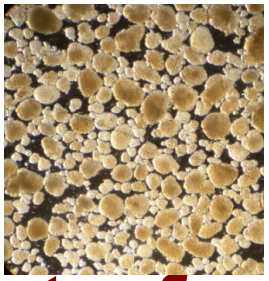

# Future Therapies in the Treatment of Diabetes: Islet Transplantation

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Hospital of the University of Pennsylvania

Congenital Hyperinsulinism Family Conference
April 17, 2016

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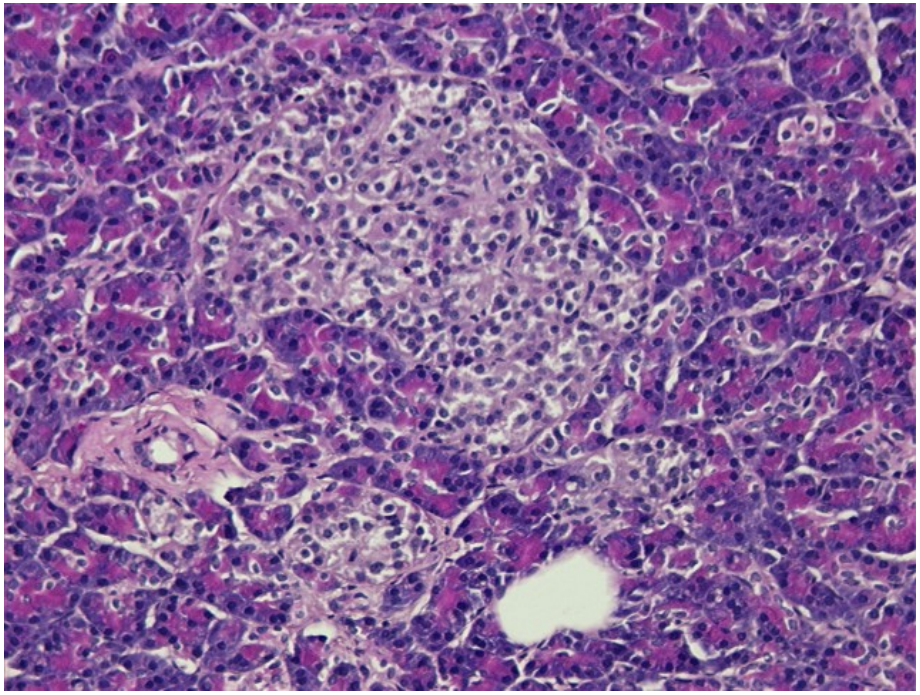
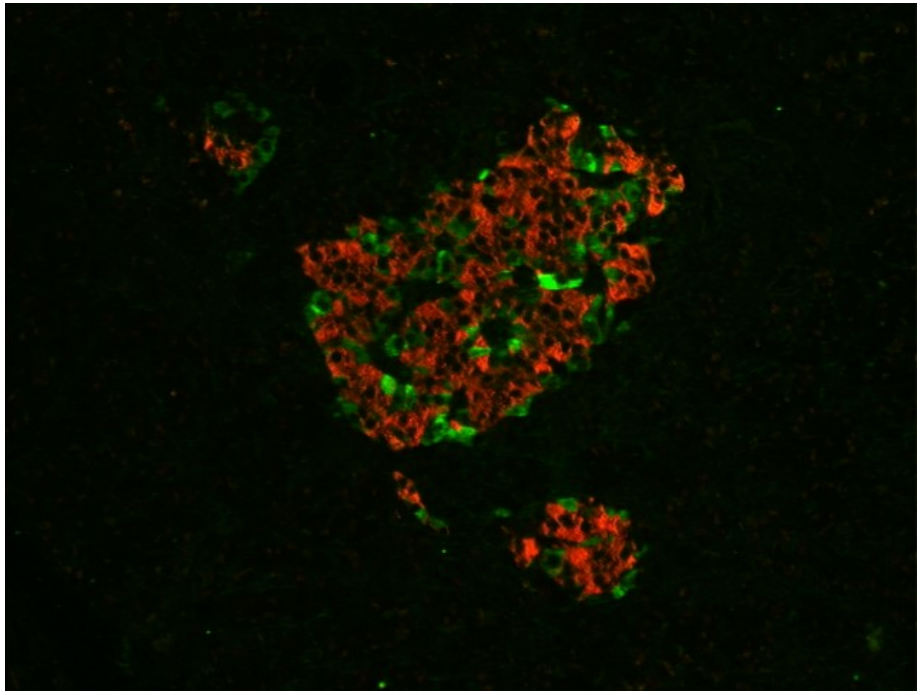
University of Pennsylvania

# Pancreatic islets of Langerhans

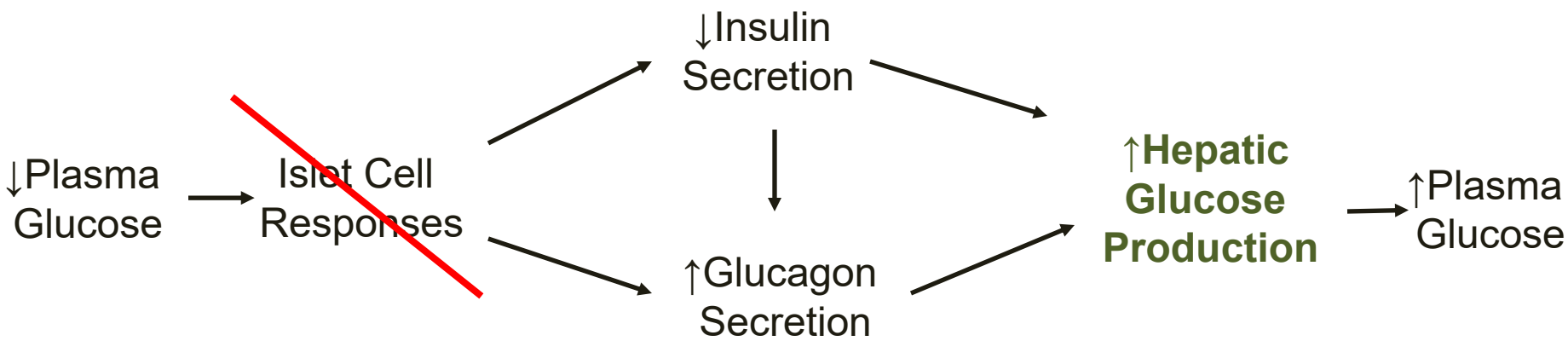
~ 1 million islets comprise 2-3% of the total pancreatic mass



