

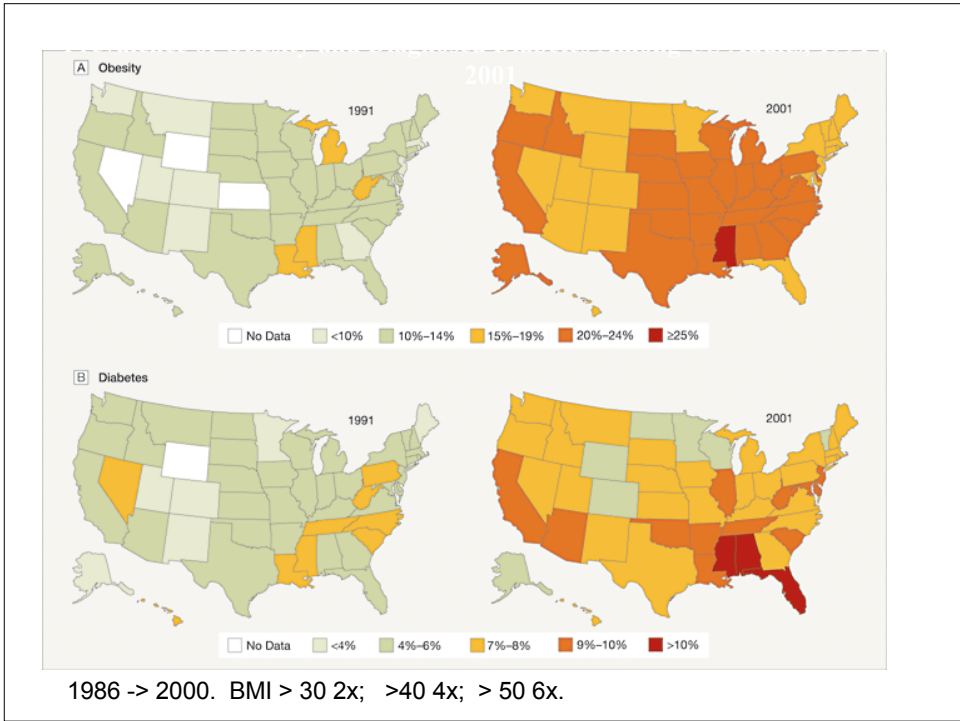
Pathophysiology of type 2 diabetes mellitus

R. Leibel
 Naomi Berrie Diabetes Center
 25 February 2008

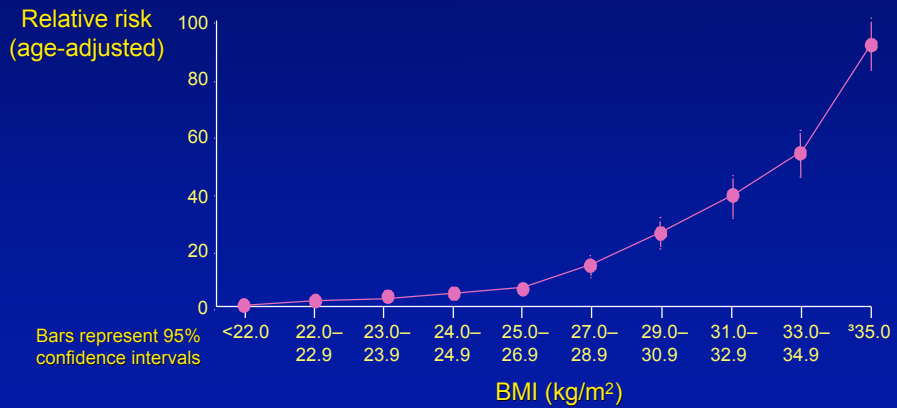
Body Mass Index Chart

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

| | | Weight (lbs) | | | | | | | | | | | | | | | | | | |
|--------|-------|--------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | 120 | 130 | 140 | 150 | 160 | 170 | 180 | 190 | 200 | 210 | 220 | 230 | 240 | 250 | 260 | 270 | 280 | 290 | 300 |
| Height | 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 |

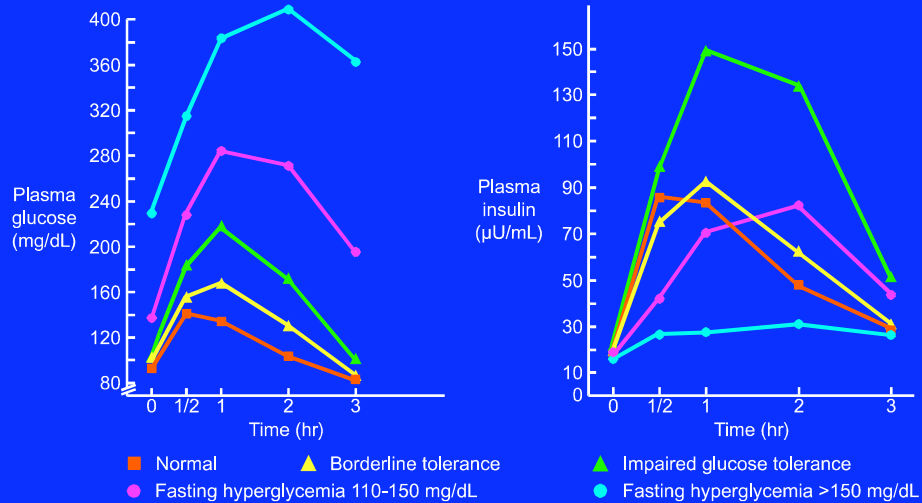


Relative Risk of Type 2 Diabetes in US Women According to BMI



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

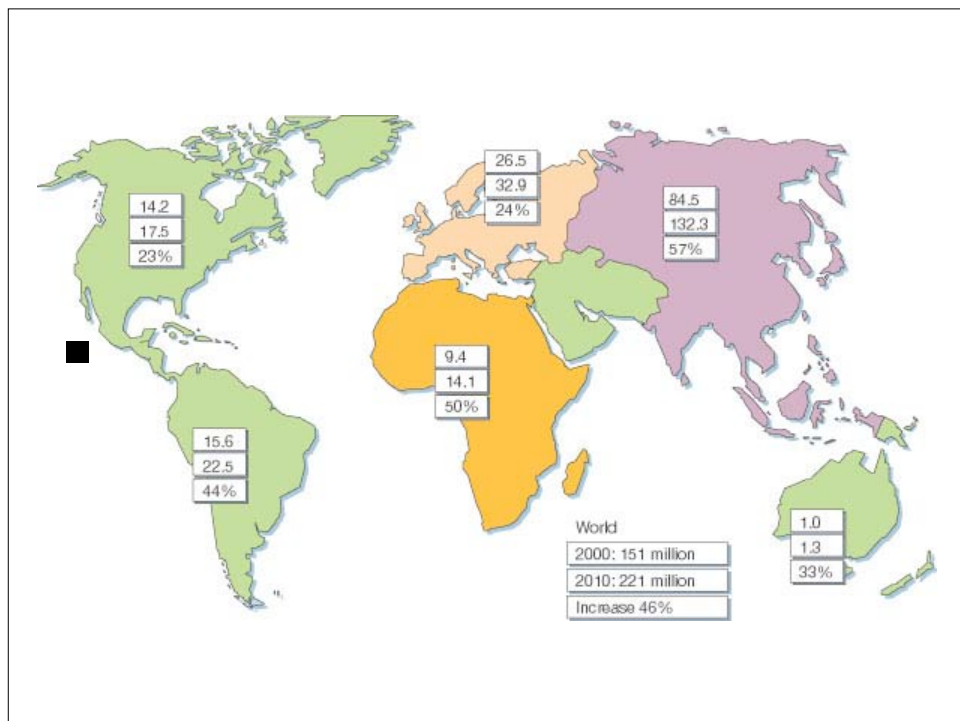
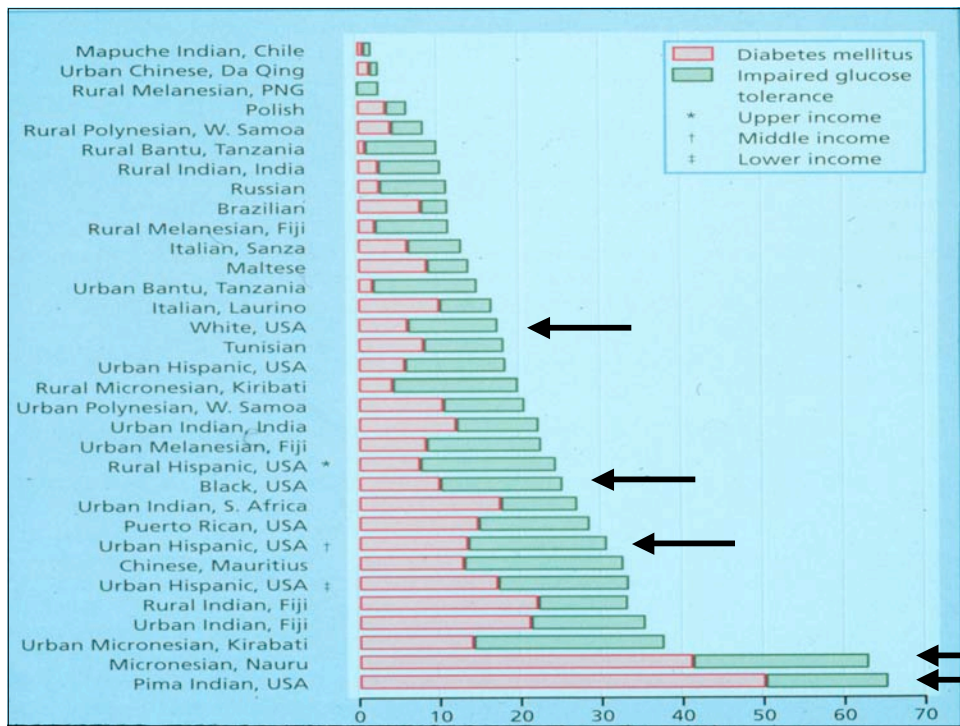
Affects 15% of Americans over the age of 60

