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Obesity and Type 2 Diabetes Mellitus - the Epidemic

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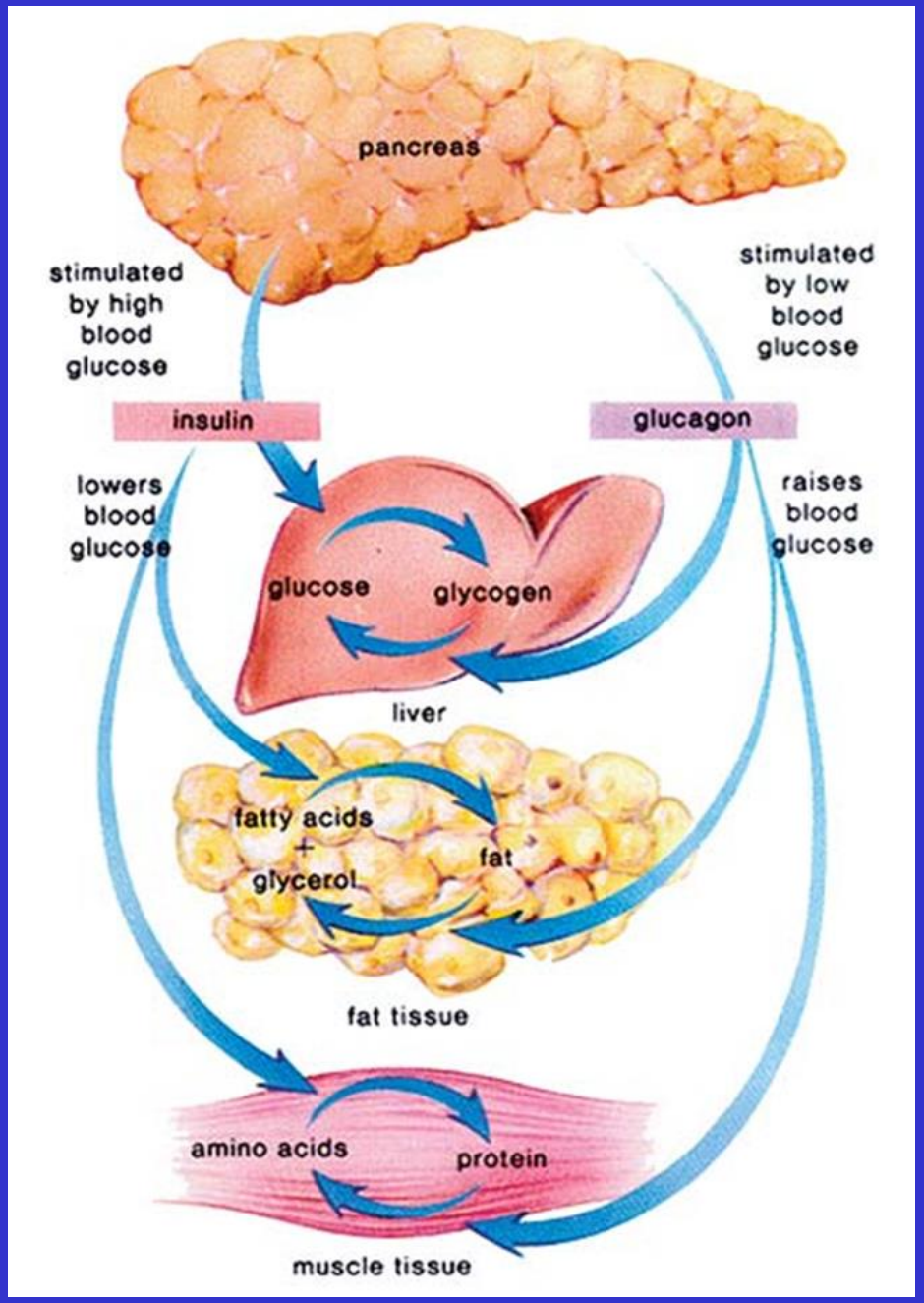
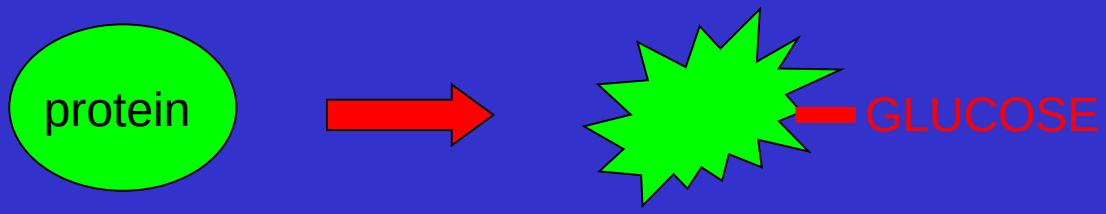


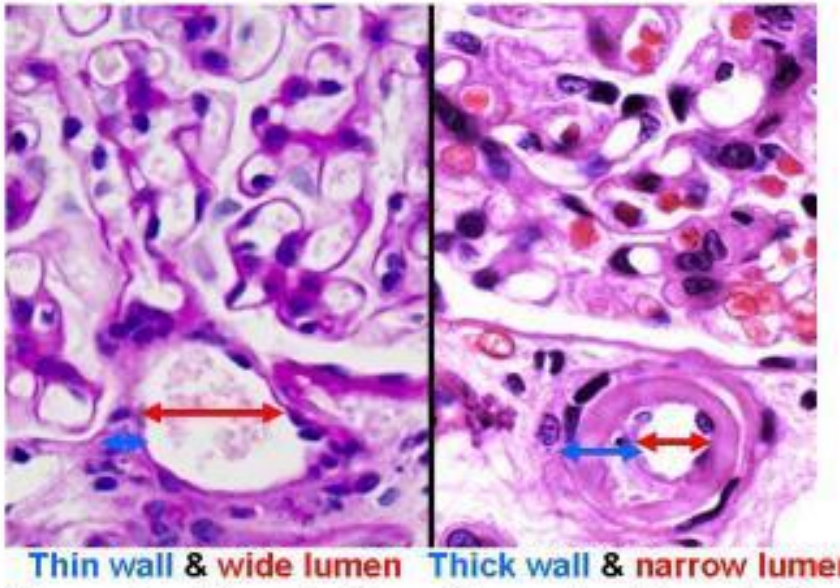
Type 1 Diabetes Mellitus, Juvenile Diabetes.
Absolute lack of insulin due to destruction of β cells in the Islets of Langerhans of pancreas that secrete insulin

Type 2 Diabetes Mellitus, Maturity Onset Diabetes.
Insulin resistance of peripheral tissues and impaired insulin secretion
- This form is very closely related to/caused by OBESITY

Diabetes Mellitus is characterized by high plasma glucose concentration.
Glucose chemically attaches to proteins and affects protein shape and function

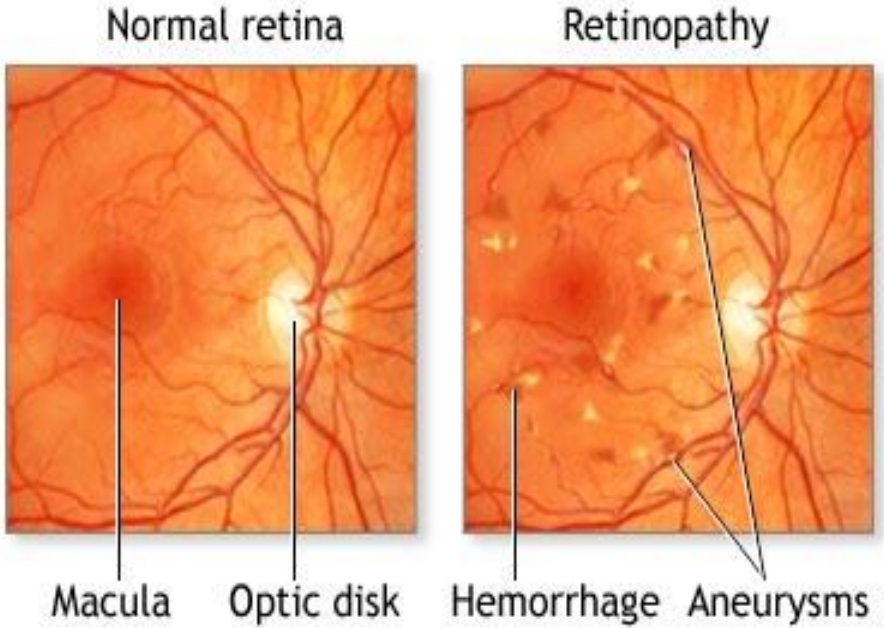


eg. glycosylated haemoglobin (hAIc) has reduced ability to carry oxygen
microvascular disease eg thickened arteriole walls and capillary closure leads to – retinopathy, neuropathy, nephropathy



Microscopic photograph of a cross section of a normal arteriole next to a glomerulus. The lumen is wide open to allow normal flow of blood.

Microscopic photograph of a cross section of an arteriole with diabetic arteriolosclerosis. The lumen is narrowed by the thick wall thus reducing flow of blood.



