MUSCULAR DYSTROPHY

Researchers Call for Time Out On Cell-Transplant Research

Two years ago, several research groups around the world began testing a promising treatment for Duchenne's muscular dystrophy, a fatal condition that strikes mostly boys. Their strategy: injecting healthy muscle cells into the sick children's muscles. Animal experiments suggested that the inserted cells, called myoblasts, would fuse to the diseased muscles and restore their normal function by producing dystrophin, an essential protein lost when a mutation knocks out the dystrophin gene. The theory sounds good, but the results have been murky. The only impressive claims, from a group led by Peter Law of the Cell Therapy Research Foundation in Memphis, have been sharply criticized (*Science*, 24 July, p. 472).

Now a group of leading investigators who do basic research on muscles are calling for a halt to the human trials. They argue that the technical problems should be worked out in animals before more children are exposed to the risks of the trials. But the clinical researchers conducting these trials don't buy it; they think the strategy may still work.

The call for a moratorium went out in a letter to *Science* after a Gordon Conference held in Tilton, New Hampshire, from 14 to 19 June, where muscle researchers, including Henry Epstein of Baylor College of Medicine, heard the results of a recently completed human trial. What Epstein and his colleagues learned convinced them it was time for basic researchers to speak up. Like other cell-transplant trials, they say, the study—by Robert Miller of the California Pacific Medical Center in San Francisco and Helen Blau of Stanford University—showed so little evidence that the treatment works or that the implanted cells are even surviving that there was no justifying the risk of the immunosuppressive drugs and general anesthesia used in the grafting.

Epstein and his colleagues concede that the patients opt to take the risk, but the letter's signers doubt that dying boys or their families are in a position to give true informed consent. "The children themselves don't have informed consent," says Epstein. "They rely on parents. The parents, in this case, may not have informed consent either because of the emotional issues of having a child with Duchenne's." Given all that, says Epstein, "We think it is a time for stopping and reevaluating and not going on."

Another signer, Eric Hoffman, a University of Pittsburgh muscle researcher, agrees that "there are clearly other ways to go about this more systematically than injecting patients right and left." And Hoffman isn't just another worker in the field: He's the researcher who discovered dystrophin, the protein that is the Holy Grail of the cell transplant work. Hoffman and his cosigners think more animal experiments are needed to improve the survival of the transplanted cells and their expression of dystrophin. After these technical problems are resolved, they say, the initial human studies should be carried out in adults with Becker's dystrophy, a related but less severe form of the disease, who can give fully informed consent.

But the transplant researchers apparently aren't about to pack it in. "We do not intend to stop doing patients," said Miller. "We are gearing up for the next phase to improve the efficiency of the technique."

All of the clinical scientists except Law admit that the initial results have been unimpressive. But they don't accept the reasoning behind the call for a moratorium. "The initial lack of success in an experimental work is no justification to advocate its cessation," said George Karpati, head of a research group at the Montreal Neurological Institute that tested myoblast treatments in eight Duchenne's boys and is planning future human trials.

Nor is the treatment unjustifiably dangerous, says San Francisco's Miller. "We are up to 60-plus patients [worldwide] and no boy has been harmed. None of us have seen any significant clinical problem or complication, including from immune suppression." As for the issue of informed consent, several of the researchers countered by pointing out that institutional review boards—which exist to protect patients from risky or harmful experiments—have approved all of the current studies.

For now, the appeal looks unlikely to stop the research unless the federal government steps in or funding dries up—and there aren't any signs, for now, that that's about to happen. Lawrence Shulman, director of the National Institute of Arthritis and Musculoskeletal Disorders, declined to comment on the moratorium call. His institute is not funding any of the human trials, though it does fund animal studies. That leaves the private Muscular Dystrophy Association (MDA), the sole financial supporter of the ongoing clinical trials, with the final say.

And MDA's science and technology director, Donald S. Wood, is noncommittal. He calls the scuffle "a legitimate scientific disagreement." But as far as the association's funding policy goes, he said, there will be no changes. "The MDA will continue to fund the human trials."

–Larry Thompson

Larry Thompson is a science writer living in Bethesda, Maryland.

Dear Editor,

The undersigned are active researchers in the field of muscle development and disease who are concerned about recent studies of human myoblast implantation in male children afflicted with Duchenne's muscular dystrophy, often referred to as "myoblast therapy." The present studies indicate only limited survival of the implanted myoblasts, little or no expression of dystrophin by these myoblasts (1,2), and no significant improvement in the clinical status of these children (3).

For these reasons and because potential risks to the children exist from the immunosuppression (1,3) and general anesthesia (3) used in these experiments, we urge the cessation of further initiation or expansion of these studies until additional research on the biology of implantation, development, and gene expression of myoblasts in animal models and adult human subjects provides a firmer basis for "myoblast therapy" than now exists. For example, specific lines of animals suffer from disorders very similar to the human dystrophy. Well-controlled experiments in these animals conducted according to humane animal welfare guidelines could provide the development of proper muscle cell culture and implantation techniques that permit sufficient proliferation and dystrophin expression to ameliorate the dystrophy. When implantation appears successful and therapeutic in such experimental models, then these techniques could be tested in adult human subjects who have given their fully informed consent in order to ensure applicability to humans.

Only after successful outcomes in such studies are achieved, should trials of "myoblast therapy" in children afflicted with muscular dystrophy or any other neuromuscular disease be reinitiated.

REFERENCES

1. I [illegible] Nature 356, 435 (1992).
2. [illegible] Worton, *Muscle & Nerve*, in press
3. P.K Law *et al*, Cell Transplant. 1, 235 (1992).

Henry F. Epstein
Donald A. Fischman
David Bader
Jean-Pierre Changeux
Kathryn Buckhold
Charles P. Ordahl
Eric Hoffman
Laurence H. Kedes
Stephen Konieczny
Leslie A. Leinwand
Anthony J. Straceski
Andrew Engel
Frank E. Stockdale
Hans H. Arnold
Vijak Mahdavi
Leland Webster
Sanford Bernstein
Richard Cripps
Stephen D Hauschka
Mary P. Wenderoth
Margarita Cervera
Karyn Esser
Edna Hardemann
Peter Gunning
M.A.Q. Siddiqui