Update on islet transplantation

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DIABETES RESEARCH INSTITUTE FOUNDATION

The Best Hope for a Cure®

- **The Challenge**
- **The Hypothesis**
- **Human Islet Isolation**
- **Prevention of Rejection/Autoimmunity**
- **Islet transplantation Safety**
- **The Translational Research Approach**
    - **Proof of Function in Animal Models**
    - **Proof of Function in Humans**
- **Possible Reasons for Islet Graft Failure**
- **Current challenges faced for islet transplantation**

Source:

Diabetes

XV century BC

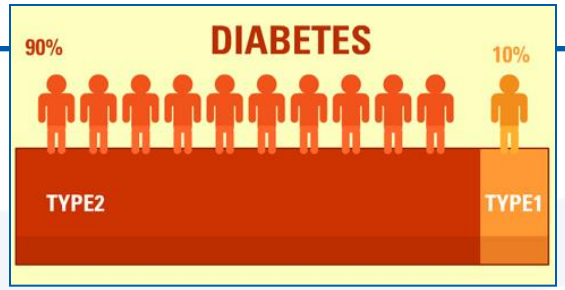
Papyrus Ebers

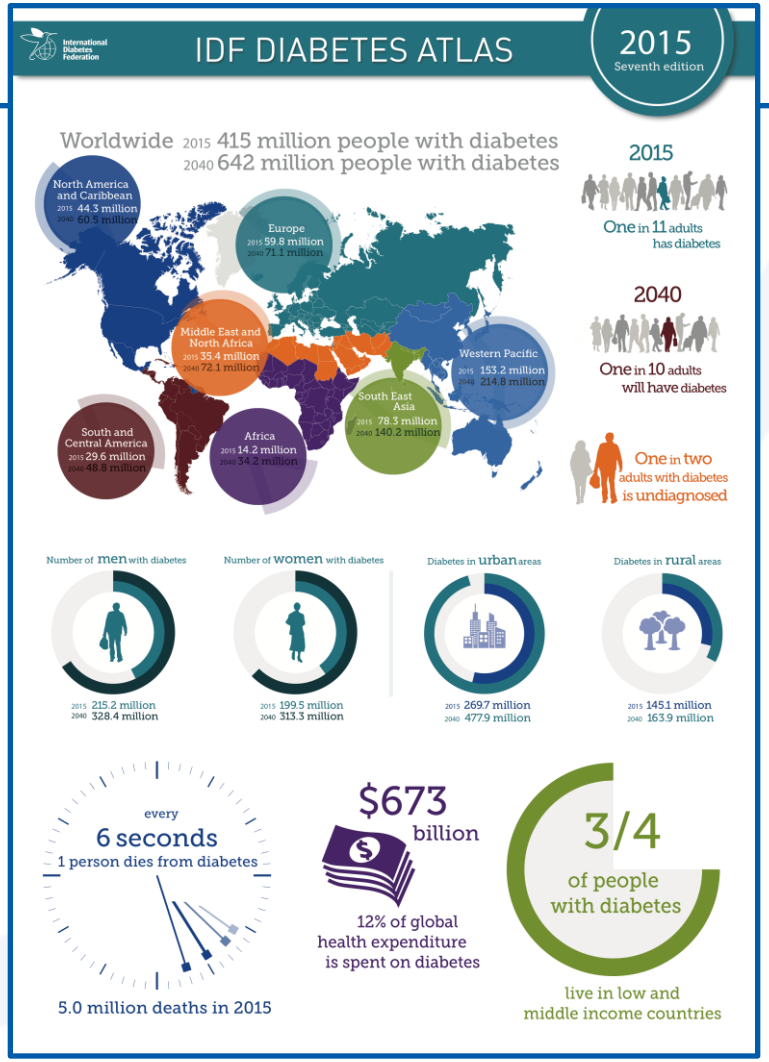
(passing of too much urine)

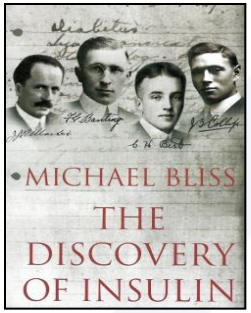
I century AD

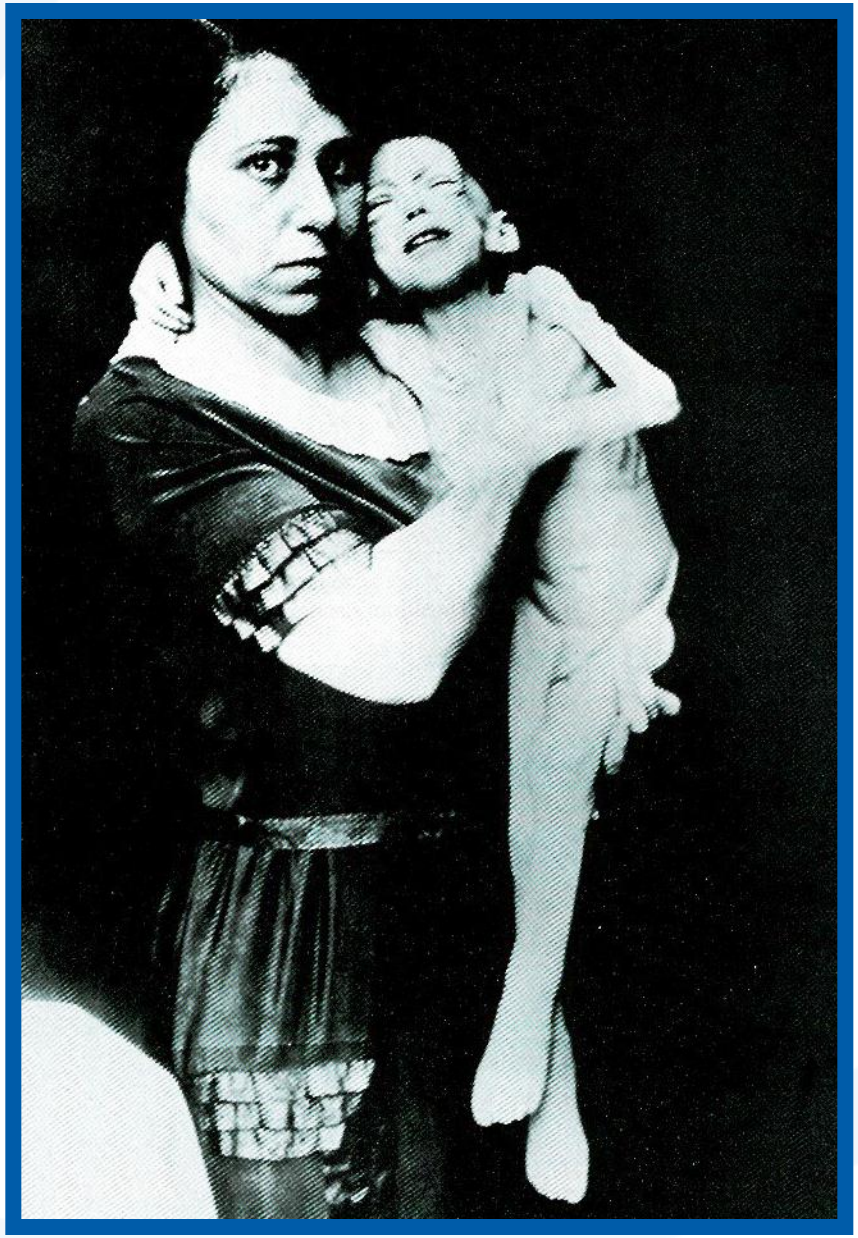
Arataeus

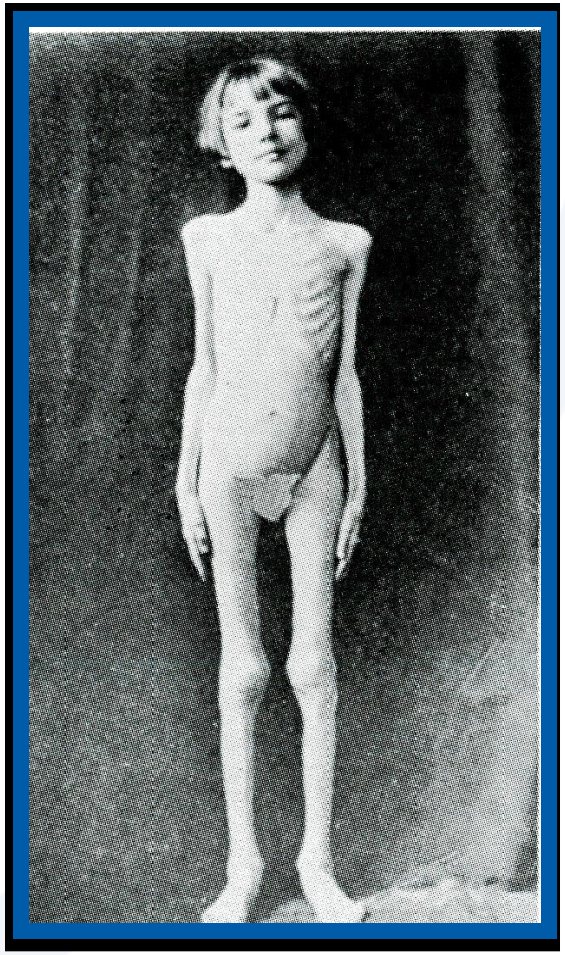
coins “diabetes” from the Greek “siphon” or “pipe- like”:“a melting down of the flesh and limbs into urine”



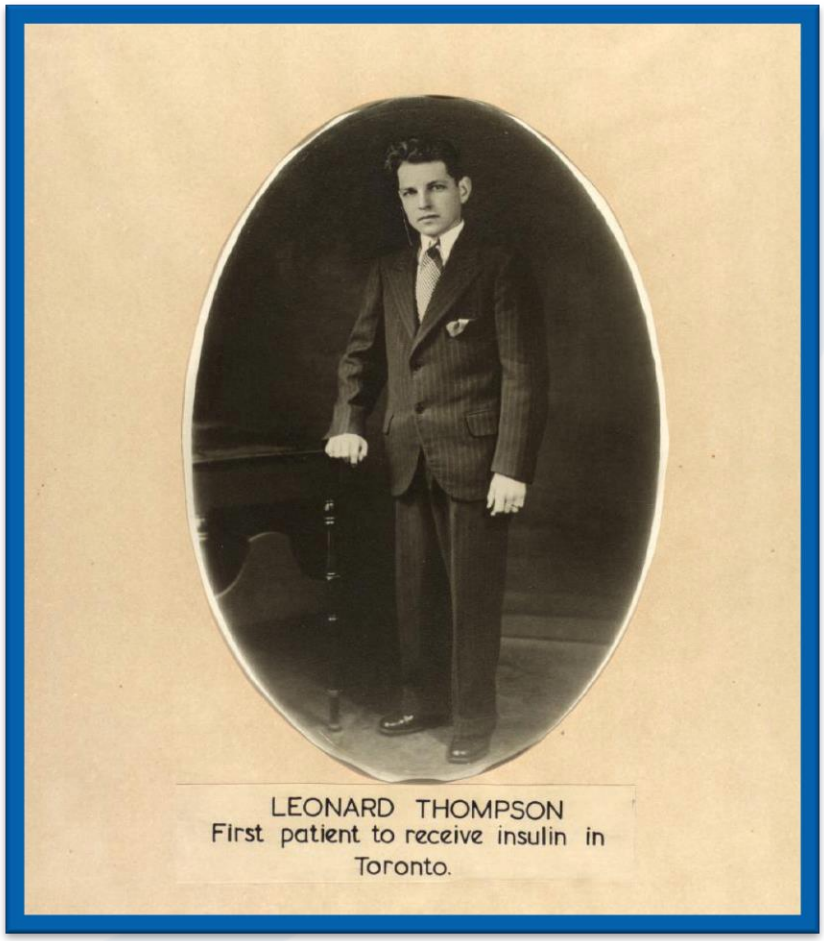


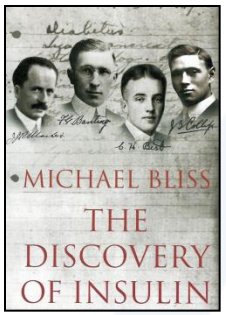

MICHAEL BLISS
THE DISCOVERY OF INSULIN





Jan, 1922


LEONARD THOMPSON
First patient to receive insulin in Toronto.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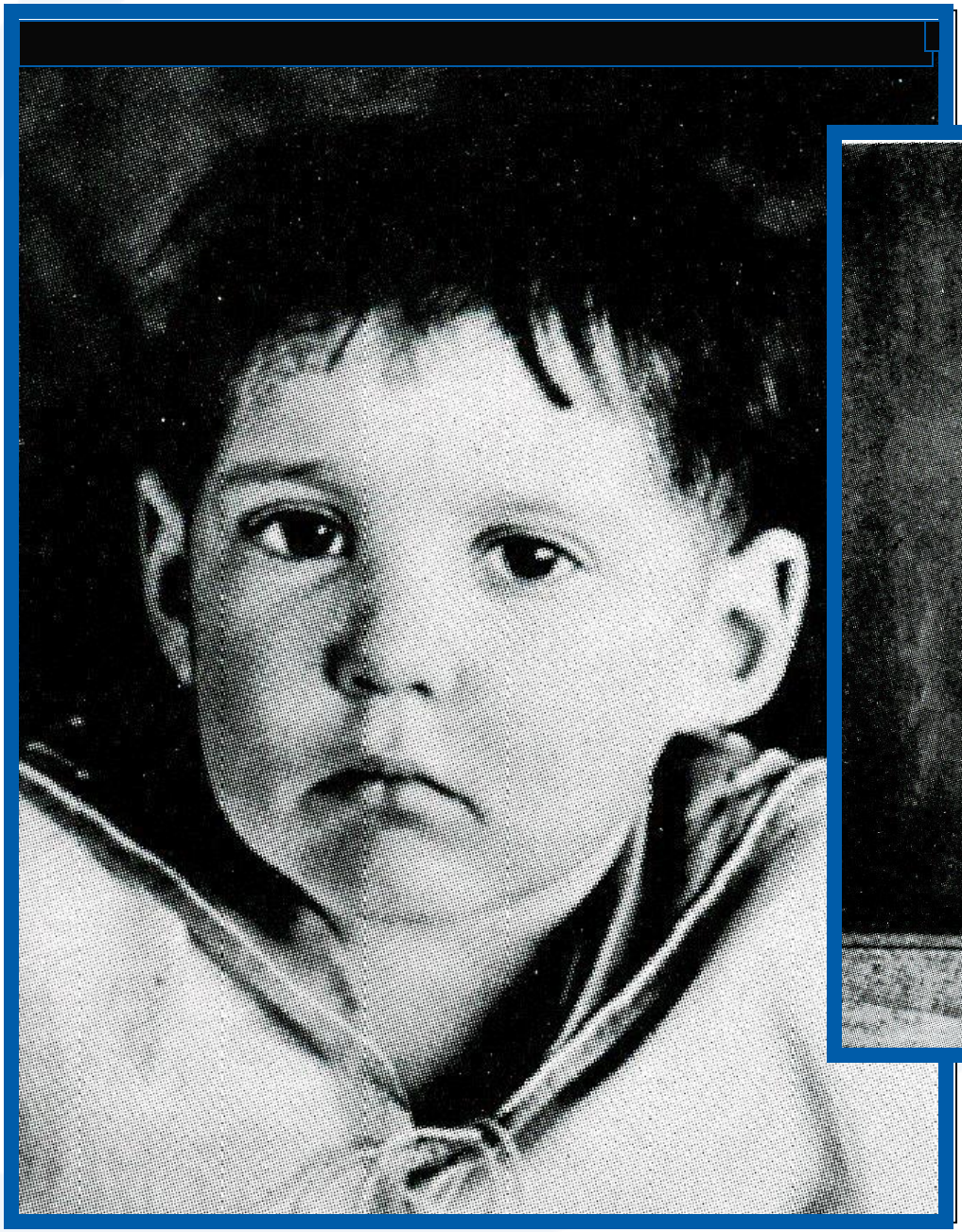
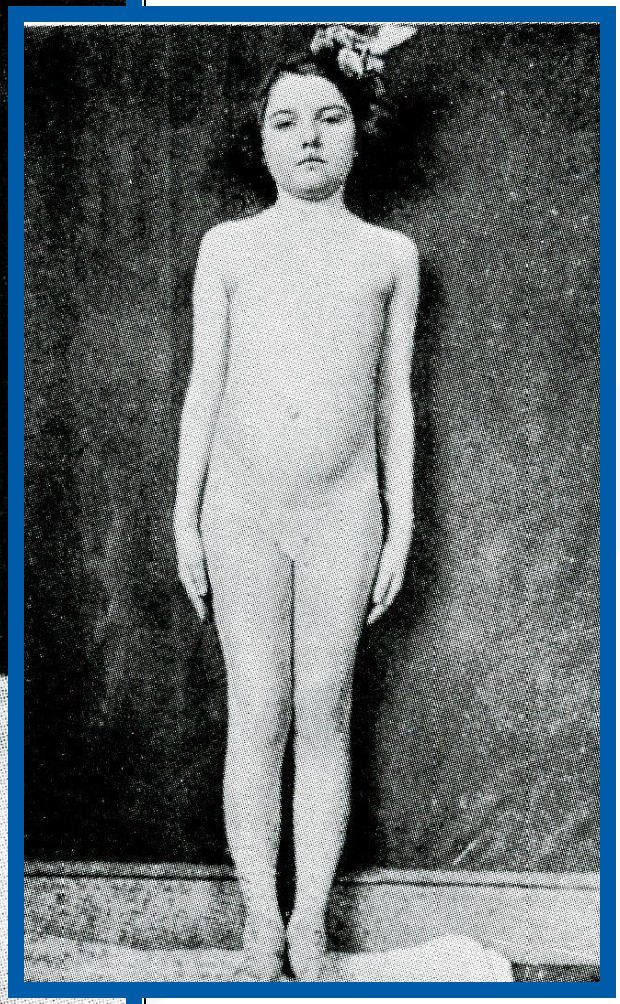
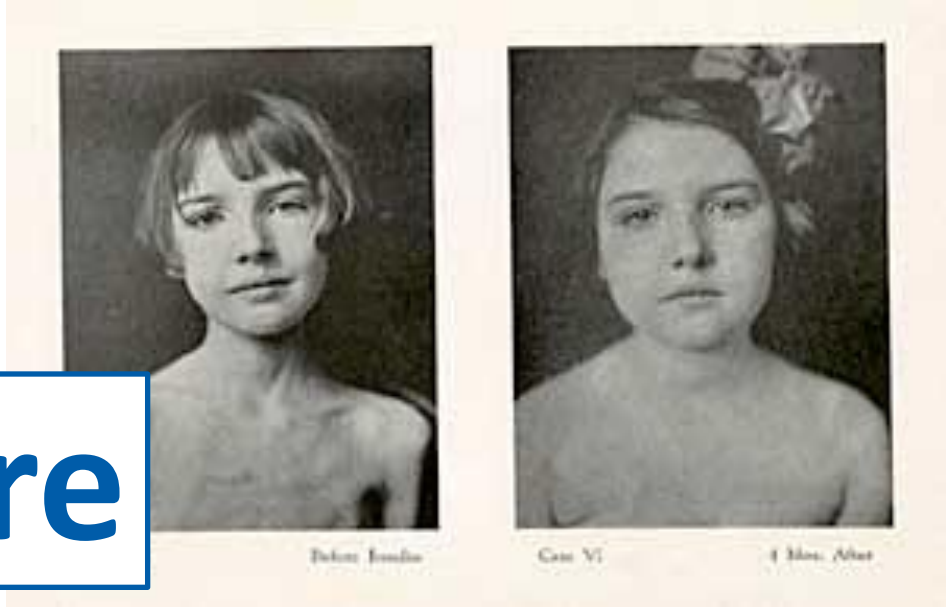
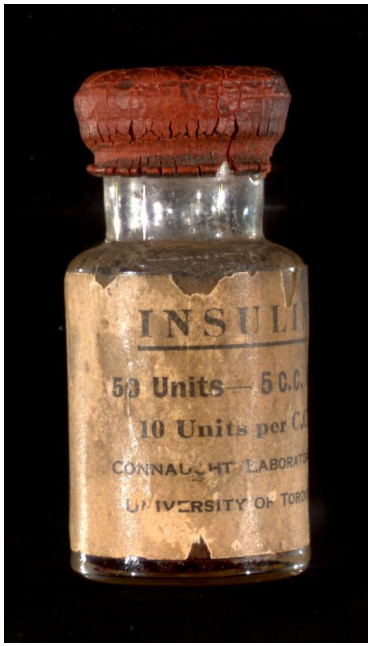


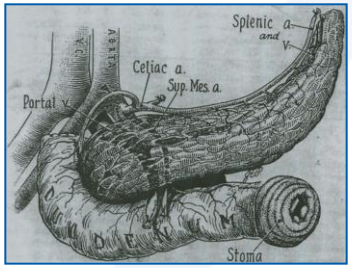




Not A Cure

- Some early users died of hypoglycemia, but insulin seemed a remarkable cure.
- By the 1940's, however, diabetic complications began to appear
- It became clear that injecting insulin was not the full answer





New achievement

Normalization of blood glucose (not merely control of blood glucose) will lead to improvements in:

- Survival
- Quality of life
- Protection from heart disease, kidney disease, retinopathy, and nerve injury

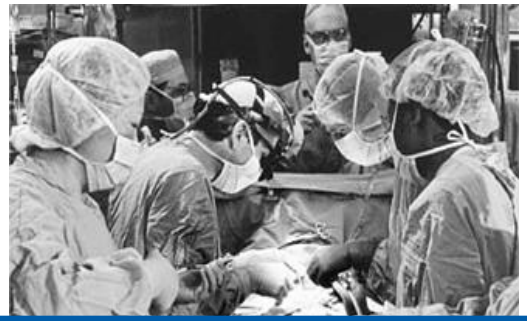
The only method that normalizes blood glucose in patients with diabetes is treatment with insulin-producing cells

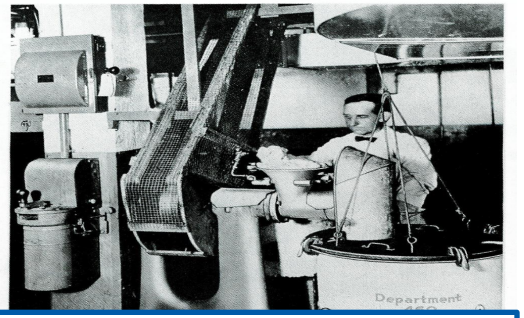
Islet Transplantation

Pancreas transplantation

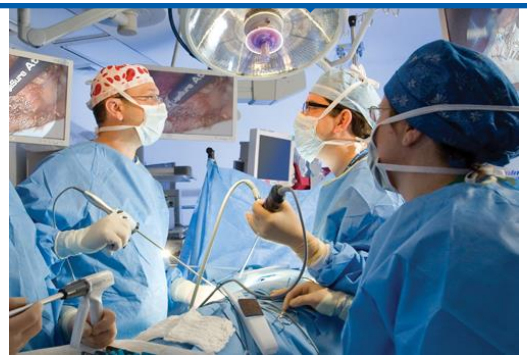
The Evolution of Treatment...

Insulin | Pancreas Transplantation | Islet Transplantation





Competitors or Allies?



