Islet Transplantation in Type 1 Diabetes

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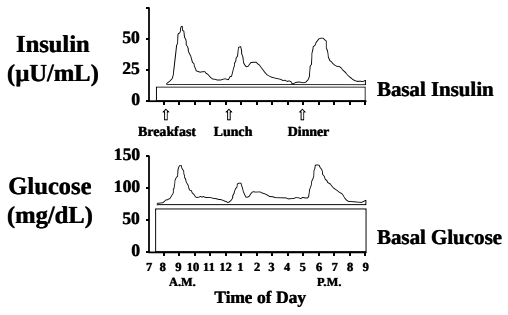
Limitations of insulin for the treatment of type 1 diabetes

- Does not mimic physiologic insulin secretion
  - Variable absorption
  - Pronounced peaks
  - Less than 24-hour duration of action
- Can cause unpredictable hypoglycemia
  - Major factor limiting the achievement of euglycemia
  - Life-threatening consequence of insulin therapy

Objectives

- Describe the rationale for pancreatic islet transplantation
- Discuss the goals of islet transplantation
- Summarize the clinical outcomes in islet transplant recipients
- Review the patient selection for islet transplantation

Physiologic insulin secretion 24-hour profile



Bergenstal RM et al. In: DeGroot LJ, Jameson JL, eds. *Endocrinology.* 4th ed. Philadelphia, Pa: WB Saunders Co.; 2001:821

Diabetes Control and Complications Trial (DCCT)

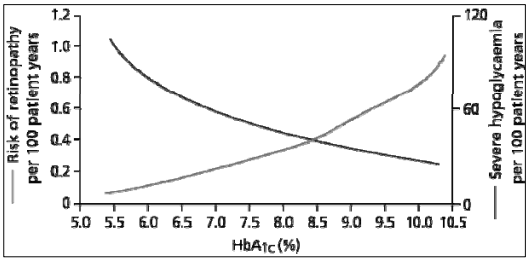
- Microvascular – risk reduction
  - Retinopathy – 63% p<0.002
  - Nephropathy – 54% p<0.04
  - Neuropathy – 60% p<0.002
- <5% of persons were able to achieve an A1C <6.1%
- Intensive insulin therapy group had 3-fold increased risk of hypoglycemia

DCCT Research Group. New Engl J Med 1993;328:977.

Alternatives to exogenous insulin therapy

- The goal of treatment for type 1 diabetes is to provide physiologic insulin delivery
- Pancreas transplantation is invasive with significant risk of complications including death
- Transplantation of pancreatic islets can provide physiologic insulin replacement in a less invasive procedure

The balance between prevention of complications and development of hypoglycemia: DCCT



DCCT Research Group. New Engl J Med 1993;328:977.

Goals of islet transplantation

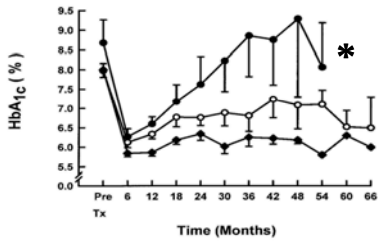
- Insulin-independence *
- Sustained insulin secretion (positive C-peptide)
- Halt progression of diabetes complications
- Improvement in quality of life
  - Amelioration of severe hypoglycemia
  - Improvement in glycemic lability
- In renal transplant recipients, to protect the transplanted kidney from hyperglycemia

Edmonton protocol for islet transplantation

- First to achieve 100% insulin independence rates at one year
- Novel immunosuppression
  - Steroid-free
  - Reduced calcineurin inhibitor use
- Better isolation techniques
- Large number of islets: avg 11,547 IEQ/kg usually requiring 2-3 islet infusions

Shapiro JAM, NEJM 2000, 343:230-238

C-peptide and diabetes control after islet transplantation



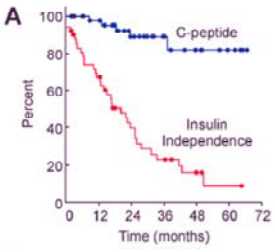
- ● Failed
- ○ Partial graft function
- ♦ Full graft function

