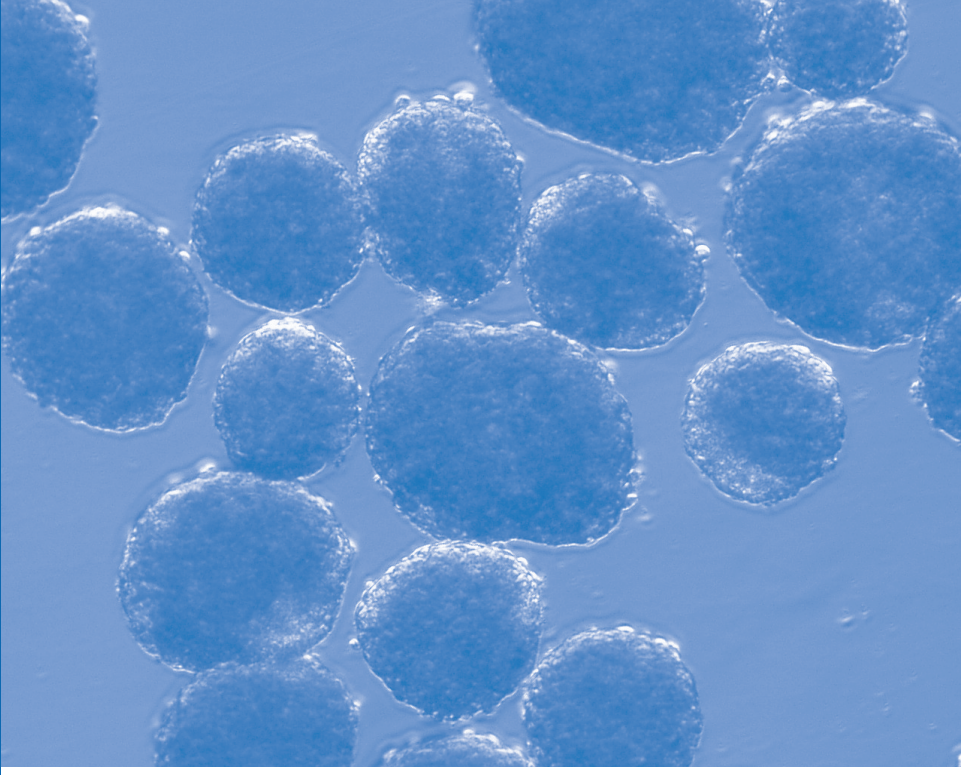


GOAL III:

DEVELOP CELL REPLACEMENT THERAPY

Why It Is Important To Develop Cell Replacement Therapy

- Benefits of Cell Replacement Therapy
- Improving Islet Transplantation Techniques
- Fighting the Immune System's Destruction of Transplanted Islets
- Making New Beta Cells

Patient Profile

- Karla Edge: Islet Transplantation Brings New Hope to a Patient with Type 1 Diabetes

WHY IT IS IMPORTANT TO DEVELOP CELL REPLACEMENT THERAPY.

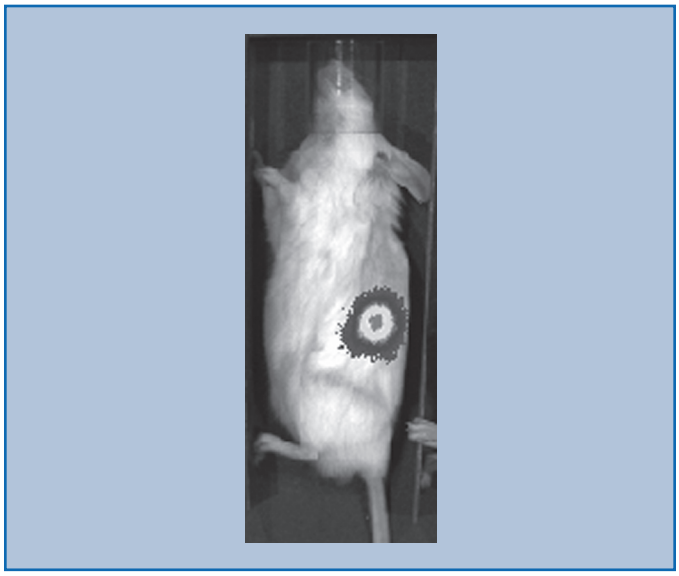
People who live with type 1 diabetes ask: "Will there be a cure for my disease? If cell therapy becomes available, will I be eligible? Are there side effects? How are scientists working to solve the problem of finding a source of insulin-producing beta cells so that all patients can someday receive an islet transplant?"