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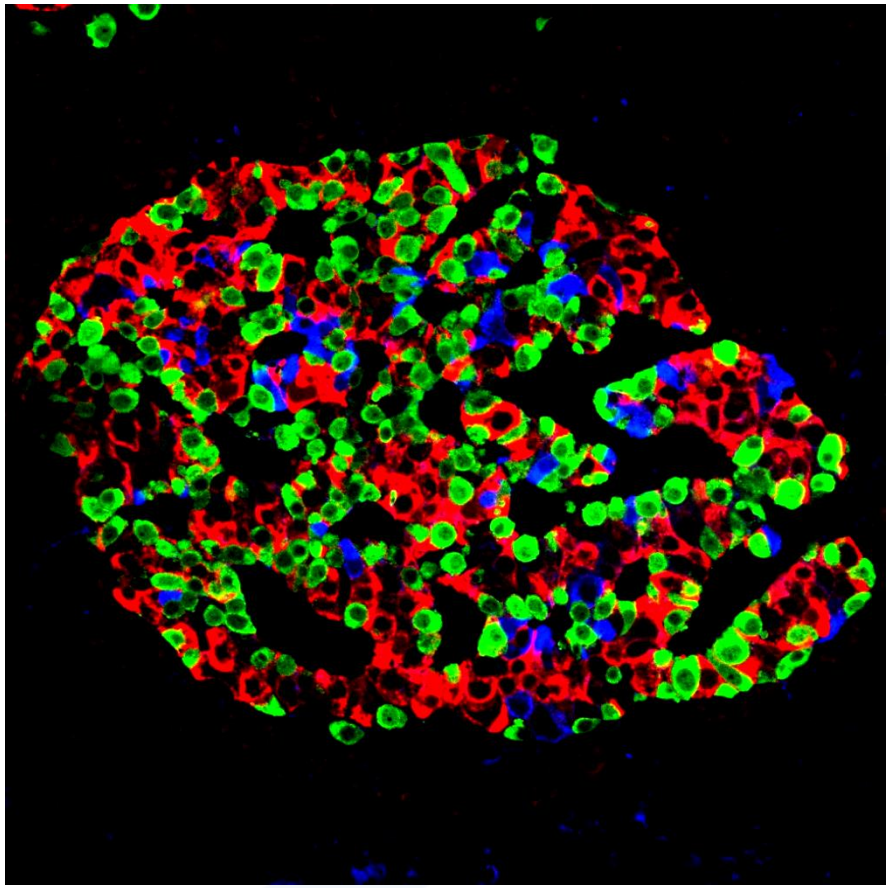
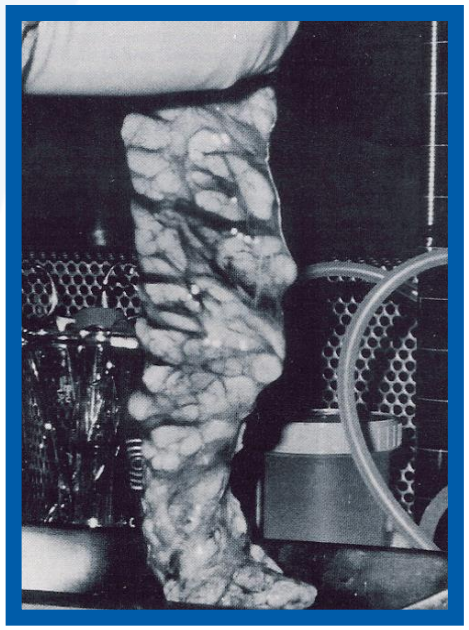
Source:

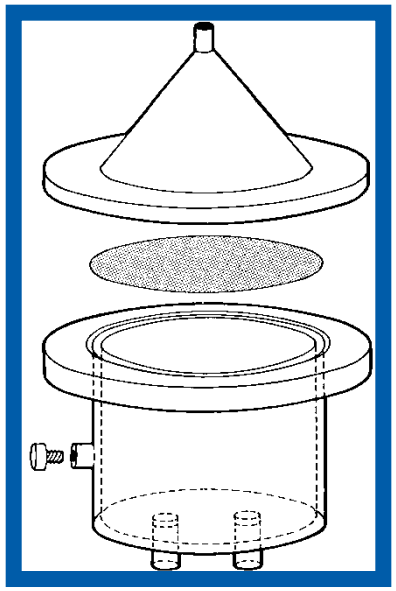
ISLETS ARE BETTER THAN INSULIN

- Make their own insulin
- Built-in glucose sensor
- Perfectly timed insulin release
- Keep glucose levels in the normal range
- Function for entire lifetime

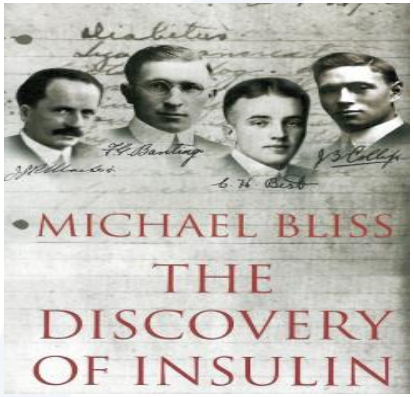


Evolution of islet isolation process…



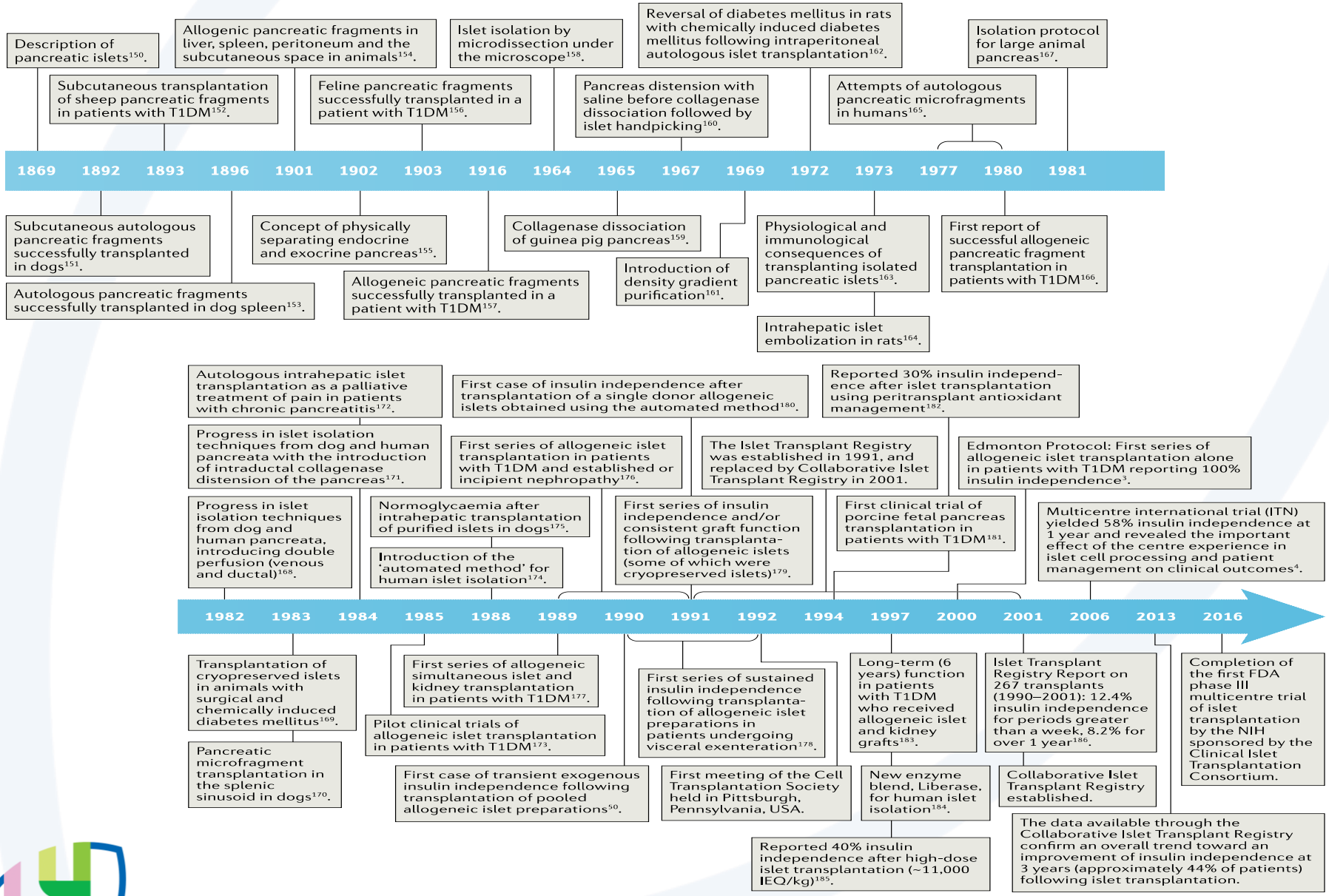


… is a story of imagination & innovation



Initial attempts to isolate islet cells from a donor pancreas involved
crude & disruptive mechanical methods.

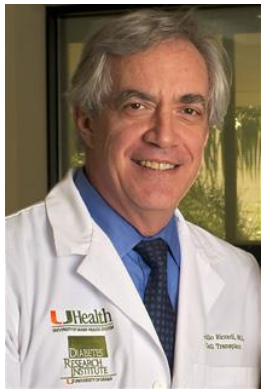
Grinding pancreas to make insulin at Eli Lilly's Indianapolis plant, 1923.
Eli Lilly and Company Ltd.

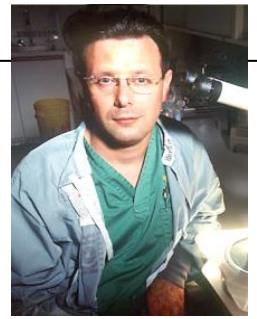


Clinical pancreatic islet transplantation

A. M. James Shapiro[1–3], Marta Pokrywczynska[2–4] and Camillo Ricordi[2,3,5]

No. of Adult Islet Allografts in Patients with Diabetes by Year from 1974 through 06/2003





ITN Multicenter Islet Trial

SingleDonor (Minnesota)

Culture + TLM

Edmonton Protocol

Liberase

Giessen Milan

Islet Autografts work

Large scale islet isolation

Rats cured

100
80
60
40
20
0

9 1 10 10 11 3 2 6 4 14 2 4 2 12 37 26 25 28 29 59 45 37 22 35 54 78 106 40

1974 1980 1985 1990 1995 2000 06/2003

No. of Adult Islet Allografts by Year

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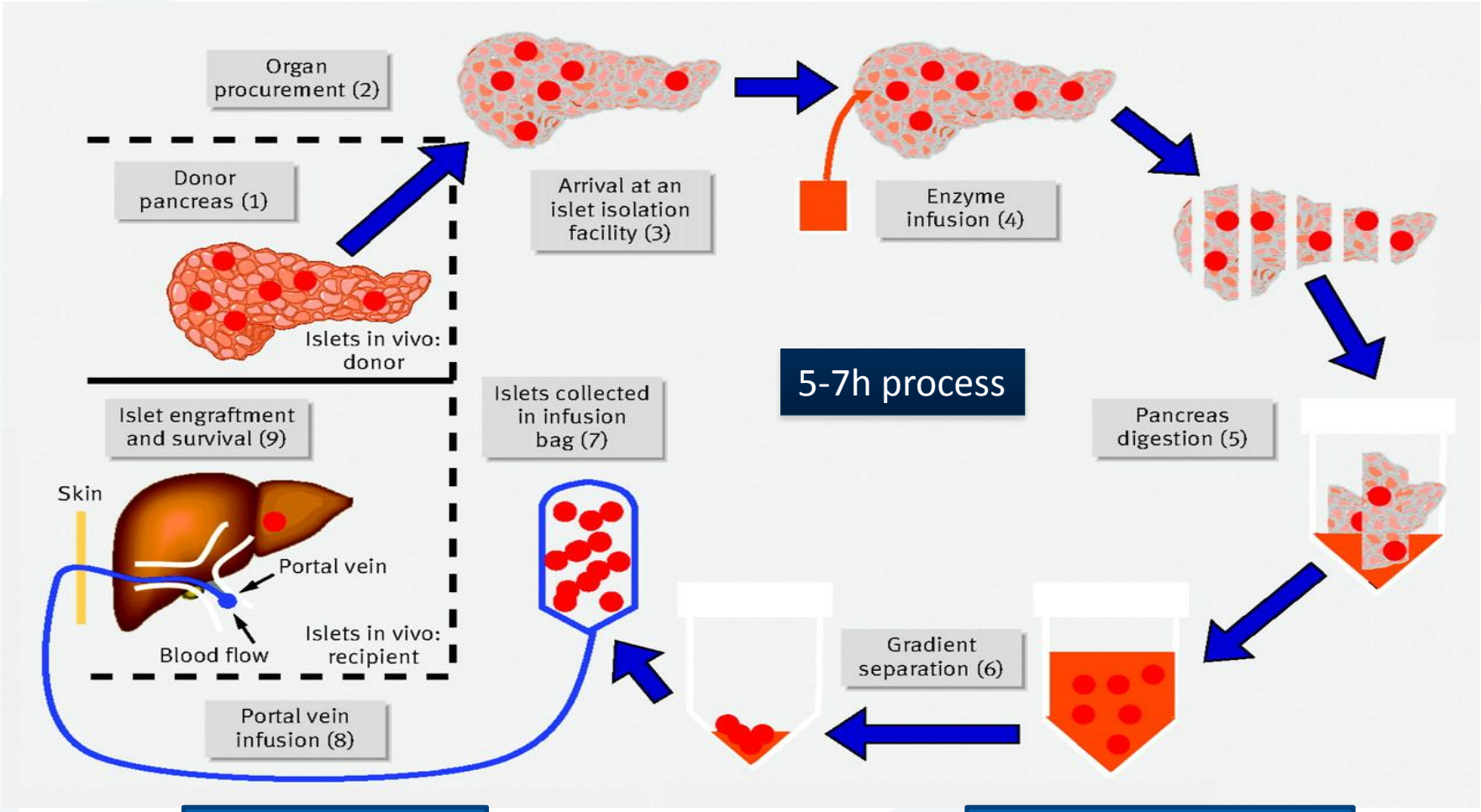
Source:

Isolation Process



1-2% of pacreas tissue volume

<5 cm3 of tissue pellet

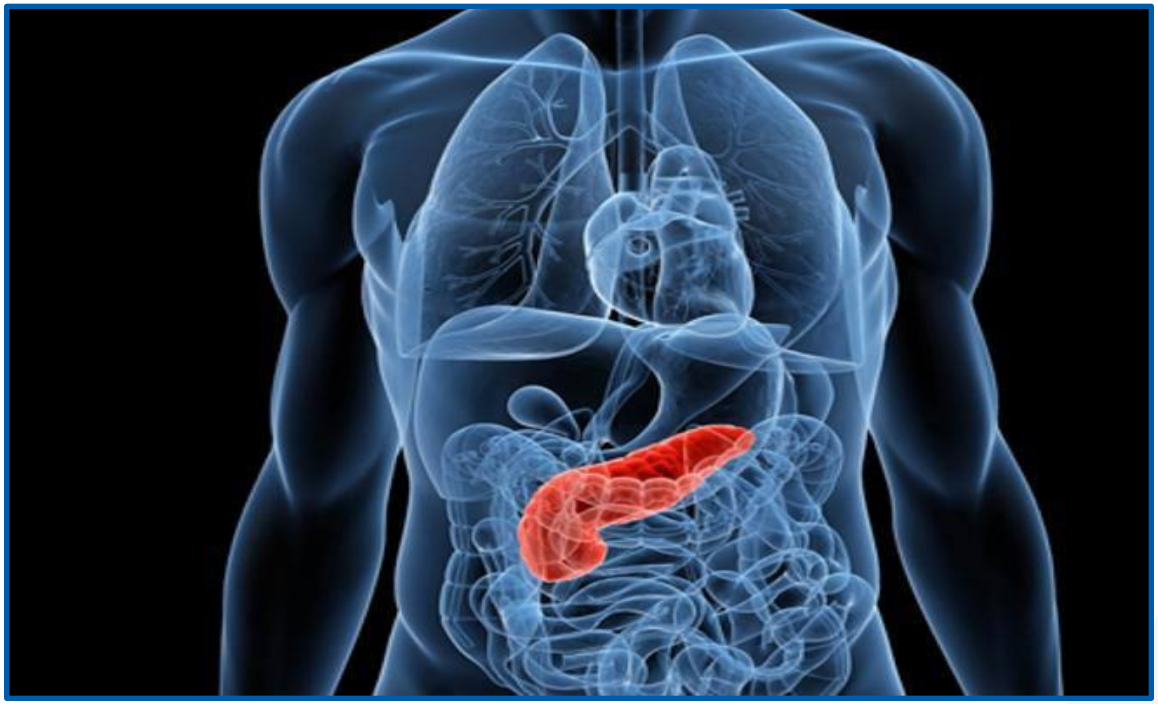
>5000 IEQ per kg of the recipient body weight

Donor Selection Criteria

BMI

CIT

Weight



Height

BSA

COD

Age

DBD/DCD

WIT

Medical/Social history

Donor management

Procurement technique

Donor Creteria Associeted with Succeful Isolation

- **Age** 20 to 50 years old

Young donors:

- generally see a higher proportion of embedded and mantled islets:

- poorer post-purification yields
- but superior function

Effect of Donor Age on Function of Isolated Human Islets

Sung-Hee Ihm, Ippei Matsumoto, Toshiya Sawada, Masahiko Nakano, Hui J. Zhang, Jeffrey D. Ansite, David E.R. Sutherland, and Bernhard J. Hering

Diabetes 55:1361–1368, 2006

Islet of Langerhans isolation from pediatric and juvenile donor pancreases Transplant International **27** (2014) 949–955

Raphael P. H. Meier,[1]* Ismail Sert,[1,2]* Philippe Morel,[1] Yannick D. Muller,[1] Sophie Borot,[1,3] Lionel Badet,[4] Christian Toso,[1] Domenico Bosco[1] and Thierry Berney[1]

- **Pancreas weight** positively associated with islet yield. Donor **BSA** predicts pancreas weight

Estimation of Pancreas Weight From Donor Variables

Tatsuya Kin, Travis B. Murdoch, A. M. James Shapiro, and Jonathan R. T. Lakey

Cell Transplantation, Vol. 15, pp. 1–100, 2006

Donor Creteria Associeted with Succeful Isolation

-BMI >30 kg/m2 and normal blood glucose levels at the time of organ donation

…but patients with levels of HbA1c >6.5% should be avoided, because of the risk of occult type 2 diabetes mellitus

Hering, B. J. et al. Single-donor, marginal-dose islet transplantation in patients with type 1 diabetes. JAMA 293, 830–835 (2005).

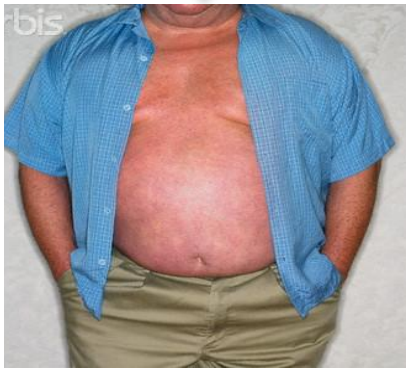
-**CIT** <12h ….as soon as possible..

-DBD>DCD ?

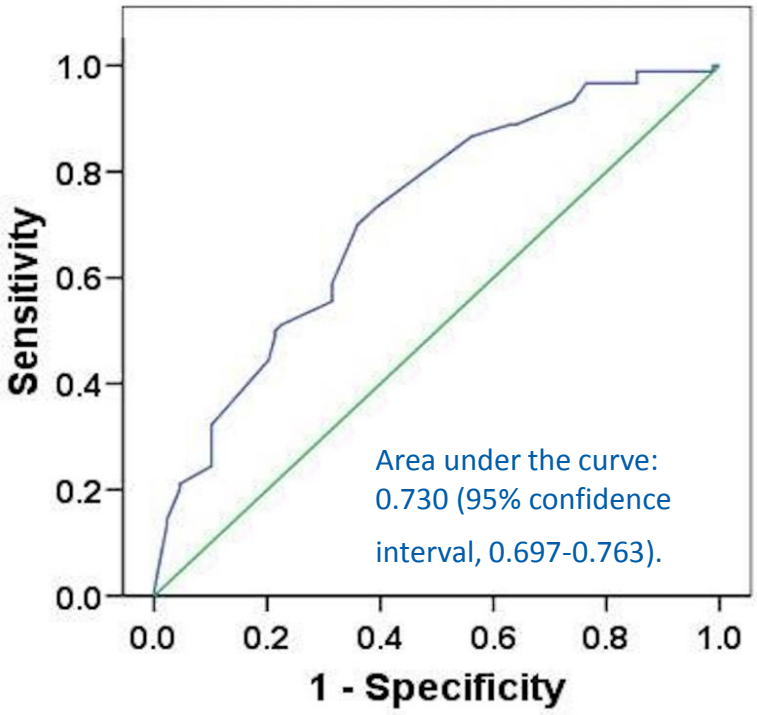
Liu, X. et al. Analysis of donor- and isolation-related variables from non-heart-beating donors (NHBDs) using the Kyoto islet isolation method. Cell Transplant. 17, 649–656 (2008).

-Moderate Alcolic consumption?

Whos islets wou you pre ?!



NAIDScore



North American Islet Donor Score

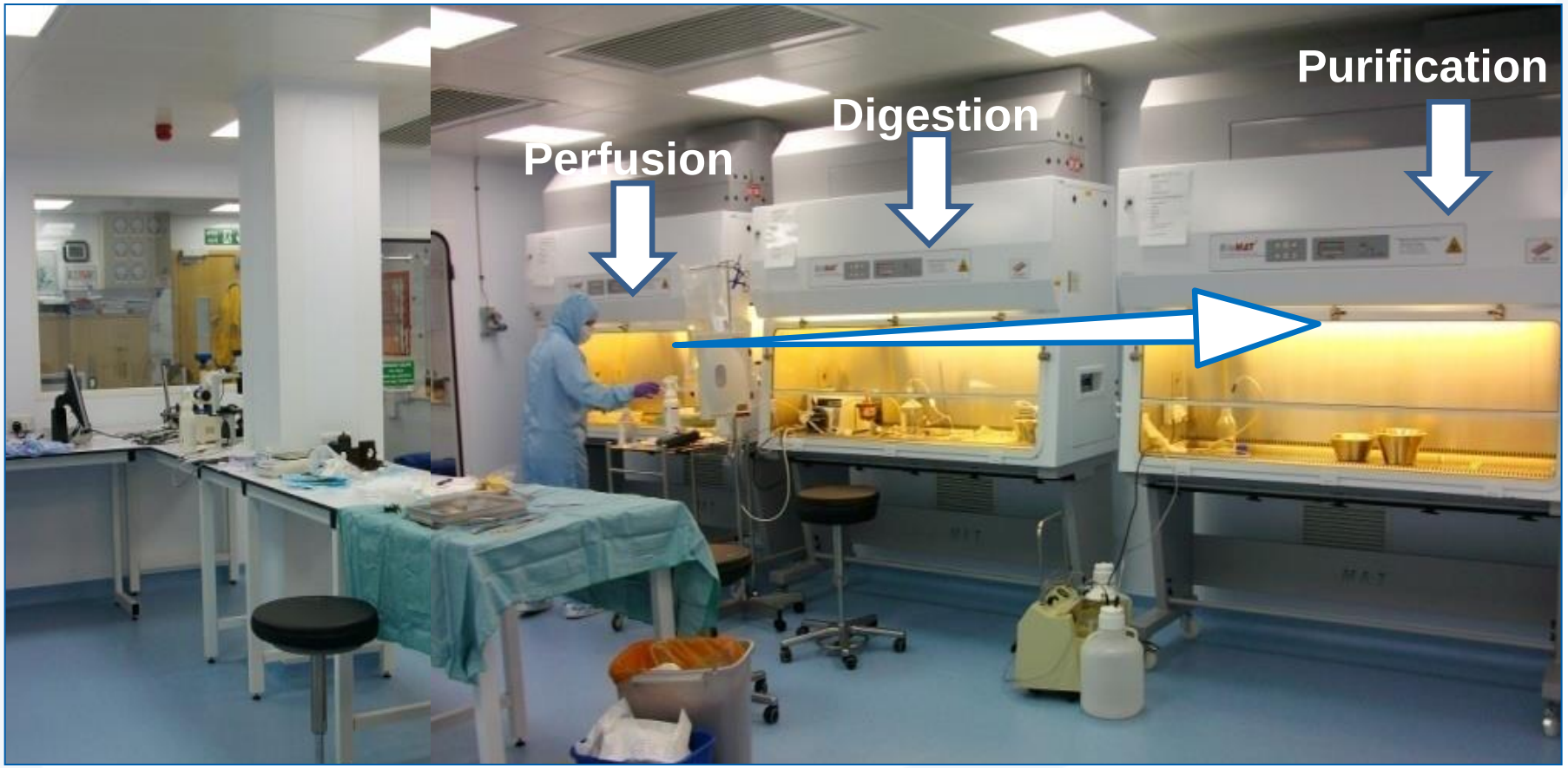
Body surface area (m^2)	
X < 1.54	0
1.54 ≤ X < 1.82	5
1.82 ≤ X < 2	10
2 ≤ X < 2.18	20
2.18 ≤ X	25
Number of vasopressor types used	
More than 2	0
Double	3
Single	10
None	15
Body mass index (kg/m^2)	
X < 20.1	0
20.1 ≤ X < 28.1	2
28.1 ≤ X < 32.5	7
32.5 ≤ X < 52.0	10
52.0 ≤ X	0
Unfavorable factors *	
At least one	0
None	35
Favorable factors †	
None	0
One	2
Two	7
More than two	15

*Unfavorable factors: age (years) <20, >75; CIT (h) ≤2, >17; body weight (kg) <55; HbA1c (%) >6.5; ALT (U/L) >1,070; AST (U/L) >580; BUN (mg/dl) ≥80; amylase (U/L) >1,500.

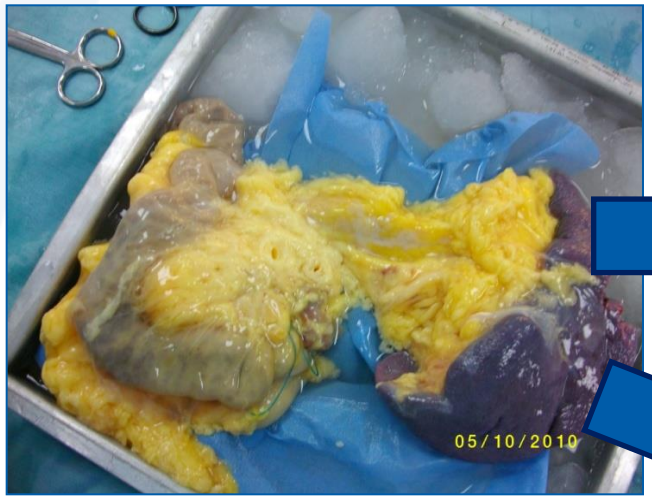
†Favorable factors: body weight (kg) >120; own team procurement; 130 < Na (mEq/L) < 160; peak glucose (mg/dl) <410.