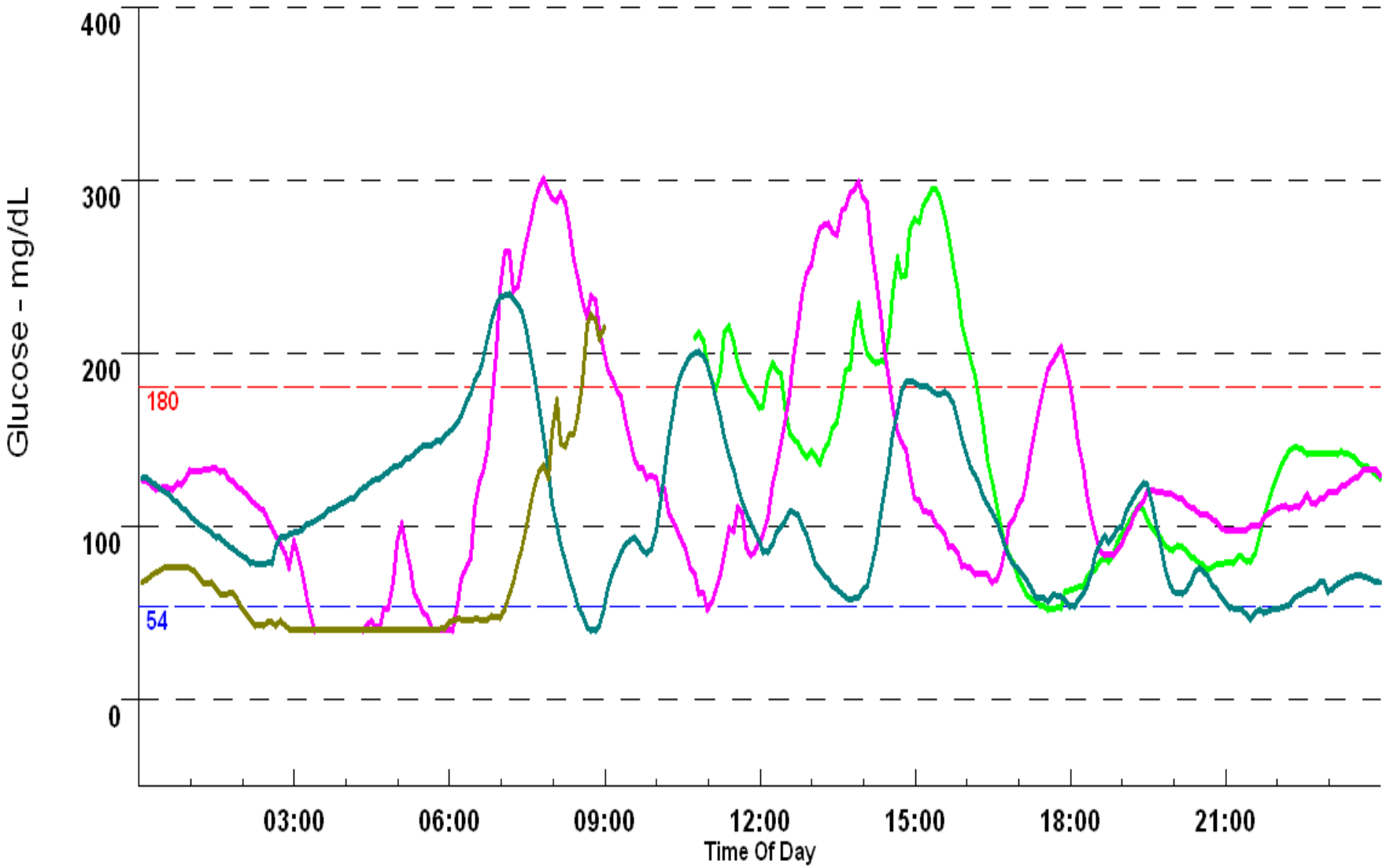


Red = β-cells, stained for insulin
Green = α-cells, stained for glucagon

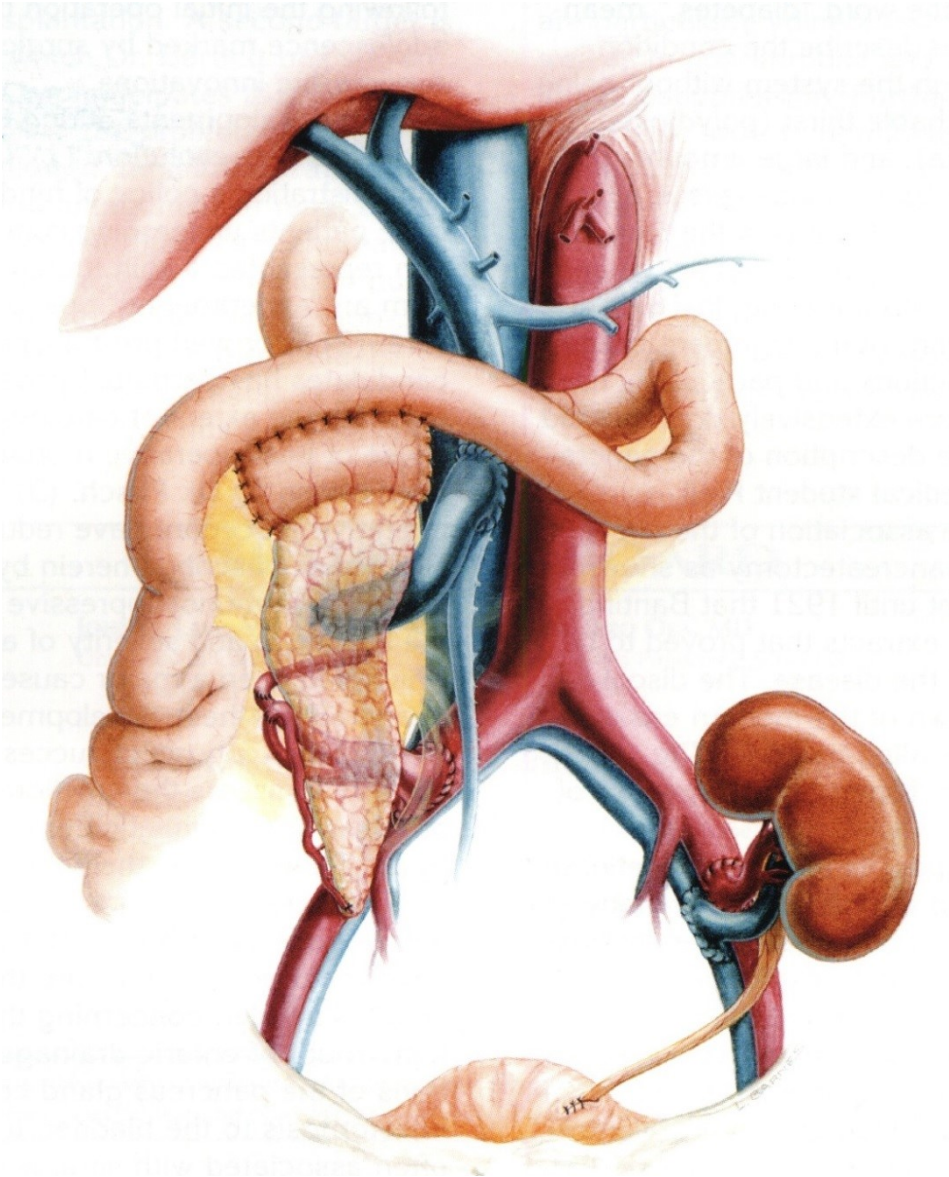
# Islet cell responses defend against hypoglycemia



