Human Gene Treatment Stirs New Debate

UCLA researchers have conducted abroad a gene experiment they are not yet allowed to do here

Public sensitivity to the subject of human genetic manipulation underlies the intense interest aroused by the news on 8 October of the gene therapy now being applied to two patients suffering from thalassemia. The treatment, devised by a team of researchers at the University of California, Los Angeles, is the first known occasion on which the technique of recombinant DNA or gene splicing has been applied to humans.

New experimental treatments of human disease are tried out daily—what makes the UCLA case apparently different? One factor is that the treatment is a form of genetic engineering, a subject fraught with social and political fears as well as sound medical opportunities. The other is that the UCLA committee which oversees the protection of human subjects has recommended that more tests of the treatment in animals should be done first. Was the committee being overcautious? Or were the researchers being overprecipitate in conducting their research abroad, before the UCLA committee had given them its endorsement?

The UCLA gene therapy is part of a plan, first conceived in 1978, which its originators hope will lead to a viable treatment of sickle cell anemia, a serious disease among black Americans. The UCLA team decided first to develop a treatment for beta-zero thalassemia, a disease in which the failure or success of the therapy would be easier to monitor. So far two patients have been treated, one in Israel and the other in Italy; in neither case are definite results yet available.

Those suffering from the disease produce almost none of the protein molecule that forms the beta-chain of hemoglobin. The therapy depends on inserting copies of the human gene for beta-hemoglobin into the patient's bone marrow cells. The novel feature of the UCLA team's approach is to insert a second gene into the marrow cells, one that gives them a selective advantage over untreated marrow cells and allows them to proliferate in the body.

The second gene, obtained from herpesvirus, specifies the enzyme known as thymidine kinase. Animal experiments conducted by the UCLA team confirm that the virus gene enzyme is slightly more efficient than the mammalian variety. The protocol for the gene therapy calls for production of both the human beta-hemoglobin gene and the virus enzyme gene by cloning copies of each in bacteria. Marrow cells taken from the patient are then exposed to the two genes in a way that encourages the genes to enter and become part of them. The cells are then injected back into the patient. Under the conditions of the UCLA protocol, probably 10,000 or so of the injected cells may contain both genes. In theory, only one cell need settle and proliferate in the marrow to give the patient useful quantities of normal hemoglobin.

Why did the UCLA team proceed without the endorsement of the university's Human Subjects Use Committee? The researchers applied in parallel for permission to conduct the experiment both in Los Angeles and abroad, at the Hadassah hospital in Jerusalem and at the University Poly Clinic in Naples. Both institutions gave their assent, and the therapy was started, before the UCLA committee made up its mind that there should be another round of tests, in monkeys, before going to humans.

Albert Barber, a UCLA vice chancellor who oversees the Human Subjects Use Committee, says that the committee deliberated long and hard over the team's proposal and called upon a number of outside reviewers. It eventually decided that the chances of successful gene transfers in humans would be enhanced by additional animal experiments, but the committee will not elaborate. However, researchers in the field suggest trying to transfer globin genes in animals to prove that such a gene transfer can, in fact, be done successfully. As to the risk of the human experiments, Barber says that, on the basis of animal work done so far, they do seem low.

The UCLA team published its preliminary experiments on animals in April this year. The researchers did not inform the NIH or the university public relations office of the gene therapy trials, hoping that secrecy would be maintained until the experiment had been reported in the scientific literature. It was agreed that none of the team would talk to the press, an arrangement that dissolved when the *Los Angeles Times* picked up the story last week. The NIH, a month ahead of the newspaper, asked on 8 September for a full account of the experiment, including whether it had been approved by human subjects committees and whether federal funds were involved.

The research team's attitude toward publicizing its work is perhaps ambiguous. Though anxious to do what is right in the eyes of their scientific colleagues, the researchers also approved a press release about their mouse experiments which contained the stirring phrase, "The revolutionary techniques appear to be useful in the treatment of cancer" (*Science*, 25 April). The epithet "revolutionary" was deleted from later issues of the press release on the advice of the associate dean of the medical school.

The researchers believe that they were not jumping the gun in carrying the technique to humans, and that an adequate basis of animal experimentation had been established. They firmly deny that they sought patients abroad in order to avoid rulings made in the United States. They needed patients who were homozygous for beta-zero thalassemia, intelligent enough to give informed consent, and with a limited life expectancy, just in case the therapy should have some untoward effect (none was detected in mice). Such patients are hard to find in the United States, where thalassemia is not nearly so common as in Mediterranean countries.

> So far, the gene therapy has not worked.

The research team intends ultimately to develop a treatment for sickle cell anemia. The disease is much harder to treat than beta-zero thalassemia because a majority of marrow cells must be replaced before the patient experiences any benefit.

The concept pursued by the UCLA team was originally developed in conversations between Winston Salser, Martin Cline, and Howard Stang.—GINA BARI KOLATA AND NICHOLAS WADE

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