Diabetes Mellitus

("If you know diabetes,

you know medicine.")

What is Diabetes Mellitus?

The

Final Common

Pathway of Expression of

Elevated Blood Glucose (Hyperglycemia) *where*

Small Vessel Complications = f([blood sugar],time)

Type 1 Diabetes in 1922

Figure 2 A 3-year-old child with type I diabetes mellitus, photographed in 1922 before insulin treatment was available.

Adam Morley sees his GP urgently

Dm1-onset

18 years old works with his father; delivery service
White North European

Since on holiday 2 weeks ago
always thirsty
always tired
ratty with family
dizzy after meals

Kylie Middleton calls her GP out

16 years old single mother
White North European

5 episodes of thrush infection in 3 weeks
dry mouth
depressed fed up
losing weight

tummy pain for 12 hours
now vomiting
feeling breathless

Geoffrey Barwick sees his GP

Dm1-LADA

55 years old solicitor
White North European

3 stones in weight loss over one year
having to get up at night 4 times to pass urine
calf cramps

“now that I’m here, difficulty keeping it up”

Barry Bramley is on the coronary care unit

Dm2-HASHD

53 years old builder
has been admitted with a suspected heart attack
White North European

nurses check his blood glucose: 21 mmol/L

Henrietta Allerton goes to Eye Casualty

Dm2- amaurosis fugax

73 year old Jamaican, retired nurse

notices sudden total loss of vision in the right eye

urinalysis shows protein and glucose
venous plasma glucose 14 mmol/L

Reverend Patrick Fitzcolton rings his GP

Dm-secondary

62 years old

recently developed polymyalgia rheumatica
has been taking steroid prednisolone 60mg daily

since starting these has needed to drink 20 pints/day
sermons have shortened as needs toilet every 40 minutes
misty vision

Mohammed Rawal sees the practice nurse

Dm2-FHx

28 year old Pakistani, taxi driver
his mother, father and 2 of his 3 brothers have diabetes

a customer (medical student) recommended he be checked out

blood glucose 17 mmol/L

Farhana Safraz attends the lipid clinic

31 year old Pakistani
has hypercholesterolaemia and hypertension
venous plasma glucose 11 mmol/L

75g oral glucose tolerance test:

fasting	7.3 mmol/L
2 hour	12.6 mmol/L

"What selfevident enigma pondered with desultory constancy during 30 years did Bloom now, have effected natural obscurity by the extinction of artificial light, silently suddenly comprehend?

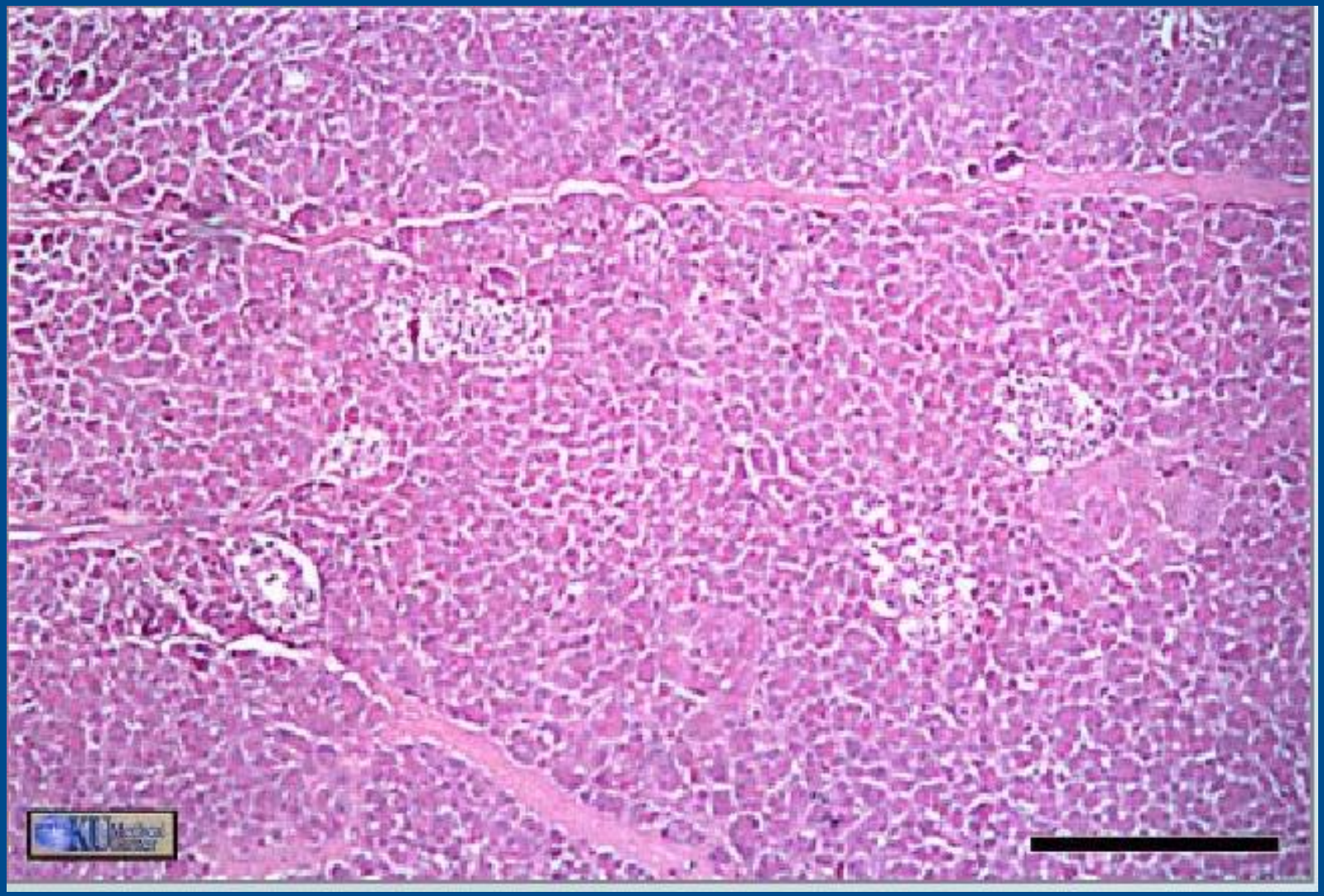
"Where was Moses when the candle went out?"

