Pathophysiology of type 2 diabetes mellitus

R. Leibel
Naomi Berrie Diabetes Center
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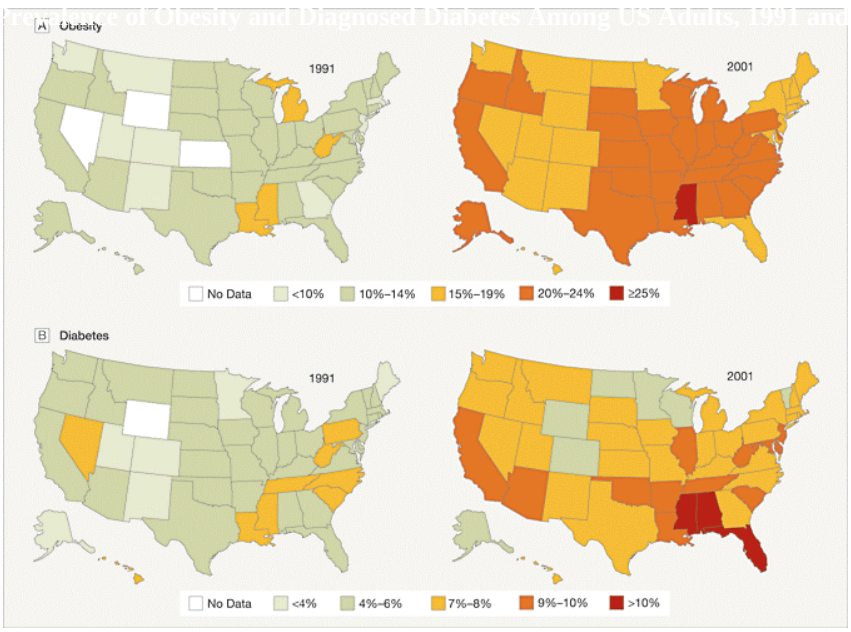
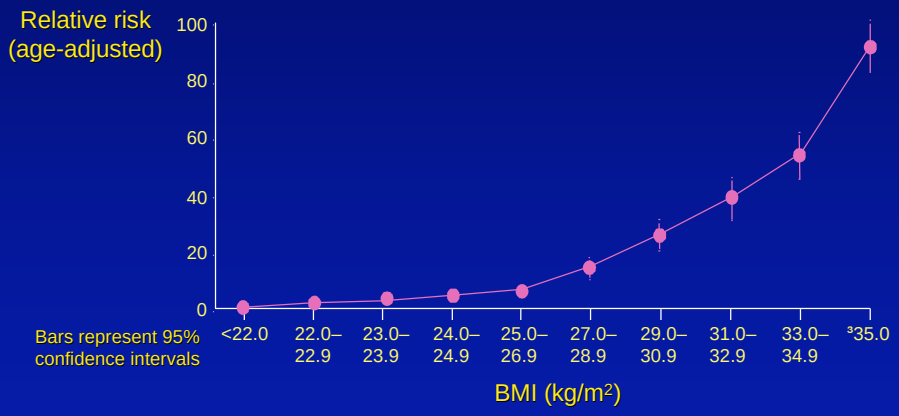
Body Mass Index Chart

25-29.9 = overweight; 30-39.9= obese; >40= extreme obesity

Height	Weight (lbs)																			
	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300
5'0"	23	25	27	29	31	33	35	37	39	41	43	45	47	49	51	53	55	57	59
5'2"	22	24	26	27	29	31	33	35	37	38	40	42	44	46	48	49	51	53	55
5'4"	21	22	24	26	28	29	31	33	34	36	38	40	41	43	45	46	48	50	52
5'6"	19	21	23	24	26	27	29	31	32	34	36	37	39	40	42	44	45	47	49
5'8"	18	20	21	23	24	26	27	29	30	32	34	35	37	38	40	41	43	44	46
5'10"	17	19	20	22	23	24	26	27	29	30	32	33	35	36	37	39	40	42	43
6'0"	16	18	19	20	22	23	24	26	27	29	30	31	33	34	35	37	38	39	41
6'2"	15	17	18	19	21	22	23	24	26	27	28	30	31	32	33	35	36	37	39
6'4"	15	16	17	18	20	21	22	23	24	26	27	28	29	30	32	33	34	35	37

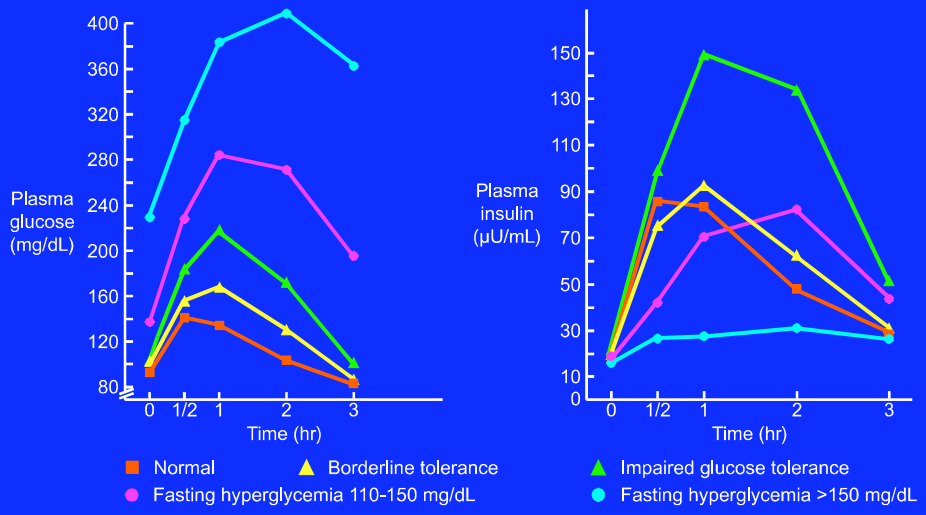


Relative Risk of Type 2 Diabetes in US Women According to BMI



Data derived from Colditz et al. *Ann Intern Med.* 1995;122:481-7.

Plasma Glucose and Insulin Profiles After Oral Glucose Challenge



Reaven GM et al. *Diabetologia.* 1977;13:201-206.

Non-Insulin Dependent Diabetes Mellitus

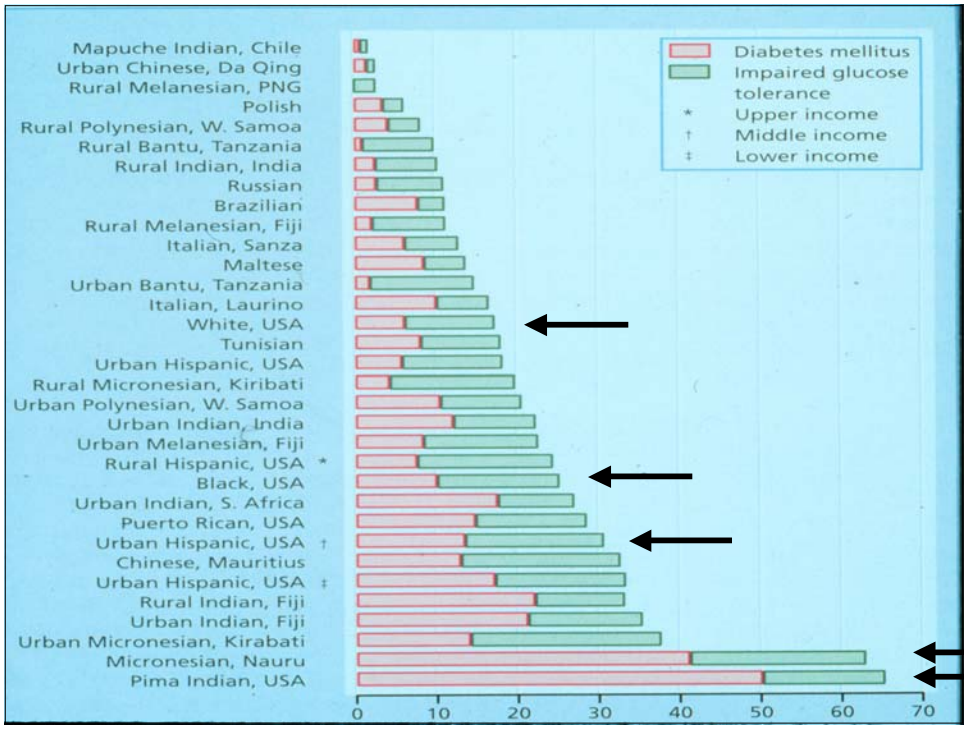
Affects 15% of Americans over the age of 60

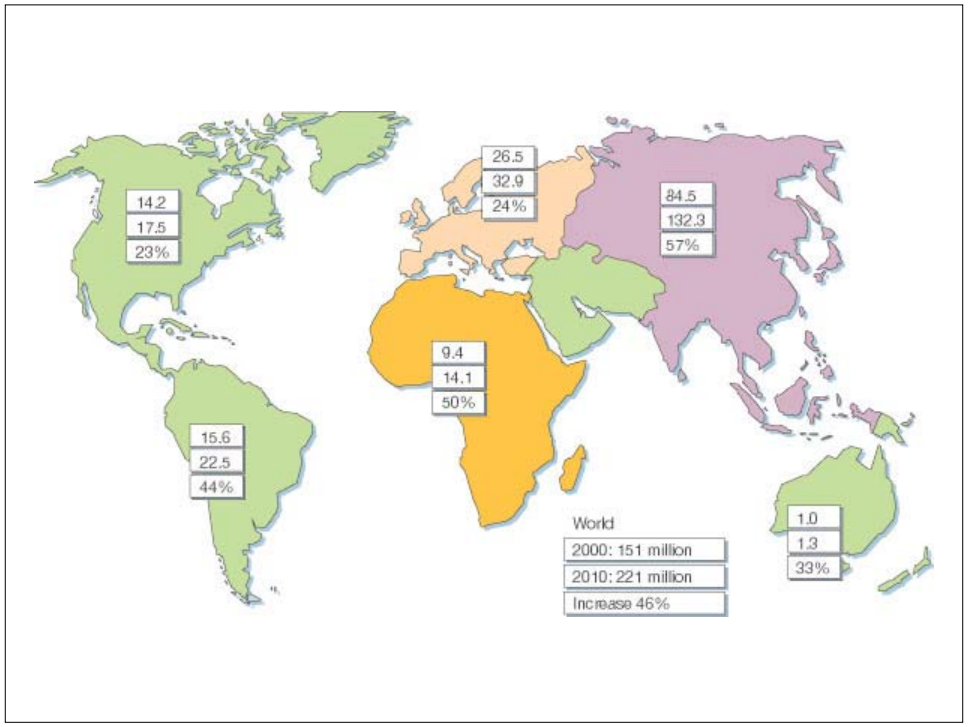
Affects 100 million individuals worldwide