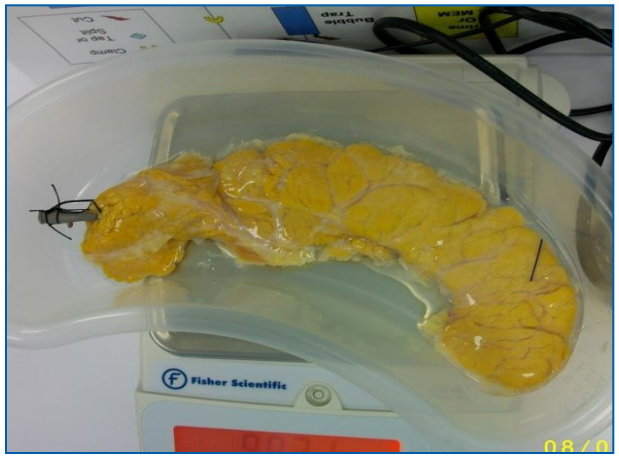
Cell Transplant. 2016;25(8):1515-23. doi: 10.3727/096368916X691141. Epub 2016 Feb 26.
A Multicenter Study: North American Islet Donor Score in Donor Pancreas Selection for Human Islet Isolation for Transplantation.
Wang LJ1Witkowski P.

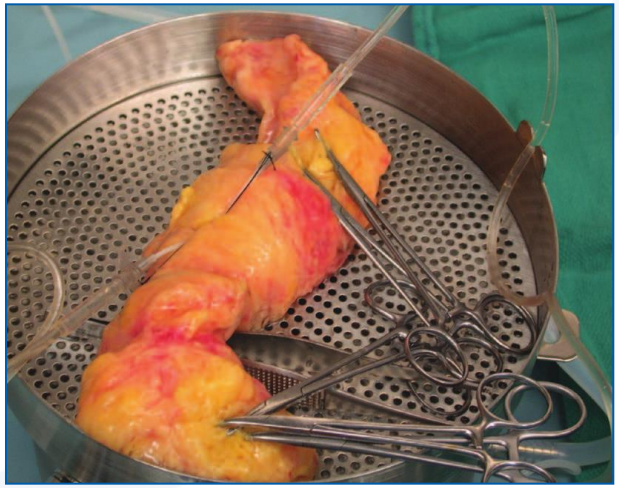
Islet Isolation facility



Organ Dissection



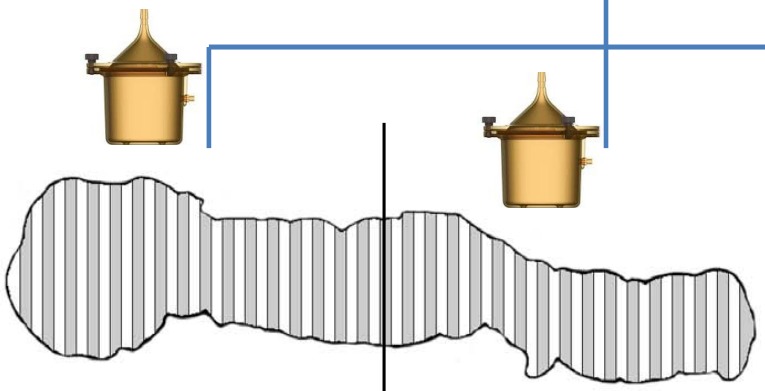




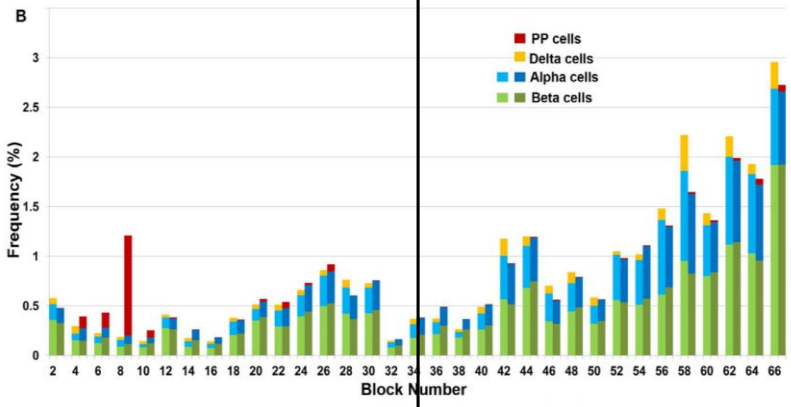
- Organ inspection
- Determine consistence and colour
- Avoid lesions, fractures..
- Avoid leaks
- Biopsy
- Bacteriology sample
- Determine pancreas weight

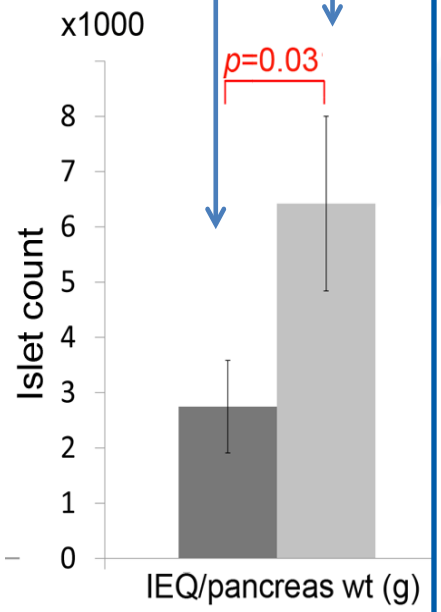
Quantitative analysis of pancreatic cell distribution in the human pancreas.

Manami Hara et al.



N=7 isolations

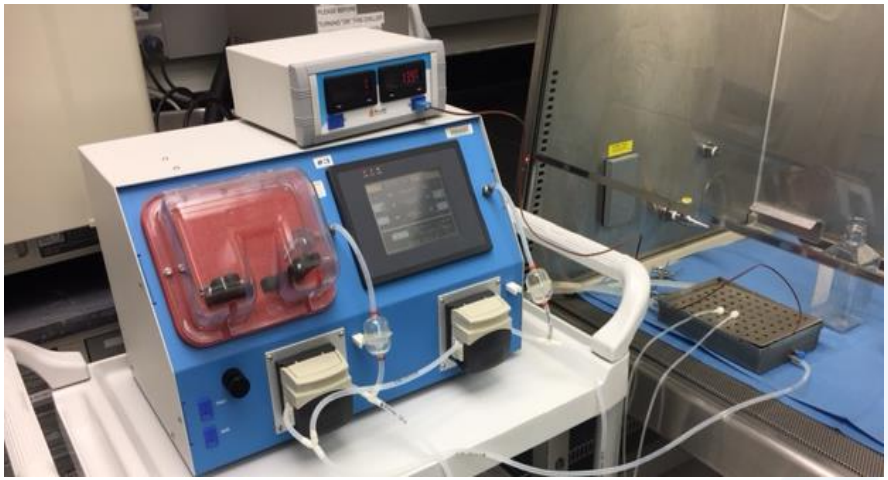


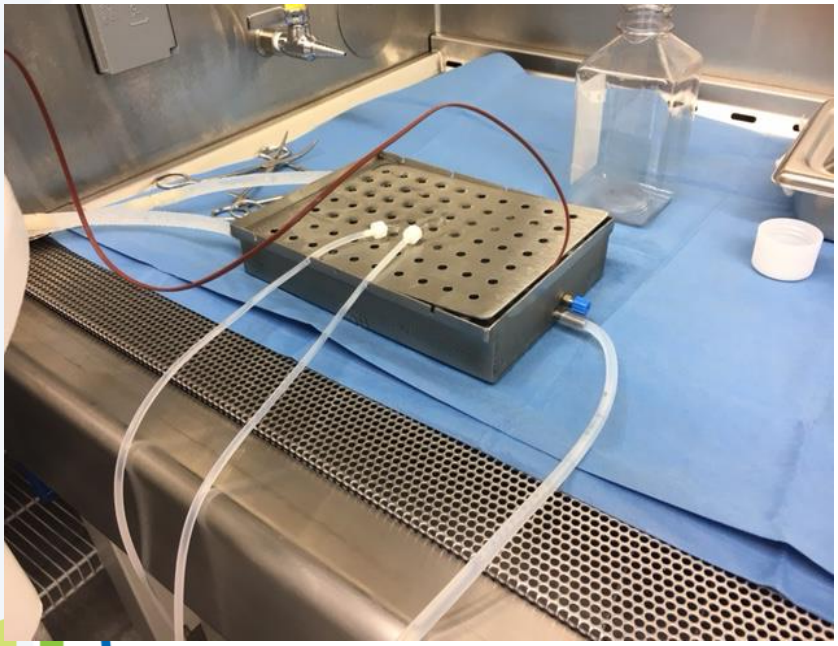


Pancreas Digestion: 3 Steps

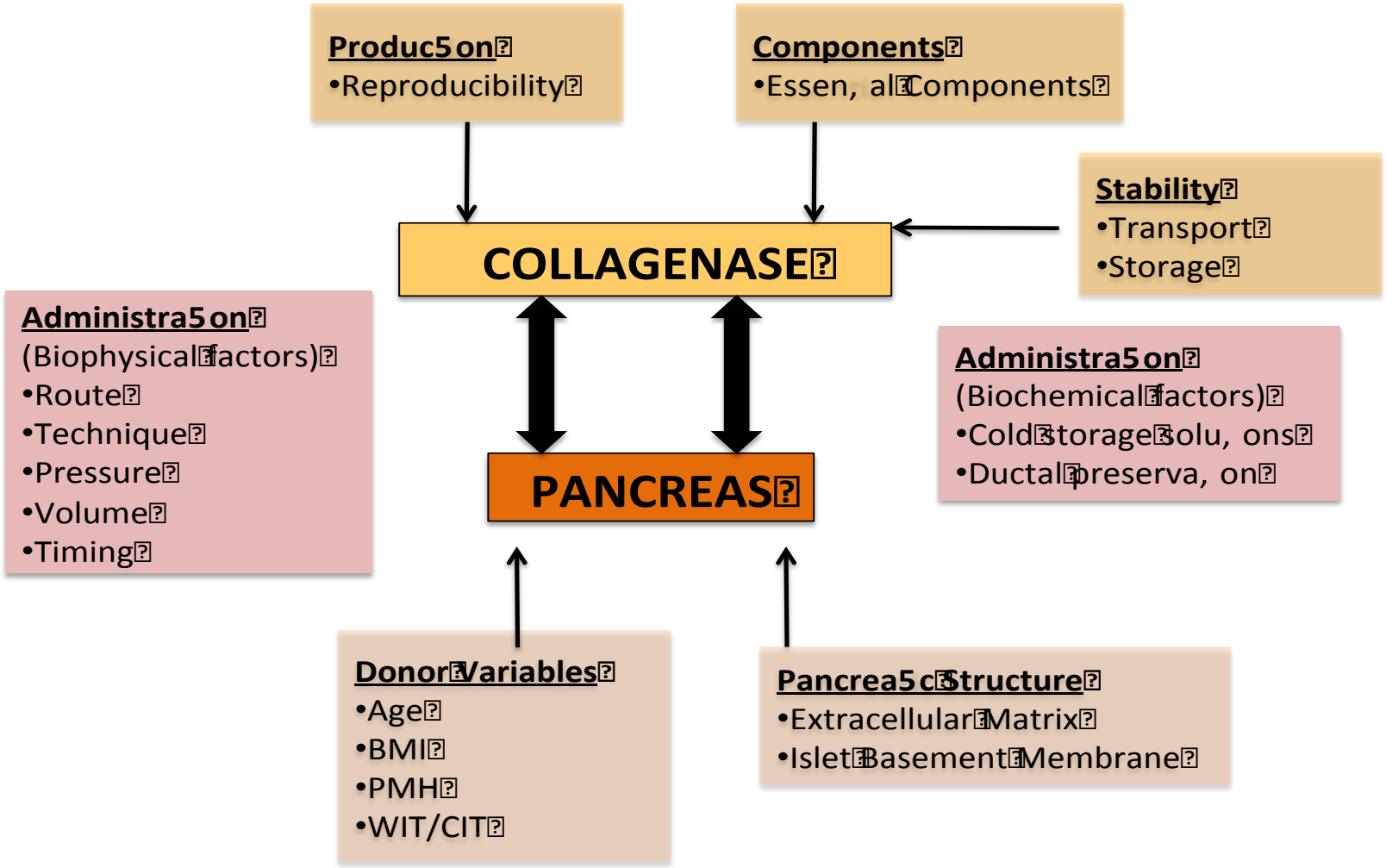
1. Physical distention of the pancreas
2. Enzymatic dissociation
3. Dilution (cessation of enzyme activity) and collection

Physical distention of the pancreas





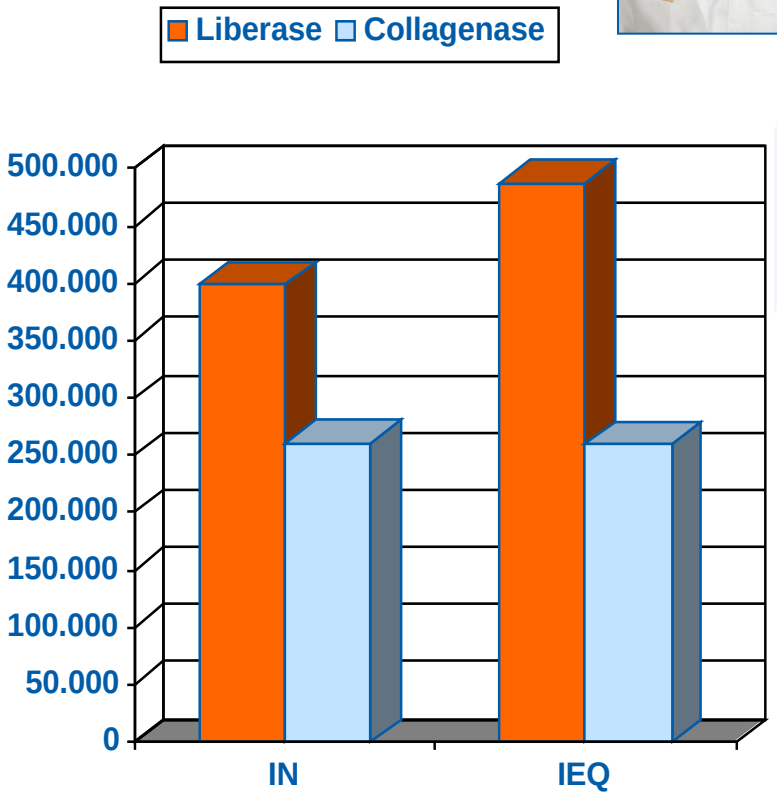
Factors influencing pancreas digestion



Diabetes 1997; 46: 1120-1123

Improved Human Islet Isolation Using a New Enzyme Blend, Liberase ™.

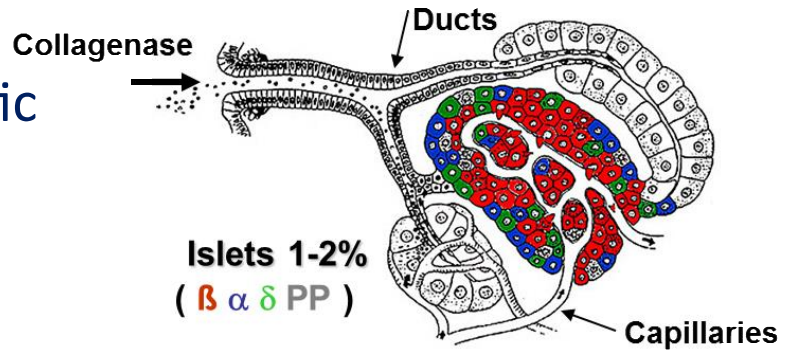
Linetsky E, Bottino R, Lehmann R, Alejandro R, Inverardi L, Ricordi C.



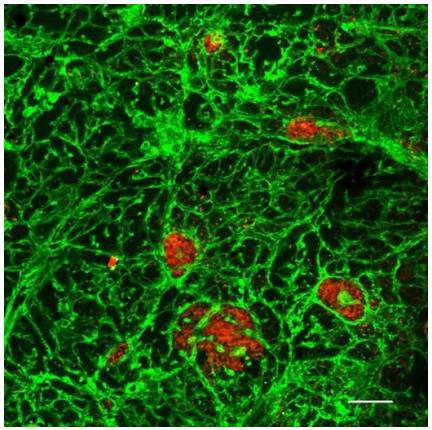
- Reduced Endotoxin
- Improved islet yields
- GMP grade

Digestion Phase Main Goal

- The need to separate one intact organ (the **islet**) from within another organ (the **pancreas**), while maintaining structural integrity as well as viability, is a unique challenge



- Efficient **diges5on** of the pancreatic extracellular matrix at the islet-exocrine interface
- Liberation of intact islets from the surrounding exocrine tissue
- Over-digestion → islet fragmentation
- Failure to digest → embedded islets

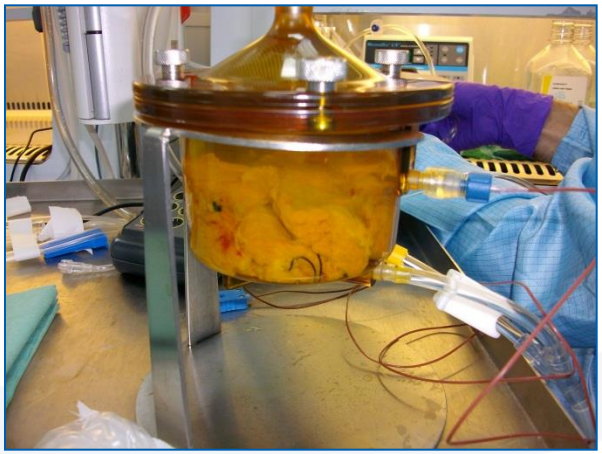


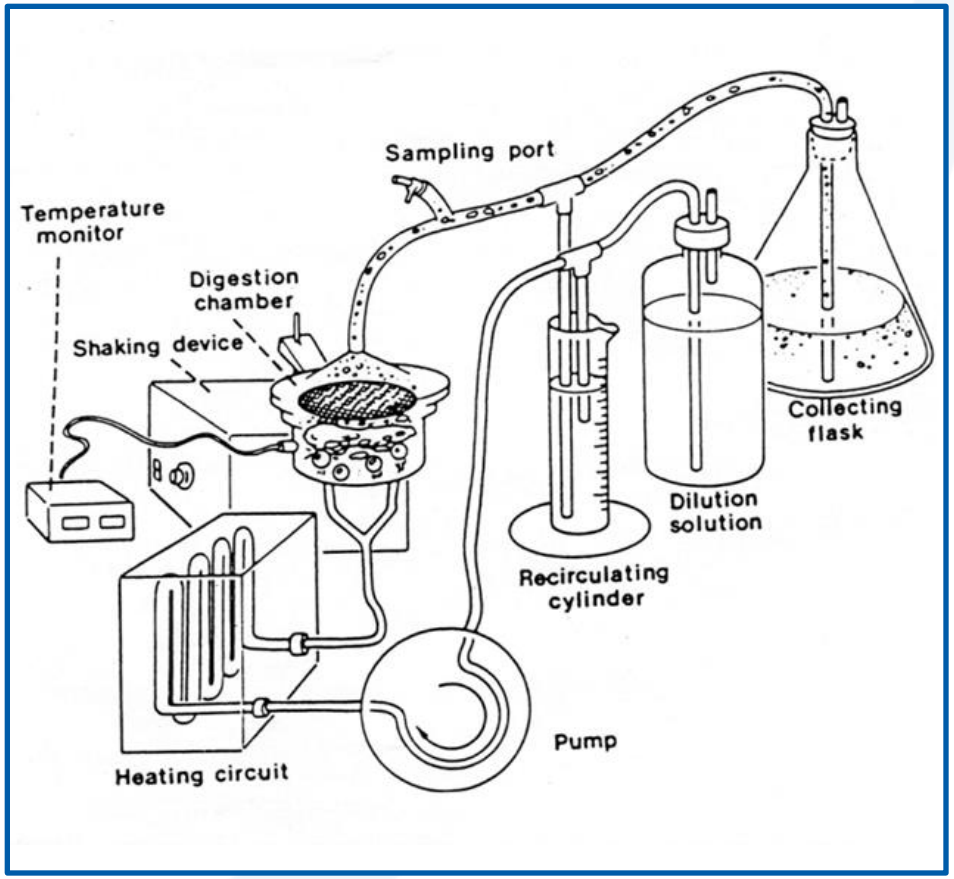
Digestion Circuit

Reprinted from DIABETES, VOL. 37, NO. 4, APRIL 1988

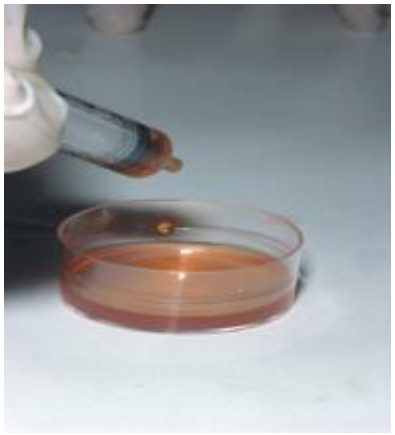
Automated Method for Isolation of Human Pancreatic Islets