# Case - continuous glucose monitoring



# Pancreas transplantation



Larsen. *Endocrine Reviews* 25: 919, 2004

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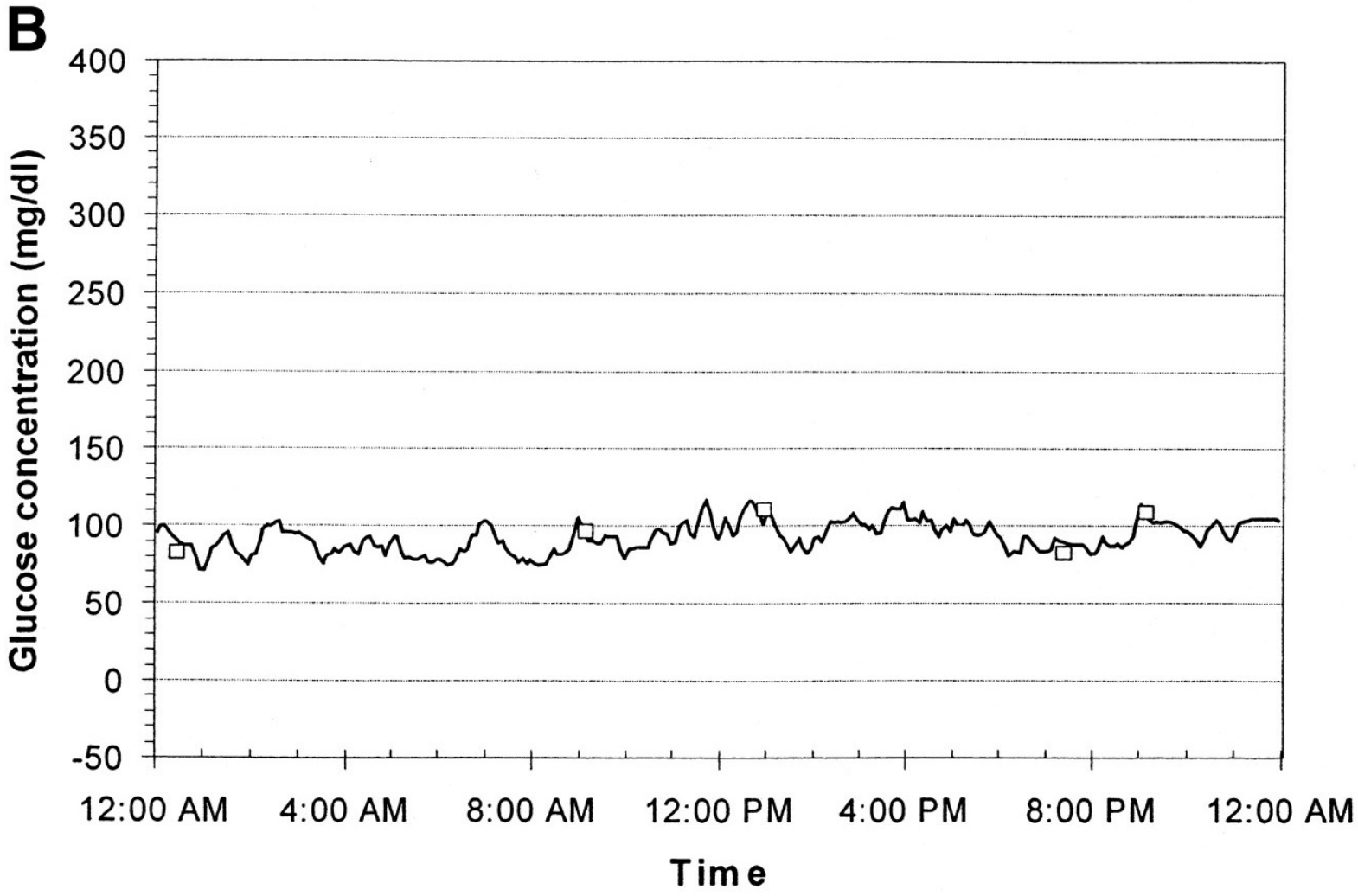
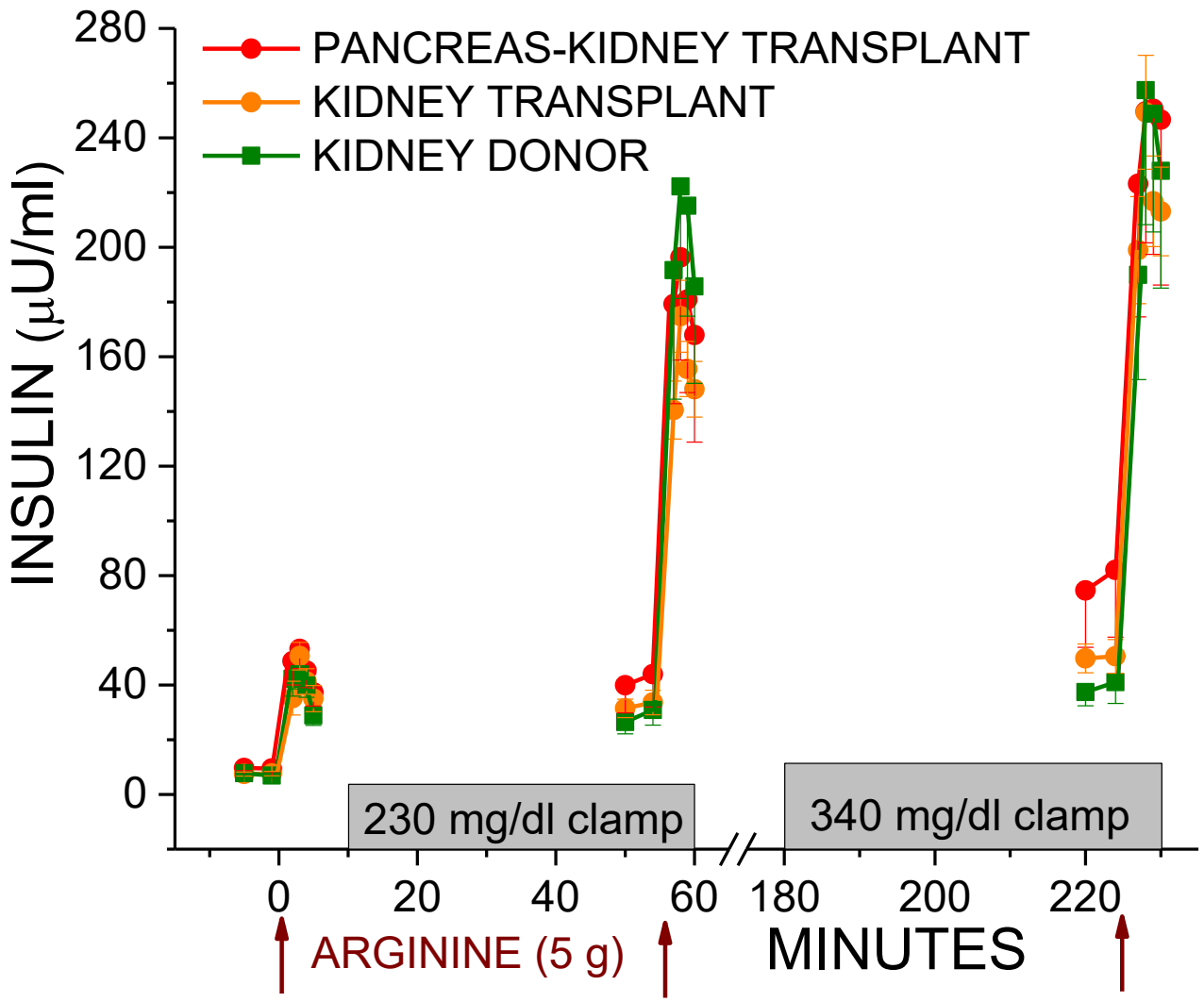
# Glycemic control in pancreas transplantation




