Issues of Beta Cell Dysfunction

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Beta Cell Meeting

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A Diabetes Puzzle

How does diabetes start?

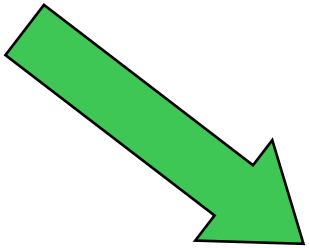
What is going on when someone's fasting glucose rises from 83 to 95 mg/dl or when postprandial glucose level start to rise?

Hypothesis: Not enough β-cells

A Simple Hypothesis:
Primacy of Reduced β-Cell Mass in Diabetes

Relative/Absolute
β-Cell Mass ↓

Glucotoxicity
Loss of β-Cell Phenotype



β-Cell Function ↓

Reduced islet mass in T2DM

Autopsy Studies

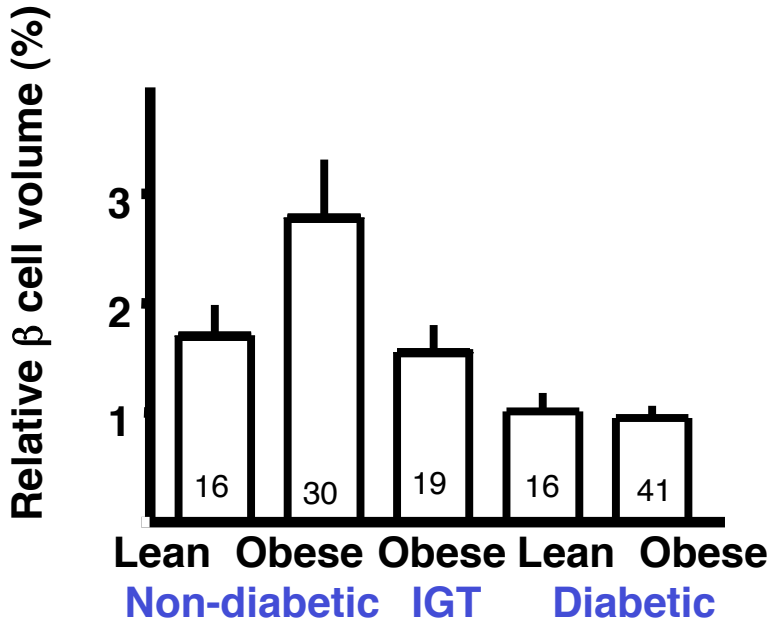
Maclean, Ogilvie - 1955
Westermark, Wilander - 1978
Saito, et al, 1978,1979
Kloppel, et al - 1985
Butler, et al - 2003
Yoon, et al - 2003

All these studies show
islet mass 40-60% of normal

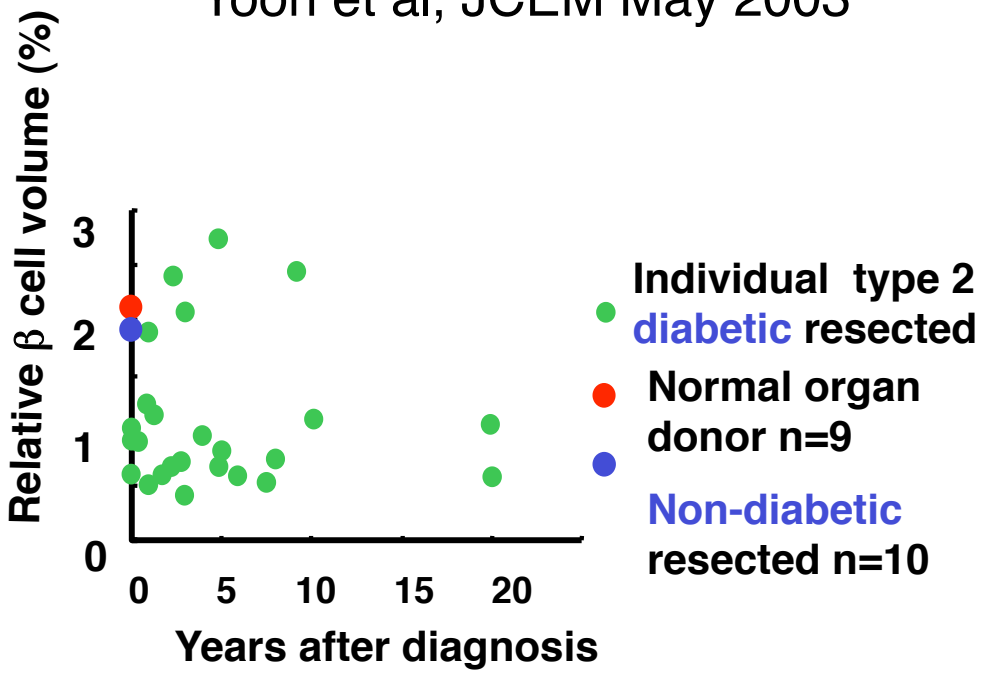
The debate is over!