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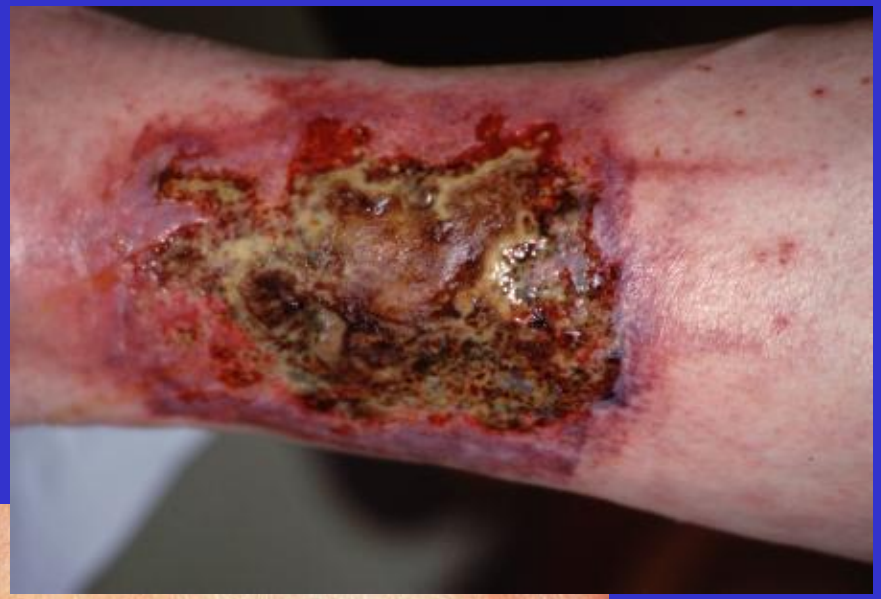
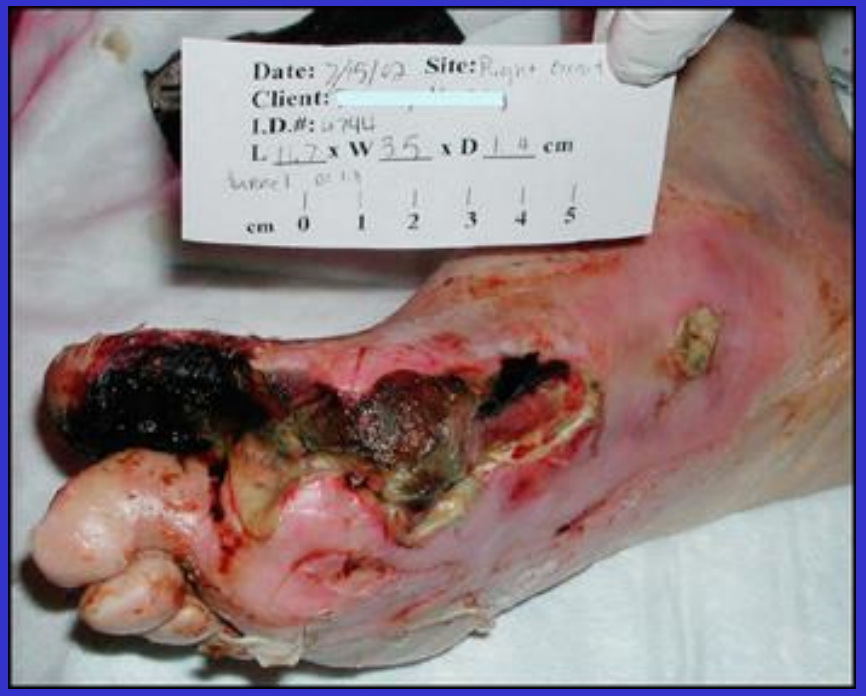
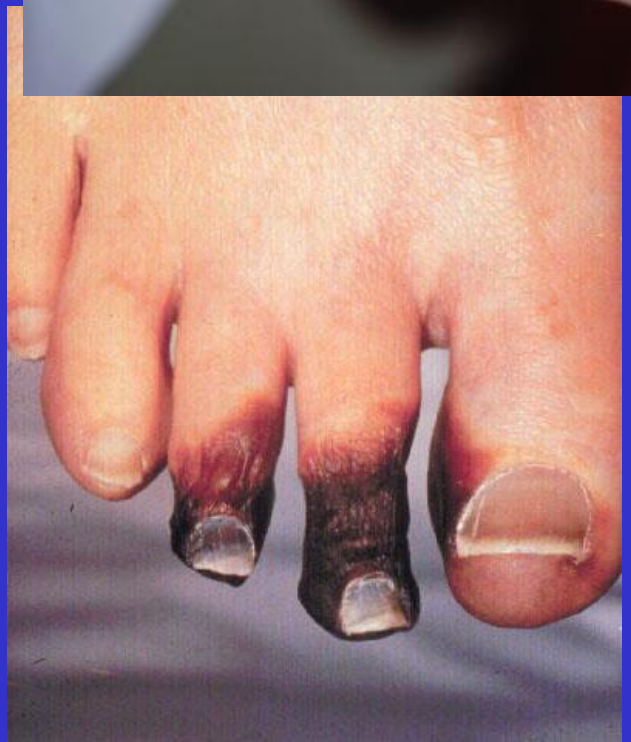
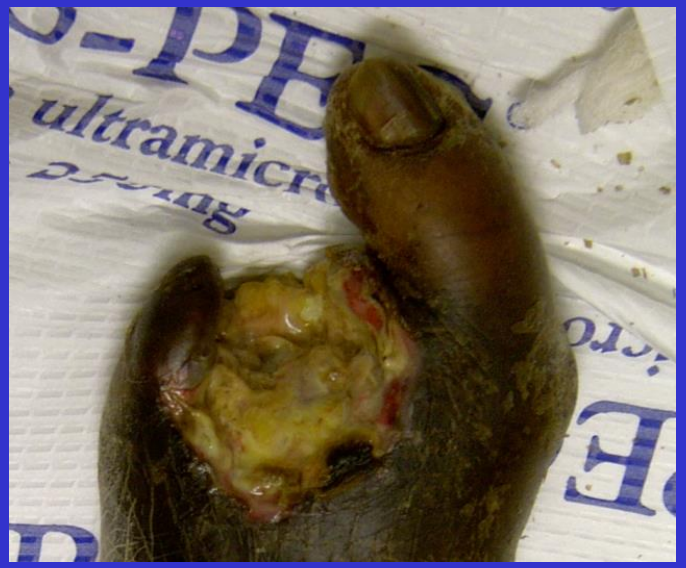






Microvascular disease, diabetic ulcers and gangrene



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Type 2 Diabetes (insulin resistance and reduced insulin secretion) is closely related to **obesity**

Obesity is defined by the "Body Mass Index"

$$\text{Body Mass Index (BMI)} = \frac{\text{Body Weight (kg)}}{(\text{Height})^2 \text{ (m)}}$$

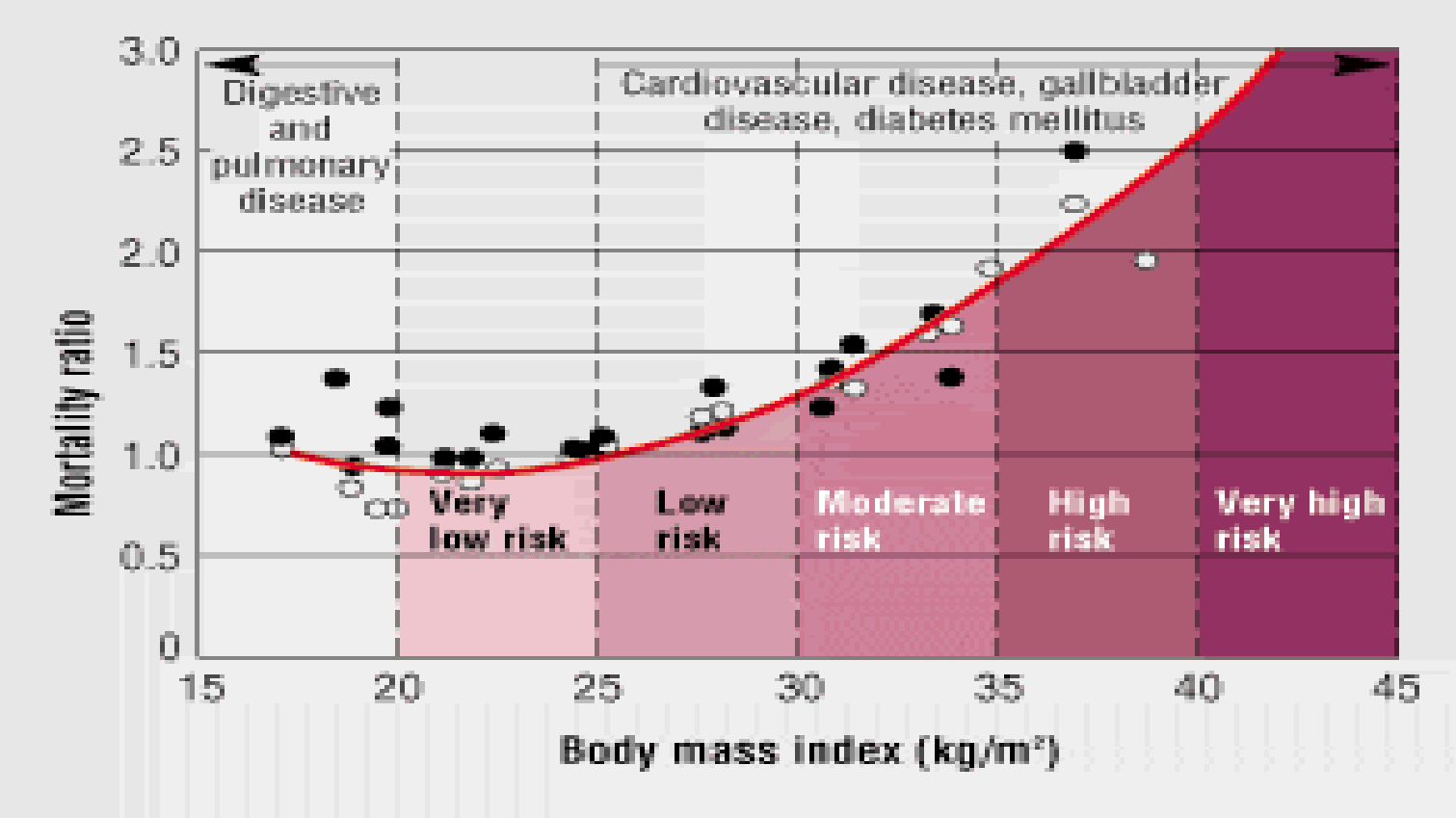

Figure 4. Relationship of body mass index to disease risks.

