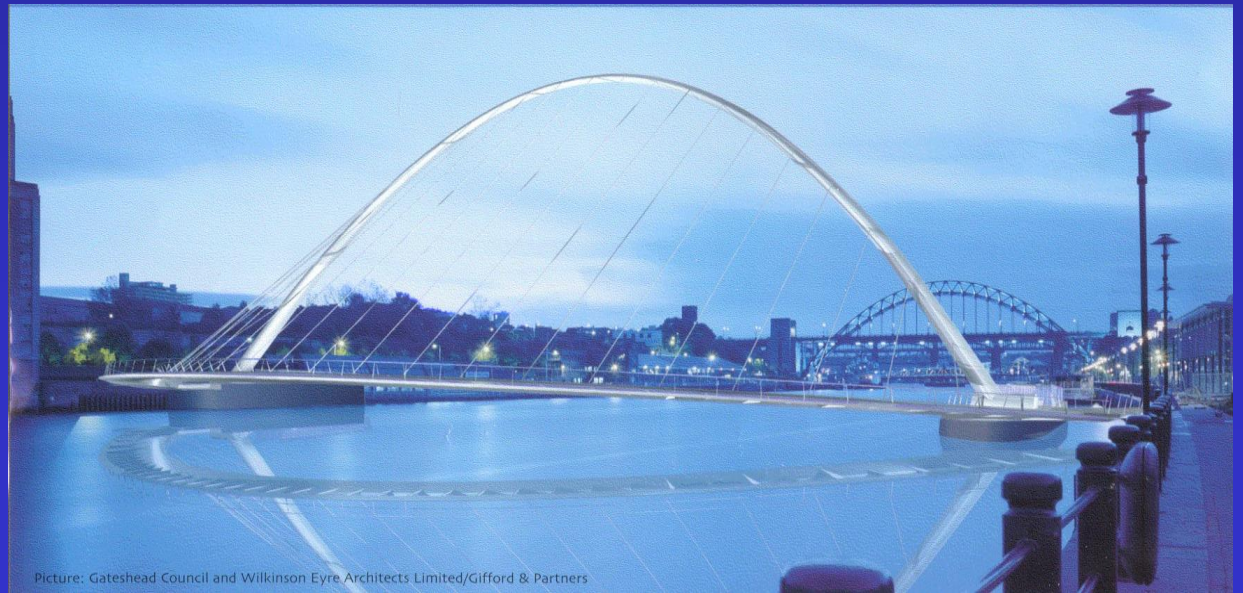
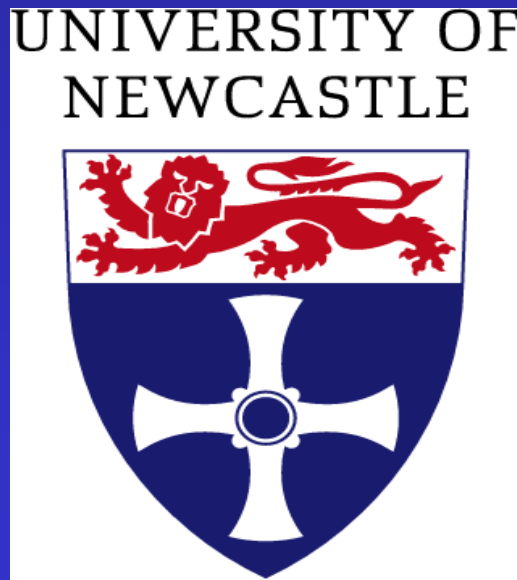


# Current and future status of islet cell replacement strategies

James Shaw: Senior Lecturer / Consultant Physician



# Overview

- Limitations of conventional therapy
- Seminal success in Edmonton
- Reproducible results world-wide and in UK
- Further innovations and future challenges

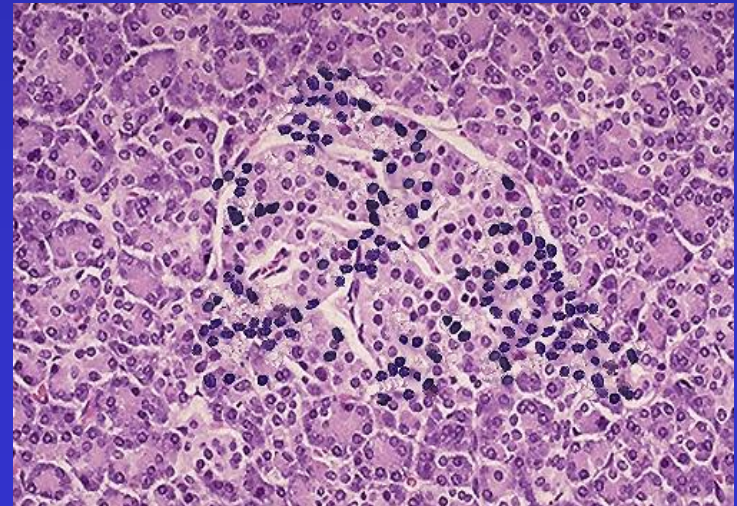


**More than 250,000 affected in UK**

**Incidence doubled every 20 years since 1945**

# Type 1 diabetes

- Auto-immune destruction of the beta cells
  - complete insulin loss: no other pathology
- Successful insulin replacement
  - restoration of normal health and lifestyle
  - prevent all complications





**‘Unspeakably wonderful!’ *Elizabeth Hughes 1907-1981***

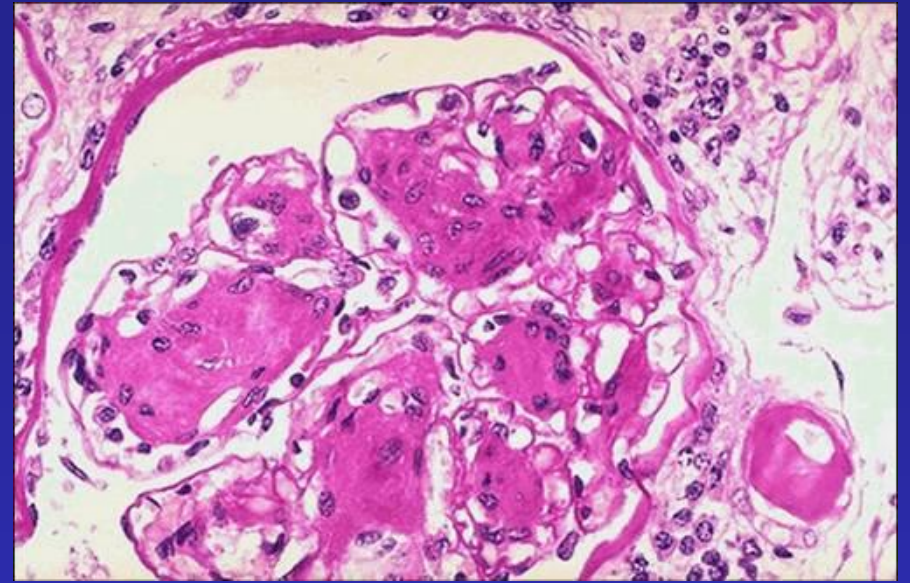
# Hypoglycaemia

‘Insulin reactions’ seen since its earliest use

*‘.....dangerous hypoglycaemia can occur without warning symptoms.....’*


*‘.....insulin is not a cure for diabetes, but a potent preparation, alike for evil and for good.’*

*Joslin, 1922*



**Major risk factor for MI / CVA**

**Life expectancy reduced up to 20 years**



Section 5:  
Clinical Trials in Diabetes

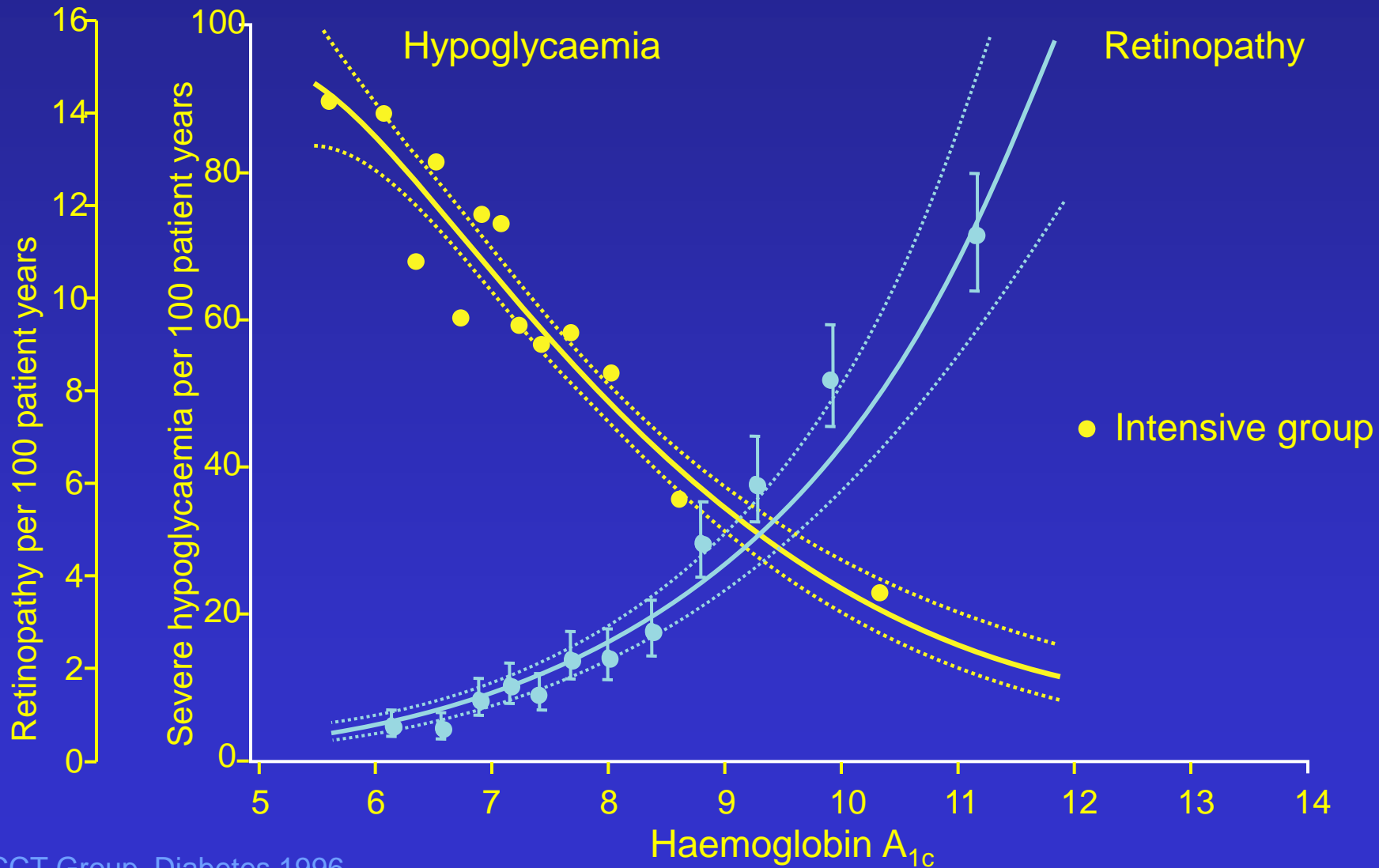
The Diabetes Control and  
Complications Trial (DCCT)

Complication	Primary prevention (Risk reduction, %)	Secondary prevention (Risk reduction, %)	Both cohorts (Risk reduction, %)
Retinopathy	76**	54**	63**
Microalbuminuria (UAE $\geq$ 40 mg/24 hrs)	34*	43**	39**
Albuminuria (UAE $\geq$ 300 mg/24 hrs)	44	56*	54*
Neuropathy	69*	57**	60**