The prospects of a cure for type 1 diabetes have improved dramatically because of research advances in cell-based therapies. Using improved techniques, researchers are now capable of restoring substantial insulin production to patients with type 1 diabetes for a period of a few years by transplanting clusters of insulin-secreting beta cells. These cell clusters, called islets, are obtained from the pancreatic tissue of human organ donors. The transplanted cells are functional replacements for those destroyed by the disease through a misguided attack by the body's own immune defense system (autoimmunity). Unfortunately, this experimental procedure—called islet transplantation—is still limited for several reasons. First, there is not an adequate supply of donor tissue to treat all patients with type 1 diabetes who might benefit from this procedure if it were to become widely available in medical practice. Second, patients who receive islet transplants require lifelong medication to keep their immune systems from rejecting the new cells as "foreign." This regimen of immunosuppressive drugs has many unwanted side effects and is a major barrier that currently limits the study of islet transplantation to adults with brittle diabetes or those who already receive immunosuppressive drugs after kidney transplantation. If these and other barriers can be overcome, the standard of practice for treating type 1 diabetes could be revolutionized. Achieving the goal of developing safe cell-based therapy would dramatically improve the health and quality of life of type 1 diabetes patients. NIH-supported research is critically important for meeting these research challenges.

Benefits of Cell Replacement Therapy

Although research advances have improved the management of type 1 diabetes, patients often have difficulty controlling their disease. No matter how vigilant patients are, they cannot achieve the exquisite regulation of blood glucose levels that is provided by a healthy pancreas. When the body's blood glucose level is not properly balanced, health complications of diabetes arise sooner and have more devastating effects over time (if glucose is too high), or an individual can become shaky, sweaty, and confused; lose consciousness; and even die (if glucose is too low). Therefore, researchers are working on ways for patients to improve control and avoid these complications. Replacing the insulin-producing pancreatic beta cells that have been destroyed by the disease would enable the body to assume its normal role of precisely regulating blood glucose levels. Patients would no longer have to check their blood glucose levels with finger sticks, inject themselves with insulin, worry about when to eat their next meal, or be plagued by the fear of life-threatening bouts of dangerously low blood glucose (hypoglycemia). Furthermore, islet transplantation can achieve the tightly regulated blood glucose control that has been shown to slow or prevent the development of long-term disease complications. In short, realizing this goal would enable patients to live a life free of the everyday burden of this disease and to be spared from developing life-threatening disease complications.

Significant progress in islet transplantation has been achieved in recent years. Several research centers have shown, on a modest scale, that people with type 1 diabetes who receive transplanted islets can remain free of insulin injections for substantial periods of time. However, major challenges must be overcome before large-scale implementation of islet transplantation will be feasible. First, the methods of acquisition and delivery of islets must be optimized in order to provide replacement therapy for all people suffering from type 1 diabetes. This includes refining the islet transplantation procedure to avoid complications, such as bleeding. Second, clinical treatments must be developed that will better combat the body's tendency to destroy transplanted islets. Third, the mechanisms of pancreatic beta cell development must be elucidated to facilitate methods for producing cells in sufficient quantities to provide an adequate supply for transplantation. Finally, safer methods of preventing rejection and recurrent autoimmunity must be developed so that the benefits outweigh the risks for patients who do not have exceptionally brittle diabetes with recurrent hypoglycemia.



In vivo imaging of islets: A mouse was transplanted with 1,000 islet equivalents of human islets expressing a luminescent marker. Non-invasive, bioluminescence imaging was performed on the anesthetized mouse, and the transplanted islets could be easily visualized.

(Image courtesy of Dr. Alvin Powers, Vanderbilt University.)

