Gene Therapy: Research in Public

With the first human gene therapy trials on the horizon, extensive review procedures are being put in place

When the first experiments in human gene therapy are initiated, sometime within the next year or two, the whole world will be watching. Although there is some precedent for human experimentation in public (the recent heart transplant cases come to mind), human gene therapy will debut under a government sanctioned policy that requires public scrutiny of a sort unprecedented in medical studies with human patients.

When the first authorized gene therapy is attempted, the pioneering research team will have received approval from its local institutional review board and institutional biosafety committee, the new Working Group on Human Gene Therapy, which is a subcommittee of the National Institute of Health's Recombinant DNA Advisory Committee (RAC), the full RAC, the director of NIH, and the Food and Drug Administration (FDA). Furthermore, every aspect of the proposed experiment will have been fully debated in public, from the technical details of the retrovirus that will be used as a vehicle for carrying a working gene into a patient's cells, to its possible implications for risks to public health, and to its implications, if any, for eugenics.

Human gene therapy, like the basic research in recombinant DNA that provides its scientific underpinning, is a subject that elicits a widespread, deep emotional response. The reaction seems embedded in feelings about the essence of humanness and "playing God" more than in a rational assessment of the technology. Ever since 1982 when Representative (now Senator) Albert Gore, Jr. (D–Tenn.), held hearings on the future of genetic engineering, the application of recombinant DNA work to human patients has been examined by scientists, ethicists, lawyers, and others who have participated in a variety of open meetings and workshops. A notable statement on the issues is contained in a recently completed report to Congress by the Office of Technology Assessment (OTA). Written at Gore's request, "Human Gene Therapy"* is a lucid analysis of the scientific and social issues.

The OTA report discusses two forms of human gene therapy that are under consideration. Somatic cell therapy, from the Greek word for body, is explicitly distinguished from germ line therapy. In somatic cell therapy, only the nonreproductive cells of the patient would be targeted for correction or repair and the genetic changes could not be inherited by offspring. Therapeutic alterations of germ cells, by contrast, would induce genetic changes that would be passed on to the patient's progeny.

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At a press conference last month at which the OTA study was released (*Science*, 21 December, p. 1404), Gore reported that a strong consensus has emerged on the acceptability of somatic cell therapy, while divisions remain about the technical feasibility and ethical validity of experiments that would alter the genetic makeup of a person's germ cells.

"Gene therapy in humans will first be done in cells from an organ or tissue other than germ cells," the OTA document says. "Therefore, because cells that are used in reproduction are not involved, gene therapy of this type is quite similar to other kinds of medical therapy, and does not pose new kinds of risks. When considering gene therapy that does not result in inherited change, the factor that most distinguishes it from other medical technologies is its conspicuousness in the public eye; otherwise it can be viewed as simply another tool to help individuals overcome an illness."

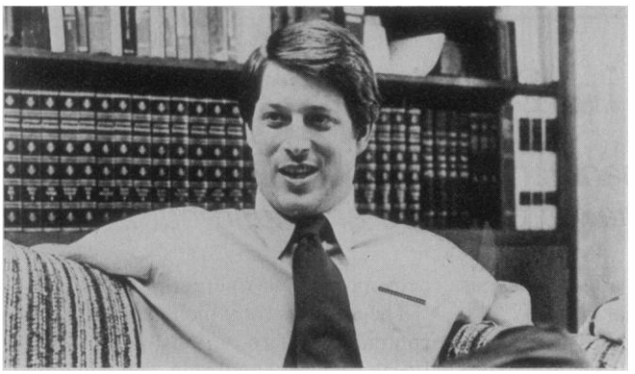
The diseases for which gene therapy is contemplated are serious, often lethal. Lesch-Nyhan syndrome, an inherited gene deficiency whose victims suffer uncontrollable impulses to self-mutilation such as biting off their fingers and lips, is at the top of the list of candidates for early gene therapy trials. Another candidate is ADA (adenosine deaminase) deficiency, a disorder in which the absence of a properly functioning gene leaves patients without an immune system. A similar immune disorder, caused by a deficiency of the enzyme purine nucleoside phosphorylase (PNP), is also a contender. One well-publicized immune deficiency case was that of "Baby David," the Houston child who lived all his life in a protective bubble until he died recently at age 12.