Age (yr) at issue of insurance policy

● 20-29 ○ 30-39

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Morbidly Obese

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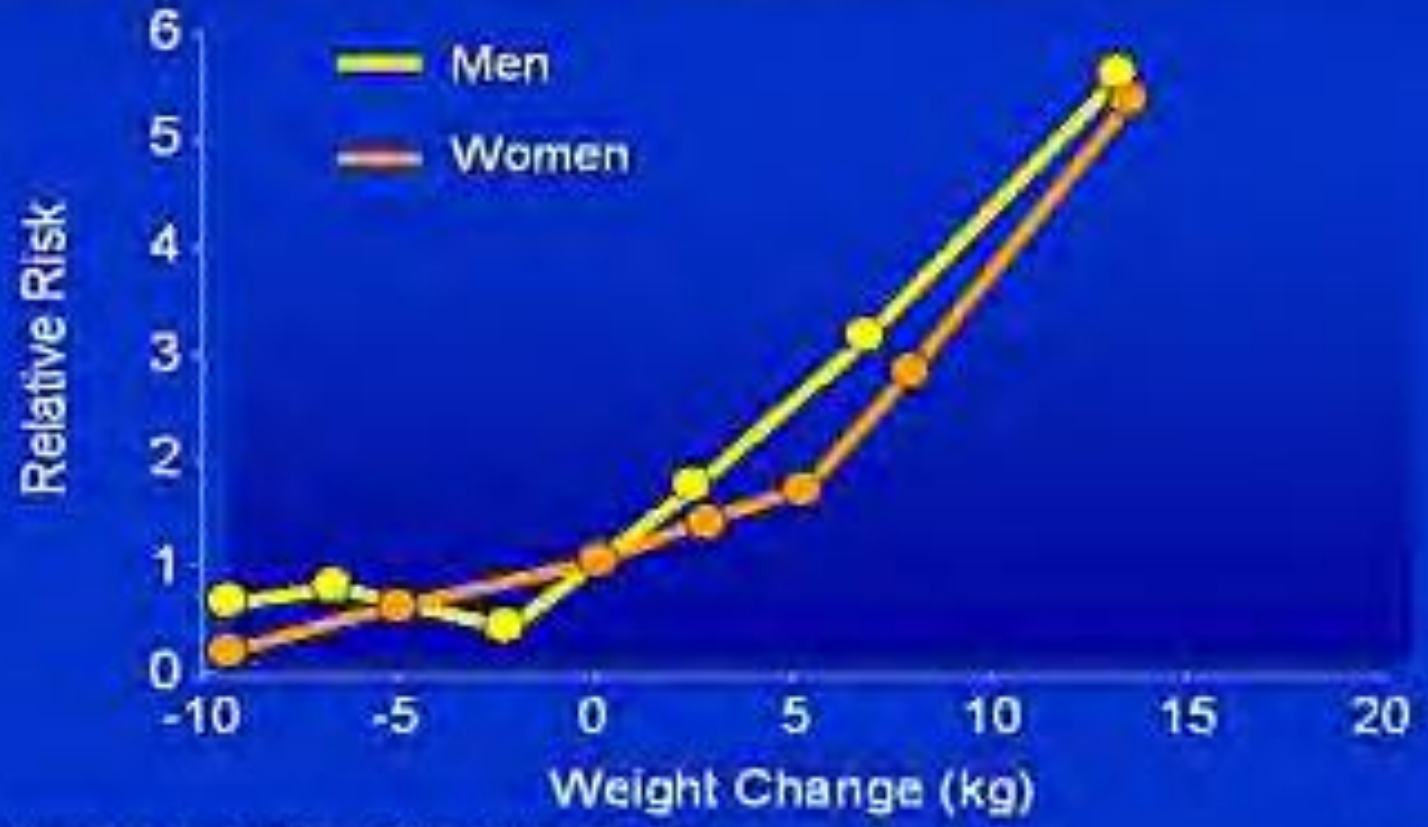
Relationship Between Weight Gain in Adulthood and Risk of Type 2 Diabetes Mellitus



Willett et al, *N Engl J Med* 1999;341:427

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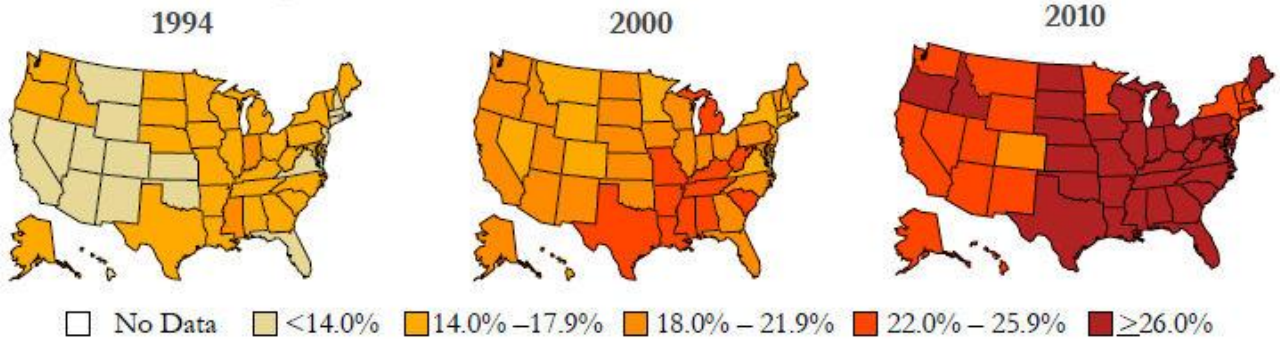
The Epidemic

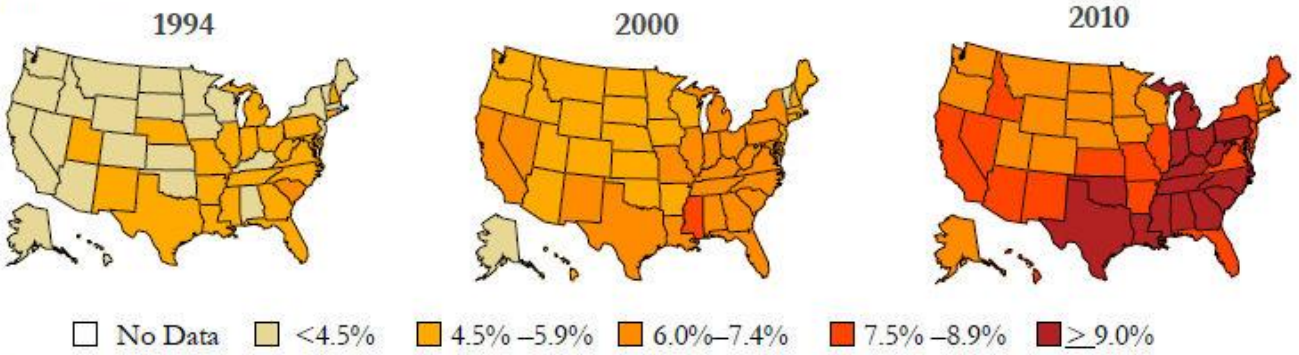
Changes in human behaviour over the last few decades are resulting in a dramatic increase in incidence of obesity and type 2 diabetes mellitus.

Age–Adjusted Prevalence of Obesity and Diagnosed Diabetes Among U.S. Adults Aged 18 years or older

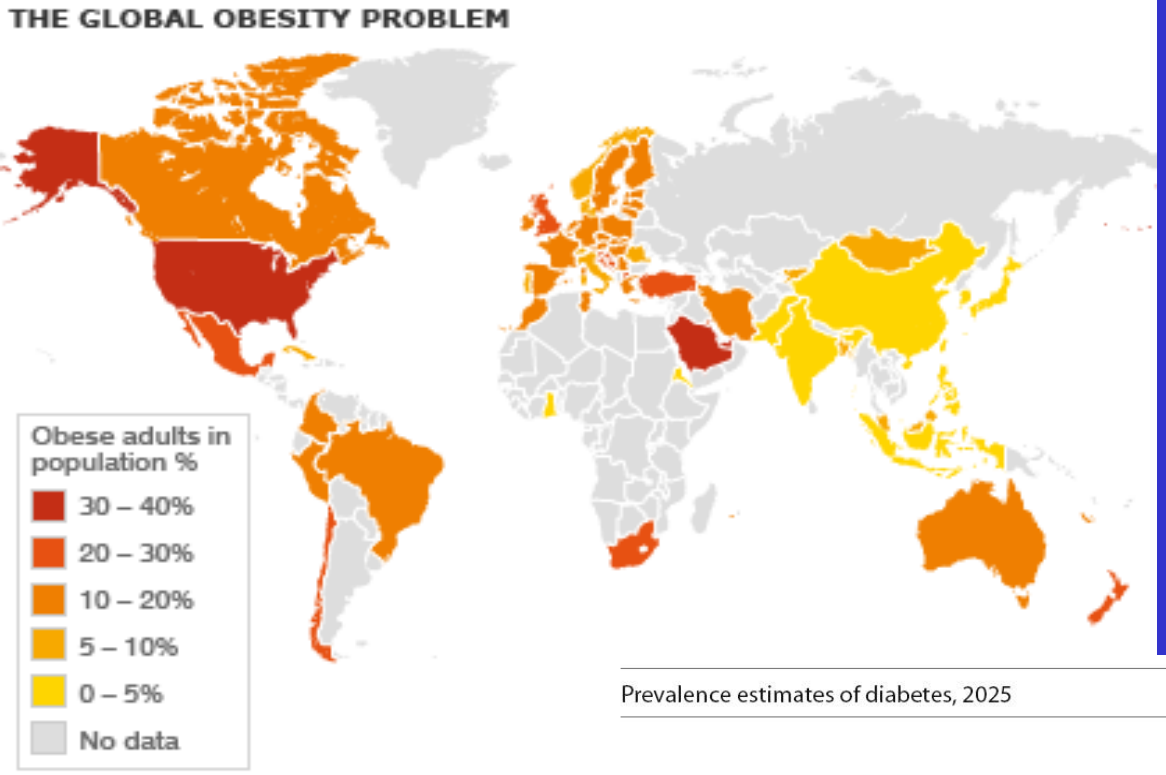
Obesity (BMI ≥30 kg/m²)