Affects 100 million individuals worldwide

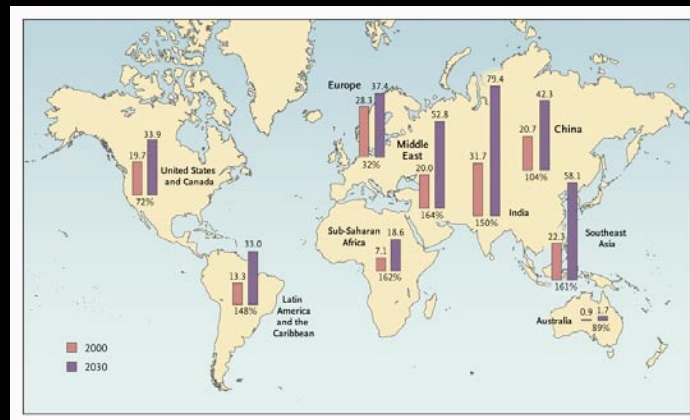
Treatment accounts for 10% of all health care expenditure in US

Complications include:

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



Millions of Cases of Diabetes in 2000 and Projections for 2030, with Projected Percent Changes



Hossain P et al. N Engl J Med 2007;356:213-215

The NEW ENGLAND
JOURNAL of MEDICINE

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
- Cushing's 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

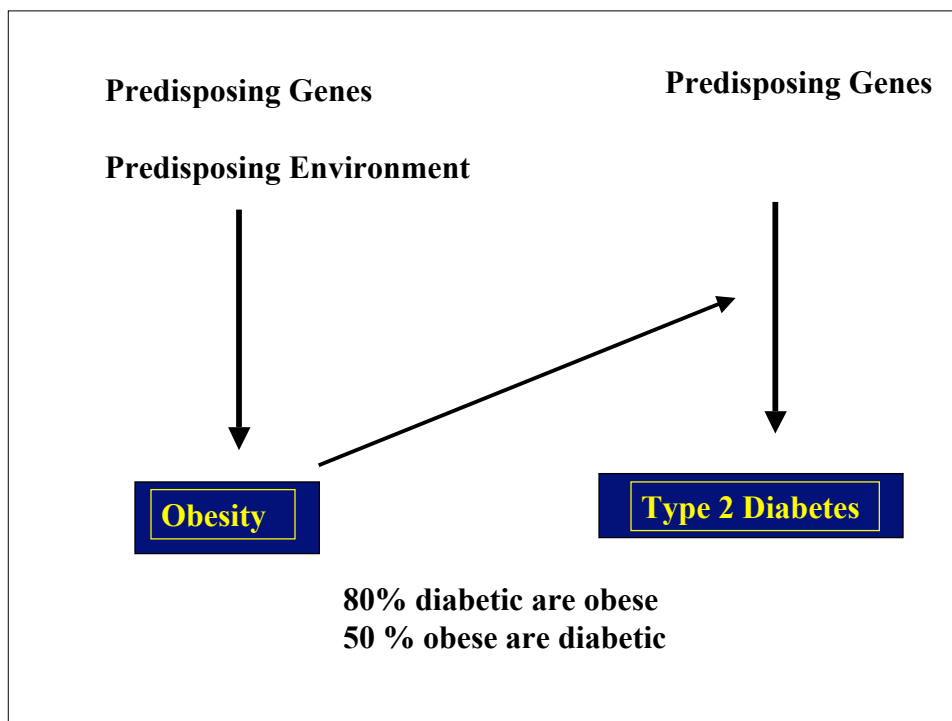
2 hour post-75gm oral glucose load plasma
glucose > **200 mg/dl**

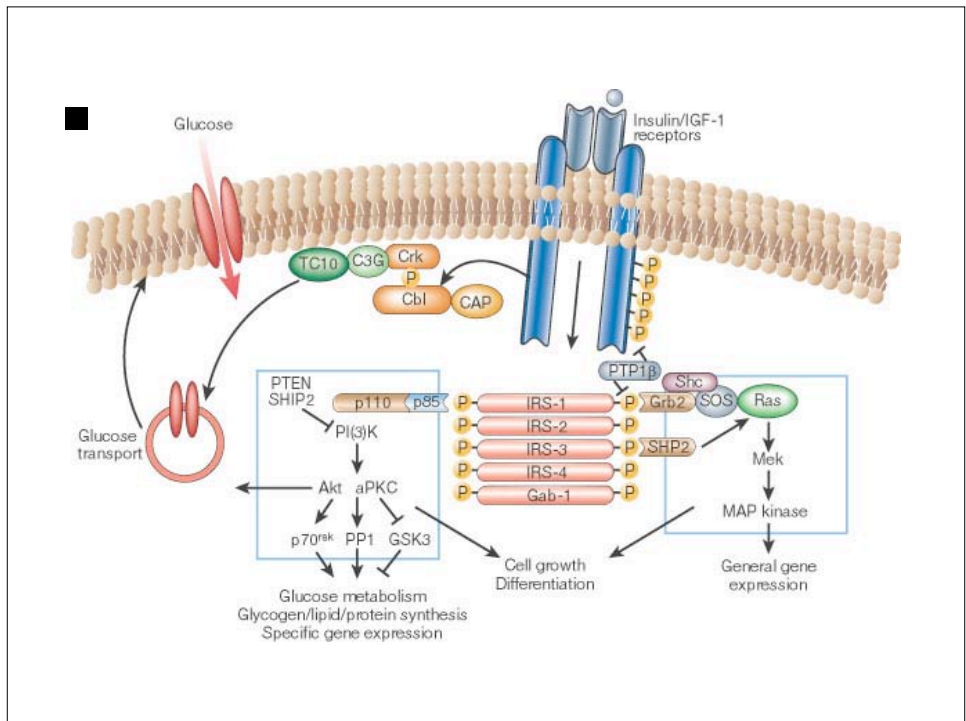
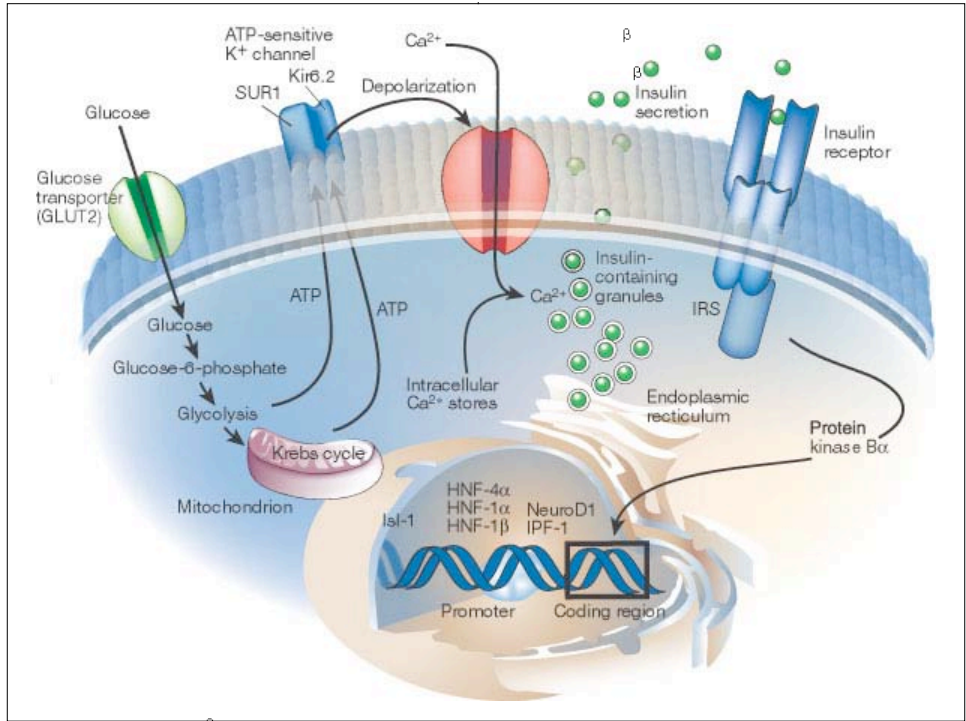
Diab. Care; 23:381, 2000

