For the moment, however, World Bank officials are hoping that the Reagan Administration will change its mind. Although the indications are that the Administration will not participate in the affiliate, it has not closed the door completely.

The statement to the Bank's executive board said that "the U.S. might be able to consider an appropriate structured Bank energy entity at some more suitable time." It added that "no inference should be drawn from this regarding the eventual U.S. position on the proposed expansion of Bank energy lending."

If it closes the door on the affiliate, however, the Administration will be passing up an opportunity to expand the Bank's energy work with little cost in public funds.—COLIN NORMAN

Gene Therapy Caught in More Entanglements

With five review committees overseeing him, a UCLA researcher did an experiment his own way

The first attempted gene therapy experiment has become further entangled in procedural problems by the discovery that it also constitutes the first known occasion on which recombinant DNA molecules have been inserted into humans.

Compounding the problem is that neither of the two American committees which considered the experiment, nor any of the three Israeli committees which approved it, were told that recombinant DNA molecules would be used: for reasons that are not yet entirely clear, all were told the opposite.

The principal architects of the gene therapy experiment are Martin Cline and Winston Salser of the University of California, Los Angeles (UCLA). An ingenious attempt to push the new genetic techniques to the therapy stage, the experiment came to public attention in October last year. After an initial wave of press interest in the first gene therapy, the publicity turned sharply negative because of criticisms from Cline and Salser's peers that the experiment was scientifically premature (*Science*, 31 October 1980).

The criticisms seemed somewhat beside the point, however, since provided that Cline and Salser had received permission for the experiment from a human subjects protection committee, they doubtless had every right to undertake it. The news that the committees may not have been given the correct information makes this shield look somewhat less reliable.

A theme that underlies the controversy over the experiment is the difference between private and public responsibility. By their own lights and in their own way, the UCLA researchers seem to have acted with scrupulous regard for their patients' interests. But for reasons that may or may not have been entirely their fault, they had difficulty in acquiring approvals from the various committees that now have public responsibility for overseeing research of this nature.

The Cline-Salser experiment, if successful, would offer a general method of treating such blood diseases as beta-thalassemia and sickle cell anemia, both of which are extremely painful, at present incurable, and kill the young. Their approach is to repair the genetic defect that is the cause of the disease by introducing the correct gene into the patient's system. Delivering the gene in sufficient quantities to be useful is one aspect of the problem; getting the gene expressed is another. Efficient expression of the human globin genes in animal cell test systems has not yet been achieved—which was the reason for much of the criticism that the experiment was premature. But with the delivery system, which at first seemed much the harder problem, surprisingly good progress has been made, at least in animal experiments. In the therapy, marrow cells are first extracted from the patient, and have inserted into them the globin gene and another gene that helps give them a selective advantage over untreated cells; they are then injected back into the patient, who must have mild radiation so as to clear niches for the returning marrow cells.

The UCLA team believed that the promising state of their delivery system merited taking it to humans. During the many months that might be needed to get the delivery method working in patients, they or someone else would doubtless come up with a solution to the expression problem. At which point there would at last exist a possibly effective treatment for a group of otherwise hopeless diseases. Cline and Salser devised protocols for treating both sickle cell anemia and beta-thalassemia. The sickle cell patients were available in Los Angeles; suitable beta-thalassemics were located in Israel and Italy. They applied for permission in all three places. But getting approval was no simple matter.

At UCLA, on their home ground, Cline and Salser ran into what struck them as a classic catch-22 situation. Each of the two committees whose approval they required—the human subjects protection committee and the recombinant DNA committee—said there was no point in considering the novel experiment unless the other committee had cleared it first.

In an attempt to break the impasse, the UCLA team asked the National Institutes of Health to put the issue before the national recombinant DNA committee. But NIH director Donald Fredrickson had no comfort to offer; he too told them to get the permission of the human subjects protection committee first.

As the first attempt to apply the recombinant DNA technique to humans, the novel experiment presented possible political problems, in addition to its scientific complexities, for whoever approved it. Asked why the NIH refused to put the question to its recombinant DNA committee, a public advisory group which costs $125,000 a year to run, executive secretary William Gartland says it was "because we didn't want a big public discussion when it might turn out to be unnecessary." The UCLA team is said to have received much the same impression of the NIH's reasons. Director Fredrickson, however, says he decided that the UCLA human subjects protection committee should rule on the experiment first "because I felt that human experimentation was a much broader issue than the recombinant DNA aspect." Because of the UCLA team's fear of being caught in a catch-22, Fredrickson told the UCLA human subjects com-

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mittee that it should take first crack at the issue without waiting for a recombinant DNA committee decision. Asked if desire to avoid public debate was also a motive, Fredrickson says he expected the decision would inevitably come to the NIH committee sooner or later, but preferred that it should come in as definite a form as possible, and therefore should be approved first in its human experimentation aspects.

Previously the UCLA team, in exploring other possible avenues out of the impasse, had developed a protocol for their experiment that did not involve the insertion of recombinant DNA molecules into the prospective patients. They would unlink the two genes from the vector used to prepare them in bacteria, and insert them in naked form into the patient's marrow cells.*

The UCLA recombinant DNA committee agreed that this non-recombinant method did not require their sanction, and the protocol then passed to the human subjects protection committee.

