UCLA Gene Therapy Racked by Friendly Fire

A buzz of scientific and ethical criticisms has enveloped the ambitious gene transfer experiment

An unusual degree of public criticism from fellow scientists has descended on the heads of Martin J. Cline and Winston Salser, the chief members of the UCLA group which is attempting the first gene therapy experiment in humans. The object of the experiment is to overcome, by insertion of human genes, the genetic defect that causes thalassemia (*Science*, 24 October).

The thrust of the criticism is that the experiment is scientifically premature, a thesis which in turn would raise the ethical issue of whether patients should yet be subjected to the technique. Beyond that is the political question of whether the promising field of gene therapy, now just beginning to enter the animal experiment phase, may not be set back if the public should acquire the notion that scientists cannot be trusted to behave responsibly.

Criticism is in one sense premature because the Cline-Salser experiment has not yet been published. There seems to be a fairly widespread view among experts in the field, however, that a sufficient basis of animal tests does not yet exist. "There is very little reason to believe, both from the molecular biology and cell biology standpoint, that an experiment like that would work," notes Philip Leder of the National Institutes of Health. According to Richard Axel, of the Columbia College of Physicians and Surgeons, "There is simply no scientific basis for expecting this experiment to work in people. A lot more has to be experimented with in animal systems. Cline has done this experiment in a mouse and, as I understand it, it didn't work. He has made a great conceptual leap from the failure in a model system to trying it in humans. He is saying, 'It didn't work in mice, so I'm going to try it in man.' "

But not everyone is ready to condemn the UCLA team. "Cline is a very bright guy who knows a lot about biology as well as being a clinician. This is a terminal disease—if I were in the patient's shoes, I'm not sure that I would not have said, 'Go ahead and try,' " remarks Jeffrey Ross of the McArdle Laboratory for Cancer Research.

The outline of the UCLA experiment seems to be as follows. Two patients suffering from beta-zero thalassemia, a disease in which almost none of the beta-chain of hemoglobin is synthesized, were the subject of the treatment. Bone marrow cells were removed from the patients and transformed with the gene for human beta-globin. (The gene was a 4.4 kilobase segment of DNA which contains the human gene complete with its intervening sequences and probably some but not all of its control sequences.) The cells were transformed at the same time with another gene, the herpes virus gene for thymidine kinase. The virus form of the enzyme, the UCLA team believes, is more efficient than the human variety and would be expected to give the treated bone marrow cells enough of a selective advantage to survive and proliferate in the patient.

The bone marrow cells were then reinjected into the patient, probably 10,000 or so of them containing the two new genes. To create space for them to settle in the bone marrow, the patient was irradiated in the thigh bone, Cline says, at a level that was "not harmful."

Although an important and imaginative experiment to try out in mice, the problem with taking it to humans, in the eyes of the critics, is that none of its three main elements can yet be called a proved technique. It is not yet clear that the herpes virus gene will give marrow cells an advantage over their untreated fellows, although Cline has some unpublished evidence that this is the case in mice, when the mice are first irradiated. It is far from clear how the human beta-globin gene can be inserted into cells in such a way that it produces beta-hemoglobin in useful quantities. Axel, who with colleagues has inserted the gene into mouse cells in culture, notes that hemoglobin is produced, but in only a fraction of the quantity produced by normal human cells. The inserted gene is also unregulated, in the sense that it does not respond to genetic controls.

The third untested element of the experiment is that of effecting the successful reestablishment of transformed cells in the bone marrow. Apart from Cline's unpublished experiments, this appears to be largely uncharted territory.

For the experiment to succeed, each of these three unknowns has to work in the UCLA team's favor, a chance that seems rather small to those knowledgeable in the field. "It doesn't make sense to do an experiment for which there is no basis in reality," is the acerbic comment of one expert.

Cline has an articulate defense against all these objections. The chief point he makes is that his critics are unaware that this is only the first in a series of experiments. He did not expect to get full expression of the beta-globin gene in his patients, a fact which he made clear to them. The purpose of the present experiment is to test the delivery system and watch for any possible toxicity. "The patients were told that the likelihood of it working was very small," Cline says; they were asked if they would participate again when the technique had been further improved.