Kessler et al. *Diabetes Care* 25: 2256, 2002

# β-cell secretory capacity in pancreas transplantation




Rickels et al. *J Clin Endocrinol Metab* 95: 1238, 2010

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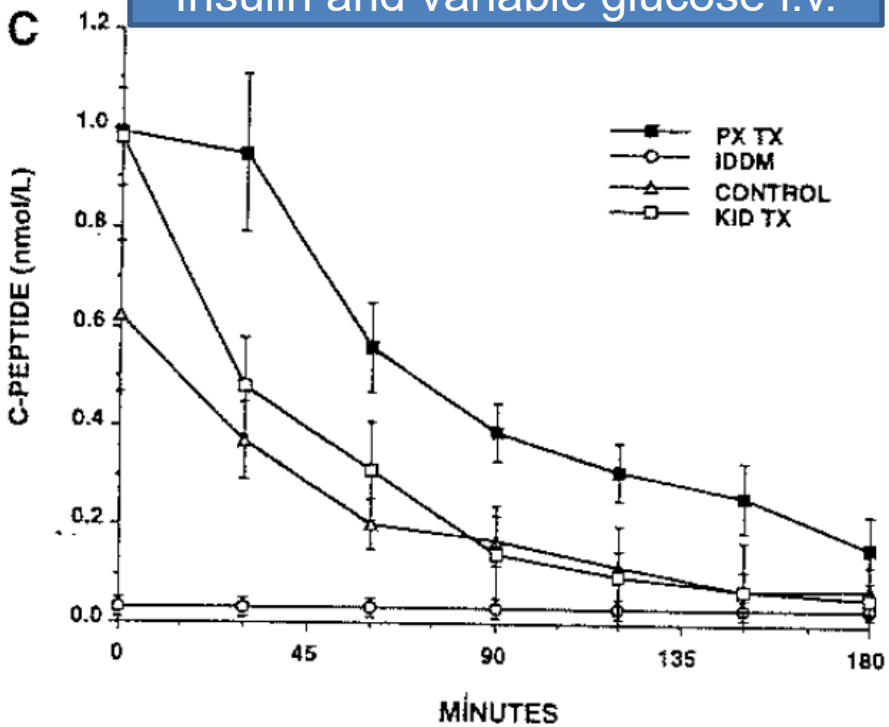
# Islet cell responses to hypoglycemia in pancreas transplantation

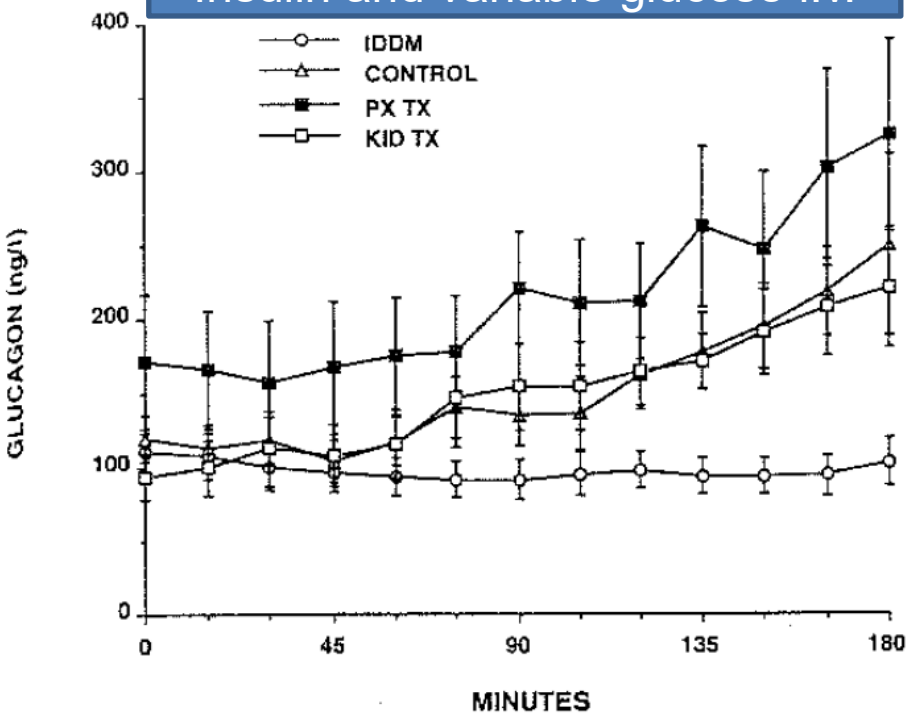
## β-cell response

Insulin and variable glucose i.v.