β cell volume in human type 2 diabetics is about 50% of non diabetic

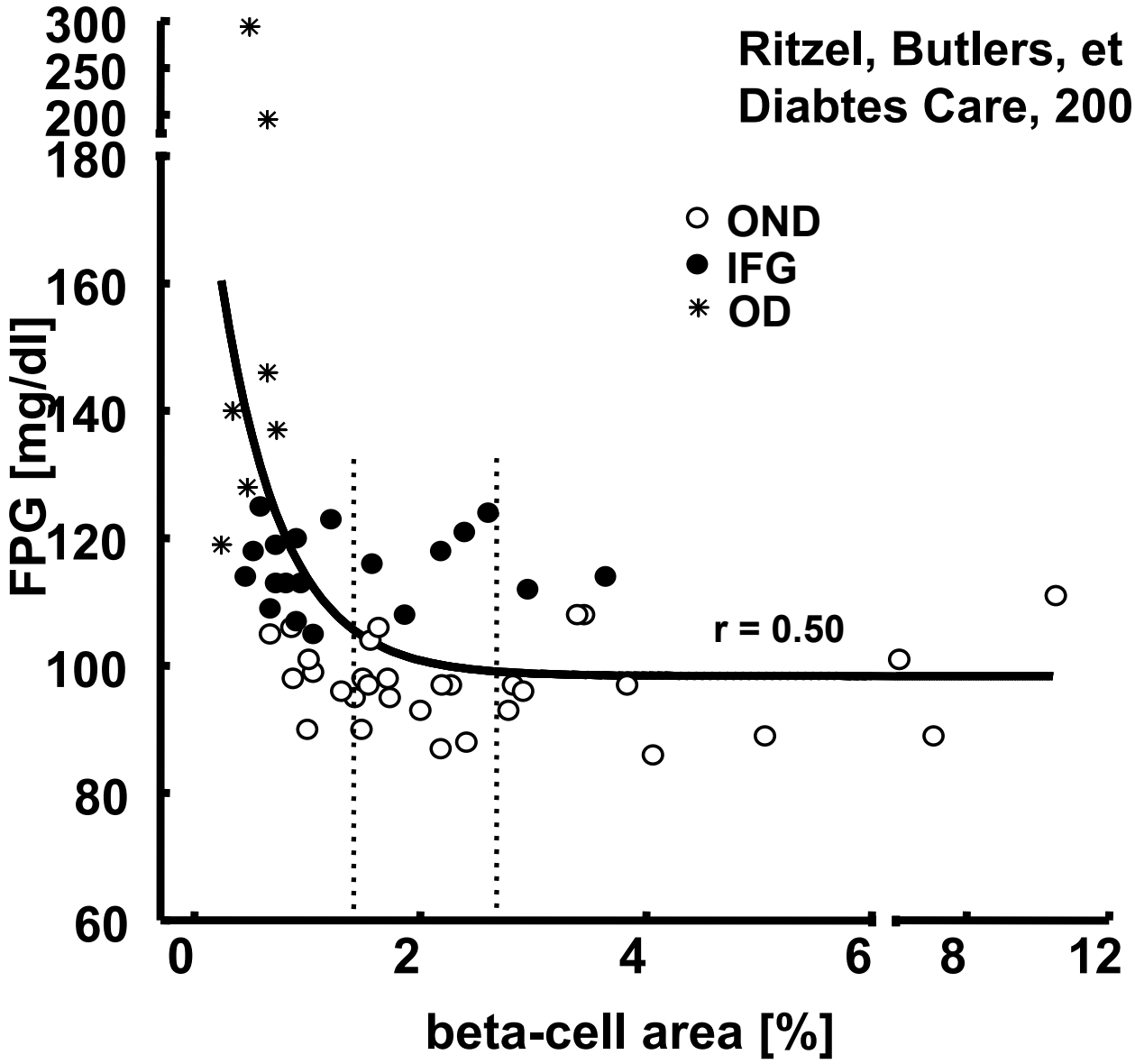
Butler et al, Diabetes Jan 2003



Yoon et al, JCEM May 2003



Beta cell mass versus glucose - humans



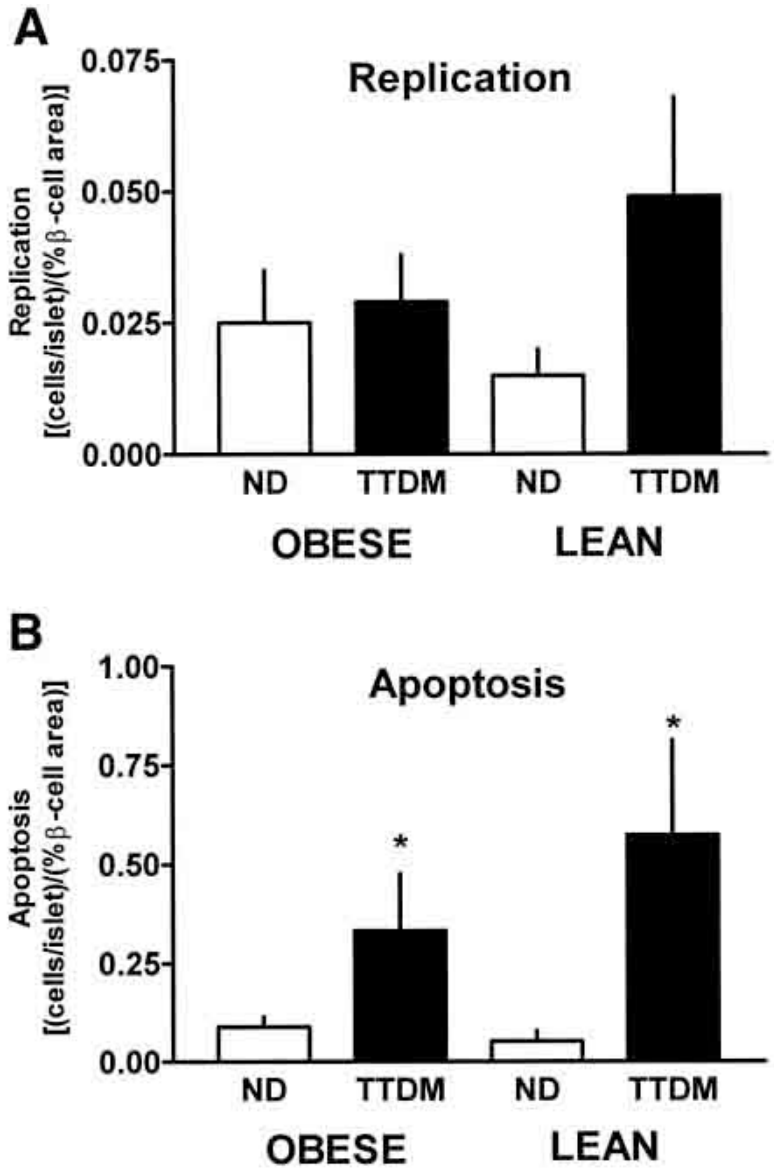
Ways to have too few β-cells en route to T2DM

β-cell death problem: Apoptosis

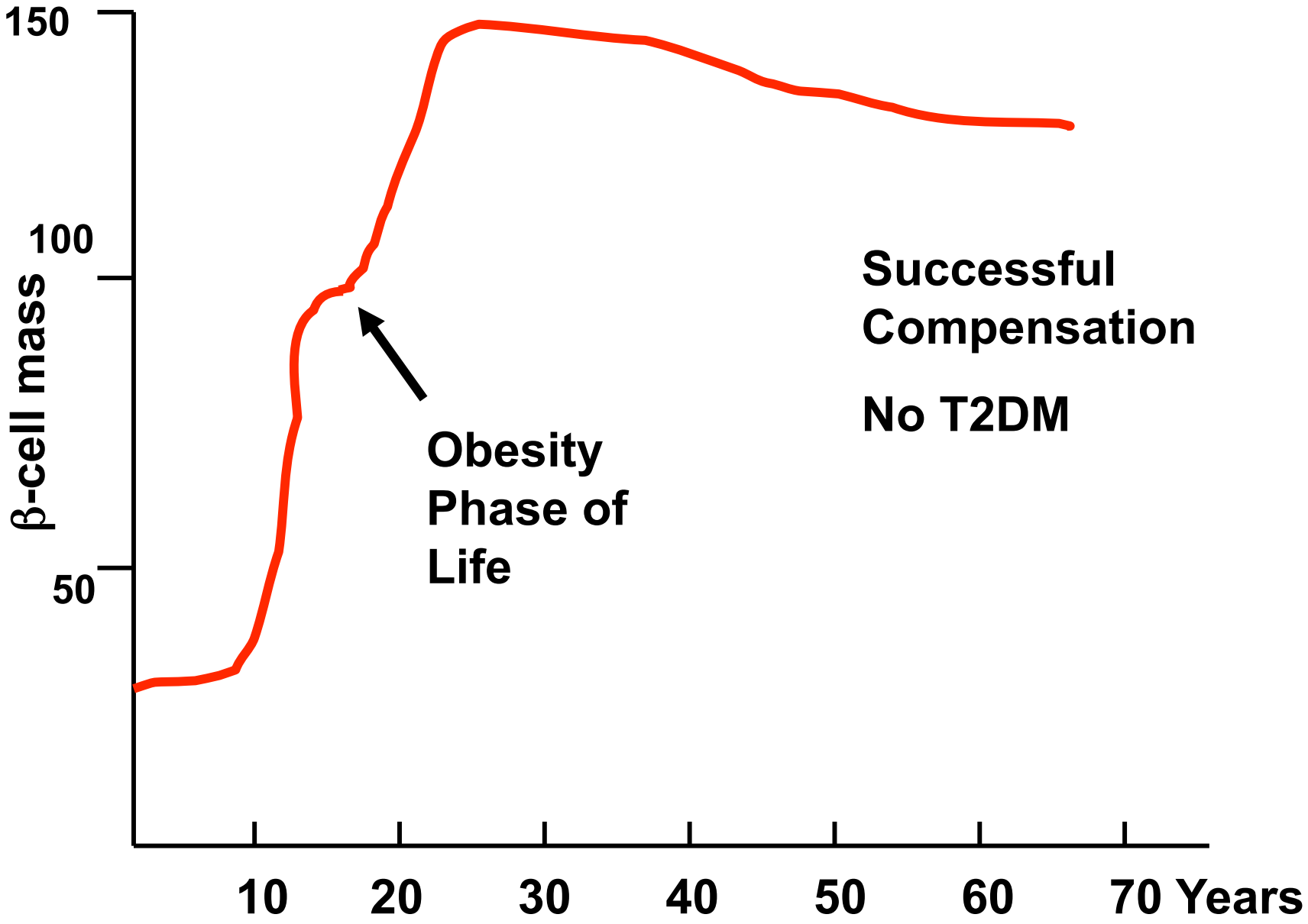
β-cell birth problem:

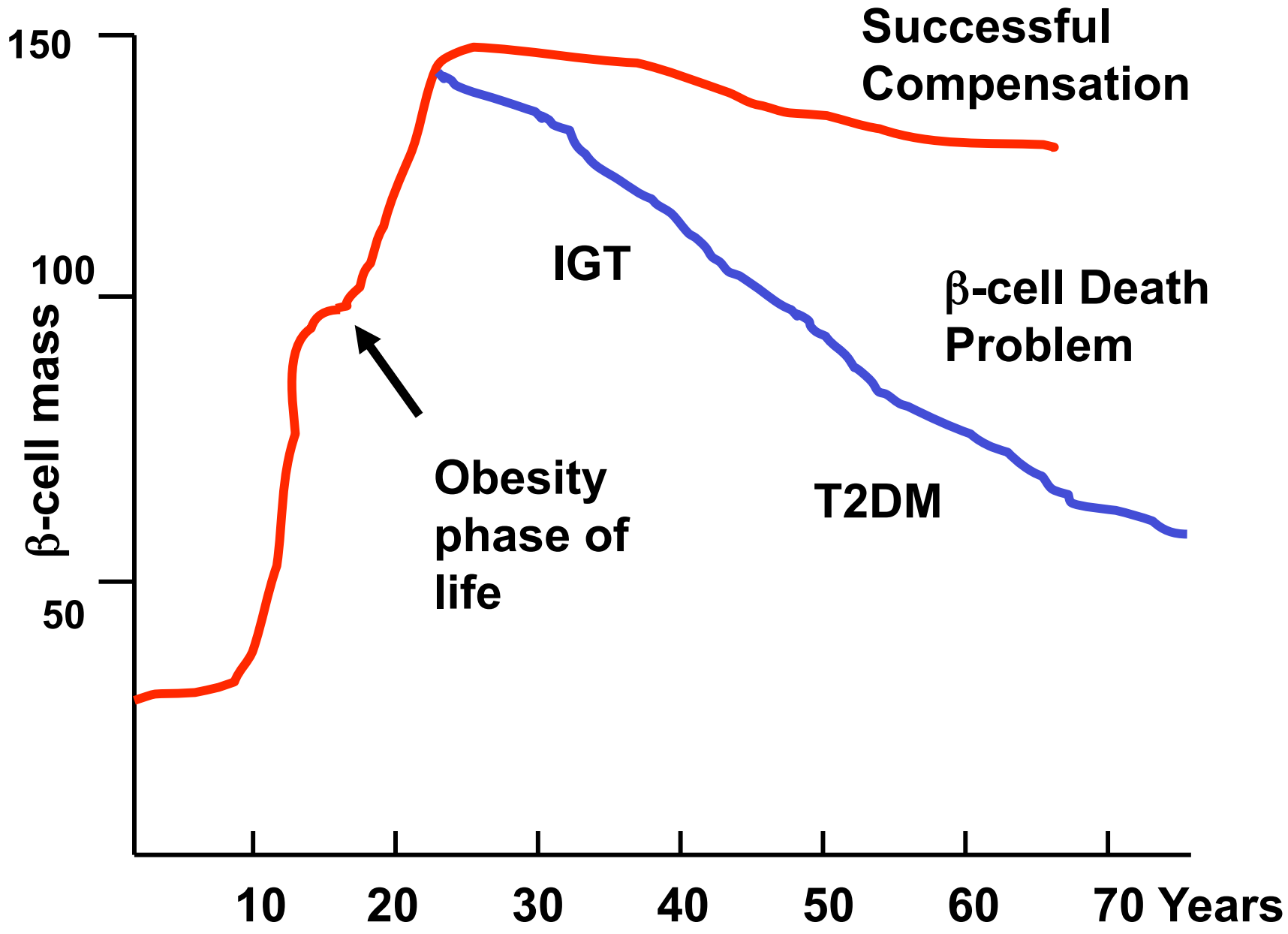
1. Not enough at the beginning: Intra-uterine growth retardation
2. Inadequate β-cell replication
3. Inadequate neogenesis

