Juvenile Diabetes –
Examining the Personal Toll on Families,
Financial Costs to the Federal Health Care System,
and Research Progress Towards a Cure

Testimony
on

Research Opportunities in Pancreatic Islet Transplantation and Thoughts on "The Pancreatic Islet Cell Transplantation Act of 2003" (S.518)

Presented by

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COMMITTEE ON
GOVERNMENTAL AFFAIRS

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Chairman Collins and members of the Committee on Governmental Affairs,

My name is Bernhard J. Hering. I am the Director of Islet Transplantation and holder of the Eunice L. Dwan Chair in Diabetes Research at the University of Minnesota, and Co-Director of the Juvenile Diabetes Research Foundation (JDRF) Center for Islet Transplantation at the University of Minnesota and the University of California at San Francisco. I currently serve as Co-Director of the NIH Immune Tolerance Network Islet Transplant Subgroup, as Medical Director of the NIH Collaborative Islet Transplant Registry, and as President of the Cell Transplant Society.

I am addressing you today on behalf of my physician-scientist colleagues. Our ability to transform the landscape of juvenile diabetes in the US in the next decade depends heavily on the federal government's efforts. Chairman Collins, I want to applaud your efforts and those of the more than thirty Senators who have Co-sponsored your legislation entitled "The Pancreatic Islet Cell Transplantation Act of 2003 (S.518)". I believe that, if passed, this bill will empower clinical researchers to expedite the translation of islet transplant research into unsurpassed, innovative treatments for individuals with juvenile diabetes and accelerate the integration of such treatments into health care delivery systems.

Although the research community has experimented with islet cell transplants for decades, they are now, at last, becoming a practical, successful, superior, and distinct therapy for patients with juvenile diabetes. This disease continues to be challenging;

with significant morbidity and major socioeconomic impact. Diabetes is a devastating burden to patients and their families, especially when acute complications are frequent and chronic complications are advanced. In the previous panel, you heard about the daily challenges people face in living with juvenile diabetes from the most effective messengers – children who suffer each and every day with this disease.

I would like to provide you with a better understanding of the science behind juvenile diabetes. Islets are clusters of insulin-producing cells located in the pancreas (Fig. 1). They make up only 1% to 2% of the total pancreas. In someone with juvenile diabetes, all insulin-producing cells are destroyed. The cells are attacked by the person's own immune system. In some patients, despite multiple daily insulin injections, frequent needle sticks for blood sugar self-measurements, and many lifestyle restrictions, blood sugar levels become erratic. The levels change rapidly from extremely high to dangerously low. This lack in control leads to acute complications, such as seizures and coma, and to chronic complications such as blindness, kidney failure, heart attack, and stroke.

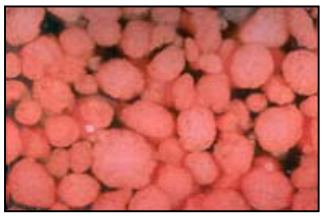
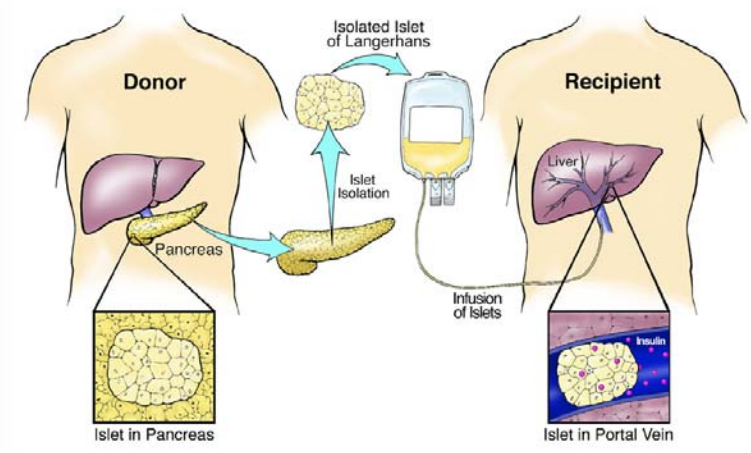


Figure 1. Human islets isolated from a donor pancreas

Please allow me to illustrate how islet transplants are unsurpassed in their potential to transform the lives of people with difficult-to-control juvenile diabetes. Lorna (who gave permission to share some of her story) is a 35-year old mother of 2 boys who developed diabetes at age 9. She completely lost her ability to sense low blood sugar levels (also referred to as hypoglycemia). Brain function is severely compromised by hypoglycemia,

leading to confusion, distorted perception of surroundings, dizziness, odd behavior, seizure, coma, and possibly death. Lorna became incapacitated by weekly episodes of severe, life-threatening hypoglycemia, requiring the help of a third person and often paramedics. As a result, Lorna lost her driver's license, was laid off at work, was divorced, and was denied the right to see her boys.