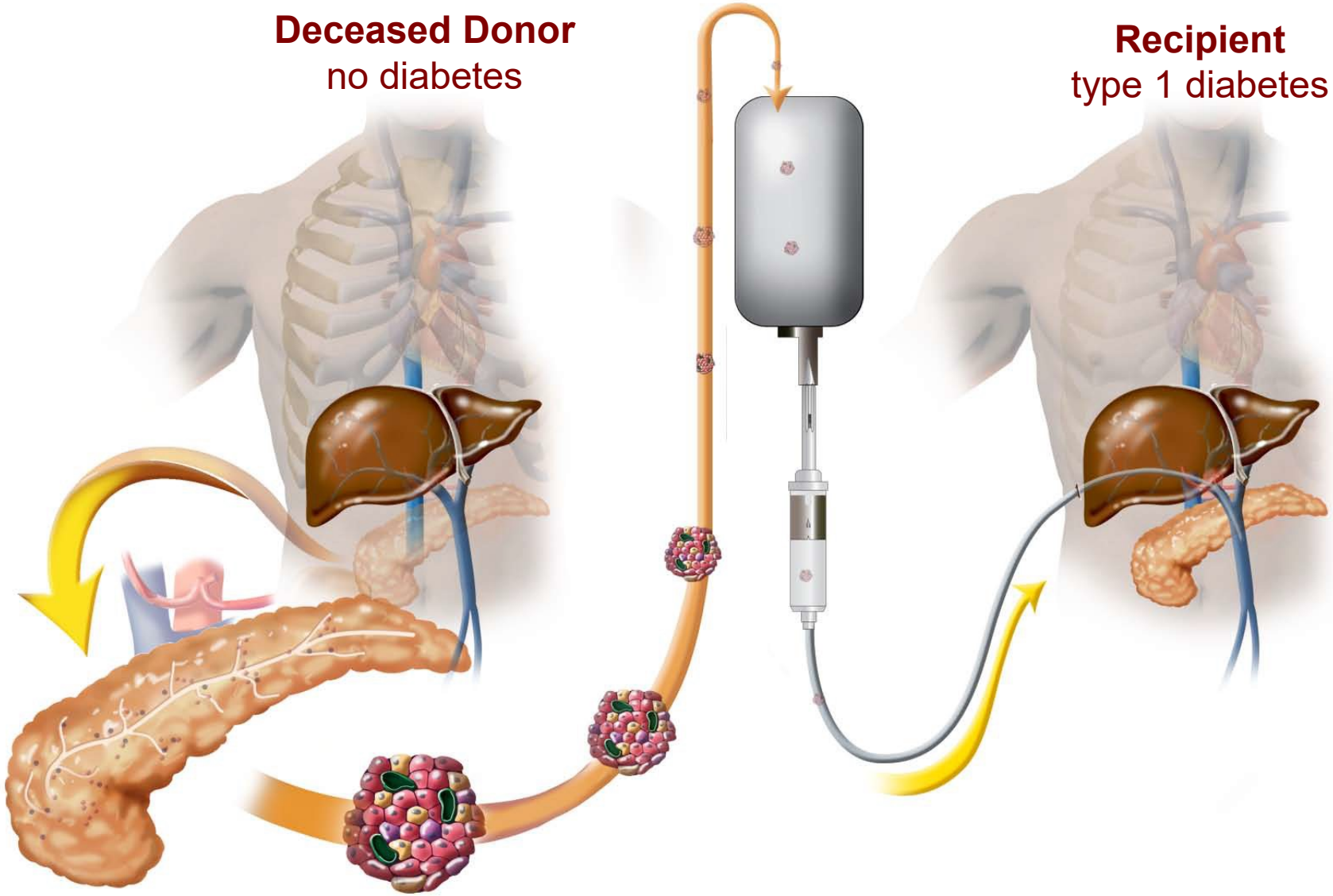

## α-cell response

Insulin and variable glucose i.v.




Kendall et al. *Diabetes* 46: 249, 1997

# Islet transplantation



# NIH Clinical Islet Transplantation (CIT) Consortium

T1D & Severe Hypoglycemia

T1D & Kidney Allograft

CIT07 (N=11/48)
Thymoglobulin
Etanercept
Heparin
Tacrolimus
Sirolimus

CIT06 (N=2/24)
Thymoglobulin
Etanercept
Heparin
Tacrolimus
MMF

Islet Transplantation #1

Insulin-Independence at day 75

Islet Transplantation #2

Primary Endpoint: HbA1c < 7% and free from severe hypoglycemic episodes at one year following the initial transplant

# Clinical endpoint – $HbA_{1c}$ <7.0% w/o hypoglycemia

| Consortium | IE/kg | HbA1c Pre | HbA1c 1 Year | HbA1c 2 Years | A1c <7% No SH 1 Year | A1c <7% No SH 2 Years |
|---|---|---|---|---|---|---|
| Australian[1] *n* = 17 | 15,366 | 8.3% | 6.5% | N.D. | 82% | N.D. |
| UK[2] *n* = 20 | 8,770 | 8.0% | 6.3% | 6.2% | N.A. | 55% |
| GRAGIL[3] *n* = 24 | 9,716 | 8.1% | 6.2% | N.D. | 83% | N.D. |
| NIH-CIT07[4] *n* = 48 | pending | pending | pending | pending | pending | pending |

[1] O' Connell ….Kay *Am J Transplant* 13: 1850, 2013
[2] Brooks et al. *Am J Transplant* 13: 3236, 2013
[3] Lablanche et al. *Diabetes Care* in press, 2015
[4] www.citisletstudy.org

