Beyond Insulin Resistance: Islet Cells as Key Drivers in Type 2 DM

Jack L. Leahy
Endocrinology, Diabetes and Metabolism
University of Vermont

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Standards of Care - American Diabetes Association

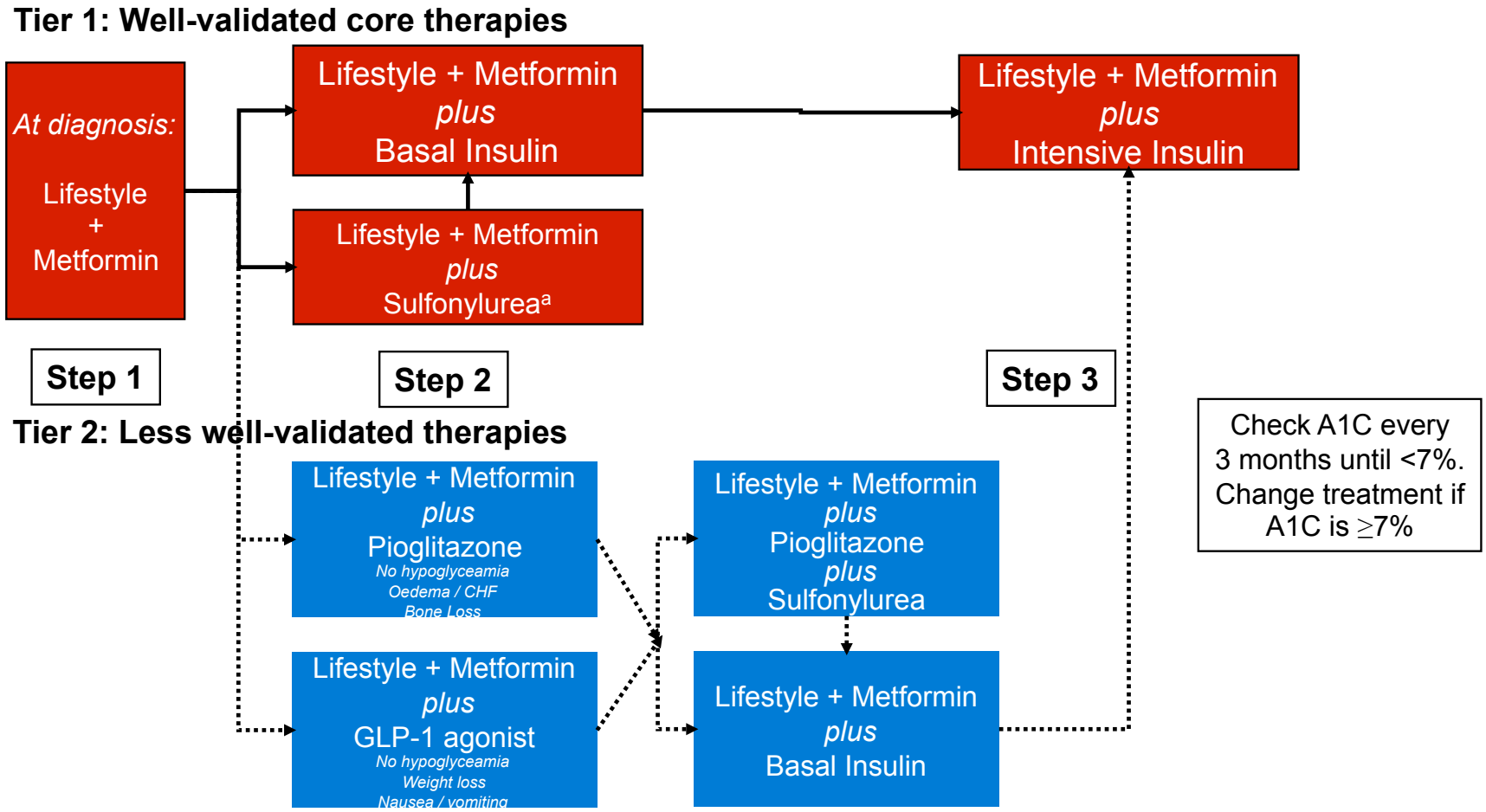
- Glycemia: HbA_{1c} <7.0%, FPG 90-130 mg/dL, PP <180 mg/dL.
- Blood Pressure: <130/80 mm Hg.
- Lipids: LDL <100 mg/dL; TG <150 mg/dL.
- Yearly:
  - Dilated eye exam; urinary protein; foot exam; flu shot.
- Other:
  - Aspirin usage; pneumococcal vaccine.