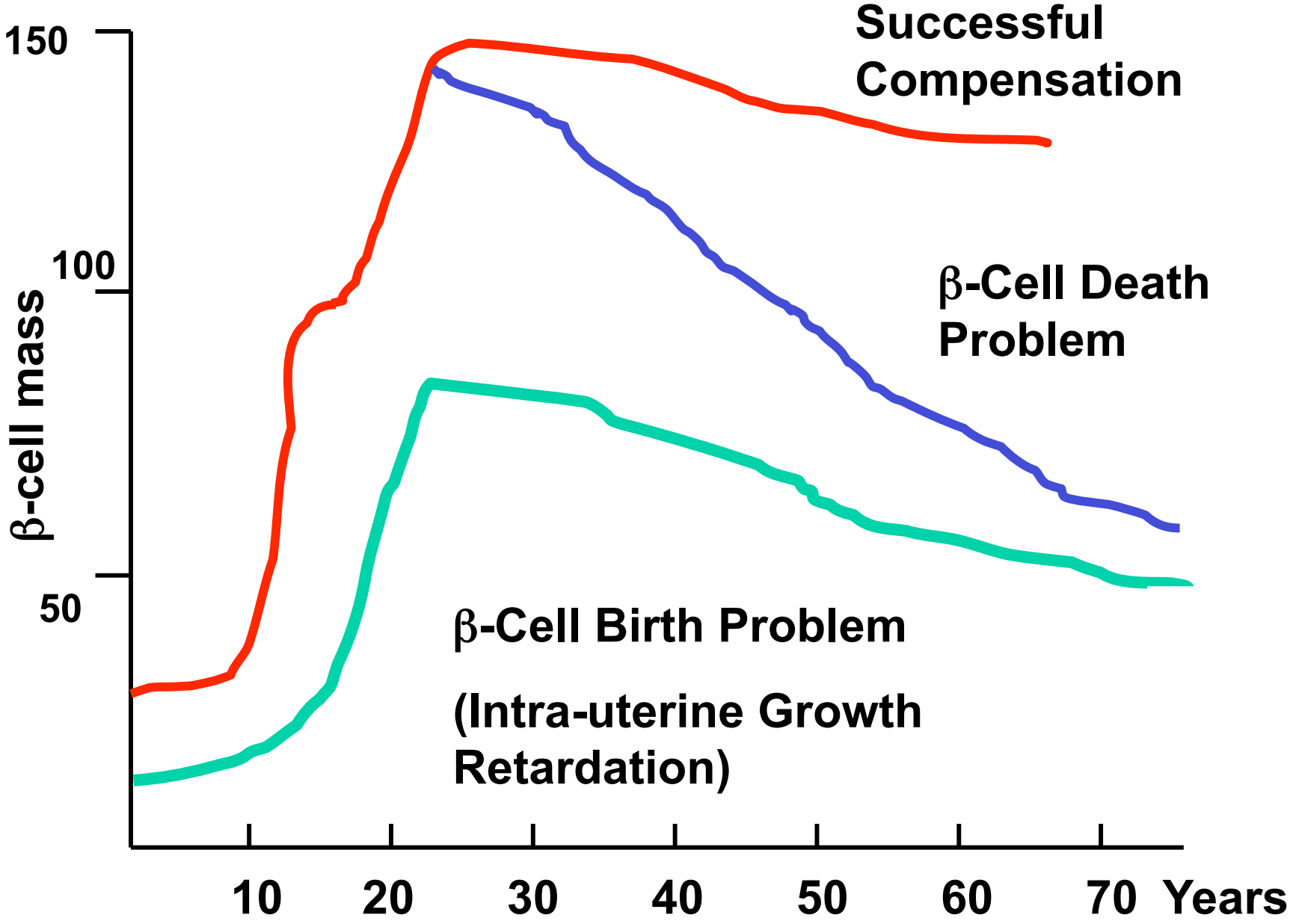
Hard to study: No good test for β-cell mass Rates of β-cell birth and death are very slow in humans.



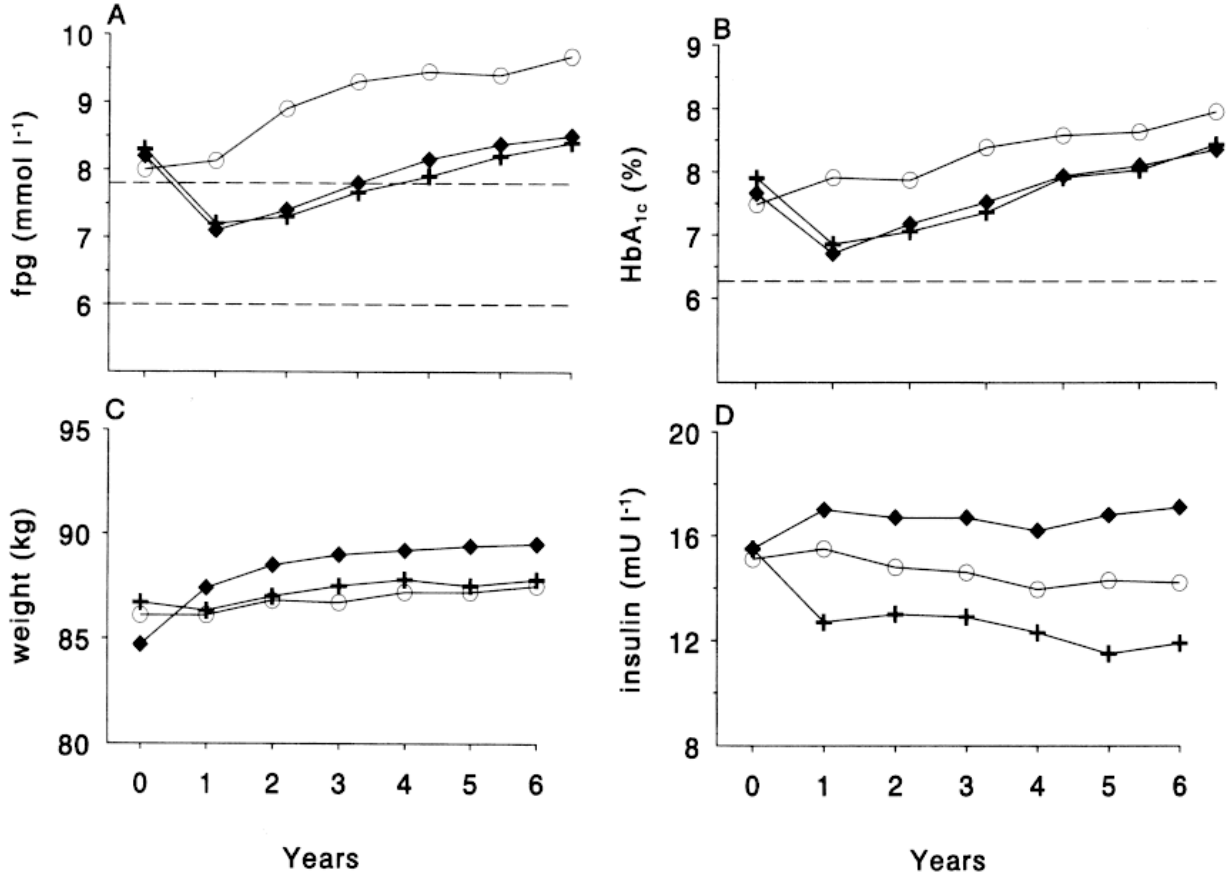
Butler AE, et al, Diabetes 52:102, 2003


150
100
50
β-cell mass
Obesity
Phase of
Life
Successful
Compensation
No T2DM
10
20
30
40
50
60
70 Years


