Cordoba 01/02/2008

Slides Professor Pierre LEFEBVRE

Clinical Research in Type 2 Diabetes : Current Status and Future Approaches

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Granada, Spain, February 2008

*Thanks to R.Bergman, P.De Meyts, L.Groop, V.Lyssenko and O.Pedersen

Diabetes + IGT In the World in 2007

~550.000.000

~13% of the Adult Population

Diabetes + IGT in the World in 2025

~800.000.000

>15% Adult Population


FATBOY SLIM
I'M
#1
SO WHY
TRY HARDER
YOU'VE COME A LONG WAY, BABY
PARENTAL
GUIDANCE
EXPLICIT LYRICS

Type 2 DM Today

- Occurs in genetically predisposed individuals
- Results from an interaction between genes and environment
- Insulin resistance contributes but B-cell failure is critical

The Genetics of Type 2 Diabetes

Status on February 1, 2008

Candidate Genes Approach
versus
Genome-wide Association Scans

Candidate Gene Approach

- Maturity-onset Diabetes of the young (MODY) : six genes indentified f.i. a mutation in the B-cell glucose-sensing hexokinase-glucokinase in MODY 2
- Neonatal Diabetes : mutations identified in the genes KCNJ11 or ABCC8 encoding for components of the B-cell KATP channel
- Other rare forms of Monogenic Diabetes : mutations in the mitochondrial genome identified in rare forms of diabetes with maternal inheritance (association with deafness in the MIDD syndrome or with myopathy and stroke-like episodes in the MELAS syndrome)

The Genome-wide Association Scans

GENE VARIANTS INCREASING RISK OF T2D

Gene	Chromosome	OR	Risk allele (%)
TCF7L2	**10**	**1.38**	**0.30**
IGFBP2 (IMP2)	**3**	**1.17**	**0.32**
CDKN2A/CDKN2B	**9**	**1.20**	**0.86**
CDKAL1	**6**	**1.12**	**0.32**
HHEX	**10**	**1.14**	**0.54**
KCNJ11	**11**	**1.15**	**0.47**
PPARG	**3**	**1.20**	**0.84**
SLC30A8	**8**	**1.12**	**0.65**
FTO	**16**	**1.23**	**0.40**

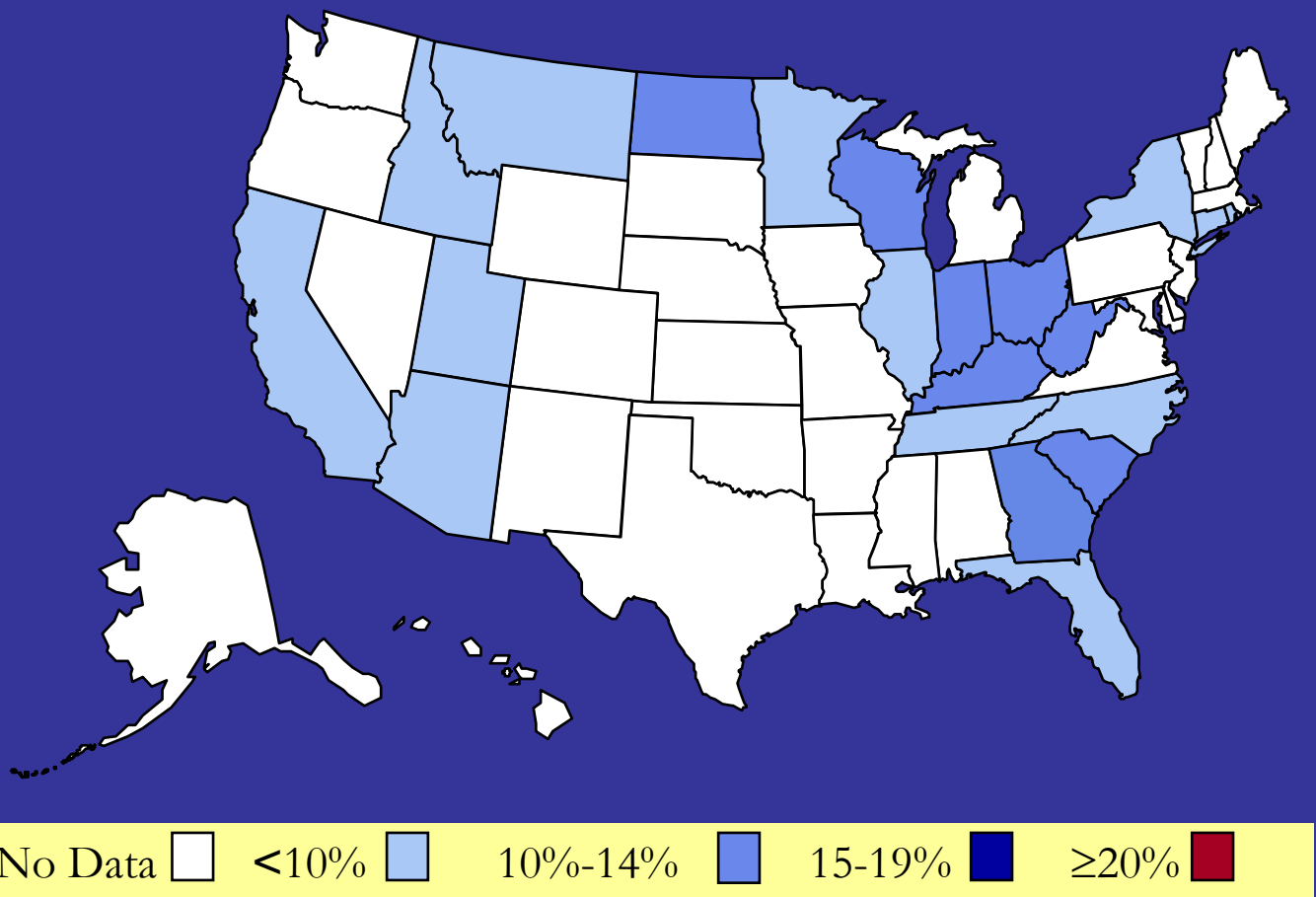
The genetic architecture of type 2 diabetes: a hypothesis for operation by Oluf Pedersen (Copenhagen)

- The genetic susceptibility to polygenic T2D is due to multiple common and rare alleles in multiple 'at-risk genes'
- All individuals have multiple 'at risk genes'
- Many of the diabetes 'at-risk genes' may earlier in evolution have been 'survival genes' or 'plus-variants' (Dr. Neel's hypothesis)
- The combination of 'at-risk genes' together with a risk environment and a risk behaviour (e.g. uterine growth retardation, toxins, intestinal ecology, infections, over-eating or a sedentary life) in critical time windows of each individual's growth, maturation and ageing are major determinants in the pathogenesis of T2D