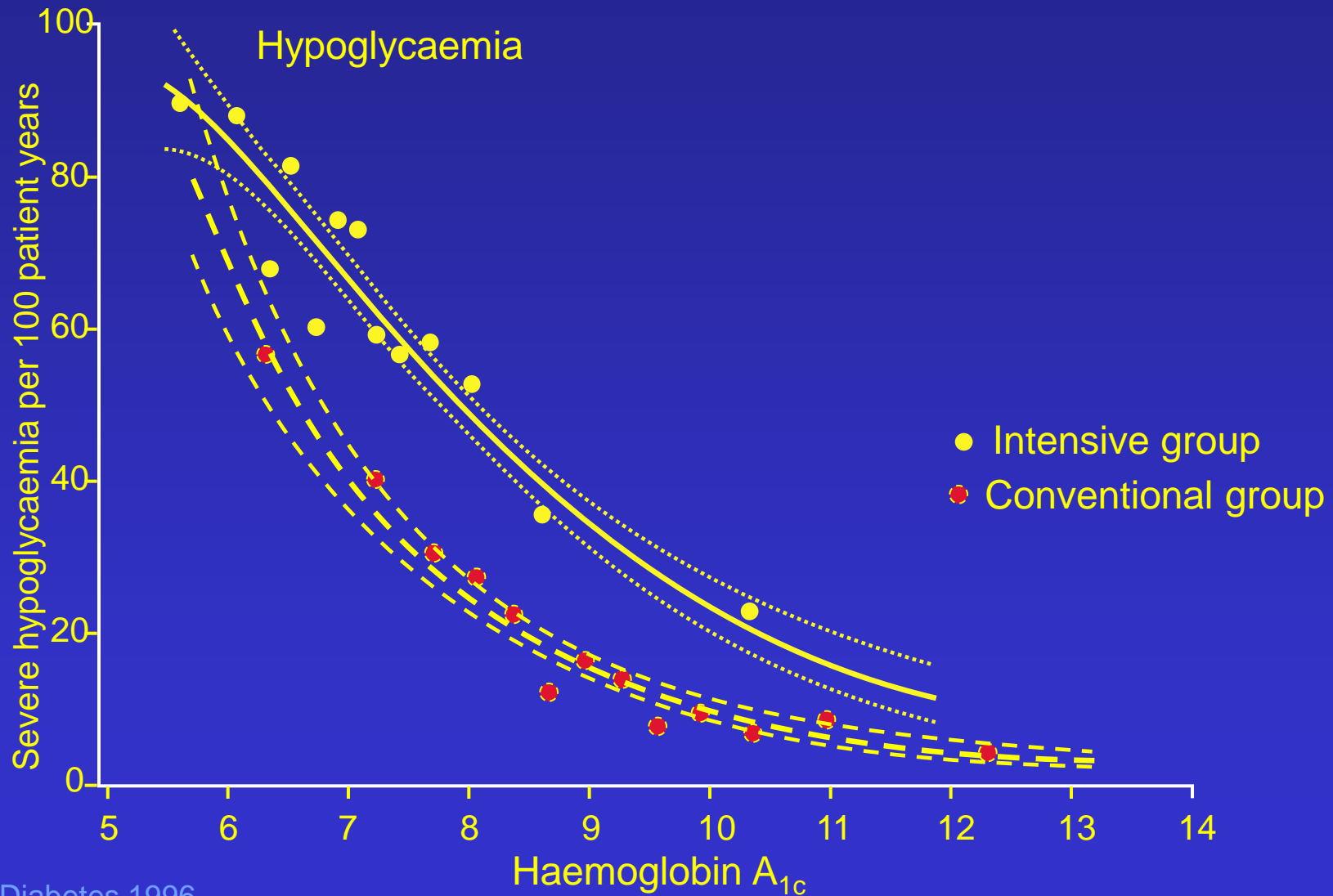
‘My greatest phobia is rats but I would rather hold a rat than have a hypo’



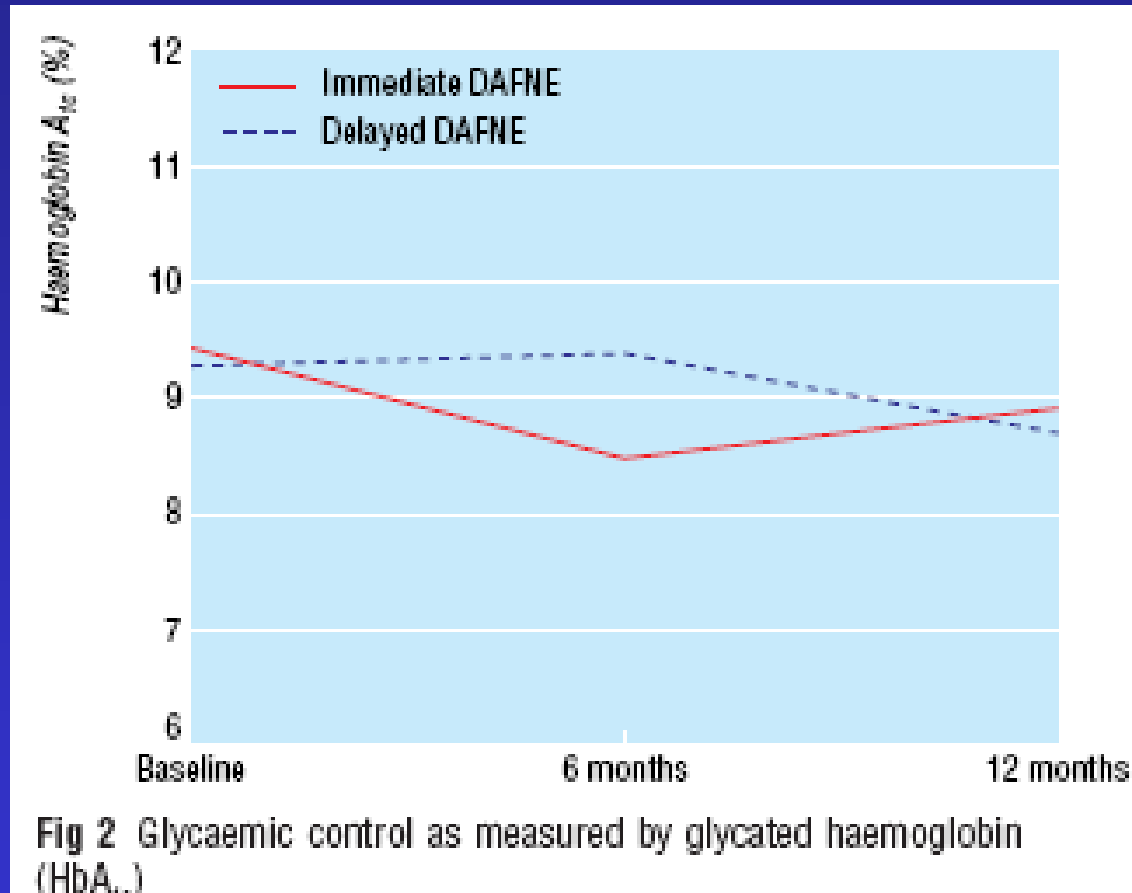
# Benefits and risks in the DCCT



# Benefits and risks in the DCCT

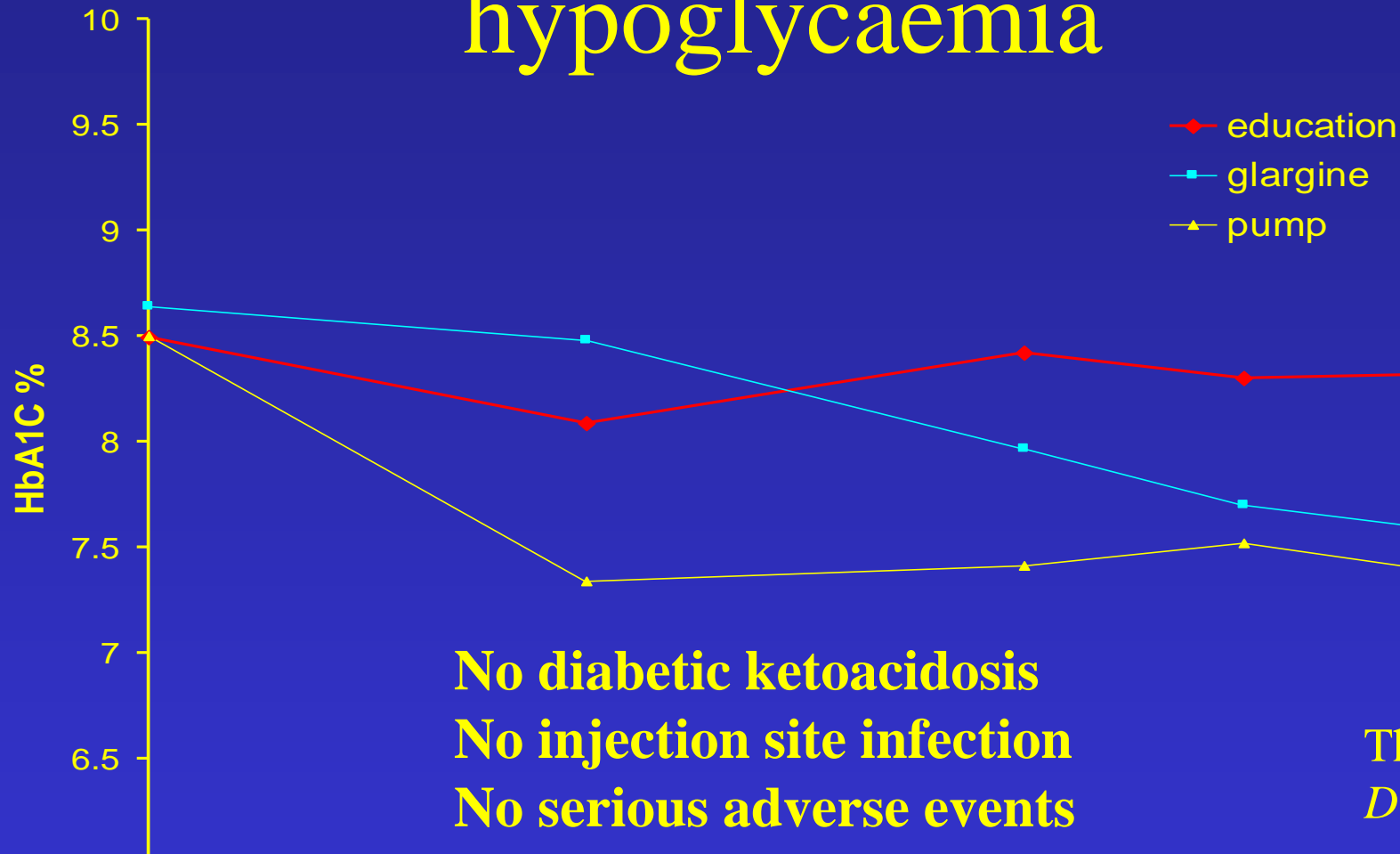


# DAFNE



**18% severe hypoglycaemia over 6 months**

# Prevention of recurrent severe hypoglycaemia



**29% severe hypoglycaemia over 6 months**

# Distribution of Blood Glucose One Week Before and During 48H-‘Closed-Loop’

E. Renard et al, Lapeyronie Hospital, Montpellier, France

<b>Reference Point Range</b>	<b>Before Closed-Loop</b>	<b>During ‘Closed-Loop’</b>
<b>&lt; 3.8 mmol/l</b>	<b>25 %</b>	<b>14 %</b>
<b>3.8-6.7 mmol/l</b>	<b>25 %</b>	<b>60 %</b>
<b>6.7 – 13 mmol/l</b>	<b>45 %</b>	<b>26 %</b>
<b>&gt;13 mmol/l</b>	<b>5 %</b>	<b>0 %</b>
<b>Average Glucose (mmol/l)</b>	<b>6.4</b>	<b>5.8</b>
<b>Daily Insulin Use (IU)</b>	<b>35</b>	<b>45</b>