AACE goals - HbA_{1c} 6.5%, FPG 110 mg/dL, PP 140 mg/dL

NCEP - LDL ≤ 70 mg/dL

ADA. *Diabetes Care* 2005;29:S4-S42

Consensus Algorithm Update 2008

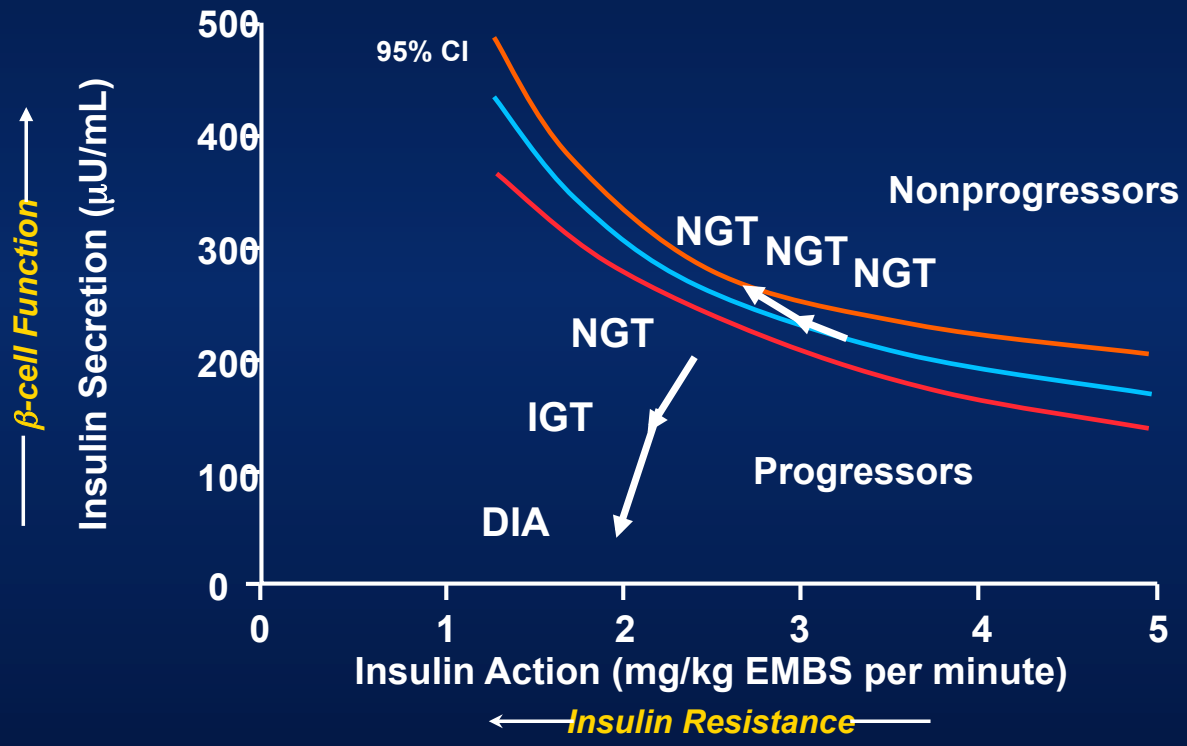


ADA/EASD Guidelines. Diabetes Care 2008;31(1):1–11

To Physiologists and Researchers, Type 2 Diabetes Is…..

