Ethical Questions Haunt New Genetic Technologies

An acrimonious battle between activist Jeremy Rifkin and NIH points to the need for a forum to debate the ethical issues that surround the new genetic technologies

ON 19 JANUARY THE UNITED STATES crossed the threshold into the much debated but still uncharted world of human gene therapy. That day, the federal government signed off on the first approved introduction of a foreign gene into humans, a research protocol that has undergone exhaustive review during the past 7 months.

Since the first gene was spliced 17 years ago, there have been countless reports, religious proclamations, and congressional hearings on what gene therapy portends—both its enormous potential benefits in treating genetic disease and its potential abuses. But as a recent meeting at the National Institutes of Health made clear, ethical questions still haunt this powerful new technology.

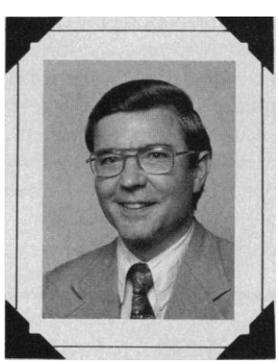
The meeting, the occasion of an acrimonious battle between activist Jeremy Rifkin and the Recombinant DNA Advisory Committee, or RAC, also made clear that despite the detailed consideration and anticipation of the first gene therapy protocol over the past 6 years, there is still no agreed upon forum to debate the contentious issues that seem certain to arise.

At the 30 January RAC meeting, Rifkin, perennial critic of modern technology, launched a frontal attack to block the landmark experiment just 2 weeks after the government had approved it. He called for a moratorium on the experiment and all human gene therapy research until NIH sets up a special committee to evaluate the ethical and social implications of this work. As he was speaking, his lawyer was filing a suit in federal court to enjoin the experiment on the grounds that the painstaking review procedures NIH followed were flawed (*Science*, 10 February, p. 734).

The experiment in question, scheduled to begin within a few months, is not technically considered gene therapy, but the distinction is a fine one. Using the tools of recombinant DNA, NIH researchers Steven Rosenberg, French Anderson, and Michael Blaese will insert a marker gene—not a therapeutic gene—into ten terminally ill patients to track the progress of a promising but experimental cancer treatment known as TIL therapy.

Gene therapy is just a short step away, however, as this same technique can also be used to insert therapeutic genes. Indeed, several protocols are expected shortly from the same team to introduce genes in an attempt to combat AIDS, cancer, and a rare immunodeficiency disorder, ADA deficiency. Moreover, a new company, Genetic Therapy Inc., has been founded, suggesting that some, at least, think that money is eventually to be made in this now-infant field. Anderson is a principal investigator in a collaborative research agreement with the company.

Rifkin does not contend that this particular experiment is unacceptably risky or ethically dubious, nor is he opposed to gene therapy in nonreproductive cells to correct genetic diseases. Instead, he seems to be trying to hang NIH on a technicality of the review process in order to force debate on the larger issue of human genetic engineering and its potential misuse.



"Gene therapy is the most extensively debated therapy in history," says LeRoy Walters.

Rifkin assembled leaders of various disability organizations and bombarded the media with press releases before the meeting, thereby ensuring good coverage, to the obvious discomfort of the RAC, which had to conduct its meeting under the glare of television camera lights. Despite the public glare, the meeting quickly degenerated into a battle, and at its lowest moment, into name-calling, between Rifkin and at least some advisory committee members, who seemed to have difficulty separating the message from the messenger.

Rifkin accused the RAC of ignoring the social and ethical ramifications of human gene therapy, essentially saying that the questions this technology raises are too monumental for an "elite group of NIH scientists and their handpicked ethical consultants," who, he charges, have a vested interest in this research and its commercialization. Thus the justification for his proposed committee, the Human Eugenics Advisory Committee, which would be parallel to the RAC and advisory in nature but with a different composition—largely individuals in the fields of civil liberties, the rights of disabled workers, and insurance and consumer rights. The RAC, by contrast, is composed of 17 scientists and 8 public members.

