Advanced Therapy Treatment Centres

LONDON ADVANCED THERAPIES

Beta-cell replacement therapy for diabetes

James Shaw

Professor of Regenerative Medicine for Diabetes
Newcastle University

Chaired by Ceri Roberts

Scientific Training Manager – Cellular and Molecular Therapies
NHS Blood and Transplant

Funded by

UK Research and Innovation

Coordinated by

CATAPULT Cell and Gene Therapy

UKITC

UK Islet Transplant Consortium

Beta-cell replacement therapy for diabetes

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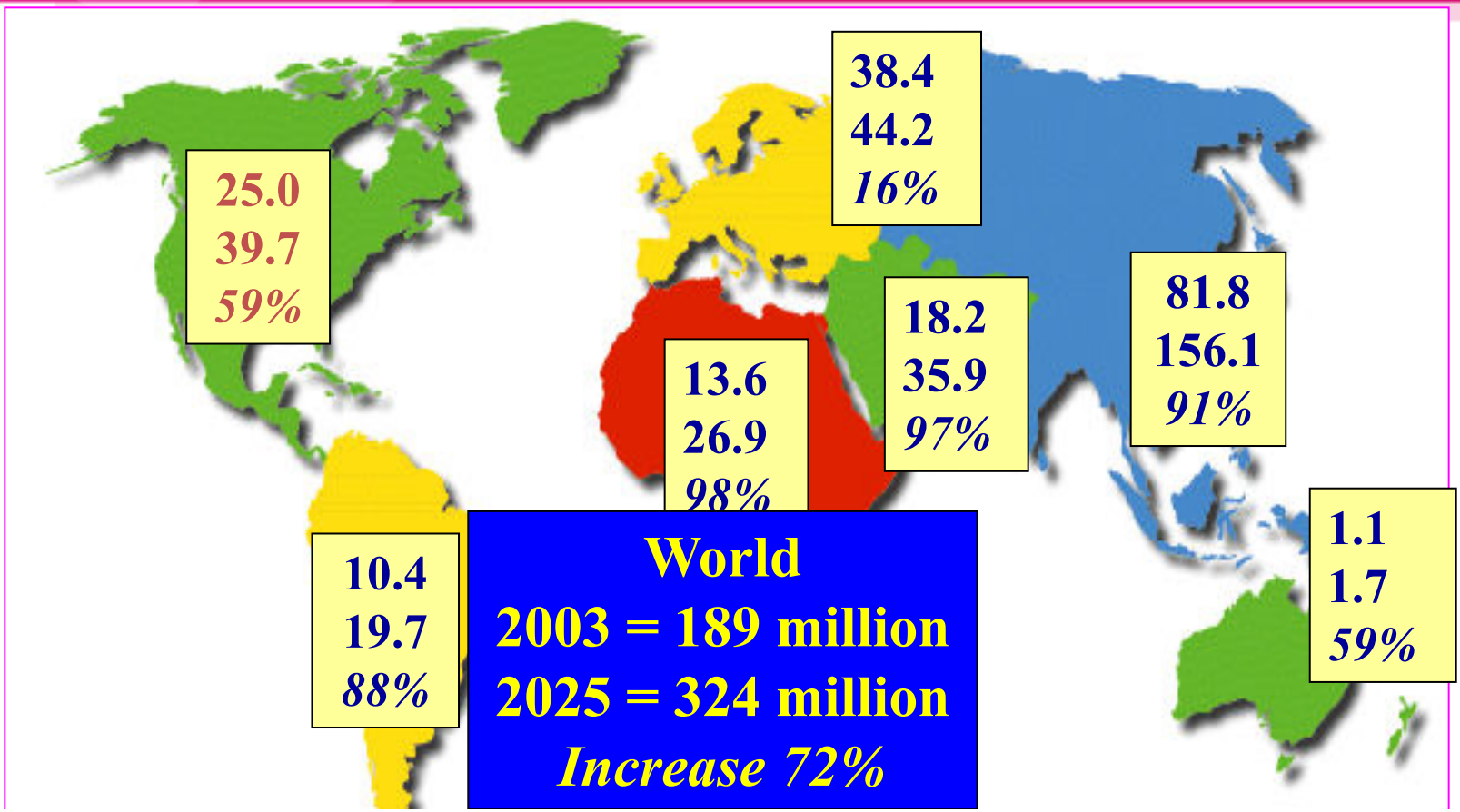
Overview

- Introduction to type 1 diabetes
- Need for beta-cell replacement therapy
- NHS-adopted islet cell transplant programme
- Addressing remaining challenges through ATs

Global predictions for the diabetes pandemic 2003 - 2025



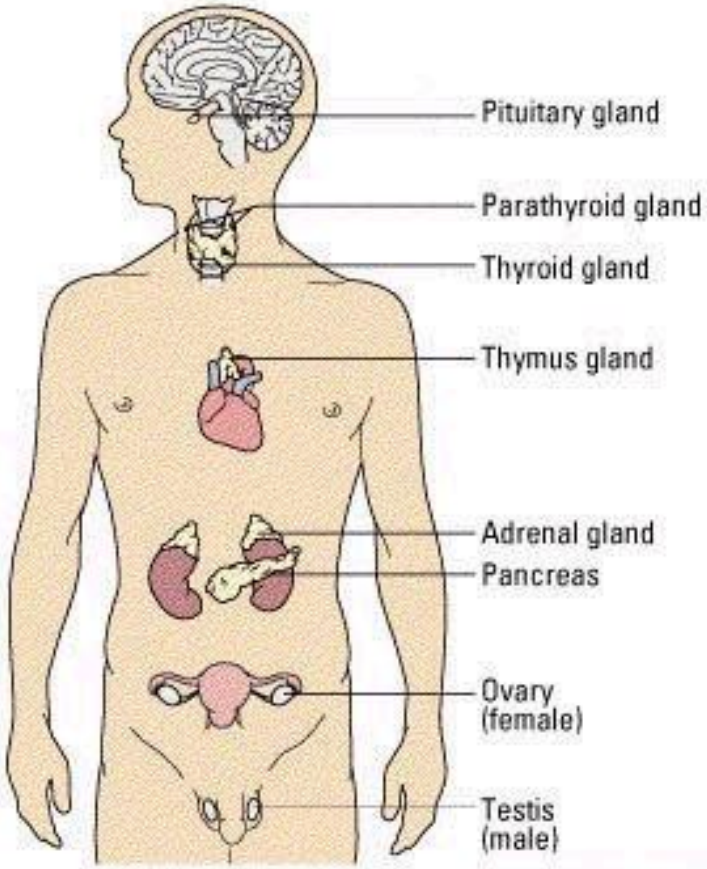
Type 1 diabetes: 30 million worldwide

Type 1 diabetes incidence increasing

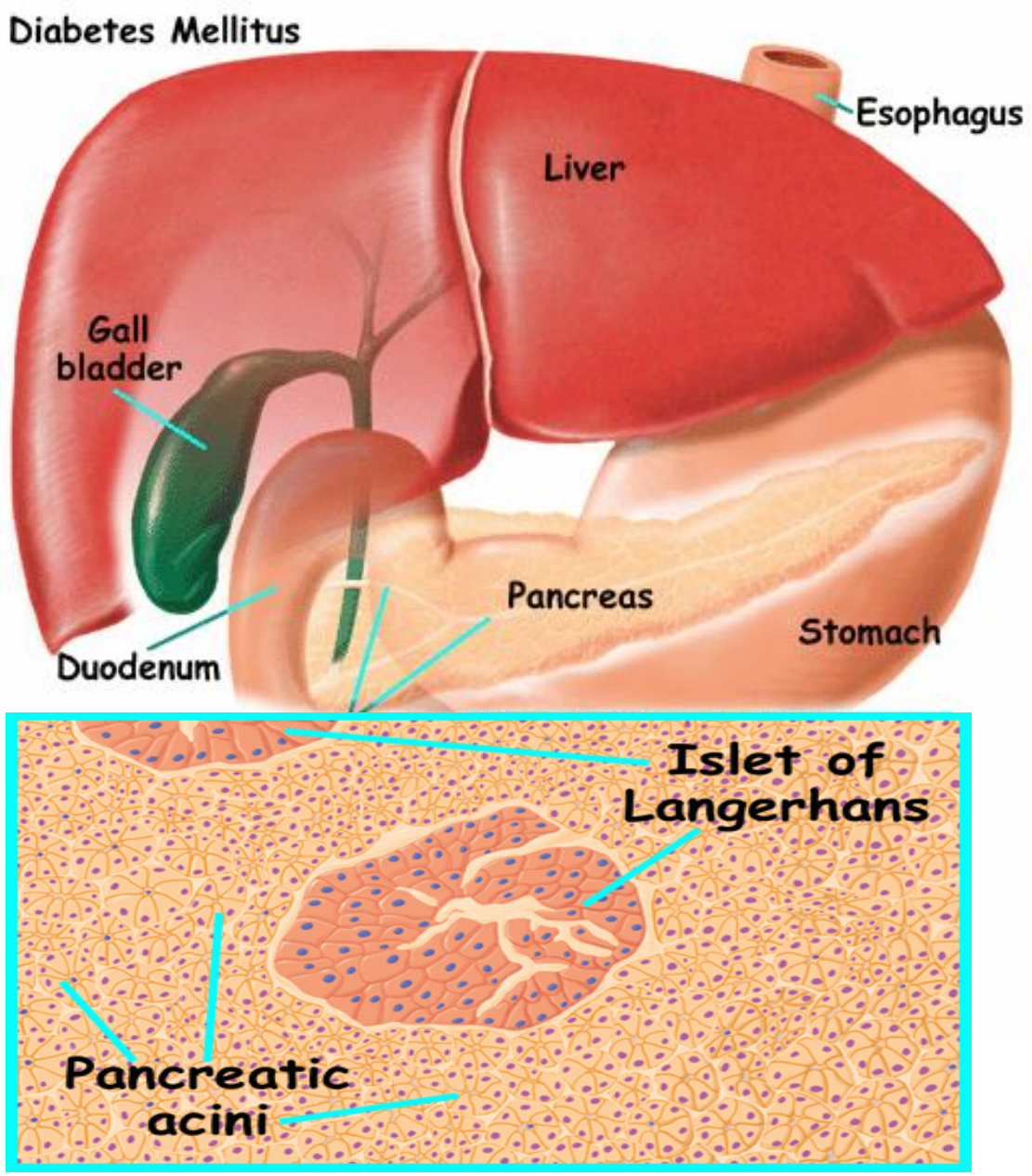
Standardised incidence rate Type 1 diabetes (age 0-14)
4.6 cases per 100 000 per year in northern Greece
42.9 annual cases per 100 000 in Finland

The Endocrine System

Glands which release chemicals directly into the blood stream.