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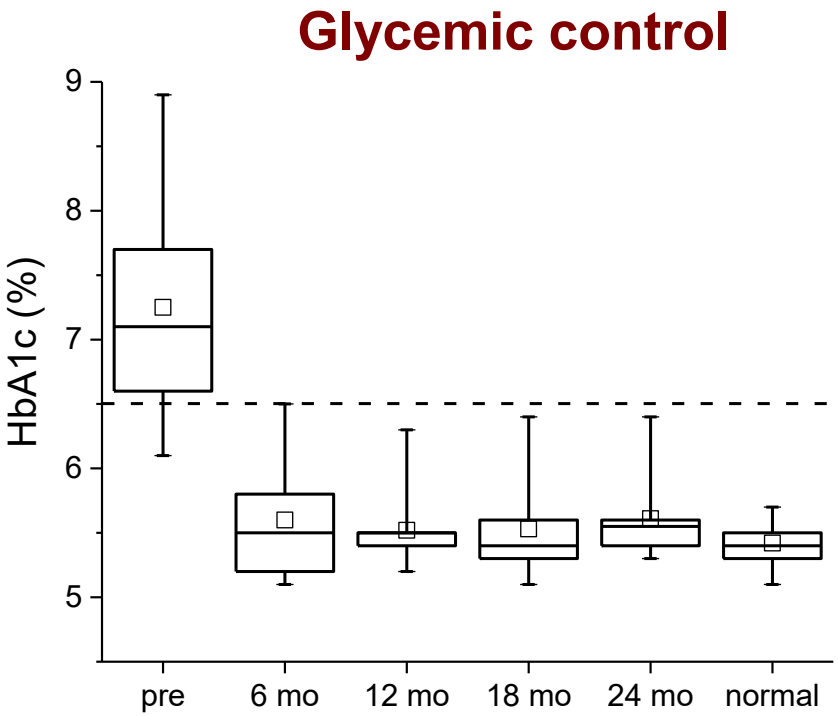
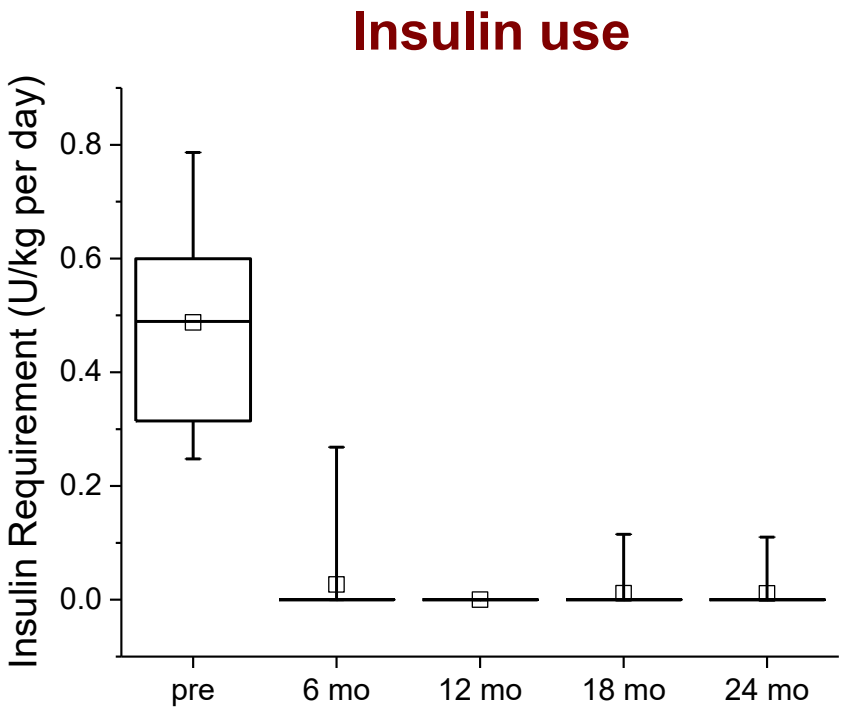
# Long term metabolic control with CIT07 at Penn