RAC members, some of whom have been wrestling with these issues since the early 1970s, were clearly offended. "Gene therapy is the most extensively debated therapy in history," responded LeRoy Walters with obvious exasperation. Walters, a Georgetown University ethicist, chairs the RAC's human gene therapy subcommittee. "I don't know of any biomedical science or technique that has had the detailed scrutiny that human gene therapy has had. There is an international consensus that somatic cell gene therapy is ethical for some diseases."

RAC member Gerald Musgrave quickly leapt into the fray, calling Rifkin a "media maven" and a "gadfly," in an exchange that at least some RAC members view as unfortunate since it gave the impression that the committee is not receptive to some of the legitimate points Rifkin and his colleagues were raising.

Several RAC members suspect that Rifkin's real intent is not to further debate, as he asserts, but to block this promising research. In particular, they chafe at his attempt to halt the gene transfer experiment, which could delay treatment for cancer patients, because of hypothetical scenarios that bear no relation to this experiment.

The accepted wisdom is that somatic cell gene therapy, at least in its early stages, poses no more ethical problems than any other new medical therapy. The common analogy is to organ or bone marrow transplants, which introduce not just one foreign gene but a host of them, in a crude fashion, to make up for the body's own shortcomings. By contrast, it is generally agreed, gene

therapy in germ line cells—that is, in sperm, ova, or embryos—will raise distinct issues, as changes would be passed on to future generations.

The RAC's human gene therapy subcommittee will not now entertain proposals for germ line therapy. But already some investigators are saying that if and when the formidable technical obstacles can be overcome, germ line therapy may be the best approach for certain diseases—perhaps those that affect multiple organs—and they balk against shutting the door on it.

Rifkin and several of the disability advocates challenged the assumption that somatic cell gene therapy is virtually issue-free, pointing out that the potential for abuse exists even now. It ranges from subtle questions, such as judgments as to what constitutes a "good" or a "bad" gene to problems like coercive therapy.

"Believe it or not, we are not all in a rush to be cured or prevented," said author Anne Finger, who had polio. "The issue of 'cure' is not entirely clear-cut. There are tradeoffs," added Debora Kaplan of the World Institute on Disability in Berkeley, California. "Not everyone offered a cure will take it. We are concerned about pressure to undergo treatment as it becomes available."

The fear voiced repeatedly at the meeting is that in crossing the threshold into direct genetic manipulation, society may be headed down a "slippery slope" in which the outcomes cannot be easily controlled. Rifkin raised the specter of "engineering" workers to render them less susceptible to chemical carcinogens in lieu of cleaning up the workplace.

Such scenarios are not farfetched, said Evan Kemp, a member of the Equal Employment Opportunity Commission, who noted that "real issues are coming up right now in the workplace" concerning women and reproductive rights and mandatory testing for conditions such as bad backs.

That is "*the* disconcerting scenario," says researcher Anderson of Rifkin's workplace scenario. "Everyone on the subcommittee and the RAC is as opposed to that scenario as Rifkin is. It just isn't an issue."

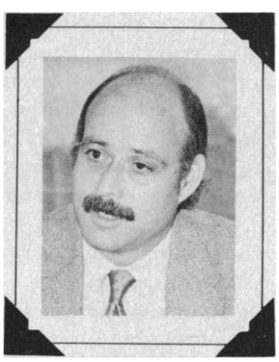
What the various advocates called for, often eloquently, was not a halt to gene therapy research but simply a broader forum—and not necessarily the one Rifkin suggested—so that different perspectives on these issues could be heard.

Most on the RAC agree that the issues raised are real and vexing, if not necessarily relevant to gene therapy. Nonetheless, they voted to "respectfully decline" the proposal, saying that the RAC and its human gene therapy subcommittee, which is headed by an ethicist, are well equipped to handle the questions that accompany gene therapy. And for the broader issues that Rifkin and his associates raised—issues that fall outside the purview of the RAC—committee members say that other mechanisms are in place to deal with them.