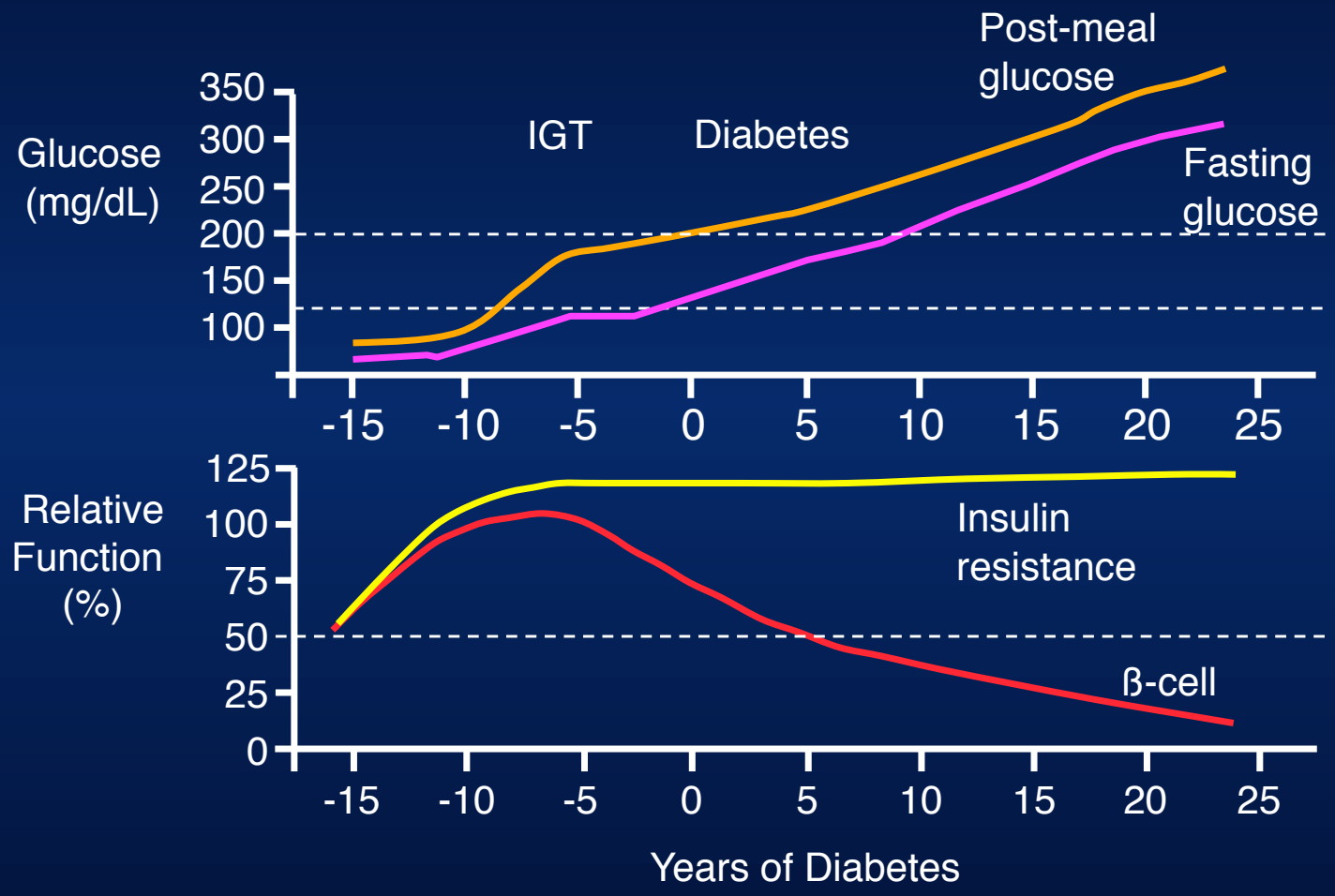
- Reasonably good understanding of pathogenesis:
  - Relative roles of ß-cell dysfunction and insulin resistance.
  - Genetic susceptibility.
  - Defects at late-stage normal glucose tolerance, prediabetes, and full blown type 2 DM.
- Defining tissue metabolic dysfunction AND some mechanisms AND few treatment/prevention strategies:
  - Incretin therapies.
- Placing physiological context to clinical terms:
  - *Treatment failure.*
  - *Treatment durability.*

Declining ß-Cell Function: Best Correlate of Progression



Weyer C et al. *J Clin Invest*. 1999;104:787-794.