Clinical Definition Impaired Glucose Tolerance

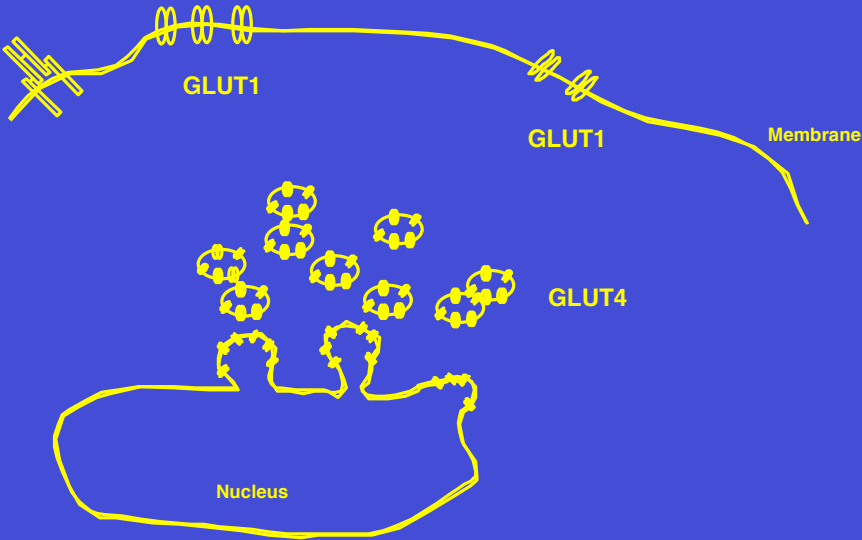
Fasting (post-absorptive) plasma glucose: **100-125 mg/dl**
or
2 hr (OGTT) plasma glucose: **140 - 199 mg/dl**

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

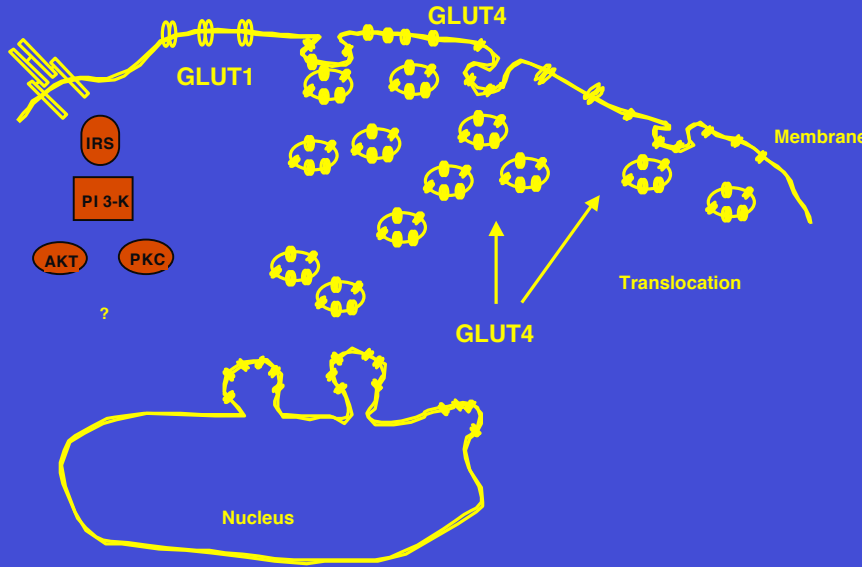


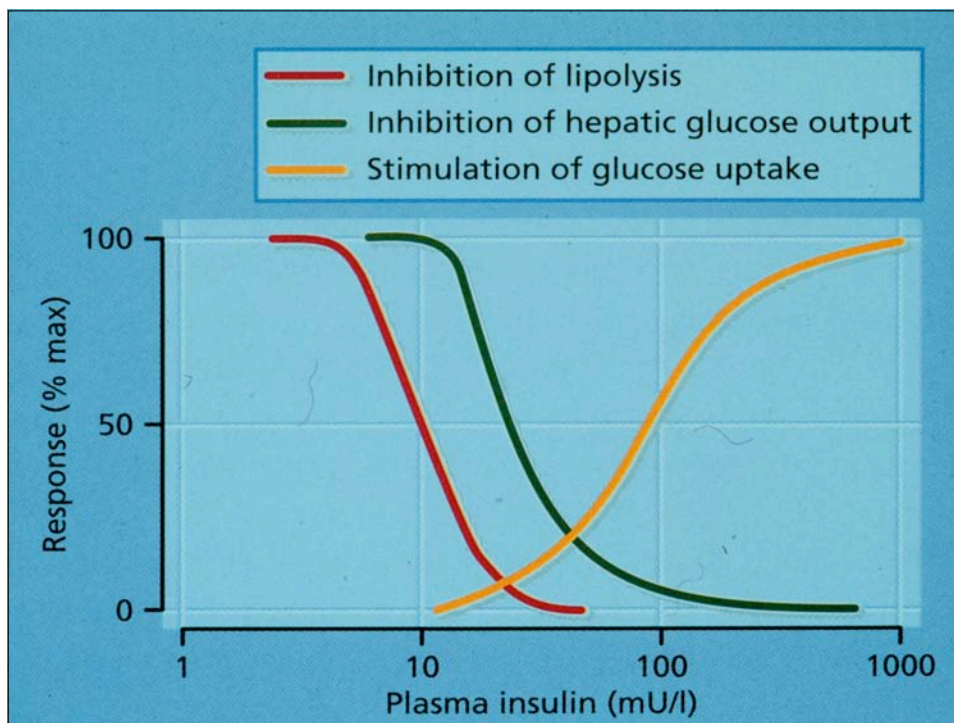
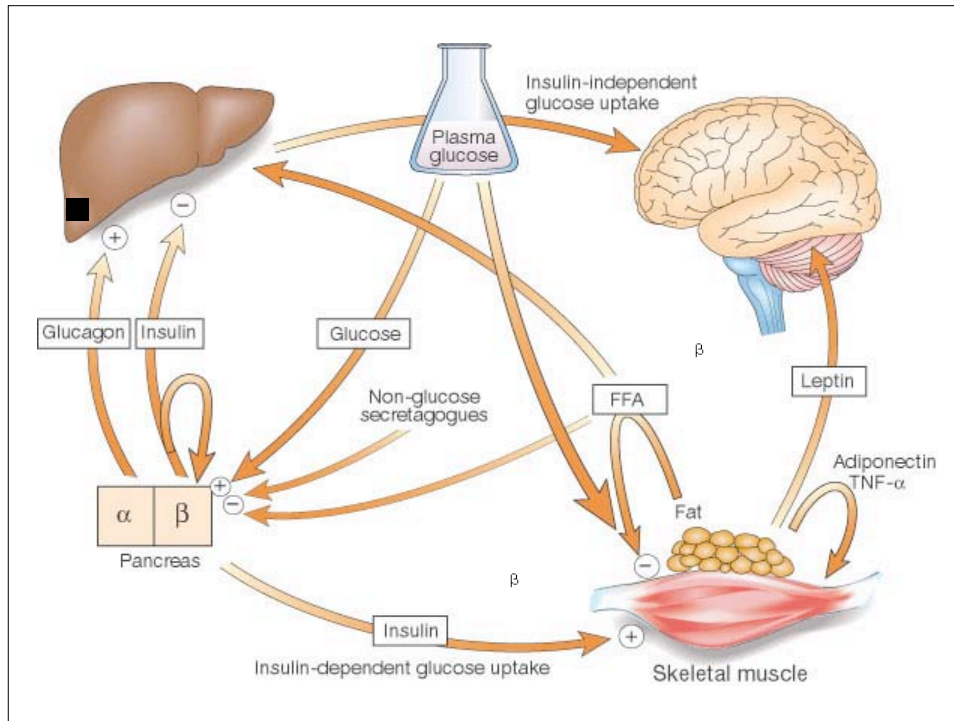


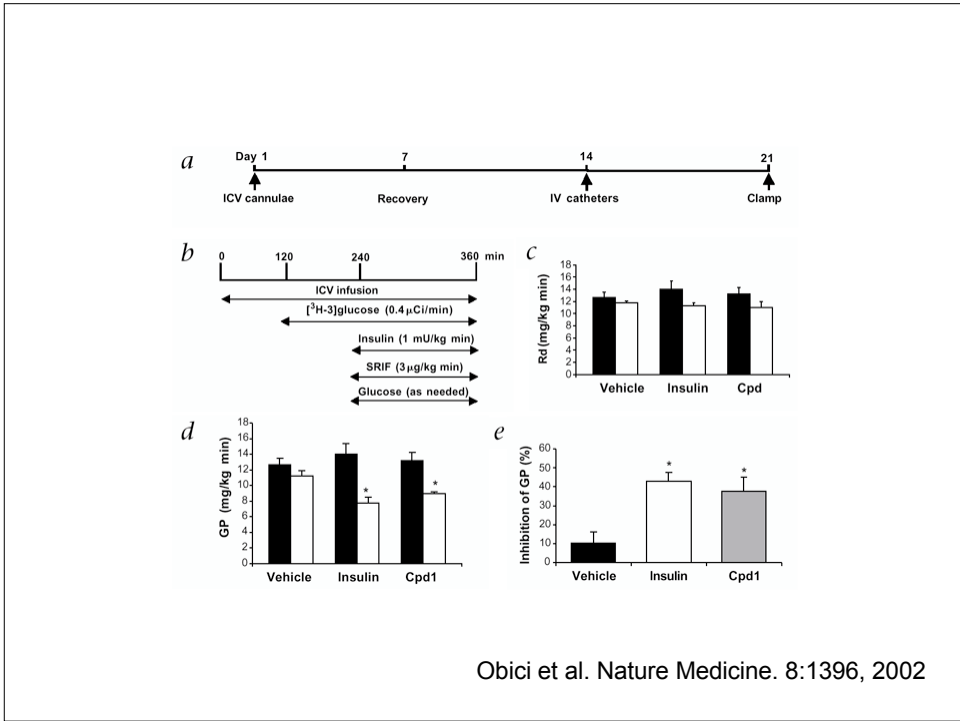
In the absence of insulin, GLUT4 is localized to an intracellular compartment