Improving Islet Transplantation Techniques

In current methods of islet transplantation, insulin-producing cells are taken from a donor human pancreas and transferred (or grafted) into an adult patient, most commonly in the liver. Once implanted, these grafts begin to make and release insulin in response to the body's needs. The transplanted cells thus enable the patient's efficient use of glucose for energy and keep the level of glucose in the blood finely balanced. The goal is to transplant a sufficient quantity of insulin-producing cells to keep the blood glucose level as close to normal as possible—with little or no reliance on external insulin administration.

Researchers have confirmed that islet transplant recipients are able to maintain near normal blood glucose levels, which is the primary and most highly desired outcome. However, they also have observed that success of the transplantation process varies greatly and wanes over time, underscoring the need for further research on methods of obtaining islets for transplantation and maintaining functioning transplanted islets. Progress has also been made in developing laboratory tests to ensure that high-quality islet cells are used for transplantation and in refining the technique for implanting donor islets into patients—both of which are key to optimizing the success of the treatment.

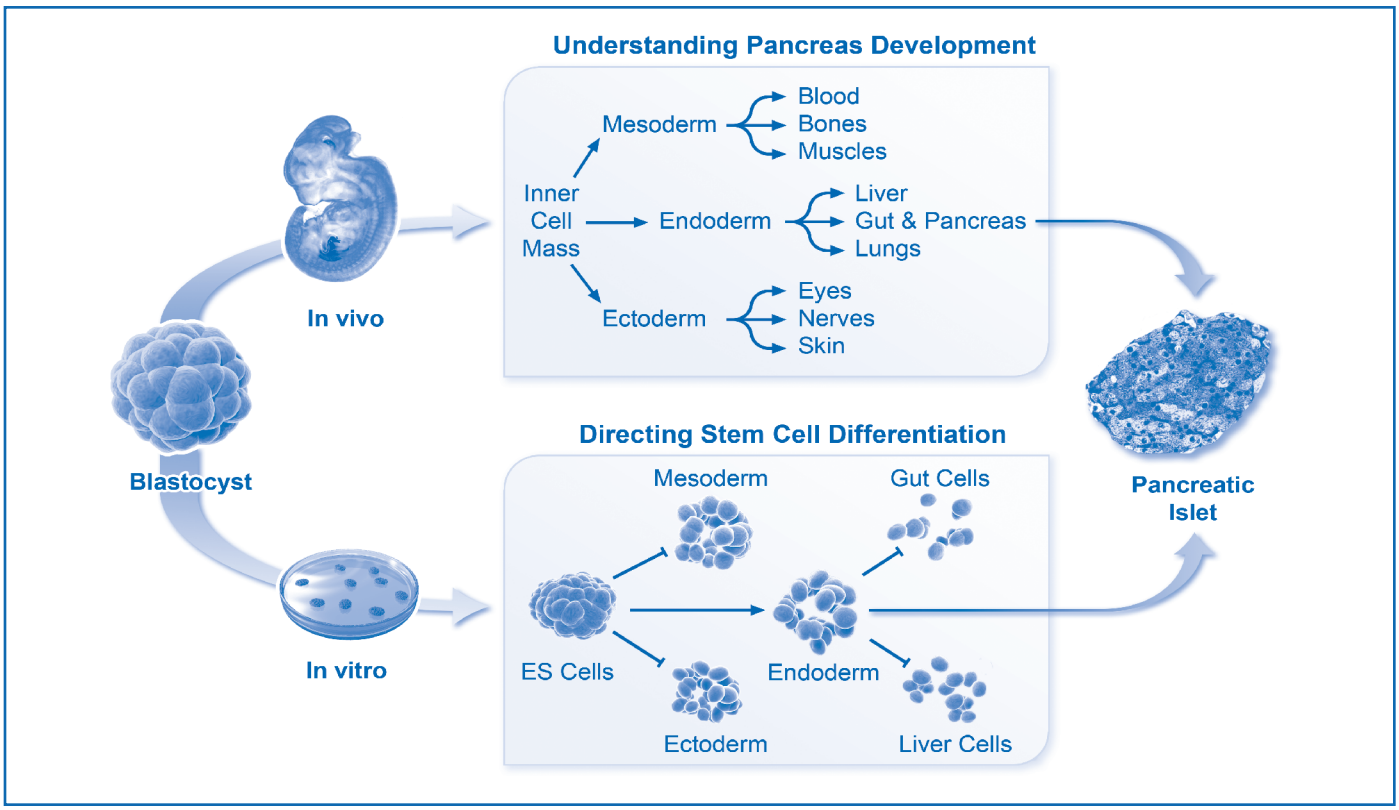
Limitations remain for the expansion of the islet transplant technique. For example, during the many steps that occur prior to the transplant surgery, the fragile islet cells must be collected and handled very carefully so as to preserve their health and function. Improper handling of cells renders them of little benefit to the patient. Likewise, these healthy donor cells must be implanted into the patient in an environment that continues to promote good health and function. Many of the complex details of what constitutes this type of environment are not yet completely defined. Scientists are investigating alternative surgical sites, as well as sophisticated biomaterials that may protect the islet graft from destruction by the immune system. Improving the collection and transplantation methods for islets is crucial for immediate expansion of the technology. If cell survival is enhanced, a lower number of cells is required, and thus a greater number of patients can undergo this life-altering treatment. To reach the goal of improving islet transplantation, future research will need to focus on improving the processing and handling of islets, developing techniques to measure viability and predict success of the islets prior to transplant, and developing and refining islet transplant techniques.