In August of 2000, Lorna was admitted to the General Clinical Research Center at the University of Minnesota for an islet transplant under a protocol supported by the Juvenile Diabetes Research Foundation. She was taken to a radiology suite, where a local anesthetic was given and a catheter was placed (under ultrasound guidance) through her skin into the portal vein of her liver. Islets isolated from a cadaver donor pancreas were resuspended in buffer, transferred to a transfusion bag, and infused over 20 min through the catheter into her portal vein (Fig. 2). Infused islets were then carried by her blood to smaller branches of the portal vein, where they lodged, engrafted, and resumed tightly controlled secretion of insulin in response to her blood sugar levels. The catheter was then removed and she was discharged to home 2 days later.



Lorna's blood sugar levels returned to normal (Fig 3). She was able to completely discontinue insulin injections 1 month after her islet transplant. Since her islet transplant, she has not experienced a single episode of severe hypoglycemia. She learned to love life again, rediscovered her ability to make contributions to the world, regained control over her destiny, received her driver's license back, found a new job, married a paramedic who had repeatedly saved her life while she was diabetic, closed on a new home, and was granted authorization to take care of her boys again - all in the first year after her transplant. Now, almost 3 years after her islet transplant, Lorna continues to be insulin-independent. She still takes immunosuppressive medications to prevent rejection of her transplanted islets. But she has not experienced any severe adverse events. You will hear another remarkable success story from Anne Seidel following my testimony.

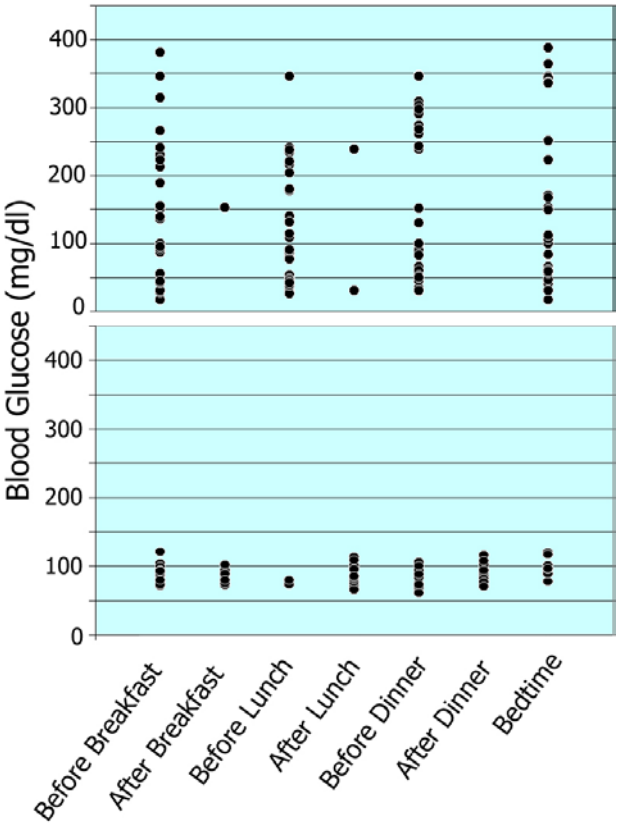


Figure 3. Blood glucose control during the month before islet transplantation (upper panel) and after islet transplantation and discontinuation of insulin injections (lower panel). Normal range is 70-120.

For patients like Lorna, insulin is survival, and an islet transplant is return to life. We have since performed islet transplants in 17 additional recipients at my Center. Diabetes was completely reversed for all but 2 of them and major complications were not encountered. Islet transplants should be considered for treating diabetes in selected patients. Islet transplants are now a clinical reality, not just a topic for experimental research.

Let us now assume for one moment that someone has a 35-year-old daughter who suffers from juvenile diabetes complicated by recurrent episodes of severe hypoglycemia, that she meets all accepted medical criteria for an islet transplant, that she has a good health insurance plan, and that she wants to proceed with an islet transplant. Will she be able to undergo an islet transplant?

Most likely no. There is a severe shortage of pancreata for islet transplants; funding in this area has not kept pace with the science; and regulations must be changed to provide incentives for additional procurement of pancreata for islet transplantation and research. And insurance coverage of islet transplantation is currently not available, thereby largely restricting them to patients meeting the very stringent eligibility criteria of research protocols.

Currently, I estimate that NIH grants will cover a mere 20 to 40 islet transplants in the US over the next 12 months. And even then, coverage would be sadly incomplete, leaving the patient and the clinical investigator with the burden of substantial uncovered

expenses, such as the costs for immunosuppressive medications required beyond the study period, the costs for donor pancreas acquisition and transportation, and the costs for additional personnel in order to be in compliance with increasingly complex regulations that have turned what should be patient-oriented research into a morass of hard-to-follow, often unnecessary rules (1).