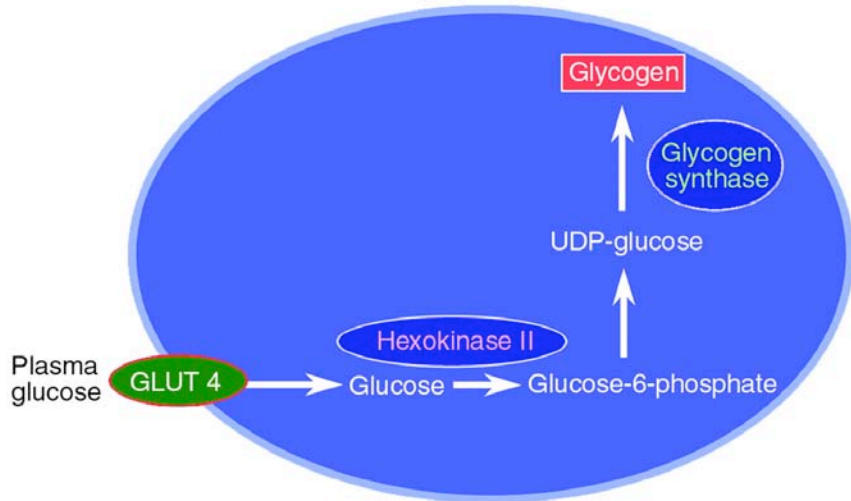
In the presence of insulin, GLUT4 translocates to the plasma membrane



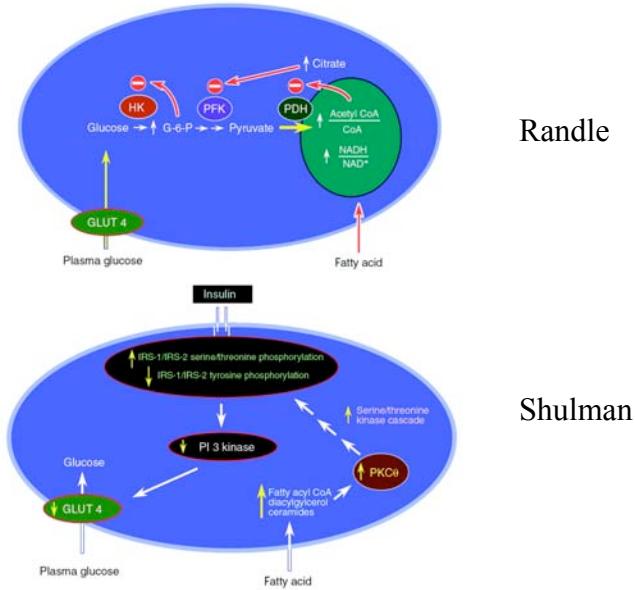




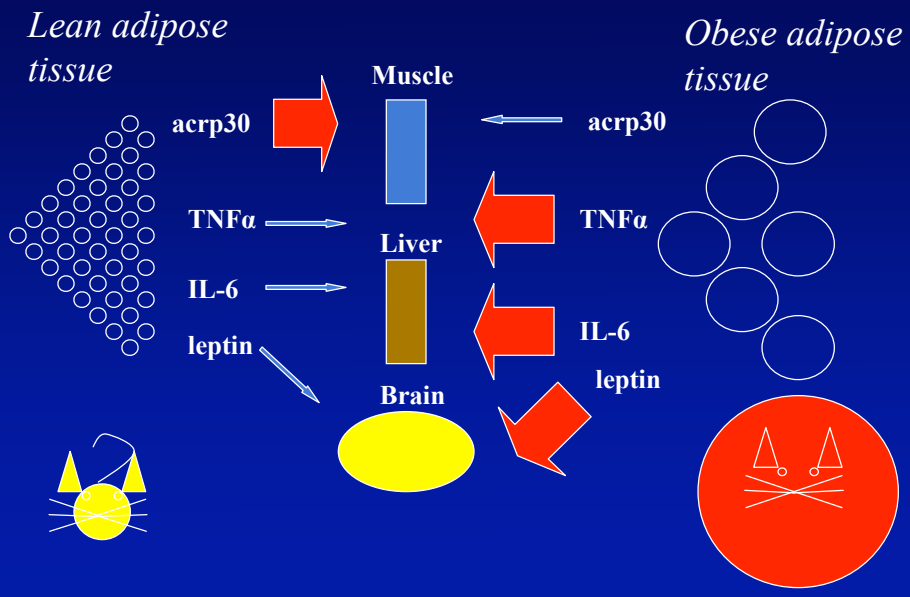
Potential rate-controlling steps in insulin-mediated muscle glycogen synthesis



Mechanisms FFA-induced insulin resistance in skeletal muscle

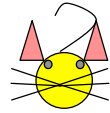


Adipose tissue is an endocrine organ.

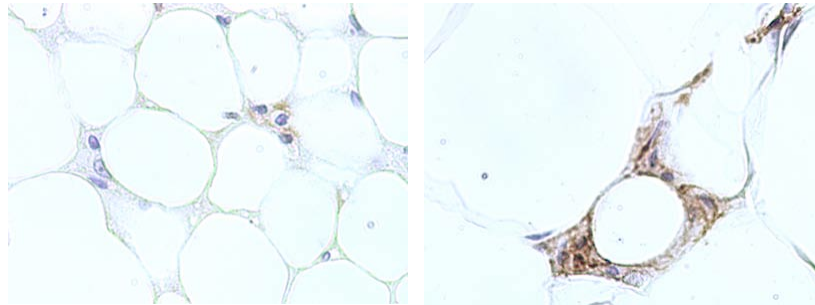
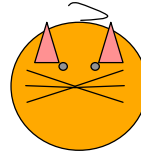


In obese mice, adipose tissue macrophages have an unusual morphology: lipid vacuoles, multinucleated.