Fighting the Immune System's Destruction of Transplanted Islets

Patients who undergo islet transplantation are required to take lifelong medications to prevent the immune system from attacking and destroying the transplanted cells. However, these drugs can cause serious and adverse side effects, can reduce the body's ability to fight infections, and also may weaken or kill the grafted cells. Researchers are gaining a deeper understanding of the concept of graft rejection and how to identify early signs of rejection, at a point when intervention is possible. It is not only important to prevent rejection, but recurrent autoimmunity must also be overcome. Researchers have developed less toxic agents to block the immune attack on the transplanted islets. These agents will soon be tested in a limited number of islet transplant recipients. In these pilot clinical trials, researchers will study new approaches to help ensure that all patients who undergo treatment have the greatest opportunity to achieve successful results. To reach the goal of reducing immune rejection and recurrent autoimmunity, future research could focus on developing novel immunomodulation strategies and technologies, as well as on creating techniques capable of monitoring and preventing autoimmunity and rejection.

Making New Beta Cells

A major restriction of islet transplantation is tissue supply, which is currently limited to donor pancreatic tissue.



Embryonic stem (ES) cells hold significant potential for deriving differentiated cell types, including insulin-producing beta cells. Knowledge of genes and signals controlling pancreatic development in the whole animal can enable test tube recapitulation of specific embryonic programs in stem or progenitor cells to produce functioning insulin-producing cells for replacement therapy in type 1 diabetes.

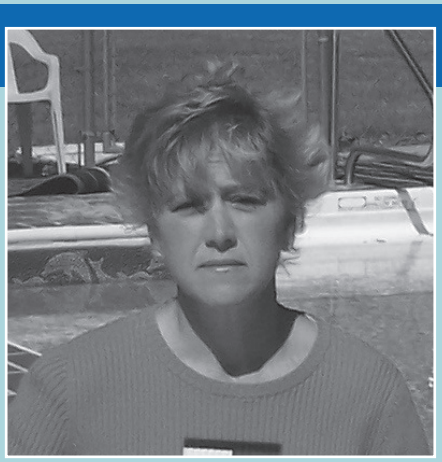
(Figure courtesy of J.P. Cartailler, Beta Cell Biology Consortium.)

However, research is under way to develop methods to regenerate beta cells within the pancreas or to generate beta cells from stem/progenitor cells. If successful, these methods could lessen or obviate the reliance on donor pancreatic tissue as a source of transplantable cells.