150
100
50
β-cell mass
Successful
Compensation
IGT
β-cell Death
Problem
Obesity
phase of
life
T2DM
10
20
30
40
50
60
70 Years


150
100
50
β-cell mass
Successful Compensation
β-Cell Death Problem
β-Cell Birth Problem
(Intra-uterine Growth Retardation)
10
20
30
40
50
60
70
Years

Progressive Loss of Glycemic Control in Obese Patients UKPDS



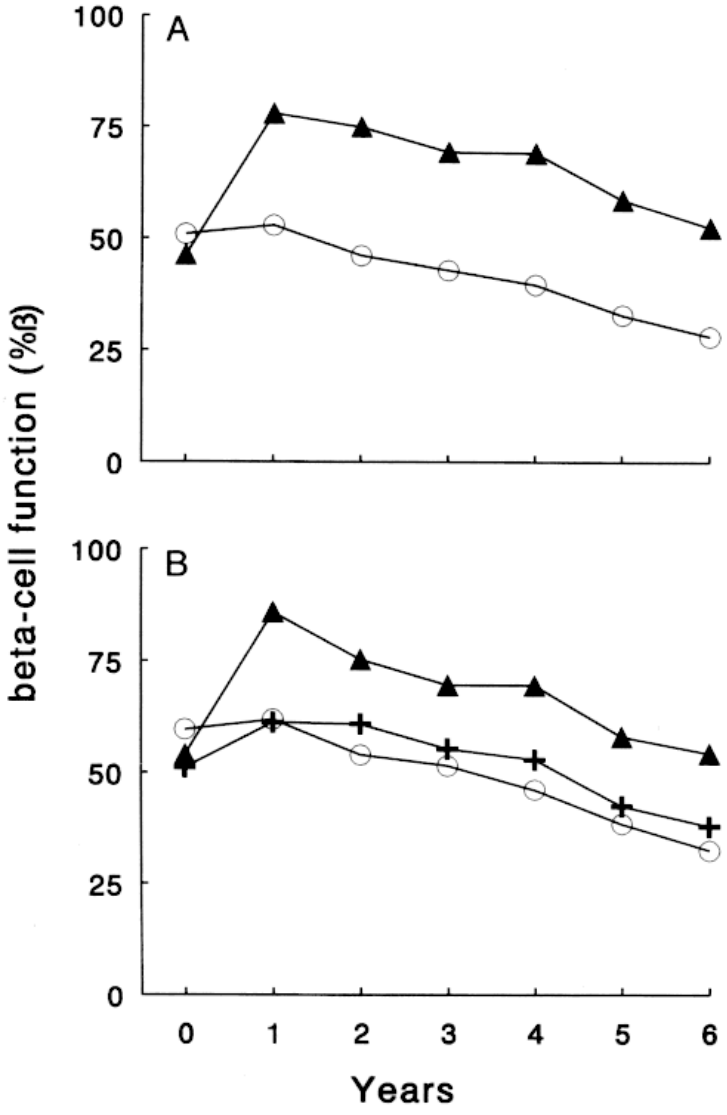
Open – Conventional

Cross – Metformin

Diamond - Intensive

UKPDS – Diabetes 44: 1249, 1995

Progressive Loss of Beta Cell Function in UKPDS – HOMA Studies



Black diamonds- Sulfonylureas

Open circles – Diet

Crosses - Metformin

UKPDS – Diabetes 44: 1249, 1995

What Might Cause Accelerated β-cell Apoptosis in T2D?

- **Areas of focus**
  - **Glucotoxicity**
  - **Lipotoxicity**
  - **Oxidative injury**
  - **Amyloid toxicity**
  - **ER stress**

Five Stages

Stage 1: Compensation - Glucose "normal"

Stage 2: Stable Adaptation

5.0-7.3 mM (89-130 mg/dl)

Stage 3: Unstable Early Decompensation

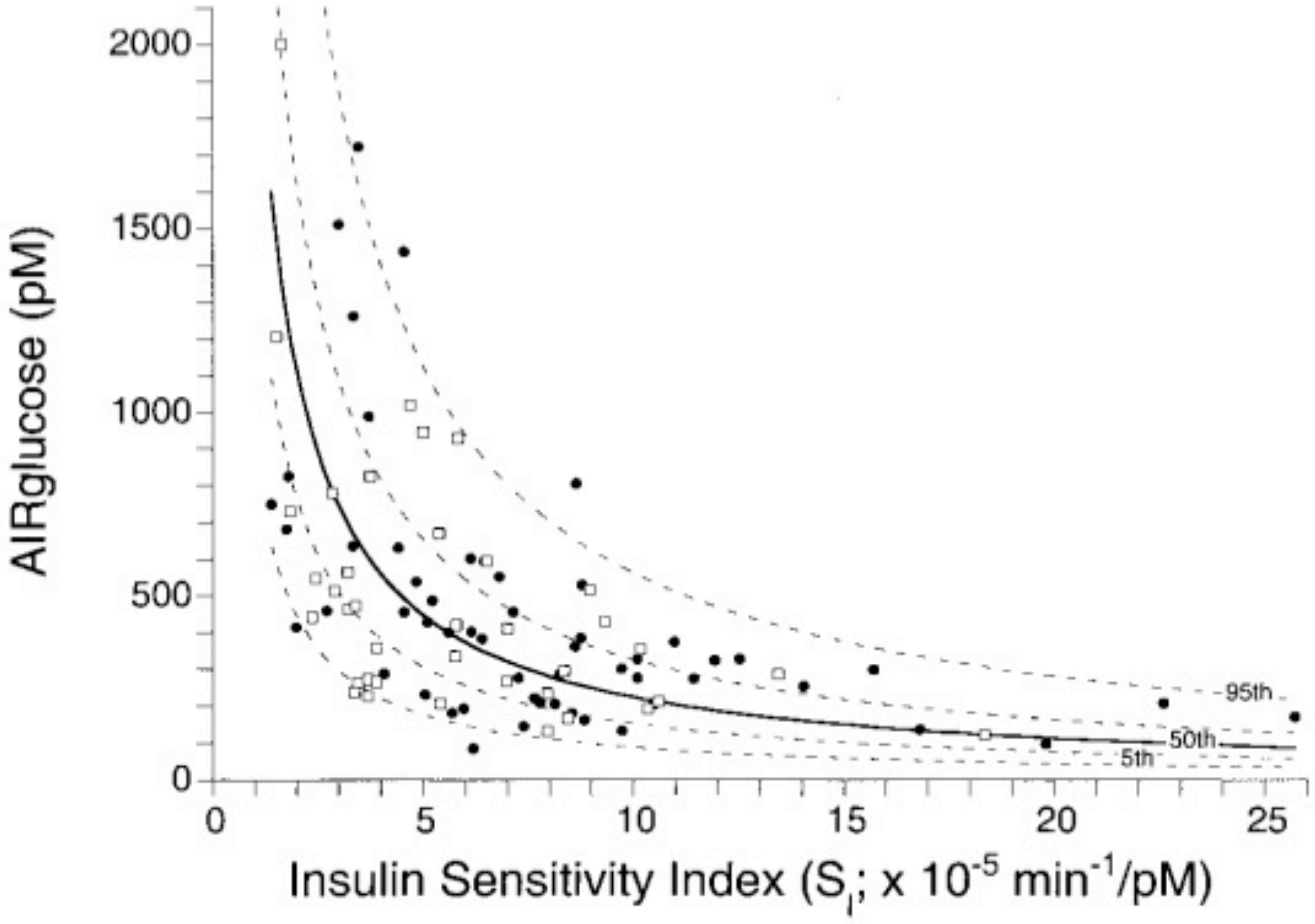
7.3-16 mM (130-285 mg/dl)

Stage 4: Stable Decompensation

16-20 mM (285-350 mg/dl)