* p = 0.025

Ryan EA, et al., Diabetes 2005; 54: 2060-2069

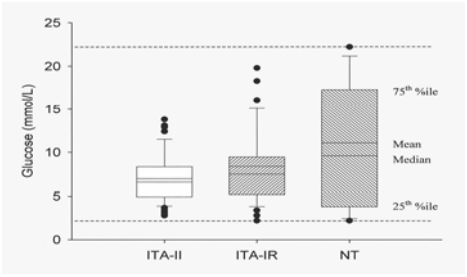
Islet transplant graft survival – 5 year follow-up

- At 5 years only ~10% remained insulin independent
- 80% have detectable C-peptide



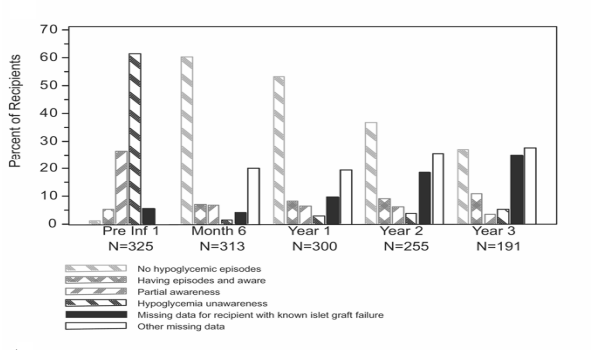
Ryan, et al. Diabetes 2005 54:2060-2069

Glycemic lability in C-peptide positive patients – CGMS®



Paty BW, et al., Diabetes Tech and Therapeutics 2006; 8:165-173

Hypoglycemia after islet transplant



CITR Update: Transplantation 2008 86: 1783–1788

Diabetes complications data after islet transplantation

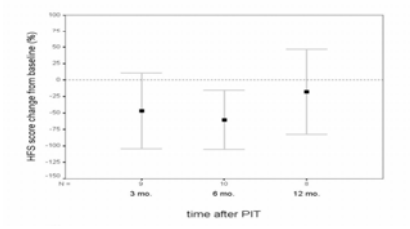
Comparison of patients with type 1 diabetes receiving islet transplantation with those on intensive insulin therapy resulted in:

- Improved glycemic control: A1c 6.7% vs. 7.8% ($p<0.001$)
- Halted retinopathy progression: 0/51 vs. 10/82 eyes ($p<0.01$)
- Slower rate of decline in GFR
- Trend toward improved nerve conduction

Thompson, et al. Transplantation 2011 86: 373-378

Quality of life improvement – islet transplantation

- Hypoglycemia Fear Survey
- Change from baseline in hypoglycemia-related anxiety



Barshes et al., Transplantation 2005: 6:1727-1730

Summary of outcomes for islet transplantation

- <10% insulin-independence long-term
- 80% remain C-peptide positive long-term
- Improved hemoglobin A1c
- Improvement in glycemic lability
- Fewer episodes of hypoglycemia and improved hypoglycemia awareness
- Stabilization of some diabetes complications
- Improvement in quality of life

Patient selection

- **Risk-benefit ratio: identify those that will benefit from a transplant over traditional insulin therapy given the risks of the procedure and immunosuppression**
- **Patient selection is also limited due to lack of availability of pancreata for widespread application and the high cost of the procedure**

Who should be considered for islet transplant referral?

- **Patients with type 1 diabetes and a stable kidney transplant**
- **Patients with type 1 diabetes without a kidney transplant who have:**
  - **Poor quality of life related to hypoglycemic unawareness and/or glycemic lability**
  - **Failure of intensive insulin therapy to prevent progression of diabetes complications**