The Role of the Environment

OBESITY*: Prevalence Trends

BRFSS 1985



CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

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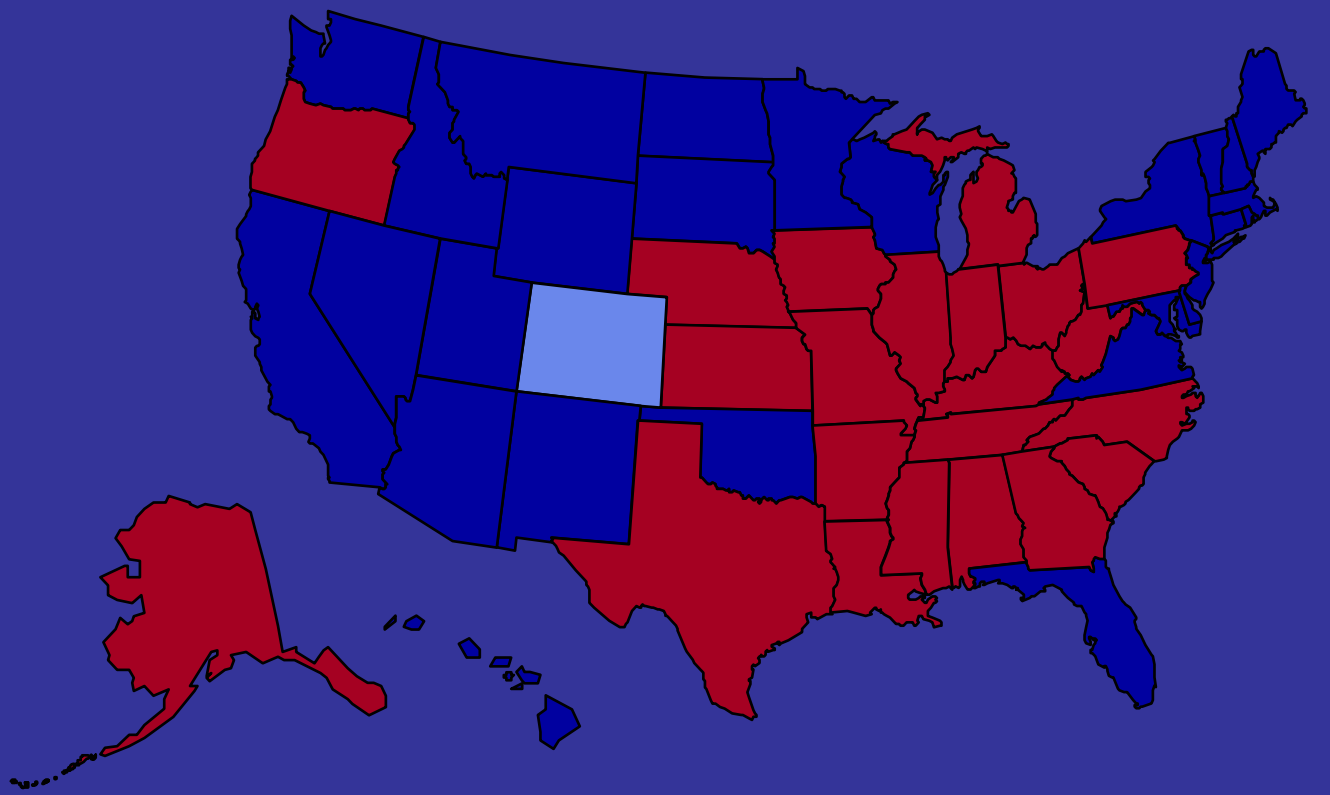
Mokdad A H, et al. *J Am Med Assoc* 2001;286:10

OBESITY*: Prevalence Trends

BRFSS 2000



CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

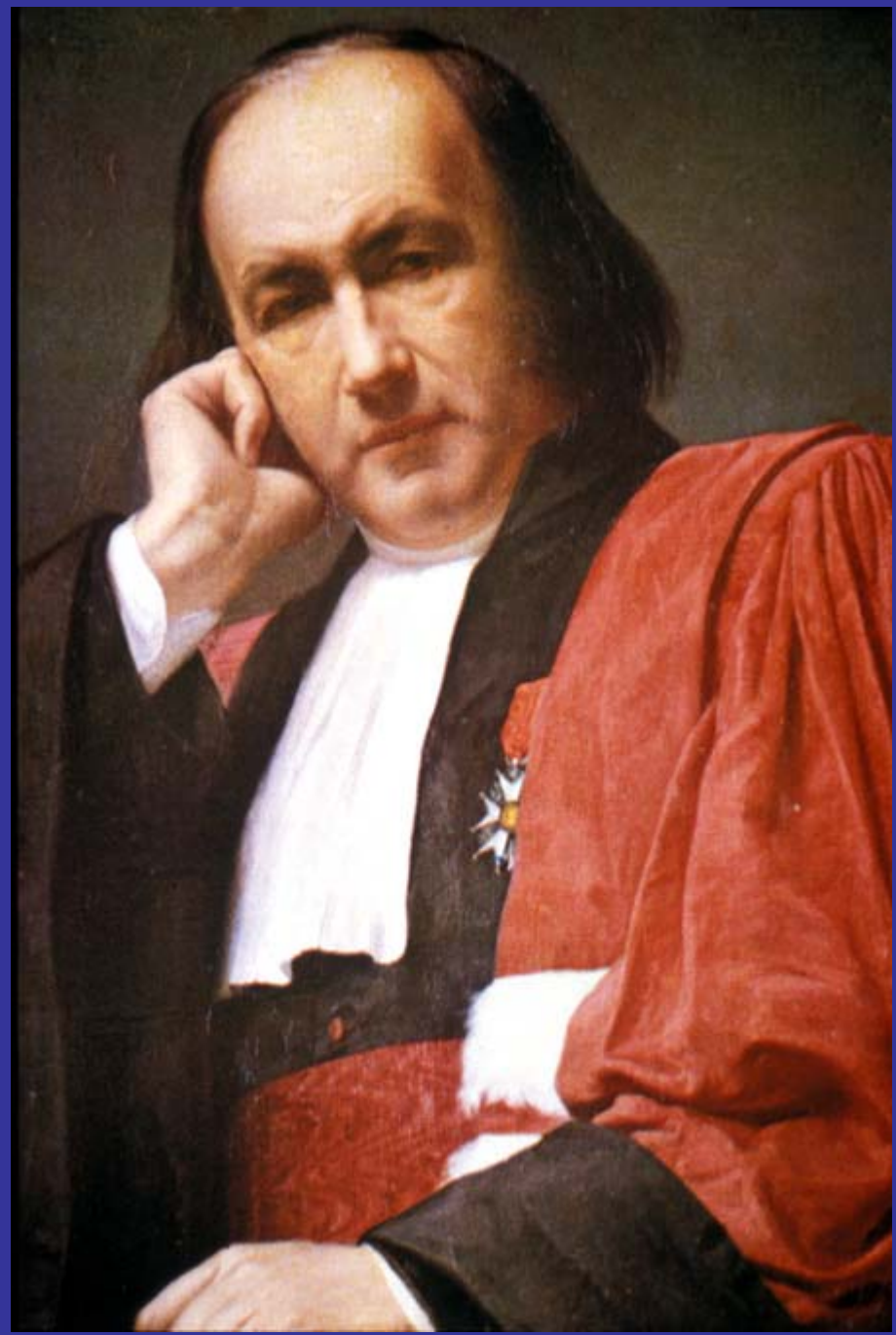
*(BMI≥30kg/m^2)