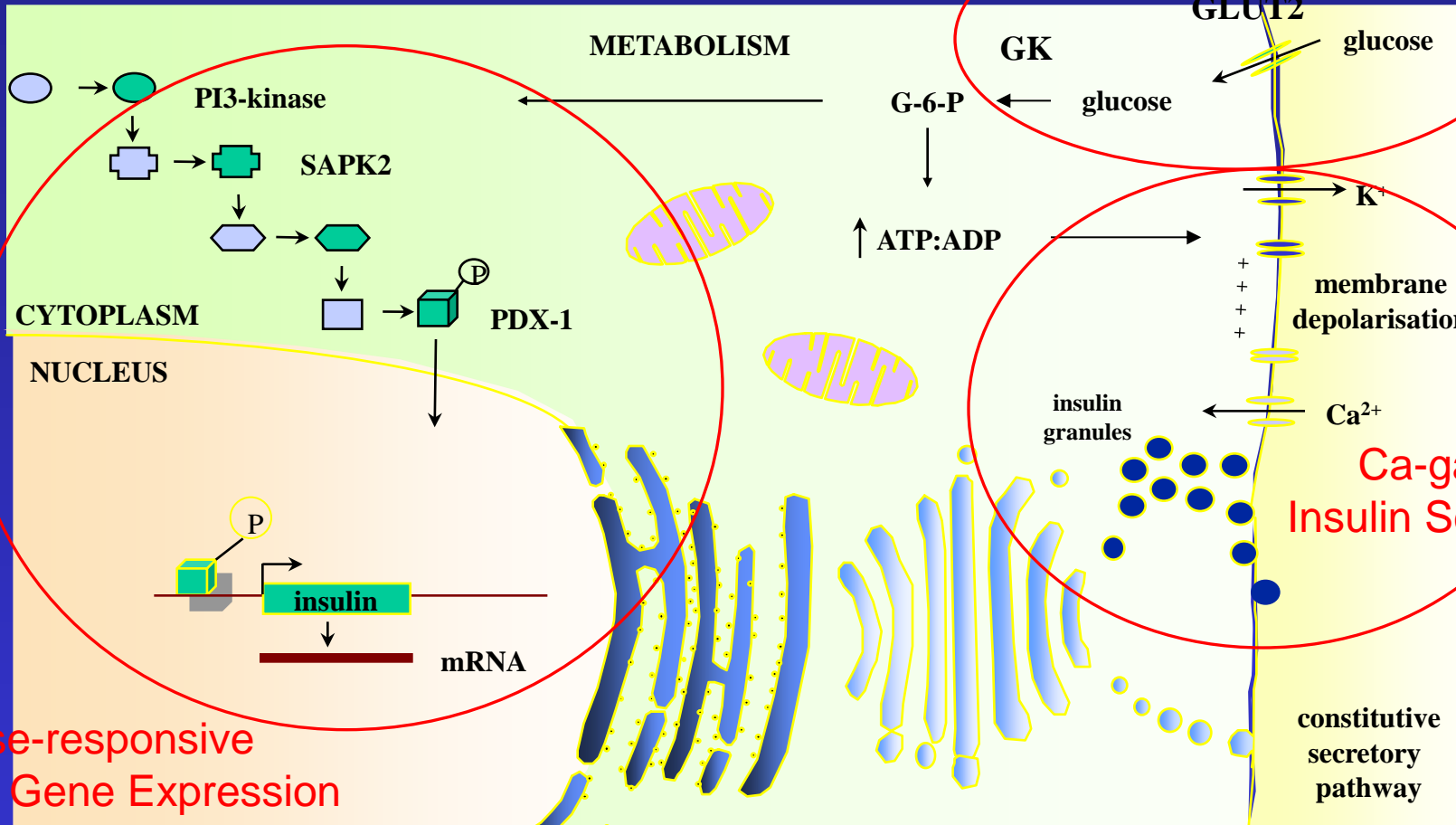
**INSULIN IS  
NOT A CURE  
FOR DIABETES.  
IT JUST KEEPS  
PEOPLE ALIVE  
UNTIL WE  
FIND ONE.**

Support the Research of the  
American Diabetes Association



# Physiological $\beta$ -cell

Glucose Sensor



Ca-gated Insulin Secretion

Glucose-responsive Insulin Gene Expression

endoplasmic reticulum      Golgi apparatus      secretory vesicles

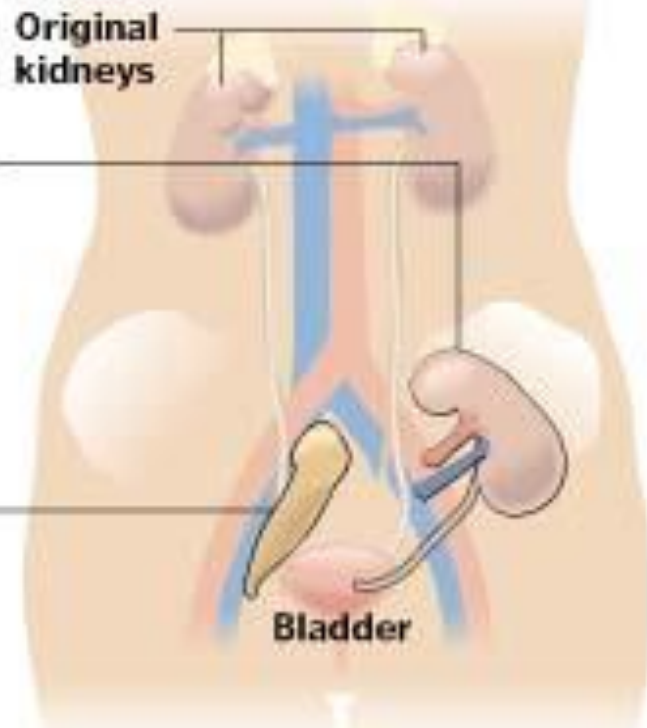
## Blueprint for a double transplant

To cure Scott Bowles' diabetes and restore his body's ability to filter toxins from his blood, doctors transplanted two organs from an accident victim. The double transplant is an increasingly popular though controversial treatment among the nation's 1 million insulin-dependent diabetics. About 1,000 such transplants are performed each year in the United States.

**How it's done:** Doctors attach a new pancreas and kidney to the major blood vessels in the lower abdomen. Scott's defective but somewhat functional pancreas and kidneys are left untouched.

**Kidney:** The new kidney gives Scott three, though his original two were damaged by diabetes. The donated kidney filters the body's natural toxins from the blood and drains them into the bladder.

**Pancreas:** The organ produces the hormone insulin. When the new pancreas is hooked up to Scott's blood supply, the organ produces insulin immediately, curing his diabetes.

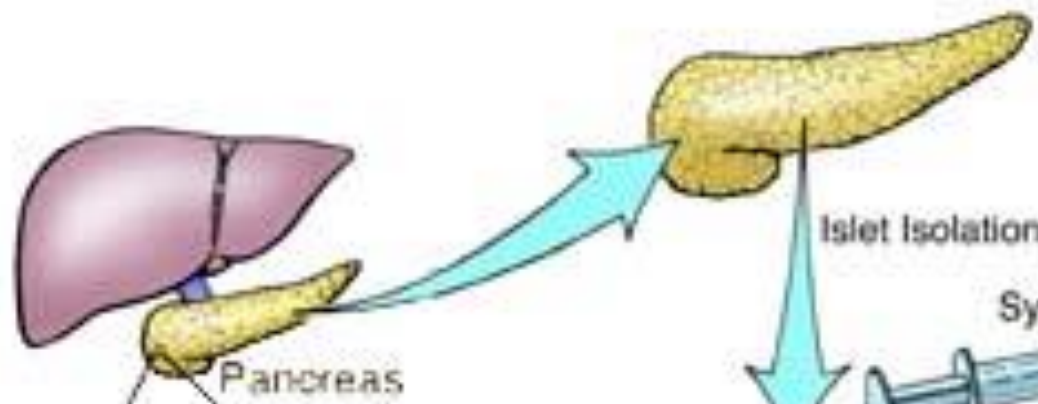




# Vascularised pancreas transplantation

- Offers the potential of ‘cure’
  - normal glucose
  - prevention of hypoglycaemia
- Requires human donor pancreas
  - long hospital stay; 20% re-operation; 5% mortality
- Requires life-long immunosuppression
  - risk of severe infection / tumours
  - combined with kidney transplant

**Donor**



Pancreas



Islet in Pancreas

Islet Isolation

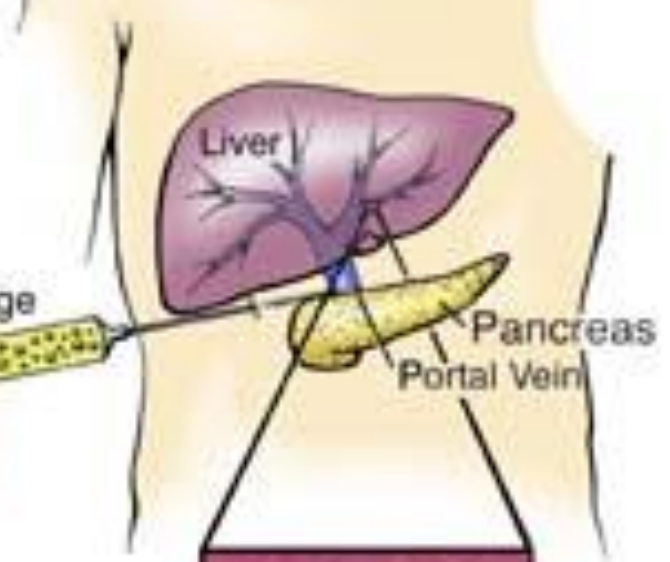


Isolated Islet of Langerhans

Syringe

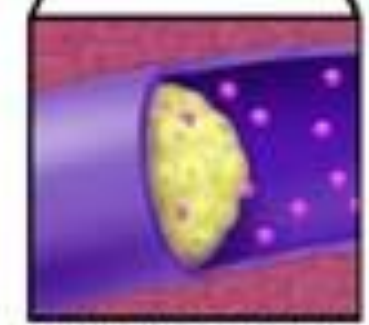


**Recipient**



Liver

Pancreas  
Portal Vein



Islet in Portal Vein

## Transplantation of Native Islets for Patients with Pancreatitis

### Islet Autografts from 1990 - 2000

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- **Institutions**

Minneapolis	54
Leicester	34
Geneva	14
Indianapolis	11
11 other Institutions	27
- **No. of cases**