Researchers have accumulated considerable knowledge about the basic biology of pancreatic beta cells, in terms of how these cells function and how they are affected in type 1 diabetes. Methods have been developed to study the genes that are uniquely active in beta cells and the proteins those genes produce. Knowledge is expanding about stem/progenitor cells that differentiate into insulin-producing beta cells. Studies have suggested that it may be possible to coax the small number of insulin-producing cells that might remain in individuals with type 1 diabetes to multiply and once again produce insulin. Of course, overcoming ongoing islet cell damage in diabetes would also be required to explore possibilities for regenerating beta cells or for boosting residual beta cell function.

Much remains to be discovered about the body's insulin-producing beta cells, as well as the stem cells from which they are derived. Specifically, the genes, proteins, and other biological compounds associated with beta cell development and the signals required for their maintenance and expansion must be elucidated. These studies could permit scientists to grow islet cells for use in future research efforts and help them recreate an environment in the transplant patient that would optimize the success of the grafted islets. This knowledge is also key to efforts to regenerate beta cells in the pancreata of patients with type 1 diabetes.

Islet transplantation is a promising therapy that can yield long-lasting and beneficial results for people with type 1 diabetes. Significant progress has been made in expanding the knowledge of islet cell biology and the processes associated with transplantation and immune rejection. However, the clinical strategy remains limited due largely to constraints in islet supply and the side effects of the drugs needed to prevent rejection and recurrent autoimmunity. Future research is needed to make islet transplantation a viable therapeutic strategy for more individuals suffering from type 1 diabetes. Addressing islet transplantation technologies, immune modulation, and beta cell development will permit researchers to move closer to a cure.



Karla Edge:

Islet Transplantation Brings New Hope to a Patient with Type 1 Diabetes

Karla Edge was diagnosed with type 1 diabetes in 1967, at age 6. As a child, her disease was relatively free of complications. However, at age 13, she started having life-threatening hypoglycemic episodes. By the time she reached middle age, the episodes had become much more frequent and severe, to the point that she was experiencing several episodes a week.

"My blood sugar was so out of control that I couldn't go anywhere by myself," says Karla. Her husband, Mike, as well as other family members and friends, felt the need to call her at all hours of the day to make sure she was okay. Her two young daughters, Talia and Tatum, worried constantly about their mother. "It was all so very scary. I felt like I was knocking on death's door," says Karla.

Living with Type 1 Diabetes

Type 1 diabetes results when the body's immune system destroys the pancreatic insulin-producing beta cells that control blood sugar levels. As a result, people with type 1 diabetes fight a constant battle to keep their levels from going too low or too high. Yet, even those who manage their diabetes well—by controlling their dietary intake and taking daily injections of insulin—are at high risk for a wide range of complications, including heart disease, stroke, blindness, kidney disease, and nerve damage.

Fortunately, 45-year-old Karla has no organ complications whatsoever as a result of her diabetes, and, "My eyesight is perfect," she says proudly. However, she developed high blood pressure during her first pregnancy, but manages to keep it under control with medication. What she wasn't able to keep under control, no matter how hard she tried, were her blood sugar levels.

A Roller Coaster Ride

When she was 18 years old, Karla went into convulsions as a result of her low blood sugar. She was taken to the hospital in an ambulance. By the time she arrived in the emergency room, her blood sugar count had dropped to 10 mg/dL. A normal blood glucose level is approximately 100 mg/dL. Karla was told that she was lucky. Just the week before, another young woman had come into the hospital with a blood sugar count of 16 mg/dL and had died.

"My blood sugar was so out of control that I couldn't go anywhere by myself," says Karla.

Since that time, Karla's life has been a roller coaster ride. She was fine as long as her blood sugar was in the normal range. But when it suddenly dropped, she would become disoriented, start slurring her words, and her eyes would dilate. "I looked crazed," she says. Karla often had to rely on close friends to give her glucose tablets to bring her blood sugar back up and to make sure she got home all right. The disease was taking an emotional toll on her family, as well. She recalls a time when she was standing in a department store checkout line with her then 6-year-old daughter. "My daughter looked up at me and knew I was in trouble. She urgently told the person standing next to us, 'Please, my mom is a diabetic and she needs help.'"