Mokdad A H, et al. *J Am Med Assoc* 2001;286:10

Understanding the Pathophysiology of Type 2 Diabetes

Claude Bernard

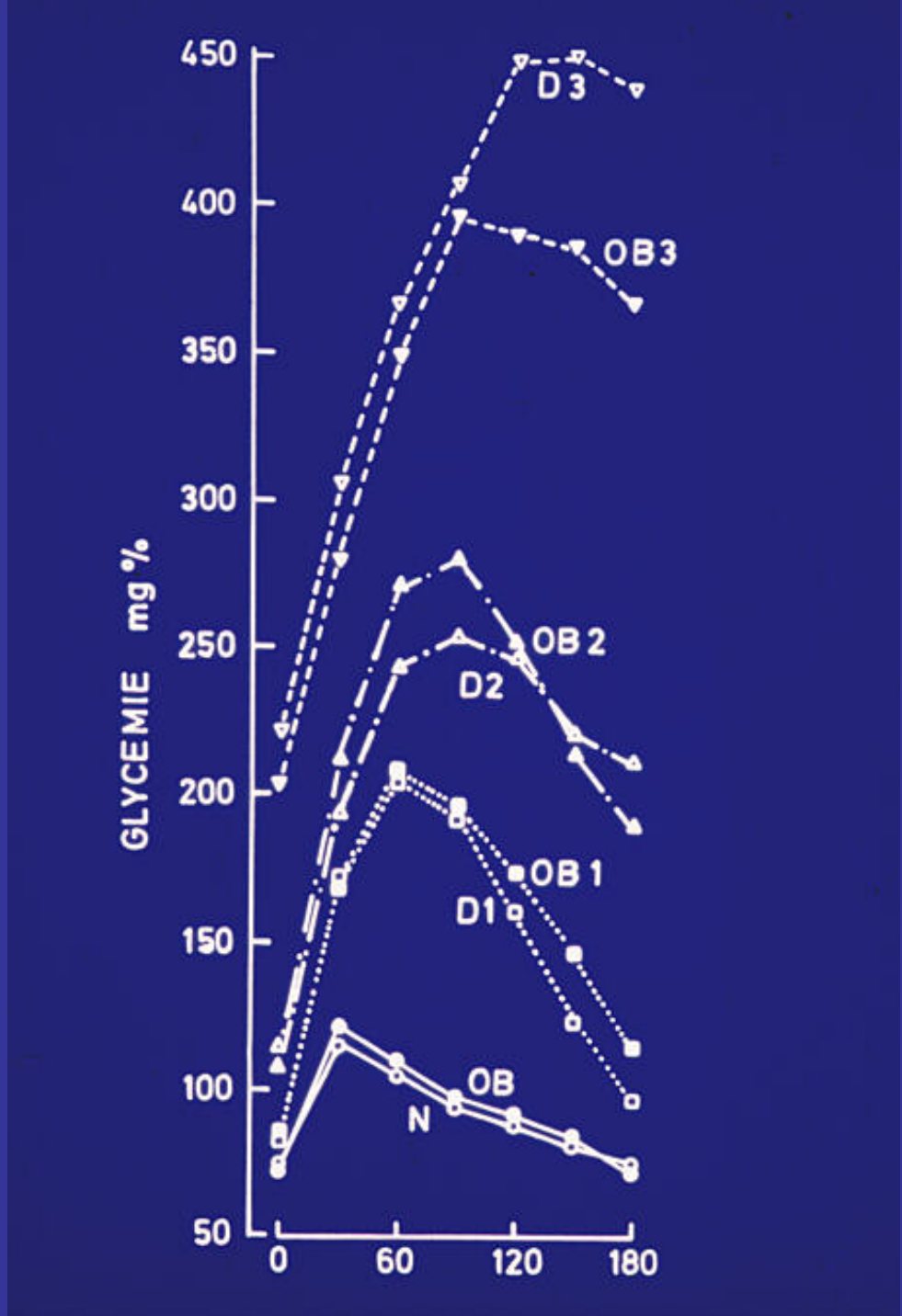
« You can understand dysregulation only if you know regulation »