-Episode 17 (Ithaca), **Ulysses**, James Joyce

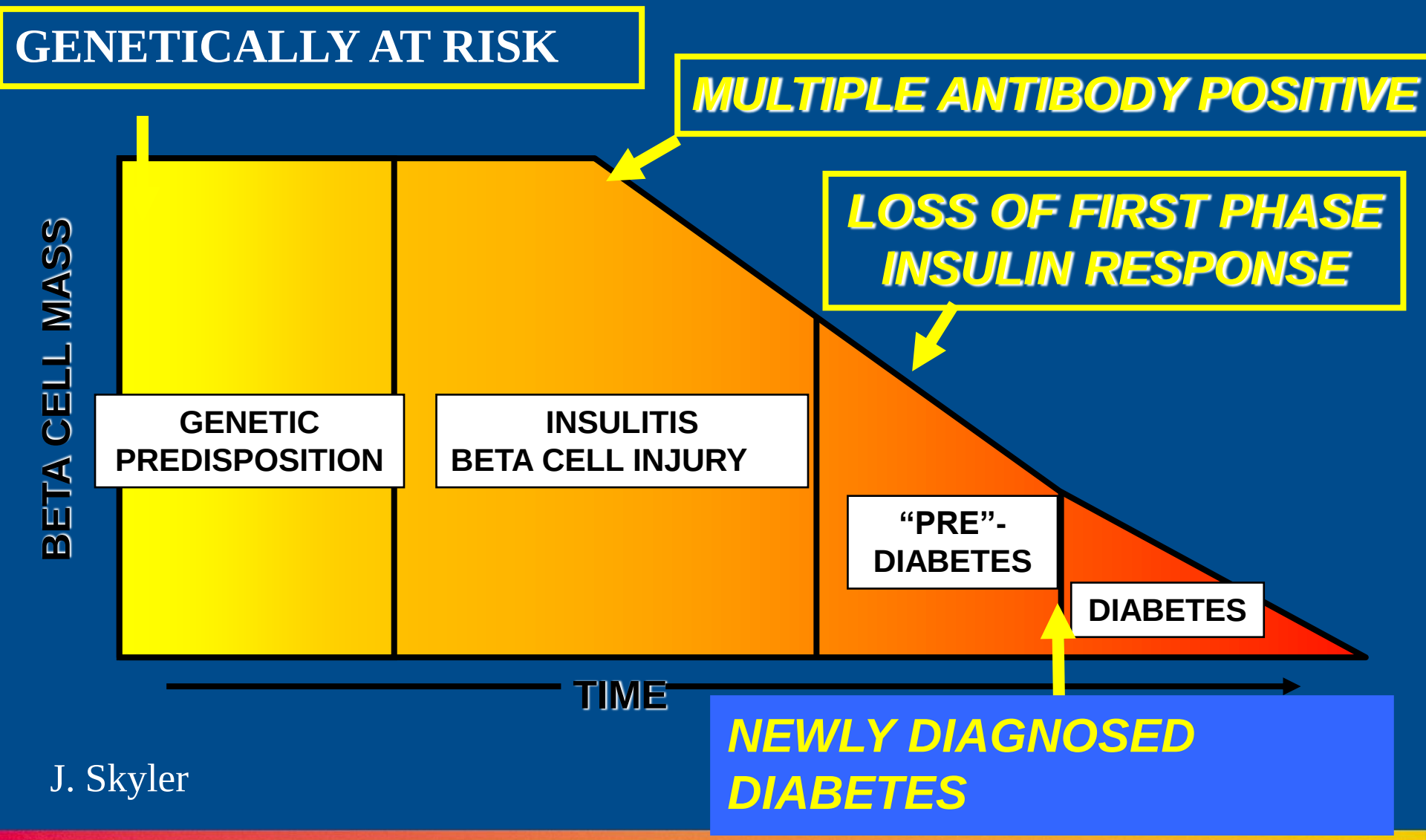
Megacepts and Caveats

- Murphy's Law can be derived from the 2nd Law of Thermodynamics - It applies quite well to genetic expression and human disease
- If a genetic "error" persists, there must be some "[*procreative*] survival" value associated with it
- From one evolutionary perspective, we are living in very anomalous times
- Fuel delivery must over-ride fuel storage
- Do we really need to know any of this?
- You may be where the light is - but not necessarily will you find the truth there ….
- Why do we always find something in the last place we look?