Hypoglycemia Score

1) Do you have symptoms when your blood sugar is low?		Always (A)	Sometimes (R)		No longer (R)
2) Have you lost the ability to recognize symptoms that used to occur when your blood sugar was low?			Yes (R)		No (A)
3) In the last 6 months, how often have you had moderate hypoglycemic episodes?					
(Symptoms of confusion, disorientation or lethargy and were unable to treat yourself)					
Never (A)	Once or twice (R)	Every other month (R)	Once a month (R)		More than once a month (R)
4) In the last year, how many times have you had severe hypoglycemic episodes?					
~~(Episodes of unconsciousness or seizure and needed glucagon or intravenous glucose)~~					
Never (A)	1 (R)	2 (R)	3 (R)	4 (R)	5 (R)
6 (R)	7 (R)	8 (R)	9 (R)	10 (R)	11 or more (R)
5a) How often in the last month have you had readings <70 mg/dl with symptoms?					
Never	1-3 times	1 time/week	2-3 times/week	4-5 times/week	Almost daily
5b) How often in the last month have you had readings <70 mg/dl without any symptoms?					
Never	1-3 times	1 time/week	2-3 times/week	4-5 times/week	Almost daily
Count as (R) if the number is GREATER for question #6					
6) How low does your blood sugar have to be before you experience symptoms?					
60-69 mg/dl (A)	50-59 mg/dl (A)	40-49 mg/dl (R)	<40 mg/dl (R)		
7) To what extent can you tell by your symptoms that your blood sugar is low?					
Never (R)	Rarely (R)	Sometimes (R)	Often (A)	Always (A)	

Reduced awareness: ≥4 R's
Aware: ≤ 2 R's

Total Number of "R" Responses:

Diabetes Care 18:517, 1995

Additional patient considerations for islet transplantation

- **Undetectable C-peptide**
- **Demonstrated efforts to control their diabetes through intensive insulin therapy**
- **Age 18-65 years old**
- **Low daily insulin requirements (<50u/day)**
- **No medical conditions that would make transplantation potentially unsafe or unsuccessful**

What should my patients know?

- Islet transplantation can be beneficial in select patients with type 1 diabetes and severe glycemic lability, hypoglycemic unawareness and recurrent hypoglycemia even in those who do not achieve full graft function.
- Benefits include improved glycemic control, reduced frequency of hypoglycemia, and halted progression of some vascular complications
- Long-term insulin independence is only achieved in a small percentage of patients

Objectives

- Describe the rationale for pancreatic islet transplantation
- Discuss the goals of islet transplantation
- Summarize the clinical outcomes in islet transplant recipients
- Review the patient selection for islet transplantation
- Describe the differences between pancreas and islet transplantation
- Describe the procedure

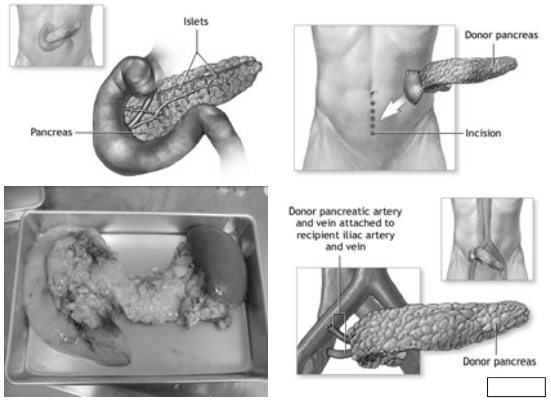
Islet Transplantation in Type 1 Diabetes

Amer Rajab, MD, PhD
Associate Professor of Surgery
Director, Pancreas & Islet Transplantation,
Comprehensive Transplant Center
Ohio State University Medical Center

Tissue replacement: whole pancreas or islet transplantation is currently the only way to restore physiologic glycemic control

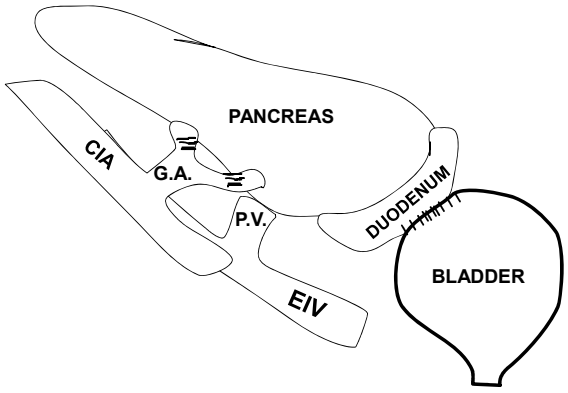
Survival

- 10-year patient survival
- Non diabetic kidney recipient 72%
- Diabetic kidney recipient 37%
- K/P recipient 60%
- K/P recipient with pancreas loss 33%
  - Tyden et al.



