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The Search for a Cure for Diabetes Takes a Controversial Turn

By: Jerome Groopman

One day in 1972, when Dana Shields was fourteen, she became so thirsty that she found herself gulping water from a faucet, unable to get enough. Soon afterward, she started to lose weight; within weeks, she had dropped about twenty pounds. At the time, Dana was competing for a place on her high school’s field-hockey team, and she attributed these symptoms to a rigorous training schedule. She cut back on exercise, but she could not gain weight. One afternoon a few weeks later, she ate a brownie, drank some Pepsi and some chocolate milk, and started to vomit. Her parents took her to the emergency room. Test results showed that Dana’s blood sugar, or glucose, was at more than six times the normal level. She had developed diabetes.

Dana (this is not her real name) had Type 1, or juvenile, diabetes, an autoimmune disease that occurs, in most cases during childhood, when T cells attack and destroy the islet cells in the pancreas, which produce insulin. (Type 1 diabetes is entirely different from Type 2 diabetes, in which the body continues to produce insulin but no longer responds to it; that disease, which generally develops in adulthood, can often be controlled by regulating glucose levels through diet.) Without the ability to produce insulin, a person cannot properly metabolize glucose, and toxic acids accumulate in the blood. Over time, serious complications may arise, among them blindness, kidney failure, extensive nerve damage, and accelerated atherosclerosis, which can lead to a heart attack or a stroke. There is a genetic predisposition for Type 1 diabetes, and thirty thousand new cases are diagnosed in the United States each year. There is no known cure.

Dana chafed at the onerous regimen she was put on: she had to test her blood sugar every few hours, and give herself multiple insulin injections to keep her glucose levels within a normal range. When she left for college, she became careless about her health. Her blood glucose often rose out of control, and she spent many weekends in the infirmary being treated for dehydration, which accompanies high blood-sugar levels. Four years after graduating, Dana, a slim woman with blond hair and blue eyes, married. At twenty-seven, she decided to have a baby, and consulted an obstetrician who specialized in high-risk cases. Shortly after the child was born, she developed retinal damage, and had to undergo a series of laser treatments to prevent blindness. “I finally grew up and realized that I needed to deal with my illness,” she told me not long ago.
Dana began to check her blood-sugar level every few hours, adjusting it with a shot of insulin. But, even with such vigilant attention, a diabetic cannot manually match the second-by-second release of insulin from the islets of the healthy pancreas, which keeps the body’s glucose level within a normal range, and Dana’s condition continued to worsen. The nerves that control the stomach and the intestine began to malfunction, so that she could not digest an ordinary meal. When she became pregnant a second time, her kidney function deteriorated. She delivered a healthy child, but her doctors concluded that she would eventually require dialysis and a kidney transplant. Seven years later, she underwent a transplant, which improved her health, but she was obliged to take strong -- and potentially dangerous -- immunosuppressive medications to ward off rejection of the new organ.

Dana, who now runs a family business in upstate New York, told me that she felt imprisoned. “Not a moment of the day went by when I didn’t think about my disease, how each activity -- whether it was eating or jogging or sitting through a long movie -- could affect my blood sugar and the amount of insulin I needed to inject,” she said. She expected more complications in the future, and she knew that there was little she could do to prevent them. She had heard reports of “breakthroughs” in diabetes research, but nothing seemed to have come of them.

Dana had not heard about extensive research into Type 1 diabetes that Canadian scientists were conducting at the University of Alberta, in Edmonton. Canada has a long tradition of diabetes research, and two Canadians, Frederick Banting and Charles Best, are credited with the discovery of insulin. At the turn of the last century, doctors knew that the pancreas played a role in regulating blood sugar but did not know how. Shortly after the First World War, Banting, a young doctor in Ontario, decided to explore the origins of diabetes. He found some laboratory space at the University of Toronto, received approval to experiment on dogs, and hired a student assistant, Charles Best. After just a few months of work, Banting and Best identified insulin, a protein that was made in the islet cells of the pancreas and had a crucial connection to the malady. Further research into Type 1 diabetics indicated that these patients’ islet cells were damaged beyond repair and could not produce insulin. Banting and Best concluded that insulin injections were the best way of controlling the swings in glucose levels. For the first time, diabetics were not totally at the mercy of their disease. Later research, however, showed that regular insulin shots did not prevent Type 1 patients from suffering the debilitating side effects. Some scientists concluded that Type 1 diabetes could ultimately be remedied only by the restoration of the islet cells themselves.