At present, only a small number of laboratories is even close to experimental gene therapy in humans, and "close" may well be a year or two away. At the University of California at San Diego, Theodore Friedmann and his colleagues, in collaboration with Inder Verma at the Salk Institute, are preparing for gene therapy in Lesch-Nyhan patients. C. Thomas Caskey and his group at Baylor College of Medicine in Houston also are working on Lesch-Nyhan. David Martin and colleagues at the University of California at San Francisco and Genentech are hoping to treat patients with PNP deficiency. W. French Anderson of the National Heart, Lung, and Blood Institute and his associates are another active group in this fledgling field.

At Harvard Medical School, David G. Nathan and Stuart Orkin, with Richard Mulligan of the Massachusetts Institute of Technology, are exploring gene therapy for ADA-deficient patients. In each case, the disease is marked by a single gene defect and the normal replacement or "therapeutic" gene has been cloned.

These diseases are rare. In the United States, there are only 200 new cases of Lesch-Nyhan reported every year. ADA deficiency, with fewer than 50 cases known worldwide, is rarer still. There are only nine known PNP cases. But as the science progresses, clinicians anticipate the day when gene therapy may be applicable to more common genetic dis-

*Human Gene Therapy. Background Paper" December 1984 (Office of Technology Assessment, Washington, D.C. 20510, December 1984). For additional reading, see "Prospects for human gene therapy," W. French Anderson, *Science*, 26 October 1984, pp. 401–409.



Senator Albert Gore

Leading congressional proponent of public debate on these issues.

eases, including Tay-Sachs disease, which occurs mainly in Ashkenazi Jews, and cystic fibrosis, which is found primarily in Caucasians. Sickle cell anemia and other hemoglobin disorders are future gene therapy candidates, as is familial hypercholesterolemia, an inherited disease that leads to early death from heart attacks. Whether certain types of malignancy might yield to cellular repair through techniques of gene therapy is a matter of speculation.

The promise is great but so, in the minds of critics who worry that the technology may get out of hand, are the risks. The question asked is this: If we can cure lethal diseases by altering an individual's genes, what's to stop us from using the technology to "enhance" human characteristics, such as strength or eye color or, even one day, intelligence?

The fact that characteristics such as intelligence may never be amenable to gene therapy does not alter the potency of the question in the public's mind.

In its analysis of the issues, the OTA study, which was directed by physician Robert Cook-Deegan, captures the essence of disagreement about the future of genetic manipulation with quotations from two persons with polar views. Jeremy Rifkin is a social activist and self-appointed critic of all work involving recombinant DNA. Says Rifkin, "With human genetic engineering, we get something and we give up something. In return for securing our own physical well-being, we are forced to accept the idea of reducing the human species to a technologically designed product. Genetic engineering poses the most fundamental of questions. Is guaranteeing our health worth trading away our humanity?"

On the other side, Ola Mae Huntley, who has taken an active interest in the issue as the mother of three children with sickle cell anemia, argues in favor of active gene therapy research. "I resent the fact that a few well-meaning individuals have presented arguments strong enough to curtail the scientific technology which promises to give some hope to those suffering from genetic disease," she is quoted as saying. Suggesting that the critics are "playing God" every bit as much as the researchers might be, Huntley declared, "I am very angry that anyone would presume to deny my children and my family the essential genetic treatment of a genetic disease. . . . I see such persons as simplistic moralists who probably have seen too many mad scientist horror films."

No thoughtful participant in the gene therapy debate seriously believes that strong differences of opinion about the ethical acceptability will ever be completely resolved. Nonetheless, there is a conviction that open public discussion may result in a useful consensus. The NIH's new Working Group on Human Gene Therapy has emerged as the likely forum for such discussion.

A year ago, the Recombinant DNA Advisory Committee, which already has authority to approve federally funded basic research with recombinant DNA technology, added to its purview experiments involving the "deliberate transfer of recombinant DNA or DNA derived from recombinant DNA into human subjects." Subsequently, it appointed the working group as a RAC subcommittee. LeRoy Walters, director of the Center for Bioethics at the Kennedy Institute of Ethics, Georgetown University, was named chairman. Members are drawn from research, medicine, law, public policy, and ethics. In anticipation of the first grant applications to try gene therapy in human patients, the working group has just issued a detailed statement called "Points to consider in the design and submission of somatic-cell gene therapy protocols." It was published in the 22 January *Federal Register* for public comment.