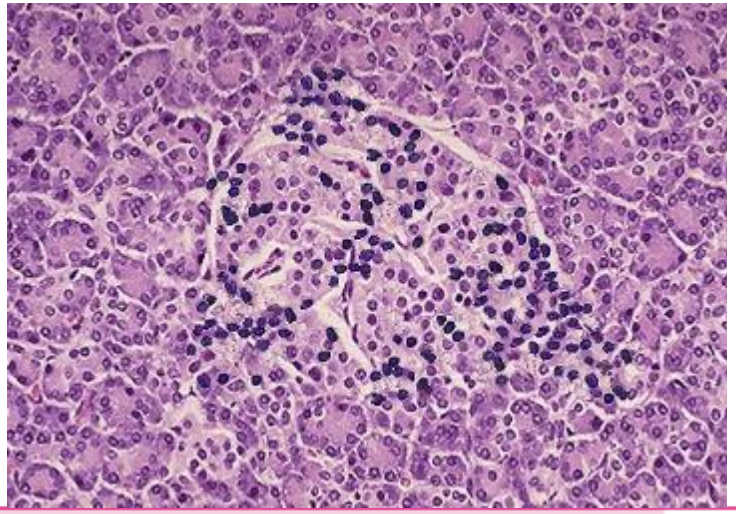


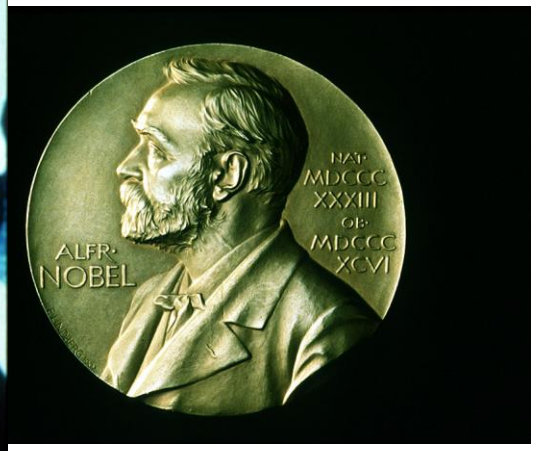
adam.com


Diabetes Mellitus
Esophagus
Liver
Gall bladder
Pancreas
Stomach
Duodenum
Islet of Langerhans
Pancreatic acini