CAMILLO RICORDI, PAUL E. LACY, EDWARD H. FINKE, BARBARA J. OLACK, AND DAVID W. SCHARP

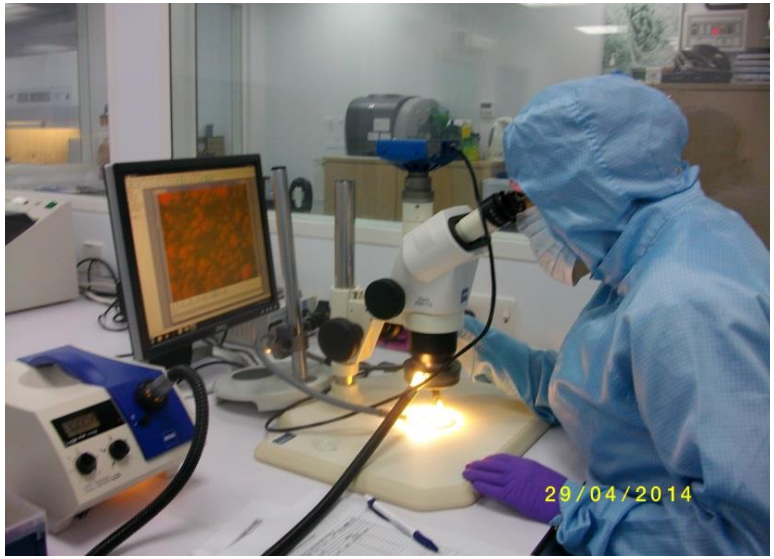




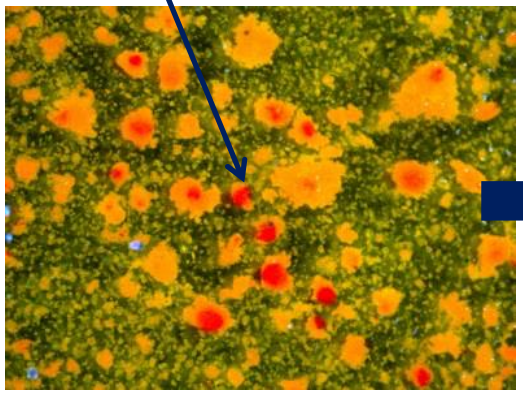
Monitoring digestion

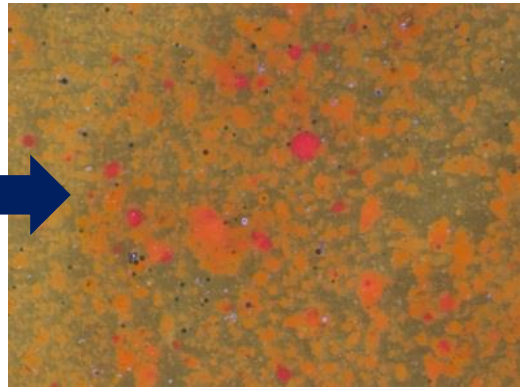


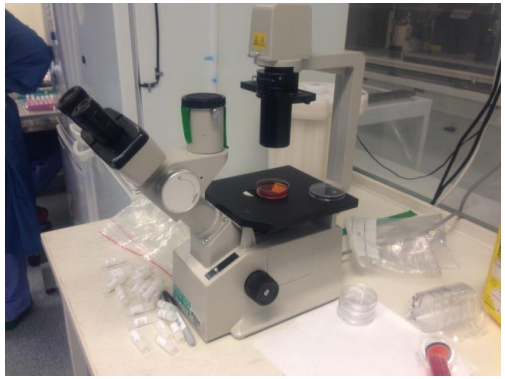
Samples taken to monitor diges, on



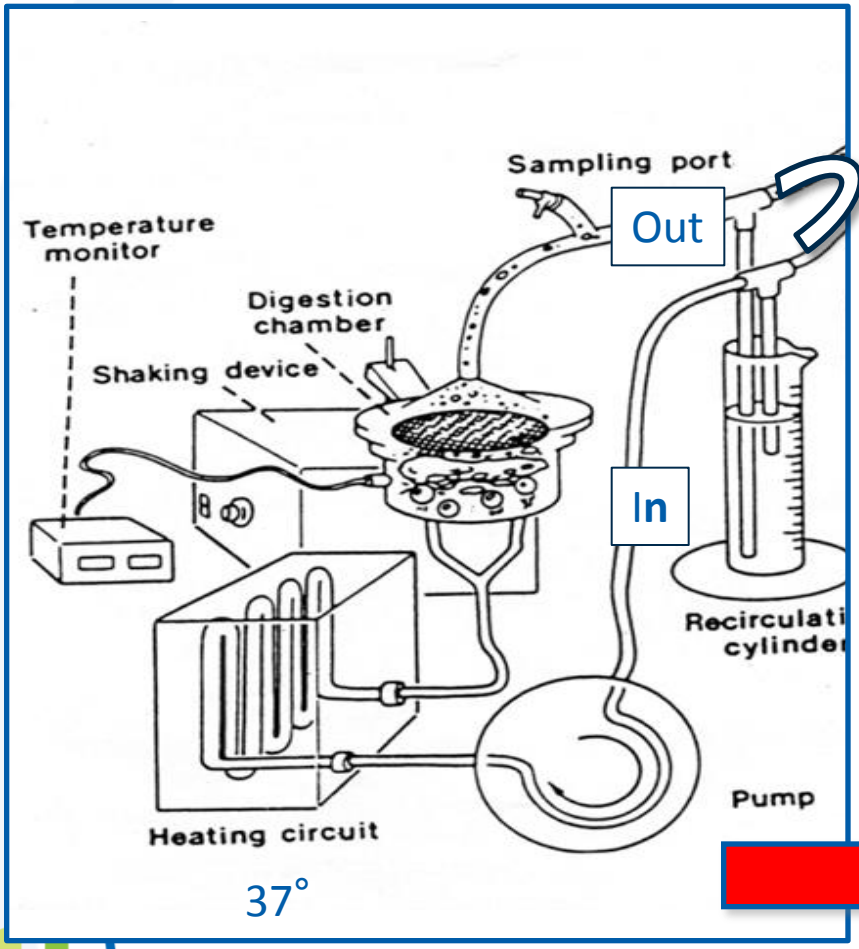
Islets stained red with dithizone

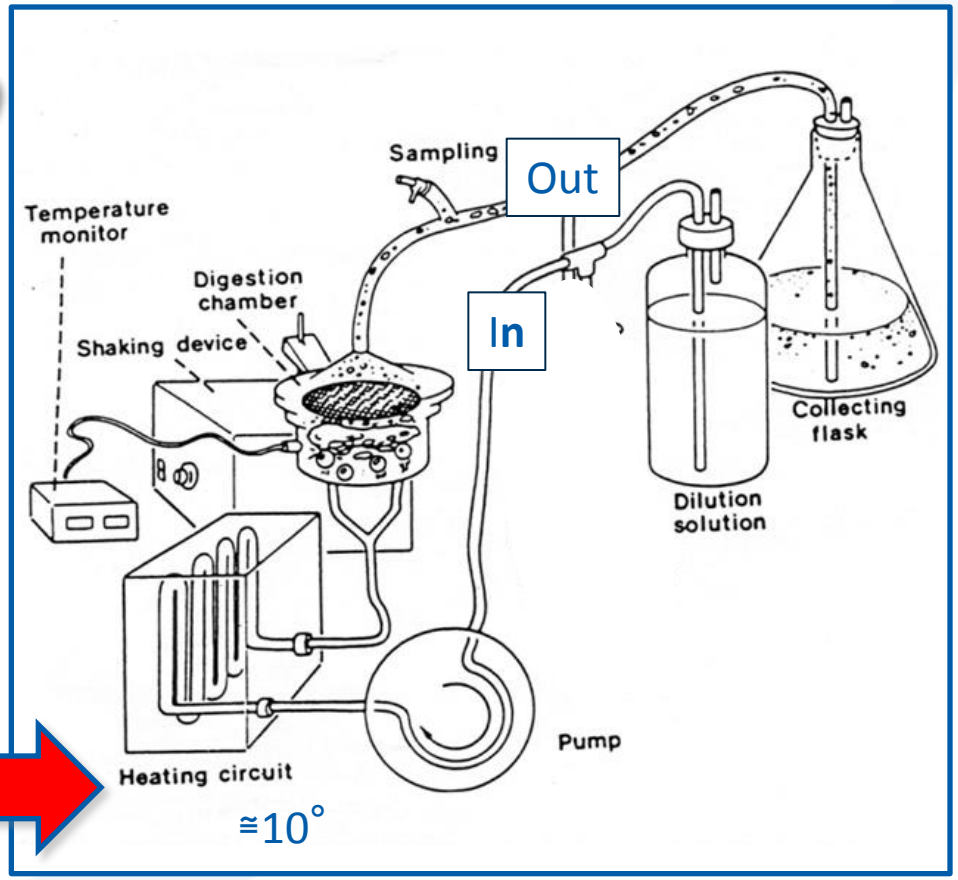






Switch

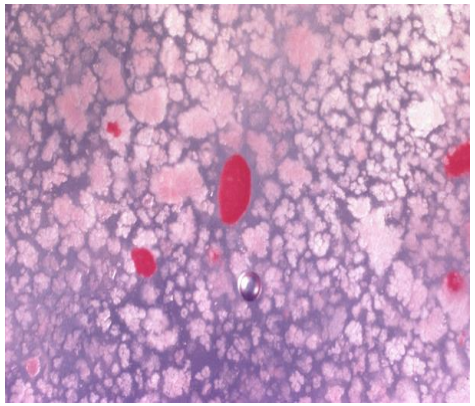

Sampling port
Out
Temperature monitor
Digestion chamber
Shaking device
In
Recirculati cylinder
Pump
Heating circuit
37°


Sampling
Out
Temperature monitor
Digestion chamber
Shaking device
In
Collecting flask
Dilution solution
Pump
Heating circuit
≅10°

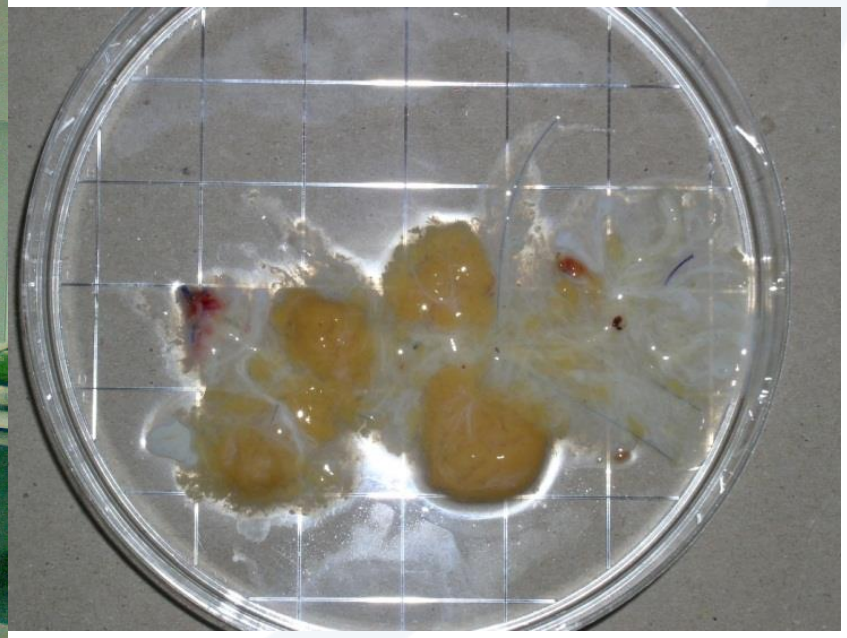
When to switch?

Dilution and collection (phase 2)

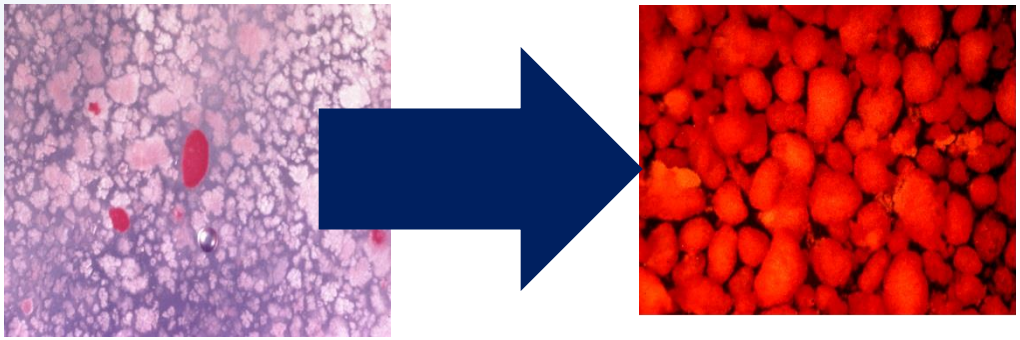
- >50% of the observed islets are completely cleaved, or
- >20% of the islets are fragmented, or
- Tissue volume in chamber has visibly reduced
- >40 islets seen (free & trapped), with acinar <300µm
- >30 min has elapsed

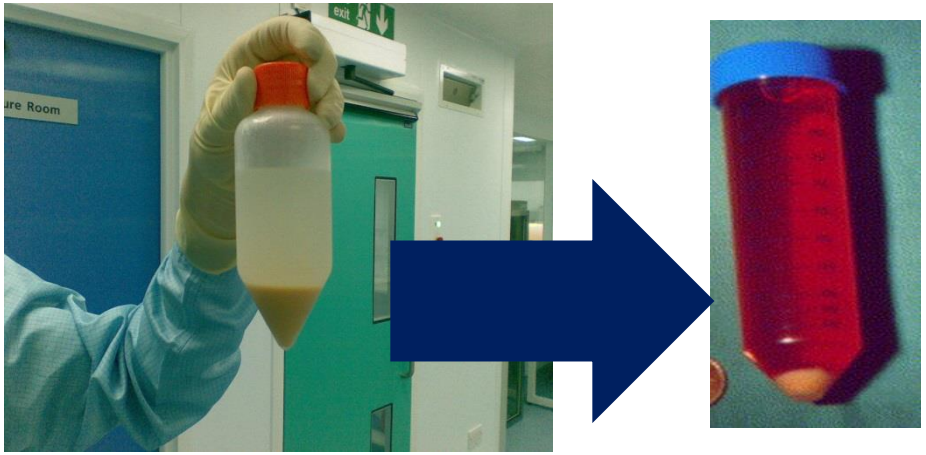


Optimal Digestion



Density-Gradient Purification





20 – 50 ml

< 5 ml

Density-Gradient Purification

Pre-Transplant Culture

Relevance

LOGISTIC FACTORS

Transplant patients from remote sites

Transport islets to remote sites

SAFETY CONCERNS

Predictive pre-transplant testing

Reduction of soluble factors infused IP

Decrease of total volume infused

INFLAMMATORY / IMMUNOGIC FACTORS

Repair mechanisms and islet metabolic recovery before ITX

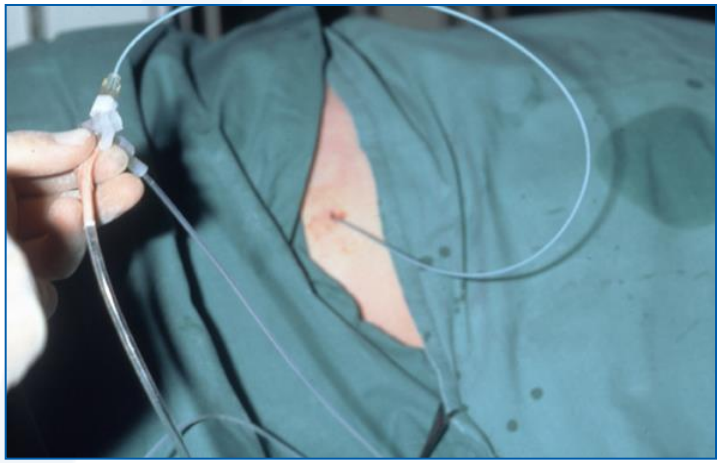
Pre-transplant immunomodulation/IS

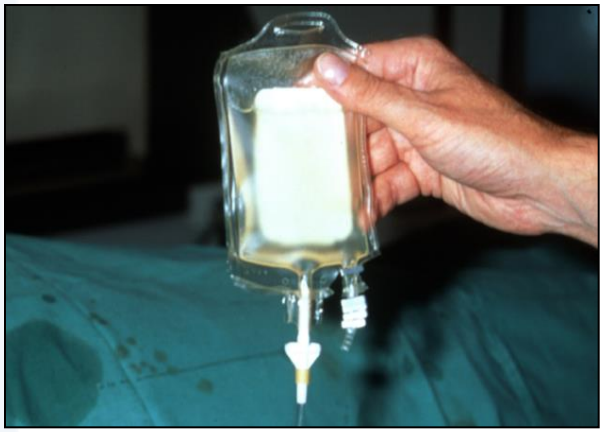
Product release criteria for clinical islet preparation

TYPE OF TEST	PRODUCT TEST	SPECIFICATION	TYPE OF SAMPLE
Safety	Endotoxin	< 5 EU/kg	Supernatant of islet suspension in transplant media
	Gram stain	No organisms detected within limits of assay	
Identity	Islet count (IE/kg)	5,000–20,000 (1st transplant) 3,000–20,000 (Re-transplants)	Islets in transplant media
	Purity	≥ 30%	
Viability	Dye exclusion (FDA/PI)	≥ 70%	Islets after overnight culture and in transplant media
Potency	Glucose stimulated insulin release (ELISA)	Stimulation Index >1	Islets after overnight culture

Curr Opin Organ Transplant. Author manuscript; available in PMC 2010 December 1.

Islet Transplant





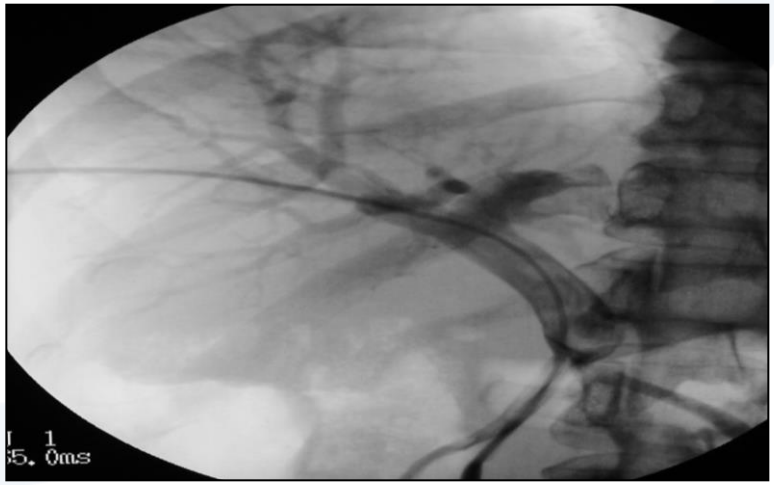
Percutaneous transhepatic approach via portal vein

(or lparoscopic / mini-lap.)

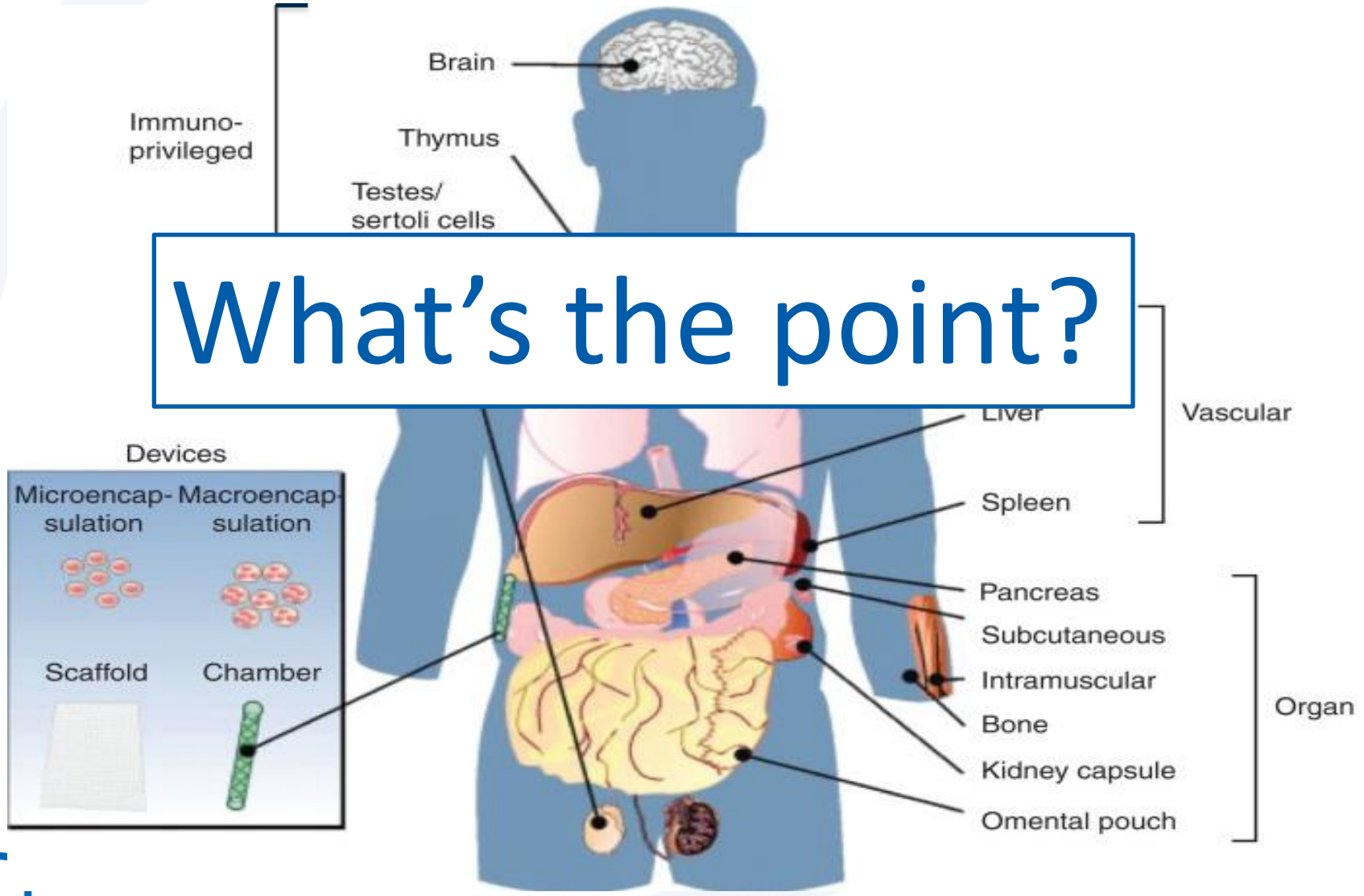
Antibiotic and Heparin cover

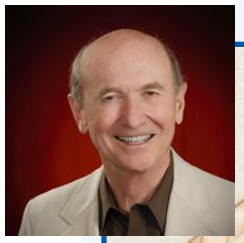
Infuse over 15-20 minutes

Monitor portal pressure throughout



Alternative islet implantation sites





R. Paul Robertson MD

Spontaneous hypoglycemia after islet transplantation: the case for using non-hepatic sites

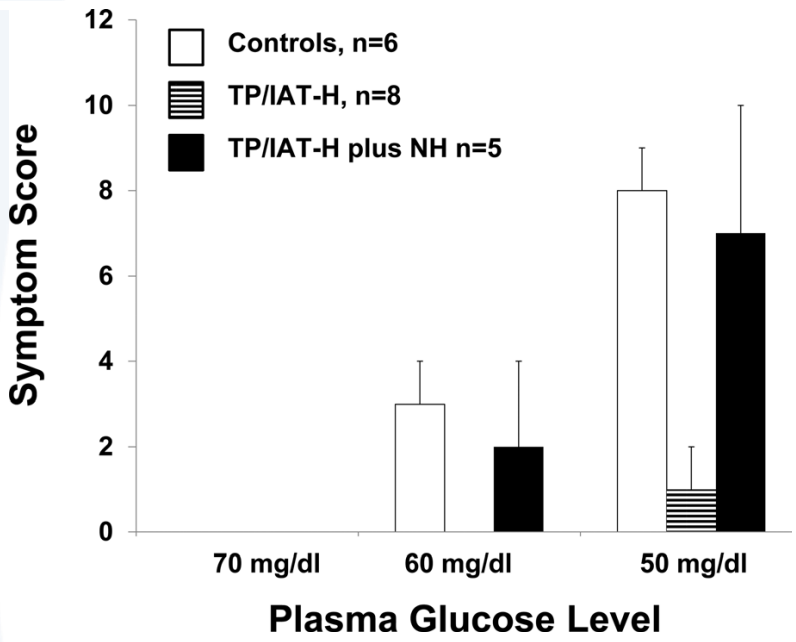
N ENGL J MED 350;7 WWW.NEJM.ORG FEBRUARY 12, 2004

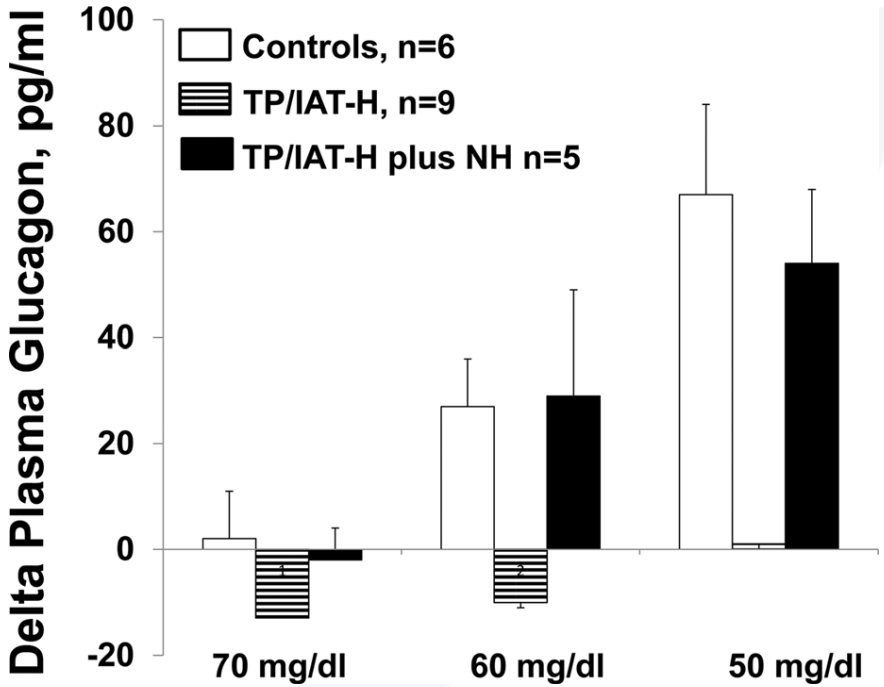
American Journal of Transplantation 2014; 14: 1880–1886
Wiley Periodicals Inc.

doi: 10.1111/ajt.12776

R. Paul Robertson MD

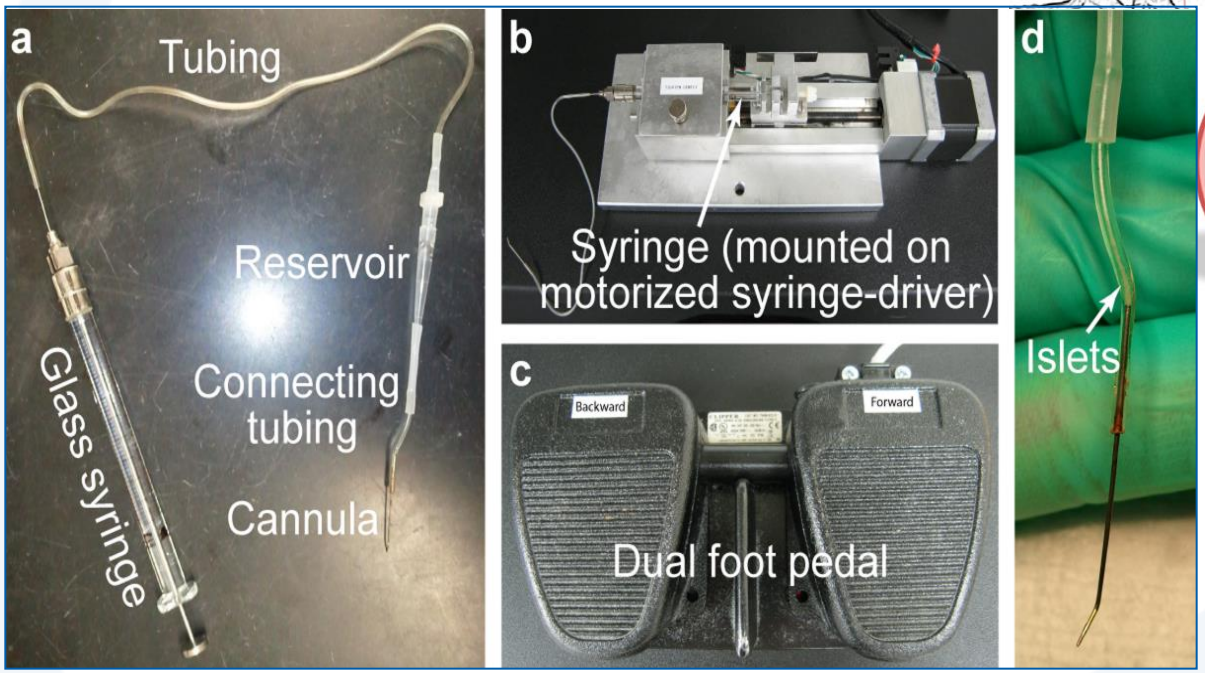
Defective Glucagon Secretion During Hypoglycemia After Intrahepatic But Not Nonhepatic Islet Autotransplantation