Lean 16-week BL6 female, omental fat

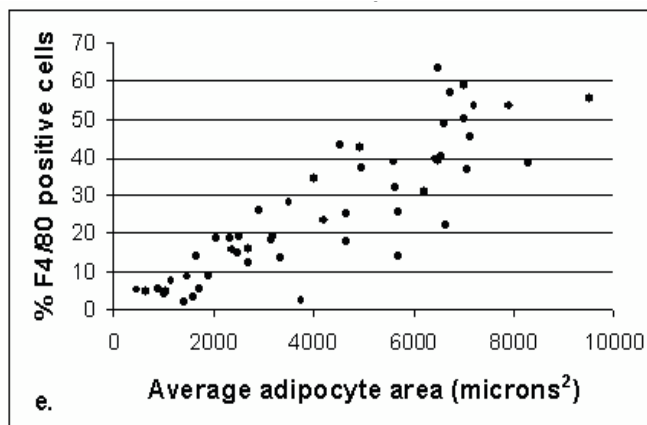


ob/ob 16-week BL6 female, omental fat



Weisberg et al., JCI, Dec 2003

Adipose tissue macrophages



Perigonadal:
 $r^2 = 0.7, P < 10^{-4}$

Perirenal:
 $r^2 = 0.7, P < 10^{-4}$

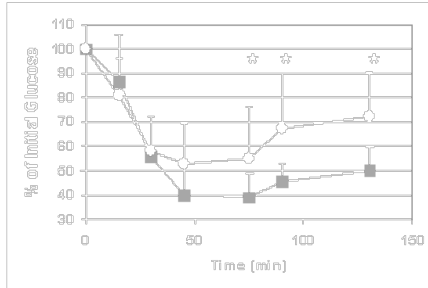
Mesenteric:
 $r^2 = 0.9, P < 10^{-4}$

Subcutaneous:
 $r^2 = 0.39, P < 0.01$

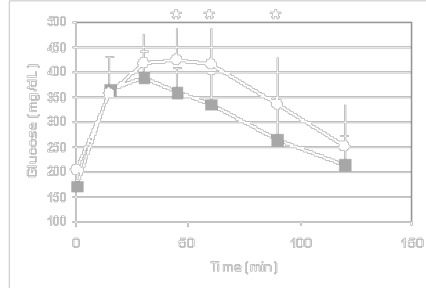
Weisberg et al., JCI, Dec 2003

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

Insulin tolerance test

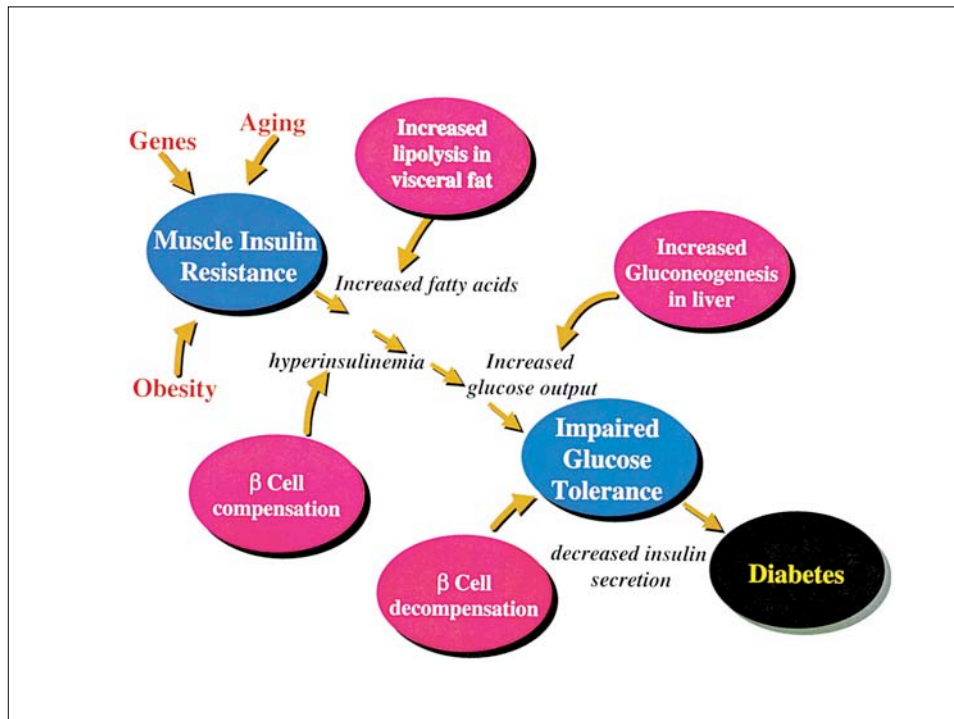


Glucose tolerance test



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

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

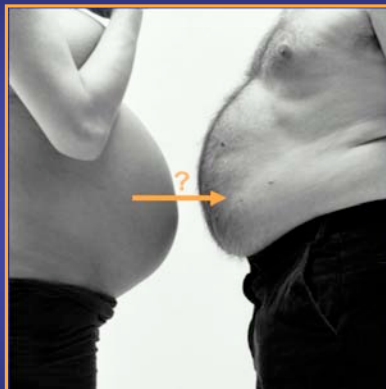


Risk Factors for Type II Diabetes (II)

“Barker Hypothesis”

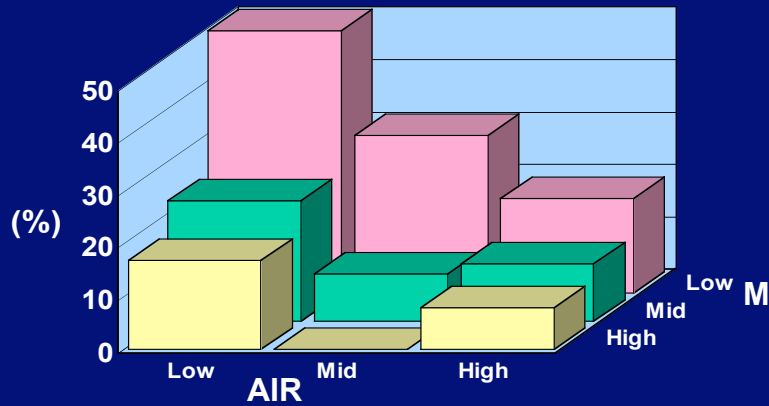
Low birth weight and slow 1st year growth lead to:

- 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

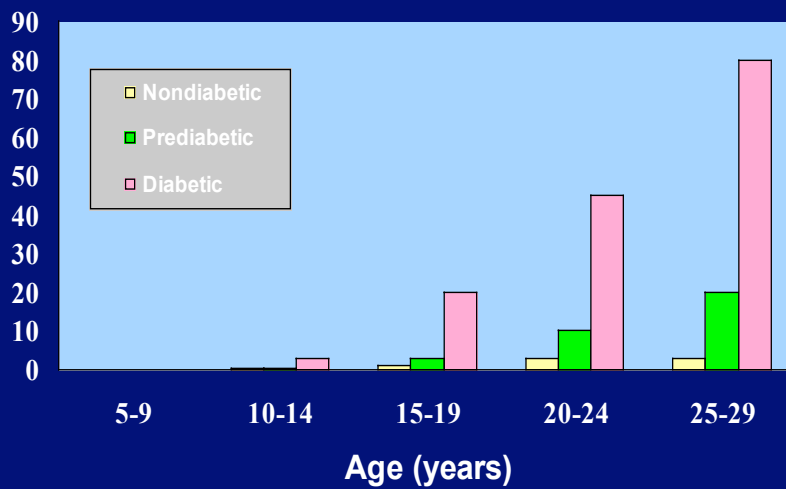


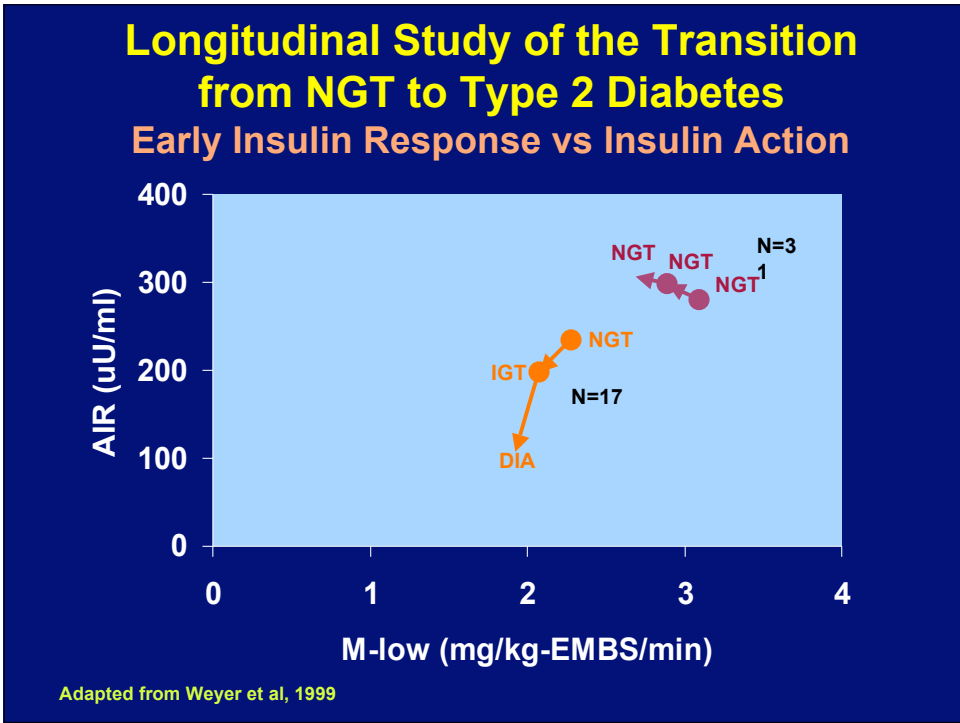
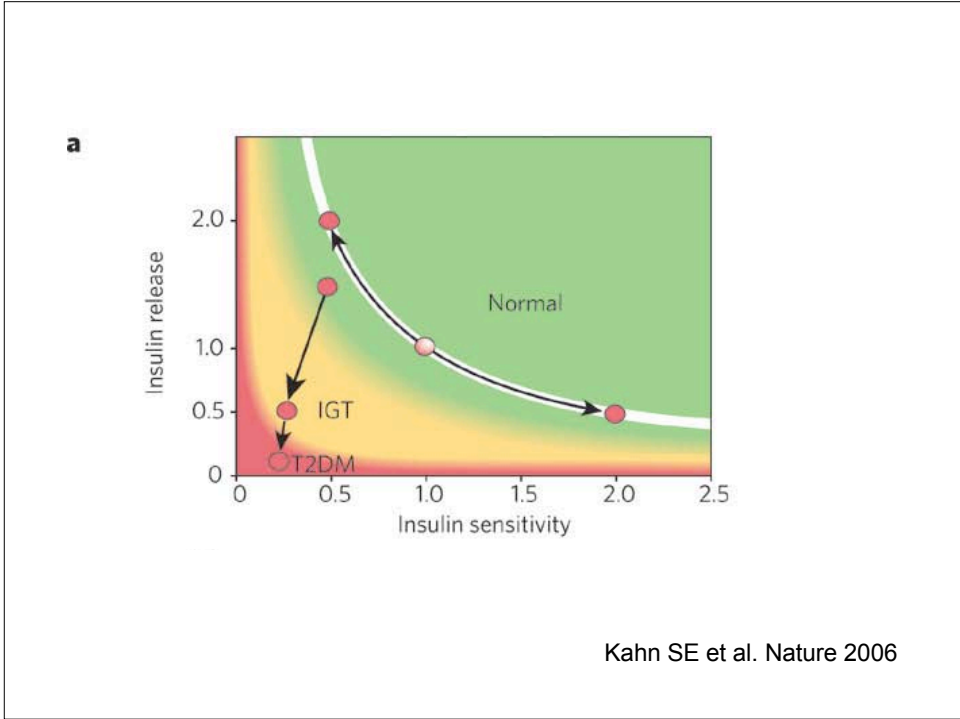
Prospective Analysis