Normal Pancreas Histology

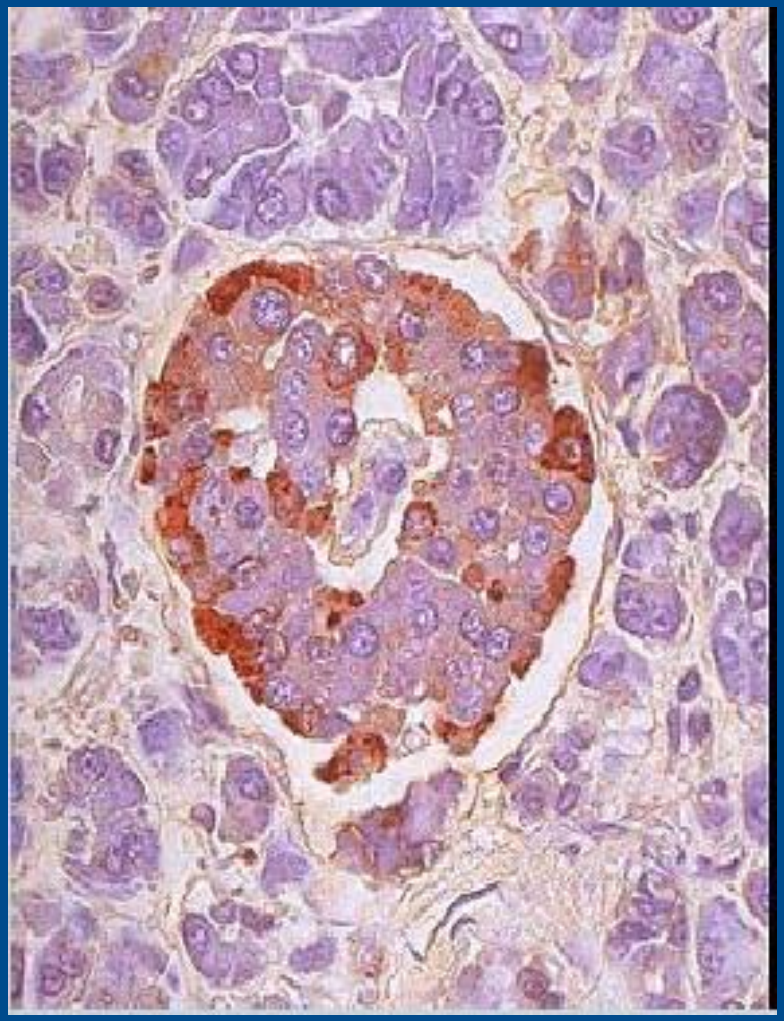


Stages in Development of Type 1 Diabetes

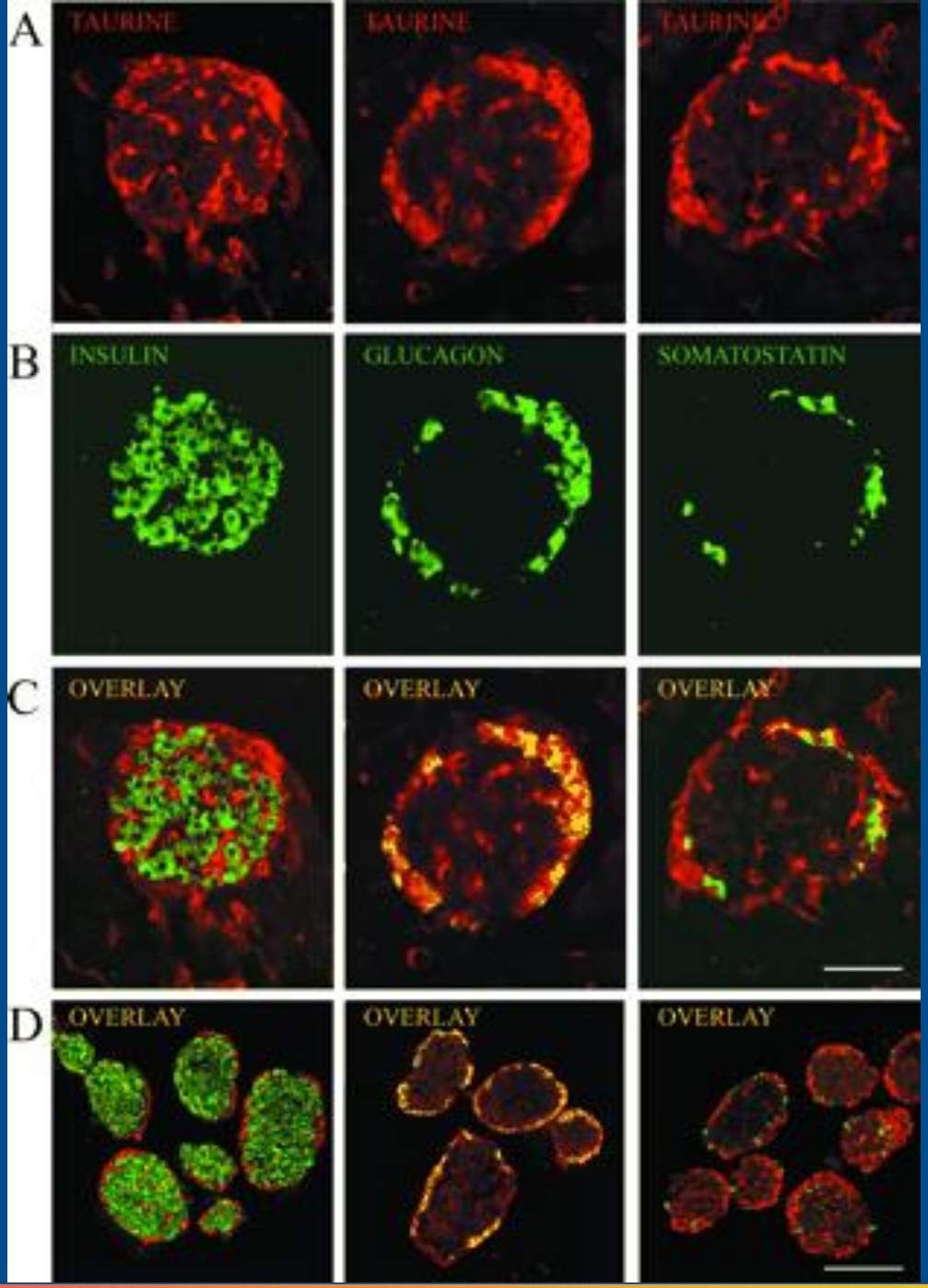


J. Skyler

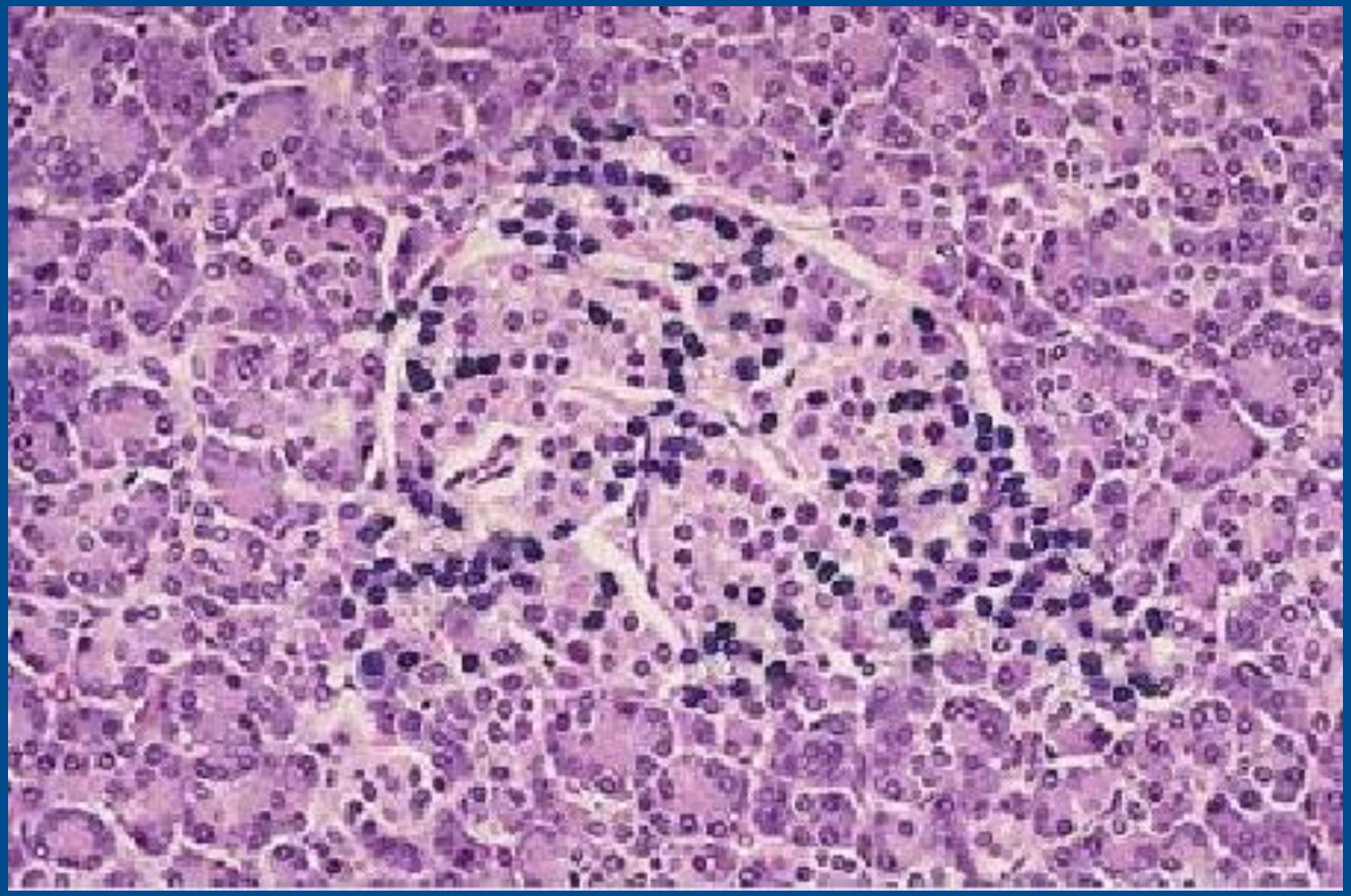