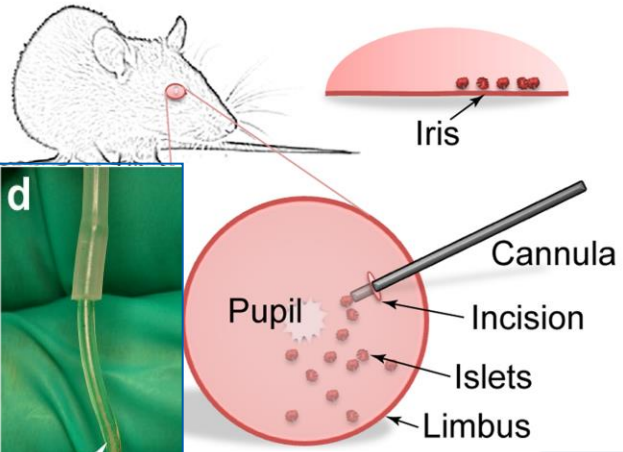




Transplantation into the Anterior Chamber of the Eye

Reverse diabetic symptoms
Monitoring of islet morphology and vascularisation
Mechanistic evaluation of islet autoimmunity

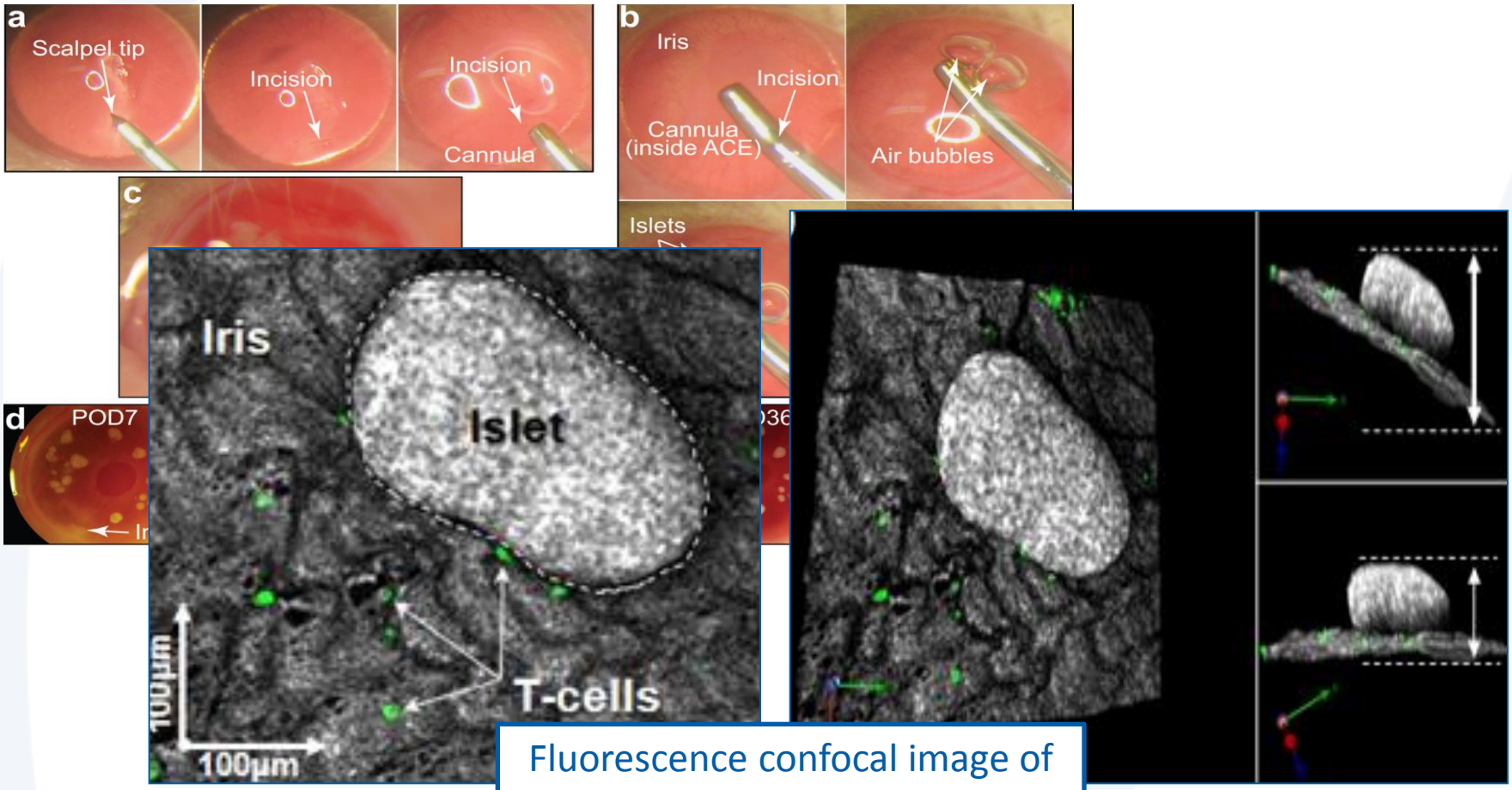




Nature Protocols **3**,2008

Per-Olof Berggren

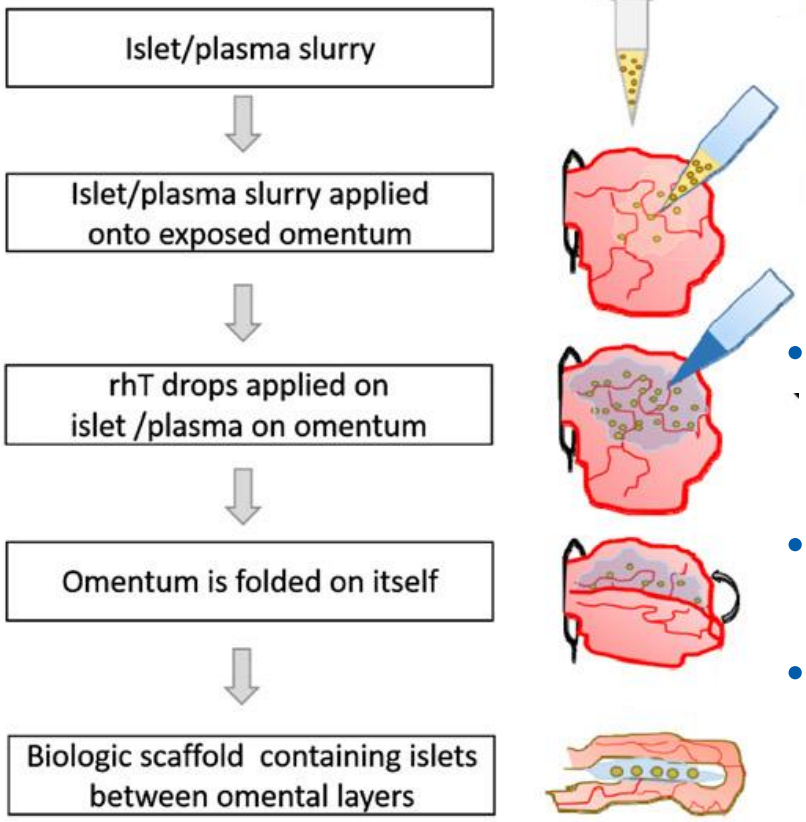
Transplantation into the Anterior Chamber of the Eye



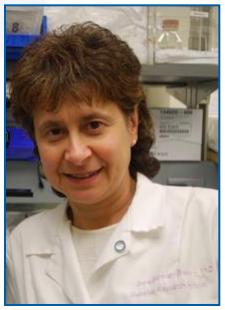
Fluorescence confocal image of a pancreatic islet i***n vivo***

Journal of Visualized Experiments March 2013

Intraomental Islet Transplantation Within a Biologic Resorbable Scaffold



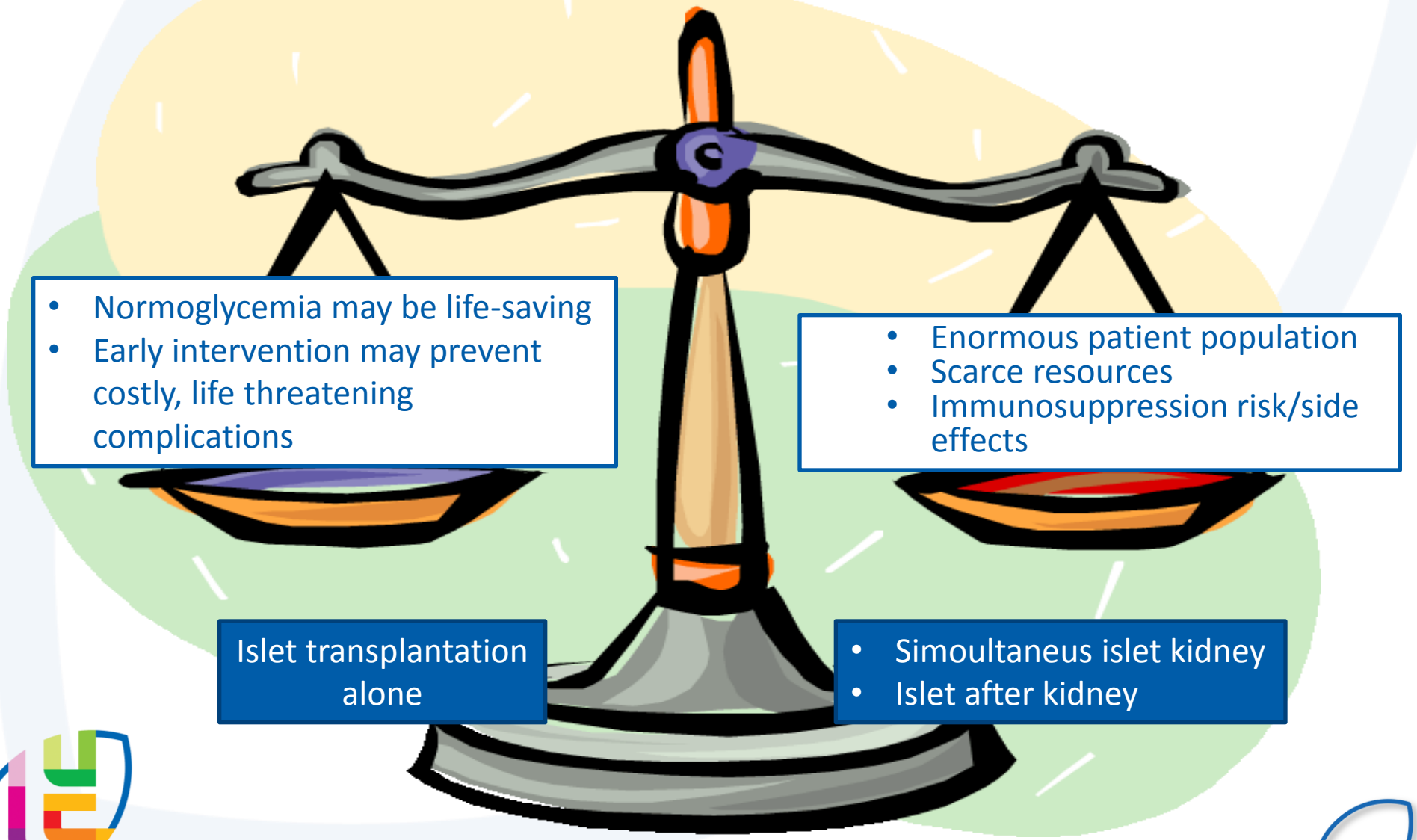
- Comparable function of intrahepatic and intraomental islets
- lower levels of serum biomarkers of islet distress
- low-purity displayed function equivalent to that of pure preparations



Dora M. Berman

Diabetes 2016;65:1350–1361 | DOI: 10.2337/db15-1525

Indication of islets transplantation



- Normoglycemia may be life-saving
- Early intervention may prevent costly, life threatening complications

- Enormous patient population
- Scarce resources
- Immunosuppression risk/side effects

Islet transplantation alone

- Simoultaneus islet kidney
- Islet after kidney

Inclusion Criteria for Allogeneic Islet Transplantation in T1DM

- Clinical history compatible with type 1 diabetes with onset of disease at <40 years of age, insulin dependence for at least 5 years at study entry, and a sum of age and insulin dependent diabetes duration of at least 28
- Absent stimulated C-peptide (<0.3 ng/ml) 60 and 90 minutes post-mixed-meal tolerance test
- Involvement of intensive diabetes management
- Three clinical evaluations during the past 12 months prior to study enrollment
- At least one episode of severe hypoglycemia in the past 12 months
- Reduced awareness of hypoglycemia
- Mentally stable and able to comply with study procedures

Clinical Islet Transplant Consortium
www .citisletstudy.org as listed at http://clinicaltrials.gov/ct2/show/NCT00434811

Exclusion Criteria for Allogeneic Islet Transplantation in T1DM

. Body mass index (BMI) >30 kg/m2 or weight ≤50 kg
· Insulin requirement of >1.0 IU/kg/day or <15 U/day
• HbA1c >10%
· Untreated proliferative diabetic retinopathy
· Systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg
· Measured glomerular filtration rate using iohexol of <80 ml/min/1.73mm2.
· Presence or history of macroalbuminuria (>300 mg/g creatinine)
· Presence or history of panel-reactive anti-HLA antibody levels greater than background by flow cytometry.
· Pregnant, breastfeeding, or unwilling to use effective contraception throughout the study and 4 months after study completion
· Presence or history of active infection, including hepatitis B, hepatitis C, HIV, or tuberculosis.
· Negative for Epstein-Barr virus by IgG determination
· Invasive aspergillus, histoplasmosis, or coccidioidomycosis infection in the past year
· History of malignancy except for completely resected squamous or basal cell carcinoma of the skin
· Known active alcohol or substance abuse
· Baseline Hgb below the lower limits of normal, lymphopenia, neutropenia, or thrombocytopenia
· History of Factor V deficiency
· Any coagulopathy or medical condition requiring long-term anticoagulant therapy after transplantation or individuals with an INR greater than 1.5
· Severe coexisting cardiac disease, characterized by any one of the following conditions:
o Heart attack within the last 6 months
o Evidence of ischemia on functional heart exam within the year prior to study entry
o Left ventricular ejection fraction <30%
· Persistent elevation of liver function tests at the time of study entry
· Symptomatic cholecystolithiasis
· Acute or chronic pancreatitis
· Symptomatic peptic ulcer disease
· Severe unremitting diarrhea, vomiting, or other gastrointestinal disorders that could interfere with the ability to absorb oral medications
· Hyperlipidemia despite medical therapy, defined as fasting LDL cholesterol >130 mg/dl (treated or untreated) and/or fasting triglycerides >200 mg/dl
· Currently receiving treatment for a medical condition that requires chronic use of systemic steroids except for the use of 5 mg or less of prednisone daily, or an equivalent dose of hydrocortisone, for physiological replacement only
· Treatment with any antidiabetic medication other than insulin within the past 4 weeks
· Use of any study medications within the past 4 weeks
· Received a live attenuated vaccine(s) within the past 2 months
· Any medical condition that, in the opinion of the investigator, might interfere with safe participation in the trial
o Treatment with any immunosuppressive regimen at the time of enrollment.
o A previous islet transplant.
· A previous pancreas transplant, unless the graft failed within the first week due to thrombosis, followed by pancreatectomy and the transplant occurred more than 6 months prior to enrollment.

Indication of islets transplantation

Condition	Procedure	Type of Transplant
Diabetes Mellitus		
Type 1	ITA, SIK, IAK	Allogeneic
Type 2	ITA, SIK, IAK	Allogeneic
Surgery-Induced Diabetes (Iatrogenic)		
Chronic pancreatitis	ITA	**Autologous**/Allogeneic
Trauma	ITA	**Autologous**/Allogeneic
Multi-visceral transplantation	Different combinations: Liver-Islet Transplantation, Bowel-Liver-Islet Transplantation, etc.	Allogeneic
Cystic Fibrosis	ITA Lung-Islet Transplantation	**Autologous**/Allogeneic Allogeneic
Benign enucleable tumors	ITA	Autologous
Borderline/malignant pancreatic neoplasms	ITA	**Autologous**/Allogeneic
Grade C pancreatic fistula requiring completion pancreatectomy	ITA	**Autologous**/Allogeneic

- The Challenge
- The Hypothesis
- Human Islet Isolation
- Prevention of Rejection/Autoimmunity
- Islet transplantation Safety
- The Translational Research Approach
    - Proof of Function in Animal Models
    - Proof of Function in Humans
- Possible Reasons for Islet Graft Failure
- Current challenges faced for islet transplantation

Source:

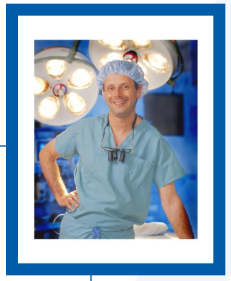
Post-transplant treatment

Induction immunosuppressive therapy

Edmonton Protocol

Inhibition of IL-2-mediated T-cell signal activation:

- **Daclizumab**
- **Basiliximab**



The New England Journal of Medicine

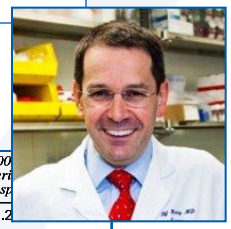
VOLUME 343 JULY 27, 2000 NUMBER 4

ISLET TRANSPLANTATION IN SEVEN PATIENTS WITH TYPE 1 DIABETES MELLITUS USING A GLUCOCORTICOID-FREE IMMUNOSUPPRESSIVE REGIMEN

A.M. JAMES SHAPIRO, M.B., B.S., JONATHAN R.T. LAKEY, PH.D., EDMOND A. RYAN, M.D., GREGORY S. KORBUTT, PH.D., ELLEN TOTH, M.D., GARTH L. WARNOCK, M.D., NORMAN M. KNETEMAN, M.D., AND RAY V. RAJOTTE, PH.D.

University of Minnesota Protocol

- FcR nonbinding anti-CD3 antibody teplizumab alone
- T cell depleting antibody (TCDAb) **ATG** and TNF-a-i with etanercept, with or without daclizumab



American Journal of Transplantation 2008; 8: 2463–2470
Wiley Periodicals Inc.

Brief Communication

doi: 10.1111/j.1600-6143.2

Prolonged Insulin Independence After Islet Allotransplants in Recipients with Type 1 Diabetes

B. J. Hering[b]

Revised UM Protocol

monoclonal antibody against CD52

Alemtuzumab

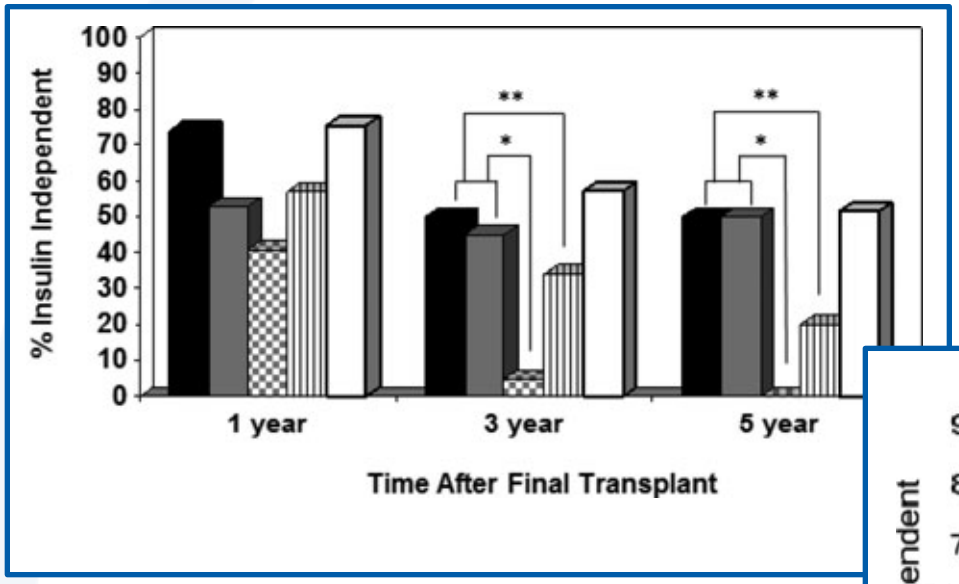
American Journal of Transplantation 2016; 16: 246–253
Wiley Periodicals Inc.

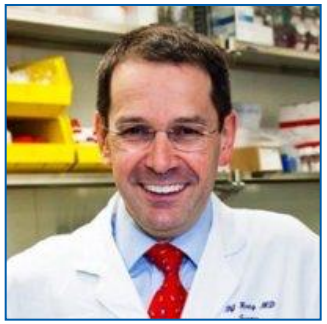
doi: 10.1111/ajt.13425

E. J. P. de Koning[1,2,*]

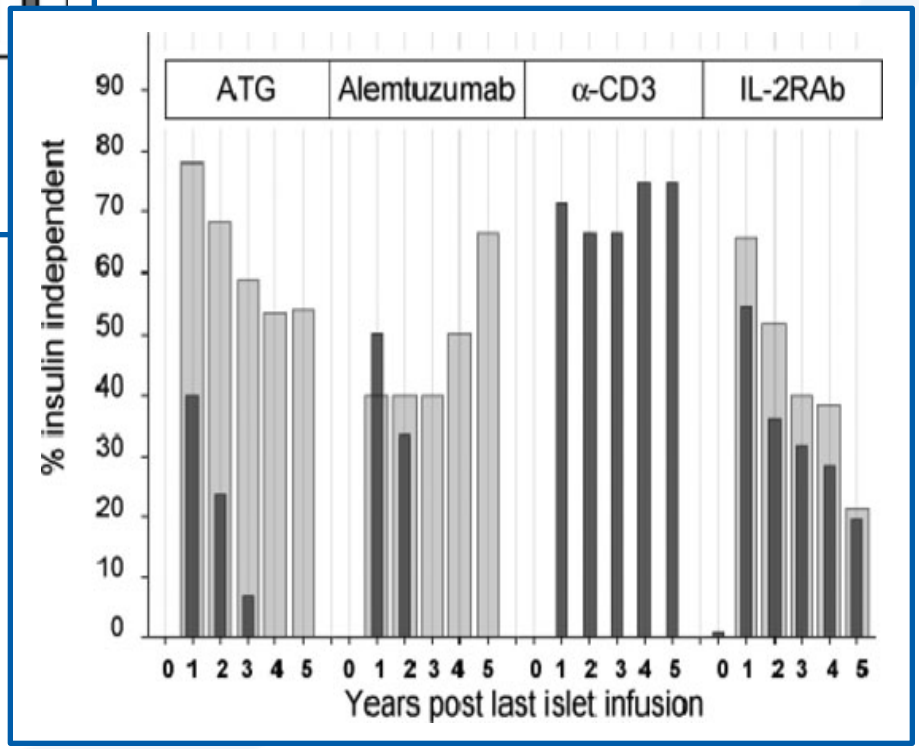
Glycemic Stability Through Islet-After-Kidney Transplantation Using an Alemtuzumab-Based Induction Regimen and Long-Term Triple-Maintenance Immunosuppression

Adjunctive peritransplant anti-inflammatory management





American Journal of Transplantation 2012; 12: 1576–1583
Wiley Periodicals Inc.