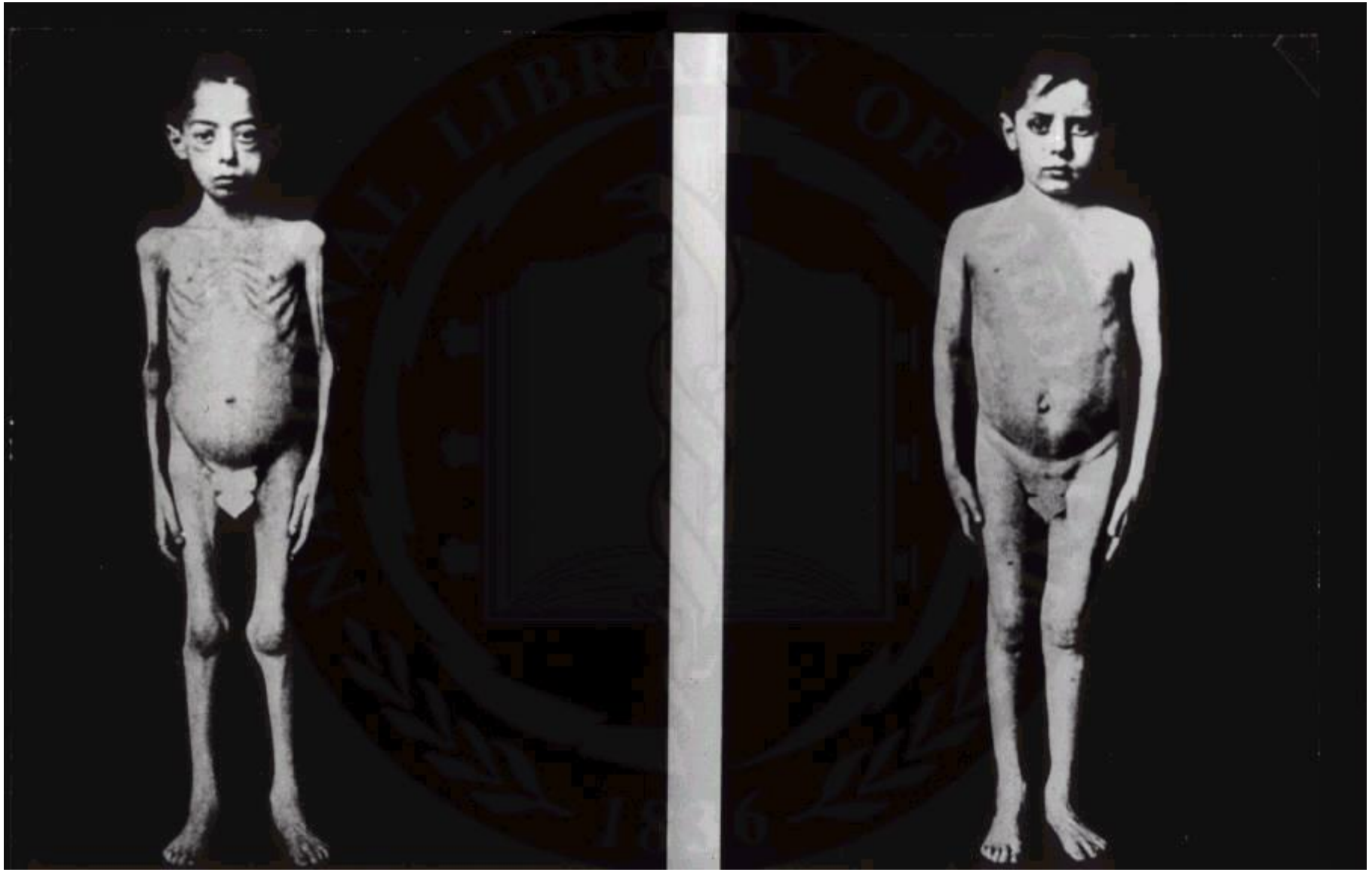
Type 1 diabetes

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

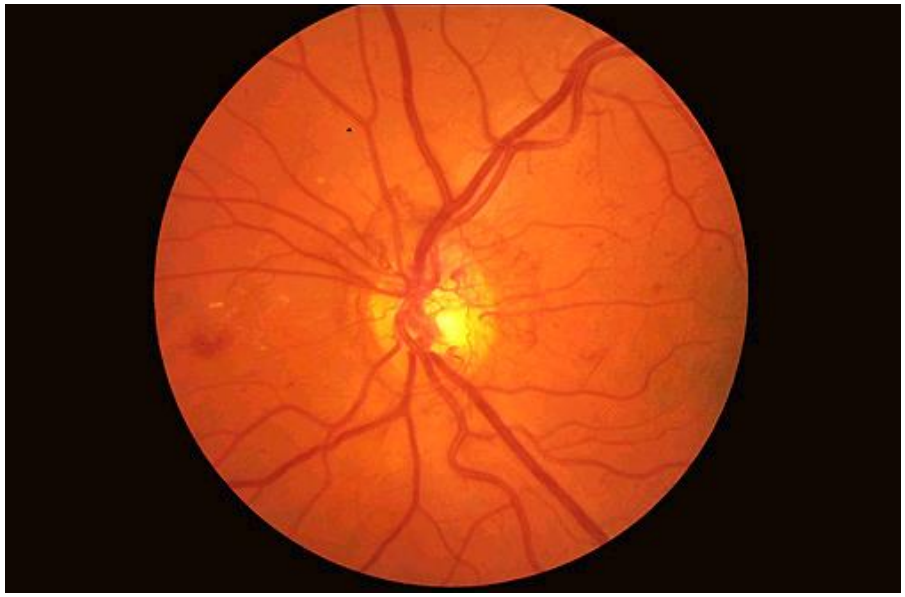


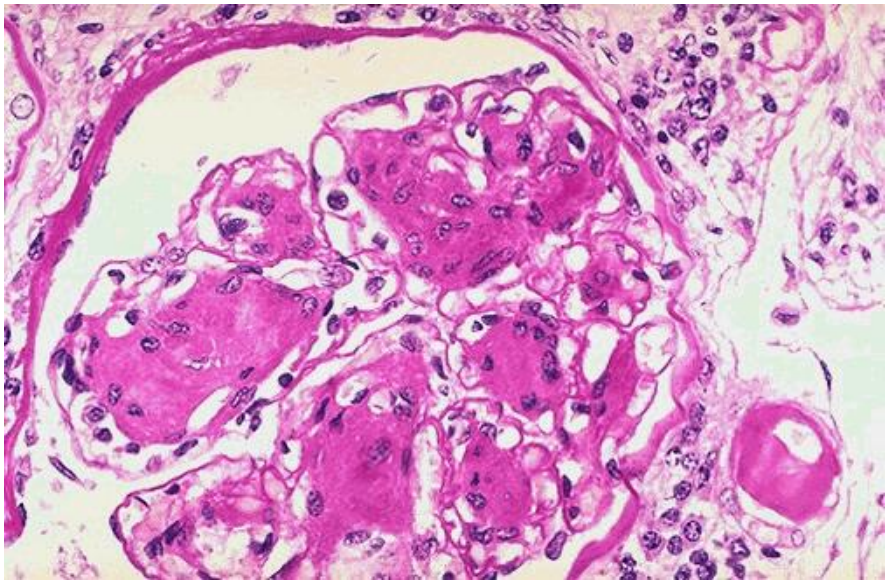


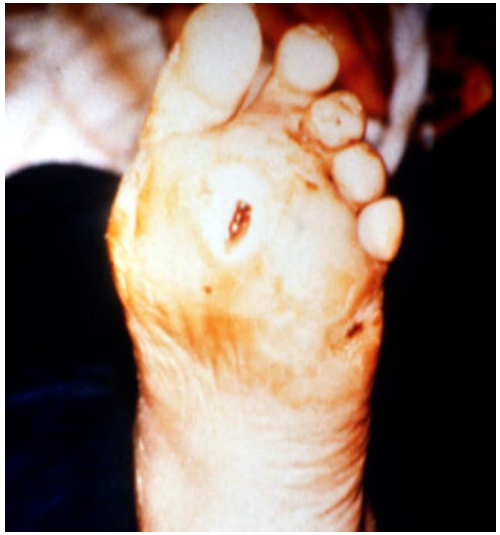
Toronto 1922



‘Unspeakably wonderful!’ Elizabeth Hughes 1907-1981

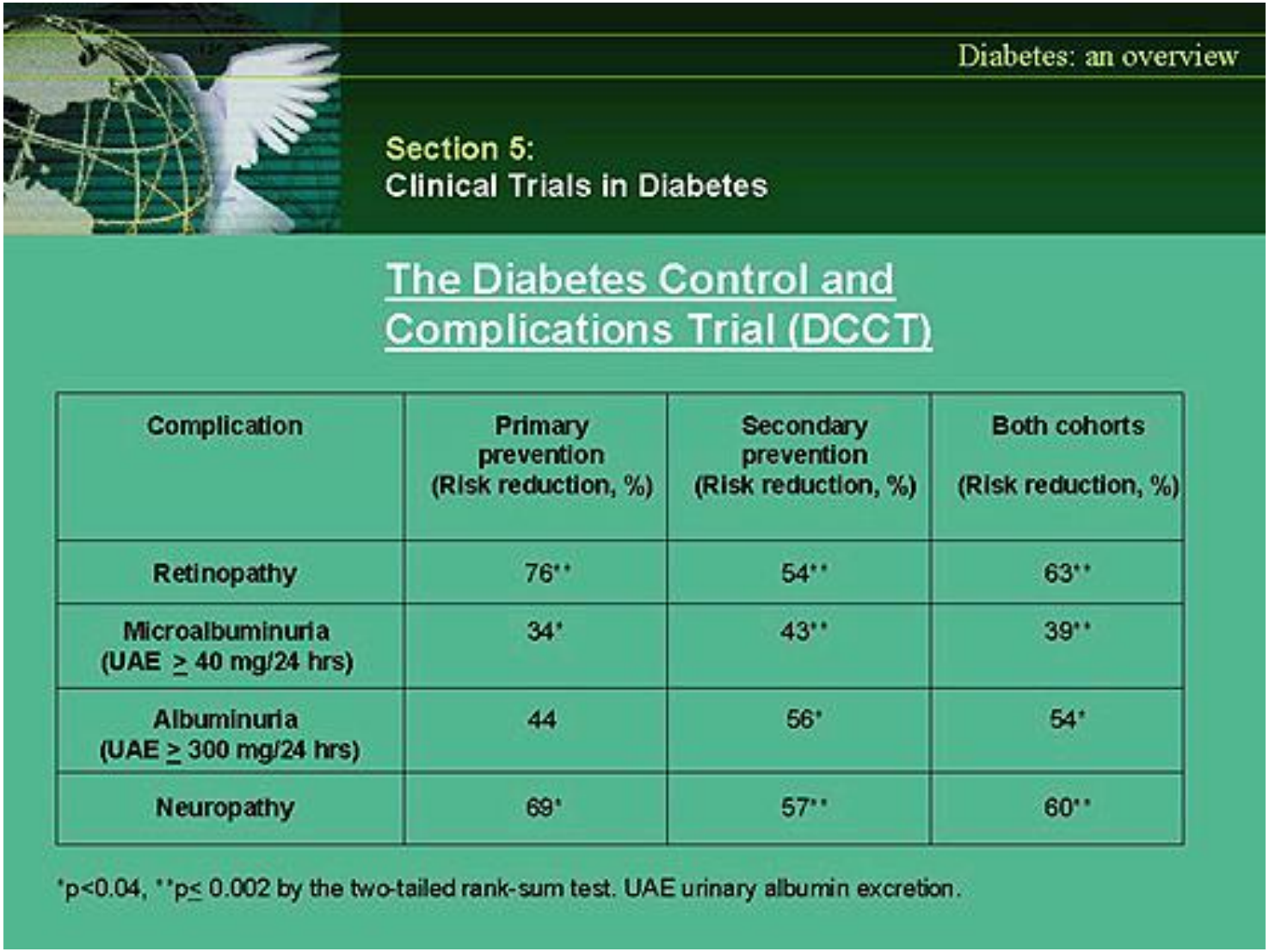






Major risk factor for MI / CVA

Life expectancy reduced up to 10 years



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

Hypoglycaemia

Discovery of insulin – one of the medical miracles of the 20th century

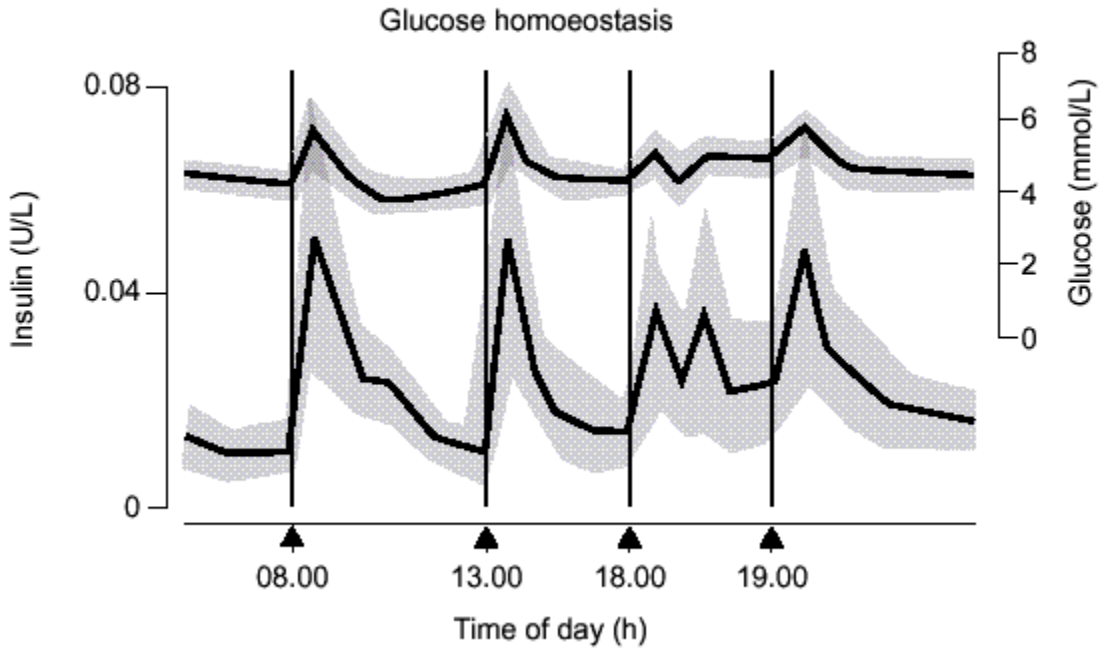
'Insulin reactions' seen since its earliest use