Normal Islet



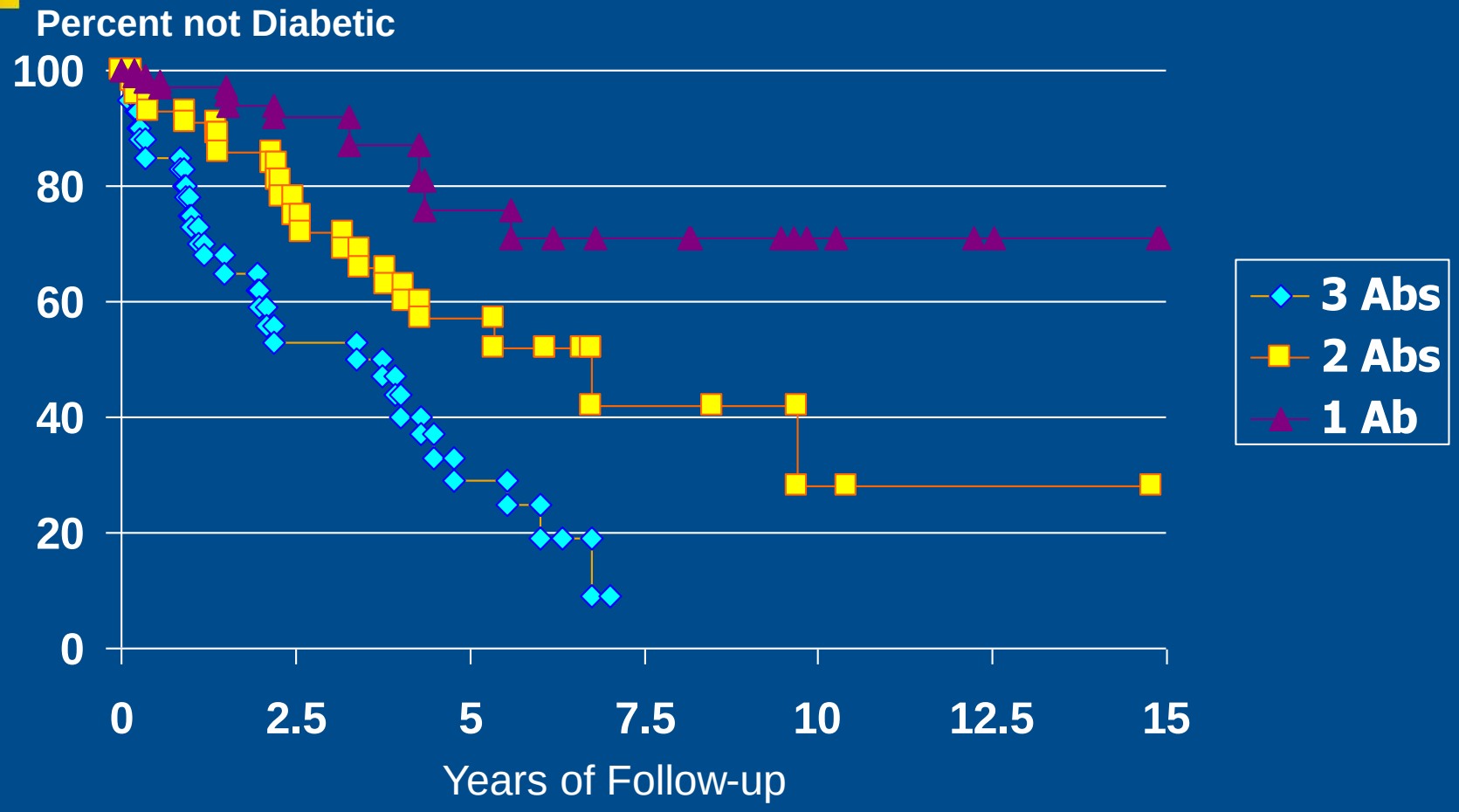
What's What and Where?



Insulitis



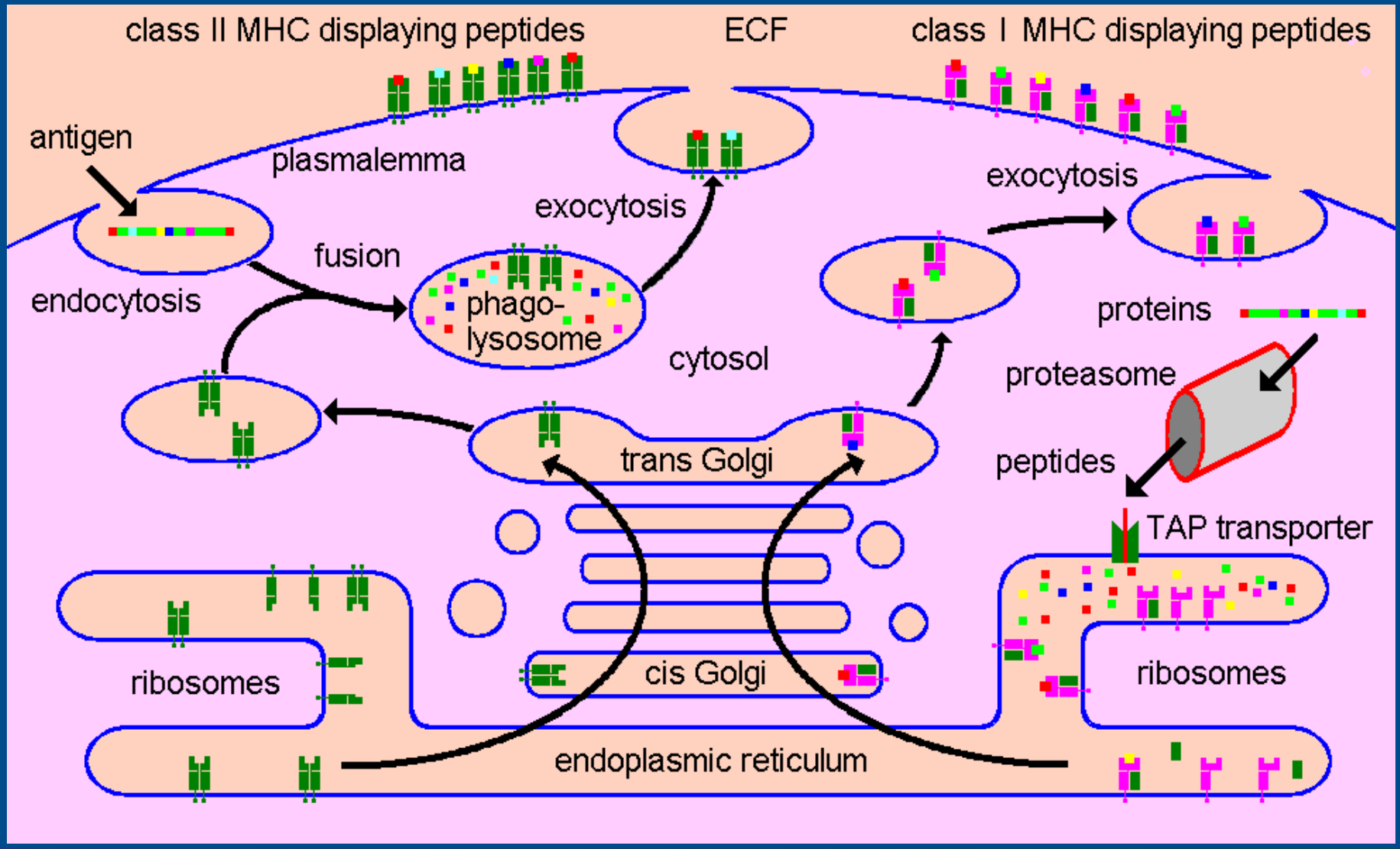
Progression to Diabetes vs Number of Autoantibodies:-GAD, ICA512, Insulin)