In 1972, Paul Lacey, a researcher at Washington University, in St. Louis, Missouri, cured diabetic rats by transplanting the islet cells from a healthy rat. Ray Rajotte, a bioengineer at the University of Alberta, attended the meeting at which Lacey presented his remarkable results. “We all sat and applauded,” Rajotte said. “We thought the cure had arrived.” Rajotte set up a program in Edmonton to develop Lacey’s work with humans. Other scientists followed suit in the United States and in Europe. Instead of grafting the donor islets into the pancreas of the diabetic rat, Lacey infused the cells into the vein that supplies the liver, bypassing the pancreas altogether. Ideally, the infused cells would form small nests in the liver and function like the
cells of a healthy pancreas, sensing from moment to moment the body’s glucose level and producing precisely the appropriate amount of insulin.

Over the next twenty years, researchers made more than four hundred attempts to apply the procedure to humans. The transplanted islet cells survived in only a handful of cases; most stopped producing insulin after a few days. No one was sure what accounted for the difference between rats and people. Some scientists speculated that in humans the attacking T cells, which caused the disease, turned against the transplanted islets, despite the use of immunosuppressive drugs. Others wondered whether the fragile cells from the donated pancreas were damaged during the transplant. By the early nineteen-nineties, scientists had largely concluded that islet-cell transplantation was futile. Many argued that it was unethical to continue to subject diabetics to a possibly harmful procedure that involved the administration of dangerous drugs. In 1996, the National Institutes of Health, the primary financial supporter of biomedical research, devoted less than three per cent of its diabetes budget to research on islet-cell transplantation.

At the same time, there was a surge in basic research into how insulin alters cell molecules. In 1990, the Juvenile Diabetes Research Foundation, a private philanthropy, began a fund-raising campaign called “The Only Remedy Is a Cure,” and its board gave millions of dollars to basic-science researchers. Yet by 1995 no significant clinical progress had been made, and key members of the foundation -- mainly parents of children with Type 1 -- were bitter and frustrated. One of the most outspoken was Emily Spitzer, a lawyer who had served on the board of directors and as a lay reviewer of research. Her seven-year-old daughter, who had had diabetes since infancy, said to her, “Mommy, you spend all this time at the foundation, and nothing has changed for me.”

In 1996, Spitzer organized a meeting of J.D.R.F. scientists to discuss research priorities. When she asked them what the foundation should be doing differently “to cure our kids,” she was met with blank faces. Then one prominent researcher spoke up: “Emily, the system is working fine. Why do you want to change it?”

Spitzer reported to the board of the J.D.R.F. that, despite the enormous sums it was spending on research, scant progress in treatment had been made. Still, no one was willing to give up. “The board had a lot of businessmen who were used to operating in a business mode,” Dr. Robert Goldstein, the foundation’s chief scientific officer, told me. In 1997, the foundation decided to pursue the cure of juvenile diabetes as if it were a business project, incorporating strict accountability and specific milestones. The board engaged McKinsey & Company, on a pro-bono basis, to assist in mapping potential paths to a cure.

Sandra Puczynski, a J.D.R.F. volunteer and a laboratory scientist whose young daughter had diabetes, was appointed to head the project. She interviewed more than a hundred researchers at universities, pharmaceutical companies, and government facilities. Each was asked to suggest ways to prevent juvenile diabetes from occurring, to maintain normal levels of blood sugar in those who had already developed the disease, and to remedy the serious complications.

One of the people she talked to was Dr. Gordon Weir, a researcher at the Joslin Diabetes Center, in Boston. Weir and his wife, Susan Bonner-Weir, had recently published an article in
which they argued that further work on the transplantation of islet cells had been wrongly neglected. “Islet transplantation,” the Weirs wrote, “may be the most emotionally charged area in diabetes research because its availability would provide the equivalent of a cure, bringing not only freedom from the burdens of injections, glucose testing, and dietary restrictions, but even more importantly, protection from the dreaded complications of diabetes.” The foundation decided to focus on islet transplantation. Many scientists were skeptical about the new initiative. “In 1997, I gave a talk at the N.I.H. outlining the decisions the J.D.R.F. had made,” Emily Spitzer told me. “A scientist from a prestigious university came up to me afterward and started yelling at me, saying that we didn’t know what we were doing, that we were bound to fail, that you can’t dictate the course of scientific discovery.”

