would like to broach the subject so that future discussions can be planned. We suggest that the RAC might wish to augment its current panel with one or more ad hoc consultants with specific expertise in transplantation."

OMB's "Mandatory Information Requirements for Federal Assistance Program Announcements" (45 FR 39592, June 11, 1980) requires a statement concerning the official government programs contained in the Catalog of Federal Domestic Assistance. Normally, NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers not only virtually every NIH program but also essentially every Federal research program in which DNA recombinant molecule techniques could be used, it has been determined not to be cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that every Federal program would be included as many Federal agencies, as well as private organizations, both national and international, have elected to follow the NIH Guidelines. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the Catalog of Federal Domestic Assistance are affected.

Suzanne Medgyesi-Mitschang,

Acting Deputy Director for Science Policy and Technology Transfer.

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