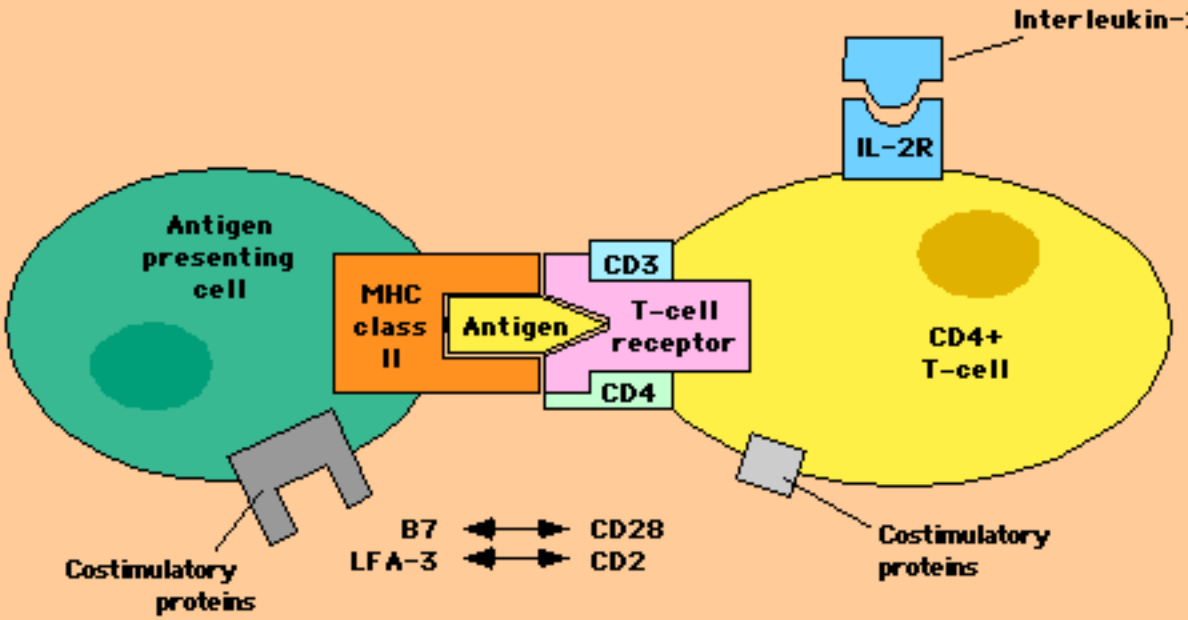
3 Ab	n = 41	17	8	1		
2 Abs	n = 44	27	15	4	2	1
1 Abs	n = 93	23	14	10	6	4

BDC

Antigen presentation

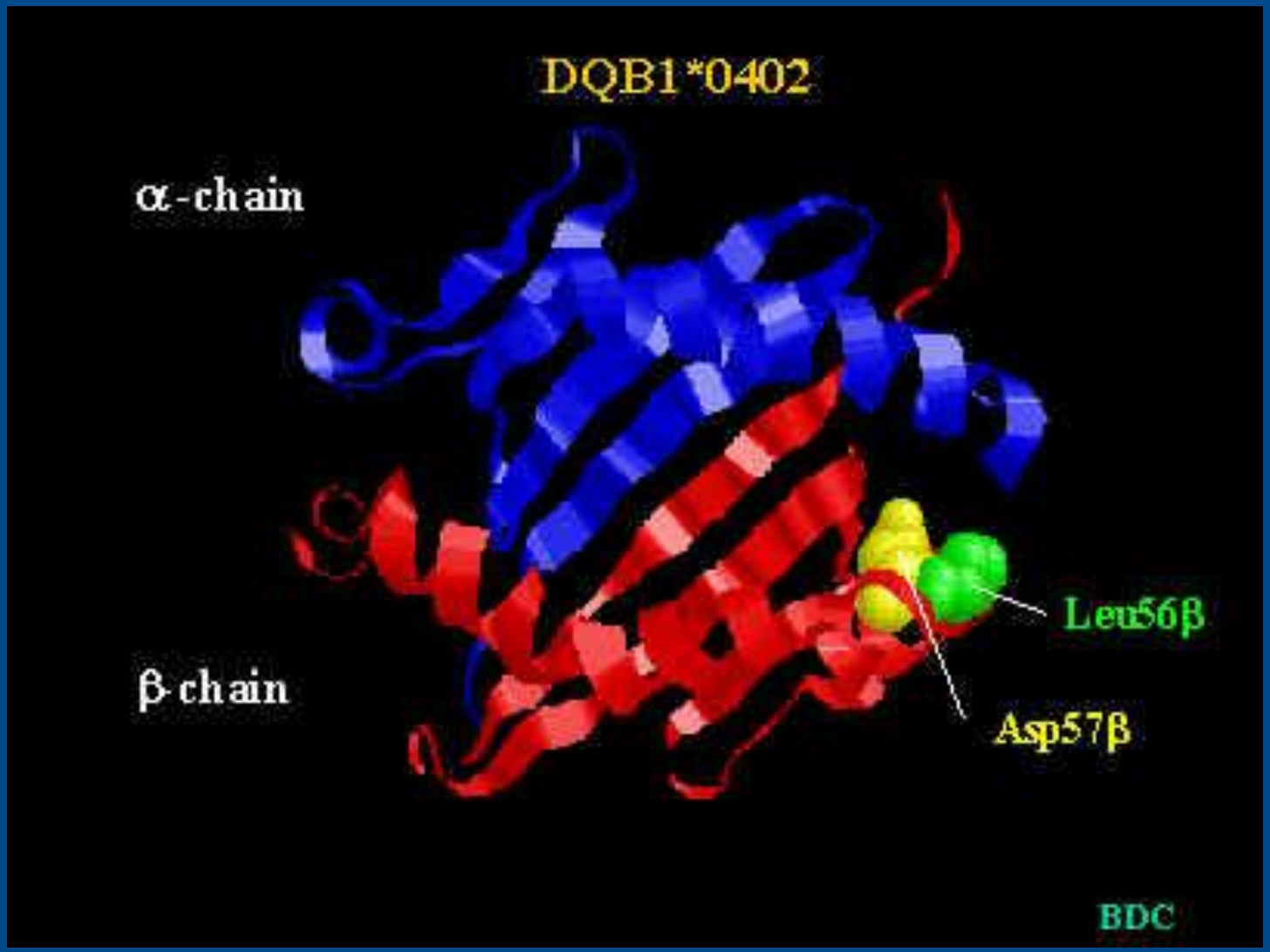


Antigen presentation-2

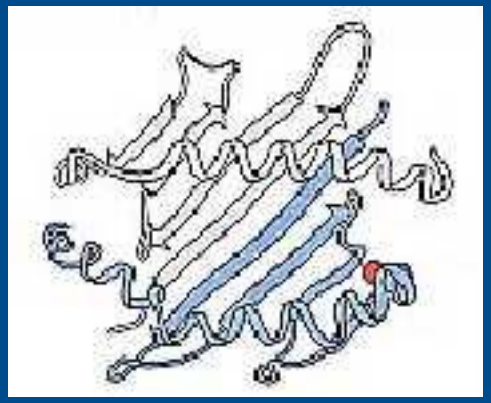


Representation of T-cell activation – Schematic representation of initiation of the immunologic response to an antigen. The antigen binds to a groove in MHC class II molecules on antigen-presenting cells (APCs, such as macrophages). This binding allows the antigen to be presented to antigen receptors on autoreactive CD4 inducer or helper T cells which, in type 1 diabetes mellitus, initiate autoimmune injury to the pancreatic ß-cells. In addition, the respective binding of B7 proteins and LFA-3 (lymphocyte functional antigen-3) on APCs to CD28 and CD2 on T cells are important **costimulatory pathways** that further increase T-cell activation. Other molecules also can participate in the immune response, such as the binding of interleukin-2 to its receptor (IL-2R).

