CLINICAL RESEARCH

A First in Cell Transplantation: Researchers Organize, Meet

How can you tell when a new field of research has come into its own as a scientific discipline? Two signs are that researchers form a society and hold an international conference. Both happened at once in the emerging field of cell transplantation, a wide-ranging discipline including projects as various as gene therapy and transplantation of fetal tissue for treating Parkinsonism. The initial meeting of the Cell Transplant Society drew 500 researchers to Pittsburgh from 1 to 3 June, to write what conference chairman and surgeon Camillo Ricordi of the University of Pittsburgh calls "the next chapter in the history of transplantation."

The preceding chapters in the history of transplantation told the story of organ transplants, and the current work could represent a significant advance over organ transplantation because transplanted cells can carry out an impressive range of specific functions. Potential applications discussed at the meeting included treatments for diabetes, cancer, Parkinsonism, muscular dystrophy, cirrhosis of the liver, heart attacks, and genetic diseases. Although bone marrow cells are the only ones routinely transplanted today, many other cell types are being groomed for that purpose, among them pancreatic islet cells, liver cells, myoblasts, and epithelial cells.

"This is an ideal time to come together," said Paul E. Lacy of Washington University in St. Louis, a leader in experimental efforts to transplant pancreatic islet cells. "Five years ago," Lacy added, "this meeting could never have happened; these fields were not far enough advanced." In many ways, however, they still aren't very advanced. The obstacles reported at Pittsburgh considerably outnumbered successes, and the chief impediments include: generating enough donor cells, maintaining donor cells in culture, knowing the location in the body where they are most likely to survive, manipulating the "microenvironment" of the transplant sites with growth factors and other stimulants to sustain the cells, overcoming immune-system rejection, and making sure the transplants function as intended.

In spite of such obstacles, plenary speaker Peter J. Morris of Oxford University, whose work is on the immune effects of cell transplants, said, "I'll be surprised if by the year 2000 cell transplantation is not an accepted therapy for several diseases, especially Type I diabetes." A review of the conference's more intriguing sessions suggests which diseases those might be:

Islet cells. Several groups reported progress in constructing artificial organs containing islet cells for treating diabetes. These cells produce the insulin the body needs to use the sugar glucose. Lacy's group reported preliminary work on the use of a bioengineered hollow-fiber device, made by CytoTherapeutics of Providence, Rhode Island, in which rat islet cells were suspended in a seaweed-based gel and enclosed in a semipermeable membrane implanted under the skin. The devices performed "very nicely" in rats, Lacy said; the St. Louis group is now testing them in dogs.

Liver cells. Michio Mito reported results of 10 experimental liver cell transplants in humans performed in Japan over the past 3 years, six by Mito's group at the Asahikawa Medical College. One transplant involved a man who had ascites (an accumulation of fluid in the abdomen) associated with cirrhosis of the liver. The condition disappeared following transplantation of liver cells into the spleen; the man was able to return to work 11 months later. But Mito noted that it is difficult to determine how big a role the transplanted cells played in recovery.

Getting prolonged function is a problem that bedevils liver cell transplants, according to Achilles Demetriou of Vanderbilt University, who described transplants into rats. "We can get good cells for several months. The point is, when you go back a year later, the cells are no longer working."

Adrenal cells. Moses Goddard and Patrick Aebischer of Brown University and CytoTherapeutics reported some arresting preliminary results from transplanting dopamine-secreting PC12 cells from a tumor derived from rat adrenal cells into the brains of monkeys that had been chemically treated to induce a dysfunction similar to Parkinsonism. The PC12 cells were placed in semipermeable capsules, then implanted in the brains of the monkeys; four of five showed "significant behavioral improvement."

Immune tolerance. One of the most intriguing results came from Suzanne Ildstad of the University of Pittsburgh, who described apparent cases of "donor-specific immune tolerance" induced by transplants across species. Following irradiation to kill off their bone marrow, mice received simultaneous transplants of bone marrow and islet cells from rats, yet survived indefinitely without showing the rejection that almost always follows transplantation across species. Descendants of the transplanted bone marrow cells had apparently been "educated" in the thymus to recognize the rat cells as part of the self. The Pittsburgh group now claims that the effect has been achieved with less harmful doses of radiation, suggesting that cross-species transplantation might ultimately be a clinical possibility.

Ildstad's results complemented recent research on immune tolerance within a single species by her Pittsburgh colleague, transplant surgeon Thomas Starzl. Starzl described "two-way traffic" of donor cells out of a transplanted organ and of host cells into the graft tissue without rejection. This so-called chimerism was discovered recently in intestine and liver transplant recipients, but a retrospective examination of long-surviving patients who received kidney transplants in the 1960s showed similar "seeding" of the host by donor cells that normally trigger an immune response. Surprisingly, several organ recipients who had these migrating cells—known as dendritic cells or passenger leukocytes—had discontinued immunosuppressive therapy on their own yet continued to tolerate the donated organ.

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Heads together. Thomas Starzl *(left)* confers with Camillo Ricordi, first president of the new Cell Transplant Society.

One impression left by the Pittsburgh meeting was that although significant problems remain unsolved, the imagination with which new approaches are being tried is striking. A remark made by Daniel Marelli of McGill University about his experiments aimed at transplanting skeletal muscle cells to improve heart performance could equally well apply to the entire field: "Our results circumstantially support the concept, but are far from being conclusive." Researchers have 2 years—the next conference is in Minneapolis in 1994—to bring the Pittsburgh 500 and their colleagues one step closer to realizing Peter Morris' prediction.

–Stephen S. Hall

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