'.....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

24-hour plasma glucose and insulin profiles in healthy individuals

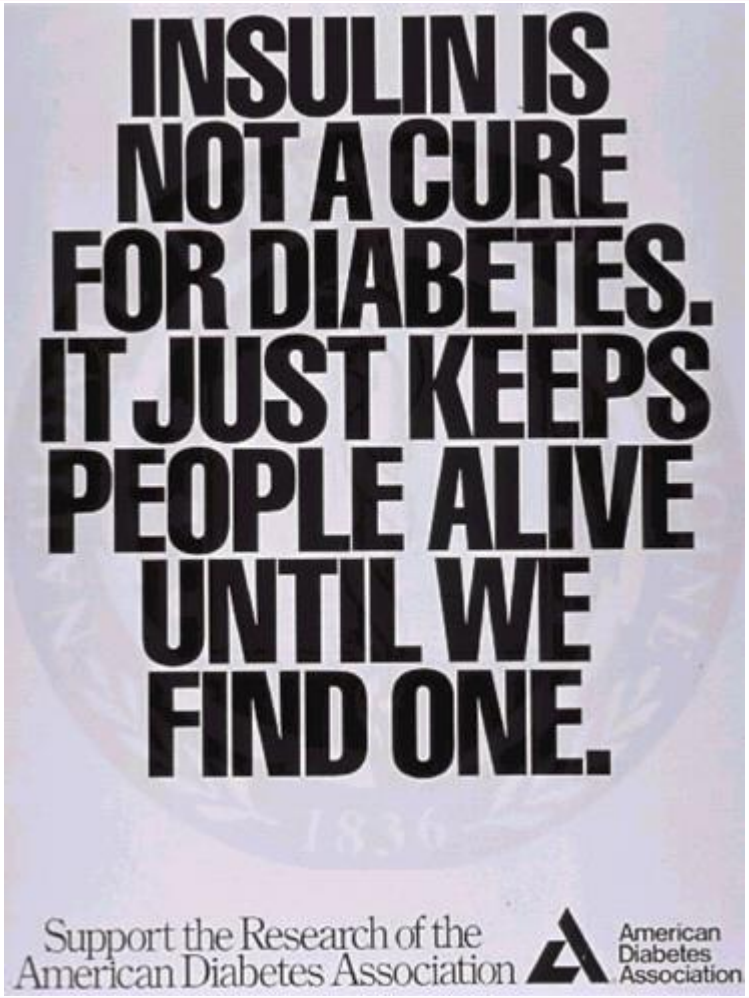


Owens DR et al. Lancet 2001;**358**:739–746

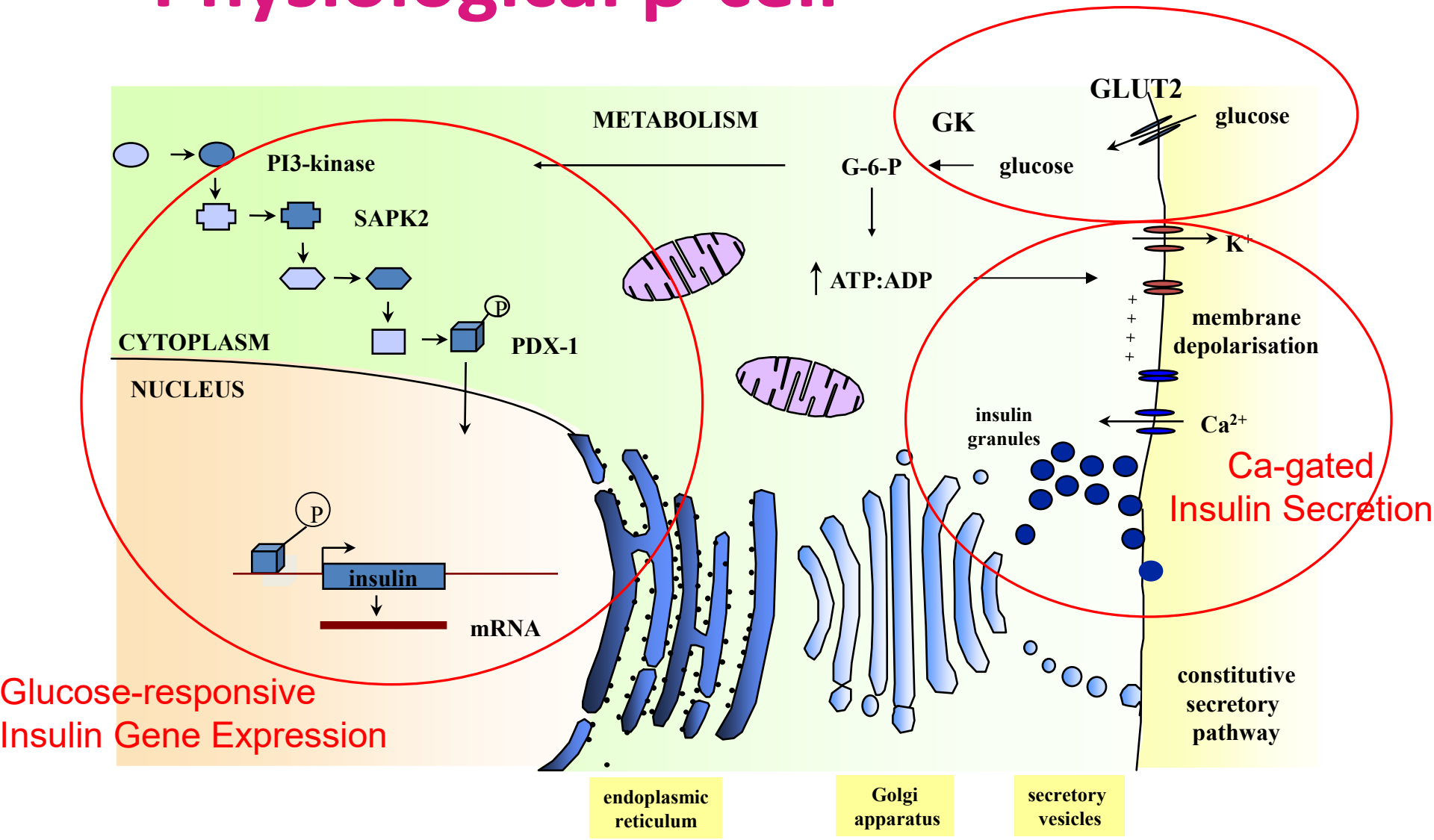
Conventional therapy

- 100 years' experience with insulin therapy
  - hypoglycaemia remains limiting factor for optimal control - 50% PA
- Closed loop – biochemical hypoglycaemia
  - Those at highest risk have not yet been studied

Exogenous insulin replacement – inextricably linked to hypoglycaemia


INSULIN IS NOT A CURE FOR DIABETES. IT JUST KEEPS PEOPLE ALIVE UNTIL WE FIND ONE.
Support the Research of the American Diabetes Association
American Diabetes Association

Physiological β-cell



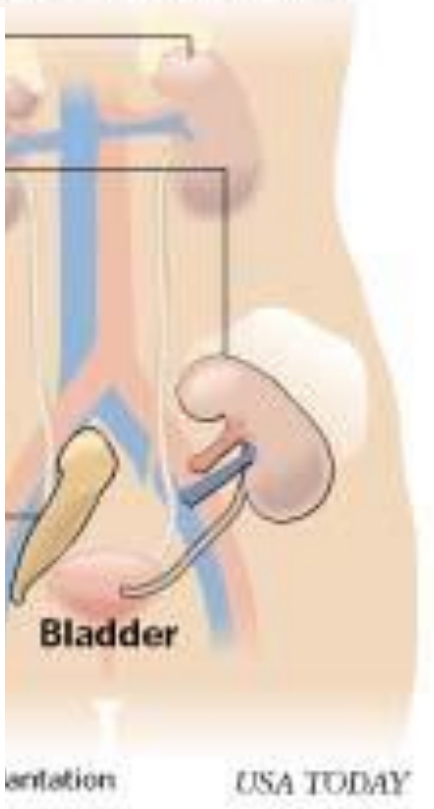
Blueprint for a double transplant

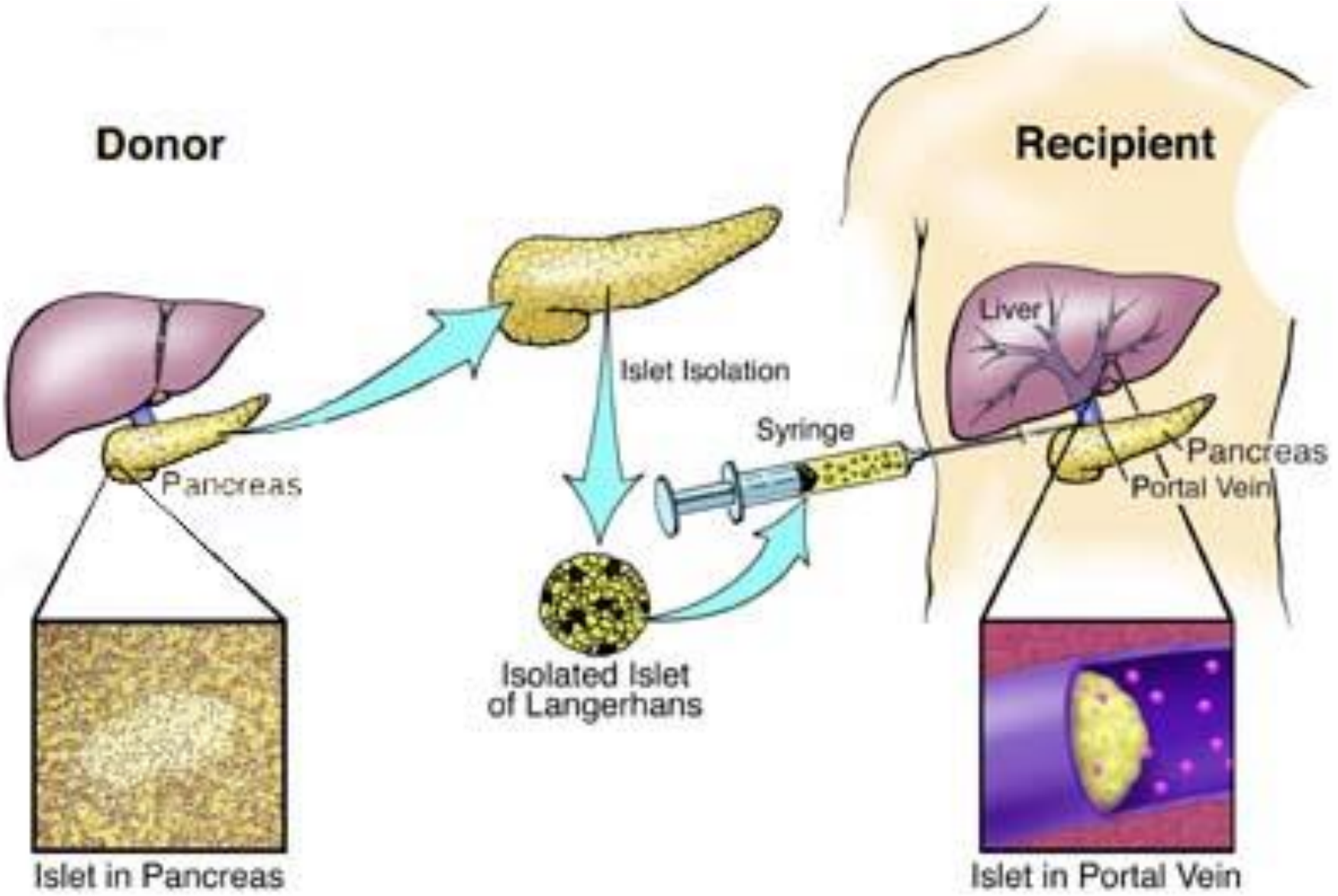
To cure Scott Bowles' diabetes and restore his body's ability to filter toxins from his blood, doctors transplanted two organs from an accident victim. The double transplant is an increasingly popular though controversial treatment among the nation's 1 million insulin-dependent diabetics. About 1,000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