For many of these issues, however, like genetic screening, privacy of genetic information, and discrimination, it is not at all clear where to turn. The Congressional Biomedical Ethics Board, which was recently rescued from a premature demise, appears to be in for rough sledding. Similarly, plans to reconstitute the Ethics Advisory Board within the Department of Health and Human Services now seem stalled.

The congressional board was created in 1985 but nearly went out of existence last summer without having done anything. The logjam came in appointing the committee of outside experts to advise the board, which consists of six senators and six representatives.* The sticking point was abortion.

The board, split equally on abortion and right-to-life issues, spent nearly 3 years haggling over who should be on the committee. They finally turned to the Office of Technology Assessment and the Institute of Medicine to winnow the list of 140 nominees for them. That done, they completed appointing the 14-member committee last summer, just in time for a last-minute reprieve—a 2-year reauthorization—from an increasingly impatient Congress. Once the committee was appointed, however, one member died, and the board once again seems unable to agree on a replacement.



Jeremy Rifkin accused the RAC of ignoring the social and ethical ramifications of human gene therapy.

The committee, chaired by Alexander Capron of the University of Southern California Law School, met for the first time in December. It met again last week to begin planning its three mandated studies on human genetic engineering, fetal research, and nutrition and hydration of dying patients. The first study should delve into just the sort of issues that came up at the RAC meeting, including genetic screening, privacy of genetic data, and civil rights. But whether the board can escape the deadlock of the past few years remains to be seen.

What the board actually accomplishes will depend, to a large extent, on how it fares in the appropriations process. As envisioned, it will have a sizable staff and hold hearings and public meetings, truly serving as a forum for debate. But for this year the board is surviving on a carry-over budget of a quarter-million dollars and is limited to a staff of two, barely enough to tackle even the first study. For next year the board is asking for $2.5 million, but prospects are uncertain.

Whatever the budget, the board cannot take on the task of reviewing individual research protocols for their social and ethical implications, a function that Robert Cook-Deegan, the board's new acting executive director, thinks is important. "There needs to be something in place to react to proposals," says Cook-Deegan, "but Congress can't do it. We are not a traffic cop, and we can't be one. We will look at broader policy issues." Similarly, he says, the issues arising from the potential misuse of gene therapy or genetic screening are broader than research and broader than the RAC and even NIH. The logical place to address them, he says, would probably be in the Department of Health and Human Services.

But the department's proposed Ethics Advisory Board, which on paper would serve just that function, has become mired in the contentious issues of fetal research and in vitro fertilization and may never emerge.

The board was originally created in 1975 to advise the HHS secretary on the ethical suitability of research proposals involving in vitro fertilization, fetuses, and pregnant women. Specifically, the 1975 regulation said that no proposal involving in vitro fertilization can be funded unless it is reviewed by the board, which began functioning in 1978. But the board was disbanded 2 years later, resulting in a curious Catch-22: all in vitro fertilization research proposals must still be reviewed by the nonexistent board. The upshot has been a de facto moratorium on all in vitro fertilization research in this country.

In 8 years the Reagan Administration made no move to reestablish it, which is not

*Board members are Senators Dale Bumpers (D–AR), David Durenberger (R–MN), Gordon Humphrey (R–NH), Edward Kennedy (D–MA), and Don Nickles (R–OK), and Represenatives Thomas Bliley, Jr. (R–VA), Thomas Luken (D–OH), J. Roy Rowland (D–GA), Thomas Tauke (R–IA), and Henry Waxman (D–CA).

Watkins Takes the Helm at DOE

Admiral James D. Watkins, President Bush's choice to head the Department of Energy (DOE), says the most serious problem before the department is the operation of the nuclear weapons materials production plants and the nuclear waste program. The DOE weapons program has failed to keep pace with the operating standards of the civilian nuclear power industry, he told members of Senate Energy and Natural Resources Committee during a confirmation hearing on 22 February.