The Pancreas

- The pancreas is <u>two</u> organs
- The exocrine tissue = 80-90%
- The endocrine tissue = islets of Langerhans (2%)
- Diabetes: Dysfunction of the islets only



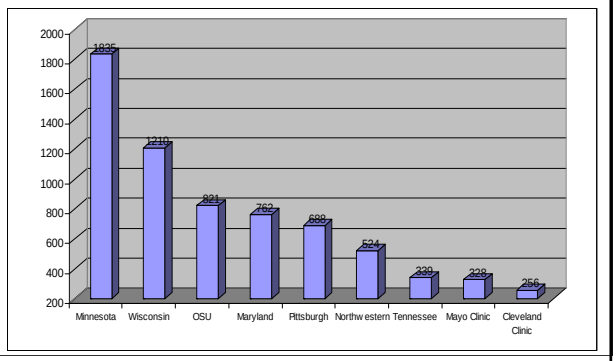
Statistics

- Number of transplant centers performing pancreas transplant: 107
- Total number of pancreas transplants: 17,888
- The total prevalence of diagnosed Insulin Dependent Diabetes Mellitus (IDDM) in the United States (all ages, 2005) is approximately 1,400,000-2,800,000 people
  - (http://diabetes.niddk.nih.gov/dm/pubs/statistics)

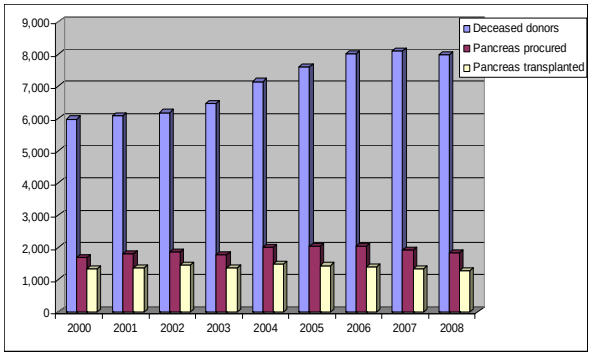
Statistics

- OSU (1988-2010): 856 total pancreas transplants
  - K/P: 756
  - Pancreas: 110
- Graft survival:
  - One year: 82% (5 year 71%)
- Patient survival
  - One year: 93% (5 year 90%)

Transplant center ranking by total number of pancreas transplants



National Data (OPTN)



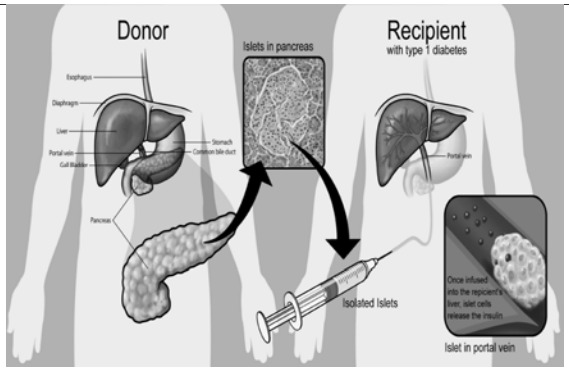
Anatomy of the Pancreas

- 75-125 g
- 15-20 cm long
- 80-90% Exocrine: acinar cells and ductular network
- 2% Endocrine: islets of Langerhans
- Remaining: connective tissues: vascular, nervous, lymphatics

Islet Sources

- Only pancreata not used for whole organ transplantation are considered for islets:
  - Donors with significant atherosclerosis
  - Donors with prolonged down time, hypotension and hyperglycemia
  - Donors with extreme age
  - Fatty pancreas
  - Fibrotic pancreas
  - Pancreatitis
  - Pancreas with duodenal, parenchymal or splenic injury

Islet Transplantation



from Wikipedia, the free encyclopedia (Islet transplantation PLoS Medicine.jpg)

Pancreas VS Islet

• Pancreas	• Islet
• Maximally Invasive	• Minimally Invasive
• Recipient Selection	• All Diabetics Qualify
• Limited Supply	• Potential for Unlimited Supply
• Immunosuppression Required	• Manipulate Islets for Tolerance
• Preservation Time Limited	• Longer Time Permitted
• Re-Transplant is difficult	• Can be repeated multiple times