Whole pancreas transplantation

- Offers potential of a 'cure'
  - normal glucose
  - prevention of hypoglycemia
- Major operation – 3-5% mortality
  - 20% reoperation – may lead to graft pancreatectomy
- Requires life-long immunosuppression
- Combined with a kidney transplant




Donor
Recipient
Islet Isolation
Syringe
Liver
Pancreas
Portal Vein
Pancreas
Isolated Islet
of Langerhans
Islet in Pancreas
Islet in Portal Vein

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.

- 7 Type 1 patients with severe hypoglycaemia
  - metabolic instability
- 2-3 donors for each recipient
- Steroid (cyclosporin)-free immunosuppression
- All off insulin at 1 year

Successful but very expensive to set up in all transplant centres

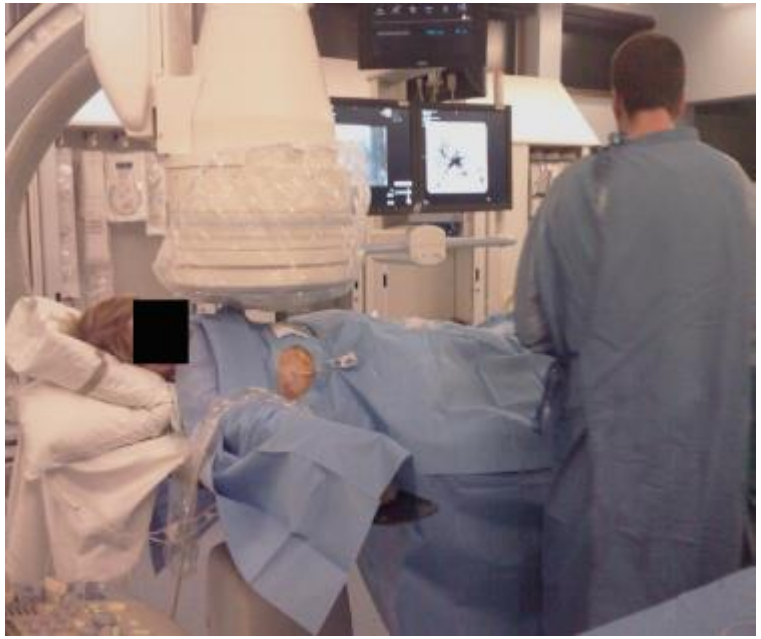
10% insulin independence at 5 years

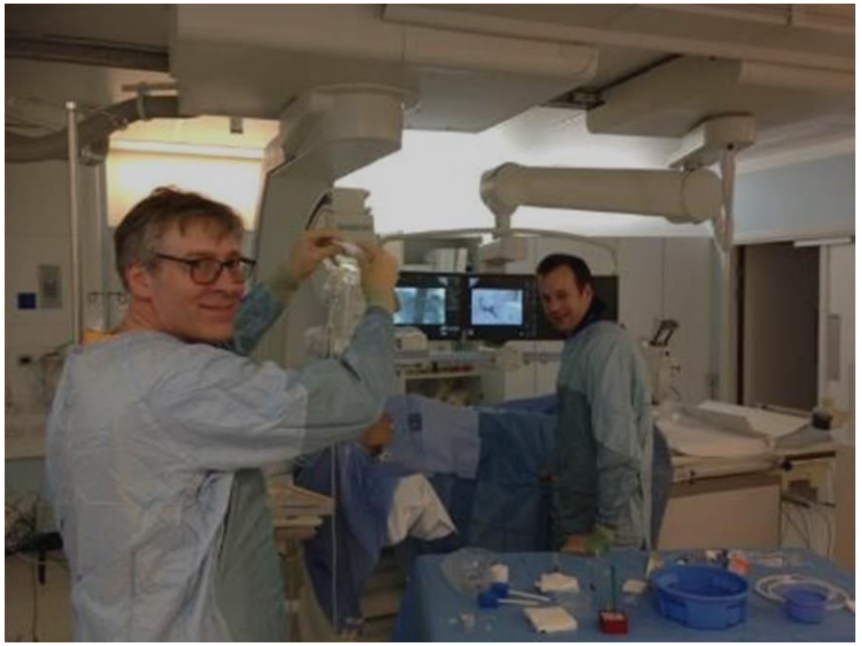
NCG islet transplant centre

First health service funded programme as an established clinical intervention

NHS / NICE: prevention of SH / HbA1c <7%

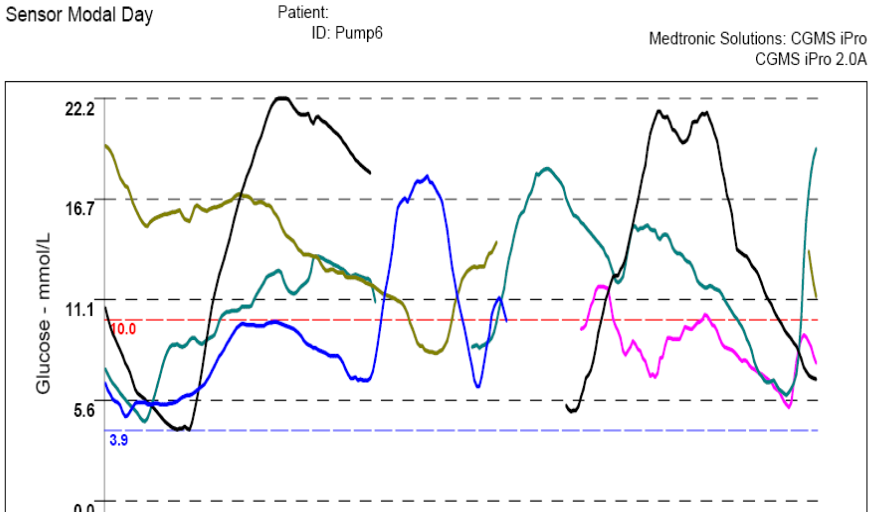
irst UK recipient of transported islets Octobe 2008 – 56 transplants to date



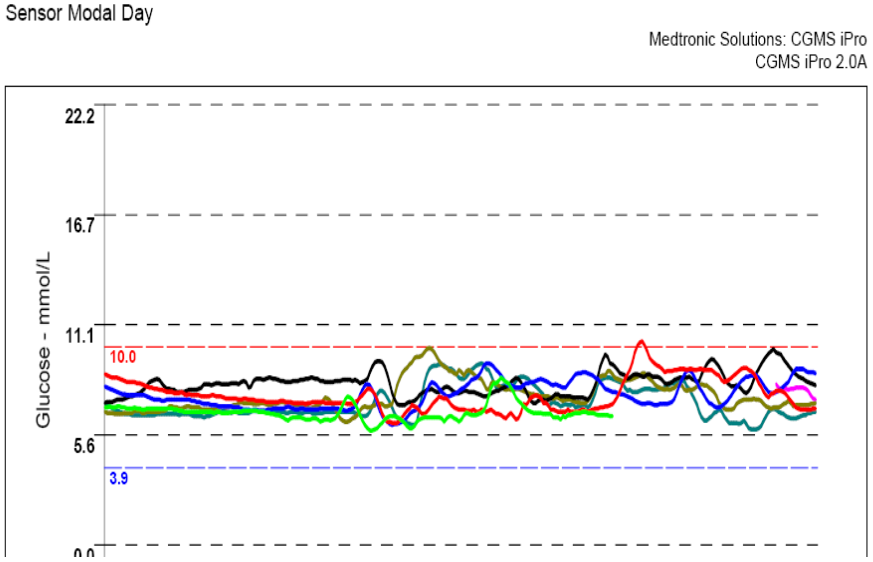


Aldibbiat A *et al., Cell Medicine* 2012
Brooks A / Oram *et al., Diab Care* 2014, 2015
Brooks A *et al., AJT* 2013, 2015