For the past several months, experts in the field have predicted that the first gene therapy experiment would take place sometime in 1985. However, a review of the working group's requirements—particularly one on the desirability of prior tests in primates—suggests that the first human trials may be farther down the road. Although the working group contends that the "points to consider" document is meant to offer guidance only and says that "Not every point mentioned . . . will necessarily require attention in every [grant] proposal," any researcher who expects to make it through the complex and very public approval process had better think twice before skipping any of the questions on the protocol exam.

First, the gene therapy protocol must describe in extensive detail the technical aspects of the intended experiment. Thus, a researcher is asked to answer the following questions among others (paraphrased from "points to consider").

- Why is the disease a good candidate for gene therapy?
- Is the therapy expected to cure the disease or halt its progress?
- What alternative therapies exist? How effective are they?
- What is the structure of the cloned DNA that will be used? If a virus will be used to carry the DNA into cells (as is likely), describe its structure and purity.
- What makes you think the therapeutic gene will be inserted where it belongs in the patient's cells and what evidence is there that it will be expressed usefully in the patient?
- Has an experiment similar to the one proposed been carried out in nonhuman primates, specifically with a view to determining whether the retrovirus carrier has recombined in the animal with any of its own viruses to produce some new organism?

This last question, about experimentation in primates, raises controversial issues. To begin with, not everyone agrees that primate studies ought to be a necessary prerequisite to human gene therapy trials. According to Walters, even the working group is divided and it is not clear how members would vote were a proposal to come before them. A strong case can be made that mouse data are sufficient, especially in light of the hopeless nature of the diseases. However, now that the subject of primate studies has come up, it will be difficult politically to skip them. But the political ramifications of the issue are deeper still, as evidenced by what has happened to a grant proposal from Theodore Friedmann of UC–San Diego.

Friedmann and his colleagues are as far along as any reserach team with plans for human gene therapy trials. He has yet to submit a proposal to the NIH.

However, a general outline of the research steps he anticipates following en route to a human test has been submitted to and approved in principle by the UC institutional review board. At present, what Friedmann does have before the NIH is a proposal for a grant renewal for 5 years. That proposal includes a request for funds for primate studies of the safety and efficacy of insertion of the HPRT (hypoxanthine-guanine phosphoribosyltransferase) gene that is deficient in Lesch-Nyhan patients, and indicates that the appropriate collaborators have already been lined up.

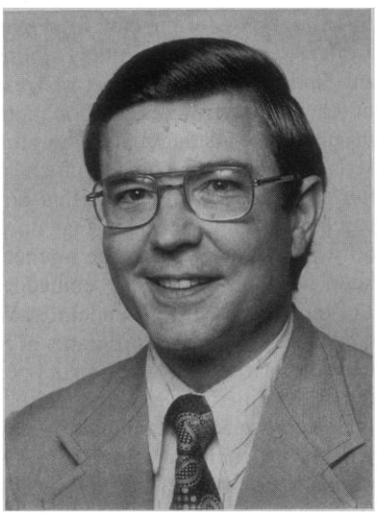
The study section that has reviewed Friedmann's grant turned the primate work down and recommended that the grant as a whole be cut back from 5 years to 3. Thomas Caskey, the Baylor geneticist also working on Lesch-Nyhan, is chairman of that study section. Caskey was not available to speak with *Science* about the study section's action, but others who are knowledgeable about the matter have commented off the record.

The study section's stated reason for dropping Friedmann's primate request—the reason given on the "pink sheet" that researchers receive after their grants have been reviewed—is that it is scientifically too soon to contemplate putting genes into primates.

Says one observer, "That's just incredible, especially if you're talking about a 3- to 5-year grant. Other investigators will be ready for primate studies very soon but Friedmann is ahead. We have the vectors. He should be in primates already." Friedmann so far has had success in getting expression of the cloned HPRT gene in cells in vitro and also has reported successful studies in mice.