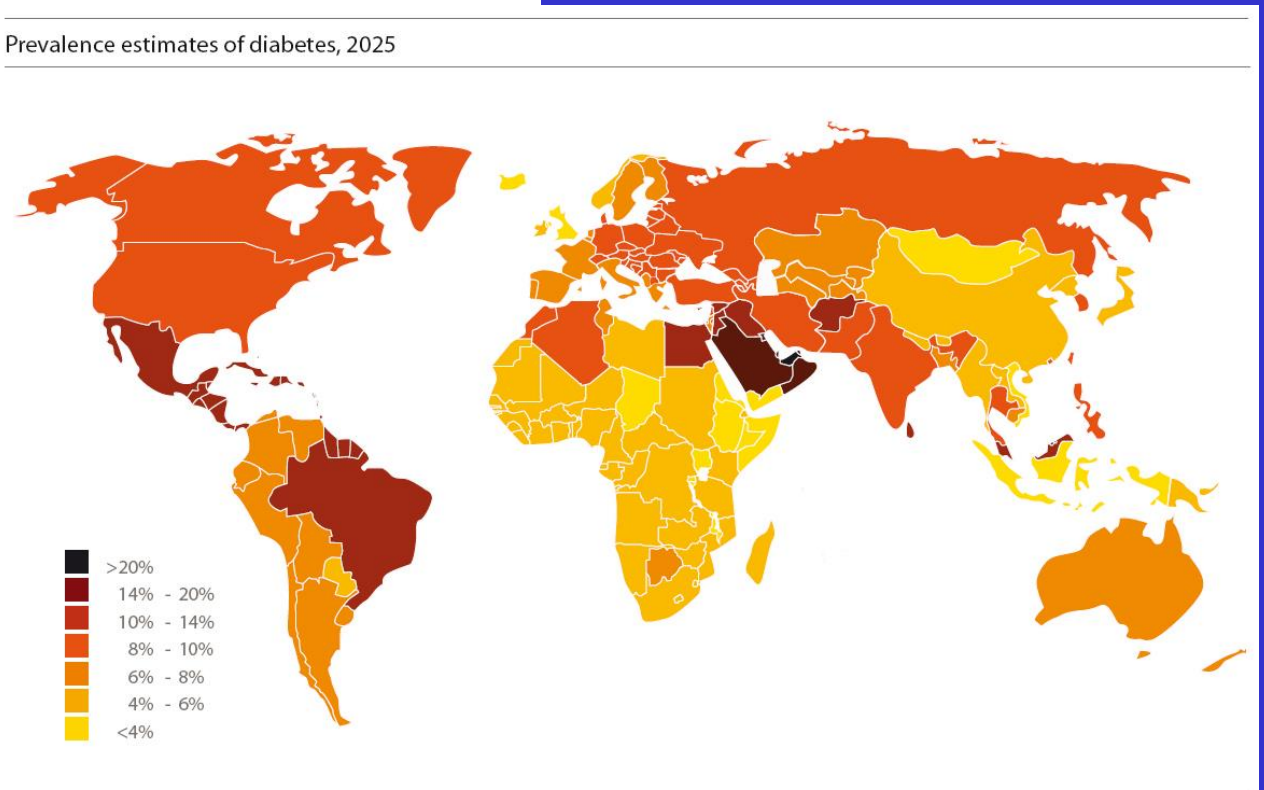
Diabetes



CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics



Few countries have a diabetes prevalence less than 4%. The International Diabetes Federation estimates that by 2030 the global prevalence of diabetes will be 7.8%, with 438 million suffering from the disease. Another 8.4% (472 million) will have impaired glucose tolerance (a precursor of type 2 diabetes).



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The human species evolved with a **thrifty genotype** - the ability to store energy producing substrates in “times of plenty” that could be used “when food was scarce”.

But now food is always abundant and we are victims of our own evolution storing calories that we do not need and becoming obese.

Certain individuals may have a genetic make up that makes them eat more and store more fat.

This kind of genetic susceptibility coupled to a modern lifestyle with less exercise and an abundance of high calorific food, has lead to the epidemic in obesity and Type 2 Diabetes.

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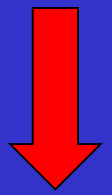
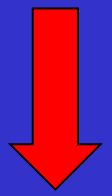
Genetic differences

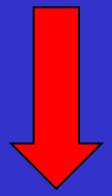
Gene = DNA (Genome)



m RNA



Protein eg receptor (Proteome)



Function in cell eg Insulin signalling (Phenotype)

There may be slight differences in genes between individuals (Single nucleotide polymorphisms).

This might mean that the protein produced may be very slightly different between individuals. (This explains eye colour, blood group, body shape etc)

This also applies to proteins in the cell.

For example: You might mean have protein receptors that are very slightly better at responding to insulin than I have.

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It's not fair!

Why the difference?

Genetic?

Environmental?

Both!!!

How have the genes responsible for predisposition to diabetes been identified?

1. Genetic Animal models of obesity and diabetes:

The ob^-/ob^- mouse is deficient in leptin, a hormone released by adipose tissue that binds receptors in the hypothalamus and reduces appetite. The ob^-/ob^- mouse overeats and becomes obese and develops type 2 DM.

The mouse on the left is unable to produce leptin, resulting in obesity.

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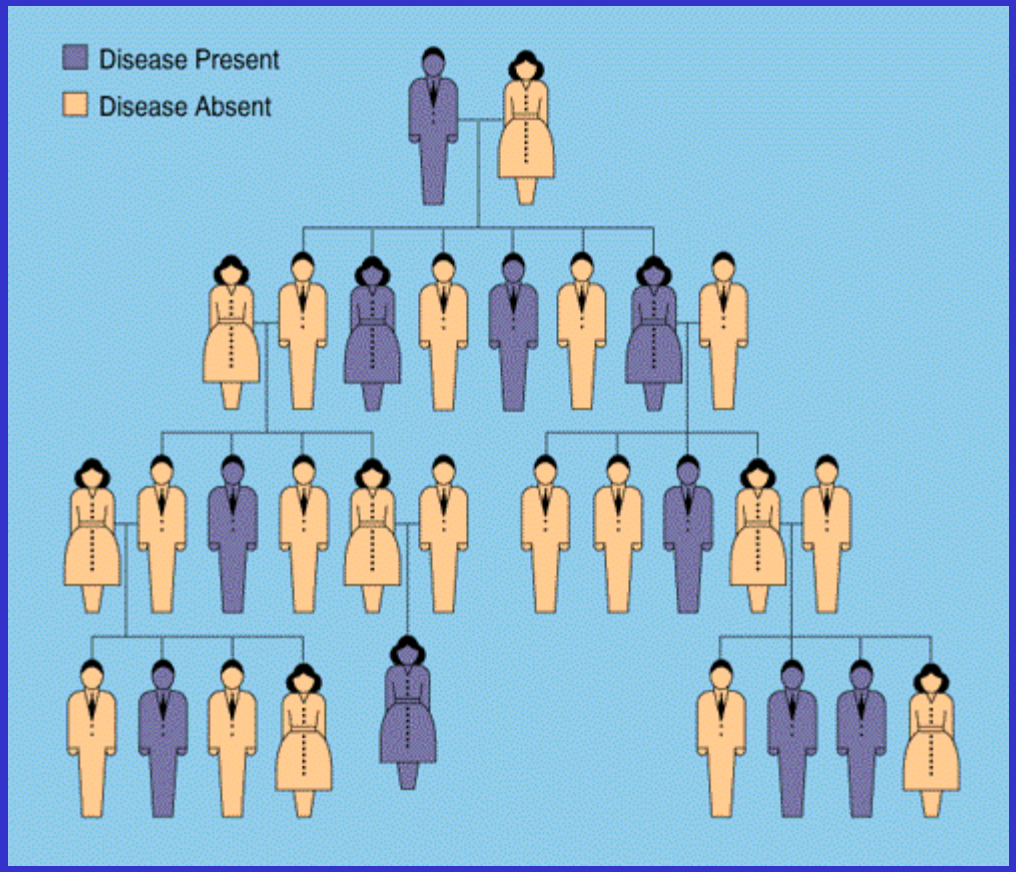
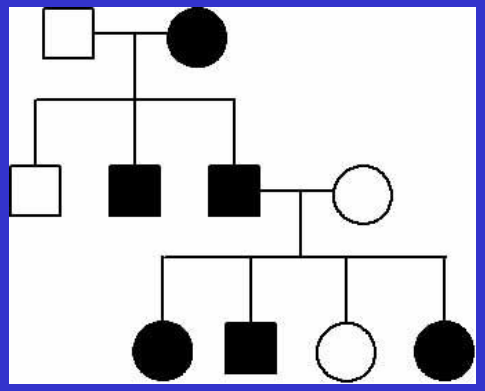
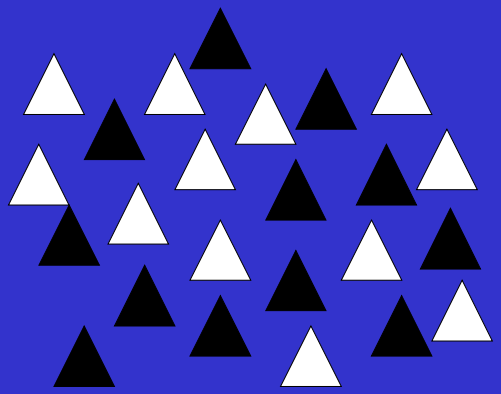
Examine the human genome in patients with diabetes to see if a particular gene is always defective – linkage analysis in families, association studies in patient cohorts



Family with type 1 diabetes (●)

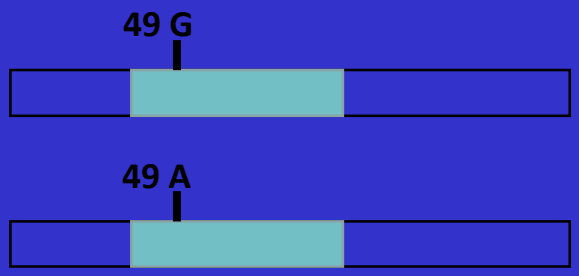


Patients with type 1 diabetes (▲)



100% diabetic family members ● ■

100% non-diabetic family members ○ □



CTLA4 gene
Chromosome 2

20% diabetic patients ▲

80% diabetic patients ▲

100% non-diabetic patients △

Linkage analysis shows that all of the members of this family that have type 1 diabetes have inherited the G polymorphism (mutation)

Association shows that a significant number (20%) of type 1 diabetic patients have the G polymorphism (mutation)

The CTLA4 gene produces a protein that inhibits the T-lymphocytes (white blood cells) that cause autoimmune destruction of the beta cells that secrete insulin. Thus polymorphisms in the CTLA4 gene could predispose to type 1 diabetes. Linkage and association analysis of chromosome suggest this.