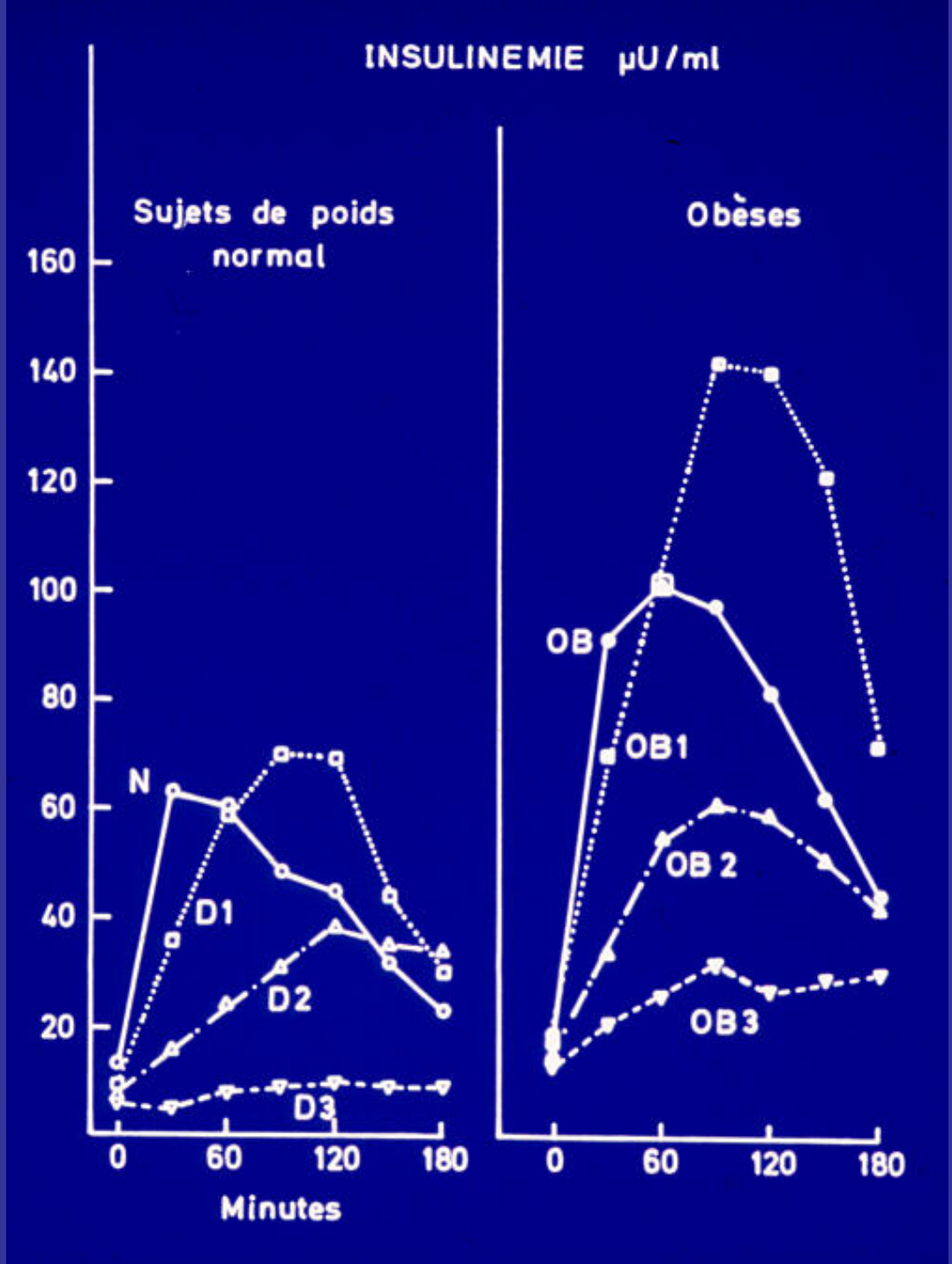


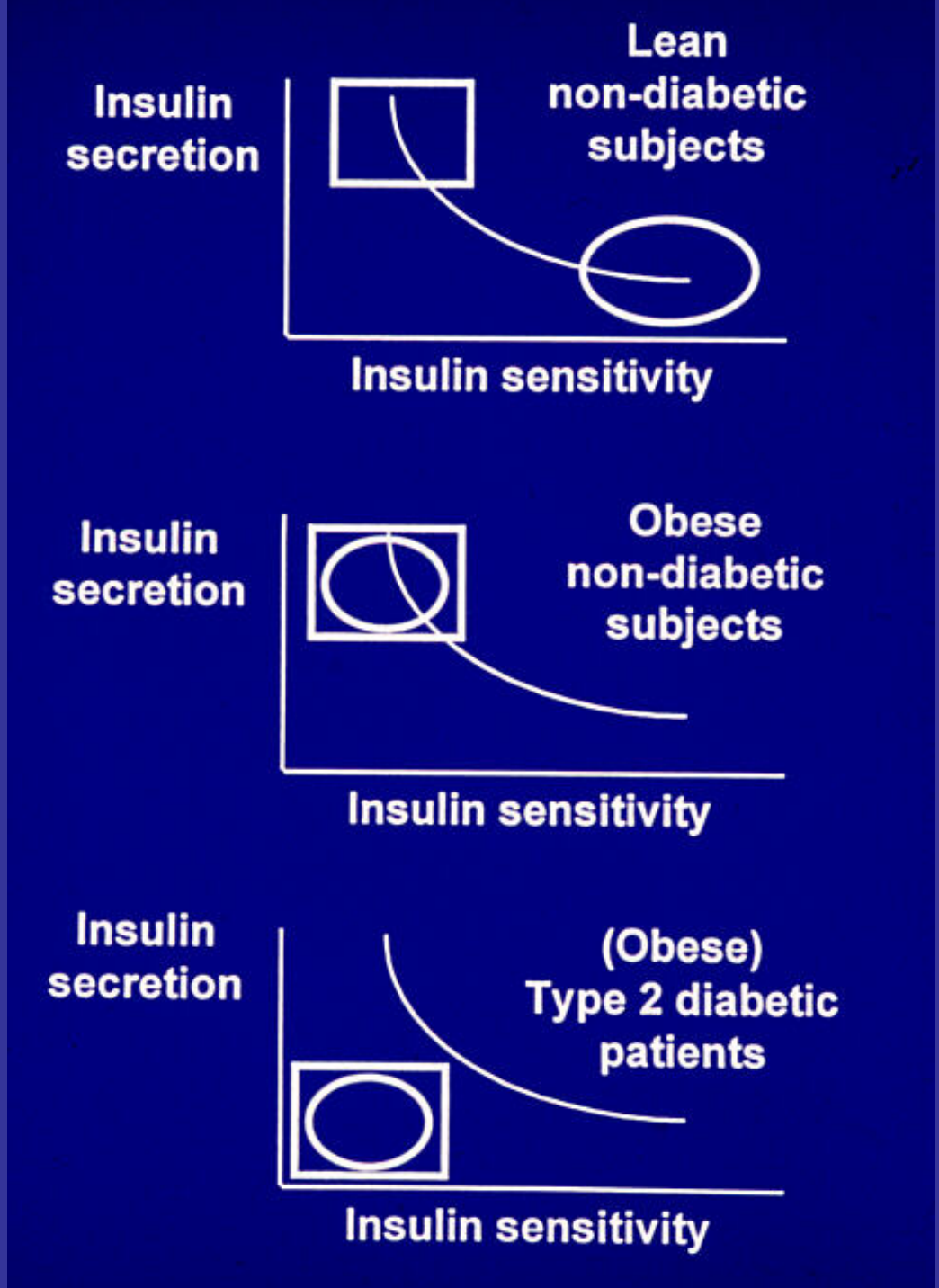
The Top Three Tools for a Better Understanding of the Pathophysiology of Type 2 Diabetes