But the foundation’s directors were prepared to invest hundreds of millions of dollars in islet transplantation, and they named four priorities: to refine the techniques of the transplant; to stop the autoimmune attack on the islet cells; to foster tolerance of the foreign cells in the recipient; and to cultivate a ready source of islets for the procedure. The J.D.R.F. established a number of research centers at prominent medical schools in the United States, including Harvard, the University of Washington in Seattle, and the University of California at San Francisco. Once again, however, a breakthrough occurred in Canada, at the University of Alberta.

Rajotte’s research team was on the verge of shutting down when the university decided to turn to Dr. James Shapiro, a transplant surgeon in Edmonton, to revitalize the program. Shapiro had experimented with islet transplantation in small animals when he was a medical student in Newcastle, England, more than a decade earlier. At six feet two, with dark hair and glasses, Shapiro is an imposing figure, and he speaks in clipped sentences that suggest the speed at which his mind works. “Every experiment I did as a student was a failure,” he said to me recently. “Moreover, I was told by my colleagues, ‘The islet program is dead, collapsed. You’re thirty-six, and this will be the end of your career. You’re crazy to consider the university’s offer!’” But, spurred by the challenge of finding a cure for a devastating disease, Shapiro accepted the offer.

In September, 1998, Shapiro and Jonathan Lakey, another young scientist in Edmonton, flew to Giessen, Germany, where the international registry of islet transplantation is kept. “We stared and stared in detail at the records of each of the four hundred and fifty failures in diabetes,” Shapiro recalled. These results contrasted sharply with a seventy-per-cent success rate of islet transplantation among patients who suffered from chronic inflammation of the pancreas but did not have Type 1 diabetes. In these cases, the procedure involved removing the patient’s pancreas, obtaining a large number of islets from it in the laboratory, and then infusing the cells back into the patient. No immunosuppressive medications were necessary, since the patient was receiving his own cells. Shapiro and Lakey surmised that the immunosuppressive drugs given to diabetics, particularly corticosteroids, were lethal to the transplanted islets.

They explored the idea of using a combination of newer immunosuppressive medications, such as tacrolimus and sirolimus, but found that many were considered incompatible. “It was an absolute no-no in the field to pair drugs like tacrolimus and sirolimus,” Shapiro told me. One day, however, he came across reports from researchers in Halifax, Nova Scotia, who had
concluded that, at least in mice, these new drugs could be mixed. Still, Shapiro knew that many experiments that had succeeded with mice failed with people.

“My intuition, when I stood at the bedside of patients, was that no animal model was going to predict what might work for humans,” he told me. “I knew that we had one shot in Edmonton to make islet transplantation work. There was no time to change one variable and then another variable and then another and come up with the answer.”

Lakey took charge of the effort to obtain large numbers of healthy islets to transplant. A former student of Rajotte’s, Lakey had been working on islet-cell extraction since his undergraduate days, in the mid-eighties. He believed that the transplants were failing because the patients had not received a sufficient number of high-quality islet cells. In partnership with the medical-technology company Roche Diagnostics, and researchers at the University of Miami, Lakey developed a mixture of enzymes which broke down the tissue of the pancreas efficiently, freeing the embedded islets without injuring them. The marketing department at Roche called this enzyme mixture Liberase.

In Edmonton, Lakey and Shapiro used the enzyme mixture to extract large numbers of intact islets. And they decided to administer the new, allegedly incompatible cocktail of drugs that had been endorsed by the researchers in Halifax.

Before they could proceed, members of the hospital’s ethics committee had to approve the project. “Yes, there had been four hundred and fifty prior failures of islet transplantation, and this gave everyone pause,” Shapiro told me. He pointed out to the committee that some people with Type 1 diabetes experience severe drops in their blood sugar. A complication called hypoglycemia unawareness, which prevents them from sensing the usual warning signs of a dangerous fall in blood sugar -- sweating, dizziness, nausea, palpitations -- can make these drops deadly. Shapiro argued that for such diabetics the danger of falling into a coma was greater than any risks inherent in the new treatment. Persuaded by this argument, the committee permitted the trial to proceed.