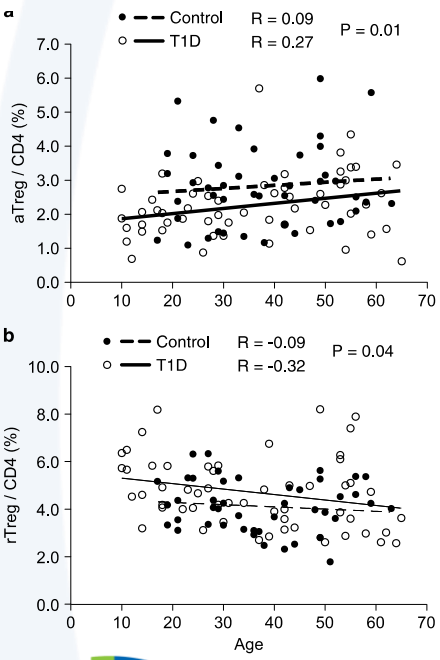
Etanercept

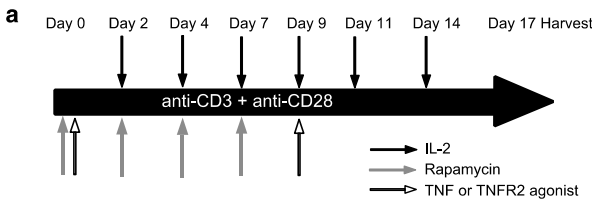
Insulin independence by induction agent, in the presence of **TNF-a inhibitor therapy** (wide bars) or absence of TNF-a inhibitor (narrow bars)

Adjunctive peritransplant anti-inflammatory management

Adalimumab

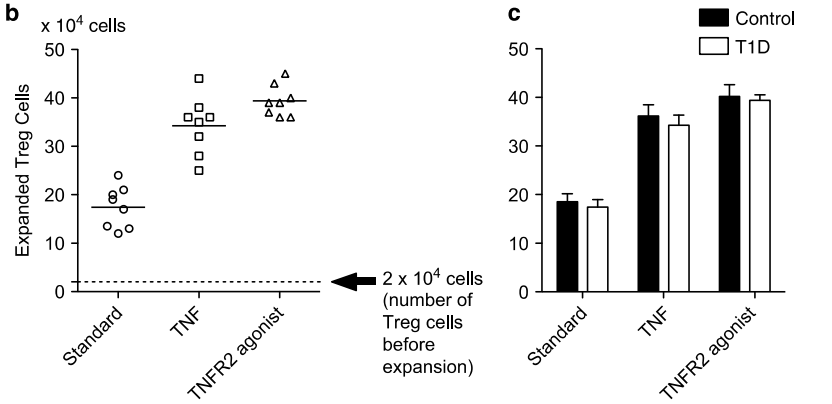
TNFa inhibitor
Treg stimulator



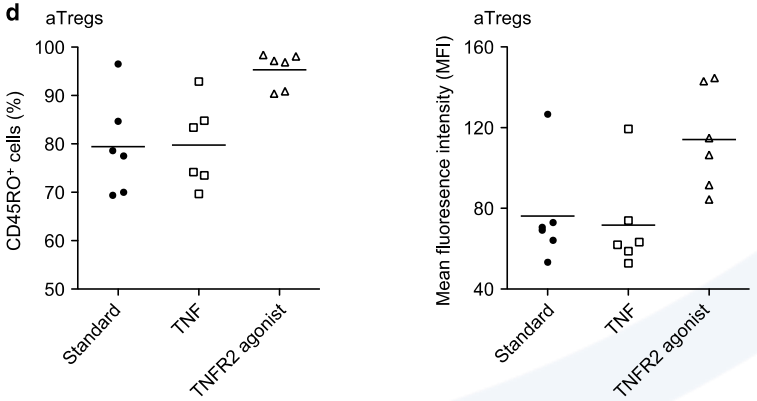


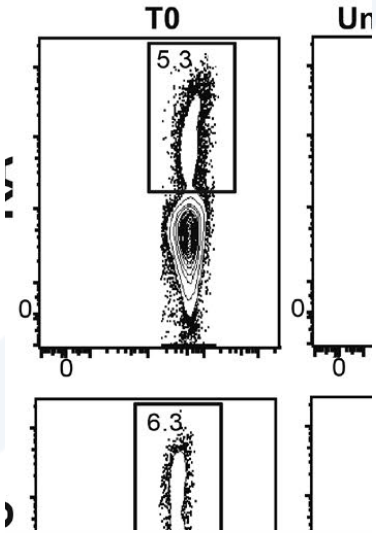
Treg activation defect in type 1 diabetes: correction with TNFR2 agonism

Yoshiaki Okubo[1], Heather Torrey[1], John Butterworth[1], Hui Zheng[2] and Denise L Faustman[1]



(Control N = 10, T1D N = 8)
Not significant between Control and T1D





Anakinra

(IL1 inhibitor) Potentiates the Protective Effects of Etanercept in Transplantation of Marginal Mass Human Islets in Immunodeficient Mice

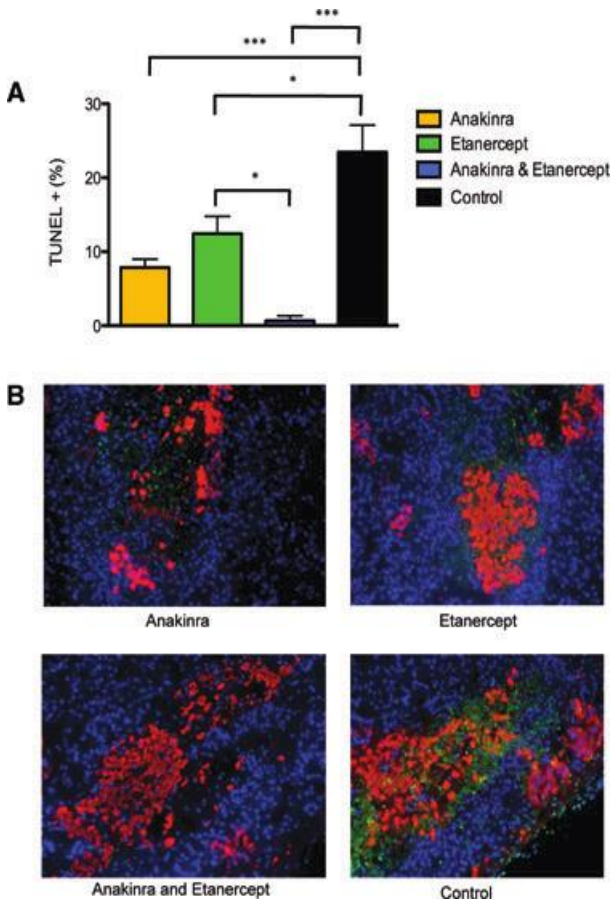


Figure 2: Apoptotic cells in human islet grafts. Twenty-four hours after transplantation, grafts were recovered from N = 3 mice per group and assessed for apoptotic cells within the islet graft using TUNEL staining. Representative figures are displayed in B. *p < 0.05, ***p < 0.001.

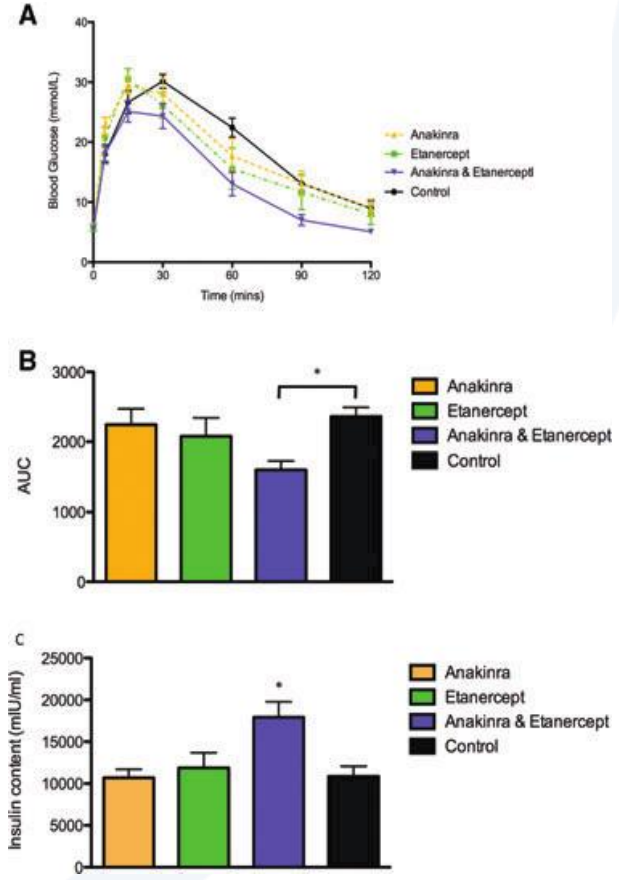


Figure 3: Glucose tolerance and graft survival of human islets. Immunodeficient mice received a marginal mass human islet graft and treated in one of four groups. After 1 month, glucose tolerance was assessed using an IPGTT (A). Area under the curve analysis is displayed in (B). Forty-eight hours after the IPGTT, grafts were recovered and analyzed for insulin content (C). *p < 0.05.

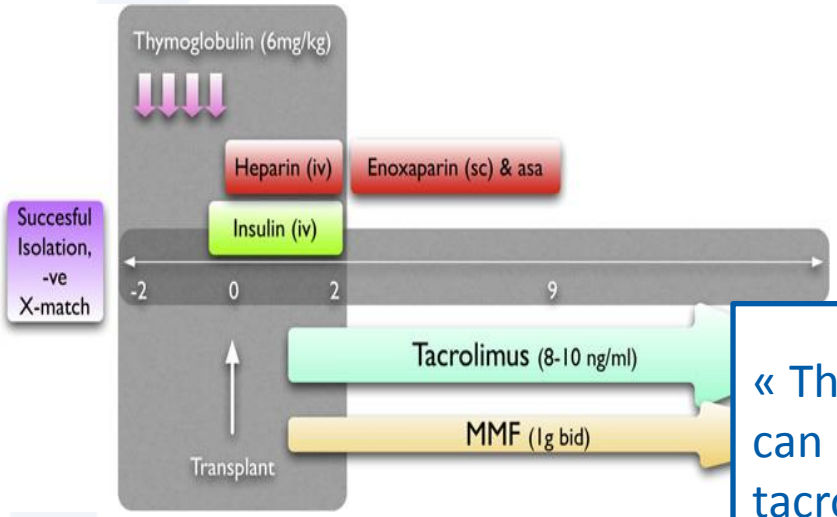
Maintenance immunosuppressive therapy

Tacrolimus

Highly effective inhibitor of both allorejection and autoimmune recurrence

General Side effects:
- Nephrotoxicity
- Tremor
- Headache…

Specific Side effects:
- Inhibits insulin secretion
- Diabetogenic



Lehman ….. Alejandro. *Transplantation* 68:1532-1541, 1999

« The fact that 5-year insulin-independence rates >50% can be achieved in patients maintained on high-dose tacrolimus indicates that the tacrolimus- related islet toxicity might be overcome **when sufficient islets are infused**, and that excellent long-term rejection and autoimmune recurrence-free outcomes are possible » *J. Shapiro*

Maintenance immunosuppressive therapy

Sirolimus

mTOR inhibition leads to arrest of the cell cycle at the G1 to S phase, and thus to blockade of growth-factor-driven proliferation not only of activated T cells, which is the basis of its immunosuppressive action, but also of other hematopoietic and nonhematopoietic cells….

…And also b-cells

Summary of studies investigating the effects of rapamycin on pancreatic β-cell proliferation

Authors (ref.)	Experimental model	Rapamycin dose	Treatment duration	Significant findings
Ex vivo				
Bussiere et al. (88)	Human pancreatic ductal cells	20 ng/mL	6 days	↓ Proliferation
Bussiere et al. (88)	Neonatal porcine islets	20 ng/mL	6 days	↓ Proliferation
Niclauss et al. (46)	Rat islets	0.1–10 ng/mL	1–5 days	↓ Proliferation
Sun et al. (96)	Porcine neonatal pancreas cell clusters	10–30 ng/mL	8 days	↓ Proliferation
In vivo				
Balcazar et al. (45)	RIP-rtTA/tetOAkt1 transgenic mi			↑ Proliferation without rapamycin,
Fraenkel et al. (65)	*P.obe*			
Niclauss et al. (46)	Muri			
Rachdi et al. (40)	βTsc			
Zahr et al. (97)	Muri			

Summary of studies investigating the effects of rapamycin on pancreatic β-cell survival

Authors (ref.)	Experimental model	Rapamycin dose	Treatment duration	Significant findings
In vitro				
Barlow et al. (36)	MIN6 cell line	200 nmol/L	24–72 h	↓ Viability, ↑ apoptosis
Bell et al. (87)	MIN6 cell line	10–100 nmol/L	1–4 days	↑ Apoptosis
Ex vivo				
Barlow et al. (36)	Rat islets	200 nmol/L	48 h	↑ Apoptosis
Bell et al. (87)	Human islets	1–10 nmol/L	4 days	↓ Viability (but not significant)
Bell et al. (87)	Human islets	100 nmol/L	4 days	↓ Viability
Bell et al. (87)	Rat islets	100 nmol/L	4 days	↓ Viability
Bussiere et al. (88)	Neonatal porcine islets	10 ng/mL	6 days	↑ Apoptosis
Johnson et al. (61)	Human islets	10–30 μg/L	24 h	↑ Cleaved caspase-3
Marcelli-Tourvieille et al. (91)	Human islets	8–32 ng/mL	120 h	↓ Apoptosis
In vivo				
Fraenkel et al. (65)	*P.obesus* rats	0.2 mg/kg/day	16 days	⇔ Apoptosis
Fraenkel et al. (65)	*P.obesus* diabetic rats	0.2 mg/kg/day	16 days	↑ Apoptosis

The New England
Journal of Medicine

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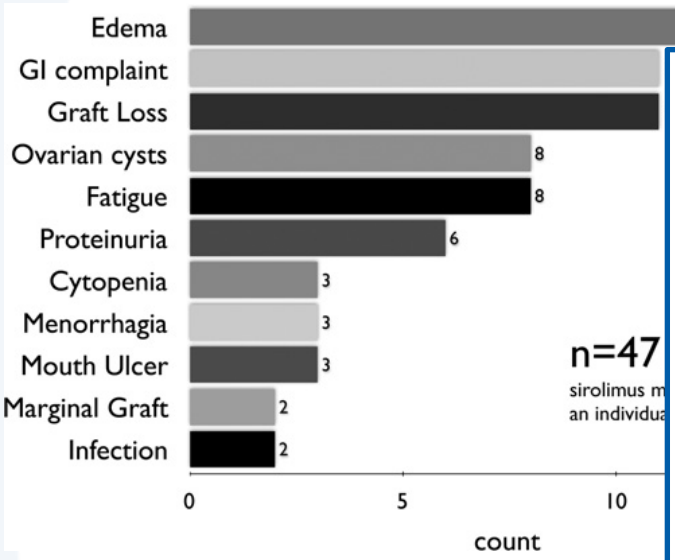
VOLUME 343 JULY 27, 2000 NUMBER 4

ISLET TRANSPLANTATION IN SEVEN PATIENTS WITH TYPE 1 DIABETES MELLITUS USING A GLUCOCORTICOID-FREE IMMUNOSUPPRESSIVE REGIMEN

A.M. JAMES SHAPIRO, M.B., B.S., JONATHAN R.T. LAKEY, PH.D., EDMOND A. RYAN, M.D., GREGORY S. KORBUTT, PH.D., ELLEN TOTH, M.D., GARTH L. WARNOCK, M.D., NORMAN M. KNETEMAN, M[illegible] AND RAY V. RAJOTTE, PH.D.

- ~~S[illegible]~~
- Tacrolimus
- Daclizumab
- No steroids



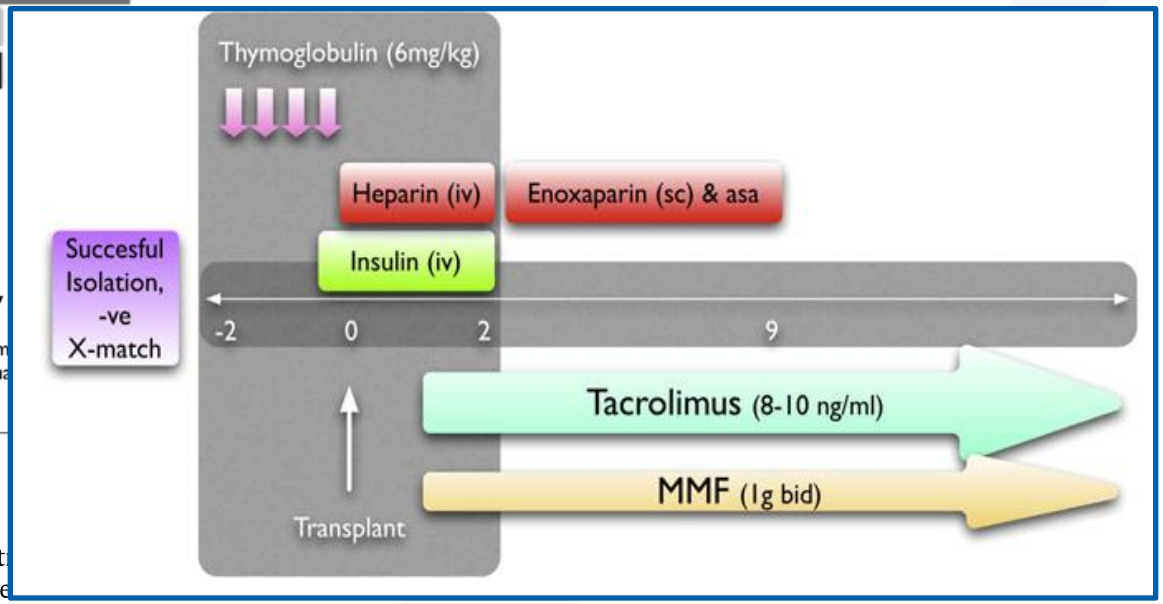


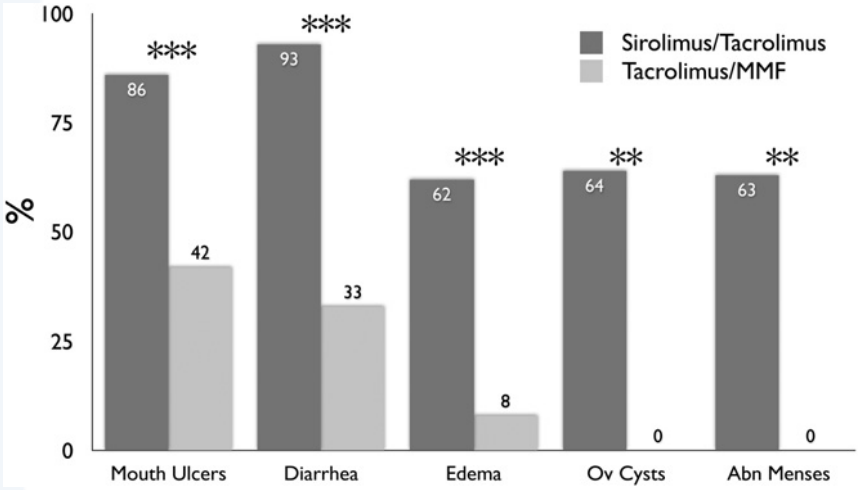
Figure 1. Reasons for sirolimus discontinuation in 47 islet t
some individuals sirolimus was withdrawn for more than 1 re

P.A. Senior et al. / Can J Diabetes 36 (2012) 32–37

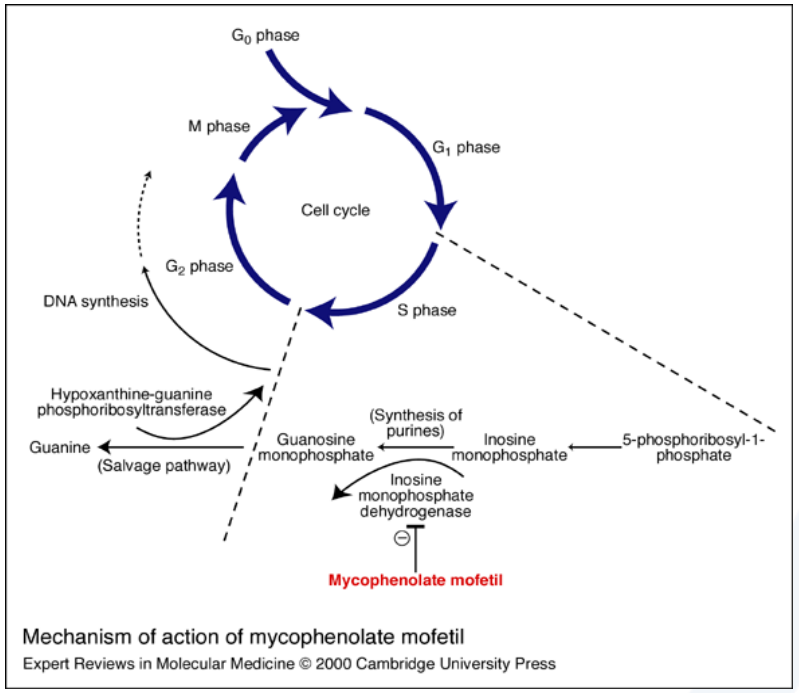
Maintenance immunosuppressive therapy

MMF

Blocking the de novo formation of GMP
Deprivation of proliferation Tand B-cell of nucleic acid .



P.A. Senior et al. / Can J Diabetes 36 (2012) 32–37



Mechanism of action of mycophenolate mofetil
Expert Reviews in Molecular Medicine © 2000 Cambridge University Press

Transplantation Publish Ahead of Print
DOI: 10.1097/TP.0000000000001543

Age and early graft function relate with risk-benefit ratio of allogenic islet transplantation under Anti-thymocyte globulin – Mycophenolate mofetil – Tacrolimus immune suppression

Da Hae Lee[1,2], Bart Keymeulen[2], Robert Hilbrands , Zhidong Ling , Ursule Van de Velde , Daniel Jacobs-Tulleneers-Thevissen[2], Geert Maleux[3], Bruno Lapauw[4], Laurent Crenier[5], Chri[illegible]phe [illegible]Block[6], Chantal Mathieu[1], Daniel Pipeleers[2], Pieter Gillard[1,2]

Clinical management

Antibiotic and Antiviral Prophylaxis.

Pneumocystis Carinii	Epstein-Barr virus	Cytomegalovirus

Thromboembolism Prophylaxis.

Early period after transplant

- added to the transplant medium
- low molecular weight heparin injections

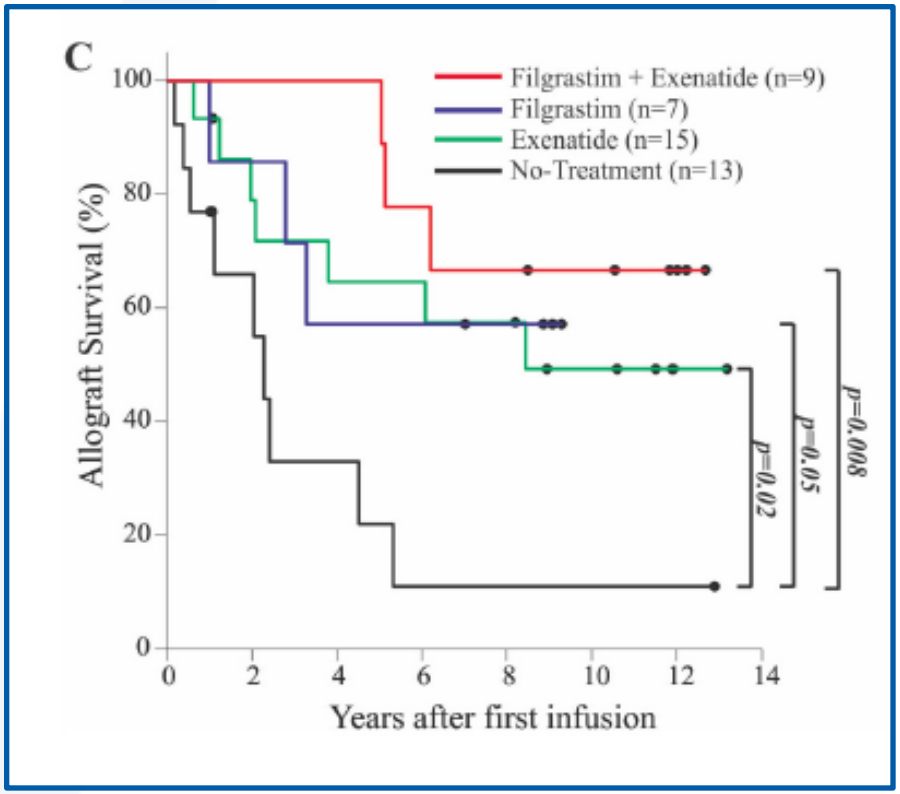
Aimed at enhancing islet engraftment in the hepatic portal system while reducing the risk of portal thrombosis.

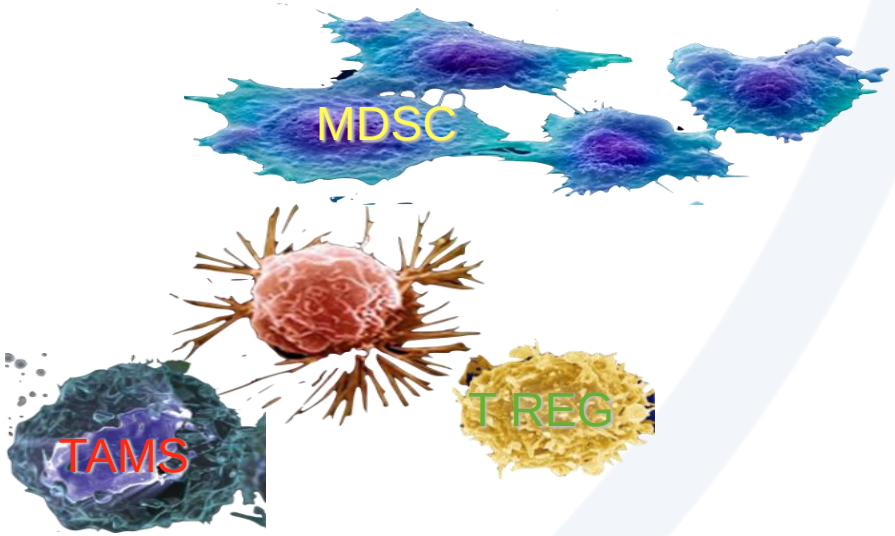
Peri-transplant Insulin Managment.