Stage 5: Severe Decompensation - DKA

The Relationship Between Insulin Secretion and Insulin Resistance



Kahn SE, *J Clin Endoc Metab*. 86: 4047, 2001

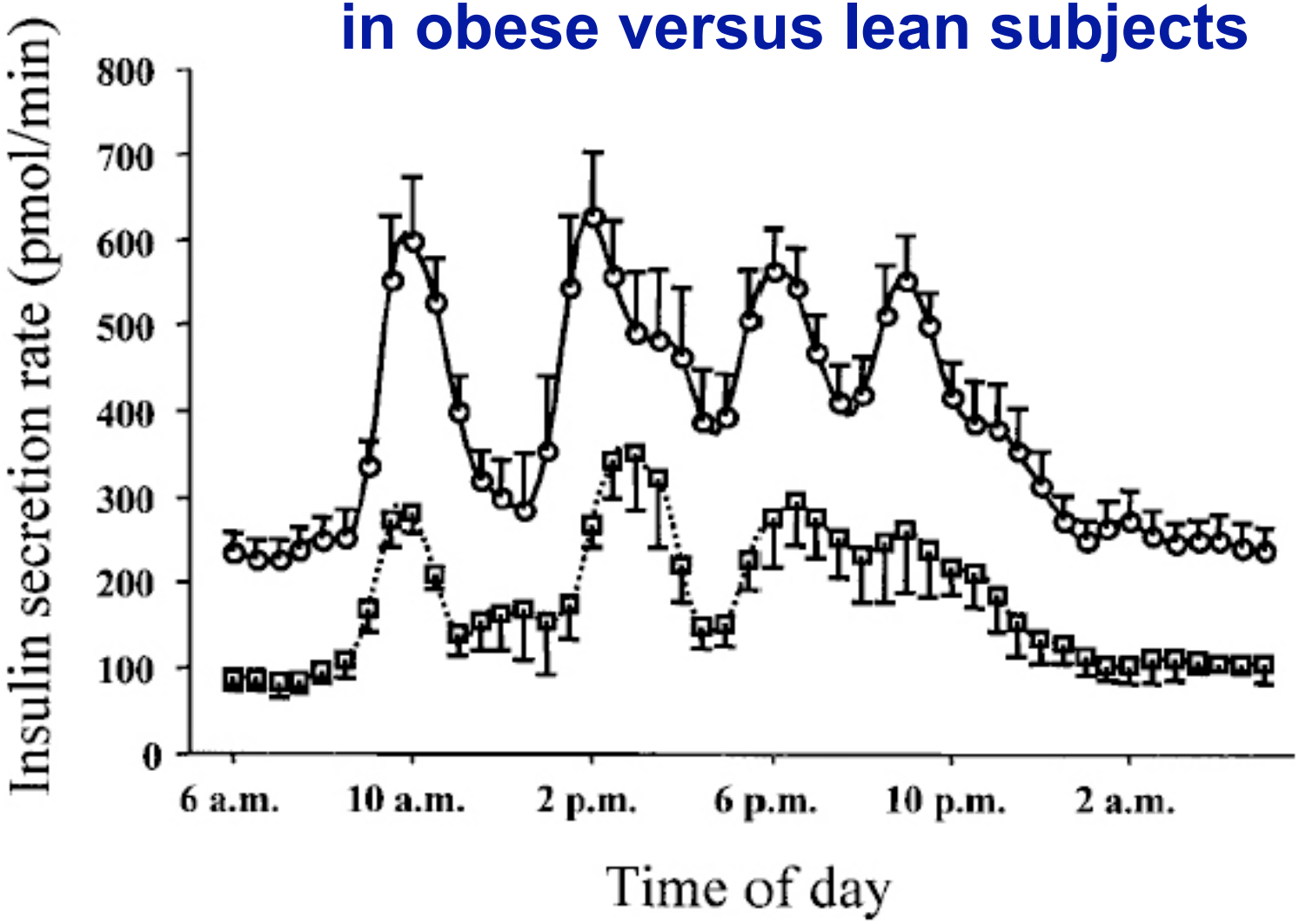
With compensation, can a given β-cell mass put out much more insulin?

Absolutely yes!

Obesity has only about a 50% increase in β-cell mass (Kloppel, Butlers), but insulin secretory output increases 100%.
(24 hr output of insulin 468 versus 235 nmol)

Camastra S, et al. Diabetes 54:2382, 2005

Insulin secretion rates over 24 hours in obese versus lean subjects



Camastra S, et al. Diabetes 54:2382, 2005

Stage 2: Stable Adaptation

Approximate glucose levels 90-130 mg/dl - Includes IGT and IFG

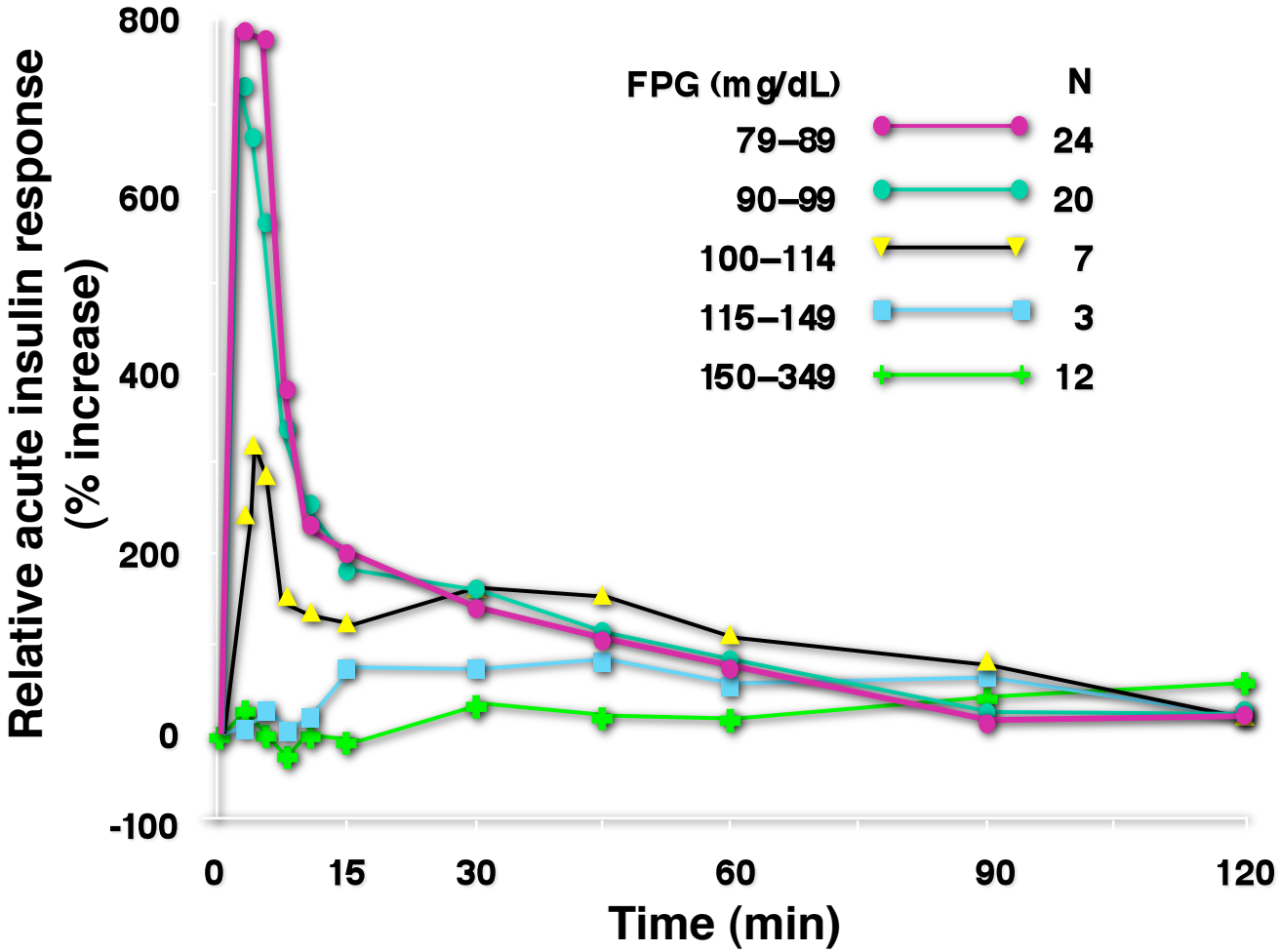
Not compensation - glucose levels not “normal”.

Beta cell phenotype altered - GSIS reduced.

Stable - Diabetes Prevention Program (DPP) IGT progresses to diabetes at 11% per year, and with diet and exercise only 5% per year.