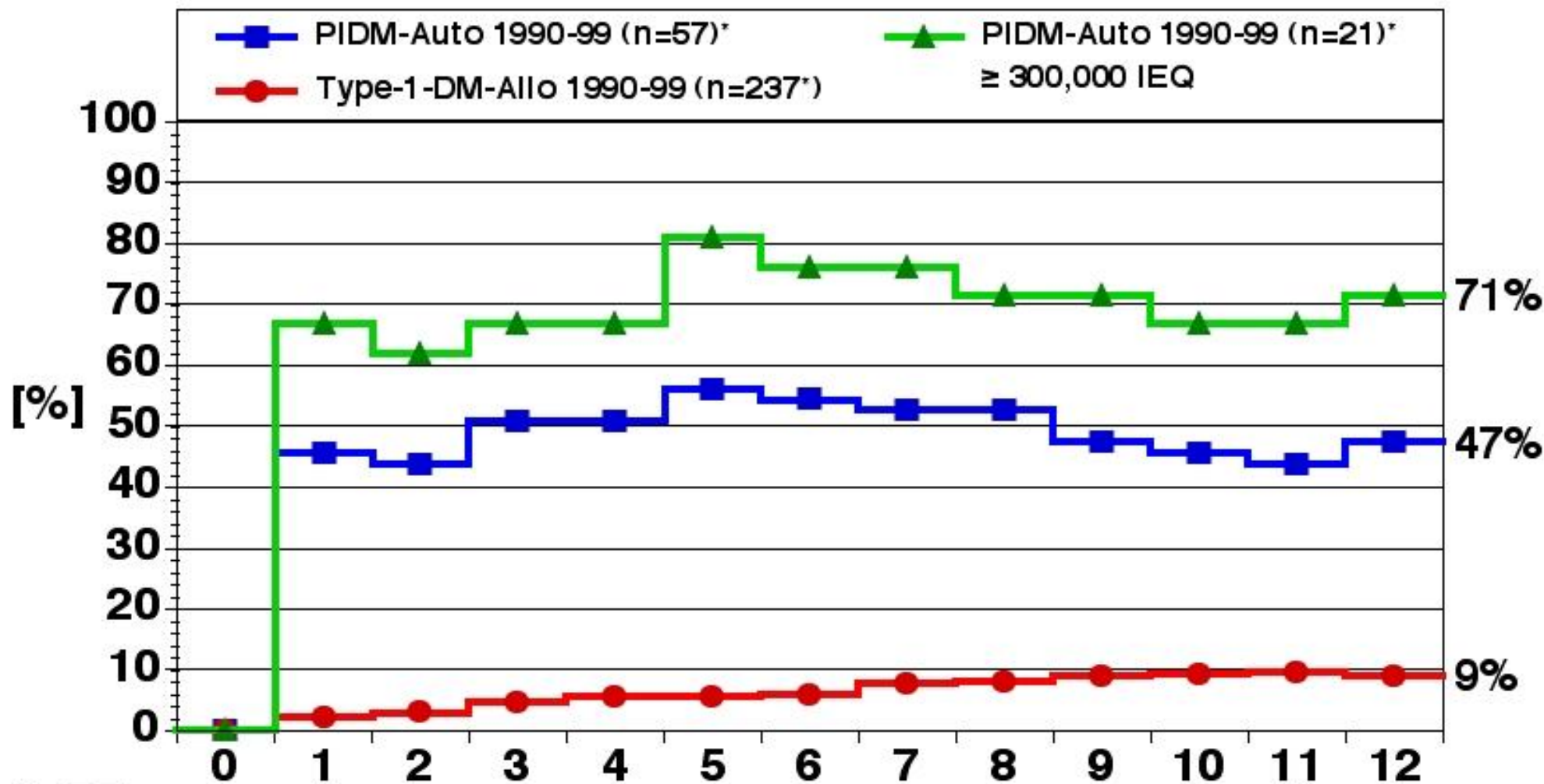
	140
• Insulin-independent $\geq 7$ days (1990-2000):	41 / 64* (64%)
• Insulin-independent at $\geq 1$ yr (1990-1999 + one year follow-up):	27 / 57* (47%)
if more than 300,000 IEQ transplanted:	15 / 21* (71%)
• Longest insulin-independence follow-up after total pancreatectomy:	> 13 yrs

\* only well documented cases

2000 data on file incomplete



# Insulin Independence Following Islet Transplantation in Man A Comparison of Different Recipient Categories



\* only well documented patients



# The New England Journal of Medicine

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VOLUME 343

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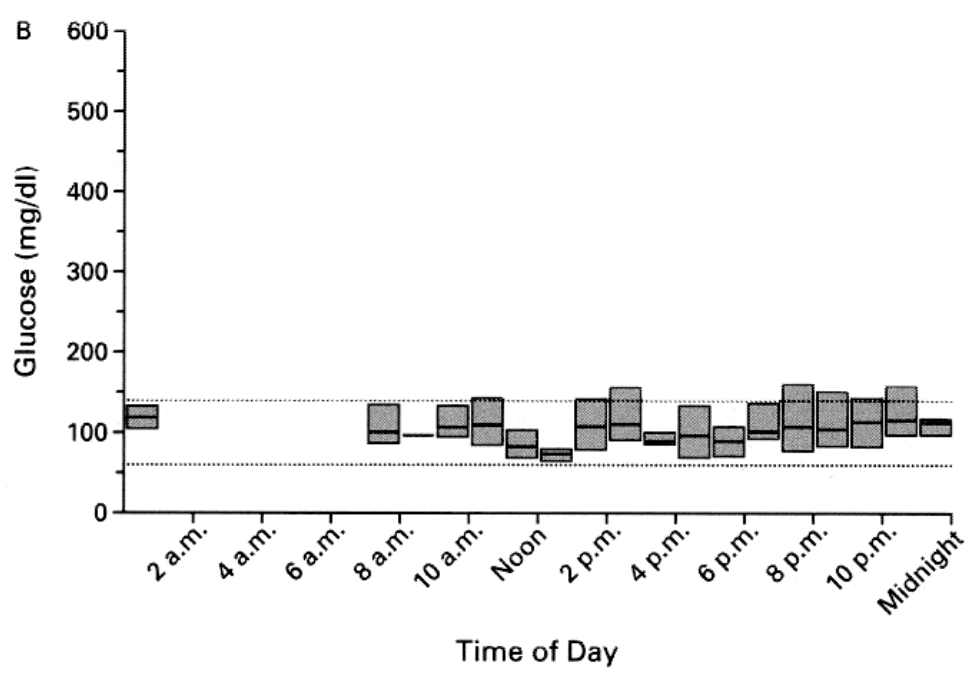
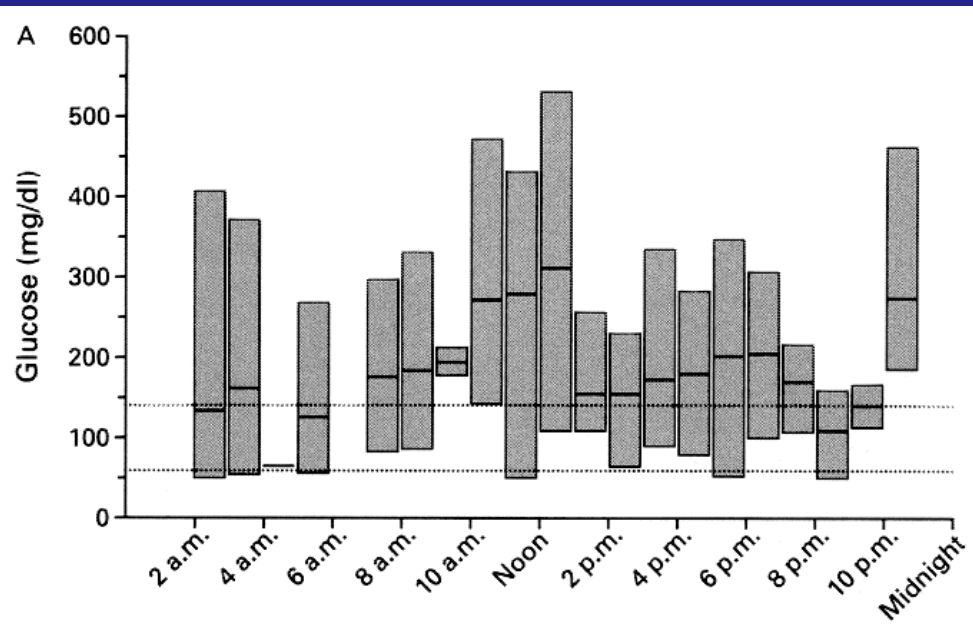
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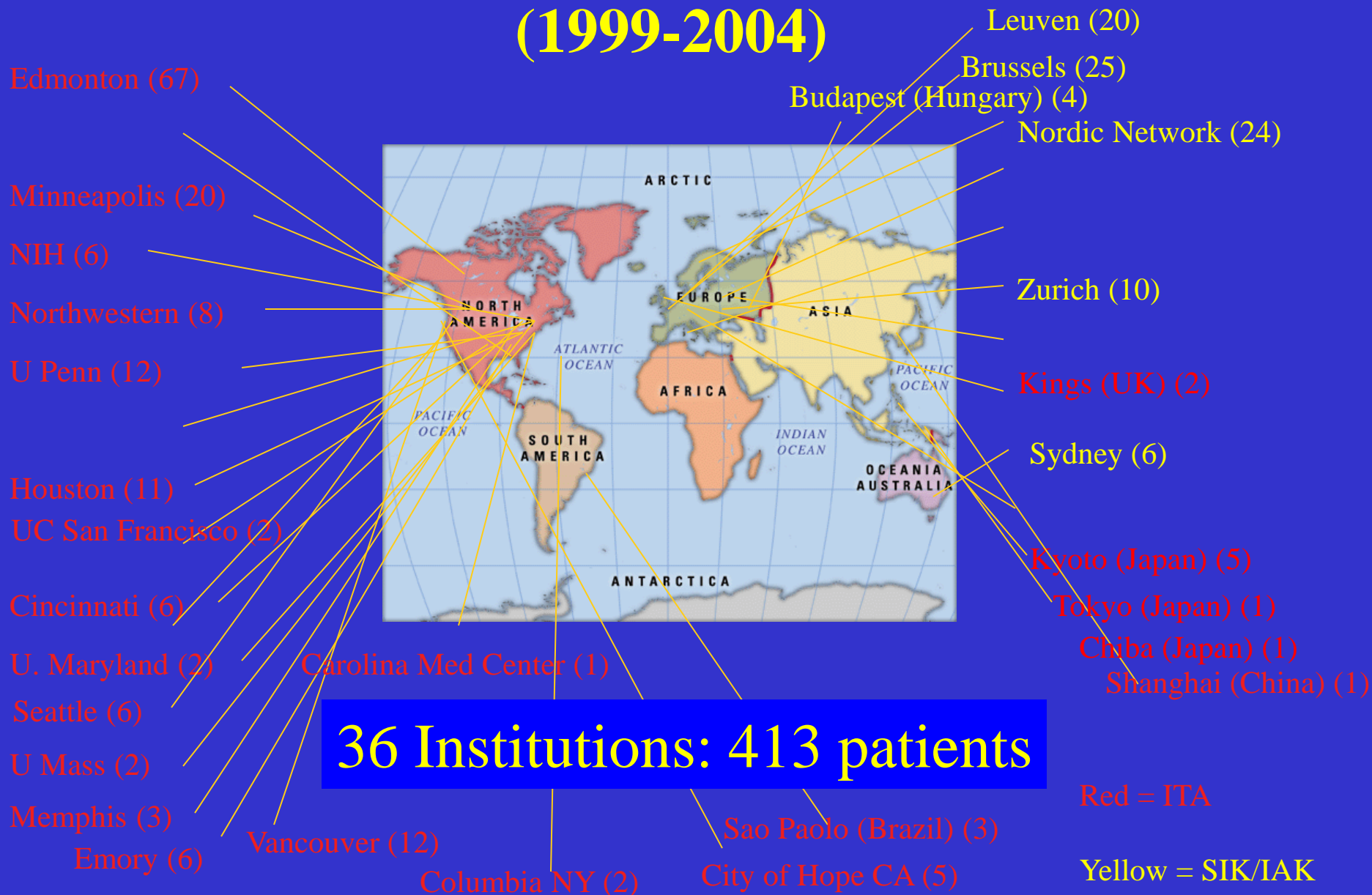
## ISLET TRANSPLANTATION IN SEVEN PATIENTS WITH TYPE 1 DIABETES MELLITUS USING A GLUCOCORTICOID-FREE IMMUNOSUPPRESSIVE REGIMEN

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.