Her diabetes affected her working life, as well. Karla worked as a data entry operator and was often late for work as a result of her hypoglycemic episodes. Her boss didn't understand the severity of Karla's condition and wasn't sympathetic to her being late or staying home from work. Over the years, the disease's impact on Karla's body—plus the emotional stress at work—had become so intense that her primary care physician strongly recommended that Karla retire early from her job, which she did at age 42.

It was about that time that Karla's sister, Kathy, read a newspaper article about an experimental treatment for type 1 diabetes, called islet transplantation, offered by the Diabetes Research Institute (DRI) in Miami, Florida. Karla immediately contacted the DRI, filled out an application, and was told she was a perfect candidate for the procedure. Although she had to wait nearly 3 years before undergoing her islet transplant, she says that it was well worth the wait.

Because islet transplants are experimental, they are available only to people who meet specifically defined criteria stated in the study protocol. To date, only adults with severely unmanageable blood sugar levels or who have already undergone a kidney transplant have been eligible.

Undergoing a Life-Changing Islet Transplant

In September 2005, Karla underwent a revolutionary new procedure for islet transplantation, called the Edmonton Protocol. Originally developed by researchers at the University of Alberta in Edmonton, Canada, the protocol uses a novel, steroid-free combination of three drugs that appears to prevent rejection, as well as halt autoimmune destruction of transplanted islets. Islet transplantation replaces the islets that have been destroyed by type 1 diabetes with islets from a donor cadaveric pancreas. The donor islets are infused through a catheter (small tube) into the portal vein of the liver. In a successful transplant, the new islets start producing insulin—eliminating or reducing the need for patients to take insulin. In effect, islet transplantation could be considered a real "cure" for the disease.

"I remember days, before the procedure, when I felt like I was 120 years old. Now I feel like I'm back in my 20s again. It's wonderful. No, it's a miracle!"

Karla's transplant was performed on September 19, 2005. She went into the procedure at about 2:00 p.m. and was given a local anesthetic, which meant she was awake throughout the entire procedure. She reports having felt very little pain or discomfort from the procedure itself and was back in her hospital room by 4:30 p.m. and released from the hospital the next day. Because the transplanted islets started working immediately, her physician reduced her insulin dosage that first day. Within 2 weeks, Karla was totally insulin-free. "It was the first time since I was 6 years old that my body produced enough insulin naturally to keep me alive," she says. "I'm very grateful to Dr. Rodolfo Alejandro, Director of Clinical Islet Transplantation at the DRI, as well as Drs. Tatiana Froud and David Baidal for their kindness and expertise," says Karla.

A New Beginning

After undergoing the islet transplant, Karla felt that her future had arrived. At the time this profile was written, she was insulin-free and says that the transplant has been a life-changing event for her for the better. "I never knew I could feel so good," says Karla. "It's amazing!"

Karla still needs to check her blood sugar before meals and two hours afterwards, as well as at bedtime. "It's always normal," she says with great relief. "It's nothing like it was before, when I had to check it every time I left the house or got in the car to drive somewhere." She

also no longer needs to eat on a regimented schedule. Moreover, she can now do volunteer work at her daughters' school without concerns about episodes of severe low blood sugar.

It has been an enormous relief for her family, as well. "Before the procedure, my husband would wake me up in the middle of those nights when I would go into a hypoglycemic convulsion, and he would have to give me an emergency injection of glucagon to prevent me from going into a diabetic coma and perhaps dying. This would happen at least once a month. He says that now he can sleep well at night, without having to worry about me."

As with any transplant, rejection is a major concern. The immune system is programmed to destroy bacteria, viruses, and tissue it recognizes as "foreign," including transplanted islets. Immunosuppressive drugs are needed to keep the transplanted islets functioning. These drugs, however, come with potentially serious side effects. Fortunately for Karla, her body has handled them well. "Aside from experiencing some nausea when I was in the hospital, I don't remember the last time I felt sick from the drugs." Nor, she adds, has she experienced any other side effects.