Treatment accounts for 10% of all health care expenditure in US

Complications include:

- Retinopathy
- Nephropathy
- Neuropathy
- Dyslipidemia
- Coronary artery disease


Mapuche Indian, Chile
Urban Chinese, Da Qing
Rural Melanesian, PNG
Polish
Rural Polynesian, W. Samoa
Rural Bantu, Tanzania
Rural Indian, India
Russian
Brazilian
Rural Melanesian, Fiji
Italian, Sanza
Maltese
Urban Bantu, Tanzania
Italian, Laurino
White, USA
Tunisian
Urban Hispanic, USA
Rural Micronesian, Kiribati
Urban Polynesian, W. Samoa
Urban Indian, India
Urban Melanesian, Fiji
Rural Hispanic, USA *
Black, USA
Urban Indian, S. Africa
Puerto Rican, USA
Urban Hispanic, USA †
Chinese, Mauritius
Urban Hispanic, USA ‡
Rural Indian, Fiji
Urban Indian, Fiji
Urban Micronesian, Kirabati
Micronesian, Nauru
Pima Indian, USA
Diabetes mellitus
Impaired glucose tolerance
* Upper income
† Middle income
‡ Lower income
0
10
20
30
40
50
60
70


14.2
17.5
23%
15.6
22.5
44%
26.5
32.9
24%
9.4
14.1
50%
84.5
132.3
57%
1.0
1.3
33%
World
2000: 151 million
2010: 221 million
Increase 46%

Definition of Type II Diabetes Mellitus

- Not absolutely dependent on exogenous insulin
- Absence of autoimmune destruction of beta cells
- Glycemia due to combined insulin resistance and relative beta cell failure
- Very common
  - 85% all diabetes
  - 5-7% of population
  - 15% of population > 60
- Most patients > 60 years old, but frequency increasing in young
- Strong genetic influence:
  - Near 100% concordance identical twins
  - 40% positive family history
- Strong environmental interaction: 50% males, 70% females are obese
- Male 3:2

Causes of Type II Diabetes Mellitus

- MODY (Mature Onset Diabetes of Youth)
- Pregnancy
- Acromegaly
- Cushings Syndrome
- Pheochromocytoma
- Hyperthyroidism
- Slow Evolving Type I = "1.5"
- Mitochondrial DNA mutations
- Insulin Gene Mutations
- Insulin Receptor Mutations

Clinical definition of diabetes

Plasma glucose > **200 mg/dl** at any time
or
Fasting (post-absorptive) plasma glucose > **125 mg/dl**
or
2 hour post-75gm oral glucose load plasma glucose > **200 mg/dl**

Diab. Care; 23:381, 2000

Clinical Definition Impaired Glucose Tolerance

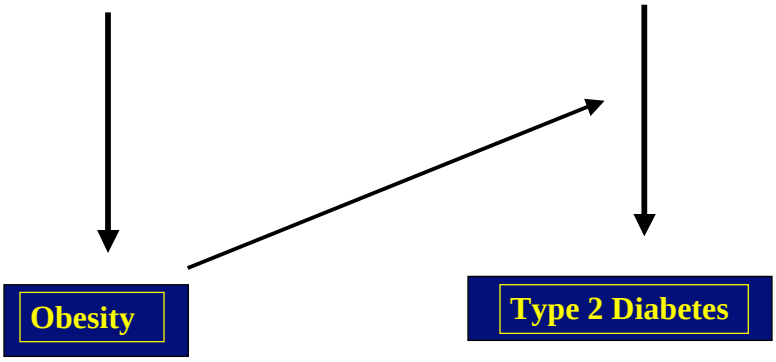
Fasting (post-absorptive) plasma glucose: **100-125 mg/dl**
or
2 hr (OGTT) plasma glucose: **140 - 199 mg/dl**