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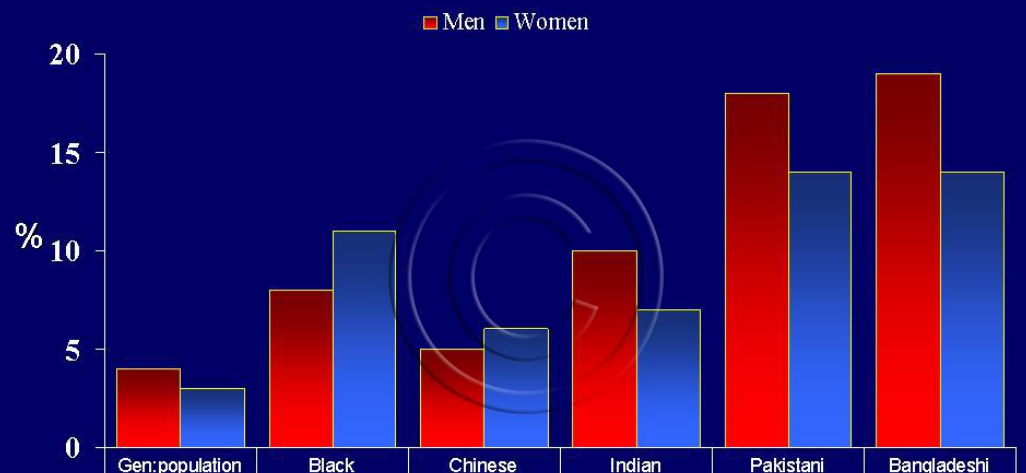
Ethnic minorities have thrifty genes that predispose to obesity and diabetes

High risk. Compared to the Pima Indians of the early 1900s (*above*), those of today (*right*) have a much more serious obesity problem—and the highest incidence of diabetes in the world.

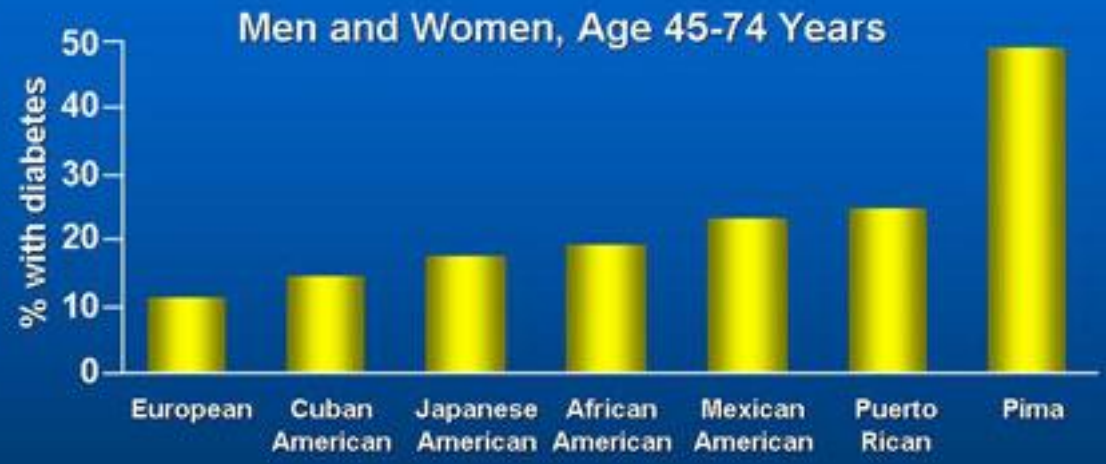
Prevalence of Diagnosed Diabetes by Ethnicity in UK (1999)



	Gen:population	Black	Chinese	Indian	Pakistani	Bangladeshi
Men	4	8	5	10	18	19
Women	3	11	6	7	14	14

www.heartstat.org

US Diabetes Prevalence by Ethnic Group



The increase in childhood obesity has revealed some children with genetic differences that make them develop type 2 diabetes at a young age MODY = Maturity Onset Diabetes in the Young

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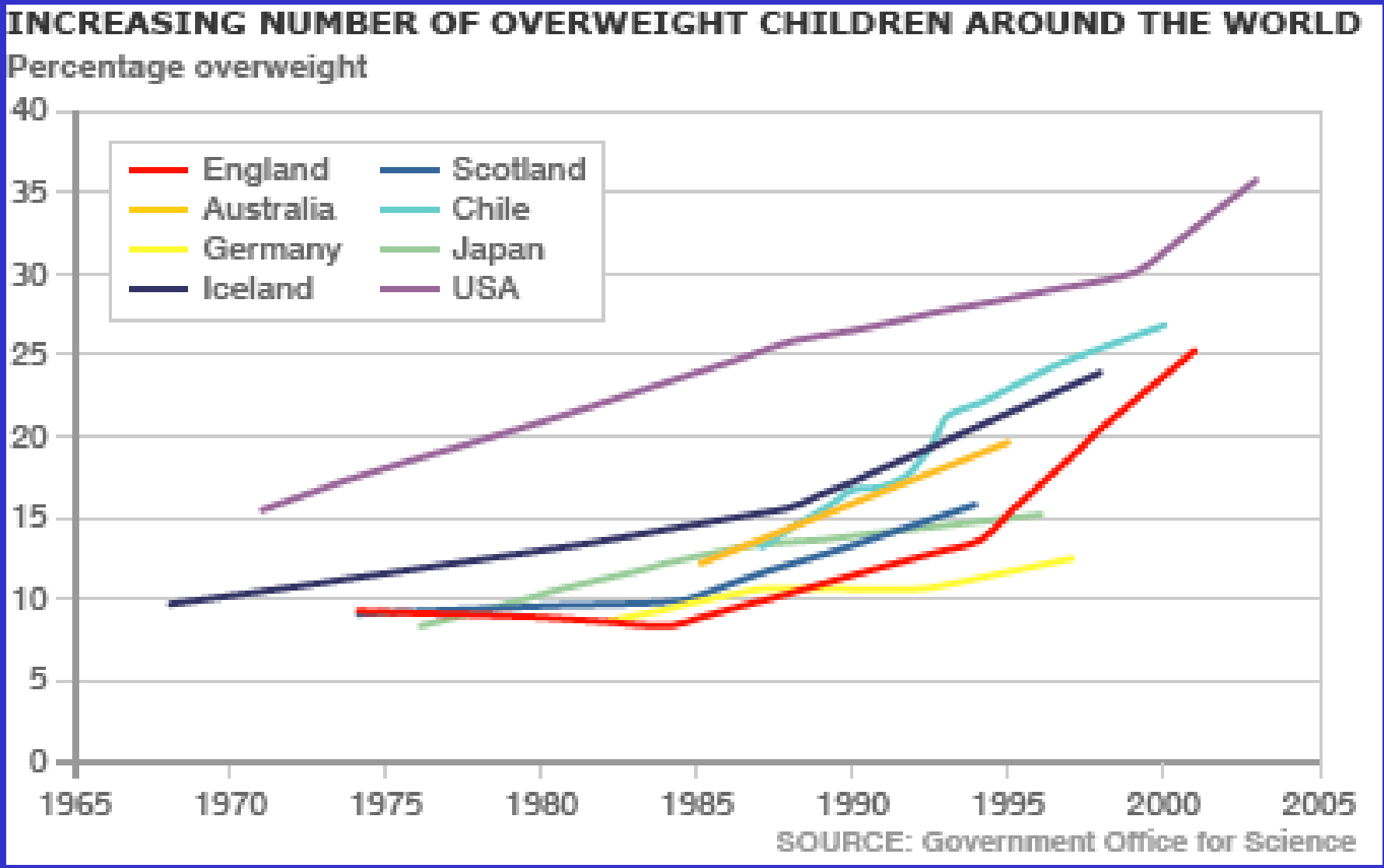