Antigen presentation-3



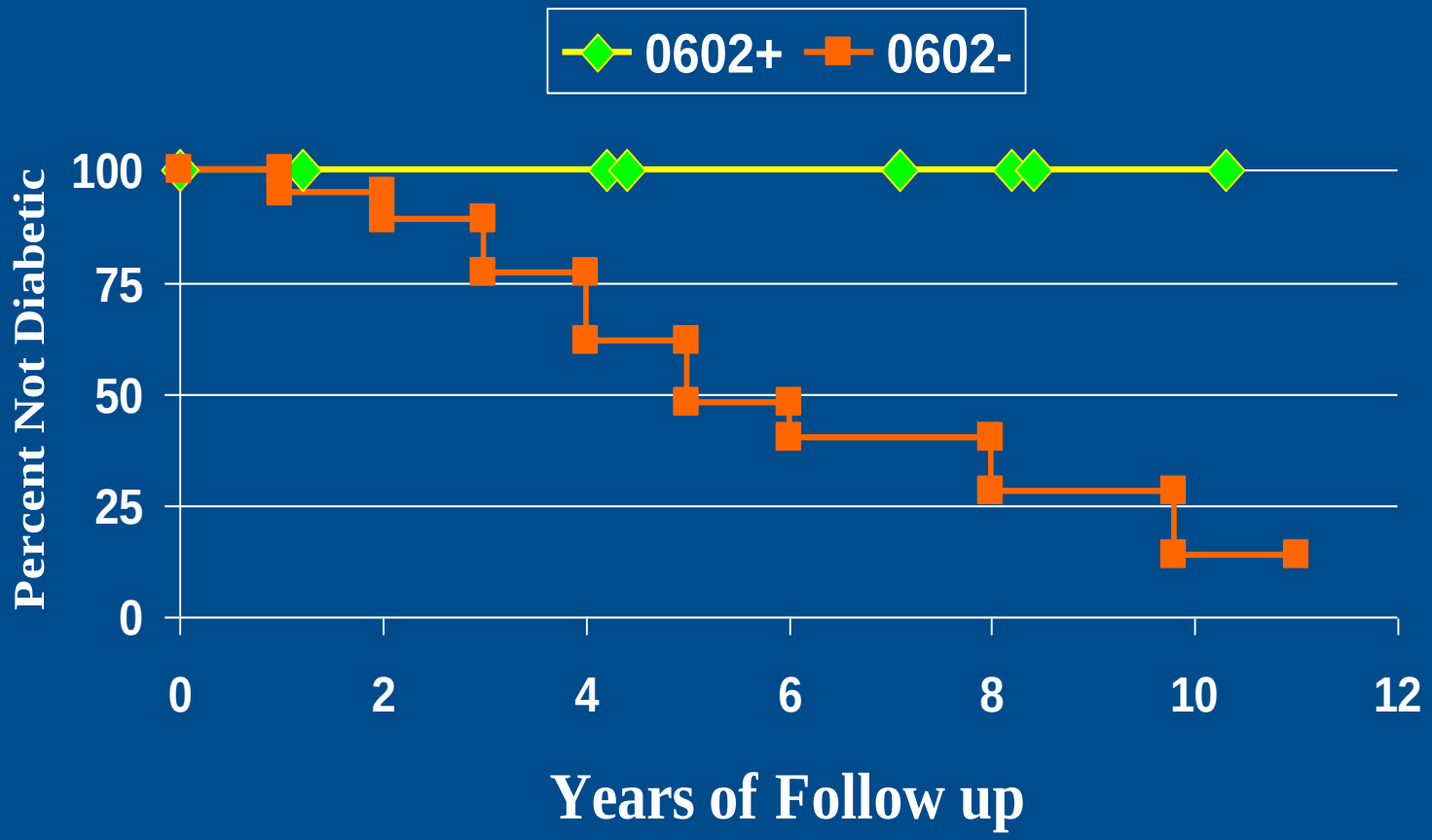
Antigen presentation-4



Asp^{57} on the DQ$_{ß}$ chain forms a salt bridge with Arg on the DQ$_{\alpha}$ chain and confers protection against insulitis

IDDM usually associates with a Ser^{57}, Val^{57}, or Ala^{57} which fails to form a salt bridge with the Arg on the DQ$_{\alpha \text{ chain}}$

Lack of Progression to DM of ICA+ 0602+ Relatives



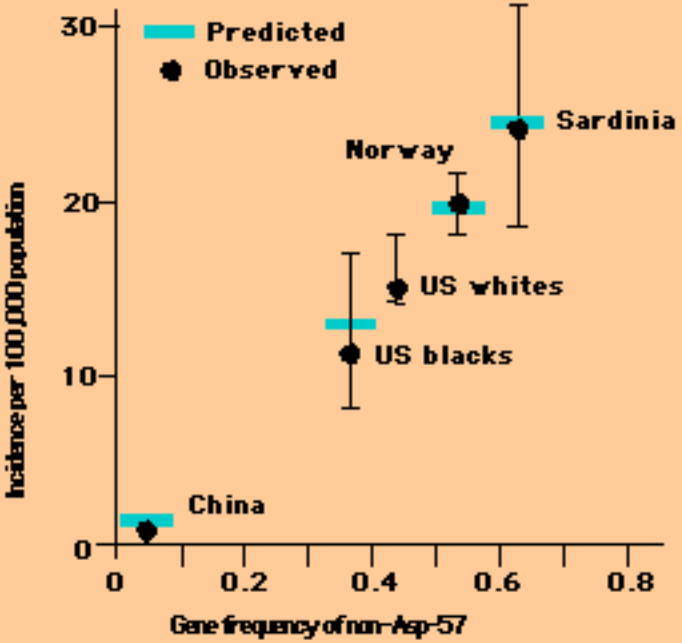
BDC

What is the selective advantage of type 1 diabetes mellitus?