Essentials For Clinical Islet Transplantation Program

- **Acquire the highly specialized islet isolation technology**
- **Establish an FDA approved islet isolation lab**
- **Apply and receive Investigational New Drug Approval (IND)**
- **Secure IRB approval**
- **Secure UNOS approval**
- ***Resources***

Human Islet Isolation

- **Standard cadaveric pancreas procurement**
- **Pancreatic duct cannulation**
- **Enzyme digestion**
- **Islet purification**
- **Quality control**

Islet Isolation Team

Jan Sirilla, RN, MSN
Administrative Director, BMT Program
- Administrative aspects of BMT Lab

Dave Krugh, MT(ASCP), SBB, CLS,CLCP(NCA)
BMT Program Quality Manager
- Oversees Quality Program of BMT Lab, including islet QC/QA

Amer Rajab, M.D., Ph.D.
Medical Director, Islet and Pancreas Transplantation
Medical Director, BMT Laboratory, Human Islet Isolations
- Procurement, perfusion & digestion phases of islet isolations
- Ensures islet products meet medical needs of patients

Lynn O'Donnell, Ph.D. **Director, BMT Laboratory**
- Responsible for operational & quality issues of BMT Lab
- Assists in islet isolations/QC

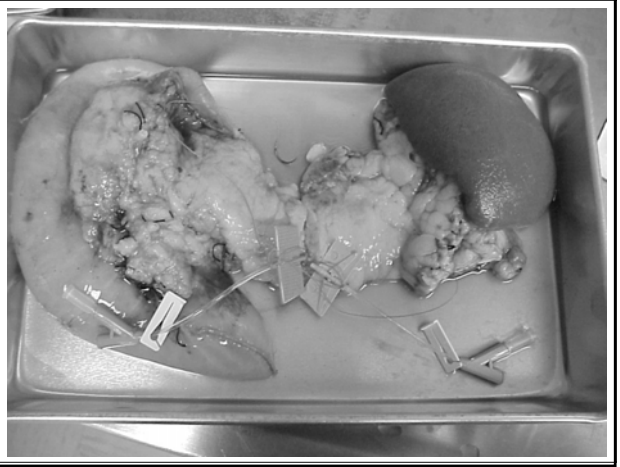
Jill Buss, M.S.
Islet Research Assistant
- Lead technologist for islet isolations
- Performs islet QC testing

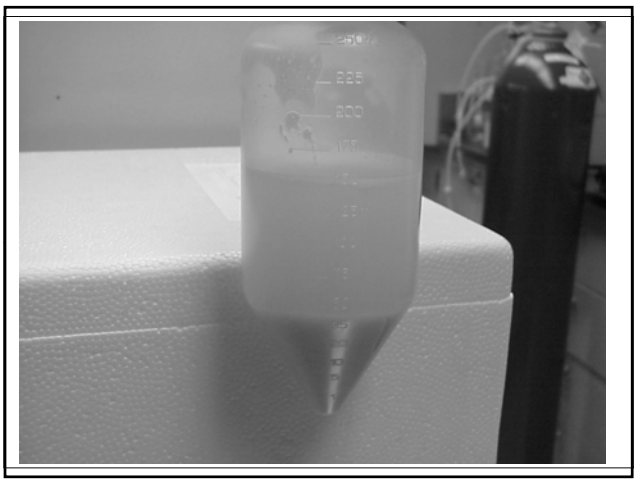
Hillary Bradbury, MT (ASCP)
Supervisor, BMT Laboratory
- Manages BMT Lab
- Assists in islet isolations
- Performs islet QC/QA

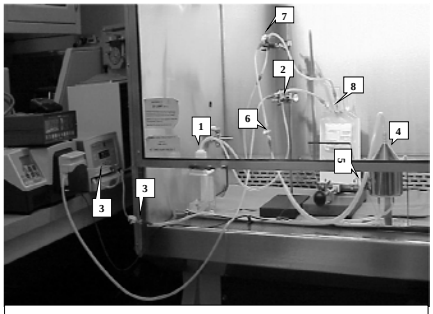
Elizabeth Diakoff, M.D.
Assistant Professor, Dept. of Endocrinology, Diabetes & Metabolism
- Assists in islet isolations

Cell Therapy Technologists, MT
- Assist in islet isolations
- Perform islet QC/QA