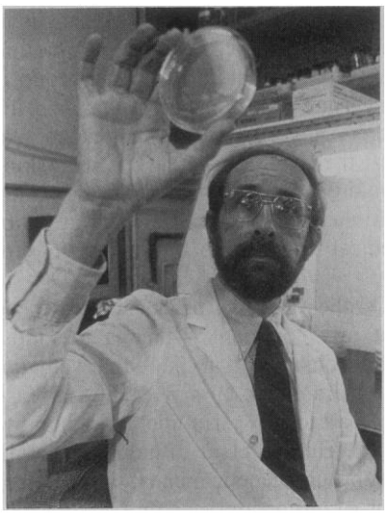
A second explanation for the study section's action points up what could be a terrible dilemma for gene therapy researchers and NIH administrators alike. On the one hand, a number of study section members are reported to favor primate tests prior to human gene therapy trials. On the other hand, some are said to fear the reaction of the animal rights activists who can be expected to argue vociferously against subjecting animals to gene experiments even though, from a scientific or medical standpoint, there is nothing unusual or especially painful about them.

The study section's action on Friedmann's grant will be reviewed at the 29 January council meeting of the National Institute of Child Health and Human Development (NICHD) which will supply funding for whatever portions are approved. The council will be asked to reconsider both the primate question and the decision to cut the grant from 5 years to 3. The entire gene therapy enterprise could come to a halt before it ever gets going if the government simultaneously demands preclinical tests in nonhuman primates but lacks the political nerve to pay for them.



LeRoy Walters

Head of new NIH review group.



Theodore Friedmann

Ready to do primate studies soon.

Once the requisite research is in hand, and one or more teams of investigators actually files a protocol for a human experiment, the role of NIH's Human Gene Therapy Working Group will become prominent.

Generally speaking, the first set of questions that the working group wants researchers to answer regarding a proposed experiment are not much different from those that institutional review boards ask about most clinical research: details about the experiment coupled with an assessment of the anticipated risks and benefits to the patient. But some of its questions go beyond the usual. For instance, under the heading "public health considerations," the following question appears: "Is it likely that the [viral] vector or the inserted DNA will be spread to the environment by treated patients?" The question calls forth an image of a patient spewing forth viruses like some fire-breathing dragon. Most experts believe the answer is an unequivocal no.

Another special issue is informed consent. The working group assumes that, because of the tremendous public interest in gene therapy, the first patients should be prepared for an onslaught of press attention. The working group clearly expects researchers to warn patients and their families and to have plans to help them cope with this invasion of privacy.

A second category of questions in the working group's "Points to consider" exam reaches into a discussion of broad social issues, admittedly going well beyond the kind of questions that researchers normally are asked to speak to as part of a grant application. According to the document, ". . . the RAC and its working group request that investigators respond to questions A and B below and discuss, at their discretion, the general issues enumerated in point C.

"A. What steps will be taken to ensure that accurate information is made available to the public with respect to such public concerns as may arise from the proposed study?" It is hardly usual to ask for a public relations plan as part of a research application. The working group view that Loma Linda (California) hospital lacked a well-thought out plan for responding to press inquiries in the case of Baby Fae's baboon heart transplant lies behind this question, in part.

"B. Do you or your funding sources intend to protect under patent or trade secret laws either the products or the procedures developed in the proposed study?" Here, too, the question is extraordinary. It reflects a view that this research must be open, as well as concern over patents that have come out of work in human in vitro fertilization. Because of the government's de facto ban on fetal research and in vitro fertilization studies, work in this area has been conducted abroad, largely in Britain and Australia, where it is well beyond the reach of NIH regulation. In fact, as the congressional report on gene therapy noted, in vitro fertilization work virtually bypassed normal stages of animal experimentation altogether. Now available as a clinical procedure at some 60 centers in

this country, it is largely in the hands of private enterprise. Thus, it may be understandable that the working group is concerned about gene therapy data being secret. Nevertheless, in its zeal to protect the public interest, it is asking would-be gene doctors for information that their colleagues in other areas of medical research are not asked to supply.

Of the final set of questions—those that are "optional"—this is the most extraordinary. "Is it likely that somatic-cell therapy for human genetic disease will lead to: (a) germ-line gene therapy, (b) the enhancement of human capabilities through genetic means, or (c) eugenic programs encouraged or even mandated by governments?"