Causes of type 1 diabetes

- 30% identical twin concordance rate
- prevalence increasing currently 0.5%
- in Europe prevalence increases toward north pole
- onset in childhood increasing
- childhood diabetes more prevalent in rural areas

Gene Frequencies - DQ-ß and DM-1



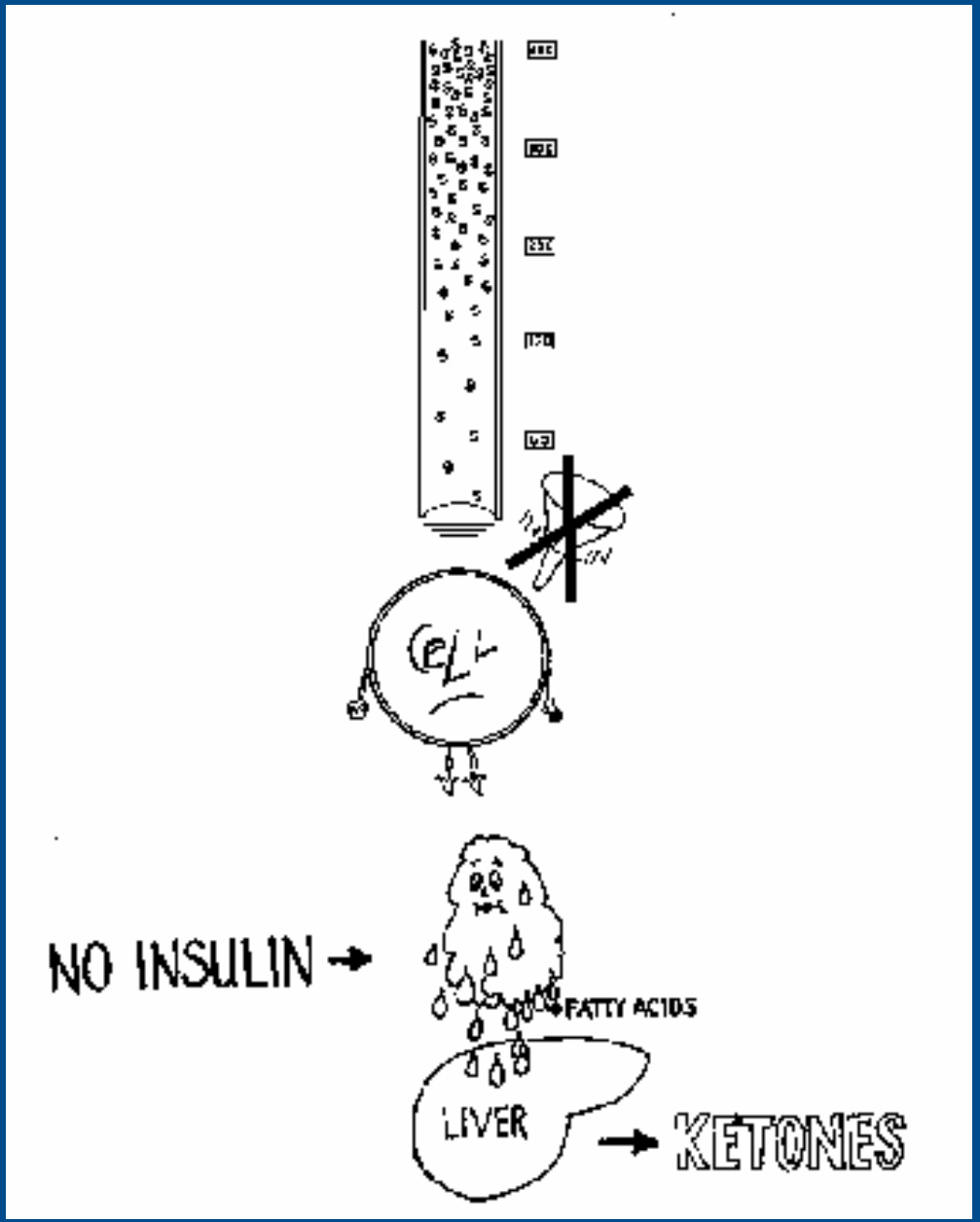
Association of type 1 diabetes with diabetogenic genes Direct correlation in different populations between the gene frequency of "diabetogenic" HLA-DQß genotypes (which lack aspartate at position 57 on the beta chain) and the predicted and observed incidence of type 1 diabetes mellitus (per 100,000 population). (Data from Dorman, JS, LaPorte, RE, Stone, RA, Trucco, M, Proc Natl Acad Sci USA 1990; 87:7370.)


Geography of Type 1 Diabetes

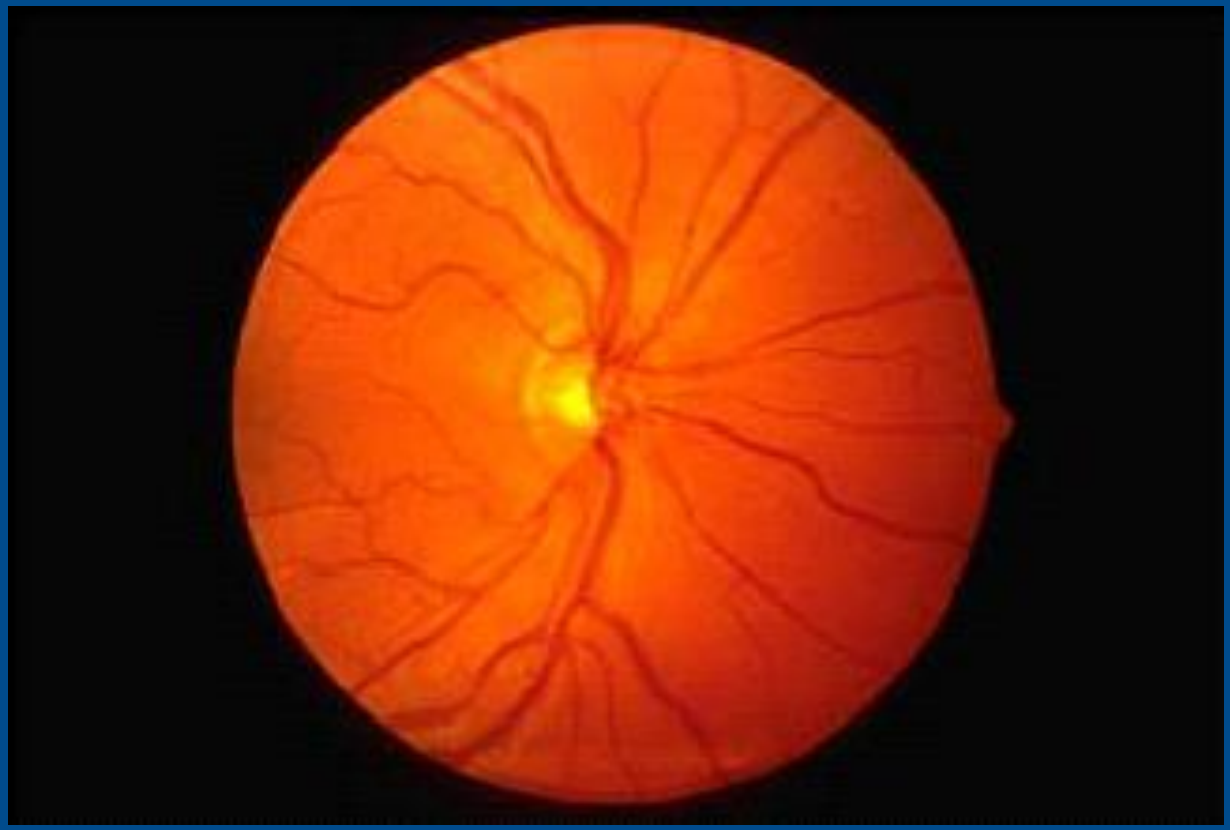
What characterizes type 1 diabetes?

- Incomplete penetrance
- Nordic predominance
- Increased glycosylation
- Increased ? depression

Type 1 Diabetes What Goes Wrong?