Diab. Care; 23:381, 2000 & update 4 04

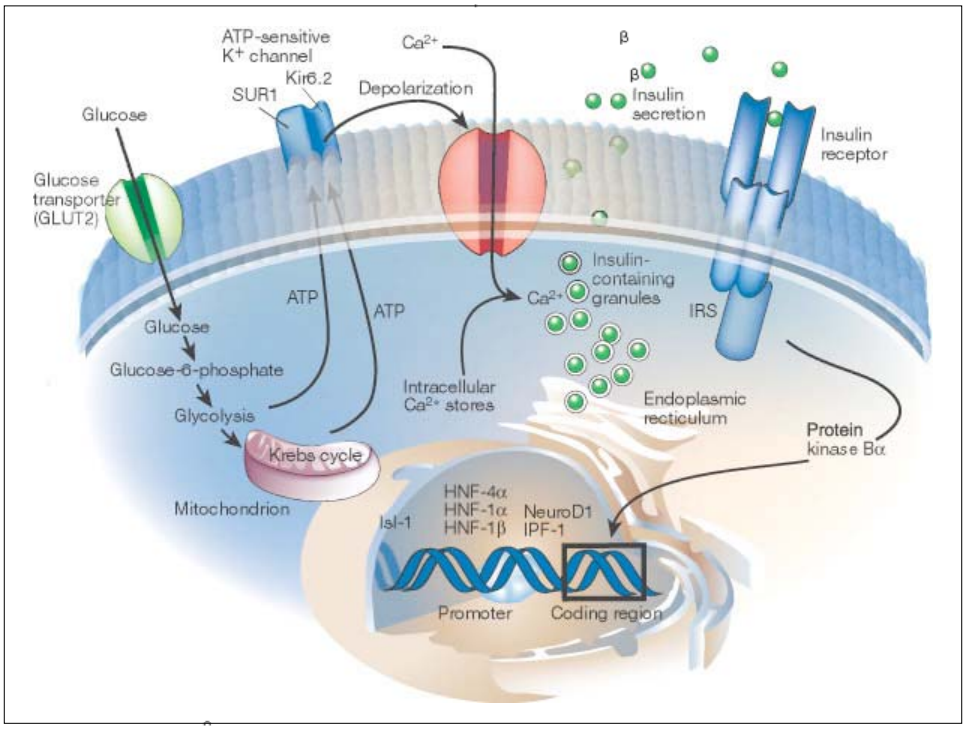
Predisposing Genes

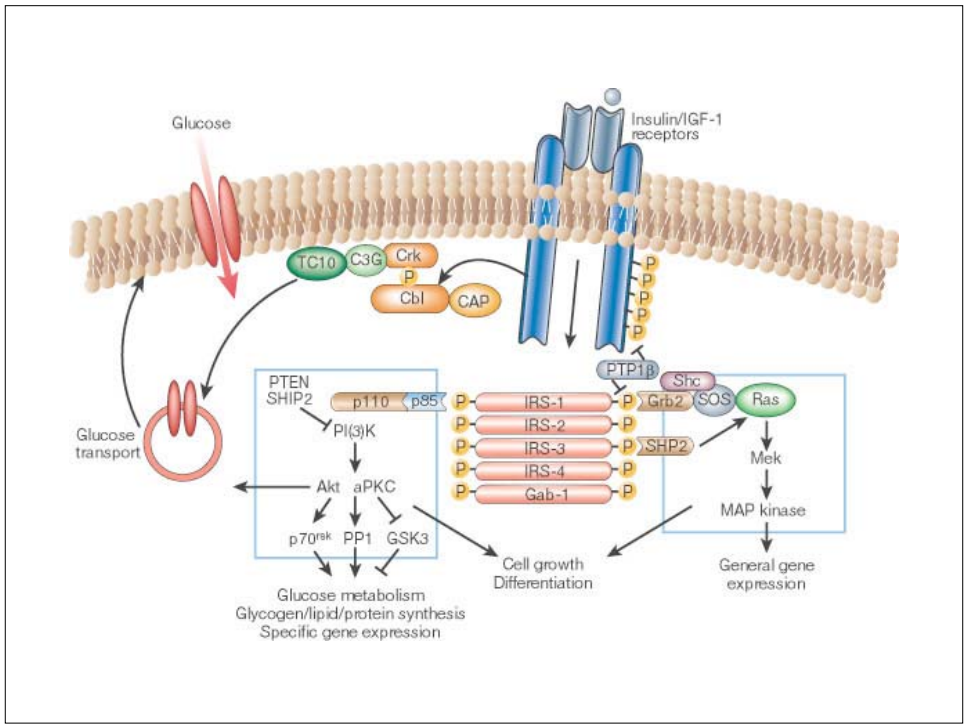
Predisposing Genes

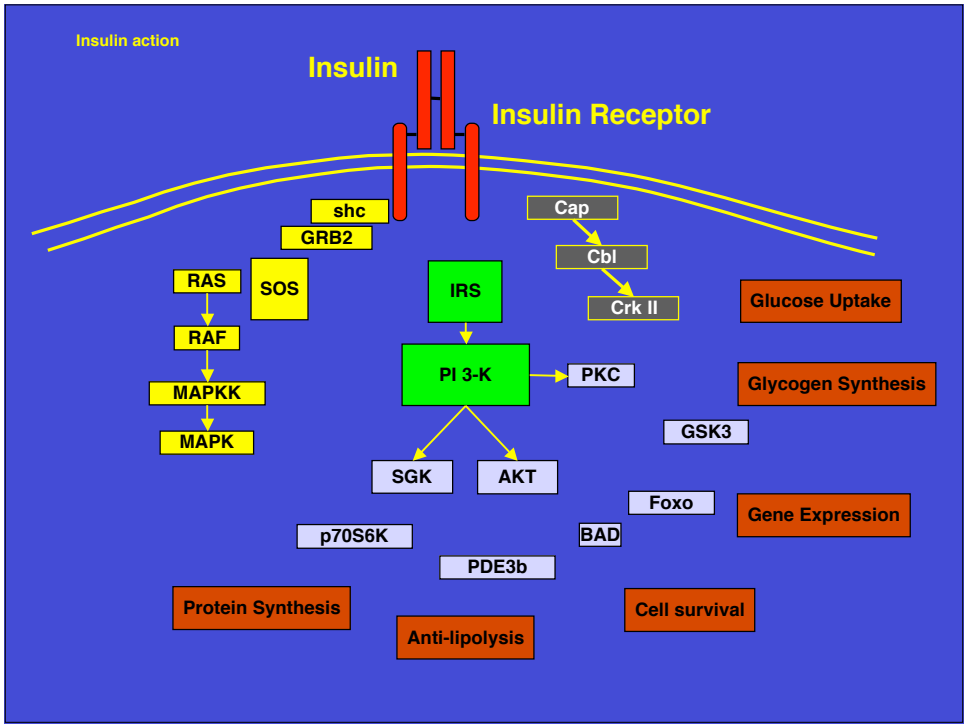
Predisposing Environment

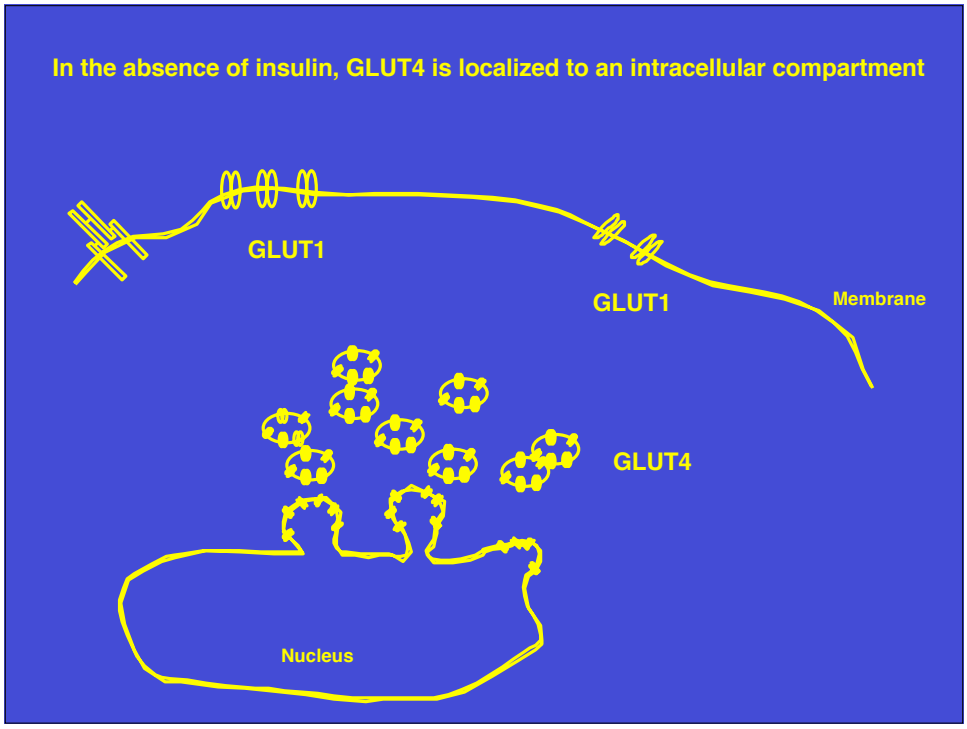


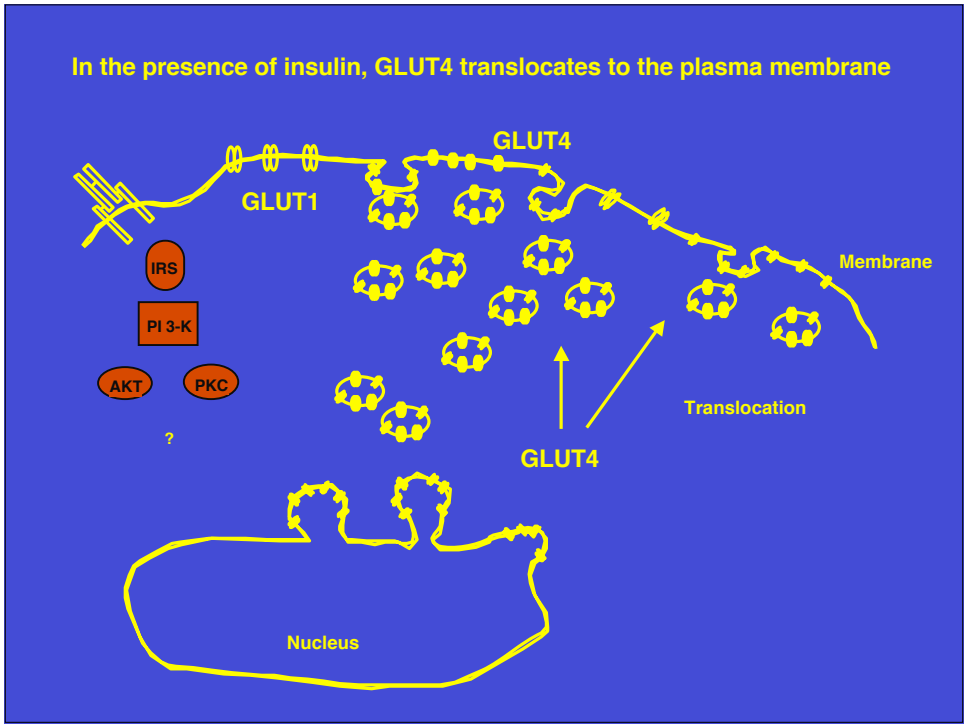
80% diabetic are obese
50 % obese are diabetic

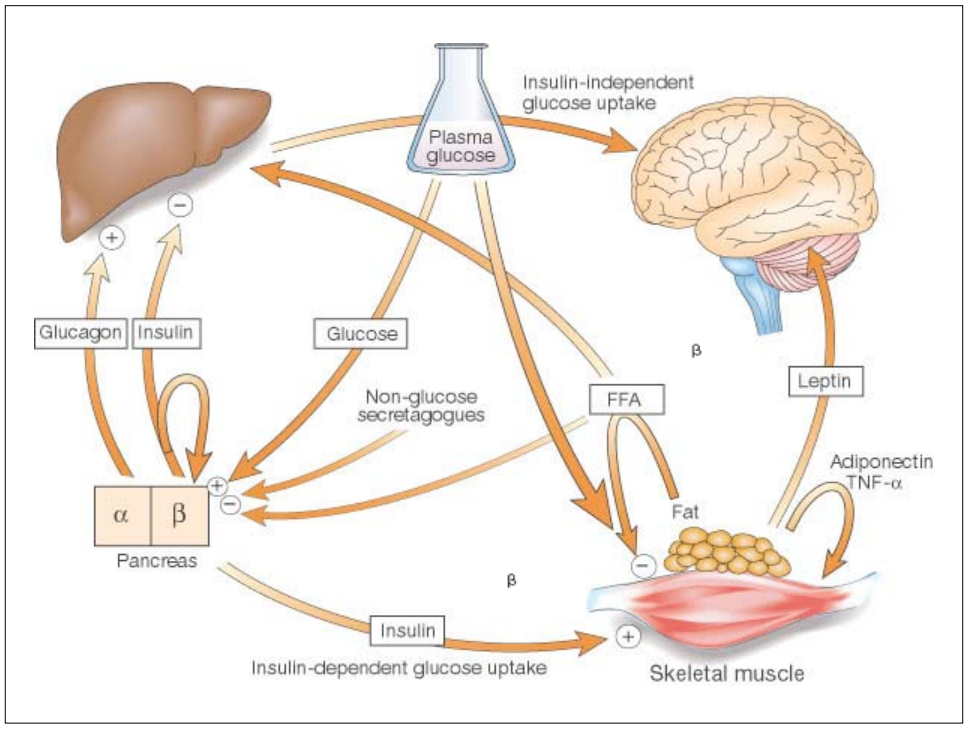


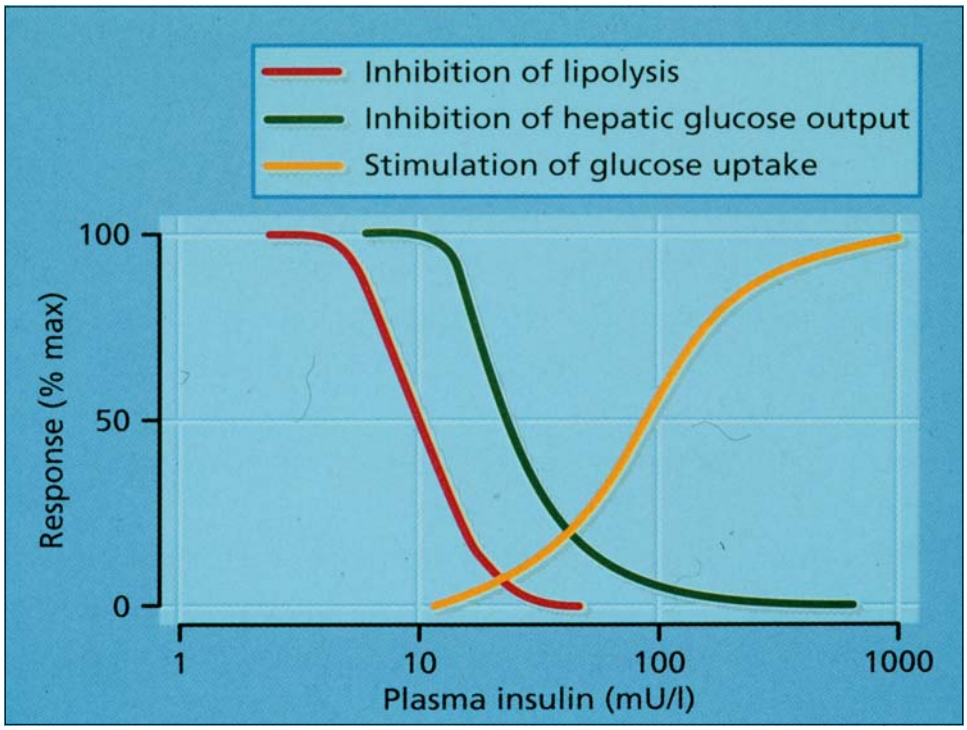

Glucose
Insulin/IGF-1 receptors
TC10
C3G
Crk
P
Cbl
CAP
P
P
P
P
P
PTP1β
Shc
Grb2
SOS
Ras
PTEN
SHIP2
p110
p85
PI(3)K
IRS-1
IRS-2
IRS-3
IRS-4
Gab-1
SHP2
Mek
MAP kinase
Glucose transport
Akt
aPKC
p70rsk
PP1
GSK3
Cell growth
Differentiation
General gene expression
Glucose metabolism
Glycogen/lipid/protein synthesis
Specific gene expression