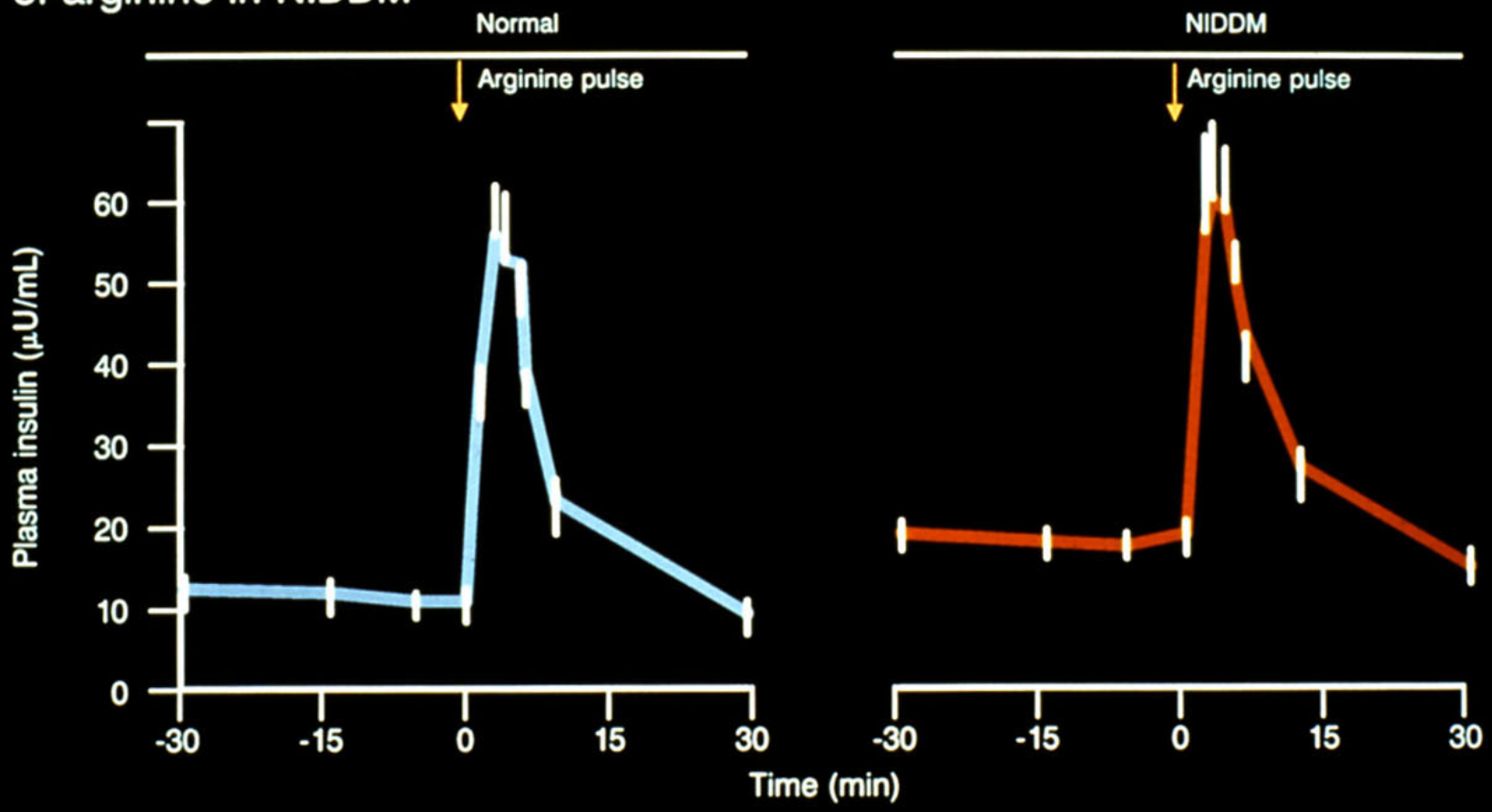
Occurs in pre-T1DM and remissions, but not as durable due to autoimmune destruction.

Effect of Fasting Plasma Glucose (FPG) on the Acute Insulin Response



Adapted from Brunzell et al. *J Clin Endocrinol Metab.* 1976;42:222.

Preservation of acute insulin secretion in response to an intravenous pulse of arginine in NIDDM



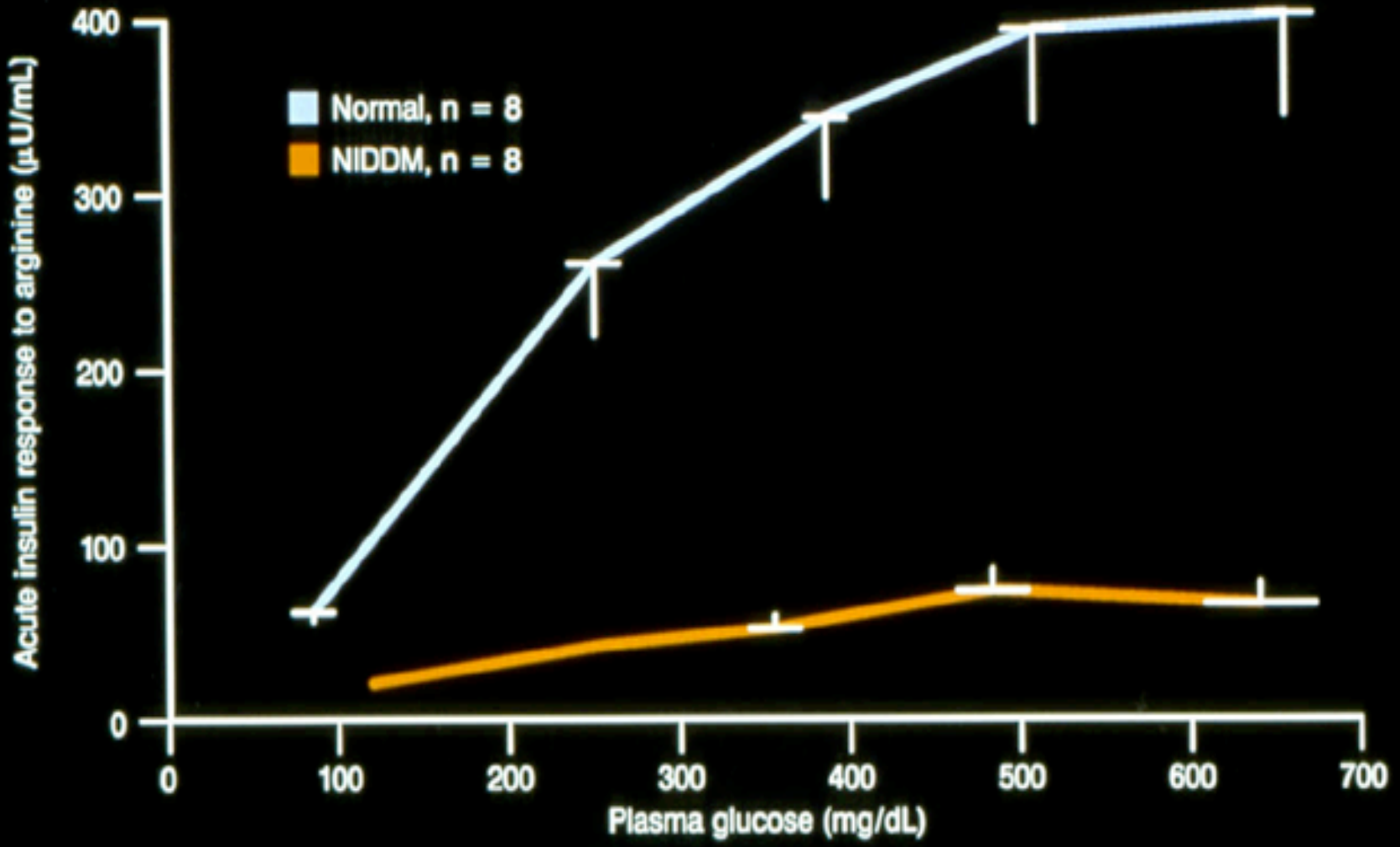
(Reproduced with permission from Ward WK, Beard JC, Halter JB, Pfeifer MA, Porte D Jr: Pathophysiology of insulin secretion in non-insulin-dependent diabetes mellitus. DIABETES CARE 1984; 7:491-502.)

With glucotoxicity in T2DM, does a given β-cell mass put out much less insulin?

Absolutely yes!

In T2DM β-cell mass is reduced to about 50% of normal, but insulin output to maximum stimulus of glucose and arginine is only about 15% of normal.

Loss of glucose influence upon arginine-stimulated insulin secretion in NIDDM



(Reproduced with permission from Ward WK, Bolgiano DC, McKnight B, Halter JB, Porte D Jr: Diminished B cell secretory capacity in patients with non-insulin-dependent diabetes mellitus. J CLIN INVEST 1984;74:1318-1328.)

Glucotoxicity Hypothesis

β-cells exposed to even mild chronic hyperglycemia develop changes in phenotype characterized by dysfunctional insulin secretion associated with altered gene and protein expression.

Competing hypotheses

Glucotoxicity: Excellent correlation between rising glucose levels and β-cell dysfunction. Molecular basis not yet established.

Lipotoxicity: Little evidence to support. High FFA in obesity associated with terrific insulin secretion. Fat may be good for β-cells.

Gluco-lipotoxicity: Fallback position. Could be true, but most evidence is from in vitro cell studies, which may not be applicable to in vivo situation. Molecular basis not yet established. Lipid accumulation in β-cells may be modestly increased but may not be harmful.