The UCLA team submitted the same non-recombinant protocol to authorities at the Hadassah Hospital in Jerusalem, where they had located a suitable beta-thalassemia patient. Like UCLA, Hadassah had two committees which had to be consulted. The Hadassah recombinant DNA committee decided that its approval was not required, but just to make sure, it referred the proposal to the Israeli national recombinant DNA committee which agreed that the experiment did not involve recombinant DNA molecules. The human subjects protection committee at Hadassah then approved the protocol.

At this stage Cline and his collaborators at Hadassah had received the sanction of three Israeli committees for the non-recombinant version of the experiment for beta-thalassemia. The sickle cell version of the experiment would later be turned down by the UCLA committee on the grounds of insufficient basis of animal experimentation, but since the review at Hadassah was no doubt equally competent, this was presumably an issue on which reasonable men might differ.

On their own initiative, the UCLA team had taken great care in selecting subjects for their first experiment. The criteria called for patients in a terminal phase of the illness, and who were intelligent enough to give truly informed consent. It was explained that the immediate procedure was unlikely to benefit them.

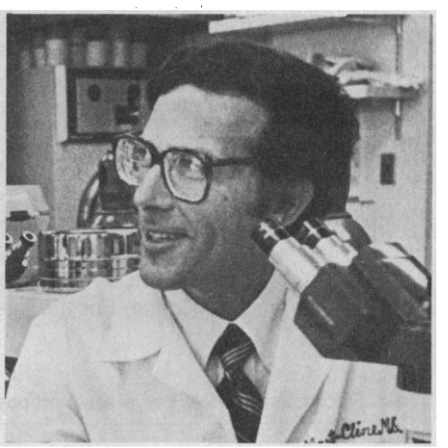
In July last year the procedure was undertaken on a 21-year-old patient at Hadassah and on a 16-year-old patient at the Poly Clinic in Naples. But in the former case at least, it was not performed according to the protocol approved by the three Israeli committees. At the last moment, without telling even his scientific collaborators at Hadassah, Cline decided to insert the genes into the bone marrow cells in the recombinant, vector-linked form, not as naked genes as specified in the protocol. Salser, who was not in Israel, declines to comment on this aspect of the incident.

"It was my decision to do it, and they were informed later," says Cline. Although he is reserving his position until the NIH completes its review of the matter, Cline states that the principal reason for the change in protocol was the evidence emerging from animal studies that the vector-linked genes were more effective. He did not tell his patient of the switch because, he says, she would not have understood such a level of technicality.

The Israeli authorities seem inclined to view Cline's actions more in sorrow than in anger. According to Samuel Penchas, associate director of the Hadassah, "I would not say Cline misrepresented the situation. He may have, in full truth, believed he had presented everything up until the last moment when he changed his mind. Personally I think it is between him and the creator. You could say, on the other hand, that at the least, once he had done it, he should have told us immediately." The Hadassah authorities only learned much later that recombinant DNA had been used. "We have no quarrel with anybody. We may feel unhappy about what it appears to us that Cline has done. Some of us do not understand why he did it, that is all," Penchas declares.

After investigating what happened at Hadassah, the UCLA authorities announced on 4 March that they had asked Cline to resign his administrative post as chief of the hematology and oncology division at the UCLA Center for the Health Sciences. But the university, in stressing its regard for his "exceptional scientific achievements," made clear that it intends to take no further action against him. Cline is still a tenured professor at UCLA. What he now faces is the verdict of the NIH committee looking into the episode.

It is easy enough to see the error Cline made in not informing the Israeli committees of the change in protocol. Since UCLA seems to claim jurisdiction over what its researchers do on other campuses, Cline also put himself in the wrong with his university. Moreover, his violation of the recombinant DNA guidelines—real if the experiments abroad came under the UCLA committee's jurisdiction, potential if not—was probably the most serious of the four infractions that are so far known to have occurred.



Protocols switched at last moment
Gene therapy pioneer Martin Cline

Yet Cline's fault was not one of avoiding responsibility. He apparently took the decision into his own hands and acted in terms of what he thought was best for the patient and for developing the new therapy. Nowadays, decisions of this nature have been transferred to committees. Some of the committees involved do not seem to have been egregiously prompt or decisive in exercising their responsibility. The NIH didn't want to touch the problem, perhaps for good reason, yet had it rendered a clear yes or no, much of the subsequent imbroglio might have been avoided. The other recombinant DNA committees approved a protocol that didn't involve recombinant DNA—a decision of no stupendous audacity. As for the UCLA human subjects protection committee, it kept on asking for more data, a request doubtless justified by the novelty of the proposed therapy, yet one in which its Hadassah counterpart did not so strenuously persist.

Cline should not have misinformed all these committees as to his intentions. But if in his heart he had said—(and there is no evidence that he did)—"To hell with them all, I'll do it my way," his sentiment would not transcend comprehension, regrettable though it would have been.—NICHOLAS WADE

*The distinction is somewhat artificial since under both protocols the genes would be prepared by recombinant DNA techniques. But in the "non-recombinant" protocol, the genes would first be severed from their vector before entering the marrow cells, whereas under the recombinant protocol the genes would enter along with the vector. The vector, pBR322, is not needed for the insertion, but removing it would also sever the link between the two genes, the globin gene and the herpes virus thymidine kinase gene.