This disconnect between the promise of basic science versus the delivery of better health in the US is of significant concern. Islet transplants for the treatment of diabetes are being covered by several provinces in Canada, where a landmark pilot clinical trial called the Edmonton Protocol was performed in 2000 (2). The steadfast commitment to basic biomedical research in the US has provided the basis for today's high success rate in reversing diabetes in human patients; it has also provided an unprecedented supply of information for further breakthroughs in clinical islet transplants. Yet, islet transplants remain largely unavailable 3 years after the demonstration of proof-of-principle. Failure to use available science is costly and harmful (3); it leads to overuse of inferior care. In contrast to Canada, we fail to deliver the best care we could for patients with difficult-to-control juvenile diabetes.

Both my learned opinion and my best bet are that one third of the gifted children with juvenile diabetes in this room will develop devastating, destructive, or deadly diabetes complications before they are 50 years old (4) -unless we enhance our preclinical and clinical research agenda markedly in the next 2 years (in order to realize a sizeable effect within 10 years). The potential short- to mid-term impact of islet transplants on

patients with juvenile diabetes prone to develop devastating complications is unmatched by any other treatment modality. "The Pancreatic Islet Cell Transplantation Act of 2003" would remove major translational blocks in the implementation of islet transplants. This bill, if passed, would lead to substantial improvements in the clinical research infrastructure and send a strong signal to all major stakeholders in health care delivery.

I want to take this opportunity to offer my highest compliments to you, Senator Collins, for authoring this bill. It addresses areas of major importance in the transition of islet transplants from clinical research to clinical care. I will make 3 suggestions.

First, it will be important to invite the active participation of all major stakeholders in islet transplant research. Addressing all concerns and legitimate requests of participating patients must be encouraged in the most proactive fashion. I also encourage inviting, via appropriate incentives, the active participation of diabetes care centers in recipient recruitment and posttransplant care. Their active participation could lead to the perception of collaborating diabetologists as transplant diabetologists. We also need to create incentives for involving other major stakeholders, such as academic health centers, the pharmaceutical and biotech industry, and health care payers. We need to overcome the fragmentation and underfunding of today's clinical islet transplant research infrastructure. We need to coordinate our research agenda around those institutions that are committed and best suited to contribute. We need to address the educational needs of payers: they stand to gain substantially from progress in the field and could prove instrumental in reducing the second translational block from clinical

studies into medical practice. We should give consideration to the foundation of a Translational Islet Transplant Network (TITN) to prioritize, coordinate, and conduct research efforts in preclinical and clinical islet transplants.

Second, the proposed 5-year demonstration project in islet transplant recipients with end-stage kidney failure will undoubtedly provide further insights into the risks and benefits of islet transplants in this subgroup of patients. It is important to emphasize that outcomes in this recipient group with advanced diabetes complications are likely to be fundamentally different from outcomes in preemptive islet transplants performed for the purpose of preventing irreversible complications. In particular, health care decision making for the latter group must therefore not await the final analysis of the 5-year demonstration project in islet recipients with end-stage kidney failure.

Finally, I urge the Committee to review the adequacy of Federal research funding for translational research of emerging concepts and strategies in the preclinical nonhuman primate islet transplant model. Removing this translational block will position established clinical research networks (e.g., Immune Tolerance Network) to capitalize much faster on the extraordinary opportunities that are increasingly presented by ongoing basic research investment. Documenting safety and efficacy of emerging concepts in preclinical nonhuman primate models is considered a prerequisite before embarking on clinical trials. Increased resource allocation should be considered for evaluating approaches that facilitate minimization of recipient immunosuppression (including innovative islet pretreatment strategies) and for developing strategies aimed at

increasing the supply of islet tissue suitable for transplant (including pig islet xenografts and living donor islet allografts).

In closing, I believe your bill will greatly enhance the islet transplant translational infrastructure and help it to operate much more efficiently. It will raise awareness; create additional momentum; and facilitate the expedient delivery of today's science and technology for the benefit of thousands of patients afflicted with juvenile diabetes. The bill will also help prepare the field to respond nimbly to the extraordinary advances that surely will emerge from stem cell biology and other high-impact, cell-based technologies of the future. Thus, this legislation will have implications well beyond its primary objectives.

As I look around the room at all of these children who are here today to take an active role in finding a cure for juvenile diabetes, I know that the scientific community and Congress must match their passion and dedication. This will not be an easy task, but progress in science has been amazing and emerging opportunities are extraordinary. Removing translational blocks (5) will allow us to reach our shared goal of a cure.

Thank you from the bottom of my pancreas (6).

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