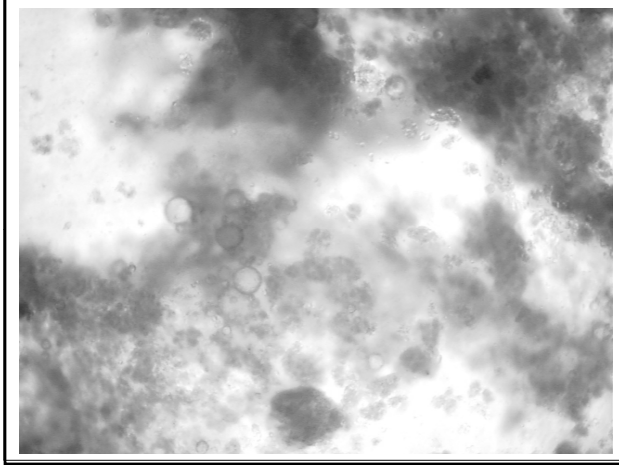
Residents & Fellows
- Assist in islet isolations

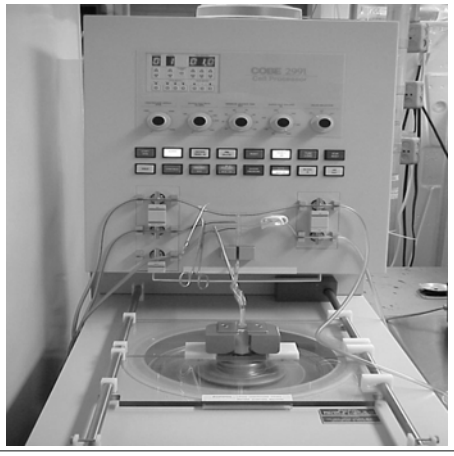


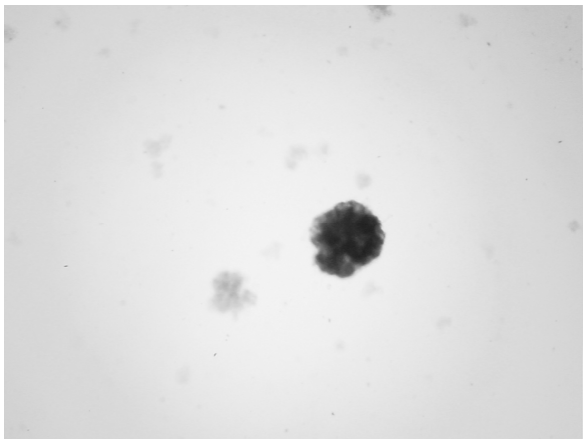




OSU islet isolation protocol IND#13038

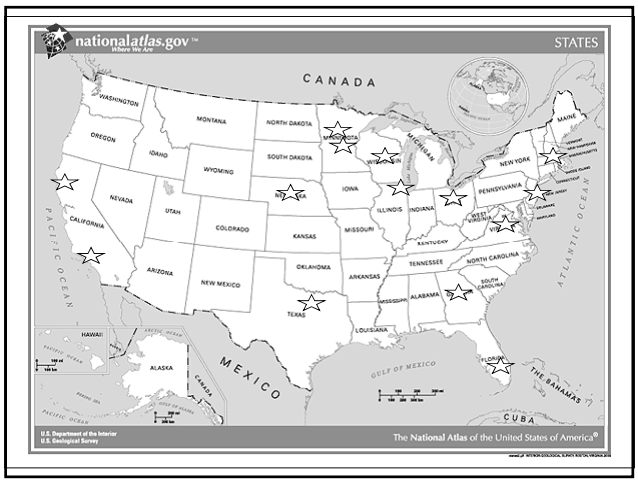






Quality Control
Product Release Criteria

- Islet Pellet Volume
- Viability Assay
  - Dithizone Staining
  - Fluroscent microsope using Calcein AM and ethidium homodimer-1.
- Islet Equivalents
- Islet Purity
- Endotoxin
- Functional Assay
  - Stimulation index: In-vitro Insulin Production in Low and High Glucose
- Sterility Testing



Islet Transplantation

- **Minimally invasive (simple injection)**
- **All diabetics qualify**
- **Potential for unlimited supply**
- **Manipulate islets for tolerance**