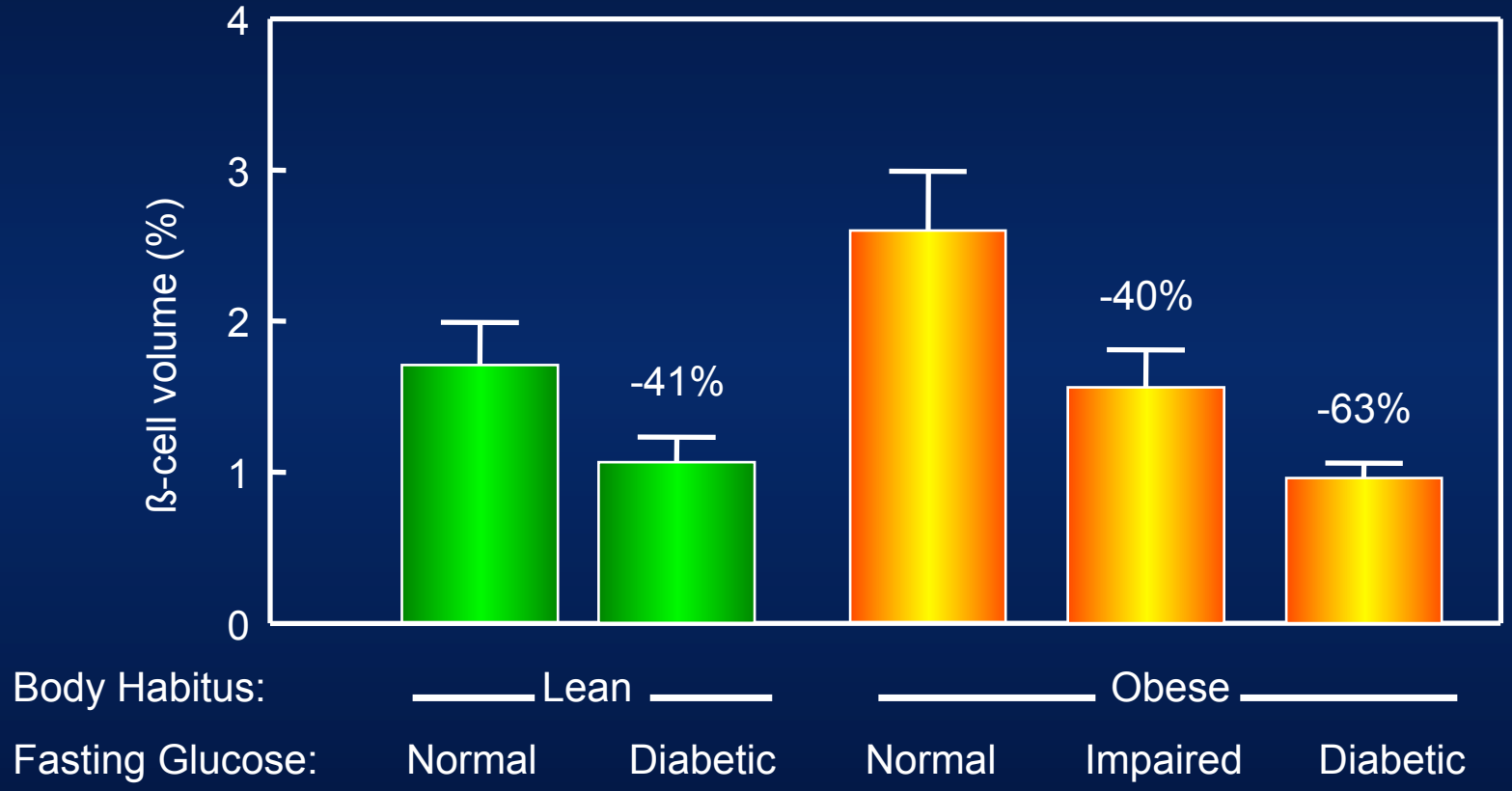
Natural History of Type 2 Diabetes



Adapted from: International Diabetes Center (Minneapolis, Minnesota).