On March 11, 1999, Bryon Best, a fifty-four-year-old teacher from Yellowknife, in Canada’s Northwest Territories, was the first person to receive an islet transplant that employed the drugs and the novel techniques devised by Lakey and Shapiro. Within a week of his second transplant, Best, who had suffered a lifetime of wildly fluctuating blood-sugar levels, required no further insulin shots, and he was able to maintain a steady glucose count. Over the next year, six more patients underwent what became known as the Edmonton protocol. The transplants worked for all of them.

Shortly before Thanksgiving of 2001, Dana Shields enrolled in an experimental trial at the J.D.R.F. Center at Harvard, which used the Edmonton protocol. For this study, the pool of patients had been expanded to include diabetics who were not experiencing life-threatening episodes of hypoglycemia. In Edmonton, Lakey and Shapiro had carried out more than two dozen transplants, with enduring success for all but four patients, who had had to begin insulin injections again, two years later. It seemed likely that in these four patients the transplanted islets
were suffering a slow attrition. The researchers were still looking for the right balance of drugs that would enable doctors to implant foreign islet cells without putting the patient at unnecessary risk of infection. To be considered for the Harvard experiment, the patient had to have received a kidney transplant and be taking immunosuppressive drugs. Dana, who qualified on both counts, signed an informed-consent document, which warned her that the treatment did not guarantee improvement and put the patient at risk of side effects, including hemorrhage, thrombosis, and infection.

The center’s director, Dr. Hugh Auchincloss, weaned Dana from her conventional immunosuppressive drugs and put her on the Edmonton cocktail. And then, along with six other study subjects, she waited. The next step required the donation of a healthy pancreas from a person whose cause of death permitted the extraction of islet cells.

In May of 2002, Dana had the first of two islet-cell transplants, at Massachusetts General Hospital; the procedure went well, and two months later she received a call telling her that it was time for the second transplant. She was taken to a radiology suite, where a technician arrived with a small plastic bag that held the purified islet preparation -- a grainy suspension with a yellowish tint that came from a donor whose blood type matched Dana’s. The small plastic packet was connected to a catheter that led into the portal vein. As nurses monitored Dana’s vital signs and glucose levels, the islet cells percolated through the catheter and into her bloodstream.

The entire procedure took less than thirty minutes. When it was over, Dana experienced some lingering nausea from the anesthetic and had to lie still on her right side for four hours. “Otherwise,” she recalled, “I felt great.” She had had her last insulin dose at eleven o’clock the night before. Four weeks later, Dana told me that she had not needed a single insulin injection since the completion of the transplant.

Three and a half years after Bryon Best had the first successful human islet-cell transplant, in Edmonton, more than a hundred and fifty patients have gone through the experimental protocol. The trials are funded by both the J.D.R.F. and the N.I.H. During the Clinton Administration, Congress significantly increased financial support for research into Type 1 diabetes, thanks, in part, to Erskine Bowles, the White House chief of staff, and Newt Gingrich, the former Speaker of the House of Representatives, both of whom have relatives with diabetes. But the procedure is still unavailable to most diabetes patients. There are only about six thousand organ donors a year in the United States, and, of these, only about twenty-five hundred provide what are called “good” pancreases. Two or more pancreases are generally required to obtain enough islets for each recipient. Given the fact that a million Americans suffer from Type 1 diabetes, each year only one or two patients in every thousand could have the procedure.

The short-term solution to the problem is to increase the efficiency of the islet-extraction process. With the sponsorship of the J.D.R.F., Shapiro, Lakey, and their co-workers are trying to maximize the yield of islets from a single donated pancreas. But, even with an increase in yield, the great majority of Type 1 diabetics will remain untreated.
In the longer term, scientists are increasingly looking to mass-produce islets from stem cells, in the laboratory. This can be done either by identifying the adult stem cells that make islets or by training primitive embryonic stem cells to become islets.