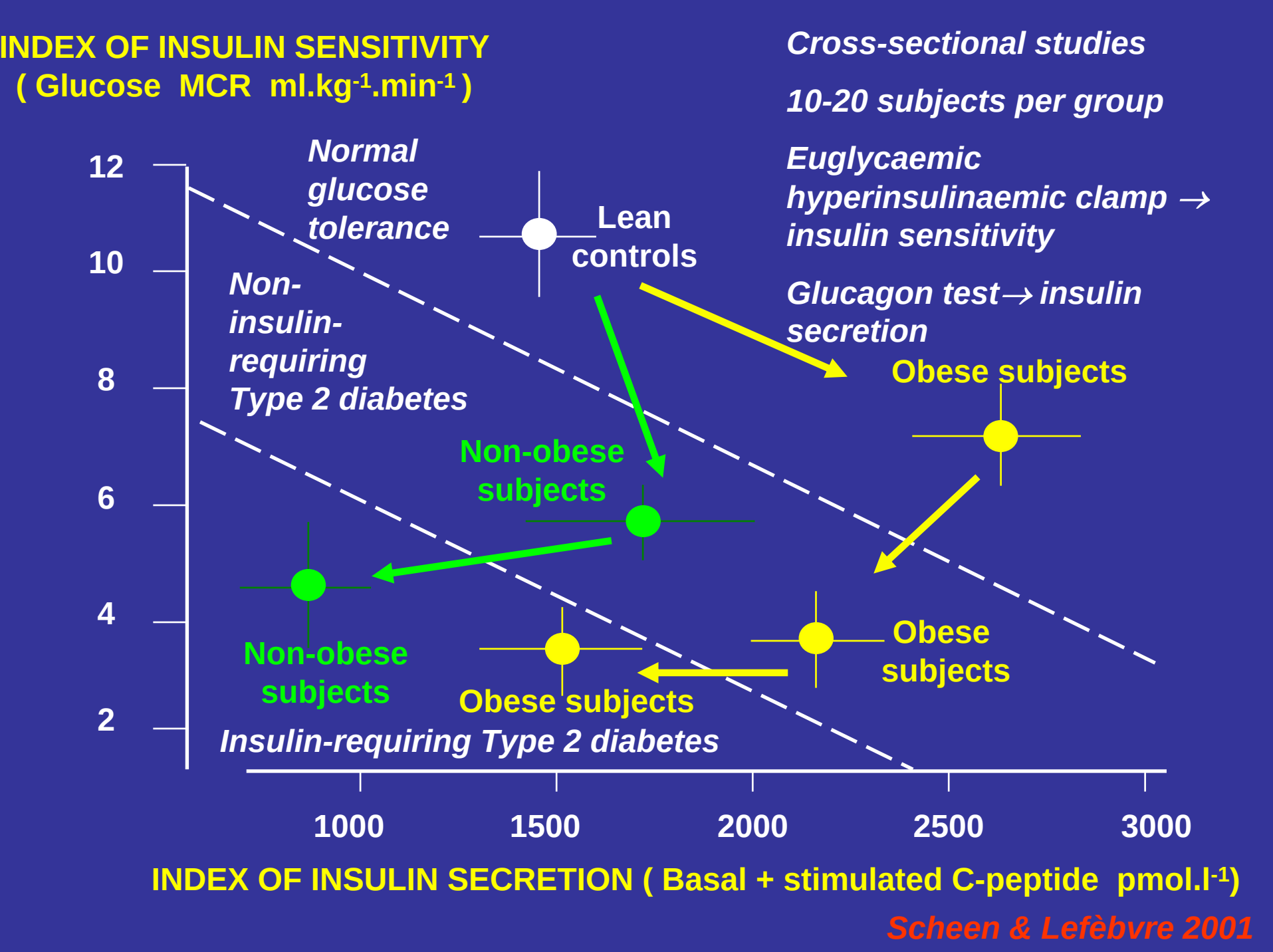
- A sensitive and specific assay of insulin in the plasma : the Yalow and Berson RIA
- A procedure to evaluate insulin sensitivity/resistance : the euglycemic-hyperinsulinemic « glucose clamp » (Andrès-DeFronzo)
- A simple procedure to evaluate the interplay between insulin secretion and insulin sensitivity : Bergman’s Minimal Model