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



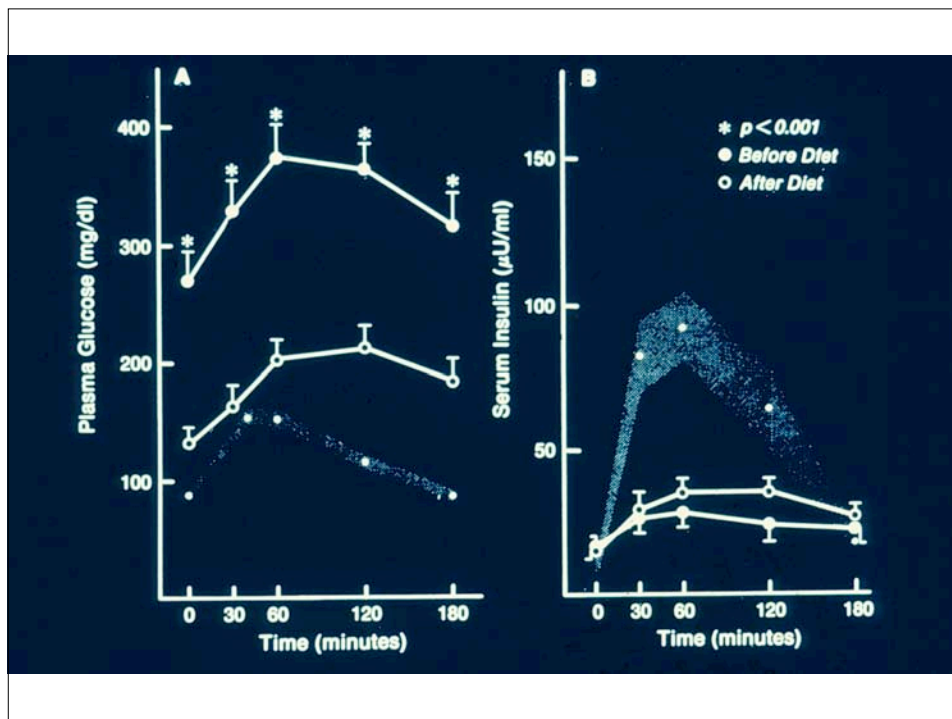
Diabetes Prevalence (%) in Offspring by Mother's Diabetes at Pregnancy

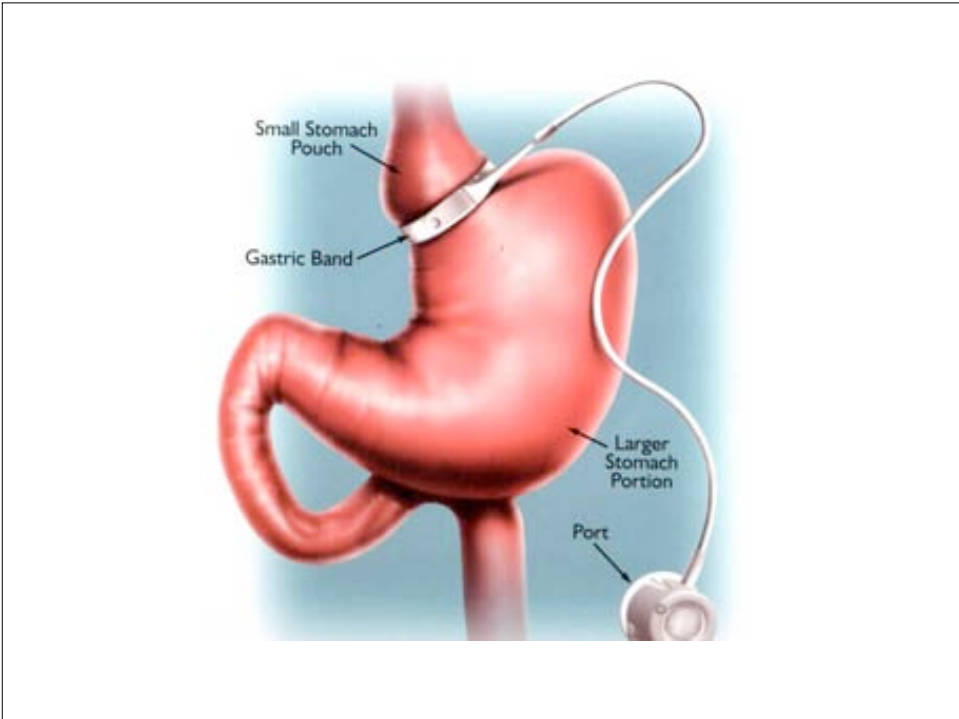
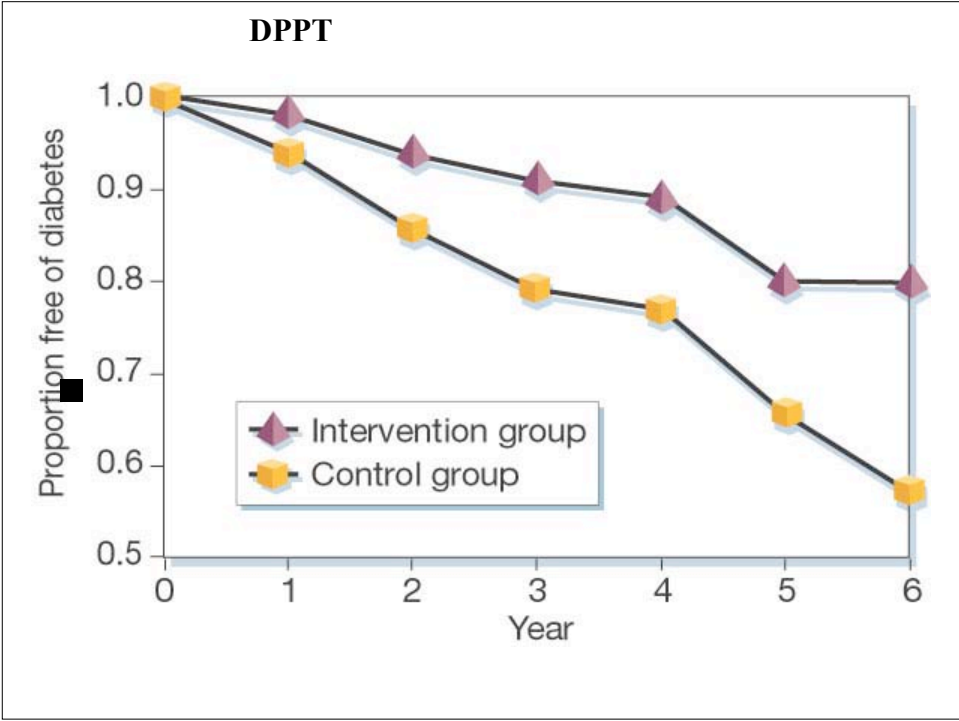




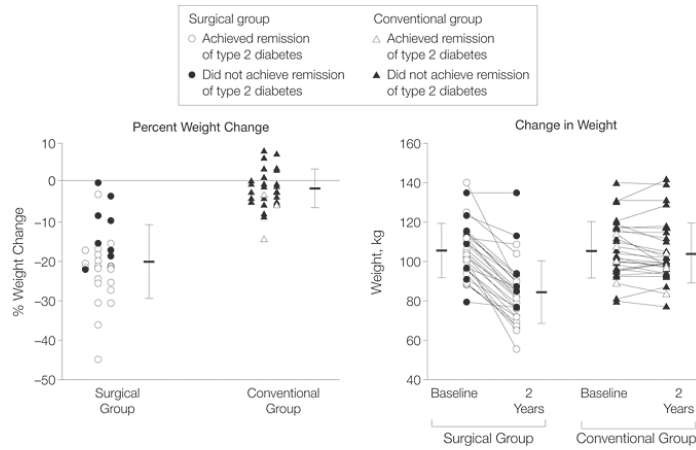
OBESITY-DIABETES

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



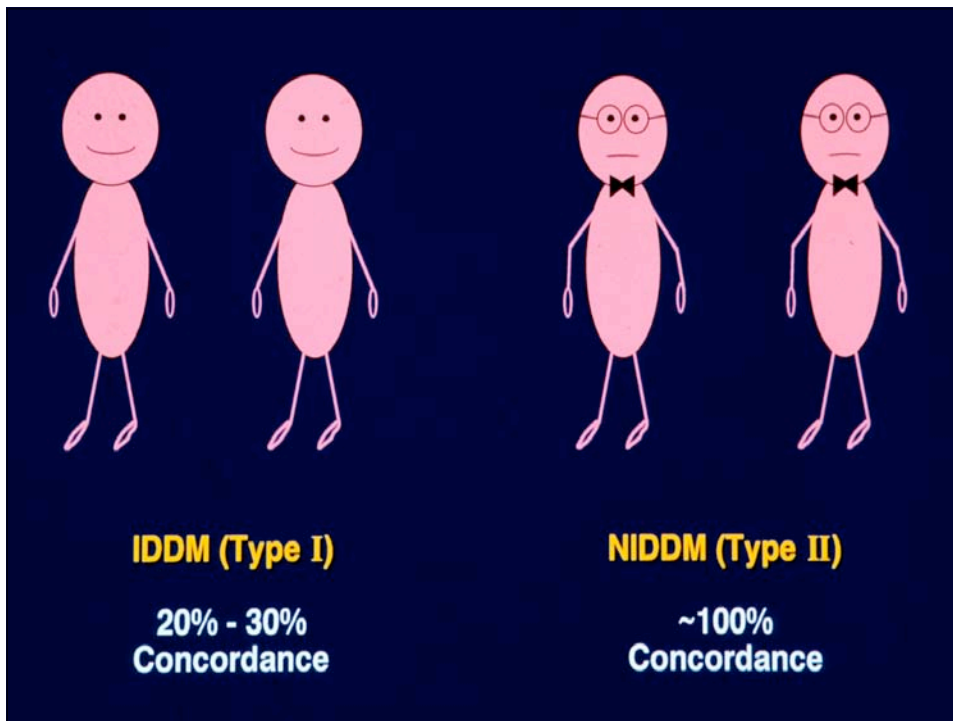


Percentage of Weight Loss Achieved Over the 2-Year Study Period (n = 60) and Individual Weight Measures at Baseline and at 2 Years



Dixon, J. B. et al. JAMA 2008;299:316-323.