Newcastle recipient CGMS

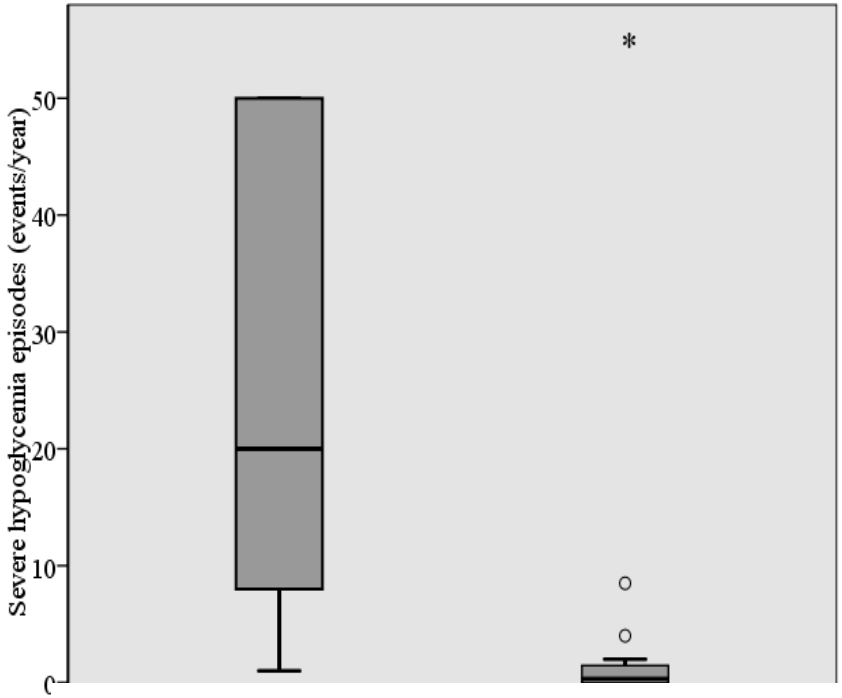


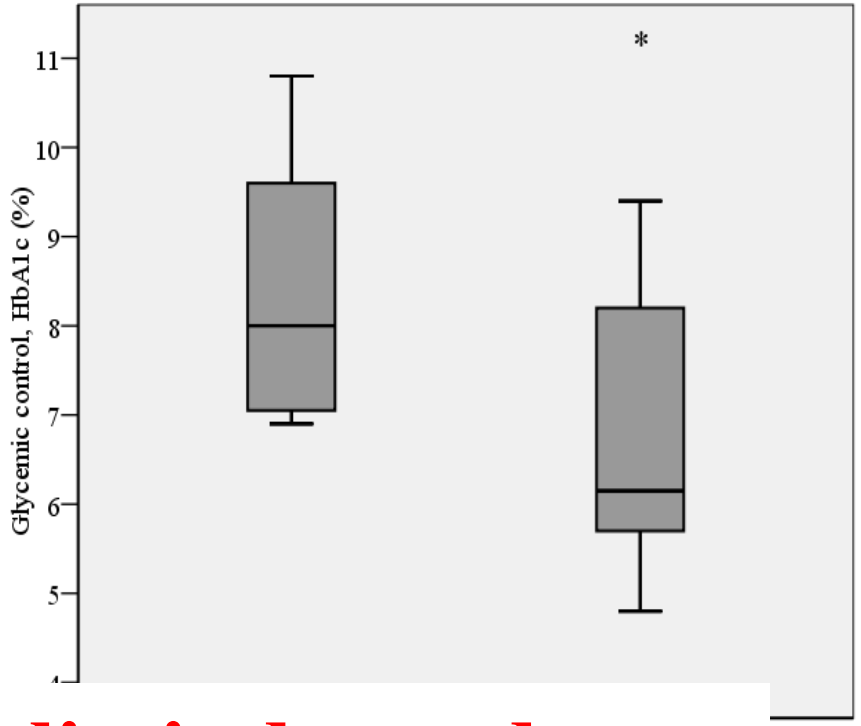
Pre-Tx



Post-Tx

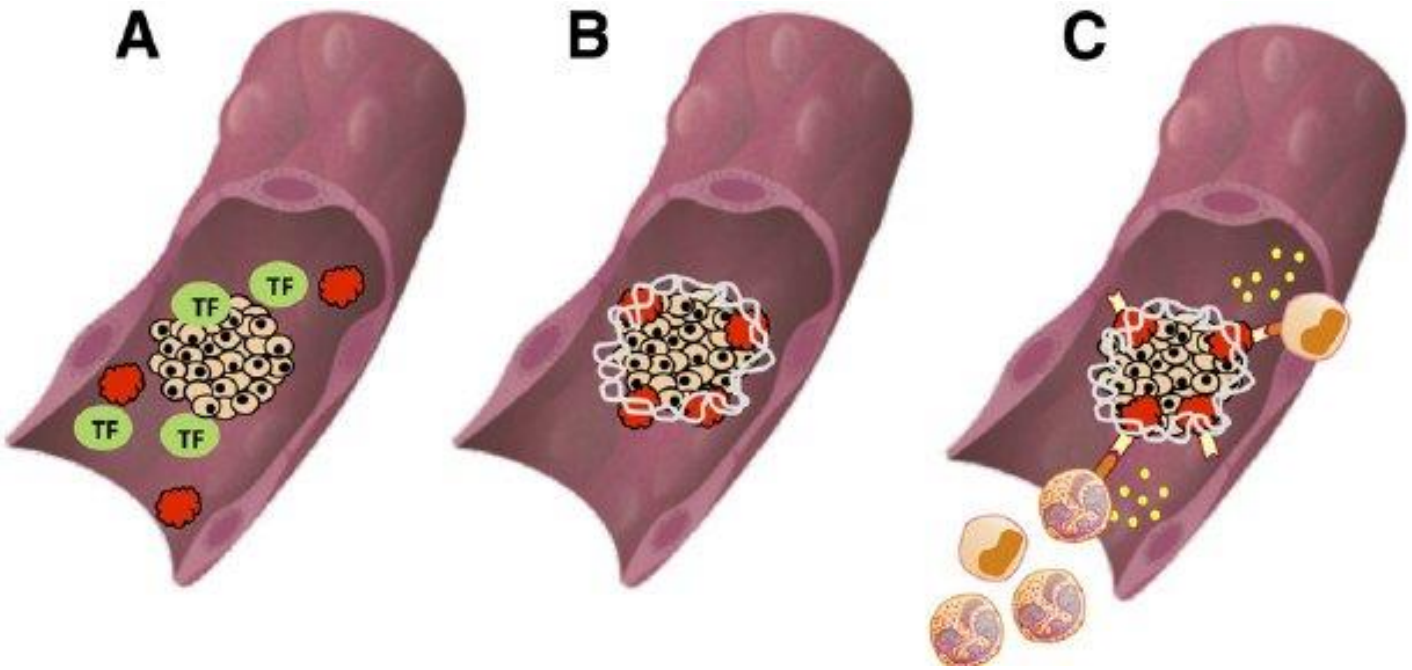
Severe hypoglycaemia / overall control





<50% sustainable insulin independence despite majority 2 transplants

Instant Blood Mediated Inflammatory Reaction



Smink AM et al., Diabetes 2013

Received: 30 May 2017 | Revised: 15 September 2017 | Accepted: 16 September 2017

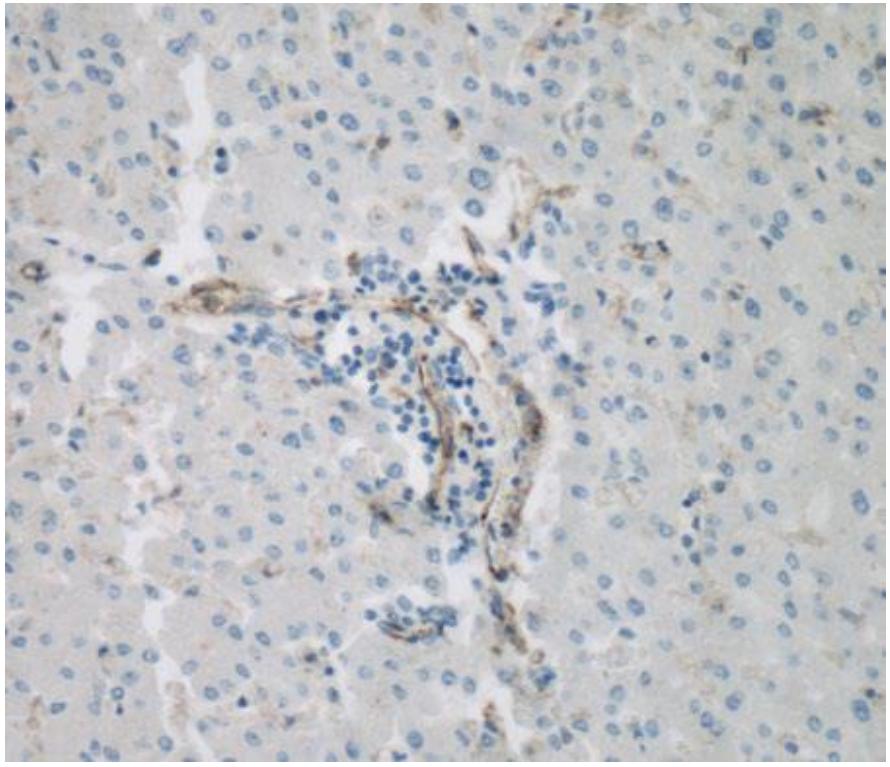
DOI: 10.1111/ajt.14521

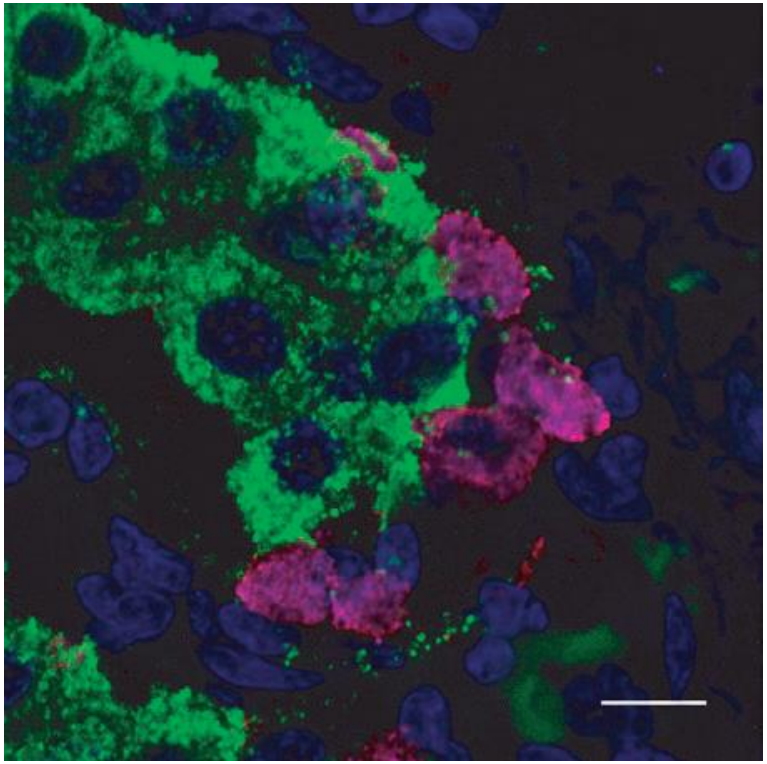
CASE REPORT

AJT

Loss of end-differentiated β-cell phenotype following pancreatic islet transplantation