> "He has made a great conceptual leap from the failure in a model system. He is saying, 'It didn't work in mice, so I'm going to try it in man.' "

Cline notes that some of his critics are molecular biologists but not clinicians (he himself is both). "Molecular biologists are criticizing a clinical experiment without really knowing its logic," he suggests. In his view, the important question is that of deciding when to make the transition from animal to human experiments, a judgment that is the responsibility of the clinician to make. "When do you make that transition? Some people say, 'It's when it's done at

0036-8075/80/1031-0509$00.75/0

Should more time have been spent with mice?

UCLA team members Martin Cline and Karen Mercola.

Harvard,' " notes Cline ironically. "I don't know that there is any defined guideline. The clinical investigator is the person who ultimately has to take the responsibility for when the transition to human studies is appropriate," he observes.

The clinical investigator, however, is not a disinterested party in deciding when to experiment on a patient, which is of course the reason for setting up human experimentation committees at the relevant institutions. If the Cline-Salser experiment had the sanction of such a committee, the UCLA team could probably be said to possess an unchallengeable right to perform the gene therapy, regardless of any criticisms of its scientific basis. Conversely, if the team did not possess such an endorsement, it could be vulnerable to criticism on both scientific and ethical grounds, not to mention those of political judgment.

Did the team act with the approval of a properly constituted human experimentation review committee? The proposal for the experiment was submitted in parallel to the UCLA Human Subjects Use Committee and to the University Poly Clinic in Naples and the Hadassah hospital in Jerusalem, where the two thalassemic patients were located. The UCLA committee decided on 22 July, after some 15 months' deliberation, that it would not permit the experiment until further animal tests had been conducted. By that time, however, the UCLA team had already received permission from the two hospitals abroad and conducted the experiment.

The UCLA team did not therefore formally disobey any decision of its home committee. But the committee was not delaying out of bureaucratic inertia or timidity. According to its chairman, UCLA vice chancellor Albert Barber, the committee felt the experiment was significant enough to require the most thorough and serious kind of review. Barber will not discuss the reviewers' objections, but the rumor among the scientific critics of the experiment is that the four reviewers made the same criticisms as they are making. These criticisms were made known on a continuing basis to the UCLA team throughout the review procedure. The UCLA committee eventually concluded that the risks to the patients outweighed the benefits and therefore disapproved the experiment.

The UCLA team was probably under no illusion about its home committee's thinking. A cardinal principle of the review system in the United States, however, is that a scientist turned down by one institutional review committee should be free to try his luck with another, the idea being that no single group should be accorded a monopoly on ethical wisdom. Even if it anticipated a veto from its home committee, the UCLA team had every right to seek permission elsewhere. Perhaps the only remaining issue is whether the quality of review in Israel and Italy was adequate. It is not yet known what review procedure was undertaken at the Hadassah hospital, but according to a report in *Le Monde* the Israeli Minister of Health himself gave authorization for the experiment.

Putting such decisions in the hands of committees should in theory sidestep the vexing questions of personal motivation. But what is giving an edge to the substantive criticisms by some of Cline's colleagues is their suspicion that he has jumped the gun out of desire for personal glory, and that the UCLA team is taking an unfair short cut to the goal of being first to apply the recombinant DNA technique in man.

The desire to be first is not shameful; the weight of the criticism probably reduces to an implication that the UCLA team somehow broke the rules of the game. Asked if personal glory was a motive—perhaps an unfair question—Cline replies: "I say the answer is no. I realize that I was taking the risk of drawing criticism for such experiments. But I don't know of anyone in the country who has precisely the same type of skills that I have, with knowledge both in the animal systems and in clinical investigations in man. I think that in that sense I must be unique. In the last analysis one must ask how responsible an investigator has been up to that point in time."

It is easy to see at first glance a case against what the UCLA team has done. The patients were unlikely to benefit, and indeed 3 months after the experiment there is still no positive sign that the inserted genes are being expressed. The radiation part of the therapy, however mild, did not do any good. The team's home committee specifically disapproved the experiment. Yet on further analysis much of the case perhaps dissolves, because the decision to go ahead with the experiment properly rested not with the investigators but with institutional committees. If hospital authorities in Jerusalem and Naples gave their permission, as they evidently did, the UCLA team had a right to proceed. They deliberately chose patients who were intelligent enough to understand the issues, and who also had limited life expectancies. They specifically told the patients, Cline says, that the immediate procedure was unlikely to benefit them. If the experiment produces useful scientific information, it was presumably worth doing.