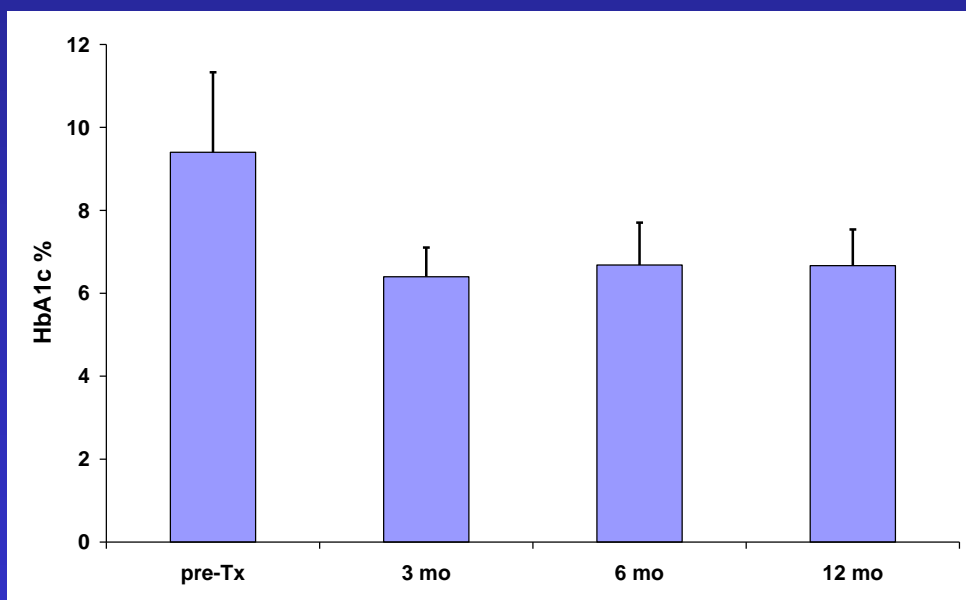
- 7 Type 1 patients with severe hypoglycaemia
  - metabolic instability
- Islets purified without animal proteins
  - immediate transplantation
  - 2-3 donors for each recipient
- Steroid (cyclosporin)-free immunosuppression
  - sirolimus (rapamycin); tacrolimus (FK506)
  - daclizumab (IL-2 receptor monoclonal antibody)



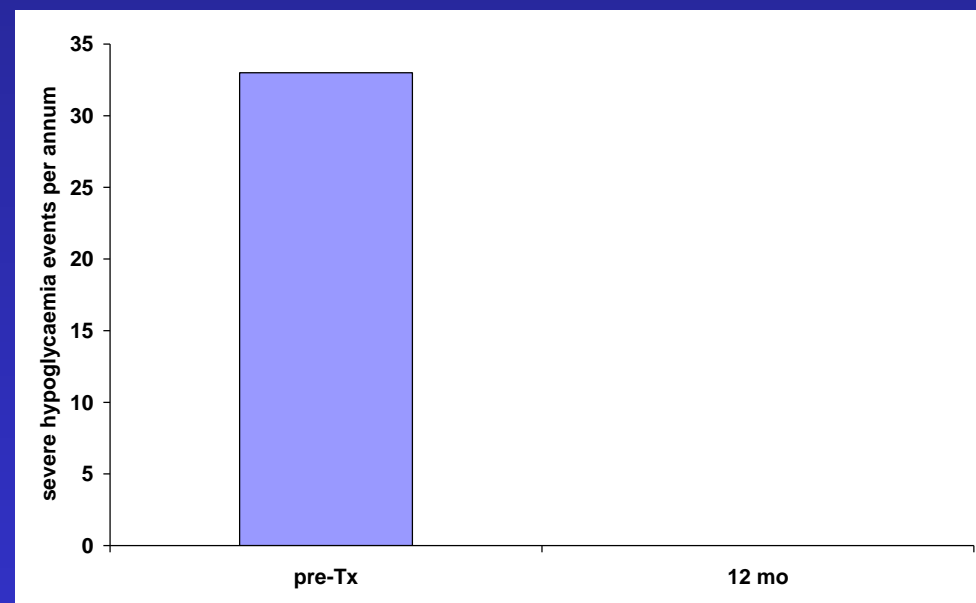
# Islet transplant activity (1999-2004)



# UKITC: first 12 patients



HbA1c



severe hypoglycaemia

Proof of principle for designated DoH funding

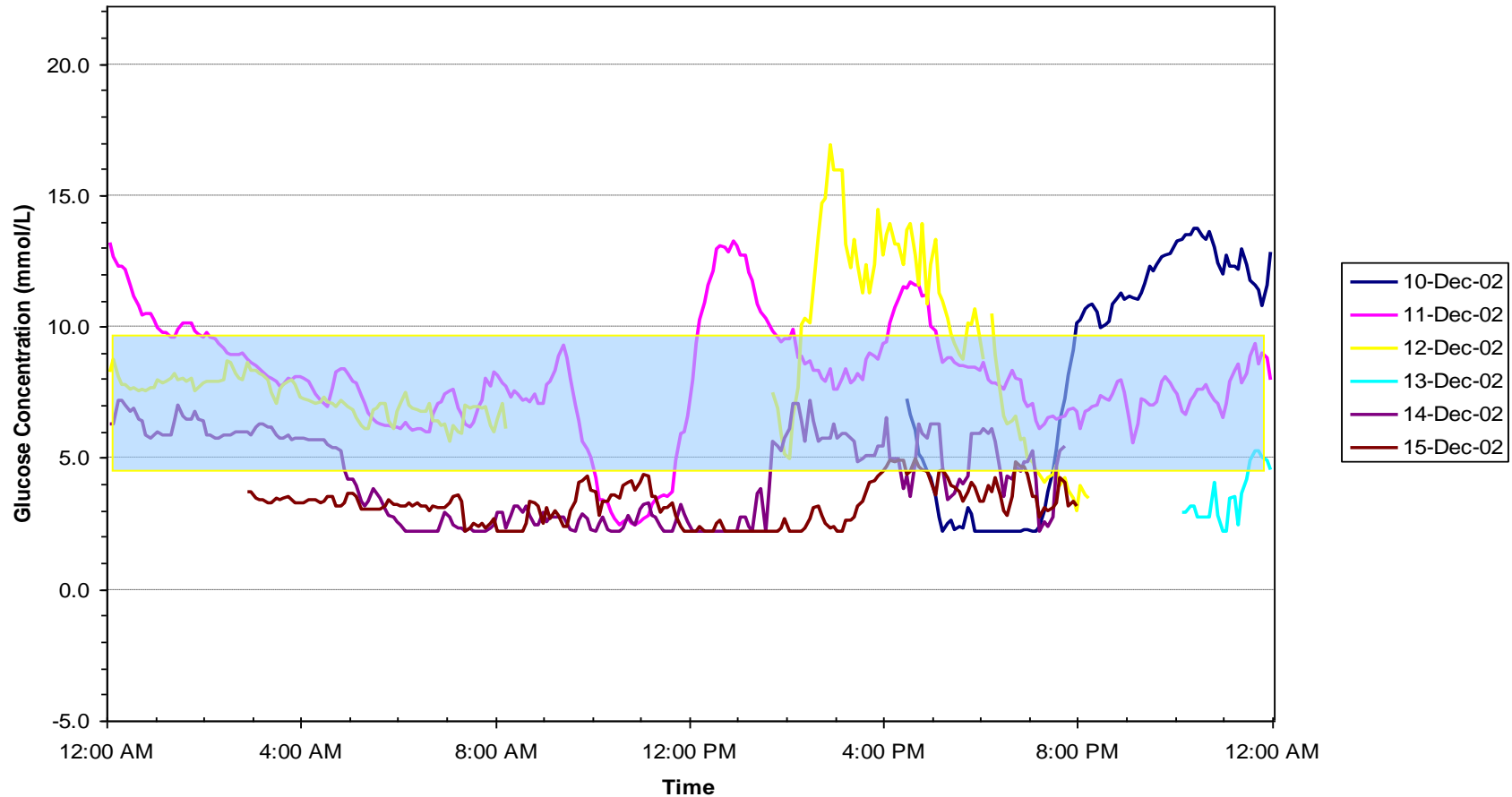


# King's College Hospital: case study

- Born 1944 - type 1 DM 1966
- Keen runner
- 1998: first reported problems with hypos after exercise
- By 2002 – recurrent severe hypoglycaemia – stopped running
- Problems persisted on insulin pump treatment despite sub-optimal control: HbA1c 8.4%
- Unable to care for grand-daughter due to fear of severe hypos

# Continuous Glucose Monitoring Pre-transplant

Glucose Sensor Profile  
Modal Day



# 2 x Islet Infusions January 2004

- HbA1c 7.4%
- Detemir 8-10 units bd
- No hypoglycaemia

Resumed competitive running including  
Great North Run & London Marathon



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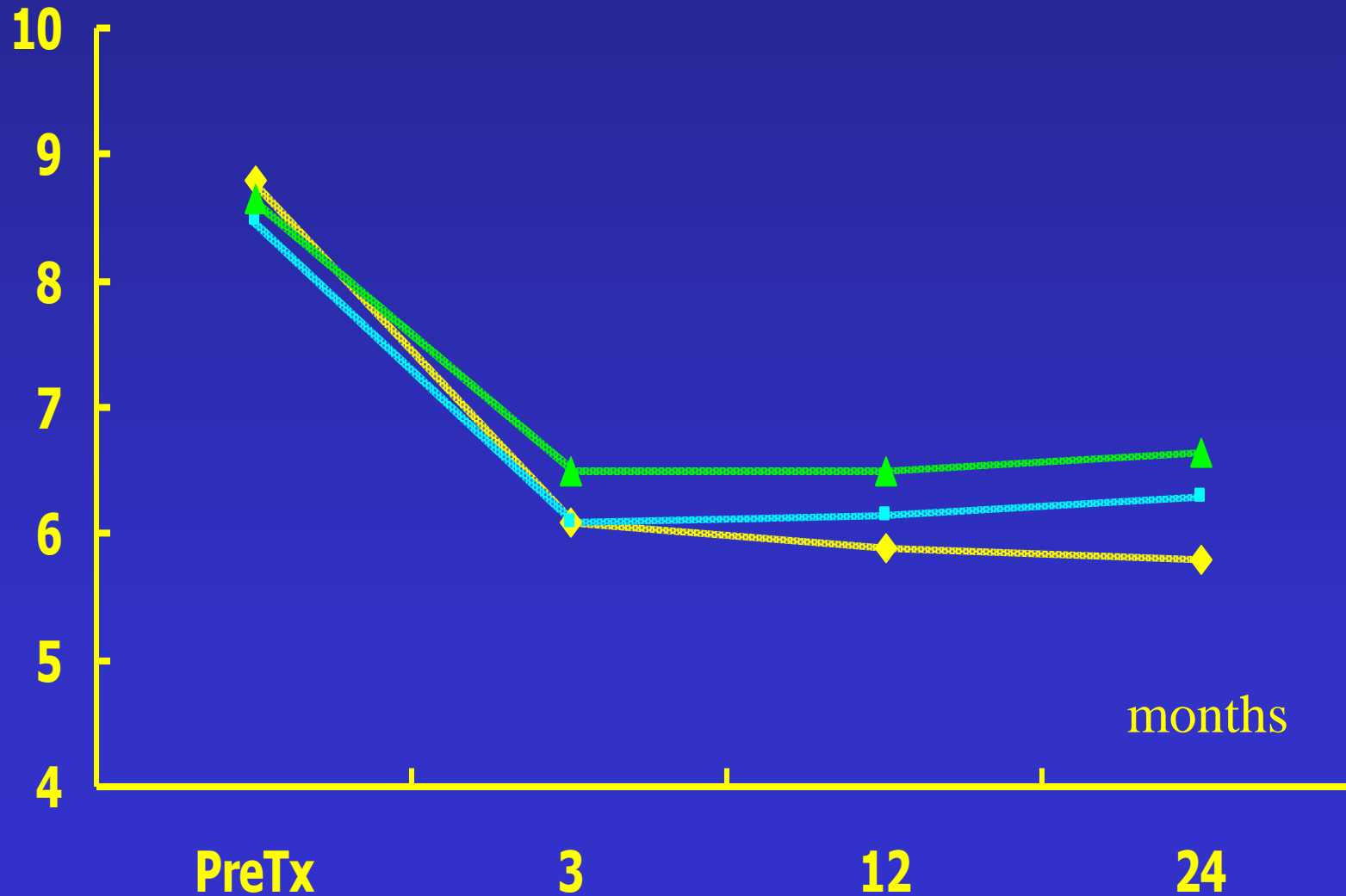
got to see me on TV, to  
torch from sprinter Kath  
handed it on to Dame  
Each torchbearer was  
of their own to keep as  
day, as well as the sport  
And it all ended in a hug  
as 70,000 people thronged  
a special concert featuring  
Ozzy Osbourne, Rod Stev  
Will Young and Jamelia.