S. J. Anderson[1] | M. G. White[1] | S. L. Armour[1] | R. Maheshwari[1] | D. Tiniakos[1,2] | Y. D. Muller[3] | E. Berishvili[3,4] | T. Berney[3] | J. A. M. Shaw[1]

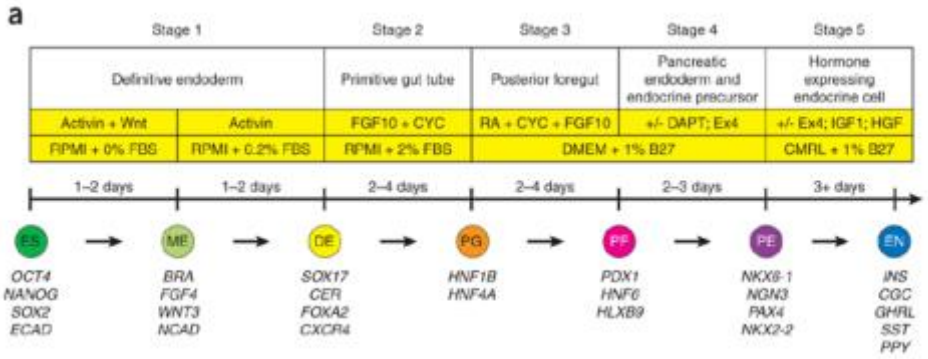




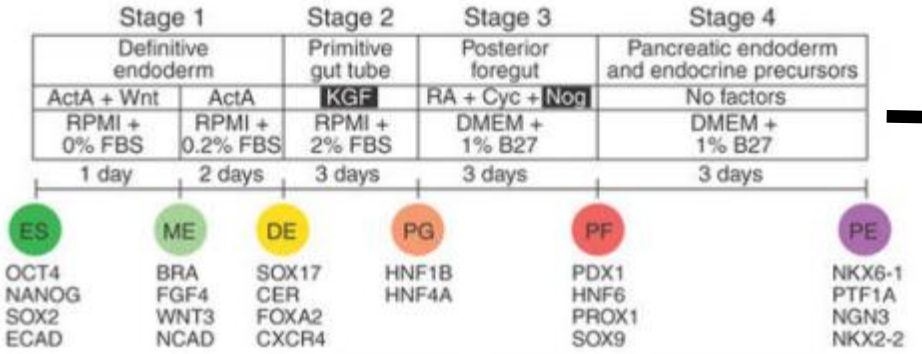
Unmet needs: sustainable insulin independence from single graft / long term immunosuppression

- Two factors preventing curative therapy for all (30 million)
  - Cannot achieve sustained insulin independence
    - from single minimally invasive procedure
  - Need for toxic life-long immunosuppression
    - to prevent allo- and auto-immune rejection

Development of ES differentiation protocol



D'Amour *et al*, 2006



Complete differentiation of pancreatic endoderm cells (PECs) in mice (fad pads)

Kroon *et al*, 2008

Cell

Generation of Functional Human Pancreatic β Cells In Vitro

Felicia W. Pagliuca,[1,3] Jeffrey R. Millman,[1,3] Mads Gürtler,[1,3] Michael Segel,[1] Alana Van Dervort,[1] Jennifer Hyoje Ryu,[1] Quinn P. Peterson,[1] Dale Greiner,[2] and Douglas A. Melton[1,*]

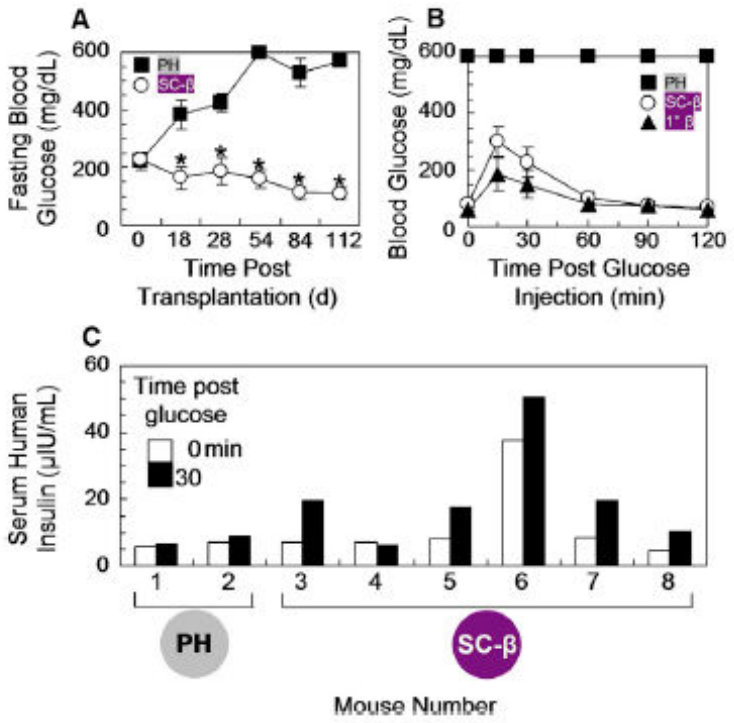
[1]Department of Stem Cell and Regenerative Biology, Harvard Stem Cell Institute, Harvard University, 7 Divinity Avenue, Cambridge, MA 02138, USA

[2]Diabetes Center of Excellence, University of Massachusetts Medical School, 368 Plantation Street, AS7-2051, Worcester, MA 01605, USA