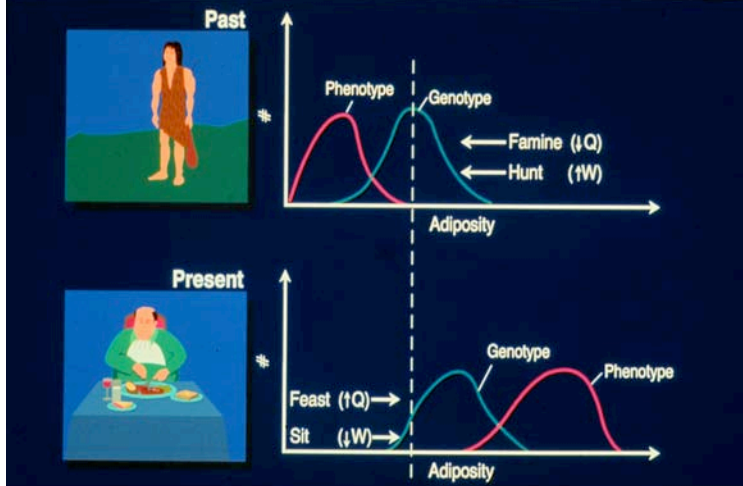
Copyright restrictions may apply.

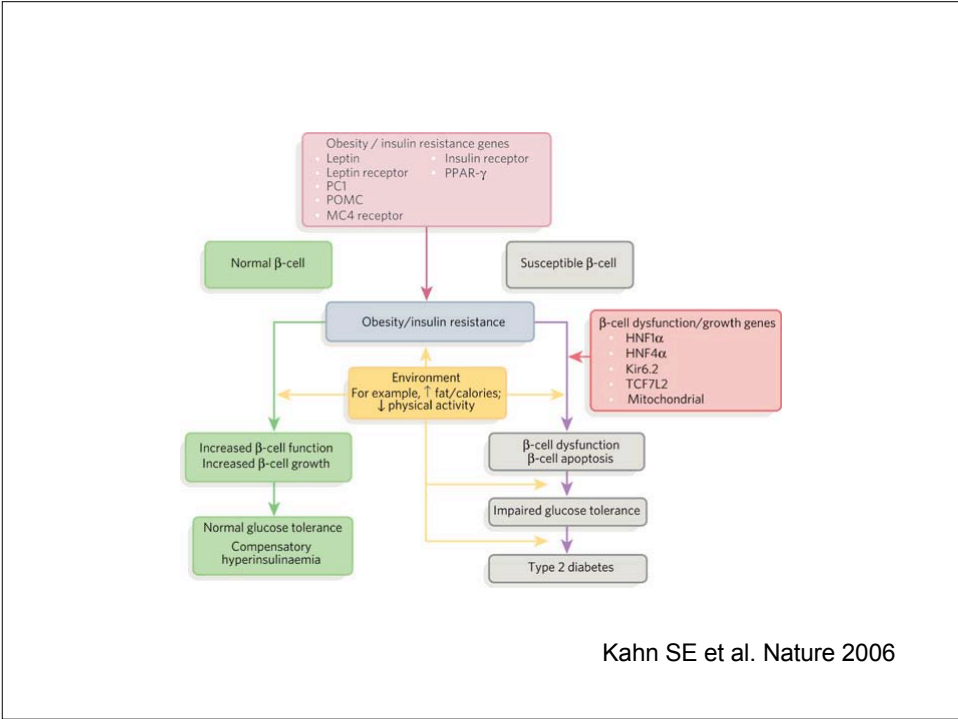


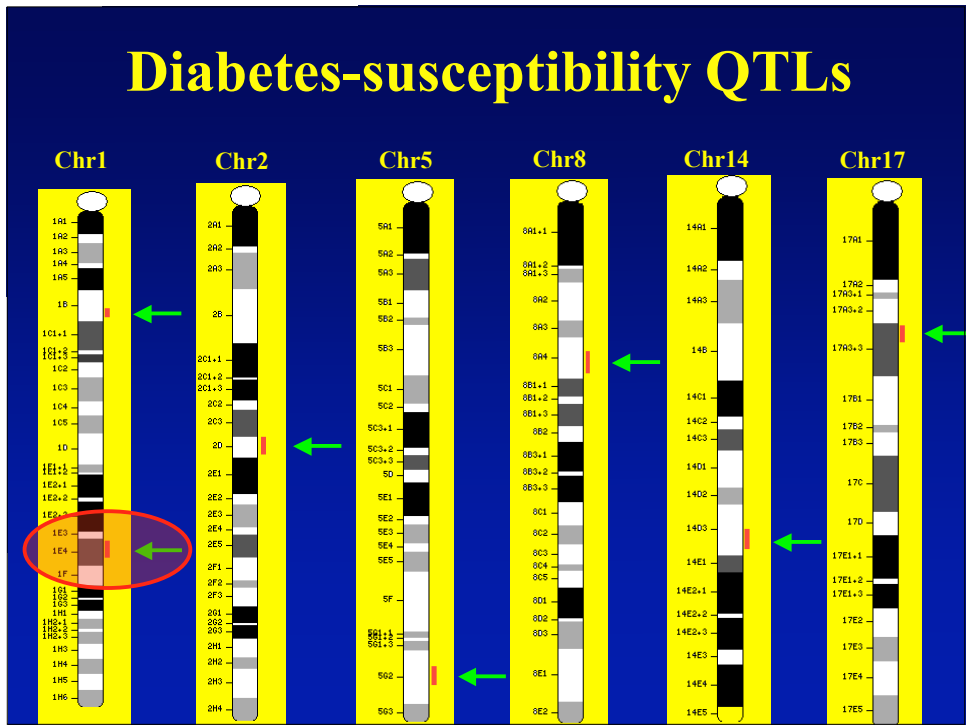
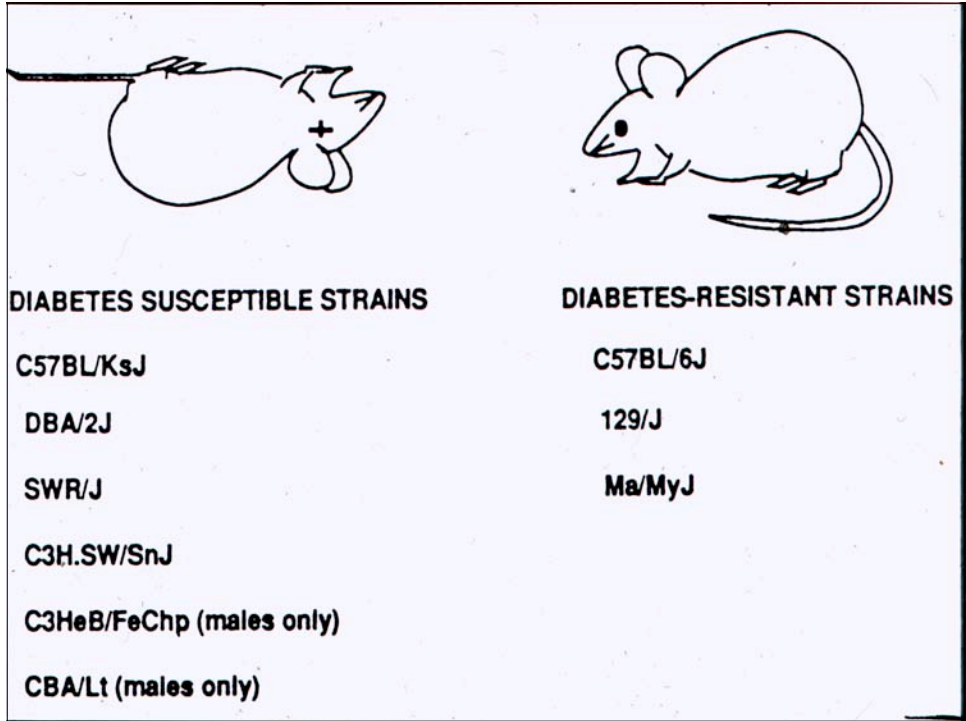
Age Adjusted Incidence Rates of NIDDM in Pima Indians by Body Mass Index and Parental NIDDM