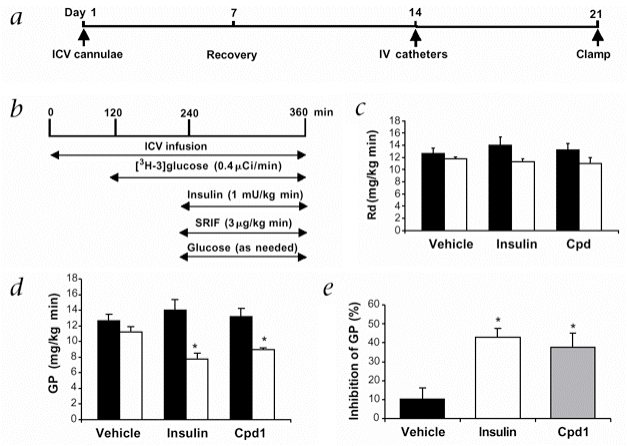

Insulin action
Insulin
Insulin Receptor
shc
GRB2
Cap
Cbl
Crk II
RAS
SOS
IRS
Glucose Uptake
RAF
MAPKK
MAPK
PI 3-K
PKC
Glycogen Synthesis
GSK3
SGK
AKT
Foxo
Gene Expression
BAD
p70S6K
PDE3b
Protein Synthesis
Anti-lipolysis
Cell survival


In the absence of insulin, GLUT4 is localized to an intracellular compartment
GLUT1
GLUT1
Membrane
GLUT4
Nucleus


In the presence of insulin, GLUT4 translocates to the plasma membrane
GLUT4
GLUT1
IRS
PI 3-K
AKT
PKC
?
Membrane
Translocation
GLUT4
Nucleus

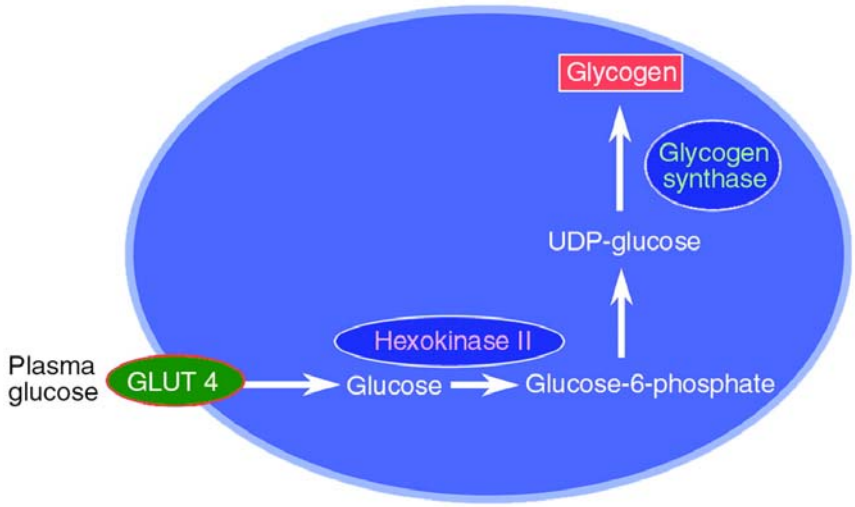

Insulin-independent
glucose uptake
Plasma
glucose
Glucagon
Insulin
Glucose
Non-glucose
secretagogues
FFA
Leptin
Adiponectin
TNF-α
α
β
Pancreas
Fat
Insulin
Insulin-dependent glucose uptake
Skeletal muscle


Inhibition of lipolysis
Inhibition of hepatic glucose output
Stimulation of glucose uptake
Response (% max)
100
50
0
1
10
100
1000
Plasma insulin (mU/l)

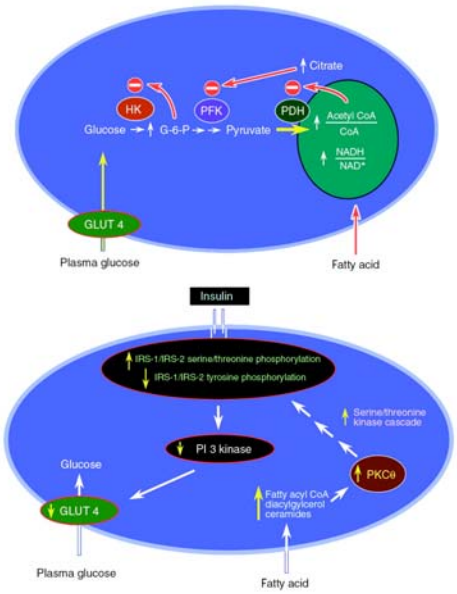


Obici et al. Nature Medicine. 8:1396, 2002

Potential rate-controlling steps in insulin-mediated muscle glycogen synthesis



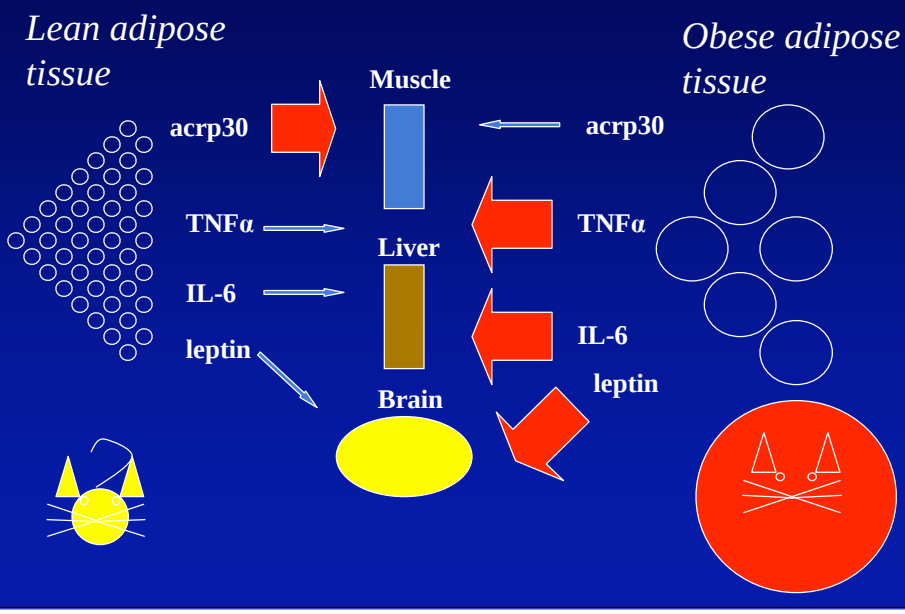
Mechanisms FFA-induced insulin resistance in skeletal muscle



Randle

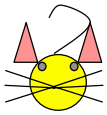
Shulman

Adipose tissue is an endocrine organ.

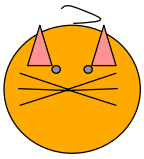


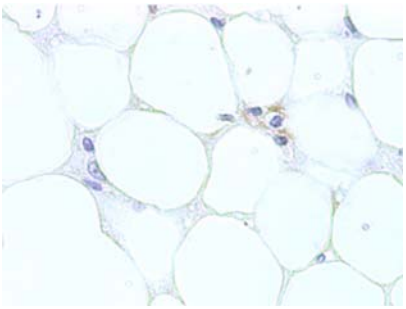
In obese mice, adipose tissue macrophages have an unusual morphology: lipid vacuoles, multinucleated.