# Edmonton protocol

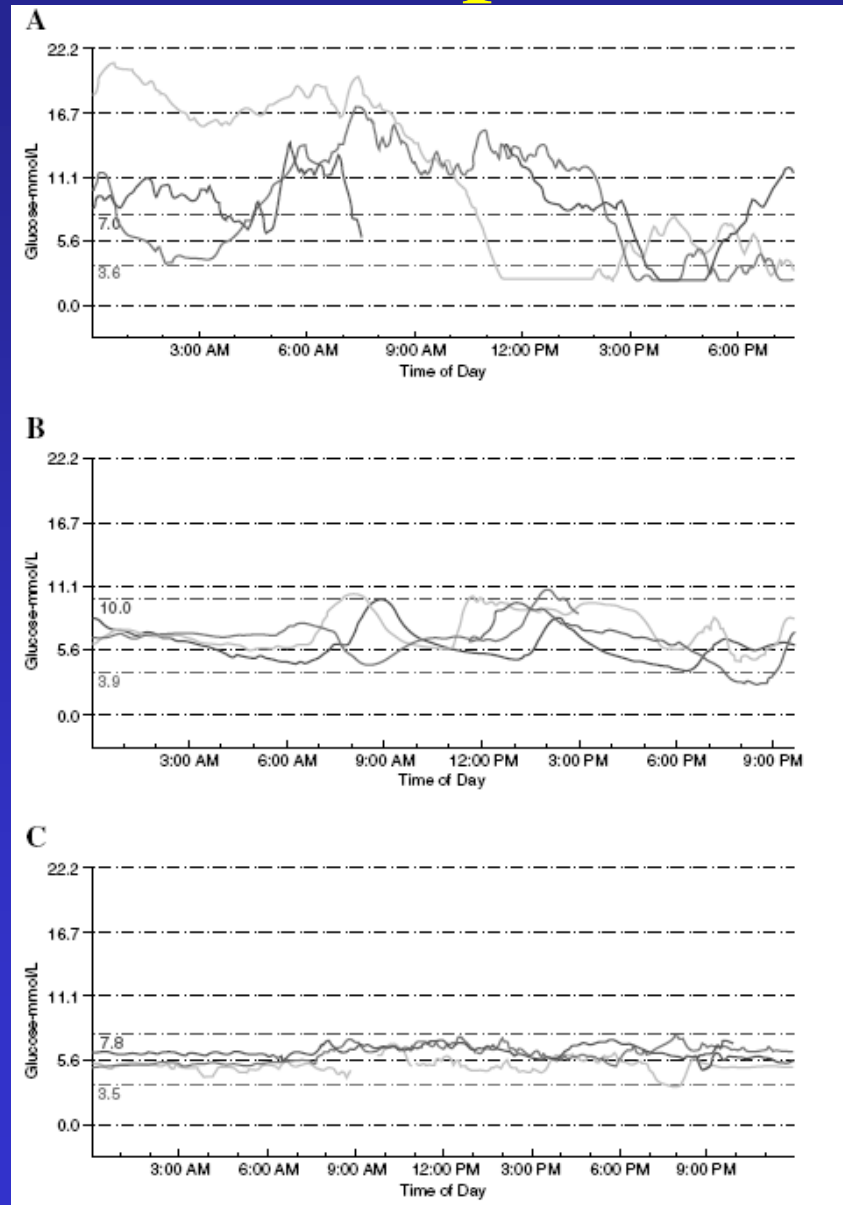
- 65 patients by 1<sup>st</sup> November 2004: 80% SH
  - 80% off insulin injections 1 year: several donors required
  - 10% off insulin injections at 5 years
  - 80% still making insulin at 5 years
- HbA1c 6.4%; majority no recurrent hypoglycaemia