Diabetes genes code for proteins that influence either

insulin secretion

or

insulin sensitivity

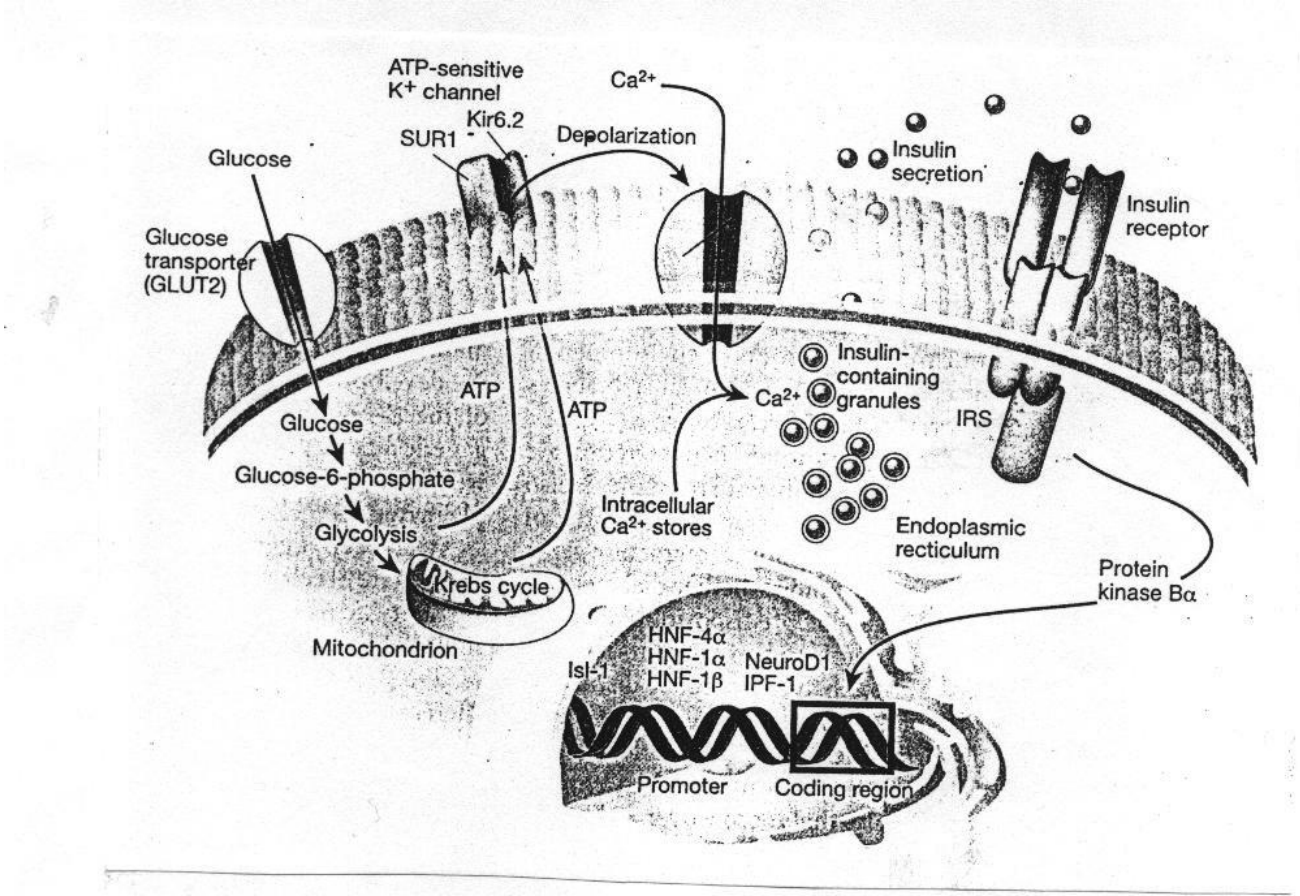
SOME CANDIDATE DIABETES 2 GENES

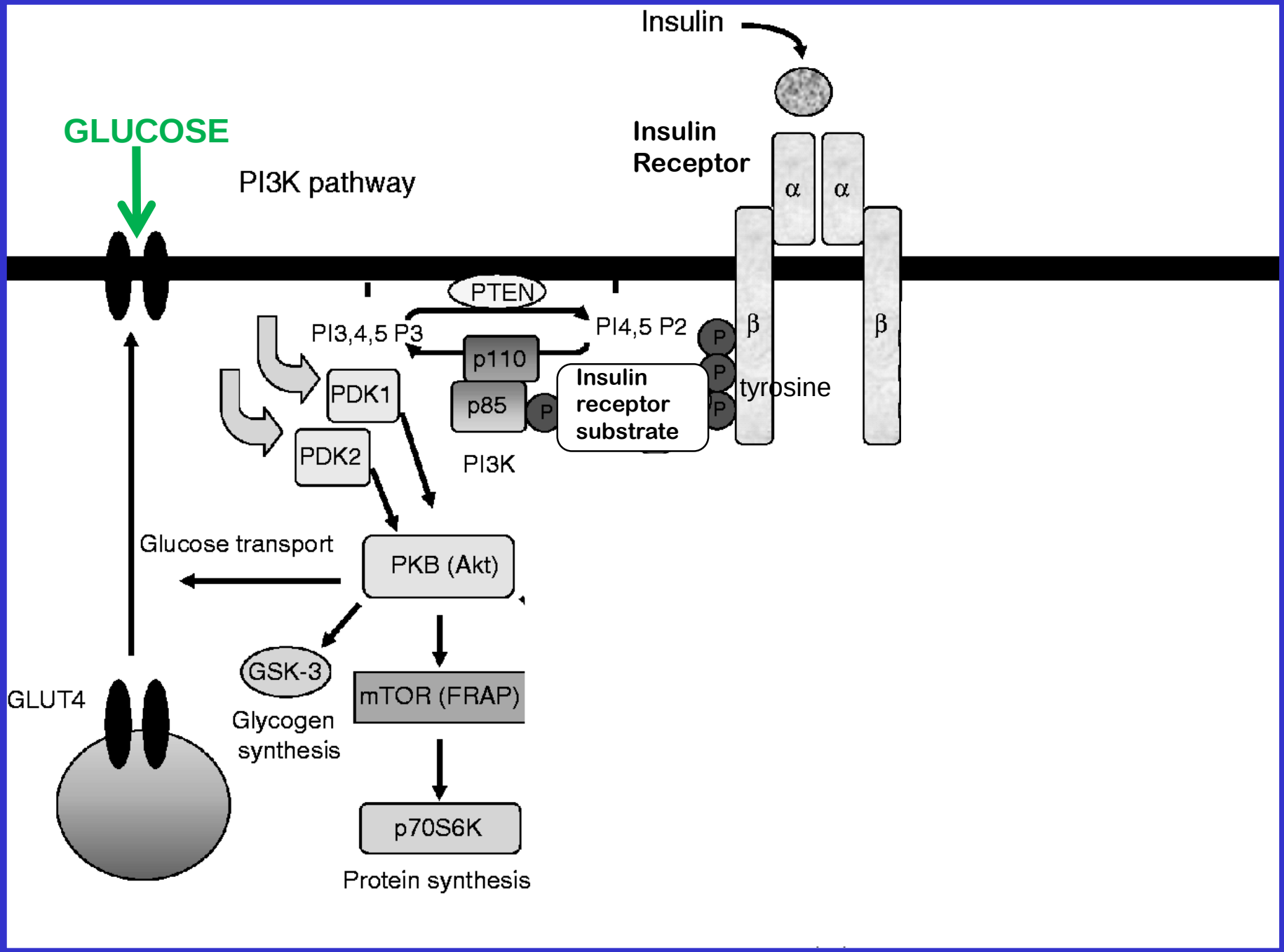
Mutated Gene	Function	Effect	Linked to
HNF-4-α, HNF-1-β IPF-1, NeuroD1	Transcription factors	↓Insulin secretion	MODY (human)
HNF-1-α	Transcription factor	↓Insulin secretion	MODY Oji-Cree diabetes
Glucokinase	Glucose metabolism	↓Insulin secretion	MODY
Calpain-10	Protease	Unknown	Diabetes 2 in Mexican and African Americans
PPAR-γ	Transcription factor	↓ Insulin sensitivity	Diabetes 2
Insulin receptor	Transmits insulin signals into cell	↓ Insulin sensitivity and secretion	Human diabetes (rare); mouse models
IRS1 and -2	Insulin signaling	↓ Insulin sensitivity	Mouse models
Akt2	Insulin signaling	↓ Insulin sensitivity	Mouse models
11-β-HSD	Glucocorticoid synthesis	↑ Blood lipids, ↓ insulin sensitivity	Mouse models
UCP2	↓ ATP synthesis	↓ Insulin secretion	Mouse models
Resistin	Fat cell "hormone"	↓ Insulin sensitivity	Mouse studies
Adiponectin	Fat cell "hormone"	↑ Insulin sensitivity	Mouse, human studies

Insulin Secretion

Glucose enters the β-cell via the GLUT 2 transporter. Glucokinase phosphorylates glucose to glucose-6-phosphate and commits it to metabolism. ATP is produced which closes ATP-sensitive K+ channels provoking membrane depolarisation that opens voltage-dependent Ca2+ channels. The Ca2+ influx releases intracellular stores of insulin by exocytosis.

Insulin binds to insulin receptors on the β-cell and stimulates transcription of the insulin gene and genes encoding proteins involved in glucose metabolism. Transcription factors implicated in this control include HNF-1, IPF-1 and NeuroD1.




Insulin
GLUCOSE
Insulin Receptor
PI3K pathway
α
α
β
β
PTEN
PI3,4,5 P3
PI4,5 P2
P
P
P
p110
p85
Insulin receptor substrate
tyrosine
PDK1
PDK2
PI3K
Glucose transport
PKB (Akt)
GSK-3
Glycogen synthesis
mTOR (FRAP)
p70S6K
Protein synthesis
GLUT4

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The causes of obesity:
30% of obesity is genetic but there is a large input from environment eg. diet

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Obesity is really all about calorie intake!!!

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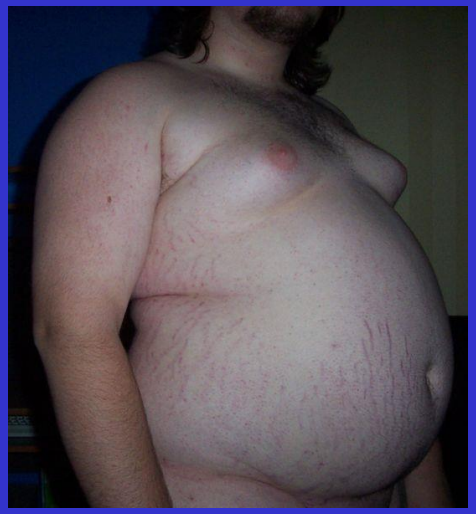
Why does **obesity** result in **type 2 diabetes**?

Waist circumference is a marker for adiposity (number and size of fat-storing cells called adipocytes).

Abdominal fat is associated with high blood levels of fatty acids and these cause insulin resistance and type 2 diabetes.