ß-cell Mass: Normoglycemia and Diabetes

An Autopsy Study

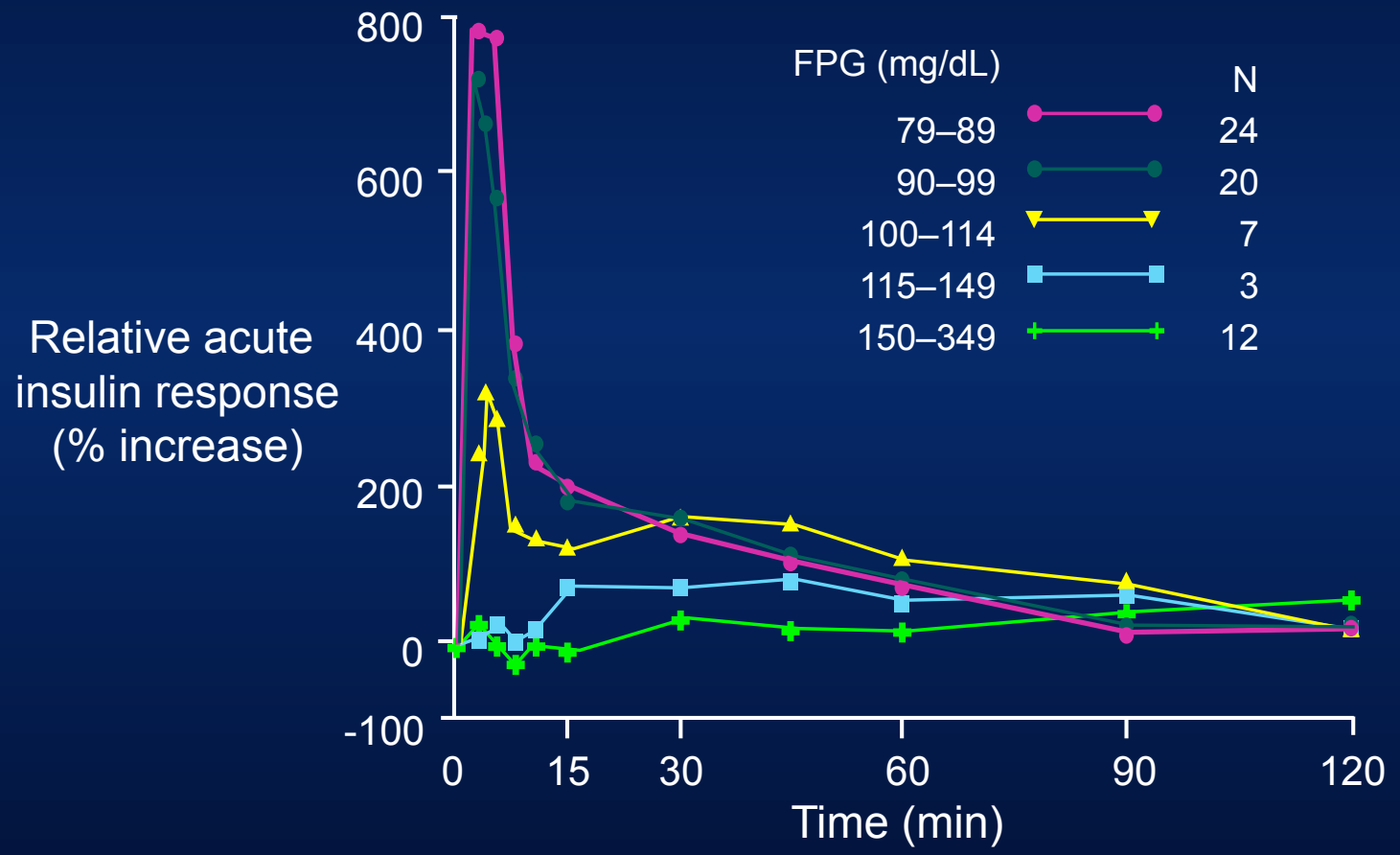


Butler AE et al. *Diabetes*. 2003;52:102–110.

Proposed Mechanisms for Lowered ß-cell Mass in Type 2 Diabetes

- Amyloid - *"Islet Alzheimer's"*