Watkins plans to overhaul much of the department's organization if his nomination is confirmed by the Senate. He assured committee members that he would be "extremely active in all parts" of DOE operations and that he would shape a new comprehensive energy policy for the country. He stressed, however, that his top priority is to straighten out the weapons program.

The retired admiral contends that a fundamental change must be made in the culture and attitude of personnel working at production plants. Over 35 years of operation, the heavy emphasis on producing plutonium, tritium, and other materials, he says, produced a system that downplays health and safety. "Problems related to safety, health, and the environment have not only been backlogged to intolerable levels, but in effect hidden from public view until recently."

The department's nuclear waste disposal program office, which repeatedly has pushed back its deadline for opening an underground repository for civilian and defense wastes, in some ways "presents nearly the same challenges as the weapons production complex," says Watkins. He concurred with Senator Bennett Johnston's (D–LA) assessment that the program "is in a shambles."

Congress got few hints from Watkins about what might be in store for the basic research programs managed by DOE's Office of Energy Research. Watkins expressed concern about low government pay scales for scientists and engineers, but did not say whether he would request higher salaries for DOE researchers. He did, however, emphasize that the department's national laboratories will be expected to step up their efforts to transfer new technologies stemming from basic research to industry.

While acknowledging that much of his professional life has centered on the operation of the nuclear navy, Watkins says he will pursue a balanced energy policy based on a "sensible economic mixture" of proven energy resources. He said that the department's clean-coal program, which could provide up to $5 billion in matching federal grants to demonstrate advanced coal combustion and cleaning processes, "will be one of my greatest personal interests."

At the same time Watkins says he will be an advocate of energy conservation and renewable energy resources such as solar power. "This is a technology. . . . It is a very definite product with a barrels-per-day equivalent that is very significant." Even so, Watkins indicated that he was inclined to support Administration plans to cut back research in these areas in fiscal year 1990. ■ MARK CRAWFORD

James D. Watkins: *The top priority is to straighten out the weapons program.*

surprising, given the vehement opposition to in vitro fertilization by the powerful antiabortion lobby. Finally, last July then secretary of HHS Otis Bowen announced plans to reestablish the ethics board with a broader charter that would cover any ethical issue associated with biomedical and behavioral research and health care delivery.

The proposed charter, published in the *Federal Register*, generated a flurry of complaints from the right-to-life contingent, however, and Bowen did not sign off on it before leaving office. It now falls to the new secretary, Louis Sullivan, whose confirmation was delayed because of the abortion issue.

At NIH, director James B. Wyngaarden does concede, unlike his advisory committee, that something more than the RAC is probably needed, but he won't be pinned down yet on exactly what. The Anderson and Rosenberg experiment is a "significant milestone" that will lead NIH increasingly into social and ethical issues," Wyngaarden told *Science*. "We fully recognize that, and we don't need Rifkin to point that out.

"I wouldn't rule out the possibility that we may set up something at NIH [to address the ethical issues], but I don't think expanding the RAC is the way to do it. And we certainly won't within my lifetime set up anything called a 'eugenics board'," he says, referring to Rifkin's proposed committee. In his view, Rifkin's proposal was a trap. "Rifkin knows full well what 'eugenics' means. And he knows we do nothing that could be considered eugenics at NIH. It is an inflammatory term, not chosen casually, I think." Wyngaarden notes pointedly that discussions about the need for increased ethical review were under way well in advance of Rifkin's appearance before the RAC.

What Wyngaarden is considering is some sort of broader committee to look at the range of issues associated not just with gene therapy but with the burgeoning genome project—the effort to map and sequence the human genome—as well. Questions of genetic screening and the privacy of genetic data have already come up in the context of the genome project. And while they are not unique to the genome project, any more than they are to gene therapy, they promise to dog it.

The details of the committee, however, are still up in the air. "We have not discussed the mechanism or the timing, and whether it should be here, in the [HHS] department, or if the congressional committee will suffice." Wyngaarden may find his options limited, however, depending on how the fledgling congressional board and still nonexistent HHS board fare in the coming months. ■ LESLIE ROBERTS