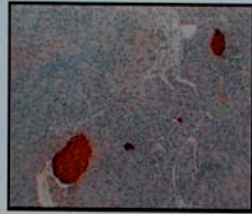
$$\text{Adiposity}(u) = f(Q) - f(W)$$



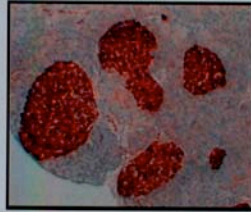




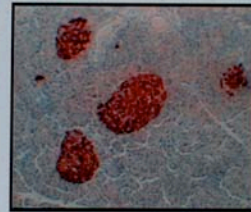
Pancreatic Grading in Genetically Obese Mice



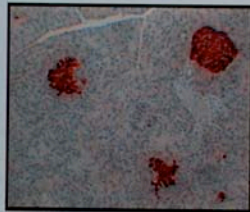
Lean



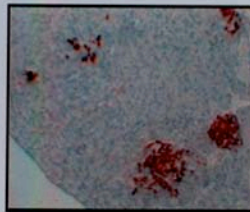
Obese Grade 1



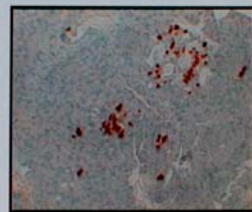
Obese Grade 2



Obese Grade 3

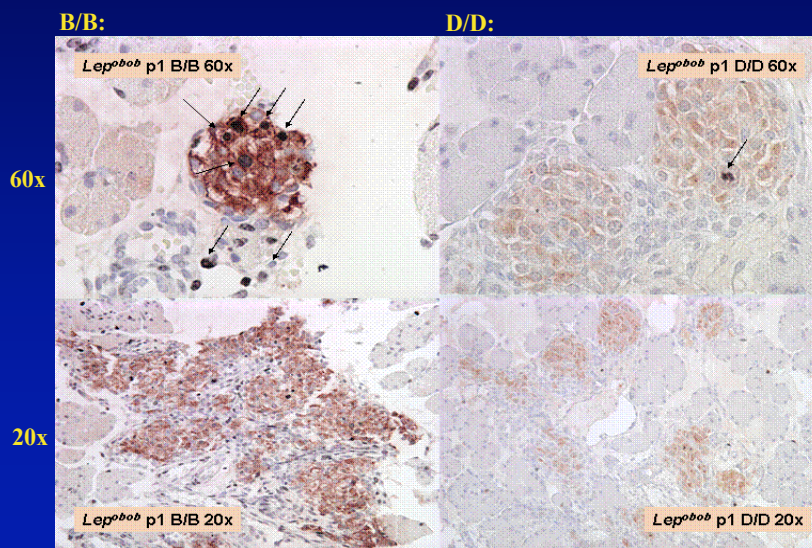


Obese Grade 4

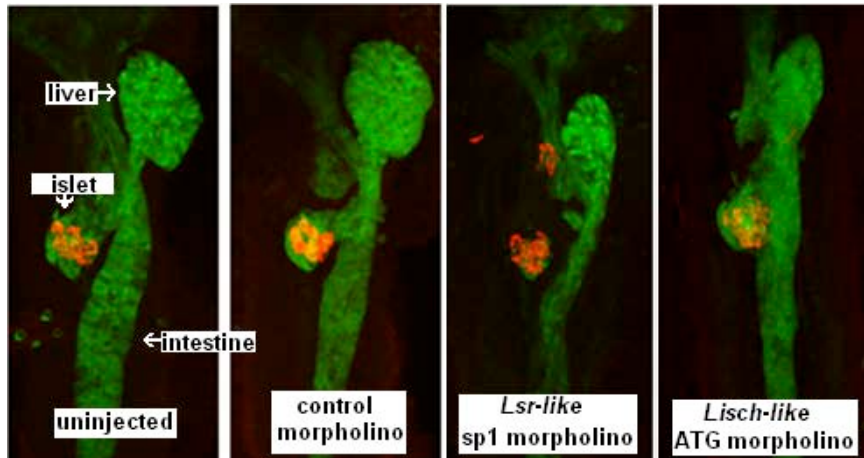


Obese Grade 5

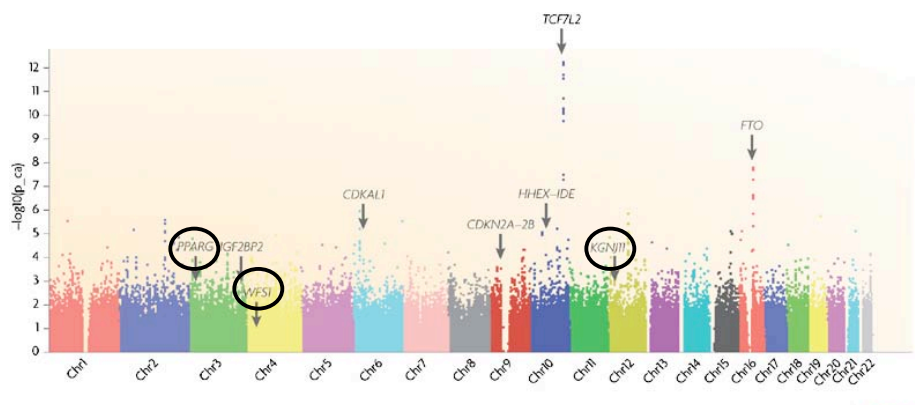
Do beta cells in D/D animals replicate as well as beta cells in B/B animals?



Zebrafish

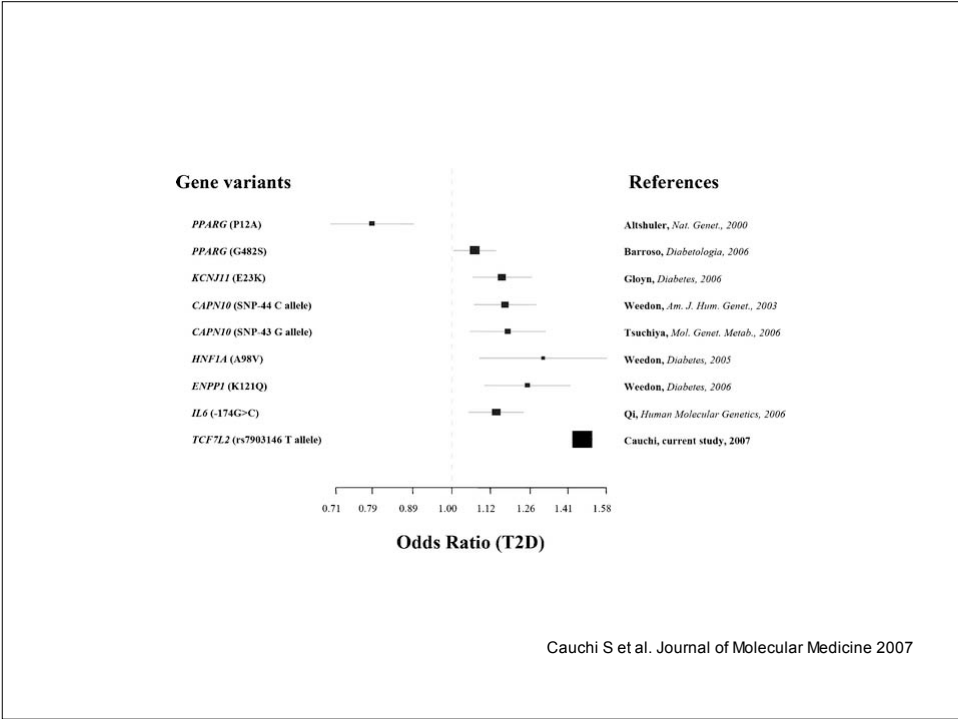


prior candidates

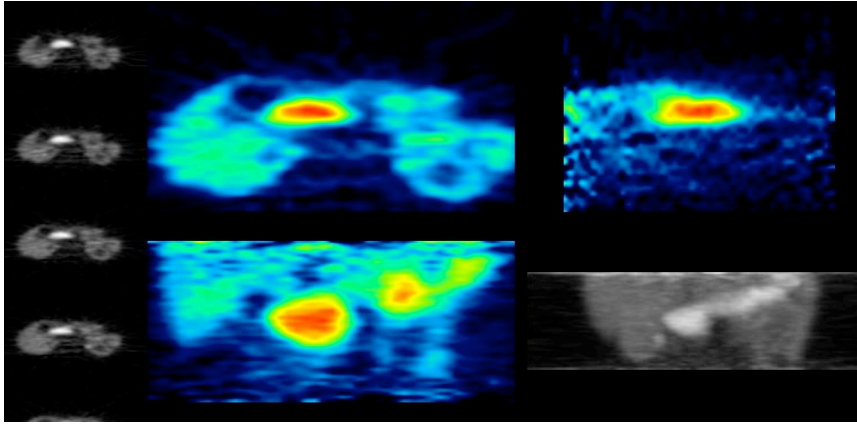


TCF2, SLC30A8 not on this affy array

Frayling. Nature Reviews. Genetics. 8:657, 2007 from Zeggini et al. Science. 316:1336, 2007



[11C] DTBZ and PET visualizes the human pancreas



END