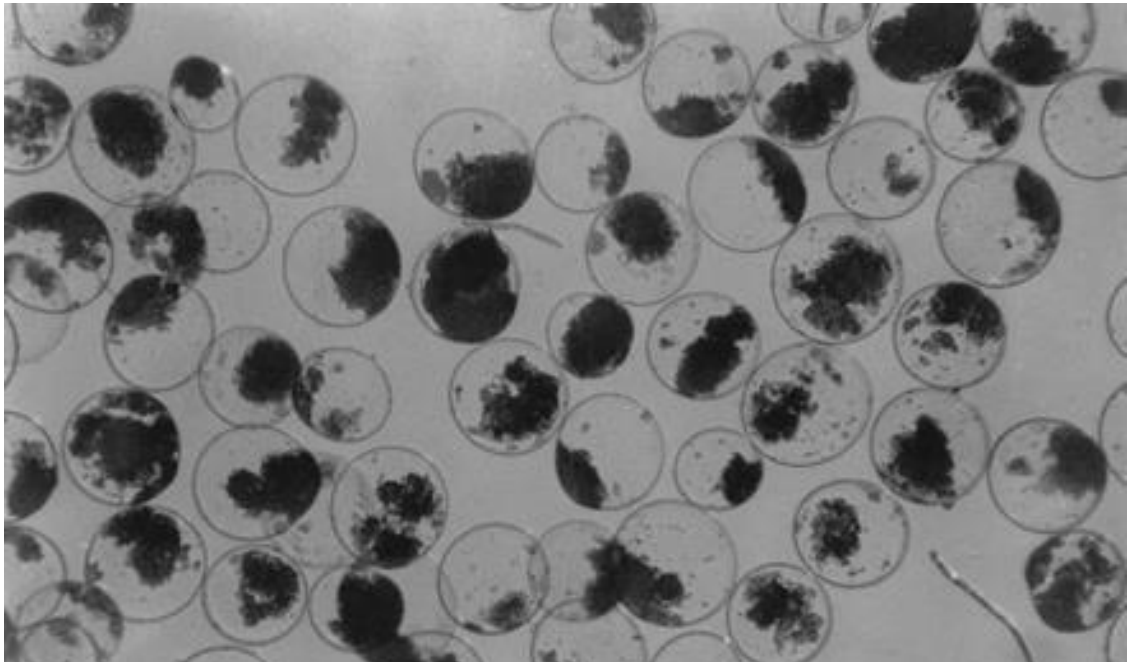
[3]Co-first author

*Correspondence: dmelton@harvard.edu

http://dx.doi.org/10.1016/j.cell.2014.09.040

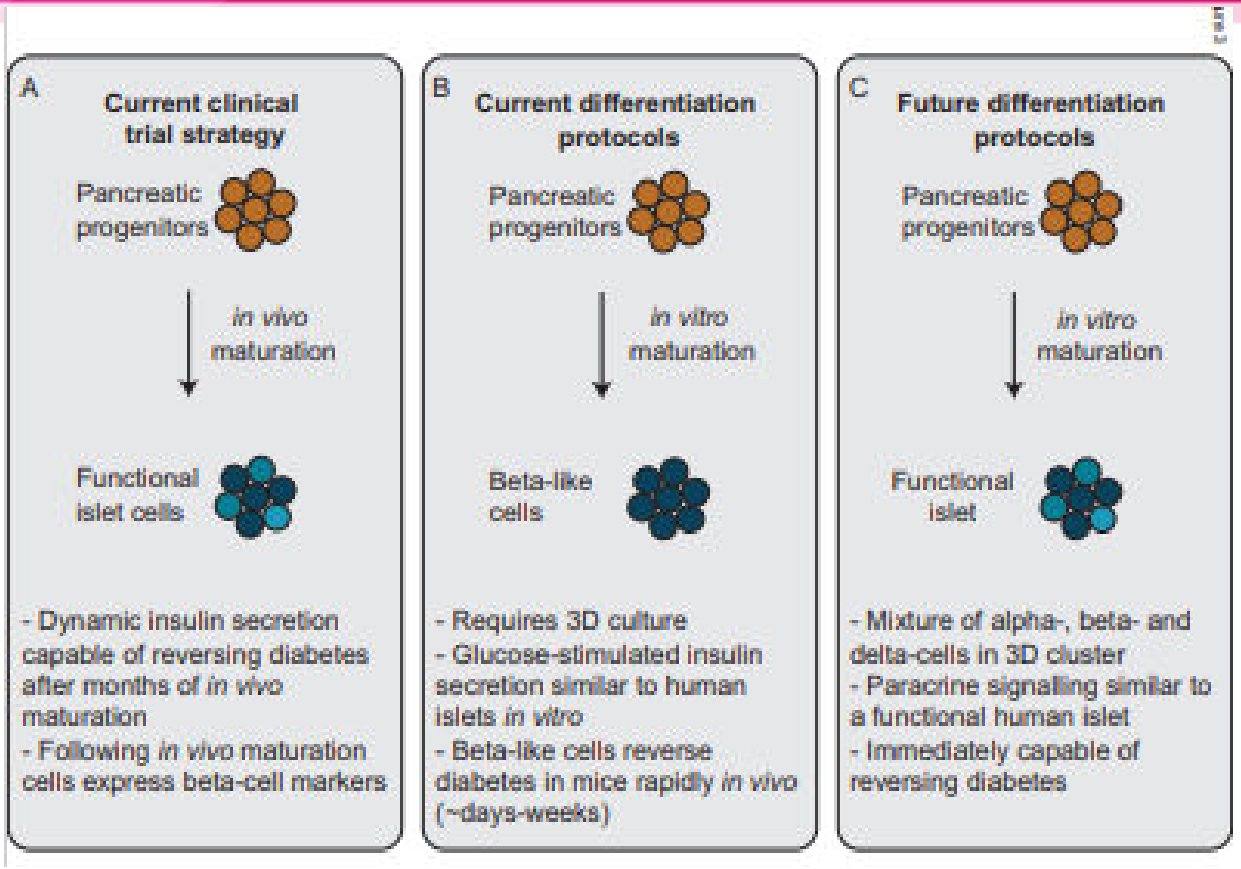


Immunobarrier encapsulation



Hypoxia appears to be main limiting factor

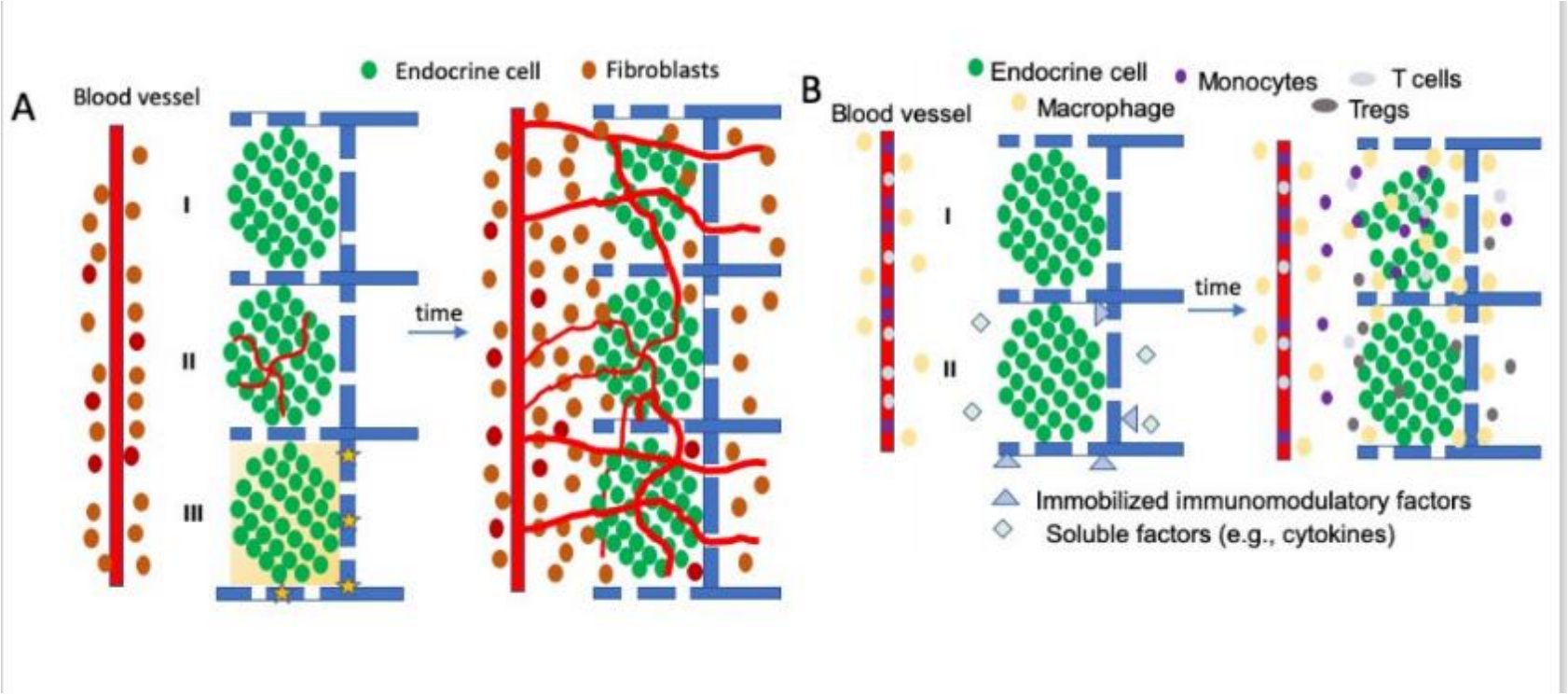
Stem cell derived beta-cell replacement therapy



Viacyte **Vertex**

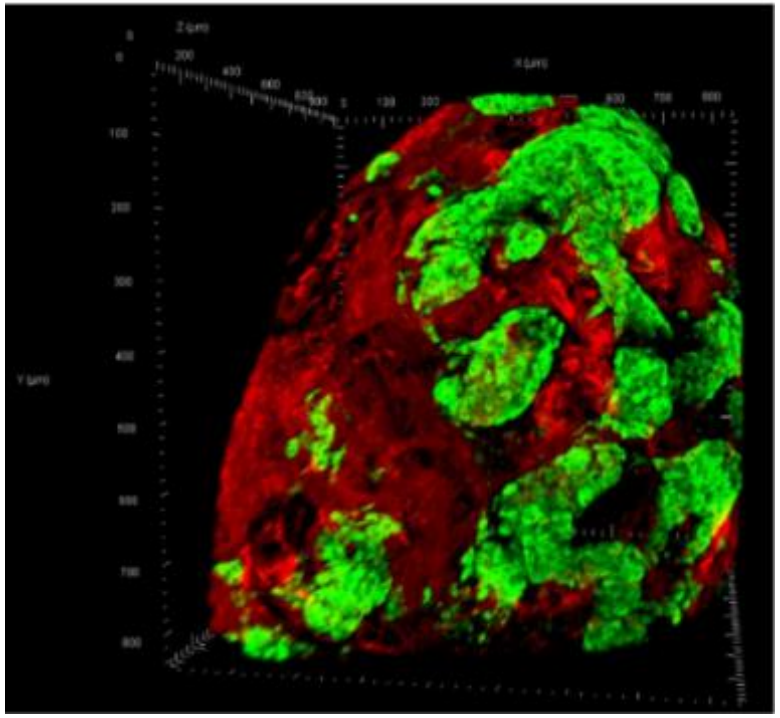
Krentz N *et al Lancet D+E* 2021 (in press)

Tissue Engineered Product:
Scaffold / Islets
Adjuvant molecules / gene therapy / cell therapy



Krentz N *et al Lancet D+E* 2021 (in press)

Northern Alliance Advanced Therapies Treatment Centre / Betalin Therapeutics UK



Engineered Micro-Pancreas
Islets (Green) fused onto decellularised Micro-Organ Matrix (Red)

Summary

- Type 1 diabetes is caused by loss of insulin production
  - Conventional therapy remains burdensome and cannot prevent risk
- Islet transplantation is minimally invasive
  - proven therapy for type 1 diabetes complicated by recurrent SH
- Conversion into a truly curative therapy for all will require
  - Sustainable single graft insulin independence
  - Avoidance of life-long systemic immunosuppression
- SC-derived beta-cells may provide sufficient numbers for all
  - Tissue engineered scaffolds may overcome innate immunity
  - Adjuvant Gene / Cell Therapy may circumvent immunosuppression

nuc DIABETES

Acknowledgements:

Leading science for better health