Updated from Rickels et al. *Diabetes* 64: 1713, 2015

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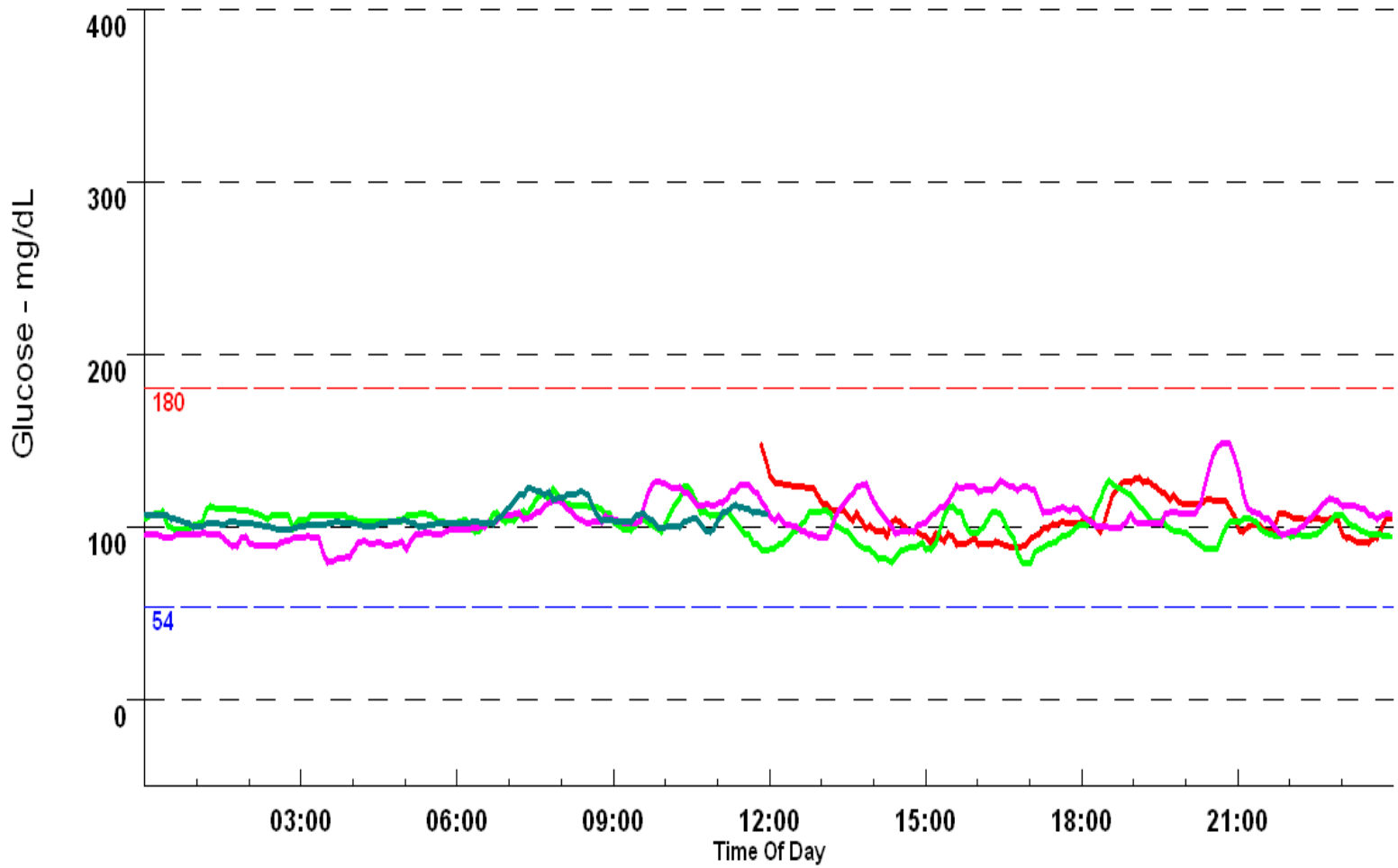
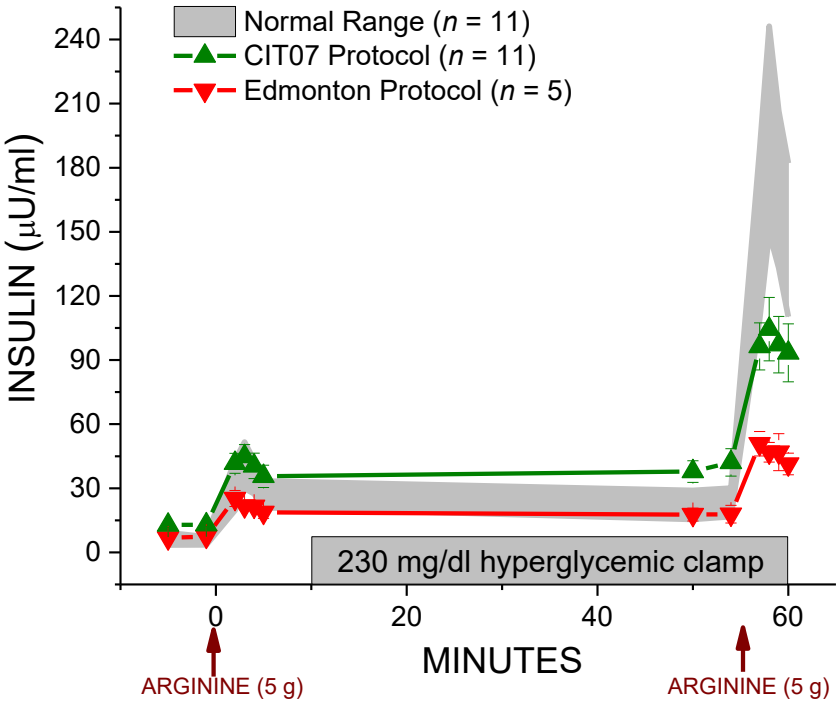
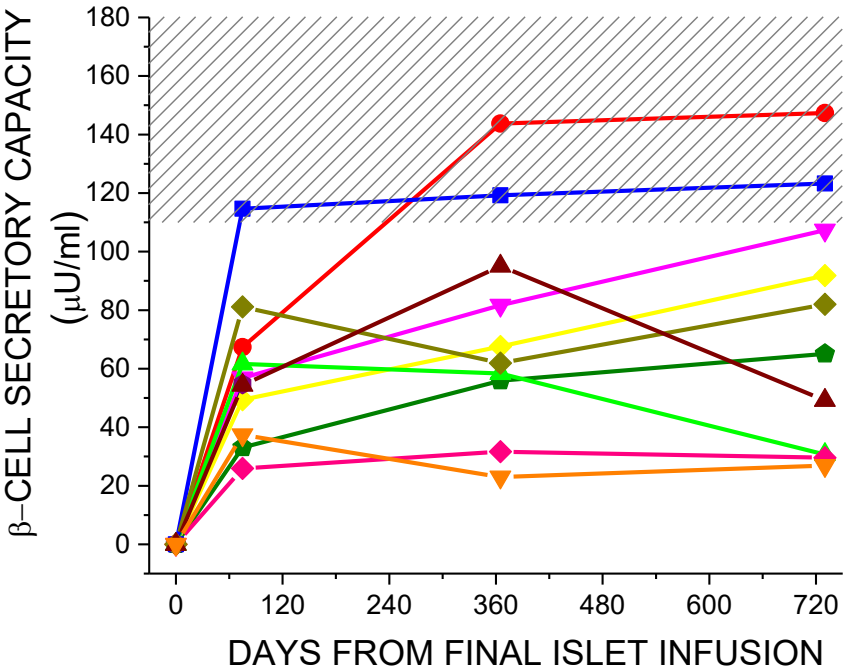
# Glycemic control in islet transplantation