L C
L C
Universitas Leodiensis

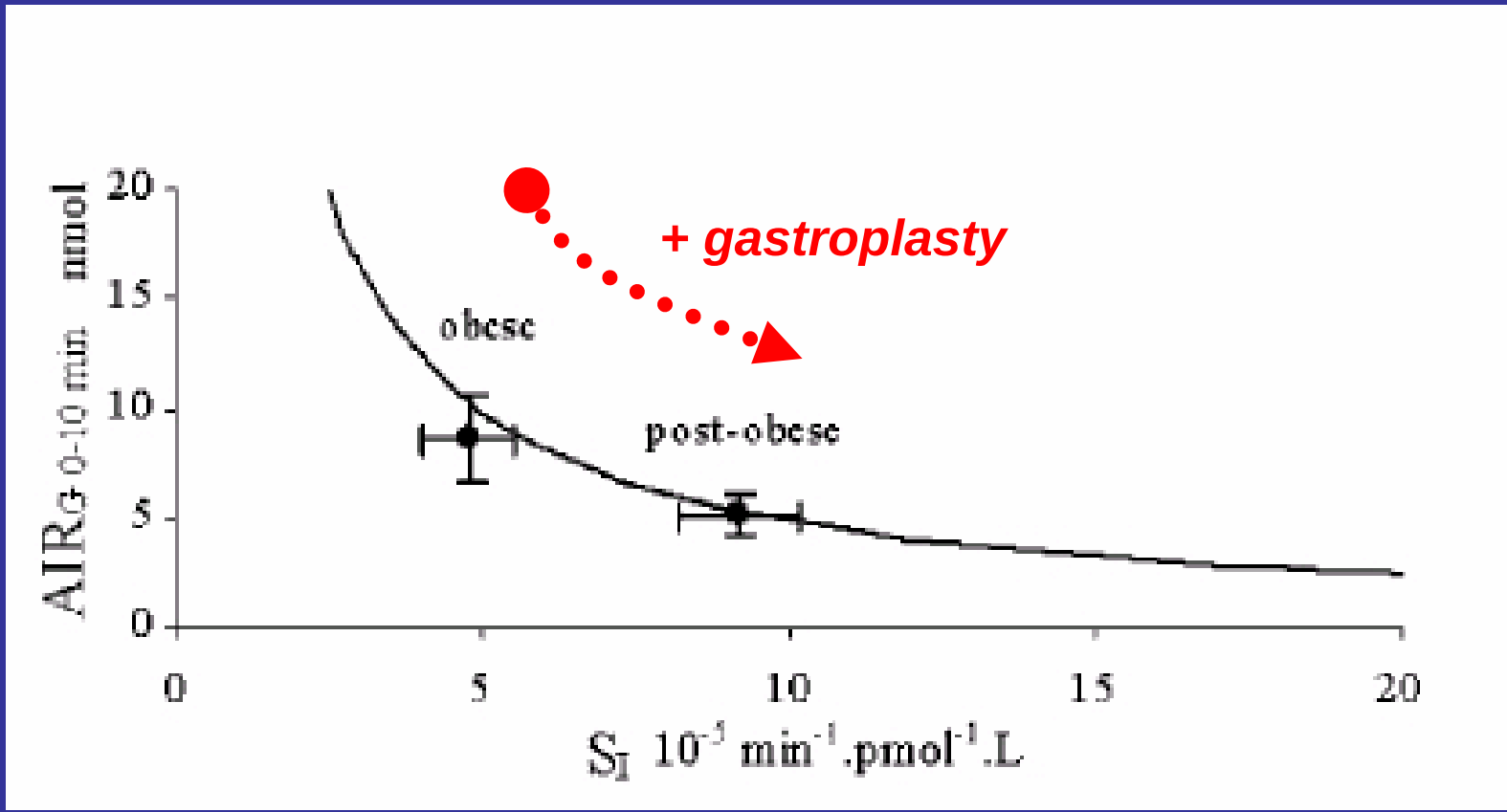

GLYCEMIE mg %
450
400
350
300
250
200
150
100
50
0
60
120
180
D3
OB3
OB2
D2
OB1
D1
OB
N


INSULINEMIE µU/ml
Sujets de poids normal
Obèses
160
140
120
100
80
60
40
20
N
D1
D2
D3
OB
OB1
OB 2
OB3
0
60
120
180
Minutes


Lean
non-diabetic
subjects
Insulin
secretion
Insulin sensitivity
Obese
non-diabetic
subjects
Insulin
secretion
Insulin sensitivity
(Obese)
Type 2 diabetic
patients
Insulin
secretion
Insulin sensitivity


INDEX OF INSULIN SENSITIVITY
(Glucose MCR ml.kg-1.min-1)
Cross-sectional studies
10-20 subjects per group
Euglycaemic hyperinsulinaemic clamp → insulin sensitivity
Glucagon test → insulin secretion
12
10
8
6
4
2
Normal glucose tolerance
Lean controls
Non-insulin-requiring Type 2 diabetes
Obese subjects
Non-obese subjects
Non-obese subjects
Obese subjects
Obese subjects
Insulin-requiring Type 2 diabetes
1000
1500
2000
2500
3000
INDEX OF INSULIN SECRETION (Basal + stimulated C-peptide pmol.l-1)
Scheen & Lefèbvre 2001

Effect of gastroplasty



Letiexhe MR, Desaive C, Lefebvre PJ, Scheen AJ

Int J. Obesity 28:2004

2008 Concept

Type 2 diabetes mellitus, in its common form, occurs in genetically predisposed individuals when insulin secretion fails to compensate for a reduction in insulin sensitivity

The Future of Clinical Research on T2 DM

Fully exploit the results of Genome-wide Association Studies

- For gaining deeper insight into the aetiopathology of the disease

- For developing new drugs affecting :
  - Beta-cell development, function and regeneration
  - Insulin sensitivity

The *TCF7L2* Story (1)

- The *TCF7L2* gene is located on chromosome 10q
- Variants of this gene have been found to be strongly associated with T2DM, initially in Icelandic individuals (Grant et al, 2006)
- The association was confirmed in numerous populations
- The minor allele frequency in control subjects is ~0.28; when present in 2 copies, the variant is associated with a ~2-fold increase of T2DM risk

The *TCF7L2* Story (2)

- *TCF7L2* , also known as TCF-4, is a transcription factor and forms part of the WNT signalling pathway acting as nuclear receptor for CTNNB1 (beta-catenin)
- The WNT signalling is critical for cell proliferation; it is important for the development of the pancreas and islets during the embryoninc growth, it influences the synthesis (and possibly secretion) of GLP-1

The *TCF7L2* Story (3)

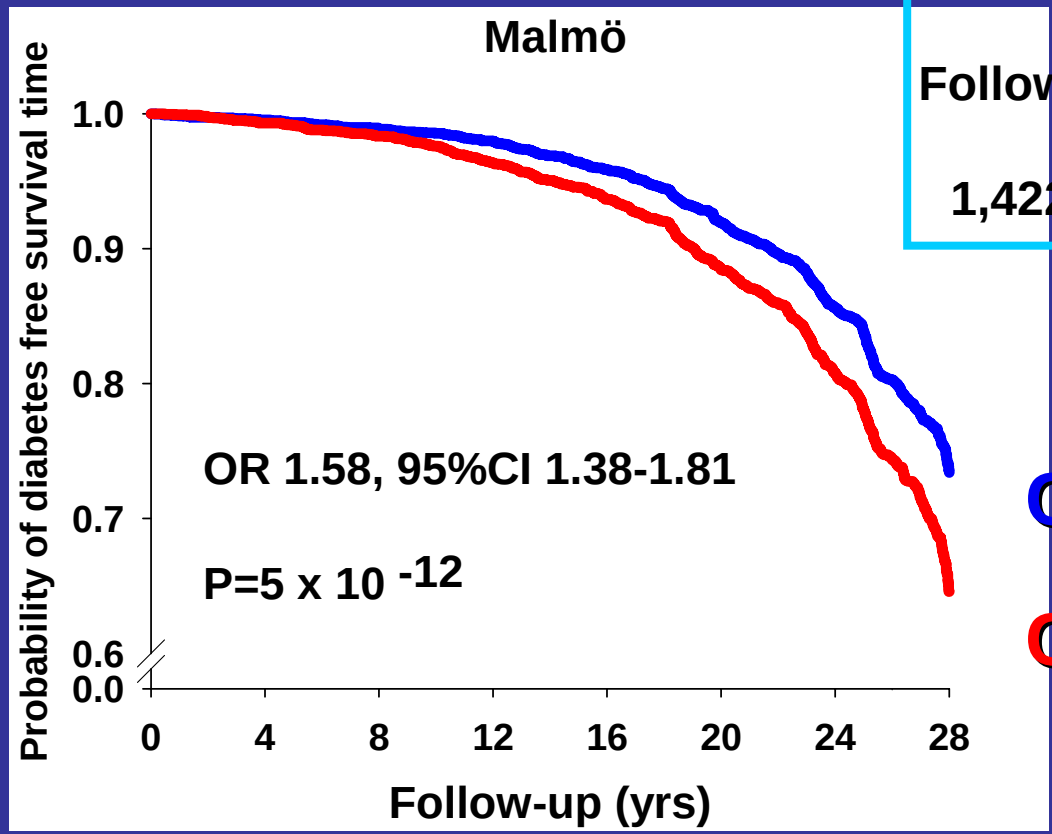
- Mechanisms by which common variants in the *TCF7L2* gene increase risk of type 2 diabetes*