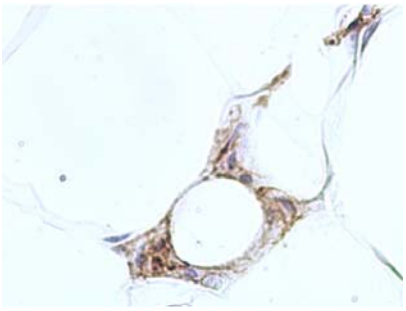
Lean 16-week BL6 female, omental fat



ob/ob 16-week BL6 female, omental fat

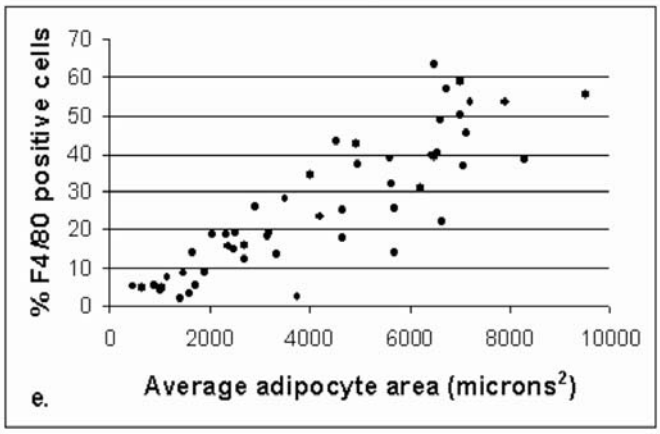






Weisberg et al., JCI, Dec 2003

Adipose tissue macrophages



Perigonadal:
r^2 = 0.7, P < 10–4

Perirenal:
r^2 = 0.7, P < 10–4

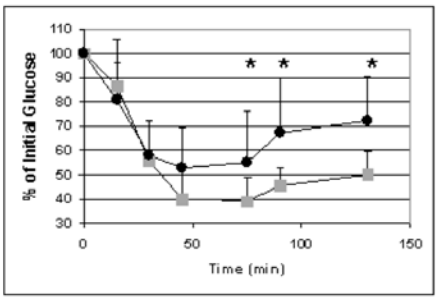
Mesenteric:
r^2 = 0.9, P < 10–4

Subcutaneous:
r^2 = 0.39, P < 0.01

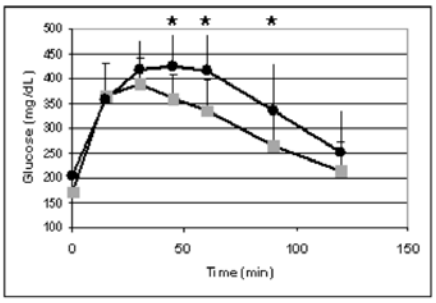
Weisberg et al., JCI, Dec 2003

Improved insulin sensitivity in *Ccr2*$^{-/-}$ mice

Insulin tolerance test

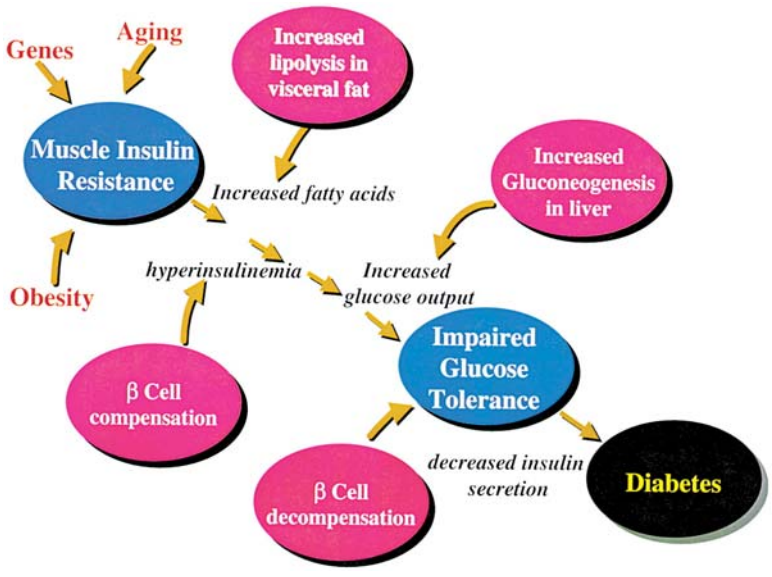


Glucose tolerance test



● = ***Ccr2*** $^{+/+}$ **with dietary obesity; 44% body fat**

■ = ***Ccr2*** $^{-/-}$ **with dietary obesity; 45% body fat**



Risk Factors for Type II Diabetes (II)

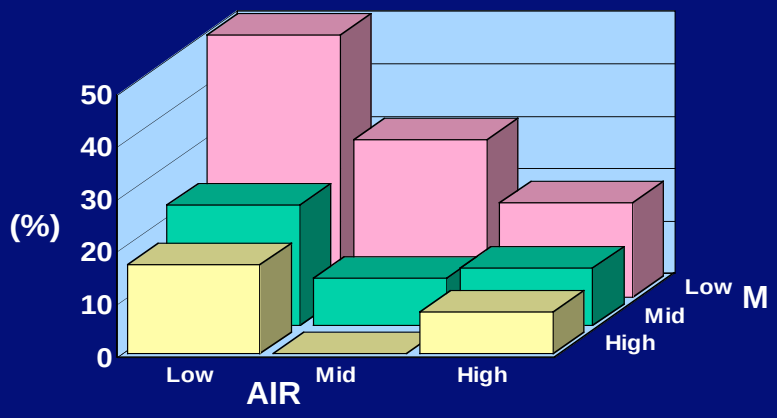
"Barker Hypothesis"

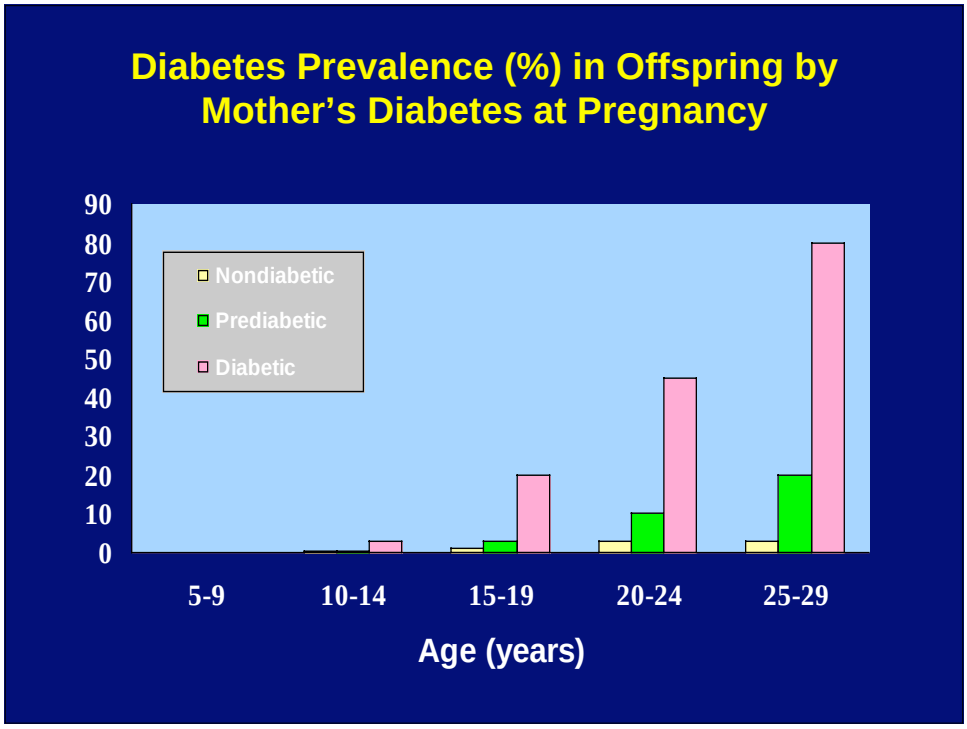
Low birth weight and slow 1st year growth lead to:

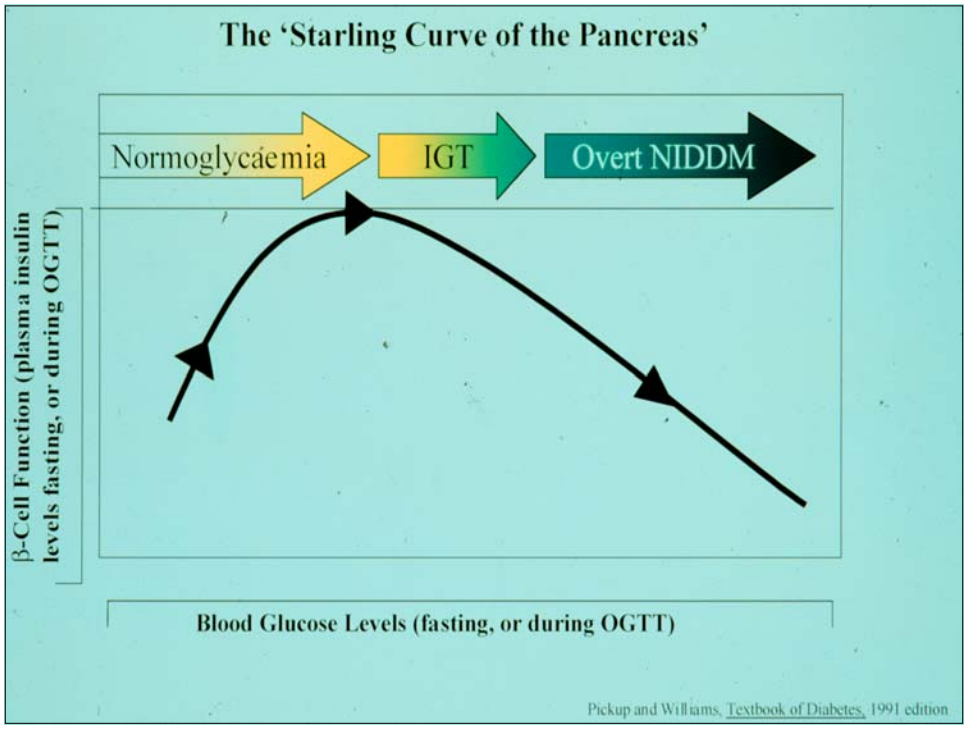
- Compromised beta cell development and increased insulin resistance
- "Thrifty phenotype"
- Insulin resistance
- Low protein intake, especially cysteine, results in decreased islet vascularity in the rat

Prospective Analysis

8 Year Cumulative Incidence (%) of Type 2 Diabetes in Pima Indians
317 NGT/62 Diabetics

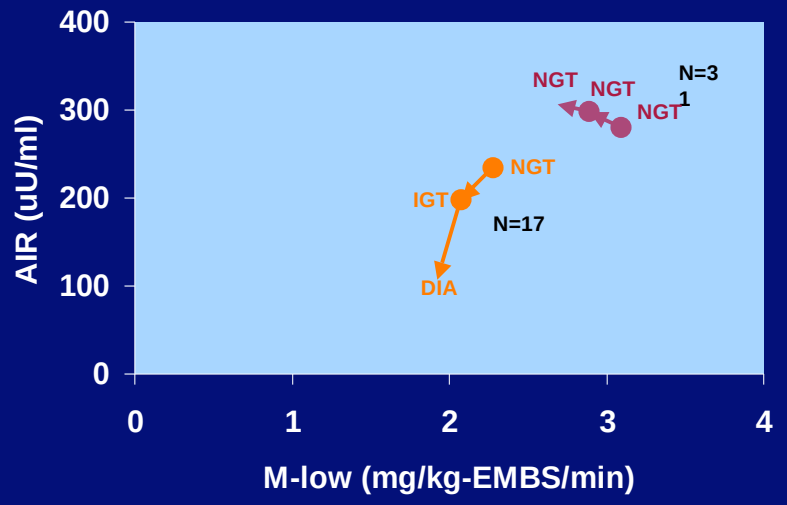



Diabetes Prevalence (%) in Offspring by Mother's Diabetes at Pregnancy
90
80
70
60
50
40
30
20
10
0
Nondiabetic
Prediabetic
Diabetic
5-9
10-14
15-19
20-24
25-29
Age (years)


The 'Starling Curve of the Pancreas'
Normoglycaemia
IGT
Overt NIDDM
β-Cell Function (plasma insulin levels fasting, or during OGTT)
Blood Glucose Levels (fasting, or during OGTT)
Pickup and Williams, Textbook of Diabetes, 1991 edition