# β-cell secretory capacity in islet transplantation




## CIT07 protocol




Updated from Rickels et al. *Diabetes* 62: 2890, 2013

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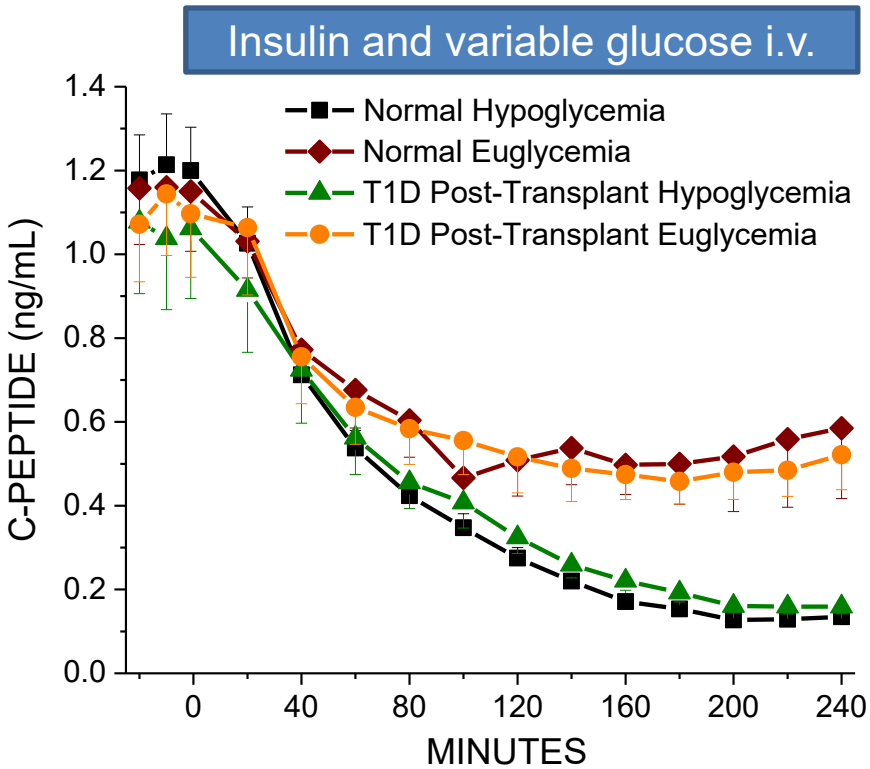
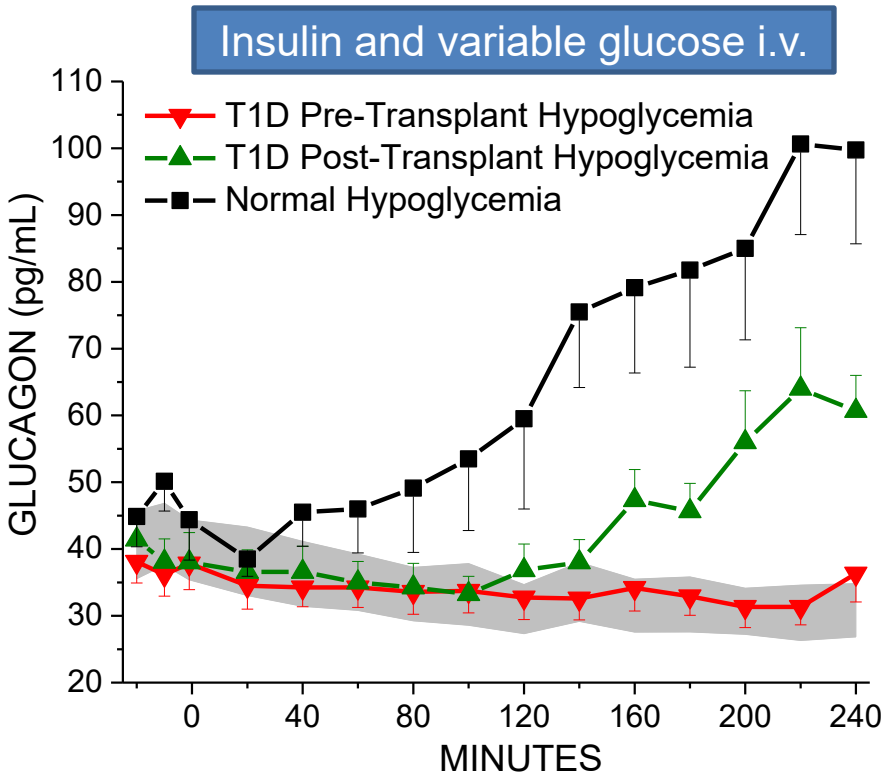
# Islet cell responses to hypoglycemia in islet transplantation

## β-cell response




## α-cell response




Updated from Rickels et al. *Diabetes* 64: 1713, 2015

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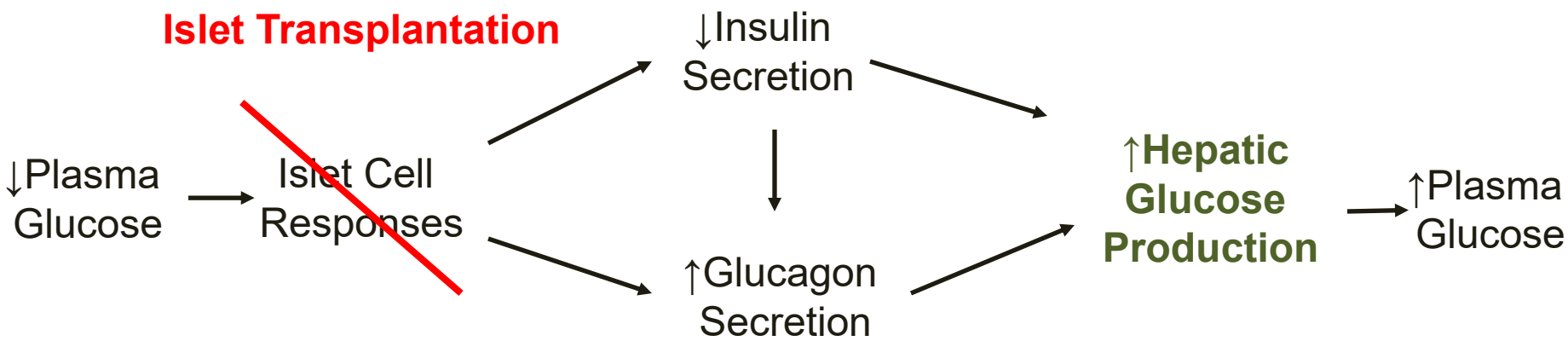
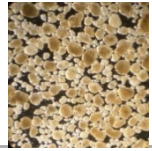
# Islet replacement restores defense against hypoglycemia



# Summary

- Intrahepatic transplantation of purified islets isolated from a deceased donor pancreas offers an alternative to whole pancreas transplantation that can restore physiologic insulin delivery and islet function, thus stabilizing glycemic control with protection against hypoglycemia
- The primary endpoint for evaluation of clinical islet transplantation is a HbA1c < 7.0% without severe hypoglycemia episodes
- Current protocols may result in recovery of sufficient β-cell secretory capacity to afford durable graft survival that resists metabolic exhaustion
- The benefits of islet transplantation on long-term improvement in glycemic control, especially amelioration of glycemic instability and problematic hypoglycemia, must be balanced against the risks for procedural complications and of the immunosuppressive drug therapy

# Acknowledgments

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