  Lyssenko et al *J. Clin. Invest.* **117:2155-2163 (2007)**

***Collaborative study Malmö, Pisa and Helsinki**

Common variants in *TCF7L2* predict future T2DM

Effect of *TCF7L2* rs7903146 on Cumulative Risk of Developing T2D



7,061 individuals

Follow-up 24 years

1,422 developed T2D

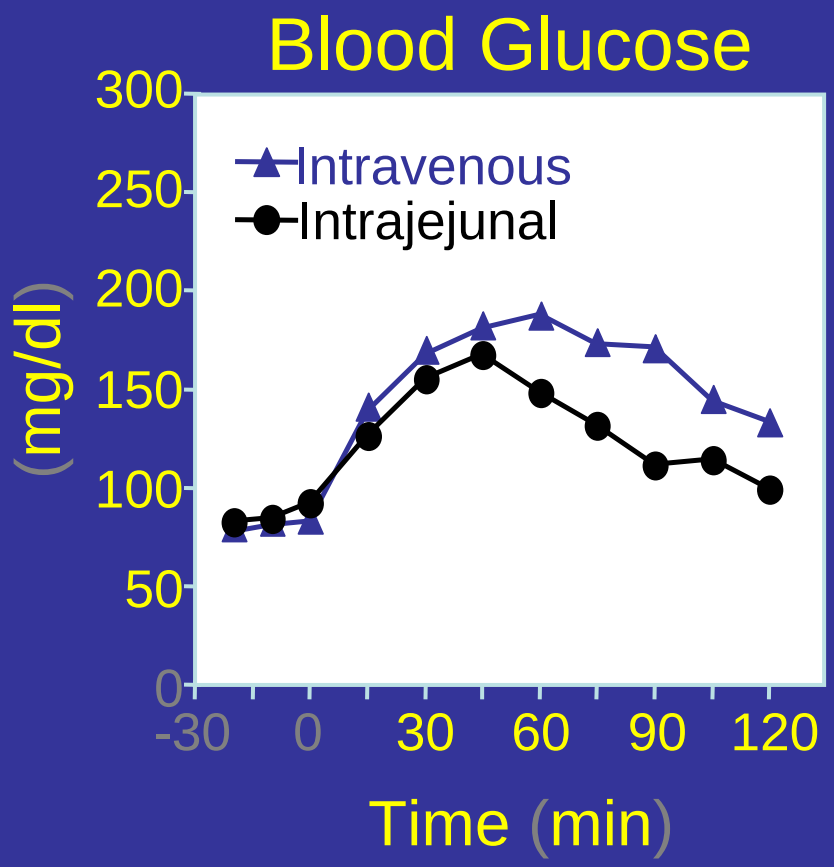
CC, non-risk

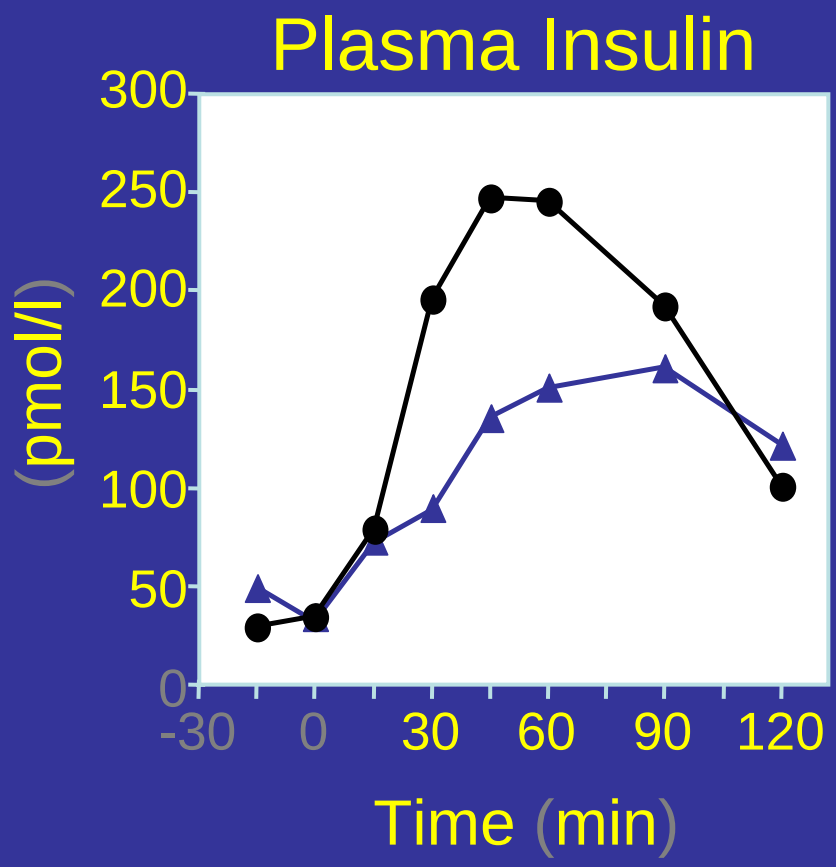
CT/TT, risk

Lyssenko *et al*. *JCI*, 2007

Risk genotypes in *TCF7L2* are associated with an impaired incretin effect

The Incretin Effect: Insulin Secretion is Greater with Oral than IV Glucose

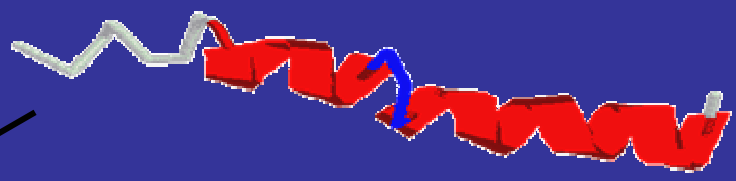




McIntyre N et al: Lancet 41:20-21; 1964

GLP-1 and GIP are Incretins Involved in Glucose Homeostasis

GLP-1: Glucagon-Like Peptide–1[1]