Longitudinal Study of the Transition from NGT to Type 2 Diabetes

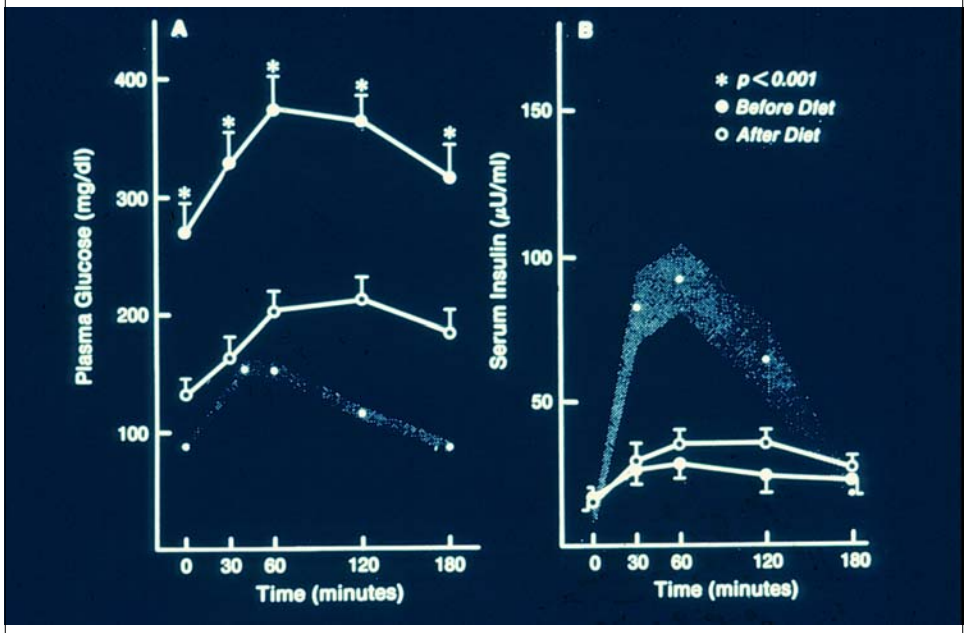
Early Insulin Response vs Insulin Action



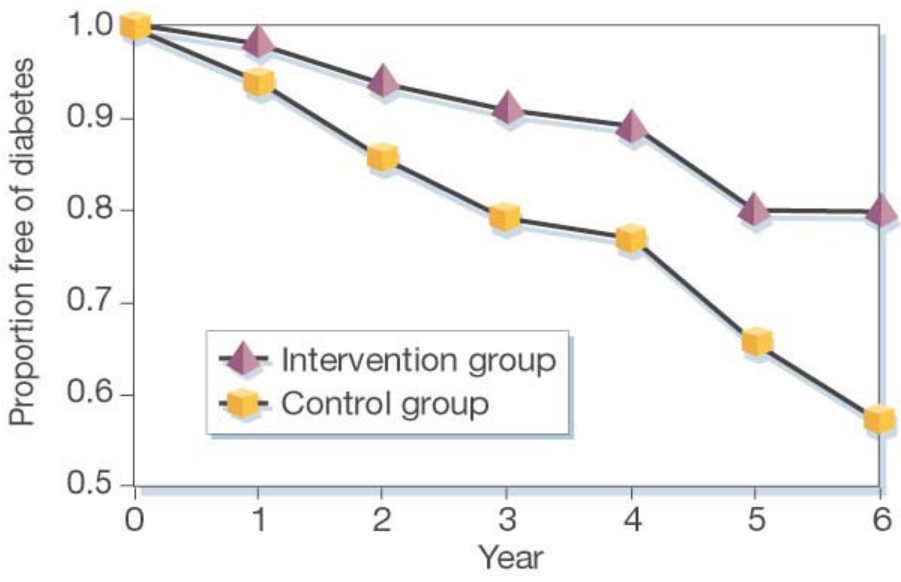
Adapted from Weyer et al, 1999

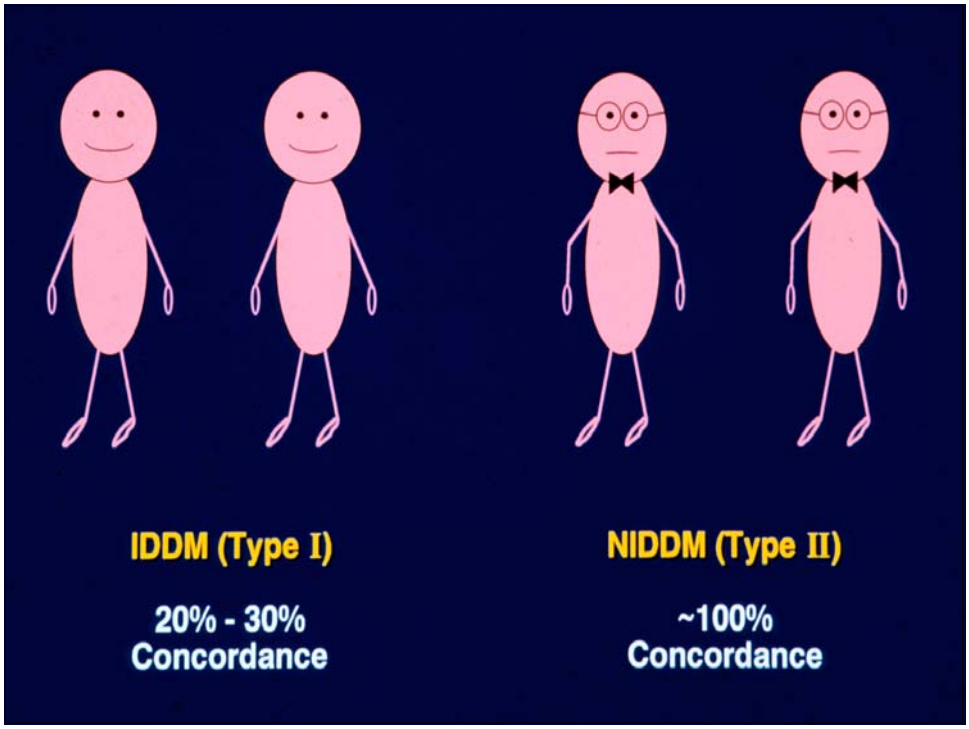
OBESITY-DIABETES

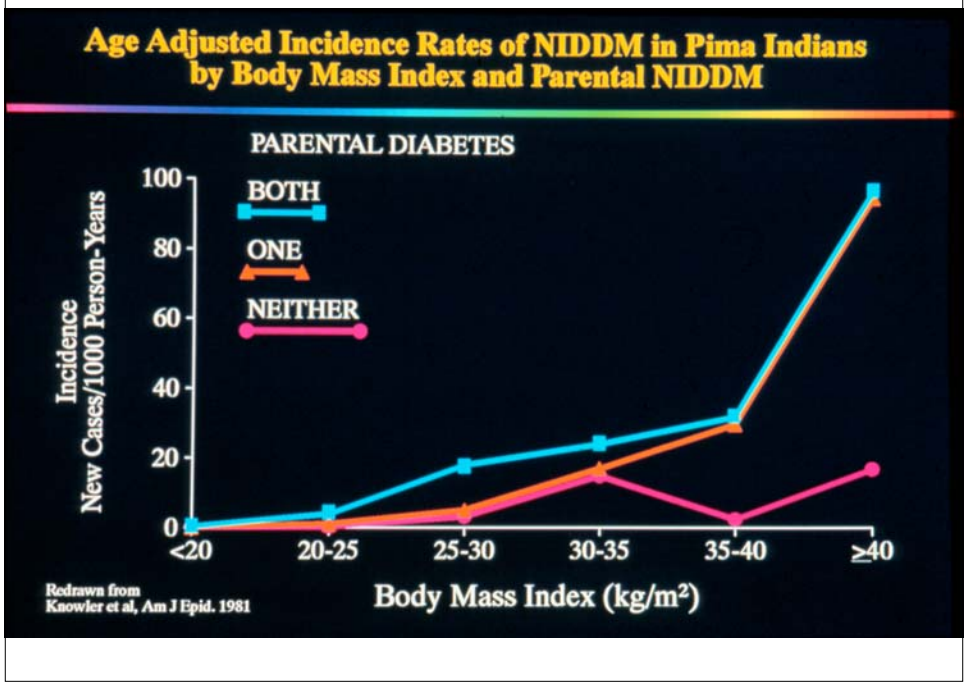
- CATASTROPHES: SIEGE OF PARIS; WWI; WWII.
- MIGRATIONS: JAPAN ------> HAWAII
  INDIA ---- --> UNITED KINGDOM
  TAKELAU ---> NEW ZEALAND
  PIMANS
- AMELIORATING EFFECTS OF WEIGHT LOSS

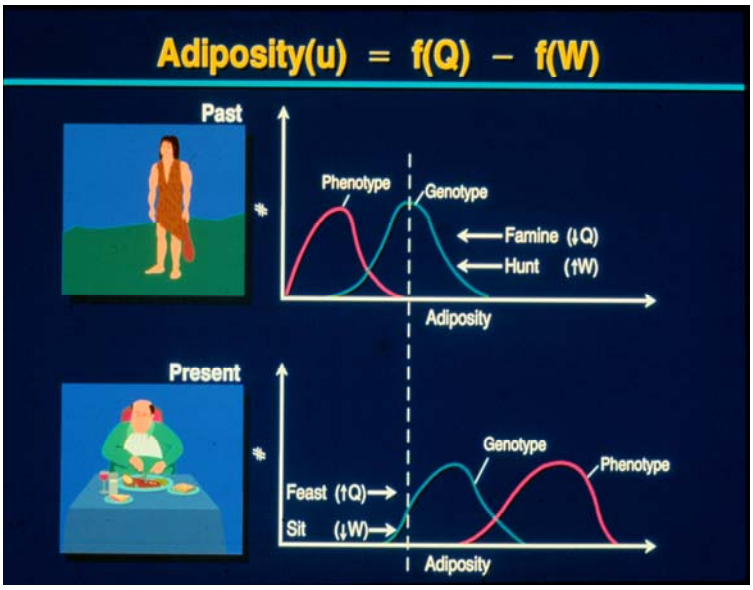

A
B
Plasma Glucose (mg/dl)
Serum Insulin (μU/ml)
400
300
200
100
150
100
50
* p < 0.001
Before Diet
After Diet
0 30 60 120 180
Time (minutes)
0 30 60 120 180
Time (minutes)