If one accepts the judgment that somatic cell therapy for the cure or alleviation of disease is fundamentally no different from other risky forms of treatment (chemotherapy and radiation therapy in cancer, for instance), it follows that these last questions become the focus of people's anxiety about where this new research may lead. The idea that one's identity is intimately tied to one's genetic makeup have been a deeply embedded part of our culture since Mendel discovered genes. The eugenics programs of an earlier time, particularly the horrors perpetrated in Hitler's Germany, raise a specter over genetic manipulation that may never be banished altogether. The questions need answering, the possible misuse of the technology needs to be anticipated.

In the absence of any other duly constituted body, the Working Group on Human Gene Therapy has become the locus for broad social discussion of these issues. All of its deliberations are intended to be open, particularly in the beginning if, as expected, the first protocols it has to review do not include proprietary information. According to LeRoy Walters, its job includes educating the public on the technical aspects of gene therapy and also on the significance of the research.

Says Senator Gore, who backs the working group but would also like to see Congress create a presidential commission with oversight in this area, "Genetic engineering shouldn't surprise us. We can see it coming, so we should be examining our choices and their ethical implications."—**BARBARA J. CULLITON**

Legislative Paralysis on the Environment

Four major environmental laws are up for renewal; EPA would like more administrative flexibility, but Congress may give it less

When legislators closed the books on the 98th Congress, they had renewed only one of five major environmental laws. As a result, the new Congress, which gets down to business this month, faces the need to rewrite the basic laws governing air and water pollution, the cleanup of hazardous waste sites, and the regulation of pesticides.

If William D. Ruckelshaus, who resigned recently as head of the Environmental Protection Agency (EPA), had his way, Congress would modify these laws in a way that would give the agency more flexibility in carrying out its mandate of guarding the environment and public health. But Congress is more likely to do the reverse. In part because of the mistrust left over from the way Ruckelshaus's predecessor, Ann McGill Burford, ran the agency, Congress will probably attempt to limit the Administration's room to maneuver by prescribing in detail how EPA should carry out environmental laws.

Ruckelshaus justly says that the agency "has now been righted" after its stormy days under Burford. Now attention has focused on environmental policy rather than personalities. On his last day as EPA administrator, Ruckelshaus argued in a wide-ranging interview with *Science* that Congress over the years has saddled the agency with unduly prescriptive laws, making it difficult for the administrator to carry them out effectively. This highly detailed legislation, for example, identifies dozens of specific chemicals or pollutants that the agency must regulate and then imposes deadlines. "That's all wrong in my judgment," Ruckelshaus said. He argues that detailed laws contribute to the ponderous pace of issuing regulations and run counter to wise decision-making.

Ruckelshaus cites as an example the one piece of environmental legislation Congress recently rewrote, which governs hazardous waste disposal. "I'm not sure [this legislation] is such an advancement," Ruckelshaus said. It states that EPA must reach specific goals by specific deadlines. "If you don't meet a deadline, certain bad things happen to you. . . . If you don't identify certain chemicals, then they can't go into landfills." As a result, he said, the agency will probably have to identify these chemicals "with imperfect information and try to regulate them. I don't think that's good public policy."

Ruckelshaus also contends that Congress should modify the mandate of the agency to take into account the cost of regulations. "We must balance [the benefits] against the other social concerns that society has to deal with," he said. Some of the statutes, such as parts of the Clean Air Act, do not give the administrator that discretion, but say he must provide "an ample margin of safety."

All of these explicit orders from Congress stem from mistrust, Ruckelshaus said. "Their argument to me is, well, you're all right, but how do we know who's coming after you and look who was in there before you. But if you treat somebody as though they're not to be trusted, it isn't very long before your mistrust is warranted." The problem, however, is not with Ruckelshaus, who was widely respected as the first administrator of EPA in the early 1970's and is regarded as the healer of a battered agency under this Administration. Congressional sources and other players in environmental issues say that the reluctance to give the administrator more rope is because of the agency's inability under previous presidents to write regulations expeditiously and because of the meddling by the Office of Management and Budget (OMB) under President Reagan.

"I understand what he's saying," says Senator David Durenberger (R–Minn.), who is chairman of the Senate's environmental oversight subcommittee. "If this was an ideal world, we might give him more flexibility, but it's not. Do I think the answer [to achieving greater progress] is more flexibility? No."

Senate and House aides who monitor EPA also say Ruckelshaus's desire for more flexibility is not unreasonable. In