- Metabolic - oxidative stress
- ER stress
- Inflammatory
- Genetic
- ß-cell balding

Fasting Plasma Glucose (FPG) and Acute Insulin Response



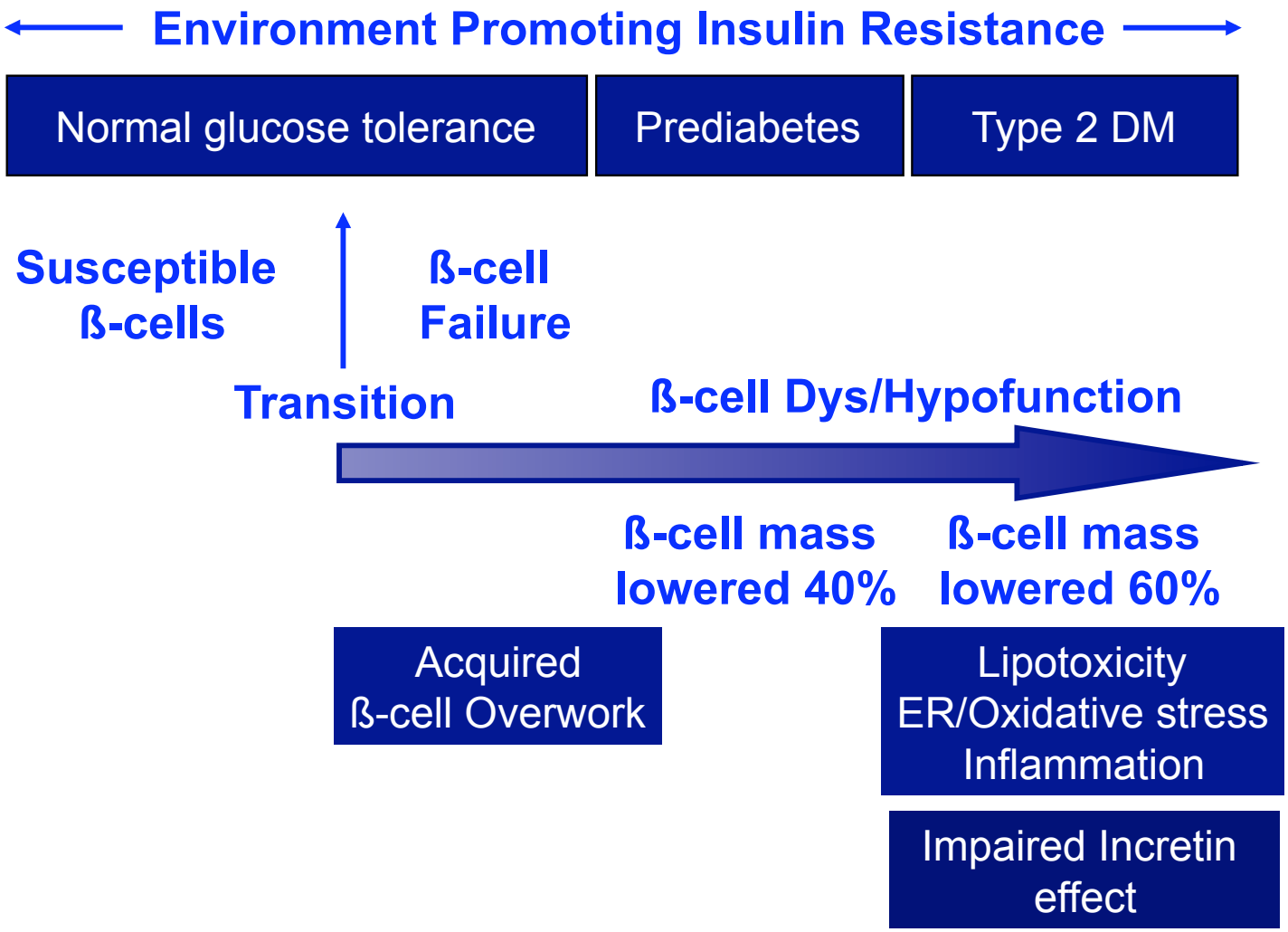
Brunzell JD et al. *J Clin Endocrinol Metab*. 42:222-229, 1976.

