New Transplant Method Evades Immune Attack

An innovative technique for transplanting pancreatic cells could offer a diabetes cure—and new avenues for transplants generally

IF ALI NAJI IS ONTO SOMETHING, there's renewed hope for the roughly 1 million Americans who suffer from insulin-dependent diabetes mellitus, or type I diabetes. The disease is caused by degeneration of the islet cells, the cells of the pancreas that produce insulin. A promising approach to curing the disease is transplantation of functional islet cells into these patients. But unless immunosuppressants (which have undesirable side effects) are used, the patients' immune systems often reject the transplants.

In this issue of *Science*, a team led by Naji, a transplant surgeon and immunologist at the Hospital of the University of Pennsylvania, reports having found a way around the need for immunosuppression (see page 1293). By transplanting islet cells into the thymus of rats, Naji and his colleagues appear to have persuaded the rats' immune system to accept the transplant as "self" rather than as foreign invader. And in so doing, they may have opened the way not only to a possible treatment for diabetes, but also to broader advances in transplantation generally.

"This is a very creative and imaginative set of experiments that will direct us to new approaches in transplantation," says Aldo Rossini, director of diabetes research at the University of Massachussetts Medical Center. "People have been looking at transplanting islets to immunologically privileged sites for a long time, but haven't done much with the thymus."

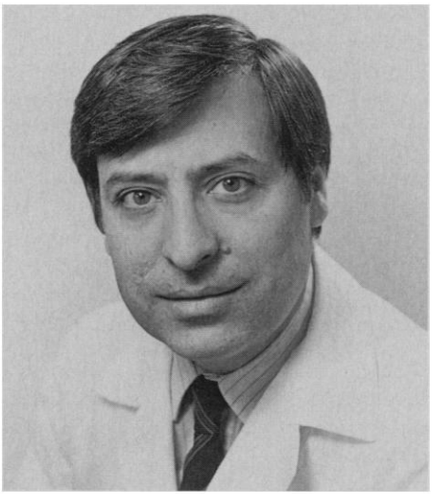
The immunological privileges of the thymus stem from the fact that T lymphocytes mature in that organ. These key cells of the immune system (among other functions) seek out and destroy foreign substances bearing antigens to which the T cells respond. It is in the thymus that each set of T cells is "educated" to respond to a particular antigen. And because the thymus is the site of that educational process, transplantation there has some special properties.

"Using the thymus as an immunologically protected host for transplantation is a tremendous advantage," Naji says. "It's almost like the graft isn't even seen there by the immune system."

Working with rats in which diabetes had been chemically induced, Naji's team injected freshly collected islet cells into each of the two lobes of the thymus. In some instances the transplant was accompanied by a dose of antibody-containing serum directed against T cells. The serum reduced the T lymphocyte population by 90%, and in the majority of those cases the transplanted cells survived indefinitely without any immunosuppressive agents.

According to Naji, reducing the number of T cells at the time of transplantation causes new T cells to mature in a thymus containing a foreign tissue that those cells recognize as part of the self and therefore tolerate. "Basically, it is like you are giving the recipient the specific antigen you want to develop tolerance to," says B. J. Fowlkes, senior immunologist at the National Institute of Allergy and Infectious Diseases, who specializes in the thymus' role in the development of immune tolerance.

Promising as it is, Naji's innovation faces several hurdles if it is to become a clinical method. For one thing, the supply of islet cells is limited, according to Hans Sollinger, a transplant surgeon and immunologist at the University of Wisconsin. Only 1000 human pancreases are available in the United States each year, Sollinger says, and two or three are needed to provide enough islet cells for one recipient. But Rossini suggested that, if the procedure proves effective in providing an immunologic sanctuary for transplanted tissue, animals might offer an additional source of islet cells.



Behind enemy lines. *Ali Naji's transplant method eludes immune surveillance.*

Even if the supply problem is solved, however, there is another obstacle: the autoimmunity that may cause the diabetes in the first place. The underlying cause of type I diabetes may be wayward T lymphocytes that attack the body's own islet cells, destroying their ability to make insulin. This problem is separate from that of graft rejection—since the subset of T cells that may trigger autoimmunity is different from those that mediate graft rejection. "Despite the tricks we can use to get around rejection, autoimmunity continues to be the big problem," says George Eisenbarth, chief of immunology at the Joslin Diabetes Center in Boston.

But that problem may also be surmountable. In follow-up experiments by the Penn team with rats that develop autoimmune diabetes, Naji said, preliminary observations suggest that islet cells continue to resist graft rejection and also function without being destroyed by autoimmune T lymphocyte attacks.

A possible next step toward clinical application may be trying islet cell transplants in larger animals. According to J. David Sutherland, director of the pancreas transplant program of the University of Minnesota Hospital and Clinic, "this is an extremely clever experiment, but the $64,000 question is: can they do this in a large animal model like a pig or dog? If it won't work in dogs, then it's just another interesting observation from small mammals that won't translate to humans."

If the Penn team's work does translate to humans, its broadest implications may come from a finding that was an unexpected bonus. After initial transplant of the islet cells, Naji and his colleagues found that subsequent transplants from the same donor into the kidney were not rejected as foreign tissue. Apparently, the education of T cells in the thymus also applies to later transplants.

"In theory," Naji says, "way down the road you might be able to implant a bit of heart or liver tissue into the thymus to modify the immune system, and then later implant the entire organ without the need for immunosuppressants." And that, he adds, could open a new avenue for transplantation research—an avenue that might one day lead to doing away with the need for immunosuppression in transplants altogether. ■ P. J. SKERRETT

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