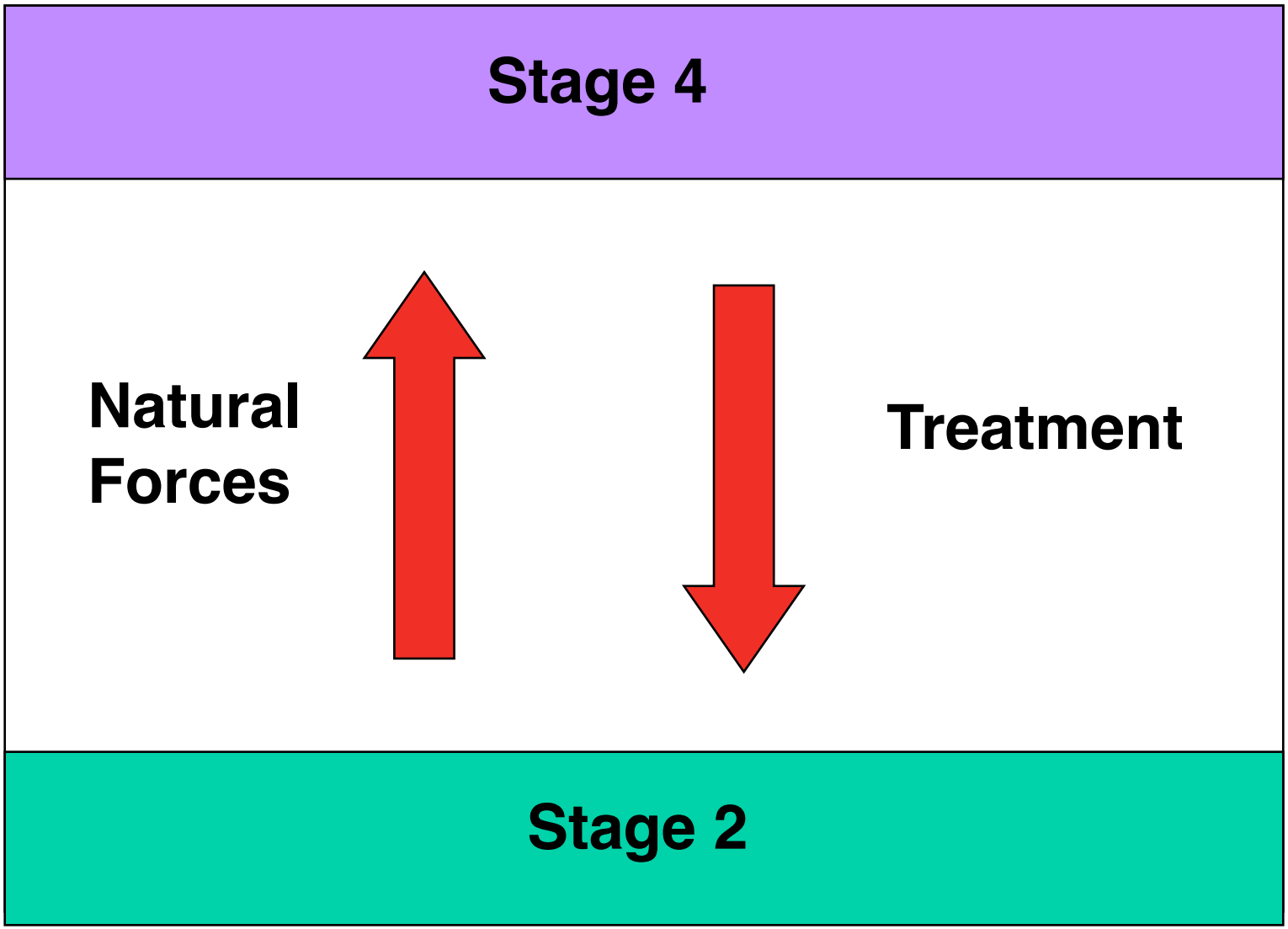
Stage 4: Stable Decompensation

Frank diabetes

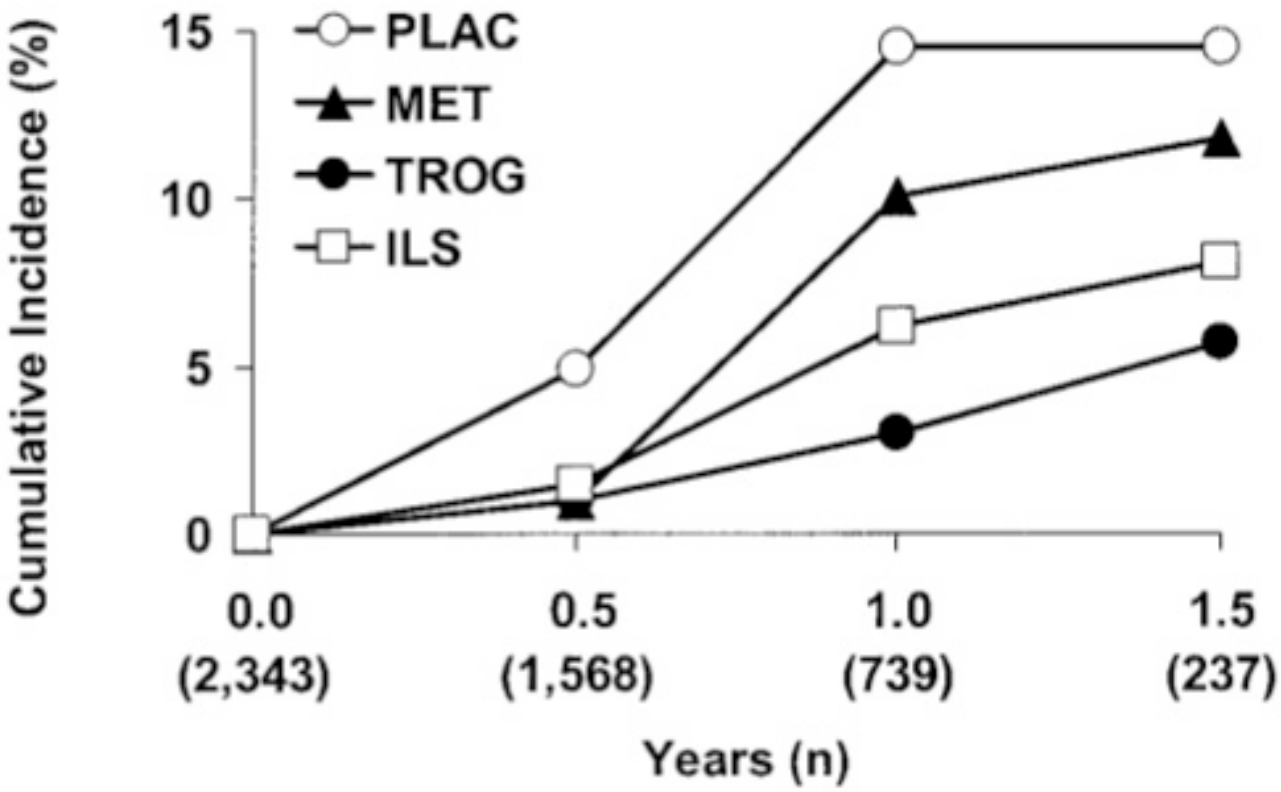
Stable because in T2DM DKA is rare and considerable amounts of insulin are produced for decades.

There is attrition of beta cells, which often leads to oral agent failure, but beta cell mass remains at 30-50% of normal.

T1DM progresses to Stage 5.

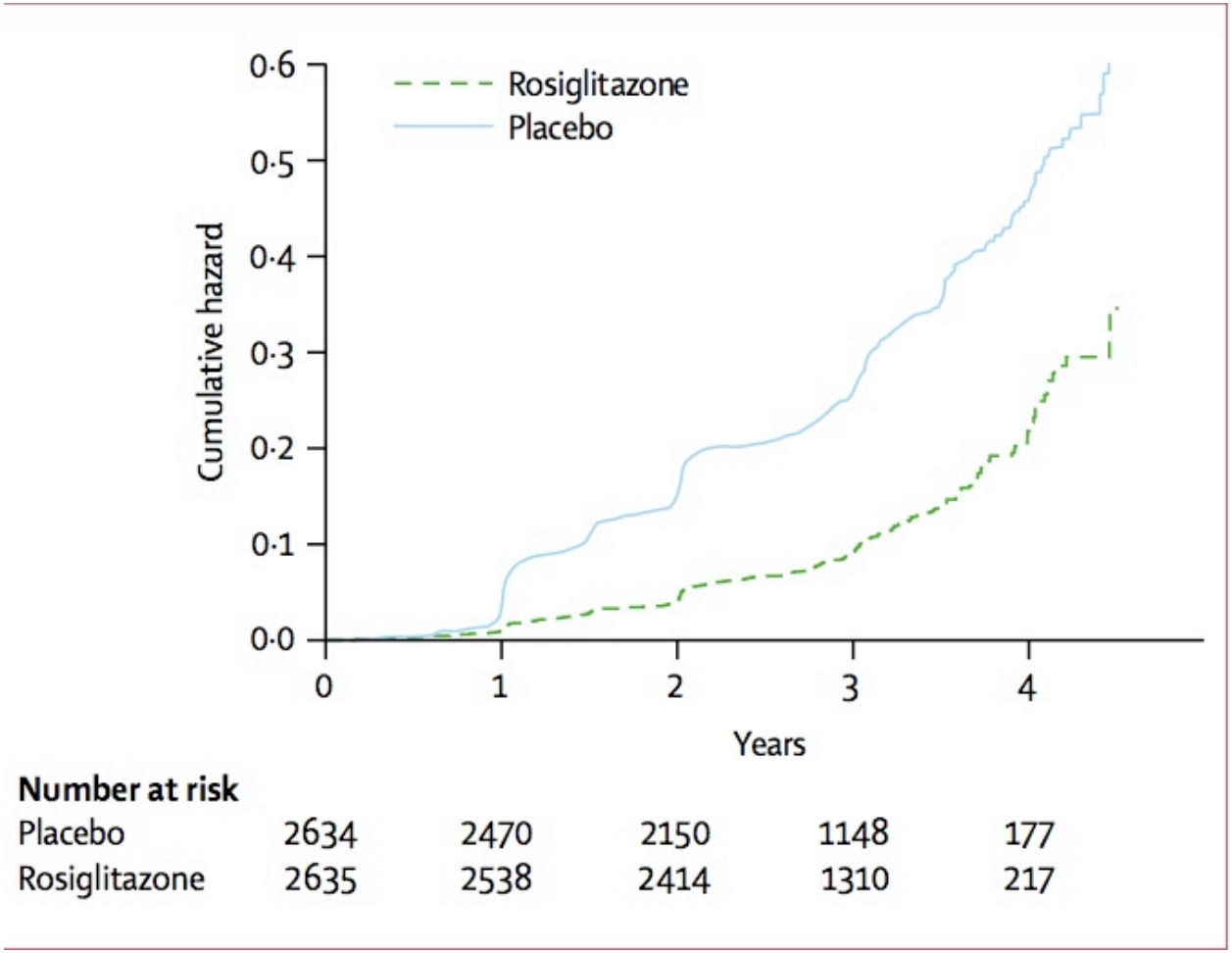

Stage 4
Natural Forces
Treatment
Stage 2

Diabetes Prevention Program (DPP) Research Group



Diabetes. **2005; 54:1150.**

The DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication)