The adipocytes here are large and very metabolically active and release a lot of free fatty acids into the blood.

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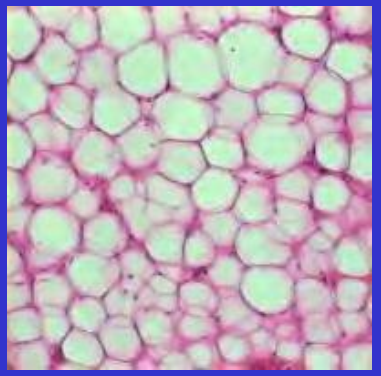


Adipose tissue

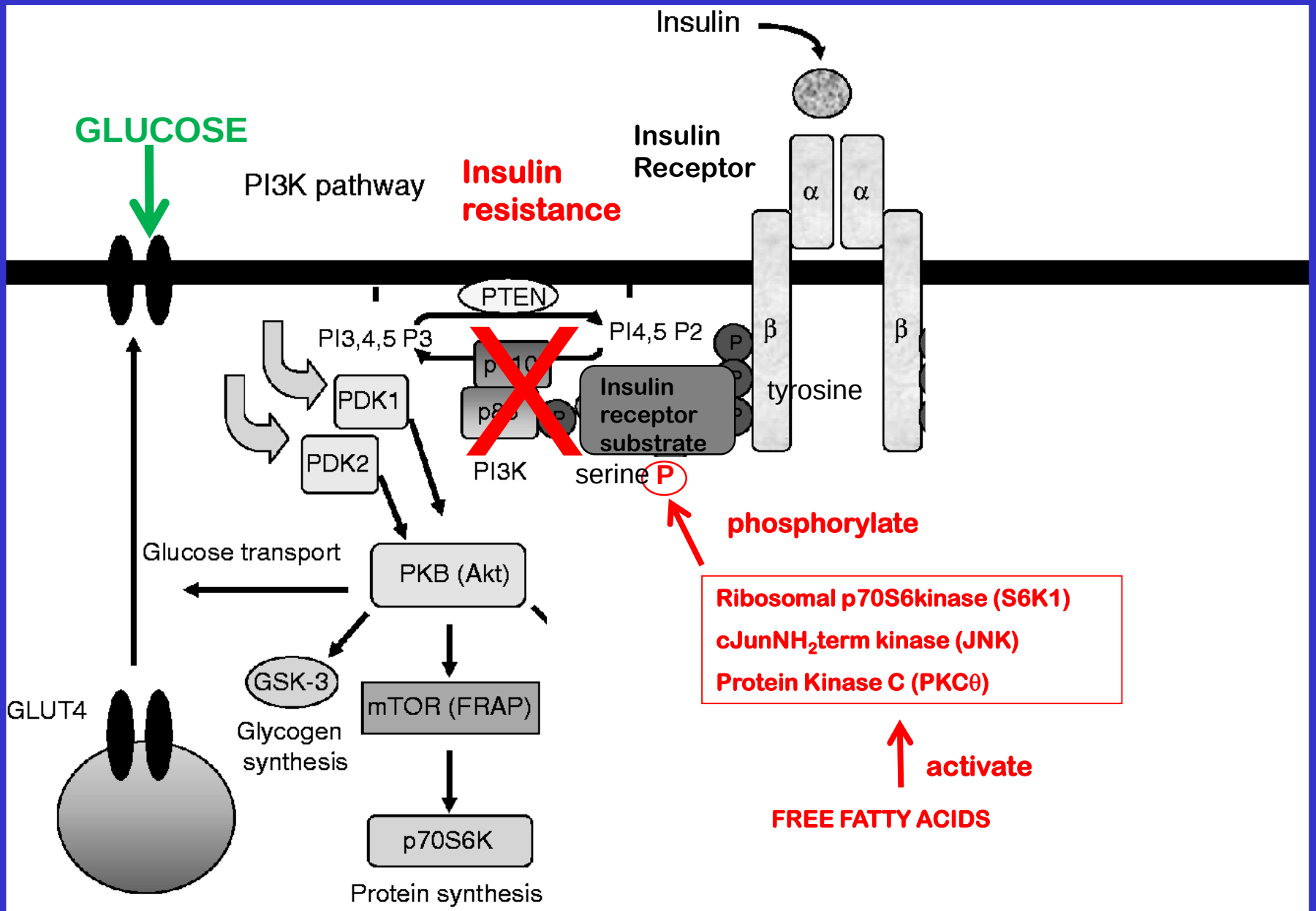
Fat stores

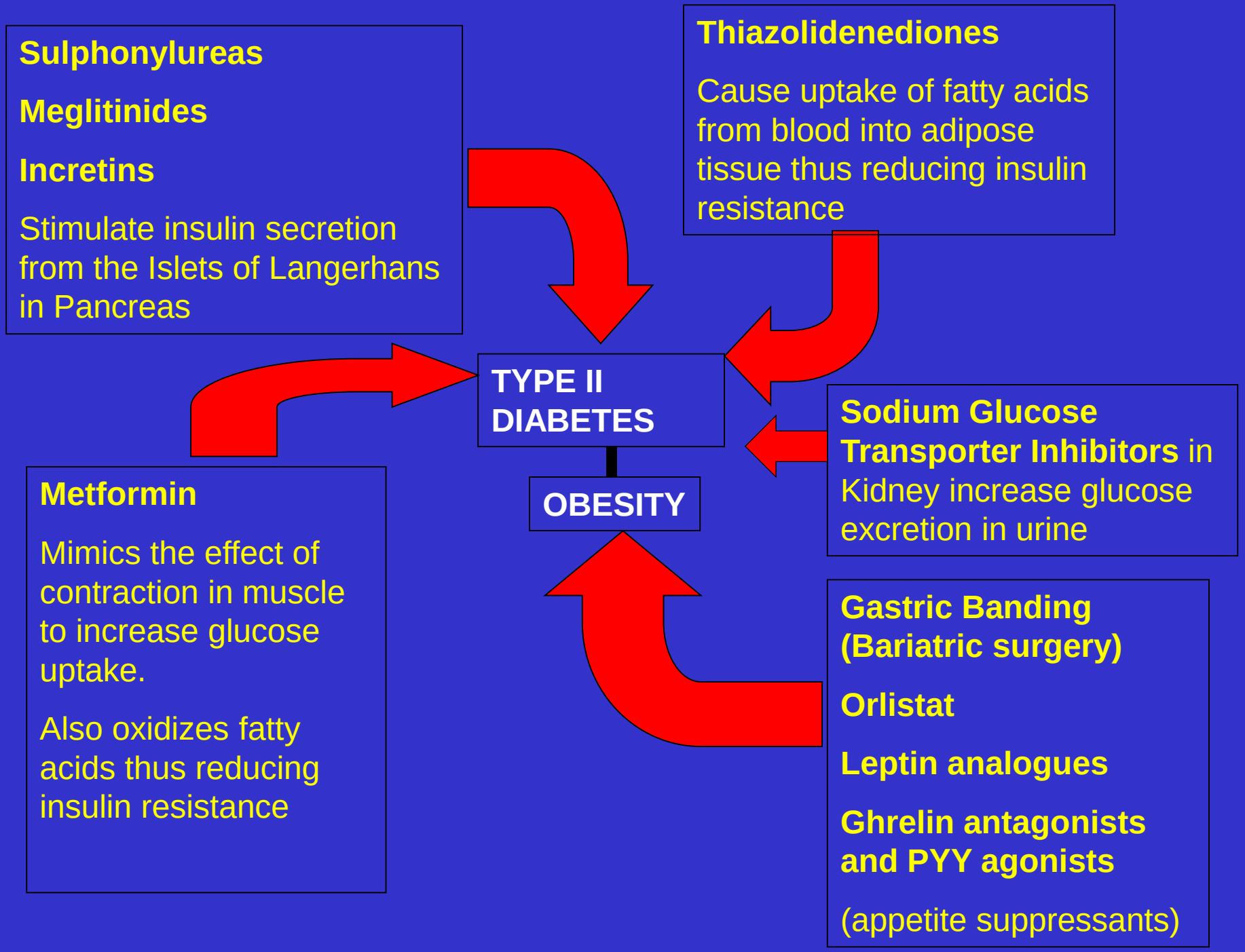
Plasma free fatty acids

Toxic to insulin secretory cells of pancreas and therefore decrease insulin secretion