N-terminal region

30/31-amino acid peptide

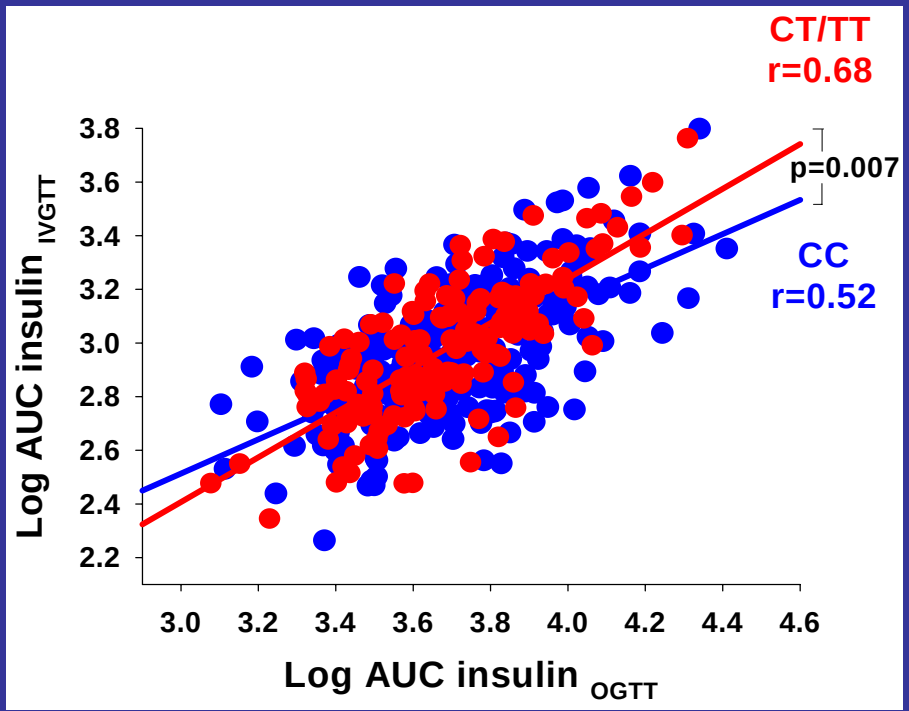
GIP: Glucose-Dependent Insulinotropic Peptide[2]

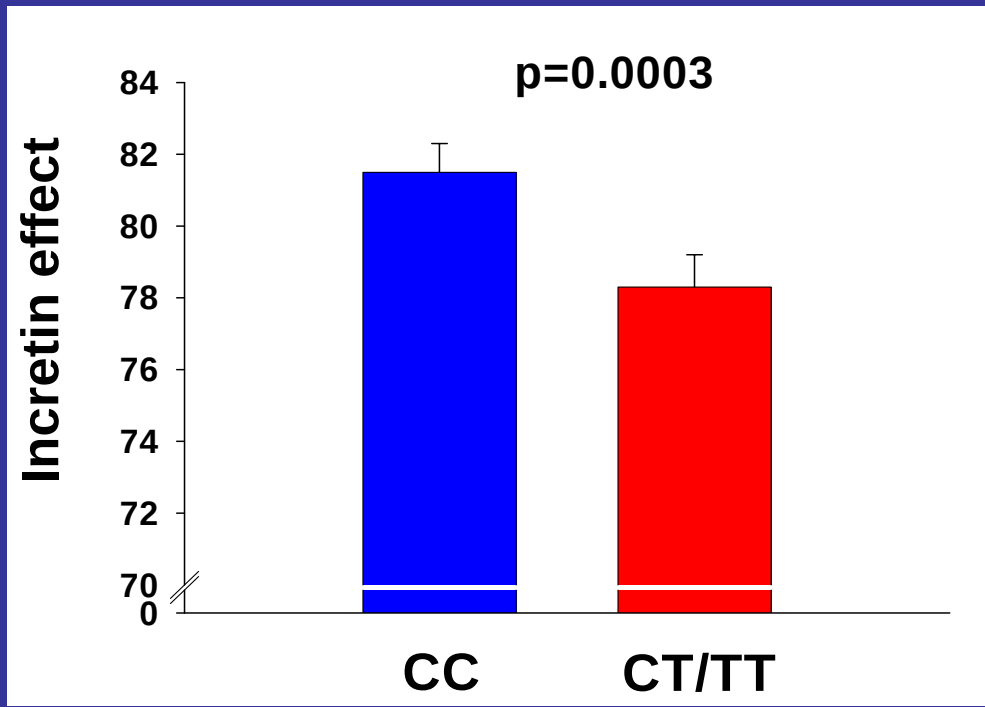
N-terminal region

42-amino acid peptide

[1] Image courtesy of Cyril Sarrauste de Menthière, PhD, Institute of Human Genetics, Montpellier, France (www.igh.cnrs.fr).
[2] Available at http://www.imb-jena.de/cgi-bin/ImgLib.pl?CODE=1t5q.

Risk genotypes in the *TCF7L2* gene are associated with impaired incretin effect





Lyssenko et al. J Clin Invest 117;2155-63,2007

Diabetologia (2007) 50:2443–2450
DOI 10.1007/s00125-007-0753-6

ARTICLE

Impaired glucagon-like peptide-1-induced insulin secretion in carriers of transcription factor 7-like 2 (*TCF7L2*) gene polymorphisms

S. A. Schäfer · O. Tschritter · F. Machicao · C. Thamer · N. Stefan · B. Gallwitz · J. J. Holst · J. M. Dekker · L. M. t'Hart · G. Nijpels · T. W. van Haeften · H. U. Häring · A. Fritsche

Consequences of reduced GLP-1 signalling in individuals with *TCF7L2 polymorphisms**

- Reduction in the « actively secreting »B-cell mass due to reduced B-cell neogenesis/proliferation and increased B-cell apoptosis leading to reduced post-prandial insulin release
- Decreased inhibition of A-cell glucagon release leading to relative post-prandial hyperglucagonemia
- Both defective insulin and excessive glucagon release lead to post-prandial hyperglycemia

*Nauck and Meier Diabetologia 2007, **50** :2413-16

Type 2 DM: Challenges for the future

- For the Epidemiologists: define incidence, prevalence and projections
- For the Health Economists: evaluate the consequences of the epidemy
- For the Basic Scientists: dissect the mechanisms involved (gene KO or overexpression in target organs , see Kahn et al)
- For the Geneticists: identify the « diabetes genes » and their interaction
- For the « Epigeneticists »: better understand the mechanisms that modify the expression of genes (like methylation of DNA or histones)
- For the clinicians: better understand pathophysiology
- For the Industry: think drug development in terms of future « personalised » treatment/prevention (Pharmacogenetics)