Intense after transplant because:

- Avoid excessive islet workload
- Prevent hypogycemic episodes

Treatment with G-CSF (Filgrastim) and GLP-1 receptor agonist Exenatide is associated with increased Long-Term Survival of Allogeneic Pancreatic Islet Grafts





- The Challenge
- The Hypothesis
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- Prevention of Rejection/Autoimmunity
- Islet transplantation Safety
- The Translational Research Approach
    - Proof of Function in Animal Models
    - Proof of Function in Humans
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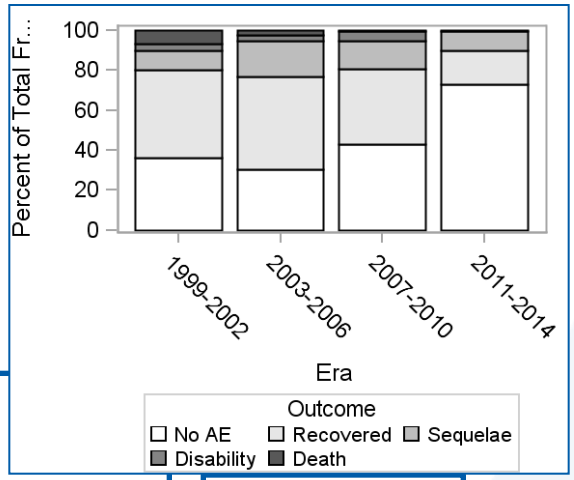
Source:

Is islet transplantation safe?

Procedure-related

Bleeding ~10-15%
Thrombosis~5%
Transaminitis~50%
Abdominal pain~50%



Immunosuppression-related

Hematological
- Anemia
- Leucopenia
- Neutropenia

Gastrointestinal
- Oral ulcers (Sirolimus)
- Diarrhea (Mycophenolic acid)
- CMV colitis

Cutaneous
- Infections
- Cancer

Genitourinary
- Urinary infections
- Ovarian cysts
- Dysmenorrhea
- Nephropathy
- Proteinuria

Metabolic
- Dyslipidemia

Neurological
- Neurotoxicity (Tacrolimus)

Respiratory tract
- Upper respiratory infections
- Interstitial pneumonitis (Sirolimus)

Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2016-.

Islet Transplantation
Piemonti L, Pileggi A

- The Challenge
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    - Proof of Function in Humans
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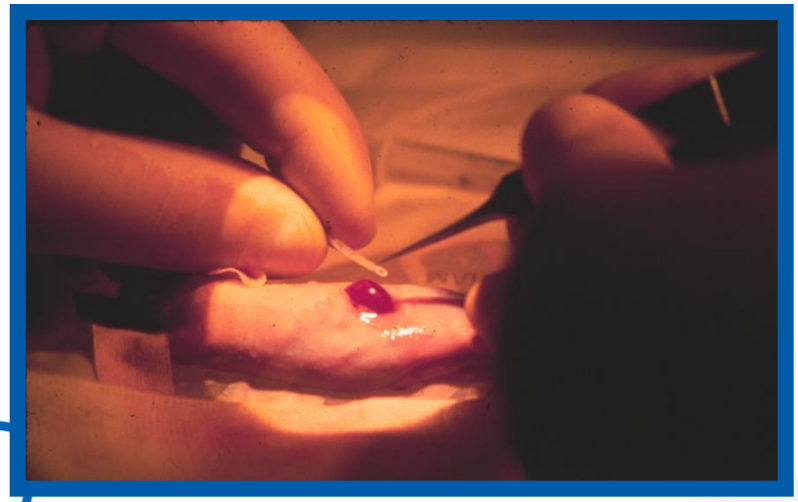
Source:

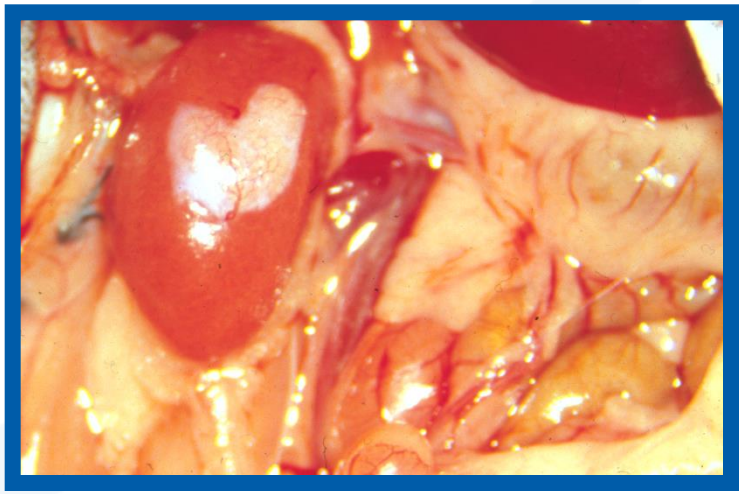
Reversal of Diabetes following Transplantation of Human islets in Mice

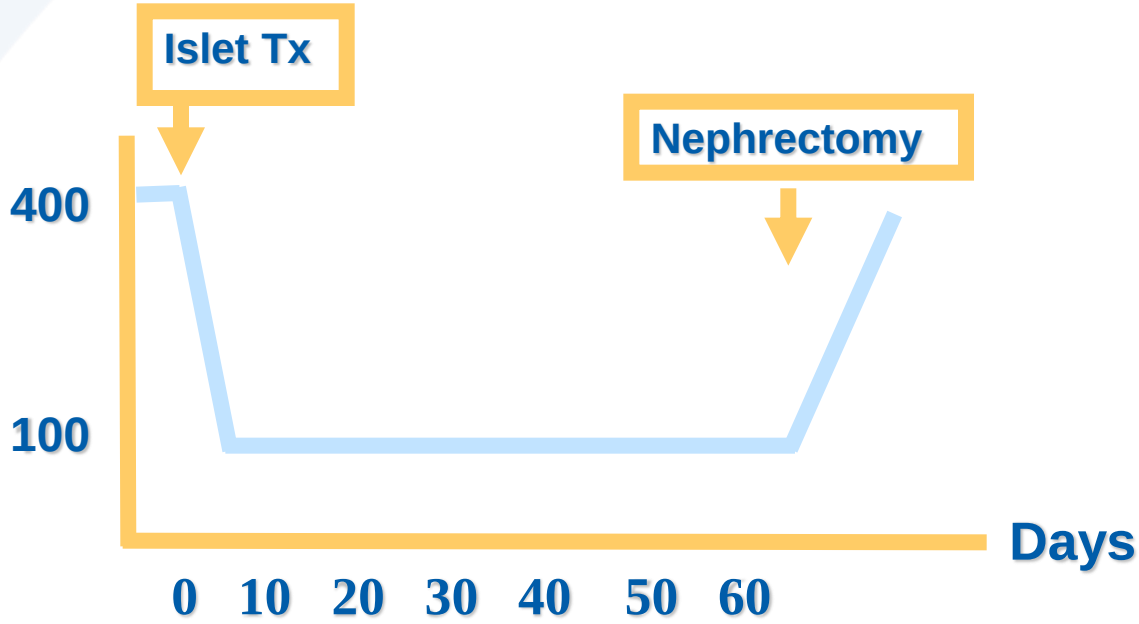
Ricordi C, Lacy PE, Sterbenz K, Davie JM
Proc Natl. Acad Sci USA 84: 8080-8084, 1987

Ricordi C, Scharp DW, Lacy PE
Transplantation 45: 994-996, 1988

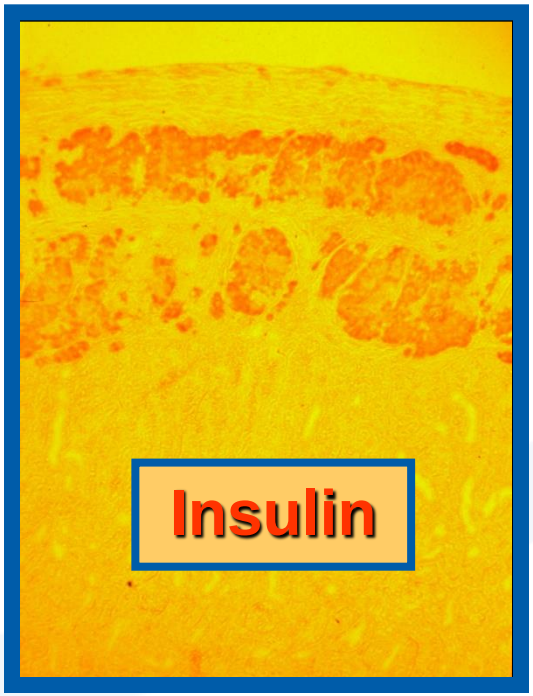
Ricordi C, Kneteman NM, Scharp DW, Lacy PE
World J Surg 12: 861-865, 1988



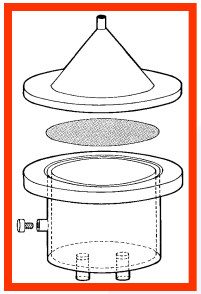



Islet Tx
Nephrectomy
400
100
Days
0 10 20 30 40 50 60


Glucagon


Insulin


Somatostatin



Insulin Independence after ITX in a Patient With Type 1 DM

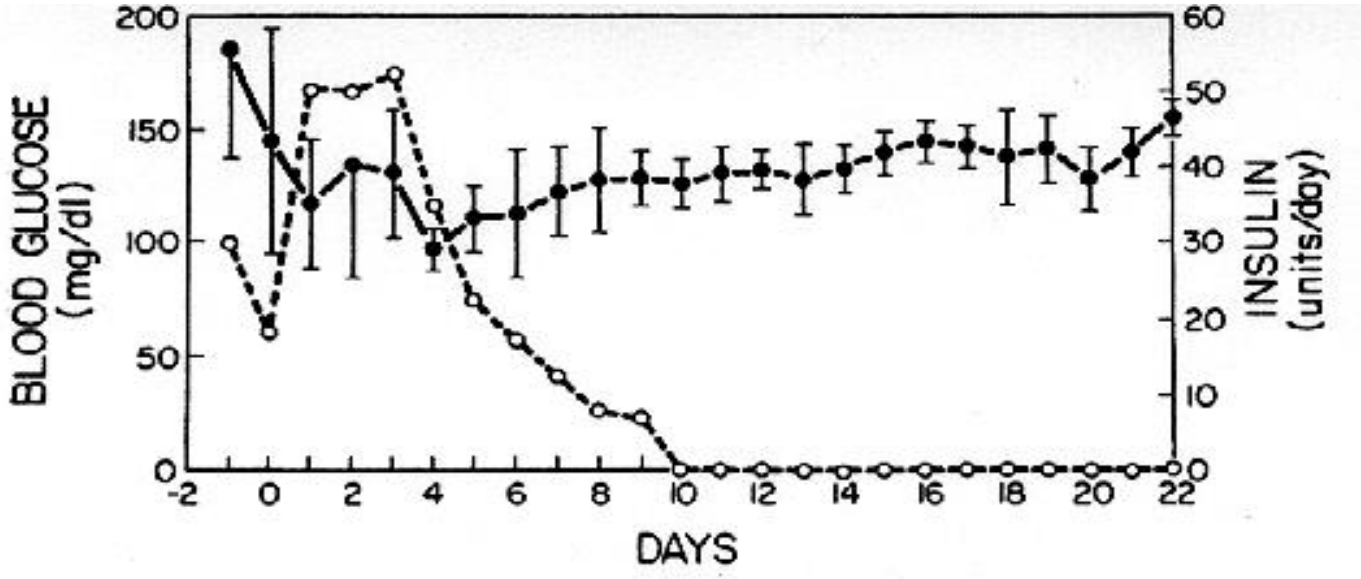
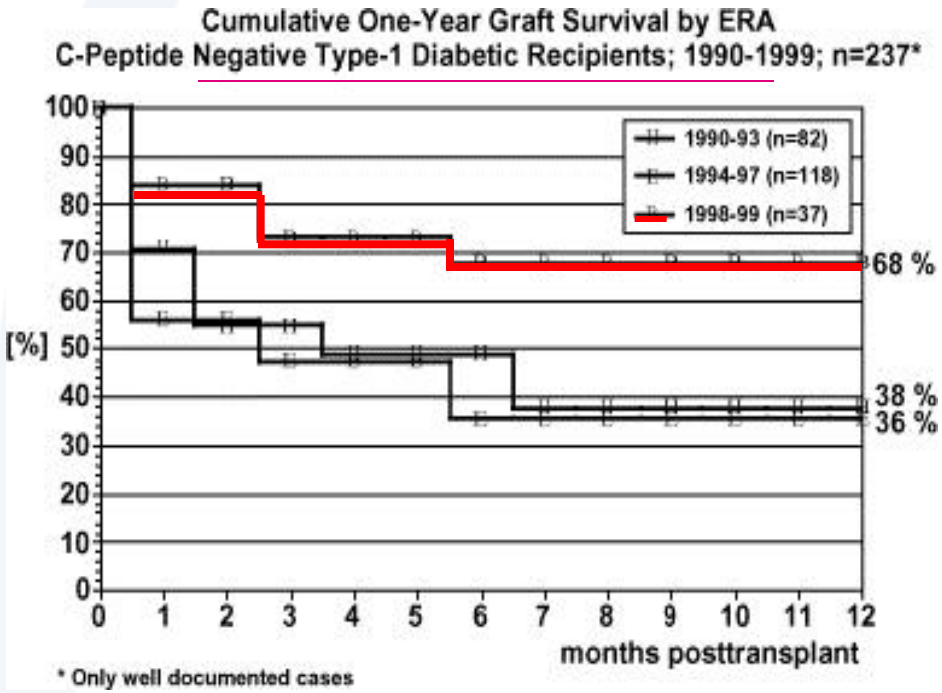


FIG. 1. Insulin glycemic profile before and after islet transplantation into patient with established kidney allograft. Average 24-h serum glucose level (●, means ± SD) is compared with 24-h insulin requirement (○).

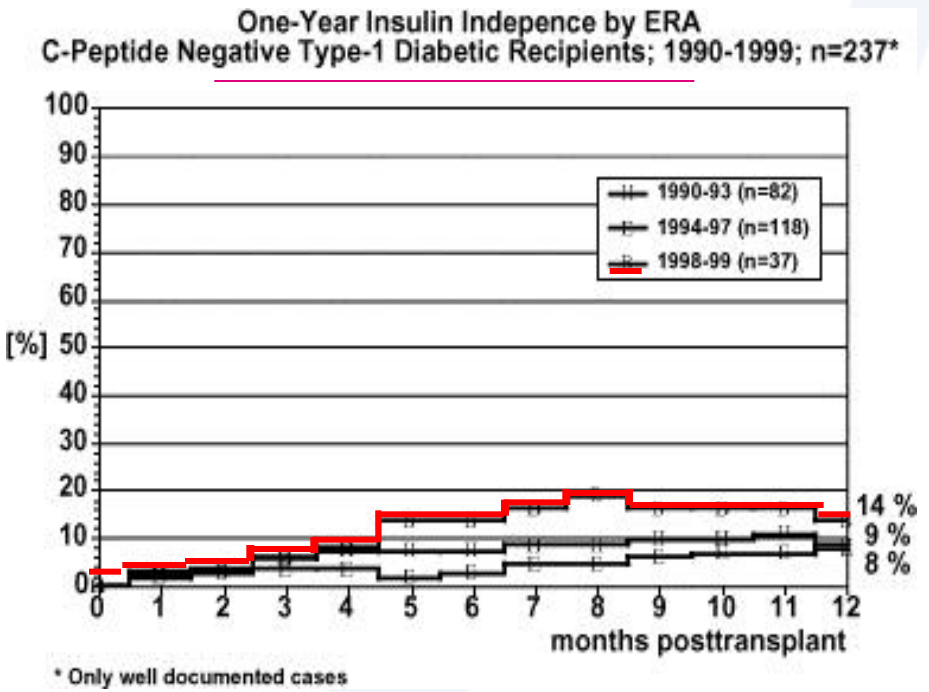
Scharp DW, Lacy PE, Santiago JV et al., *Diabetes 1990*

International Islet Transplant Registry

Graft Survival



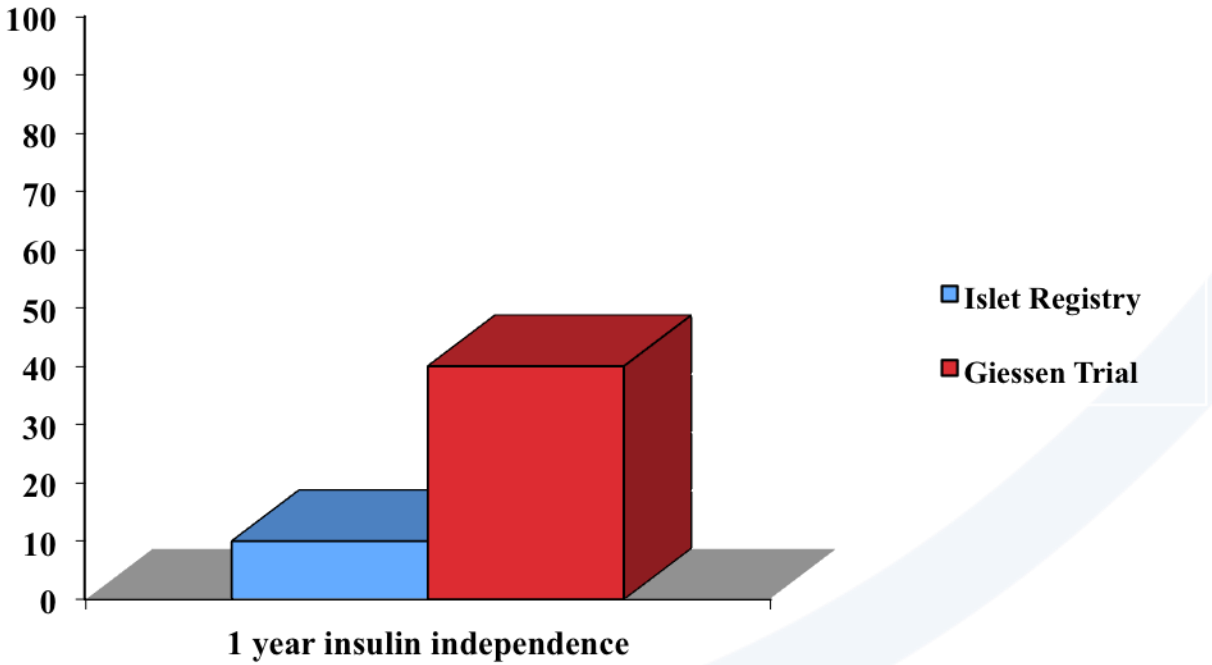
Insulin Independence



International Islet Transplant Registry. Newsletter #9. 8(1):1-20; 2001.
http://www.med.uni-giessen.de/itr

The Giessen Trial

Bernhard Hering et. al



A New Era in Islet Transplantation

"EDMONTON PROTOCOL"

The New England
Journal of Medicine

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ISLET TRANSPLANTATION IN SEVEN PATIENTS WITH TYPE 1 DIABETES MELLITUS USING A GLUCOCORTICOID-FREE IMMUNOSUPPRESSIVE REGIMEN

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- Short CIT
-
-
-
-

Immunosuppression

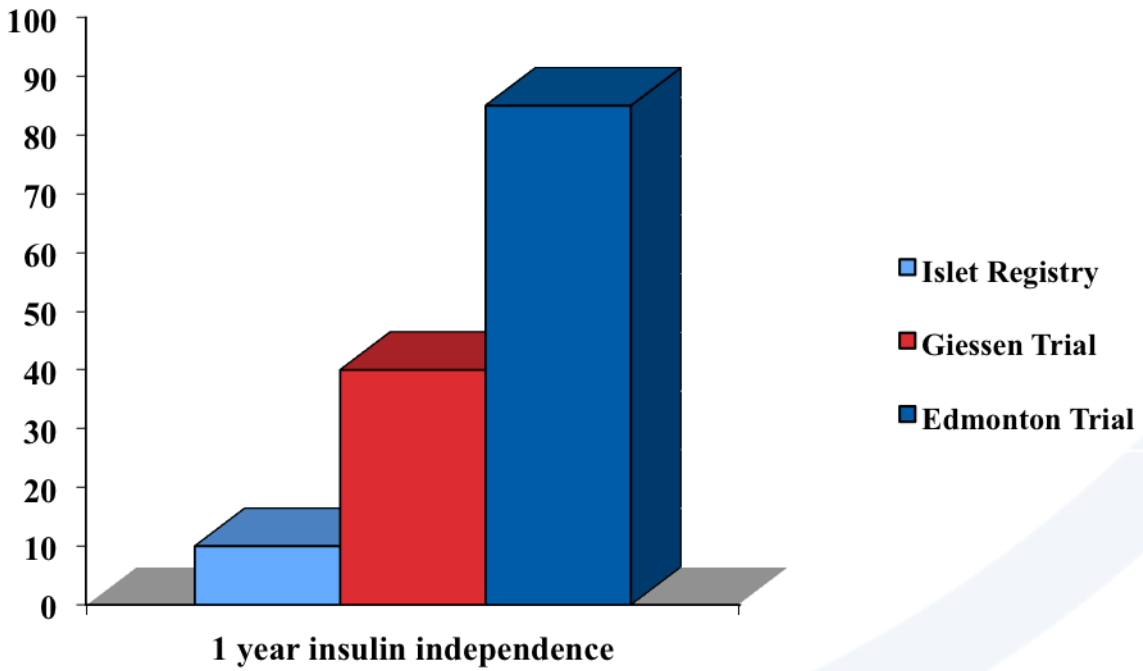
- Sirolimus
- Tacrolimus
- Daclizumab
- No steroids

Islet Transplant

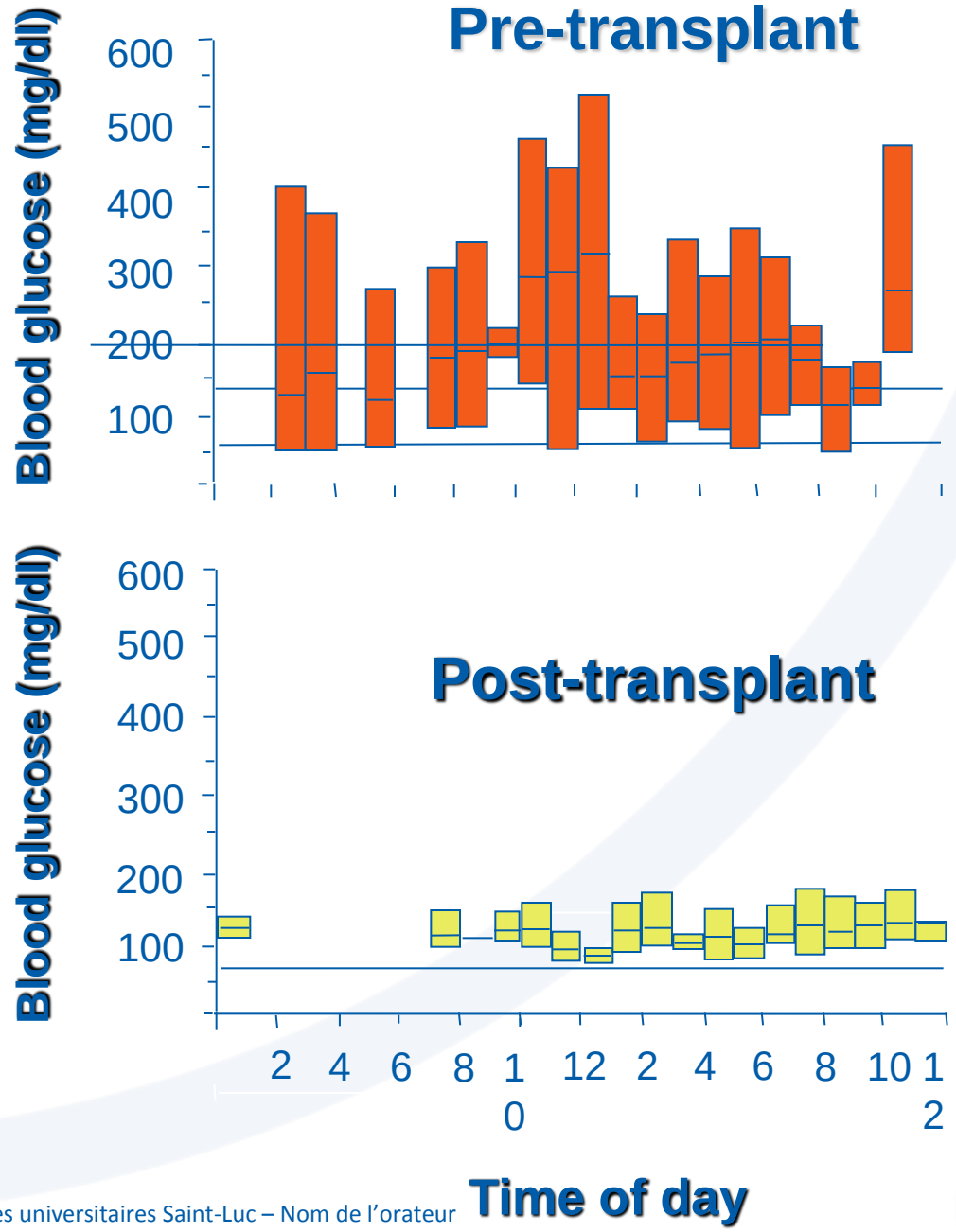
- No culture
- 2-4 pancreata

The Edmonton Trial

James Shapiro et. al - 2000



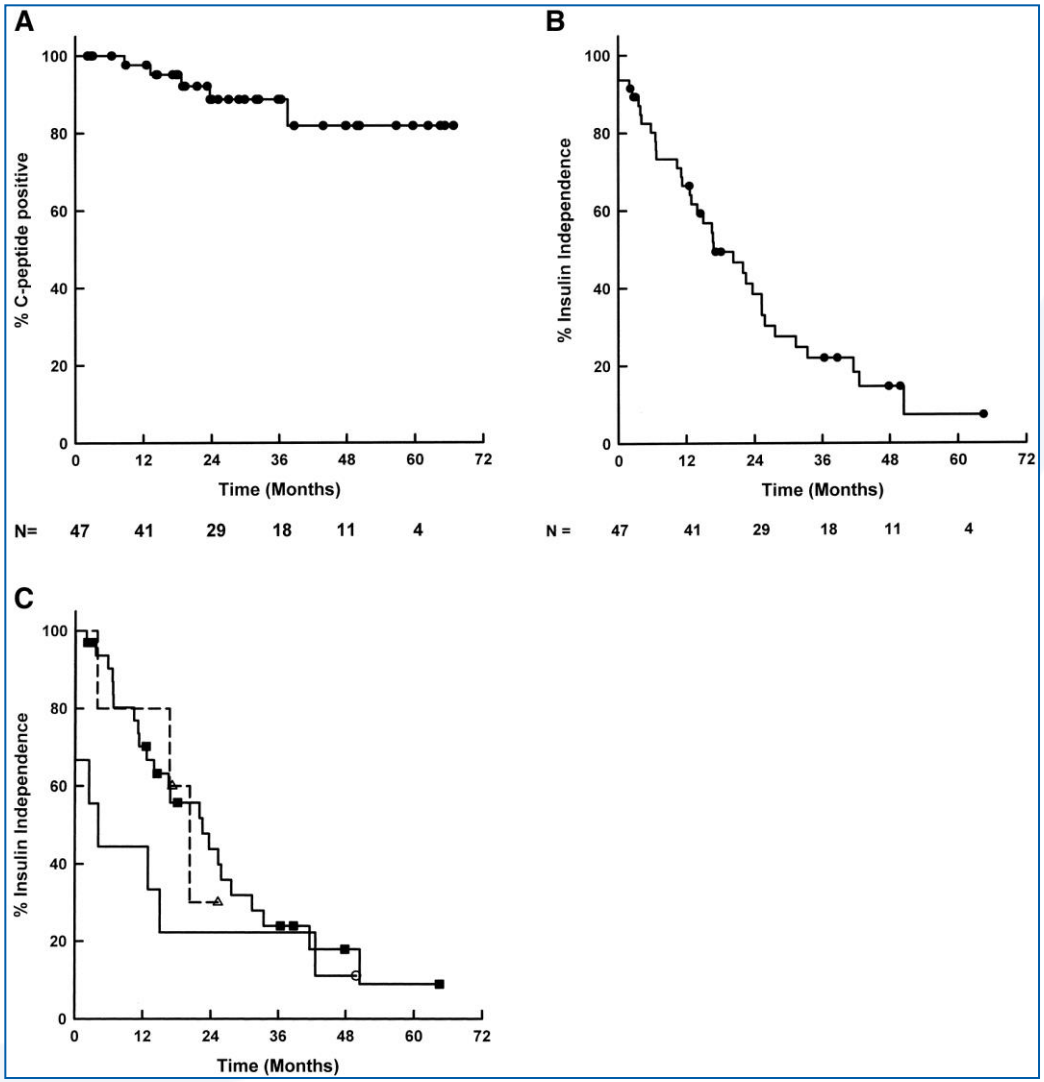
Shapiro et al.
N Engl J Med 2000; 343:230-238