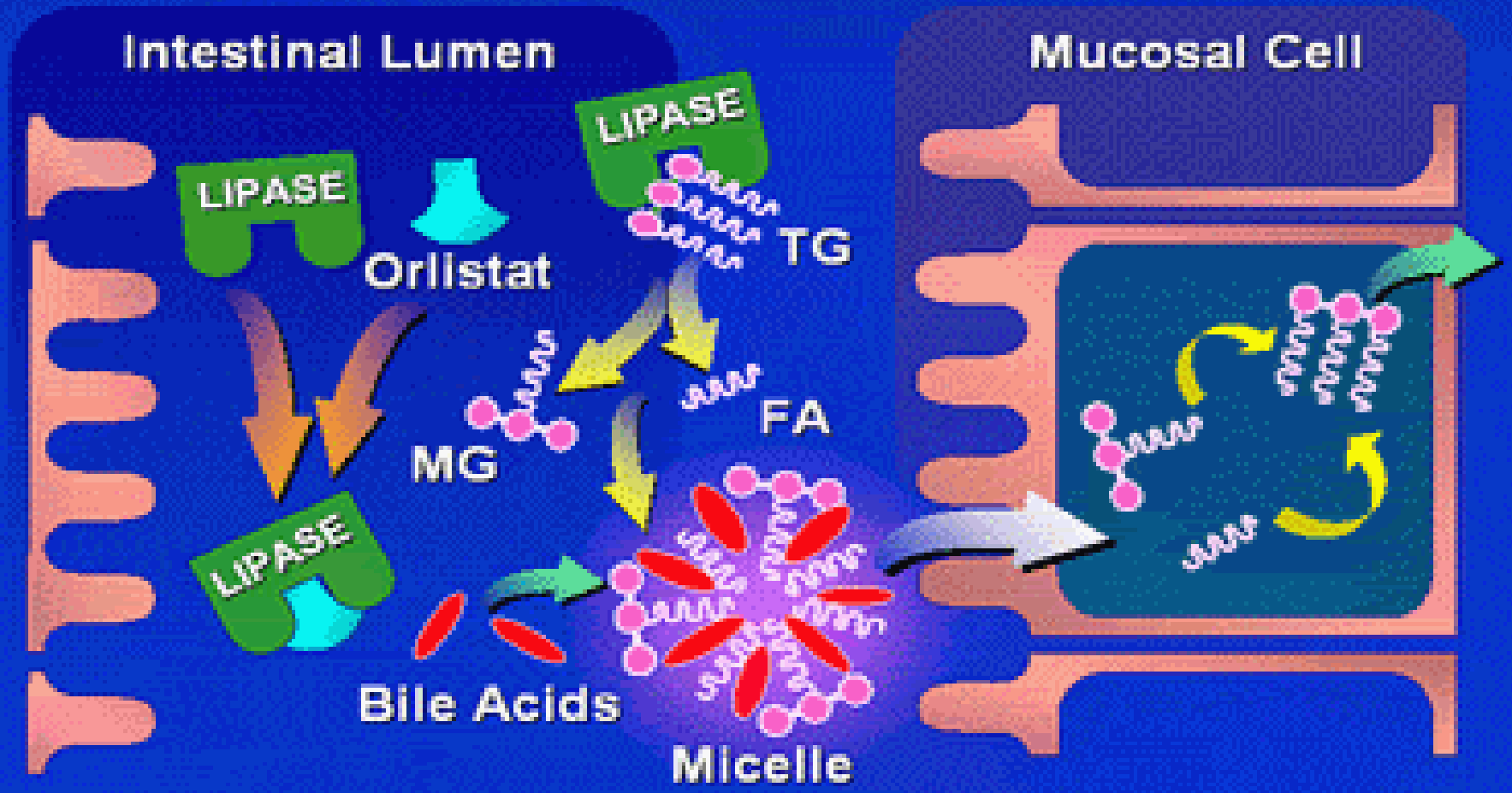
Type 2 diabetes

Inhibit the insulin signalling pathway in tissues such as muscle and therefore produce insulin resistance in muscle


Insulin
GLUCOSE
Insulin Receptor
PI3K pathway
Insulin resistance
α
α
β
β
PTEN
PI3,4,5 P3
PI4,5 P2
PDK1
PDK2
PI3K
Insulin receptor substrate
tyrosine
serine P
phosphorylate
Glucose transport
PKB (Akt)
Ribosomal p70S6kinase (S6K1)
cJunNH2term kinase (JNK)
Protein Kinase C (PKCθ)
GSK-3
Glycogen synthesis
mTOR (FRAP)
GLUT4
activate
FREE FATTY ACIDS
p70S6K
Protein synthesis


Sulphonylureas
Meglitinides
Incretins
Stimulate insulin secretion from the Islets of Langerhans in Pancreas
Thiazolidenediones
Cause uptake of fatty acids from blood into adipose tissue thus reducing insulin resistance
TYPE II DIABETES
OBESITY
Sodium Glucose Transporter Inhibitors in Kidney increase glucose excretion in urine
Metformin
Mimics the effect of contraction in muscle to increase glucose uptake.
Also oxidizes fatty acids thus reducing insulin resistance
Gastric Banding (Bariatric surgery)
Orlistat
Leptin analogues
Ghrelin antagonists and PYY agonists
(appetite suppressants)

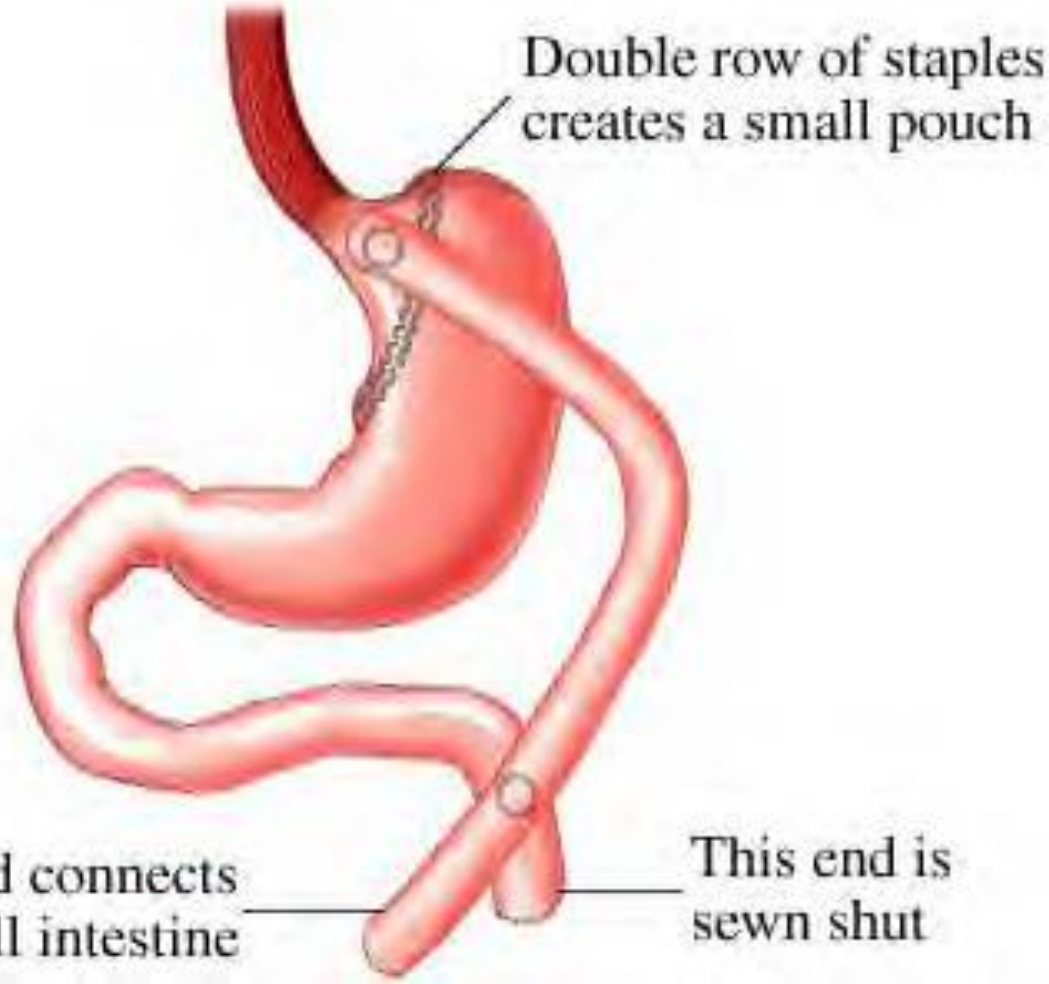
Orlistat Prevents Fat Digestion and Absorption by Binding to Gastrointestinal Lipases



TG=triglyceride; MG=monoglyceride; FA=fatty acid.

This cure works!

GASTRIC BYPASS



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Can we reduce appetite and prevent obesity?

Signals brain to stop eating

Signals brain to stop eating

Signals brain to start eating

LEPTIN is produced by adipose tissue to signal that fat stores are full

GHRELIN is produced by an empty stomach

PYY is produced by stomach when full

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The mouse on the left is unable to produce leptin, resulting in obesity.

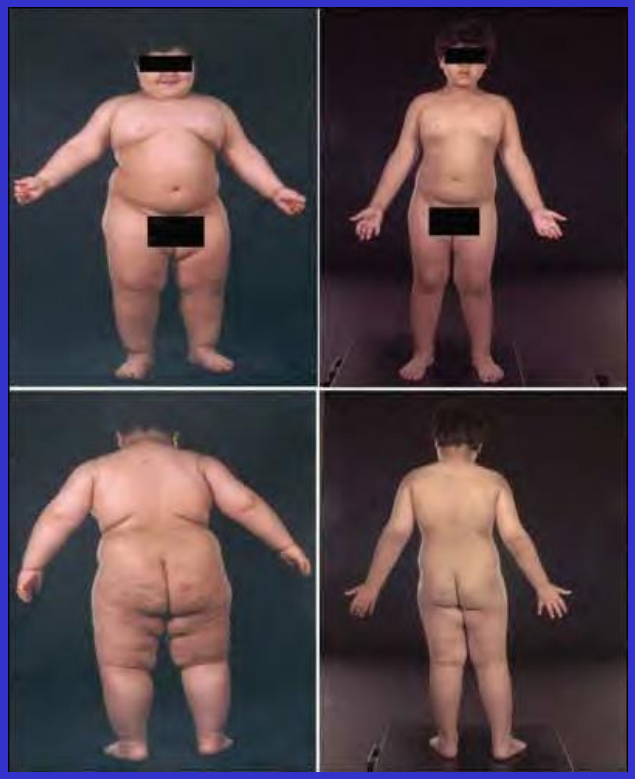
There are genetic models of obesity – the ob/ob mouse is homozygous for a mutation in the leptin gene. The fa/fa rat has a mutation in the gene for the leptin receptor

Leptin deficiency in humans is in fact rare.

Only 2 known UK cases.

Leptin administration reverses the obesity.

Human obesity actually correlates with leptin resistance – comparable to type 2 diabetes insulin resistance.



tranzyme pharma is developing TZP-301, a ghrelin antagonist for the treatment of obesity and metabolic syndrome.

AMYLIN® has developed metreleptin – a leptin analogue and agonist that is an appetite suppressant.

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FREE METRO

Ruud faces an FA ban

Tuesday October 26, 2004 www.metro.co.uk Back Page

Ronald MacDonald arrested in foiled terrorist plot to spread disease in Britain