Recovery of ß-cell Dysfunction in Type 2 Diabetes

- Insulin:
  - Overnight fish insulin (Turner 1976)
  - 1-3 months on diet, sulfonylurea, or insulin (Kosaka 1980)
  - Biostator for 20 hours (Moulin and Vague 1982)
  - 3 weeks insulin pump (Garvey 1985)
- ß-cell rest:
  - Diazoxide and insulin for 10 days (Greenwood 1980)
  - Overnight somatostatin (Laedtke 2000)
  - ?TZDs
- Lowered free fatty acids:
  - 48 hours of acipimox in family members type 2 DM (Cusi 2007)
- GLP-1 (Holz 1995)
- Inflammation:
  - Interleukin 1 receptor antagonist for 13 weeks (Larsen 2007)

Proposed Mechanisms for ß-cell Dysfunction in Type 2 Diabetes From Animal Studies

- Glucose Toxicity
- Lipotoxicity
- ß-cell Overwork/Exhaustion
- Metabolic - oxidative stress, ER stress
- Inflammatory
- Impaired Incretin Effect


Environment Promoting Insulin Resistance
Normal glucose tolerance
Prediabetes
Type 2 DM
Susceptible ß-cells
ß-cell Failure
Transition
ß-cell Dys/Hypofunction
ß-cell mass lowered 40%
ß-cell mass lowered 60%
Acquired ß-cell Overwork
Lipotoxicity ER/Oxidative stress Inflammation
Impaired Incretin effect

Type 2 DM Susceptibility Genes

TCF2	HHEX/IDE	ZJAZF1
IGFBP2	TCF7L2	CDC123-CAMK1D
WFS1	KCNJ11	AN8-LGR5
CDKAL1	FTO	THADA
SLC30A8	PPARγ	ADAMTS9
CDKN2A/B		NOTCH2

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Diabetes Genetics Institute. *Science* 316:1331-1336, 2007.
Scott, LJ. *Science* 316:1341-1345, 2007.
Zeggini E. *Science* 316:1336-1341, 2007.
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Zeggini E. *Nat Gen* Online

Tissue Gene Regulation:

- ß-cell
- Insulin Sensitivity
- Unclear

Pathogenesis Concept

- Insulin resistance occurs early – before glucose intolerance
  - Genetic?
  - Obesity, ageing, lifestyle, etc.
- If have healthy ß-cells, compensate and remain euglycemic
- If “susceptible” ß-cells:
  - ß-cell dysfunction results in imperfect compensation
  - Progress to prediabetes stage
  - Onset of acquired abnormalities
  - Hyperglycemia worsens, vicious cycle

Session 1

- Beta and Islet Cell Biology:
  - Chris Rhodes
- Beta Cell Mass Regulation:
  - Susan Bonner-Weir
- Issues of Beta Cell Dysfunction:
  - Gordon Weir
- Basic Biology of Incretins:
  - Patricia Brubaker
- Incretin Abnormalities in Type 2 Diabetes:
  - David D'Alessio