Five-Year Follow-Up After Clinical Islet Transplantation

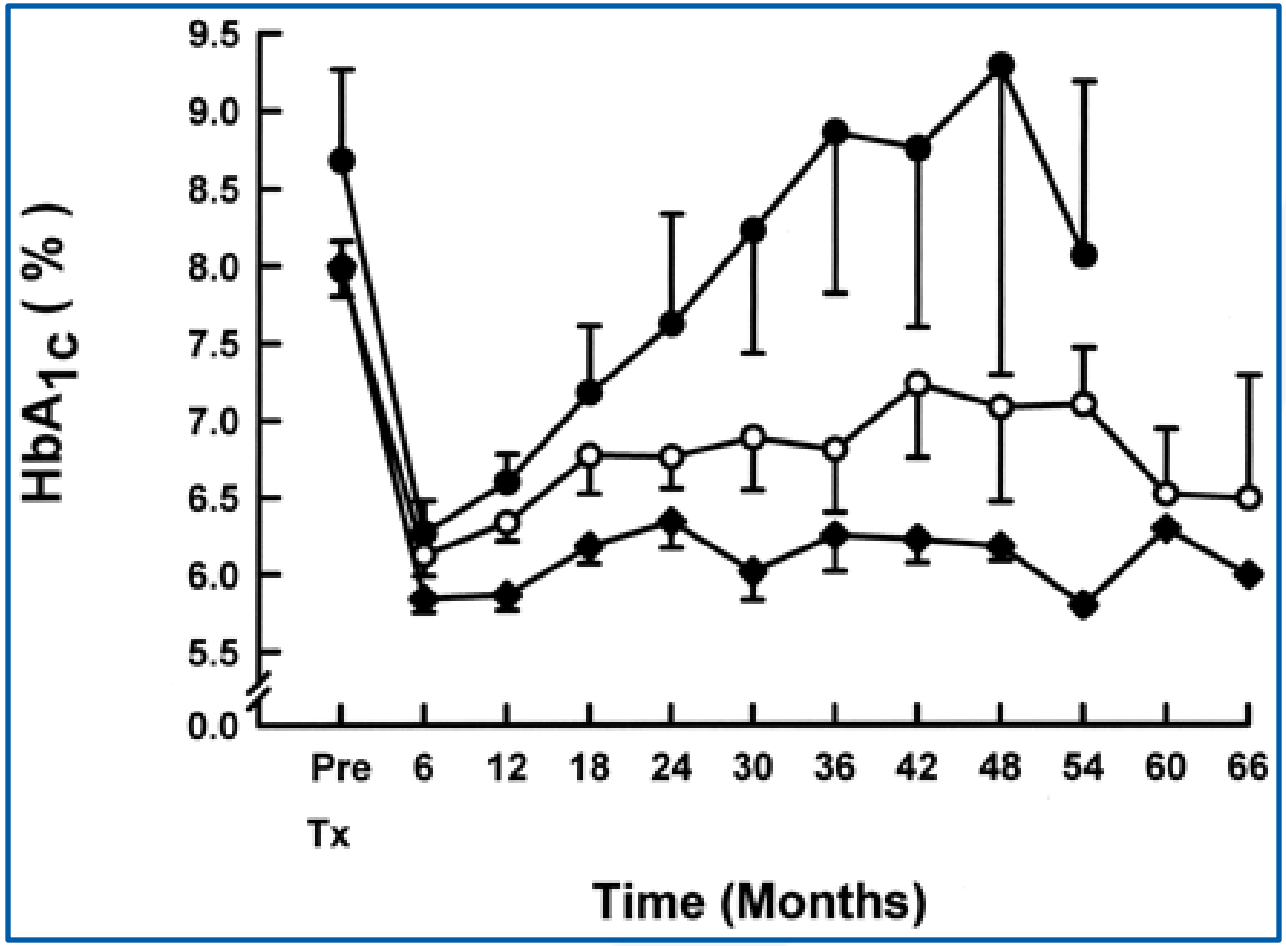
Edmond A. Ryan,[1] Breay W. Paty,[1] Peter A. Senior,[1] David Bigam,[2] Eman Alfadhli,[1]
Norman M. Kneteman,[2] Jonathan R.T. Lakey,[2] and A.M. James Shapiro[2]

At 5 years, c-peptide secretion preserved but only 11% maintain insulin independence

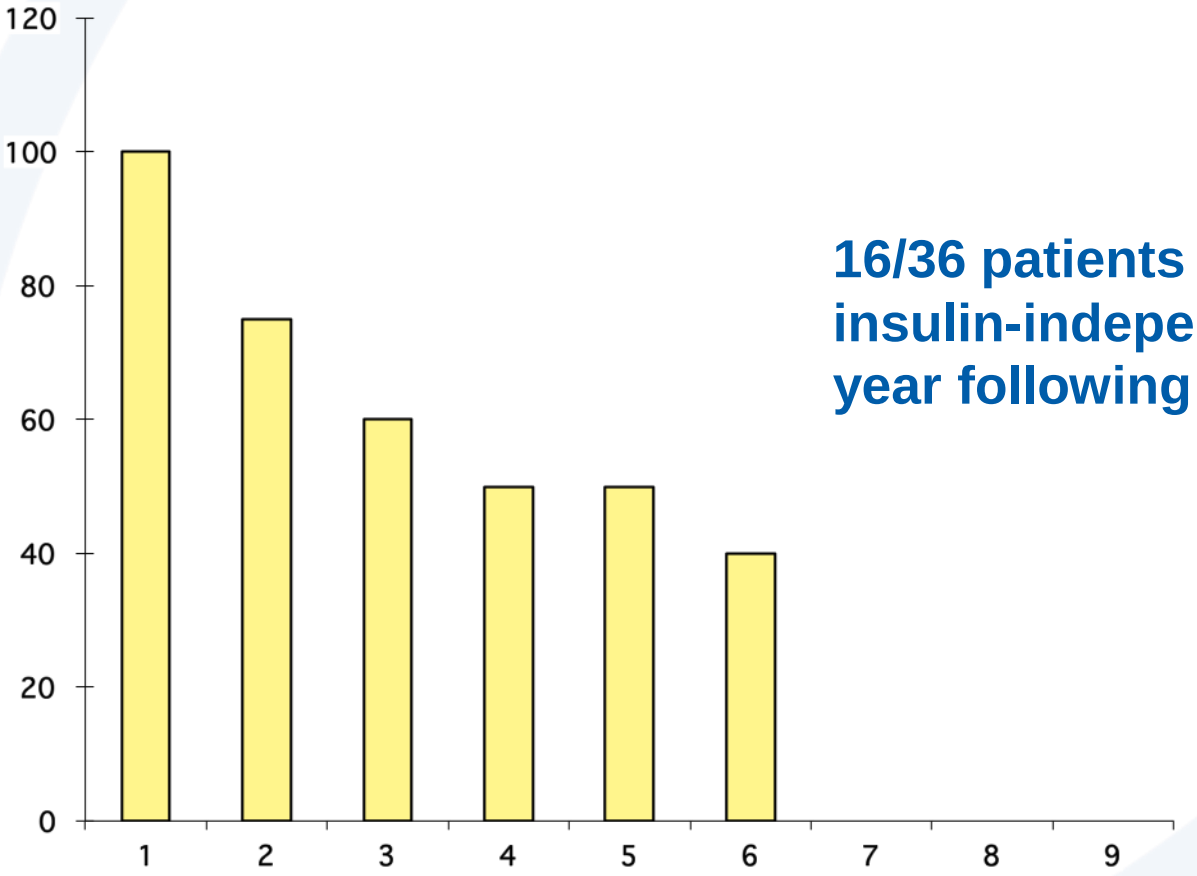


HgbA1c remains improved despite return to insulin use

- Insulin-free
- Lost function
- Primary nonftn



ITN Multicenter Trial
9 centers enrolled 3-5 patients to replicate Edmonton trial



16/36 patients rendered insulin-independent at one year following final infusion

Data presented by AMJ Shapiro at the ATC 2004

Donor selection

Relevence of culture

Single donor transplantation

The Post Edmonton Trial Era

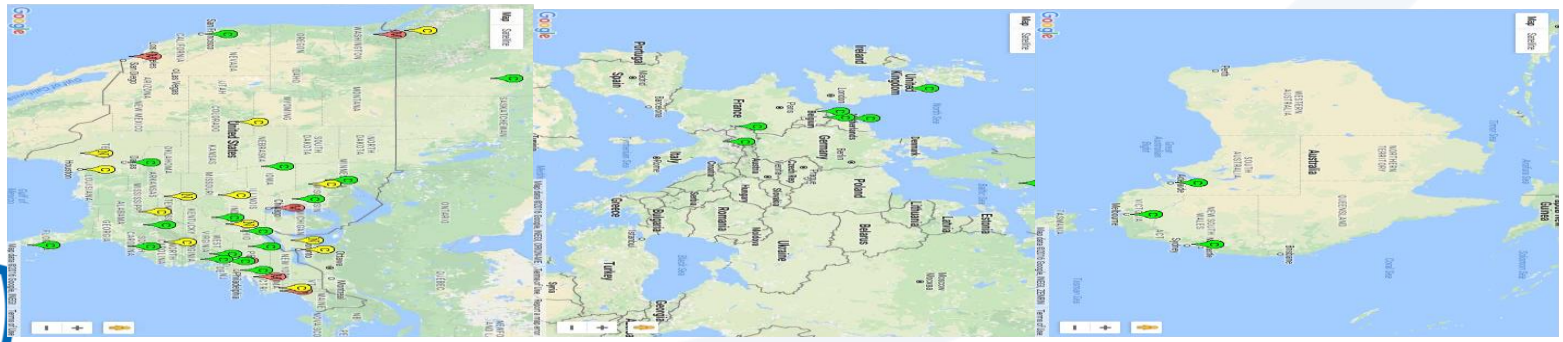
Recipient selection

Improvement of immunosuppressive drugs

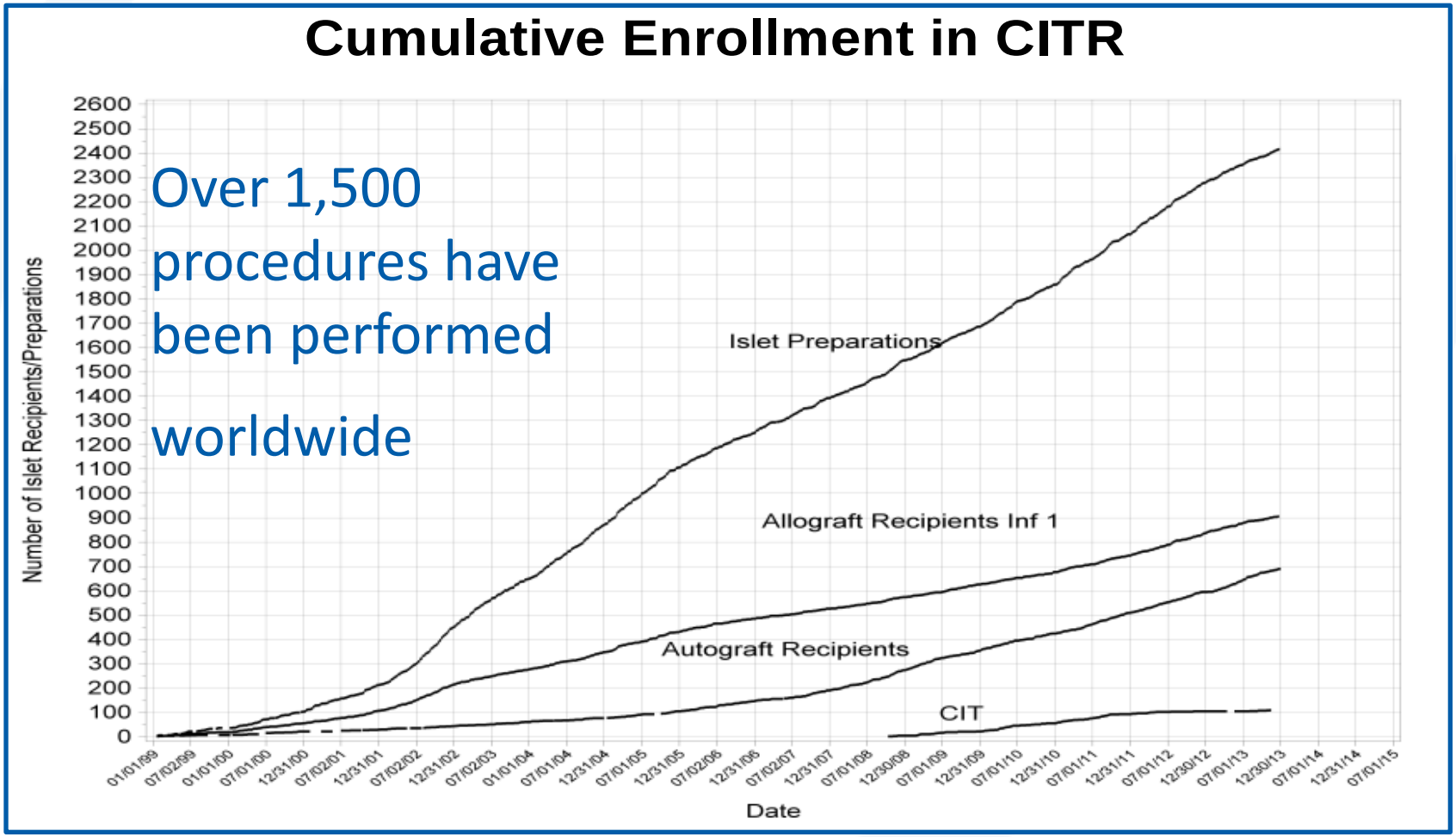
Improvement of enzyme manufacture

Clinical Islet Transplantation Consortium

The Clinical Islet Transplantation (CIT) Consortium is a network of clinical centers and a data coordinating center established in 2004 to conduct studies of islet transplantation in patients with type 1 diabetes.



Collaborative Islet Transplant Registry 2013



Islet Transplantation Alone

University of Miami

University of Illinois, Chicago

Northwestern University

University of Minnesota

University of Alberta

University of California San Francisco

University of Pennsylvania

University Hospital Uppsala, Sweden

Clinical Islet Transplantation Consortium

Harmonized process for the manufacture of allogeneic PHPI product in center-specific Phase 2 & common licensure Phase 3 clinical trials

Phase 3 Common Licensure Trial
Prospective, open-label, single-arm study
Camillo Ricordi, Chair
James Shapiro and Bernhard Hering, Co-Chairs

Primary end point:

•Achievement of an HbA1c level of ≤7.0%(rac.byADA)

And freedom from SHEs from day 28 to 365 after the day transplant

Phase 3 Trial of Transplantation of Human Islets in Type 1 Diabetes Complicated by Severe Hypoglycemia

Diabetes Care 2016;39:1230–1240 | DOI: 10.2337/dc15-1988

Key secondary end points:

•Achievement of an HbA1c level of ≤6.5% at 1 year

•Freedom from SHEs from day 28 to 365

•Insuline indipendence

- 75 clinical PHPI lots prepared
- All lots met pre-established criteria for safety, purity, potency, and identity
- Transplanted into 48 subjects enrolled in the trial
- No adverse events related to PHPI reported

- A total of 324 pancreata were processed for all CIT protocols
- 170 out of 324 lots produced met product release criteria (52.5%)
- CIT-07: 75 out of 170 lots were transplanted (44.1%)
- Final product IEQ recovery correlated with donor sex and BMI
- IEQ/g of trimmed pancreas did not differ among centers, or enzyme blends

Results

Phase 3 Trial of Transplantation of Human Islets in Type 1 Diabetes Complicated by Severe Hypoglycemia

Diabetes Care 2016;39:1230–1240 | DOI: 10.2337/dc15-1988

Work in Progress…..(compaired 2006 CIT study)

Fewer donors :1.6 vs. 2.1 donors per recipient
Better glycemic control :42% vs. 14% insulin independent at 2 years
Fewer Complications :10% vs 19% suffered intraperitoneal bleeds

1. Primary end point: 87.5% of subjects at 1 year ,71% at 2 years
2. The median HbA1c level decreased from 7.2% pretransplant to 5.6% at 1 year post-transplant
3. SHE:2 subjects at 1 year and totally 4 episodes(medically non adherent)
4. Highly significant improvements in all other measures of glycemic control.
5. Restoration of hypoglycemia awareness
6. Insulin independence in 52% at 1 year

persisted at 2 years in at least 80% of those who achieved it by year 1.

Islet Transplantation for Hypoglycemia Unawareness/Severe Hypoglycemia: Caveat Emptor

Pros:
- For most subjects (~70%), at least 2 years of improved glycemia without severe hypoglycemia
- A minority (~40%) achieve insulin independence & improved (albeit not normal) glycemia control for at least 2 years
- Procedure much less traumatic than a whole pancreas transplant

Cons/Caveats:
- Procedure-related bleeds requiring intervention
- Immunosuppression-related complications:
  - Significant and consistent renal function decline
  - Infections
  - Malignancy risk increased
- Cost!
  - Islets preparation
  - Hospitalization fees
  - Immunosuppressive medications
  - Outpatient follow-up and monitoring
- Immunosensitization risk
- Most still require insulin-based therapy
- No clear survival benefit: for solitary pancreas transplant, increased (not decreased) mortality
- Islet allograft supply limits applicability to ~1000-2000 individuals/year
- Allograft function consistently wanes with time
- Identifying suitable candidates for the limited resources difficult
- Medical treatments rapidly improving

D. Harlan Diabetes Care 2016

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- Islet transplantation Safety
- The Translational Research Approach
    - Proof of Function in Animal Models
    - Proof of Function in Humans
- **Possible Reasons for Islet Graft Failure**
- Current challenges faced for islet transplantation

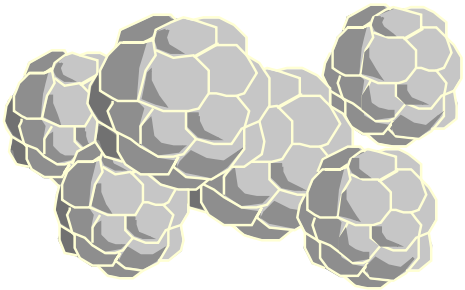
Source:

Possible Reasons for Islet Graft Failure

Insufficient islet mass

Poor quality of islets

Failure to engraft



Toxicity of anti-rejection drugs

Insulin resistance

Islets

Disease recurrence

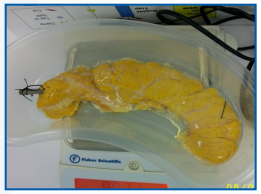
Allograft rejection

OBSTACLES TO SUCCESSFUL ISLET TRANSPLANTATION:
Low engraftment of islets

Transplant

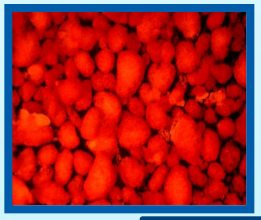
Donor

100%



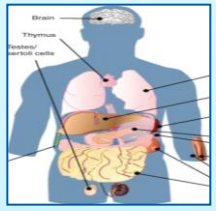
Islet isolation

50%



1 week

20%



5 year

?

Peri transplant period

Donor managment
Pancreas preservation
Pancreas digestion
Purification
Culture

Hypoxia
Poor revasularization
Exposure to blood
Proinflammatoy cytokines

Immune system
Immunosuppressive drugs
Hyperglycemia

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Source:

Current challenges faced for islet transplantation

Challenge	Possible impact	Potential solutions
Progressive graft dysfunction	Reintroduction of exogenous insulin; Destabilization of metabolic control; Supplemental islet transplant.	Incretin mimetics; Alternative islet implantation sites; Novel immunosuppressive protocols.
Multiple islet donors	Increased operational costs; Shortage of deceased donor pancreata for transplantation; Risk of allosensitization.	Improved donor selection criteria; Optimized cell processing; Alternative sources of transplantable tissue (i.e., stem cells-derived or xenogeneic islets; Alternative implantation sites.

Current challenges faced for islet transplantation

Challenge	Possible impact	Potential solutions
Chronic immunosuppression	Systemic toxicity; Increased risk of opportunistic infections; Islet cell toxicity.	Use of biologics; Immune isolation techniques; Development of immune tolerance inducing protocols.
Allosensitization	Reduced graft survival; Preclude/worsen outcome of subsequent transplantation (i.e., islet or renal)	Maximizing the success rate of single donor islet transplantation; Alternative sources of transplantable tissue; Immune isolation; Plasmapheresis / depletion of alloantibodies; Novel immunosuppressive protocols; Development of immune tolerance inducing protocols.

Current challenges faced for islet transplantation

Challenge	Possible impact	Potential solutions
Cumbersome graft monitoring	Mainly rely on metabolic function tests, but cannot discriminate between immunological and metabolic causes of dysfunction; Liver needle biopsies do not provide adequate graft tissue; MRI and PET lack the resolution to detect islets scattered throughout the liver	Improved simple metabolic measures predictive of graft dysfunction; Improved sensitivity of noninvasive imaging techniques (functional MRI?); Improved immune monitoring techniques for early detection of immune events able to discriminate between rejection and autoimmunity.

Conclusions

- Islet transplantation is a safe and effective treatment for patients with T1DM complicated by hypoglicaemic unawareness or severe hypoglycaemic events
- Remarkable progress has occurred in the clinical delivery of islet transplantation, and improvements in the outcomes of islet transplantation have accelerated over the past 16 years
- The dream that began in 1972 of transplanting islets to patients with diabetes to restore normoglycemia and to eliminate the need for insulin injections remains a work in progress and many questions still remain unanswered so...

FONDATION SAINT-LUC
Cliniques universitaires SAINT-LUC | UCL Bruxelles

Let's try to find the heart of the problem...

Fondation
Saint Luc
Merci de tout cœur!!!