One of the leaders in embryonic stem-cell research is Douglas Melton, a professor in the Department of Molecular and Cellular Biology at Harvard and a member of its J.D.R.F. Center. Ten years ago, Melton was studying how frogs develop. Then his six-month-old son, Sam, was diagnosed with Type 1 diabetes. Melton began to focus on how the different cells in the pancreas develop from primitive embryonic stem cells. Because stem cells have an apparently unlimited potential to grow and differentiate, they could provide a robust supply of islet cells. Furthermore, because stem cells are “all-purpose” cells, from which all tissues of the body develop, scientists could conceivably genetically alter them to make them impervious to autoimmune attack. Islet-cell transplants could one day be performed without patients having to wait for altruistic families to donate organs, and recipients would not have to take risky immunosuppressive drugs.

In 1994, during the Clinton Administration, the N.I.H.’s Human Embryo Research Panel, which included scientists and ethicists, concluded that stem-cell research involving human embryos, such as those created during in-vitro fertilization, should be made available for research supported by federal funds. Five years later, as the Administration, in the face of opposition from pro-life activists, was reconsidering this recommendation, Melton testified before a Senate appropriations subcommittee.

Melton, a soft-spoken man with thick black hair, now graying, and large rimless glasses, presented himself not as a renowned scientist but as the father of a child with diabetes. “Before discussing the exciting potential of stem-cell research, allow me to speak briefly as a parent,” he said to the subcommittee. “My wife is regularly up in the late hours of the night doing blood checks while Sam sleeps. We wonder, Is his blood sugar too low? Will he find the middle ground between a ‘low,’ or coma, and being too ‘high’ in the morning? I can’t recall a night since Sam was diagnosed when we slept peacefully, free of the worry that the balance between his food, insulin, and exercise was not good enough. I am unwilling to accept the enormity of his medical and psychological burden, and I am personally devoted to bringing it to an end for Sam and all Type 1 diabetics. I implore you to continue to make it possible to cure diabetes, for diabetics and their families.”

A “compromise” announced by President Bush in August, 2001 -- which allows the government to fund work with stem-cell lines that were created before the decision but blocks funding for work on cell lines obtained subsequently -- has made it difficult for such research to flourish. The number and the quality of human stem cells available for government-funded research became sharply limited. In frustration, Melton, with money from the J.D.R.F. and the Howard Hughes Medical Institute, established an independent laboratory for stem-cell research; his work can now continue unhindered by federal restrictions.

I visited Melton’s laboratory not long after Dana Shields’s transplant. In the human-stem-cell facility, four incubators held primitive embryonic stem cells in petri dishes. (The donors had specifically designated the fertilized eggs for diabetes research.) Melton put one of
the petri dishes under a special microscope. At the bottom of the petri dish was a flat bed of cells, the "feeder layer," which supports the embryonic stem cells. The stem cells were growing in a tightly clustered ball that looked like an expanding nebula. I asked how long it might take for scientists to devise a way to turn stem cells into islet cells that can sense glucose levels and produce insulin. “I don’t think it will happen before two or three years,” Melton said. “But it is something to be pursued non-stop. Embryonic stem cells have the greatest potential of any cell type to regenerate tissues.”

Meanwhile, researchers are looking for other solutions to the shortage of donated pancreases. “No one knows what will solve the islet-supply problem,” Hugh Auchincloss, of Harvard, told me. His own research involves a strategy that he calls “xenotransplantation,” in which islets from animals such as pigs would be used for human transplants. But increasing the supply of islet cells is only half the solution. The larger aim is to transplant cells that will be “tolerated” in their new home, so that patients can end their dependency on immunosuppressive drugs.

In 1998, the National Institute of Allergy and Infectious Diseases, under Dr. Anthony Fauci, established the Immune Tolerance Network, an organization of researchers who conduct innovative studies that could lead to clinical experiments in which the human immune system is “educated” to accept foreign transplants. (Some of the costs are paid by the J.D.R.F.) Scientists hope that training the immune system may help not only patients with Type 1 diabetes but also those afflicted with other disorders related to immune-system dysfunction, such as multiple sclerosis and asthma. Last May, Jeffrey Bluestone, the director of the I.T.N. and the head of the University of California at San Francisco Diabetes Center, announced that treating recently diagnosed diabetics with an antibody against T cells not only tempered the autoimmune attack but preserved insulin production in the remaining unharmed islets, for up to a year.

Four months after Dana Shields received the transplant of islet cells, we met in my office. “Now that I no longer take insulin,” she said, “I have so much extra energy I told my husband that they need to put me on Valium. It’s as if I had been carrying around weights that were suddenly removed. I feel free for the first time in thirty years.”