# Diabetes Control

HbA1c



# CGMS profiles



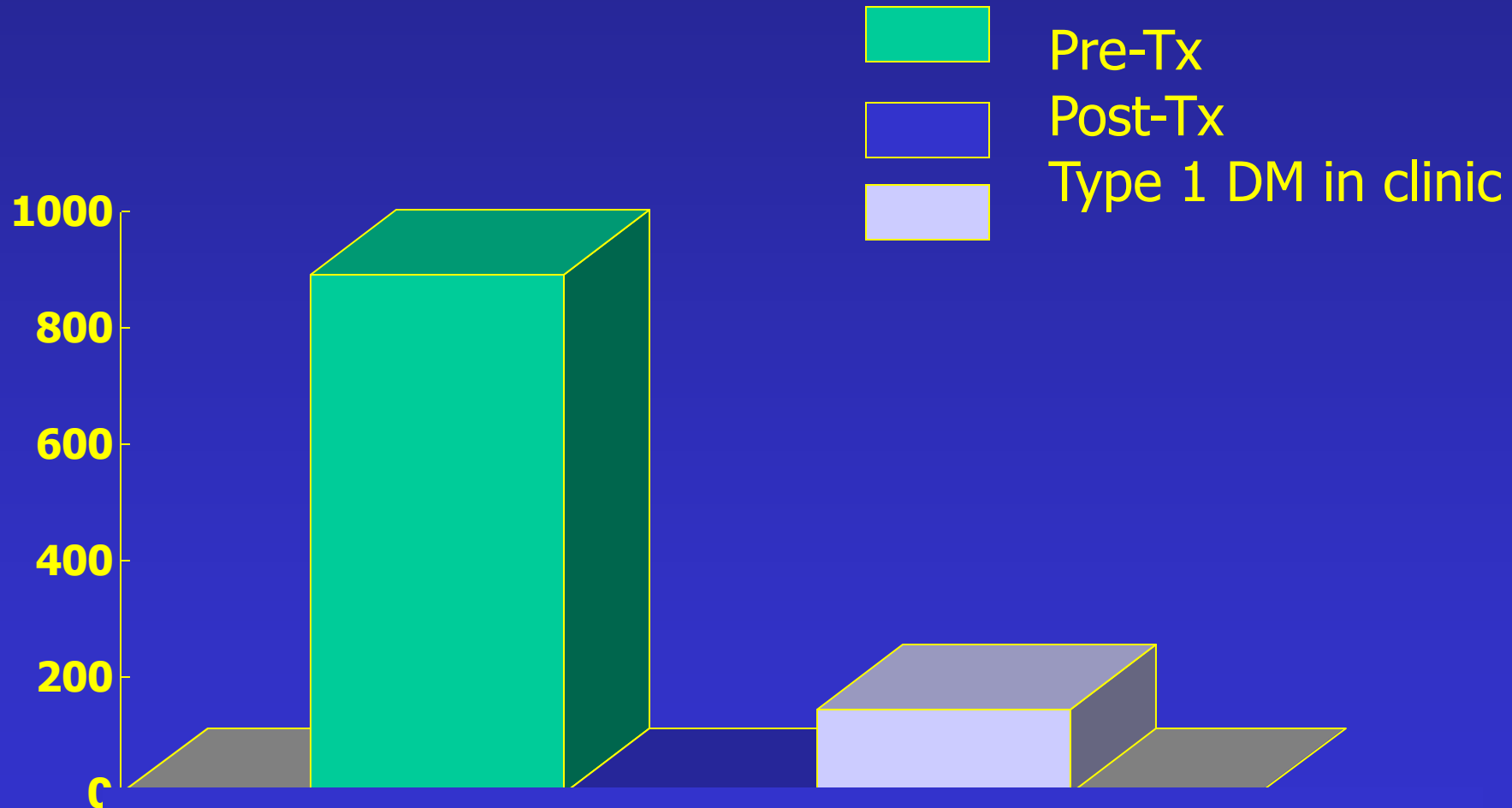
Non-transplanted

Insulin requiring

Insulin independent

Paty BW *et al.*,  
*Diab Tech Ther* 2006

# Effect of Islet Transplantation on hypoglycaemia burden



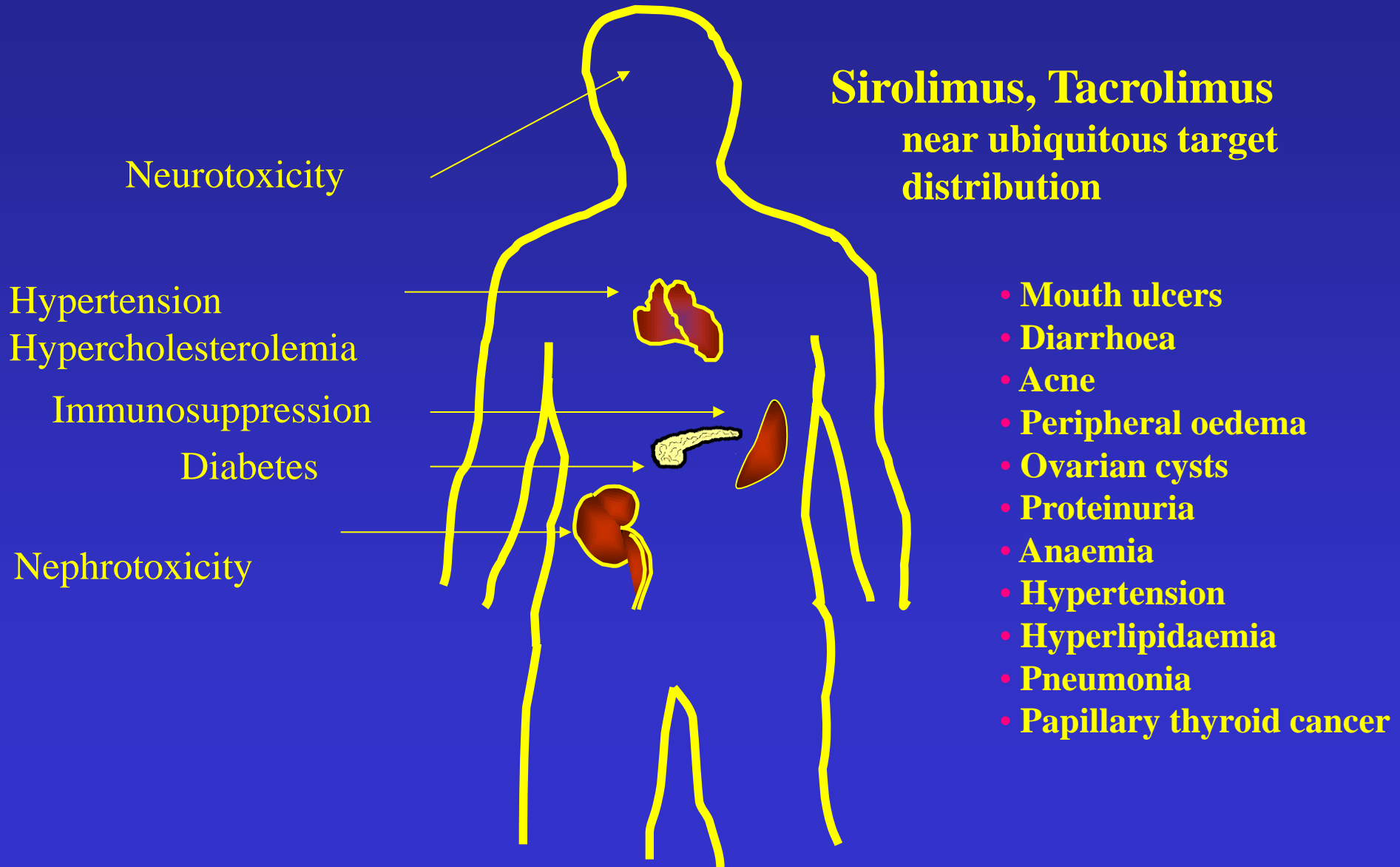
**Reduced fear of hypoglycaemia**

# Surgical complications

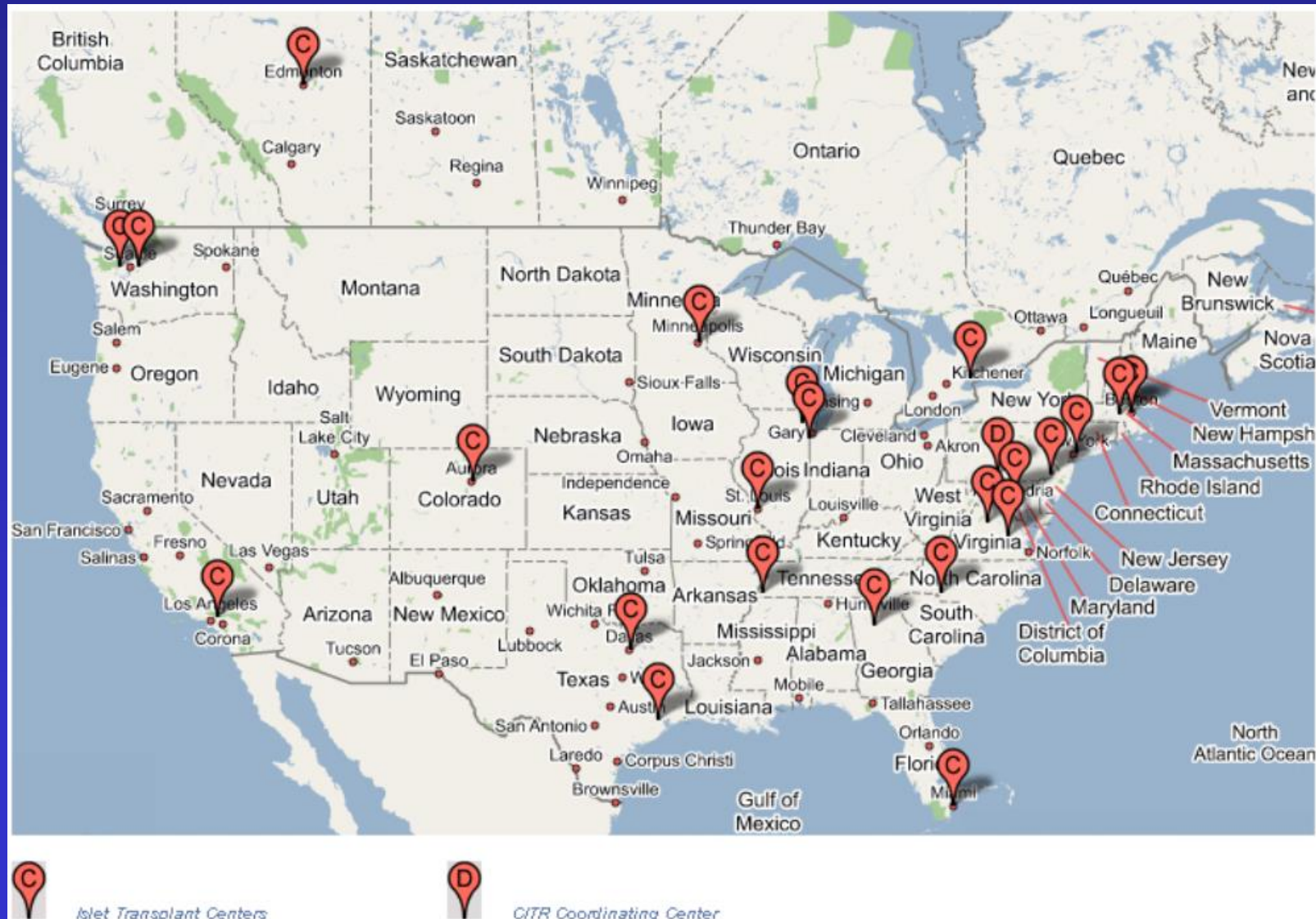
- One unrelated death
- Bleeding (4%)
  - smaller catheter / Avitene paste (0%)
- Portal vein thrombosis (4%)
- Gall bladder related (4%)
  - dye injection; bleeding; no perforations
- Transient liver inflammation
  - acute rise in portal venous pressure after 3<sup>rd</sup> transplant
  - glycogen accumulation / steatosis (MRI / IHC)



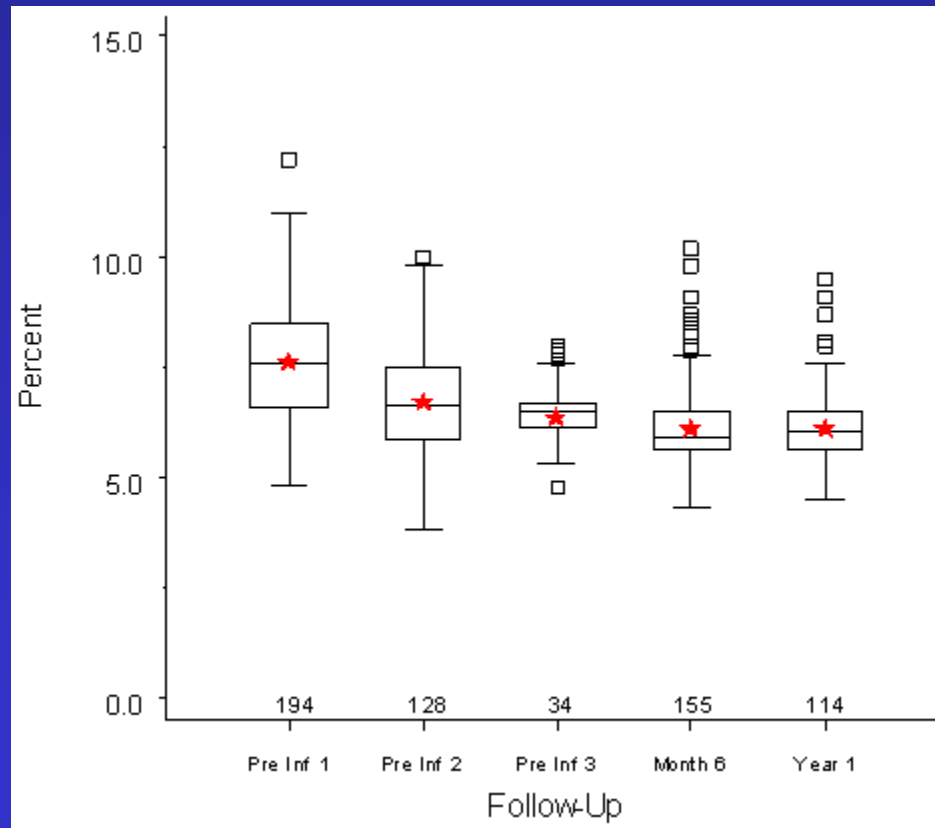
# Drug Target Distribution and Toxicity



# CITR: Islet Transplant Centres (N=23)



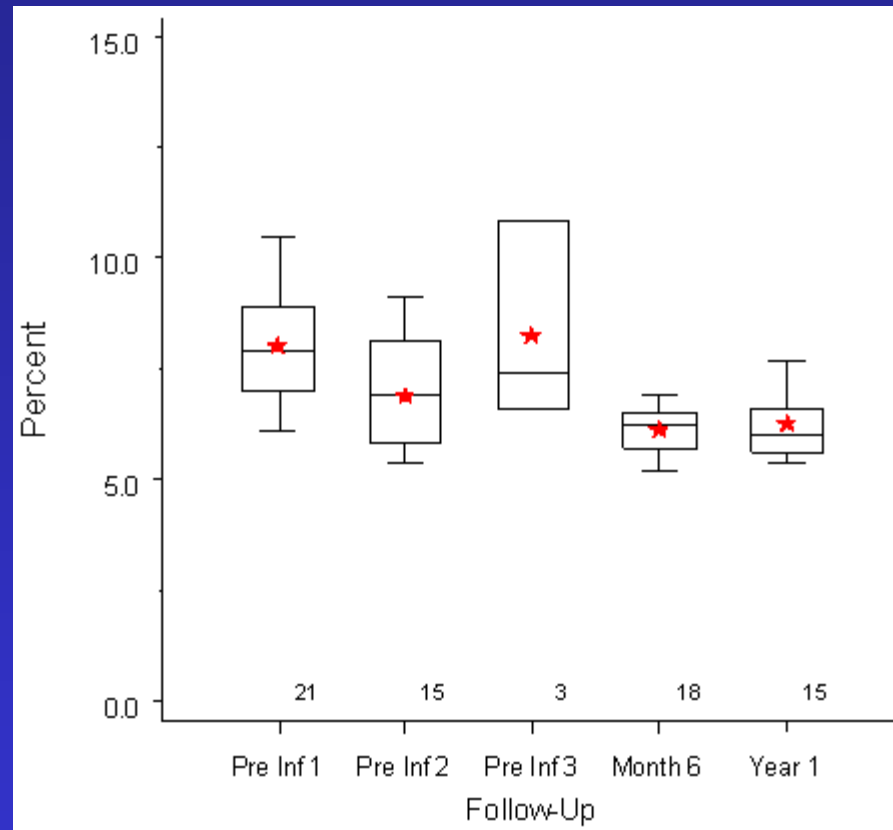
# HbA<sub>1c</sub> pre-infusion and post-last infusion: ITA 1999-2005 (n=203)



# Islet after kidney transplantation

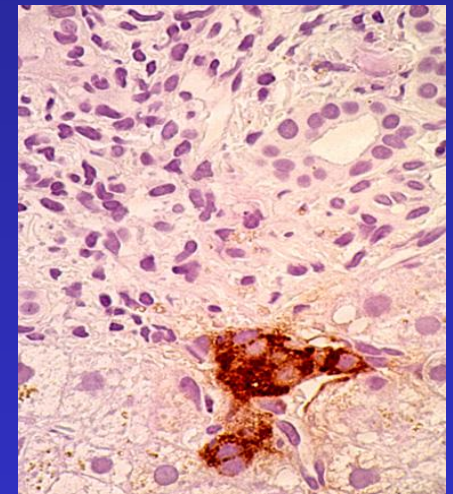
- 36 T1DM renal transplant recipients (Newcastle)
  - excellent ongoing renal function / QoL
- Mean HbA1c: 9.1%; AHA/SH: 83%
- High risk of vascular event / recurrent nephropathy
- 25% aged over 50 years: not suitable for PAK
- Liberation from insulin injections and SMBG
  - less important than avoidance of complications

# HbA<sub>1c</sub> pre-infusion and post last infusion: IAK (n=22)



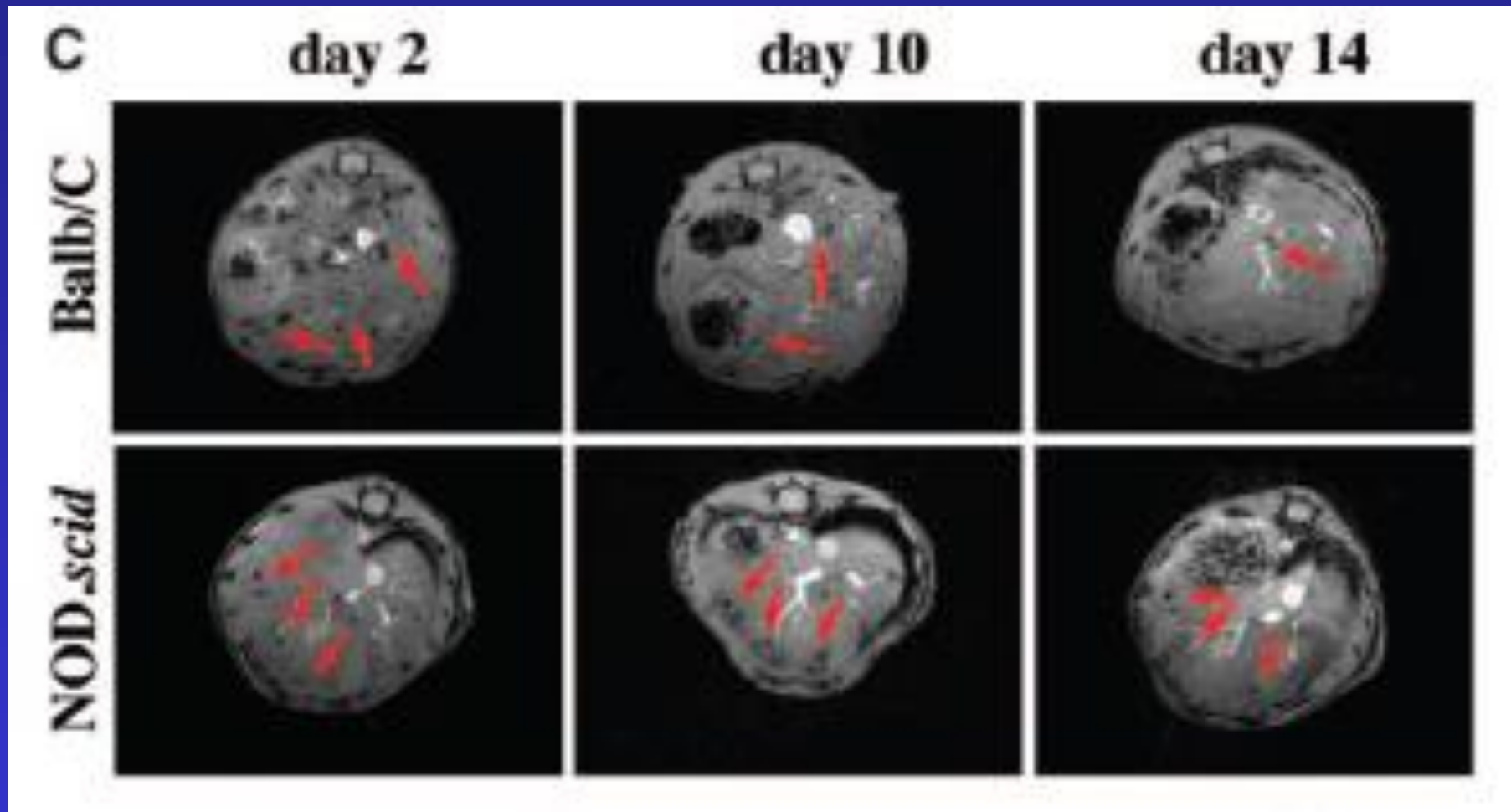
# Decay in islet function over time

- Instant blood-mediated inflammatory reaction
- Chronic allograft rejection
- Undiagnosed acute rejection
- Recurrent autoimmunity
- Drug toxicity (Tac/Srl)
- Failure of islet regeneration (Tac/Srl)