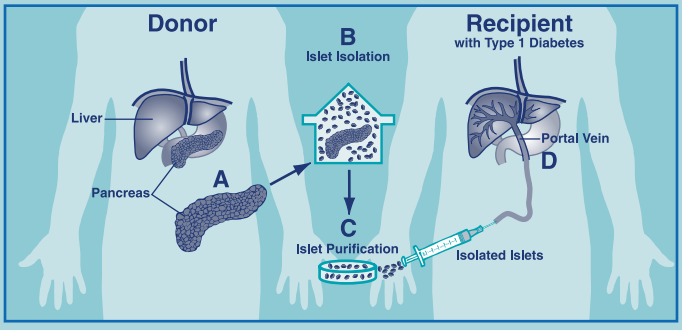
While the experiences of islet transplant recipients can vary, Karla's reactions have been very positive. Karla adds: "I remember days, before the procedure, when I felt like I was 120 years old. Now I feel like I'm back in my 20s again. It's wonderful," she says joyfully, and then pauses. "No, it's a miracle!"

Future Research: The Quest To Make Islet Transplantation a Viable Treatment Strategy for Patients with Type 1 Diabetes

The demonstrated success of the Edmonton Protocol has engendered new hope for people with type 1 diabetes. It has also benefited patients, such as Karla. However, islet transplantation using the new protocol is still very much in its infancy. For example, people who undergo a transplant may not be able to tolerate the immediate side effects of the immunosuppressive drugs, and the potential long-term side effects are not fully known.

The Collaborative Islet Transplant Registry analyzed outcomes in 138 patients at 19 medical centers in the United States and Canada. Data analysis showed that 58 percent of recipients no longer had to inject insulin 1 year after their last islet infusion; in 19 recipients, the donor islets failed to function. These data show that not every recipient becomes insulin-independent after undergoing this procedure. In addition, because islet transplants are experimental, they are available only to people who meet specifically defined criteria stated in the study protocol. To date, only adults with severely unmanageable blood sugar levels or who have already undergone a kidney transplant have been eligible.

Further research is needed to overcome the current barriers in the field of islet transplantation. To propel research progress, the NIH is supporting multifaceted research efforts, primarily with support from the *Special Statutory Funding Program for Type 1 Diabetes Research*. Major goals are to increase the number of islets available for transplantation and to reduce or eliminate the need for immunosuppressive drugs after transplant. For example, the NIH launched a major new Clinical Islet Transplantation Consortium, which is conducting multiple islet transplantation trials to improve methods of



Islet transplantation is an experimental procedure in which islets are isolated (B) and purified (C) from a donor pancreas (A) before infusion into the portal vein of the recipient's liver (D). If the transplant is successful, the new islets begin producing insulin in a regulated manner, thereby eliminating or reducing the patient's need for insulin administration.

isolating islets, improving techniques for administering the transplanted islets, and developing approaches to minimize the toxic effects of immunosuppressive drugs. The Islet Cell Resource Centers are a key resource for providing islets to the broad scientific community for use in both clinical islet transplantation and basic research studies. The Non-human Primate Transplantation Tolerance Cooperative Study Group is evaluating novel methods to induce immune tolerance to transplanted islets in non-human primates to achieve long-term graft survival. This tolerance induction approach would avoid the need for lifelong immunosuppressive therapies. To tackle the shortage of islets, researchers in the Beta Cell Biology Consortium (BCBC) are collaboratively working to understand beta cell development and function, in order to identify ways to grow unlimited numbers of beta cells in the laboratory that can be used to treat patients. Research is also under way in xenotransplantation, which studies the possible use of non-human organs (such as from pigs) for transplantation into humans.

In addition to research on islet transplantation, the NIH also supports research on other methods to replace the insulin-producing beta cells that are destroyed in type 1 diabetes. Recent studies have shown that people with long-standing type 1 diabetes have some remaining functional beta cells. Therefore, research on the mechanisms controlling beta cell growth and regeneration, such as those being pursued through the BCBC, could lead to novel therapies designed to stimulate beta cell growth in the body.

Through islet transplantation, Karla Edge has re-experienced life without the need for daily insulin administration. It is only through additional research efforts that Karla's life-changing, positive experience may become a reality for many more patients with type 1 diabetes who could potentially benefit from islet transplantation.