***Lancet* . 2006;368:1096.**

Debate about DPP

Are We Delaying the Onset of Diabetes

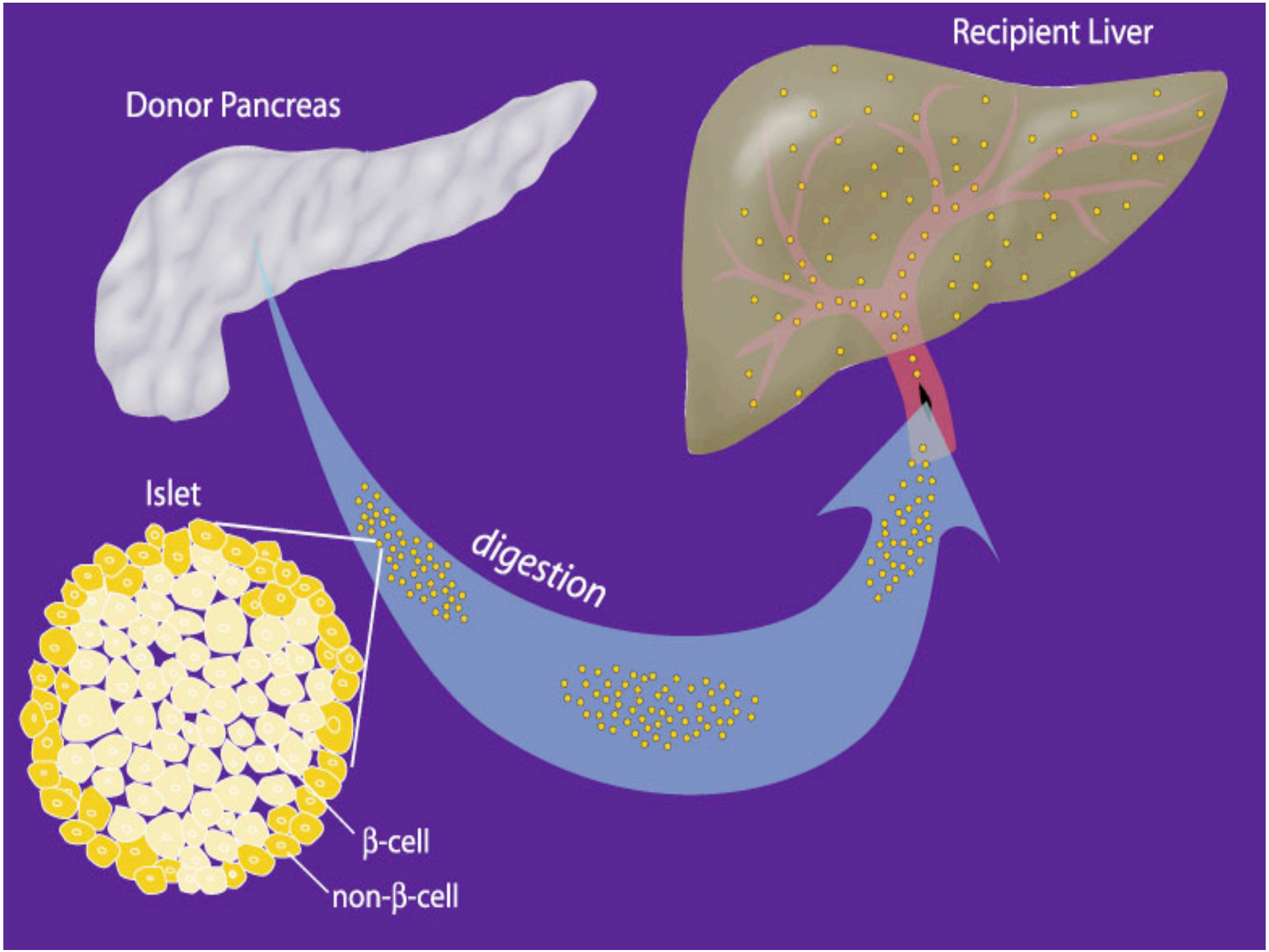
or

Preventing Diabetes?

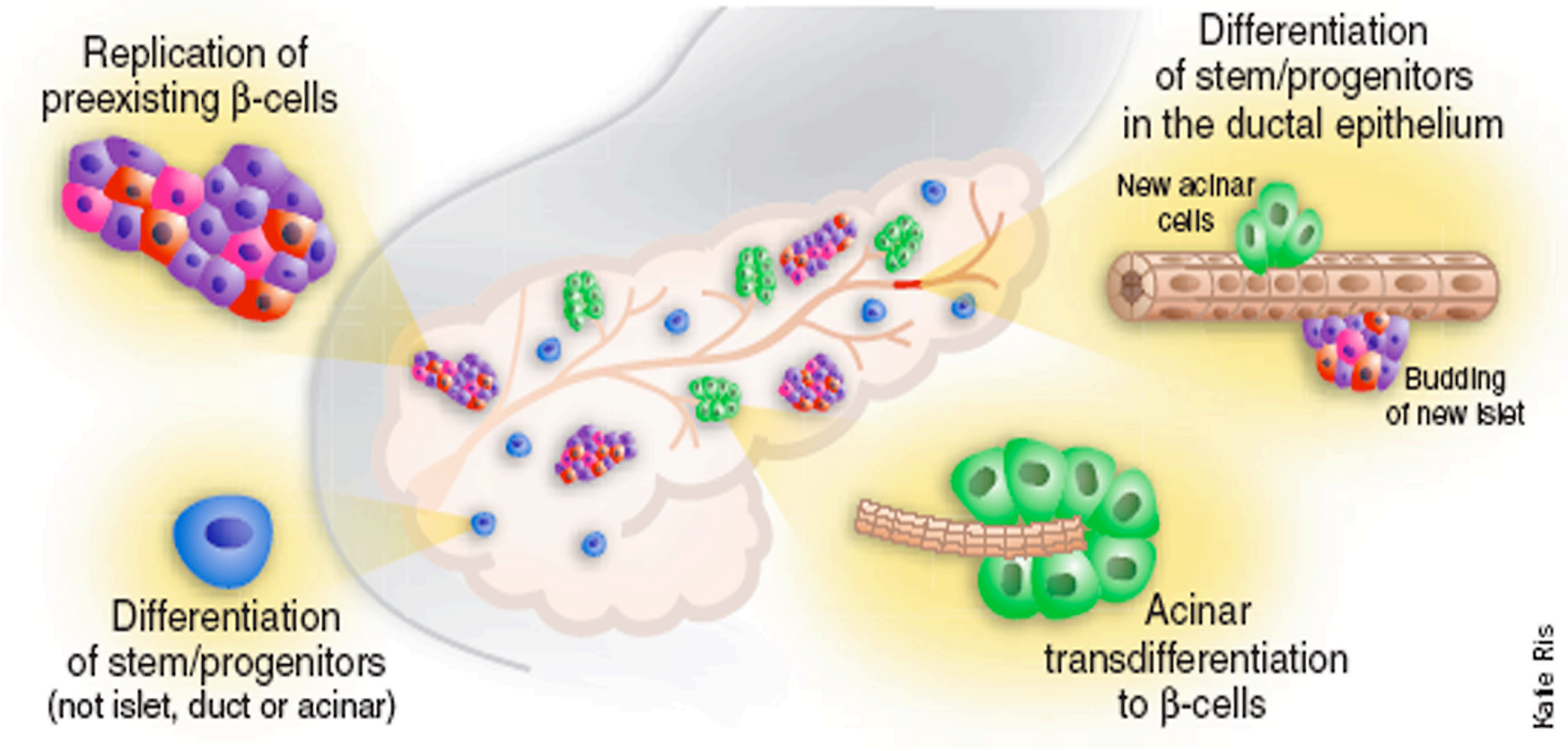
Why β-cell Replenishment?

Because the problem with both type 1 and 2 diabetes is not enough β cells.

(Of course, autoimmune destruction must be prevented too.)


Recipient Liver
Donor Pancreas
Islet
digestion
β-cell
non-β-cell

The Dream of β-cell Regeneration



β-cell Regeneration in Diabetes: The Task

- **Type 1 Diabetes:** Shut off autoimmunity, stimulate β-cell replication and neogenesis, inhibit apoptosis
- **Type 2 Diabetes:** Stimulate β-cell replication and neogenesis, inhibit apoptosis, and reduce insulin resistance

β-cell Regeneration