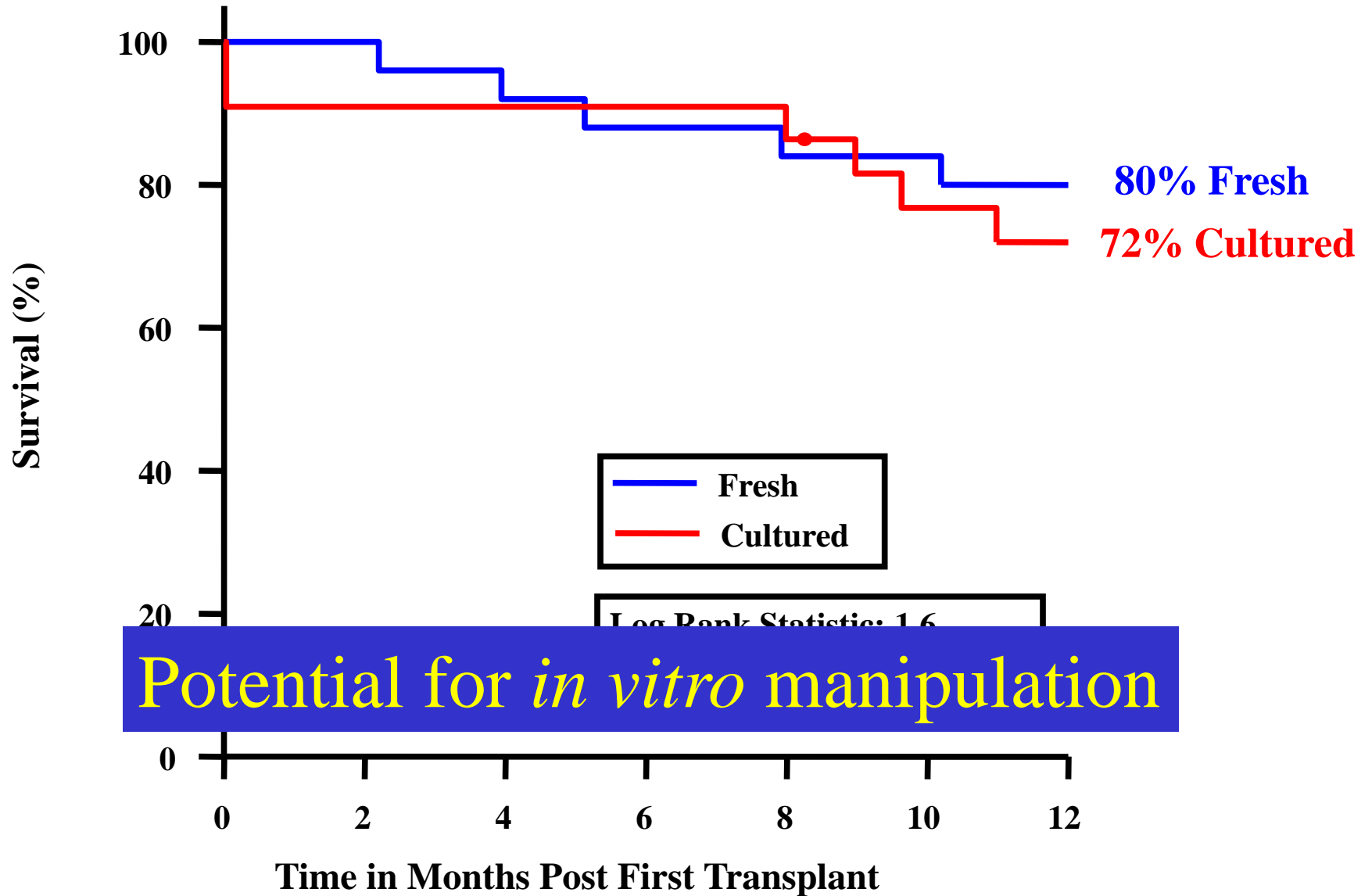
New antithrombotic protocols  
 $\beta$ -cell function / insulin resistance  
Auto-antibodies (GAD, ICA, IA2)  
T cell response  
Panel reactive antibody response  
Serial systematic graft biopsies:  
Infiltrates, islet amyloid, fibrosis

# *In vivo* islet imaging



FDA-approved Feridex labelling Bonner-Weir *Diabetes* 2006

# Kaplan-Meier Survival Curves (Insulin Independence) From time of first transplant





# Miami / GRAGIL / Nordic networks



Transport of islets between centres:  
equivalent outcomes to locally purified islets

# New model for cell-based therapy



Kings islet isolation unit



Newcastle Stem Cell Manipulation  
and Gene Therapy Unit

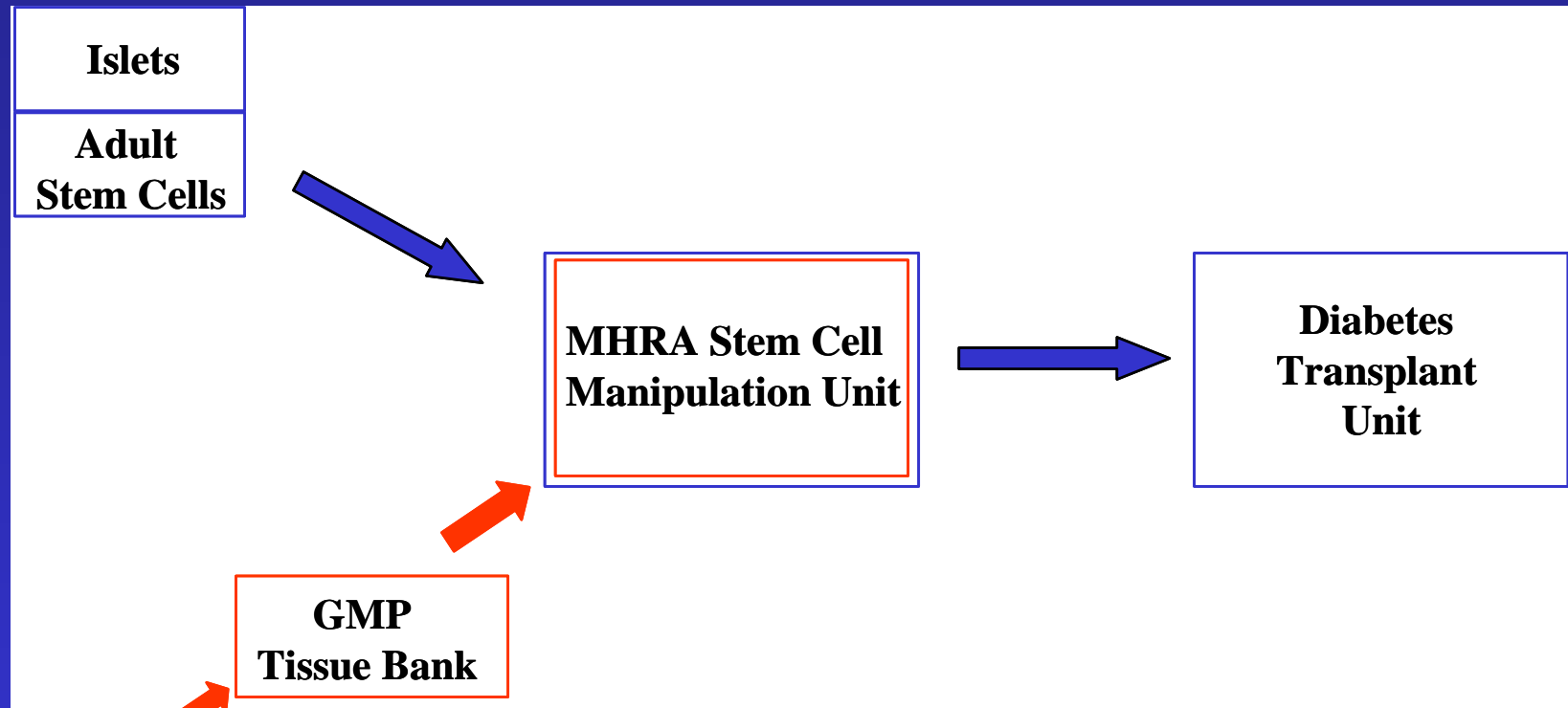
# An NHS Islet Transplant Programme

- Maximise retrieval of suitable organs
  - address mismatch: organs; isolation facilities; patients
- Equity of access to integrated NHS service
  - regardless of post-code and ephemeral research funds
- 2 isolation units: uninterrupted / quality assured
- 6 transplant centres
  - assessment; transplant; follow up
- Allocation of optimally retrieved organs
  - according to national prioritised waiting list



○ NCG islet  
○ transplant  
○ centre

# Final common pathway for accredited cell processing and clinical transplantation



**Sufficient donors for <1% T1DM**

**Porcine xenografts may provide alternative**

# Reproducible single donor success

- 8 consecutive achieved insulin independence
  - 5 (63%) maintained for greater than 1 year
- Recipient selection: weight <70Kg; <40U/day
  - donors <50 years old; BMI >27
- RATG; daclizumab; etanercept induction
  - islet culture; peri-transplant iv insulin; heparinisation
- Insulin requirement: inadequate immunosuppression
  - positive islet autoantibodies

# David Sutherland; Minnesota:

- ‘Career devoted to availing pancreas transplants for those wanting this procedure’
- ‘Pancreas transplants are associated with a relatively high incidence of surgical complications and the whole gland is transplanted solely to supply one cell – the only one missing in Type 1 diabetes, the beta cell’
- ‘If ever there was a solid-organ transplant that could be replaced by a cellular transplant, it is islet for pancreas transplantation. If there was ever an indication for wholesale transfer from major to minimally invasive surgery, this is it’

# UK Islet Transplant Consortium

- Establish  
– 18  
– no  
– No
- Recruitment  
– co  
– do  
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- Sub-  
– se  
– H

**INSULIN SENSITIVE PATIENTS**

**WITHOUT RENAL FAILURE**

**in whom**

**INSULIN THERAPY IS FAILING IN  
A BIG WAY**



# Conclusions

- Islet transplantation proven benefit
  - in T1DM complicated by severe hypoglycaemia
- Careful candidate selection imperative
  - insulin sensitive without renal failure
  - adequate trial of optimised conventional therapy
- Progress towards single donor success
- Long-term insulin independence next goal
- Conduit for all  $\beta$ -cell replacement approaches