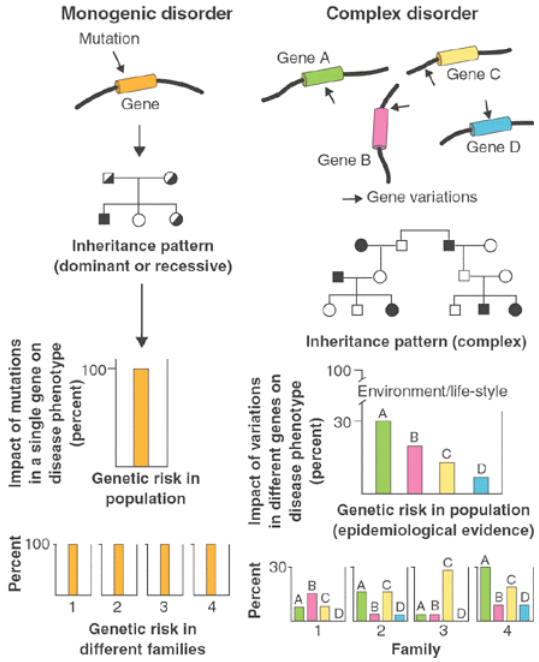
DPPT


Proportion free of diabetes
1.0
0.9
0.8
0.7
0.6
0.5
Intervention group
Control group
0 1 2 3 4 5 6
Year

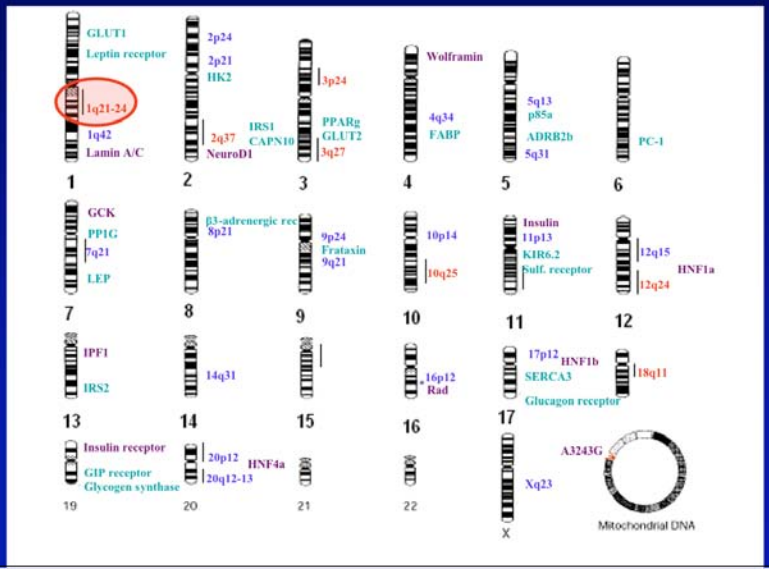

IDDM (Type I)
20% - 30%
Concordance
NIDDM (Type II)
~100%
Concordance

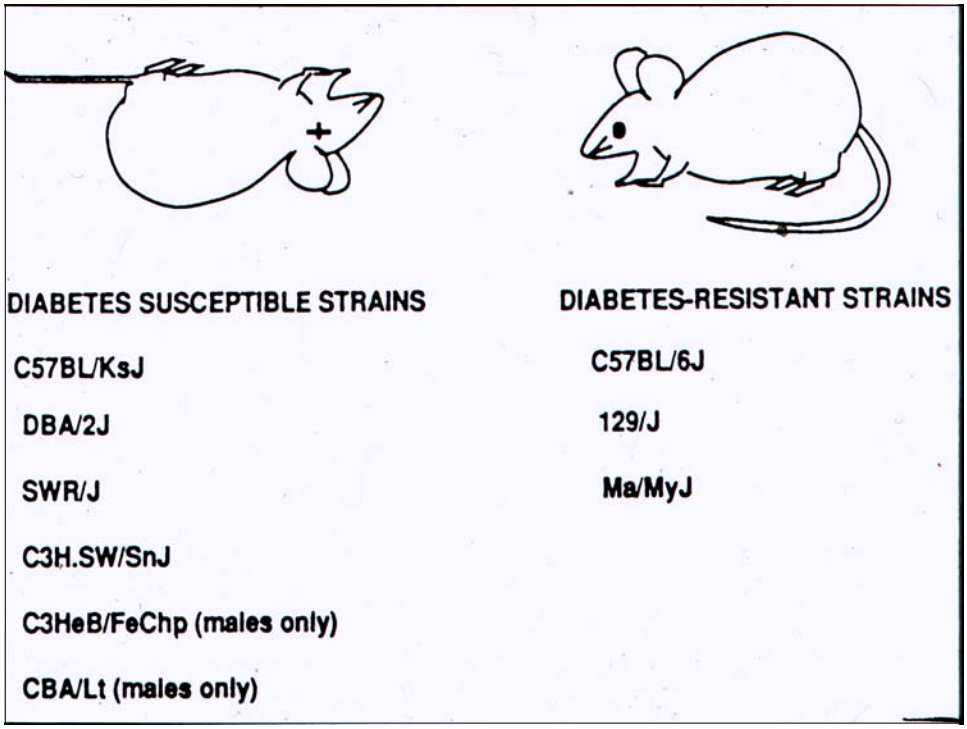

Age Adjusted Incidence Rates of NIDDM in Pima Indians
by Body Mass Index and Parental NIDDM
PARENTAL DIABETES
BOTH
ONE
NEITHER
Incidence
New Cases/1000 Person-Years
100
80
60
40
20
0
<20
20-25
25-30
30-35
35-40
≥40
Body Mass Index (kg/m²)
Redrawn from
Knowler et al, Am J Epid. 1981


Adiposity(u) = f(Q) – f(W)
Past
Phenotype
Genotype
Famine (↓Q)
Hunt (↑W)
Adiposity
Present
Genotype
Phenotype
Feast (↑Q)
Sit (↓W)
Adiposity

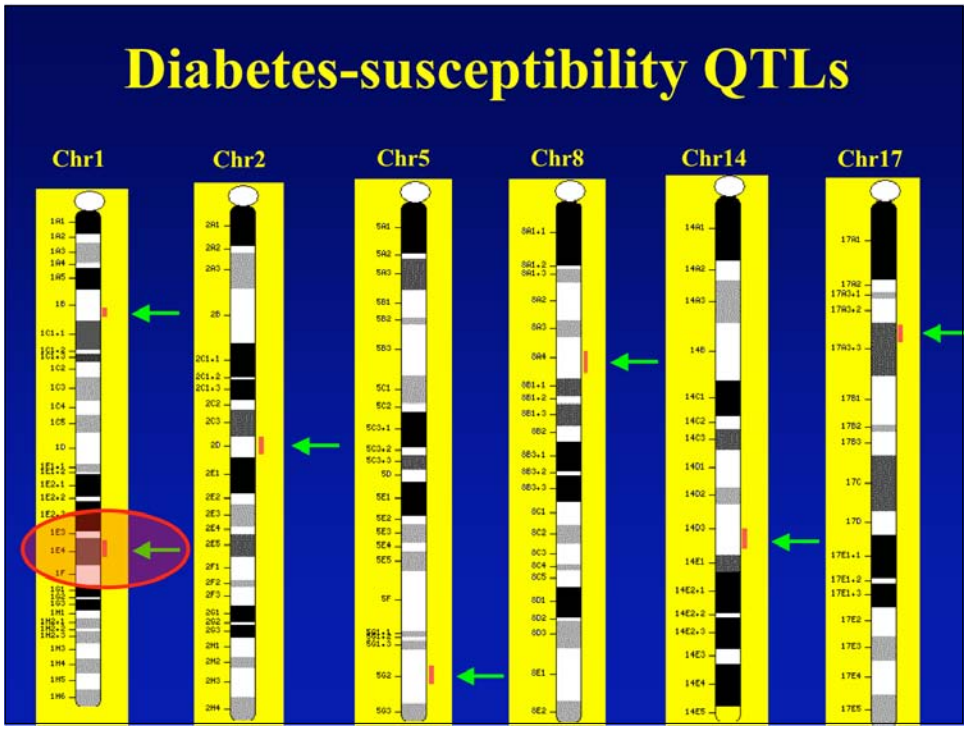

Monogenic disorder
Mutation
Gene
Inheritance pattern
(dominant or recessive)
Impact of mutations in a single gene on disease phenotype (percent)
100
Genetic risk in population
Percent
100
1 2 3 4
Genetic risk in different families
Complex disorder
Gene A
Gene C
Gene B
Gene D
Gene variations
Inheritance pattern (complex)
Impact of variations in different genes on disease phenotype (percent)
100
Environment/life-style
30
A B C D
Genetic risk in population (epidemiological evidence)
Percent
30
A B C D
1 2 3 4
Family