Even if the UCLA team had a reasonable right to do the experiment, however, their judgment of its political context can perhaps be questioned. Since the exact experiment has not yet been

made to work in animals, the judgment to go to humans was certain to be questioned. Cline and Salser argue that since there are no suitable animal models in which to study thalassemia, man is the best subject. Their colleagues take direct issue with this contention, saying that mice with alpha-thalassemia have been developed at Bar Harbor and Oak Ridge. Debate about the experiment was inevitable, and the UCLA team's hope that they could complete it in secrecy does not seem particularly realistic. A few more animal experiments obviously would have established a warmer reception for the novel therapy.

The report on the affair now being prepared by UCLA for the NIH may resolve some of the issues. Whatever its verdict, it is clear that Cline and Salser took something of a gamble, skating close to the edge of what was scientifically reasonable and publicly acceptable. But there is no evidence as yet that they transgressed either boundary, although they may have given spectators something of a fright.—NICHOLAS WADE

Study Group Agrees to Voluntary Restraints

The National Security Agency has persuaded a group of researchers to submit papers for review prior to publication

A voluntary system of prior restraints on research publications in cryptography was approved this month by the Public Cryptography Study Group, most of whose nine members represent professional societies in mathematics and computer science. The system will be tried for 2 years, reports Daniel Schwartz, the general counsel of the National Security Agency (NSA). If, after that time, the process is not found to be "useful and efficient," the NSA may decide to seek legislative authority for mandatory restraints.

The study group was formed last year by the American Council on Education (ACE), a group representing university administrators, in response to a request by NSA director Bobby Inman for a dialogue between the NSA and the academic community. The agency was concerned because mathematicians and computer scientists are beginning to publish papers on cryptography—an area that previously was the near-exclusive domain of the NSA. Academic and industrial scientists are becoming so interested in cryptography because there has been a growing demand by business and industry for secure codes to protect computer messages and information stored in computers. With the advent of electronic fund transfers and electronic mail, the need for codes has become especially pressing.

The problem confronting the NSA and the academic community is to balance the NSA's worries that open research in cryptography might imperil national security against researchers' rights to publish their work and some scientists' and industries' claim that national security is also imperiled if new developments in cryptography are kept from the private sector. Since computers are so easily tapped, it would be possible for foreign powers to wage economic warfare, for example, by intercepting corporate messages carried by electronic mail.

In a previous meeting, the study group voted to consider prior restraints on cryptography research (*Science*, 27 June, p. 1442). The meeting this month was held to discuss a paper, largely written by NSA general counsel Schwartz, detailing how such a system of restraints might operate. Although the meeting was scheduled to last two whole days, 6 and 7 October, the group quickly agreed to the restraints and the meeting adjourned at 3 p.m. on 6 October. Cochairman Ira Michael Heyman, a constitutional lawyer and chancellor-elect at the University of California at Berkeley, did not even call for a vote. Instead, he said that since everyone evidently agreed to the system of restraints, it would be written up in final form, mailed to the members for approval, and then it would become the study group's recommendations to the NSA director, to professional organiza-

Policy on Cryptography Proposals

Just 2 months ago, Leonard Adleman, a computer scientist with appointments at the University of Southern California and the Massachusetts Institute of Technology, got a disturbing call from the National Science Foundation (NSF). He was told that part of his NSF grant proposal in cryptography would not be funded by that agency; the National Security Agency (NSA) wanted to fund it instead (*Science*, 29 August, p. 995).

Adleman, concerned by this turn of events, said he did not want to accept NSA funds because he worried about what terms the NSA might extract. The NSA said that if it funded Adleman, it might try to persuade him to have part of his work classified.

In part as a result of the publicity surrounding the NSA's offer to fund Adleman's work, the directors and representatives of the NSF and the NSA held a meeting on 9 October in the office of White House science adviser Frank Press to clarify how the two agencies will handle cryptography proposals. One result of the meeting is that Adleman has been informed that he has the option of accepting NSA funds or having his proposal reviewed and, presumably, funded by the NSF. Adleman says he will choose the NSF.

It was decided at the meeting that both the NSF and the NSA will fund cryptography research. For the time being, all cryptography proposals will be sent to the NSF, who will then send them to the NSA for technical review. If the NSA wants to fund a proposal, it will inform the NSF, which will offer the researcher the choice of accepting NSA or NSF funds. In the future, the NSA plans to have its own office to handle cryptography proposals, so researchers can submit their proposals directly to the NSA if they want NSA funds.—G.B.K.

0036-8075/80/1031-0511$00.50/0