Genome-wide linkage studies for T2DM in humans

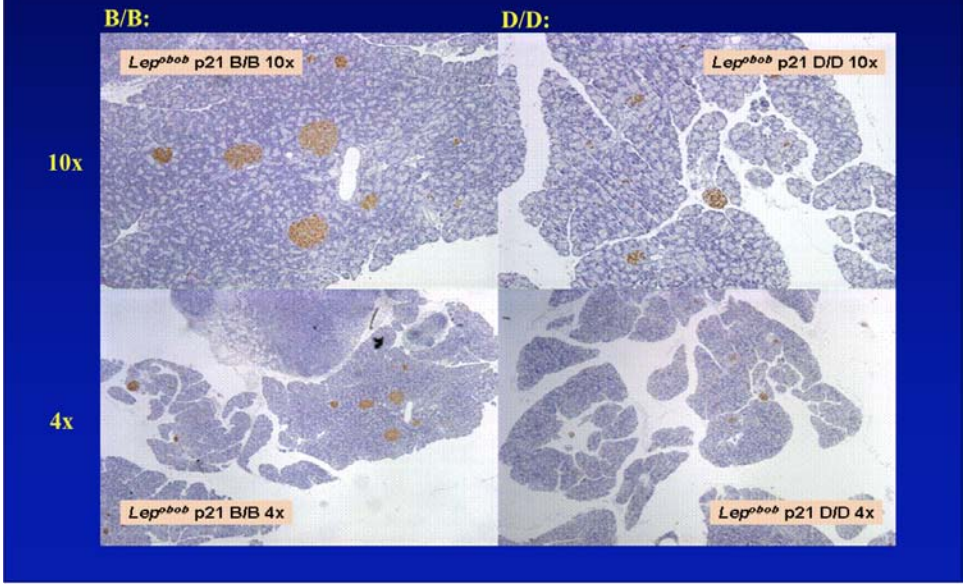




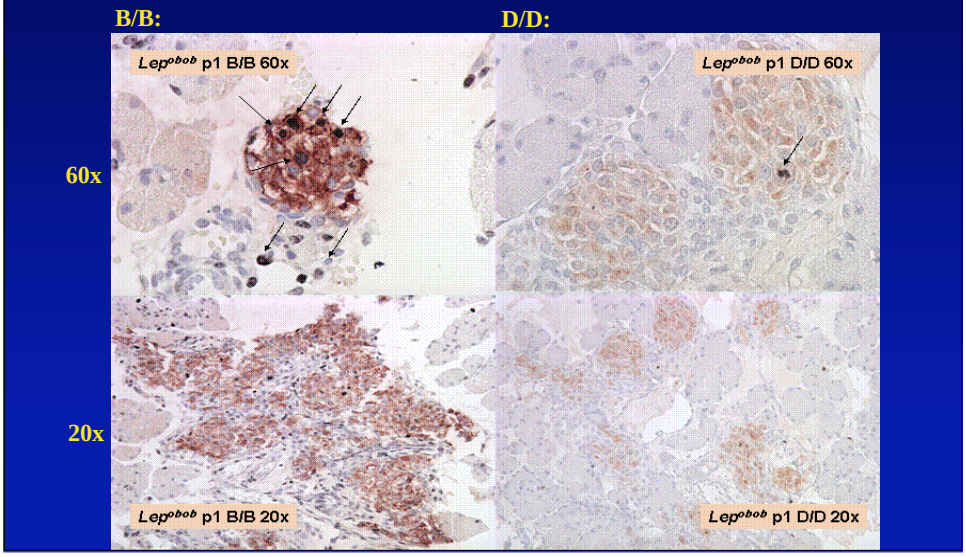
DIABETES SUSCEPTIBLE STRAINS	DIABETES-RESISTANT STRAINS
C57BL/KsJ	C57BL/6J
DBA/2J	129/J
SWR/J	Ma/MyJ
C3H.SW/SnJ	
C3HeB/FeChp (males only)	
CBA/Lt (males only)	

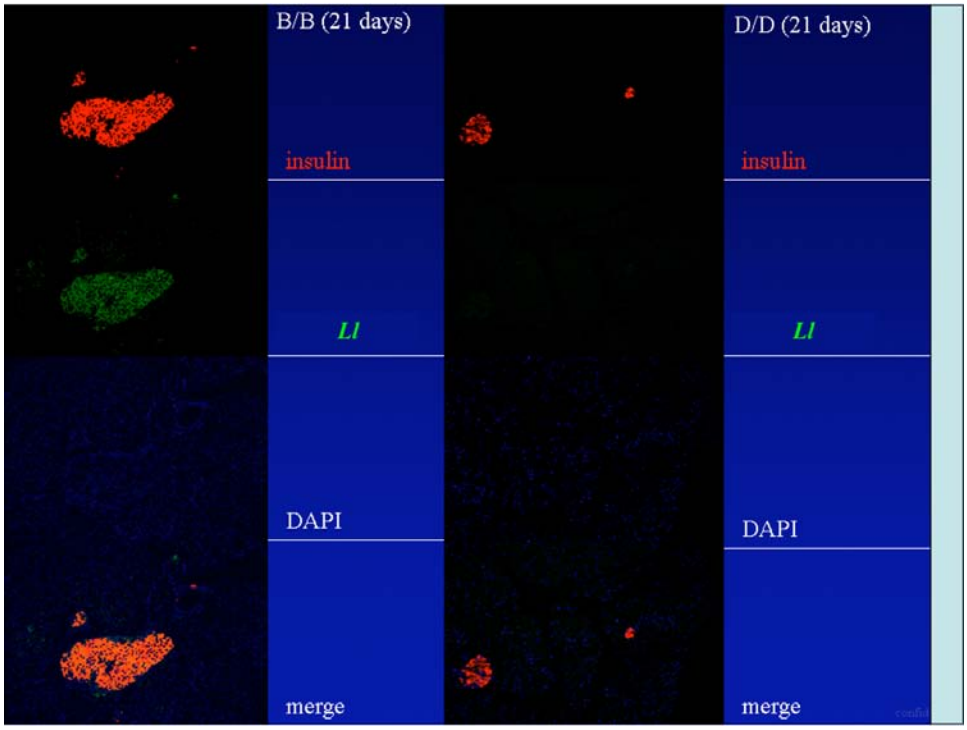


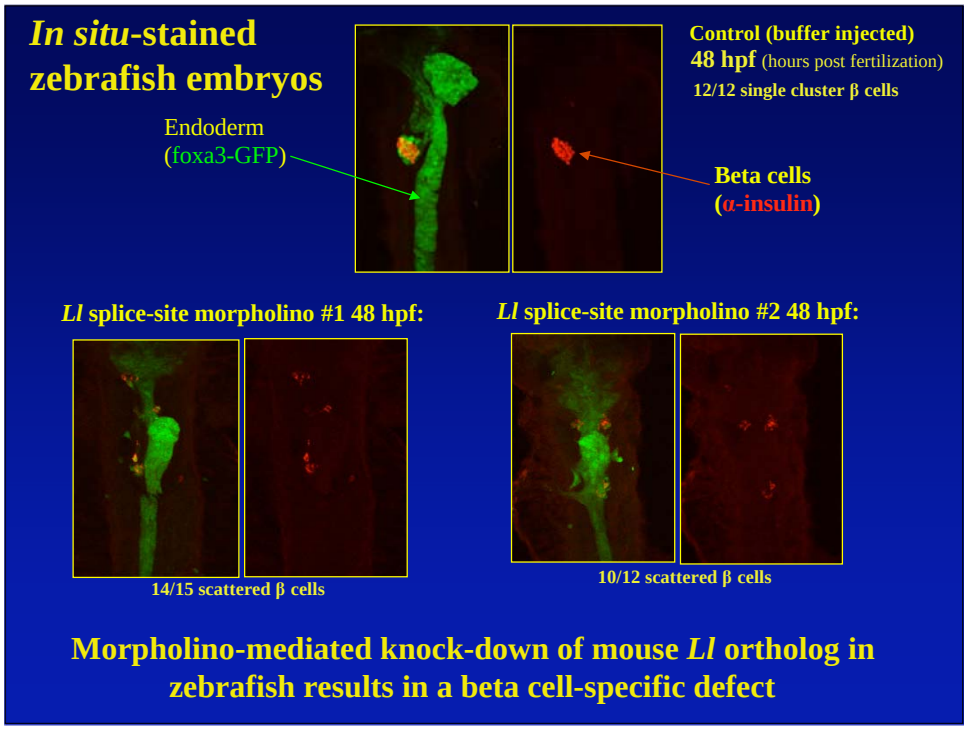
Islets in D/D animals are hypoplastic compared to islets in B/B animals

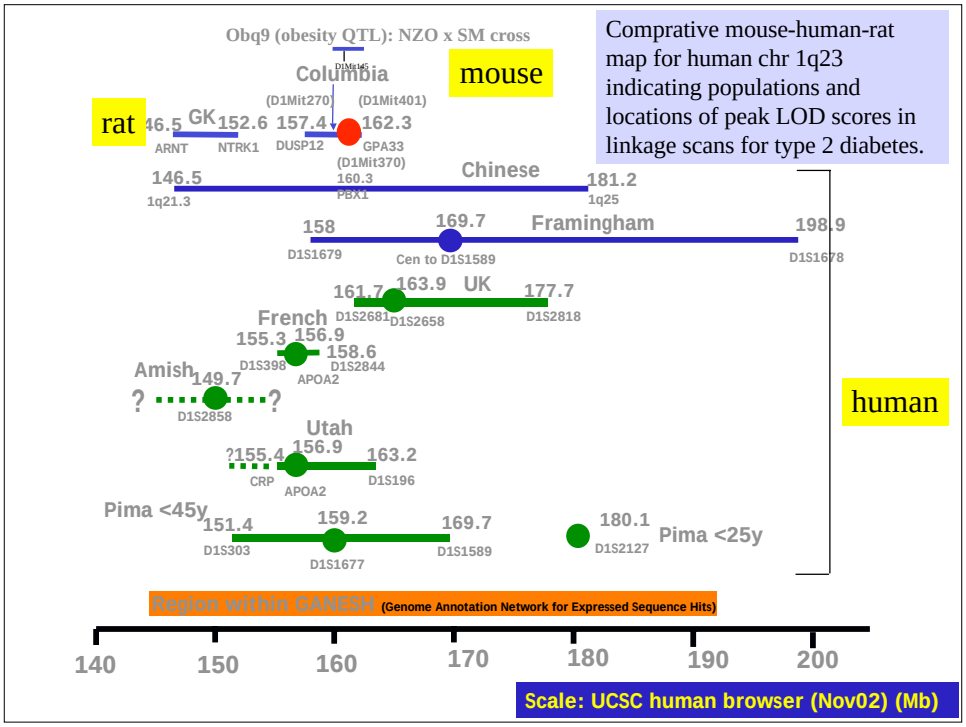


Do beta cells in D/D animals replicate as well as beta cells in B/B animals?




B/B (21 days)
insulin
Ll
DAPI
merge
D/D (21 days)
insulin
Ll
DAPI
merge


In situ-stained zebrafish embryos
Endoderm (foxa3-GFP)
Control (buffer injected)
48 hpf (hours post fertilization)
12/12 single cluster β cells
Beta cells (α-insulin)
Ll splice-site morpholino #1 48 hpf:
14/15 scattered β cells
Ll splice-site morpholino #2 48 hpf:
10/12 scattered β cells
Morpholino-mediated knock-down of mouse Ll ortholog in zebrafish results in a beta cell-specific defect



Comprative mouse-human-rat map for human chr 1q23 indicating populations and locations of peak LOD scores in linkage scans for type 2 diabetes.

END