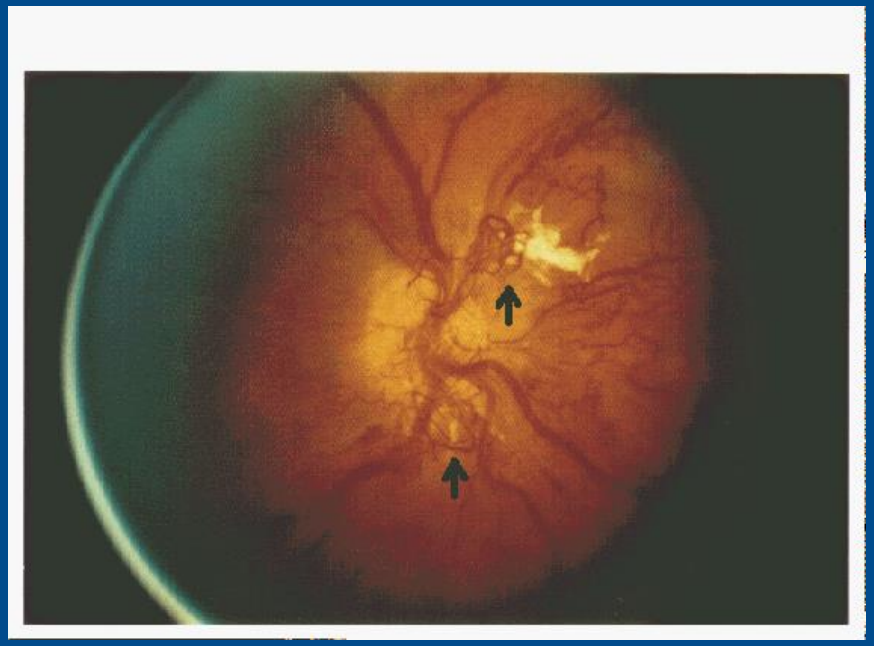


Normal Retinal Fundus

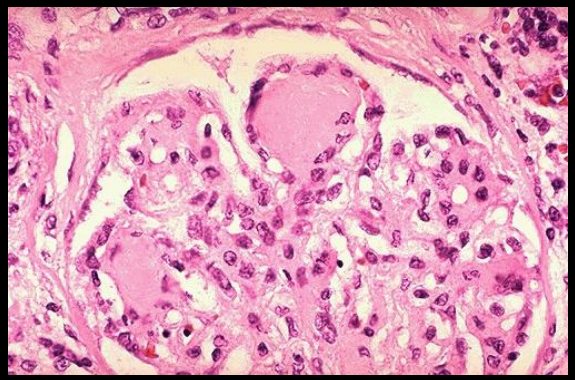


Diabetic Proliferative Retinopathy

Increased Glycosylation

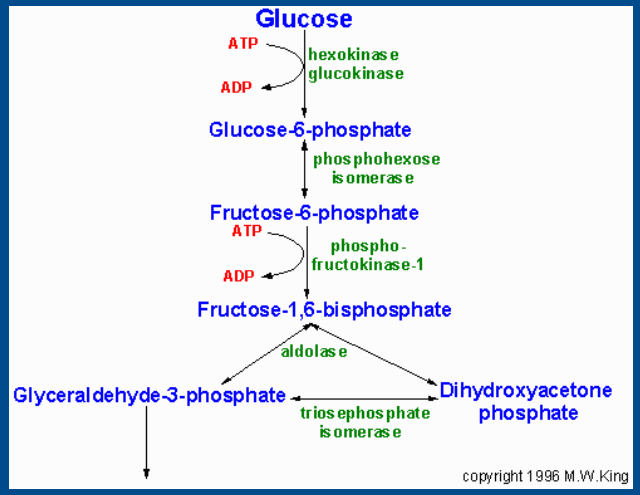


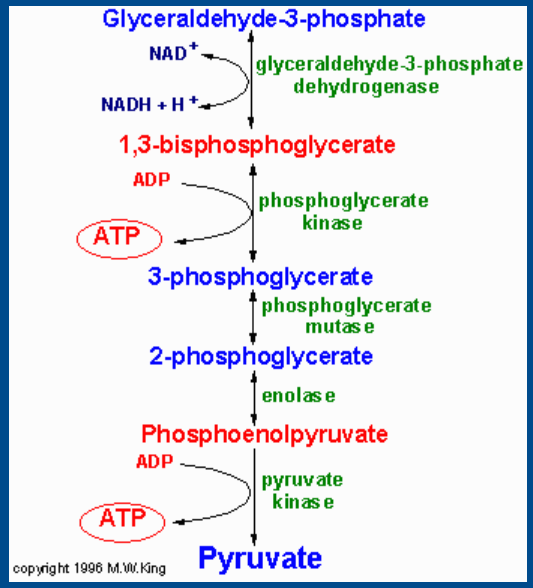
Diabetic Nephropathy



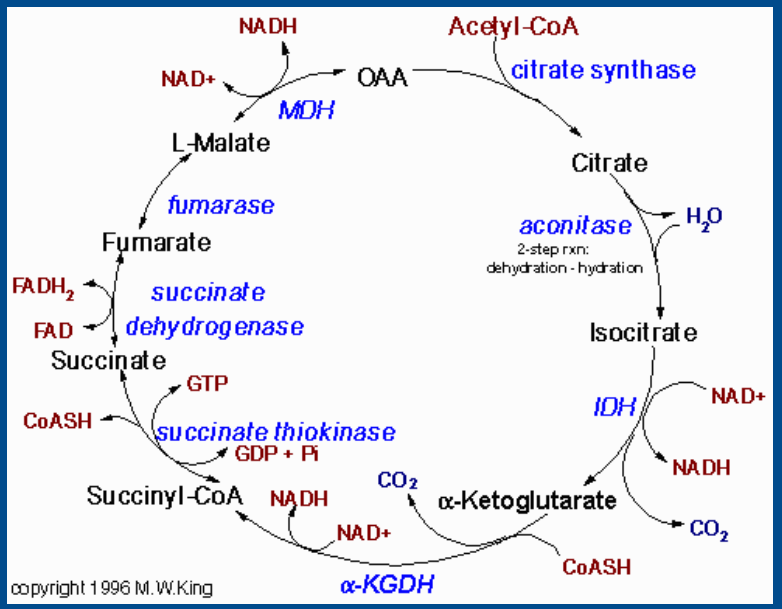
Intermediary Metabolism

Cytoplasm





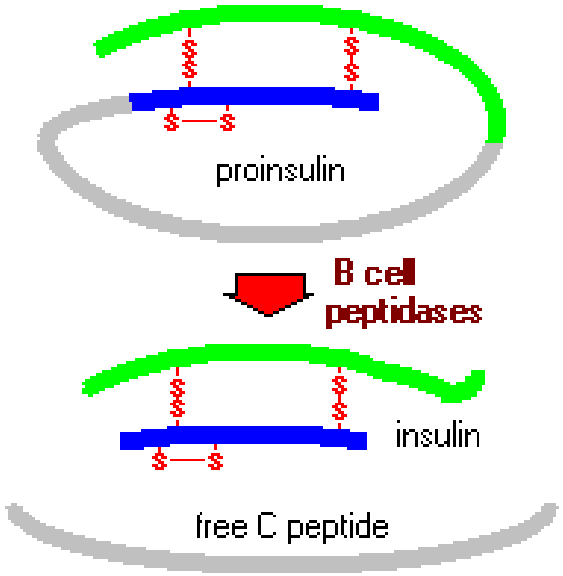
Mitochondrion

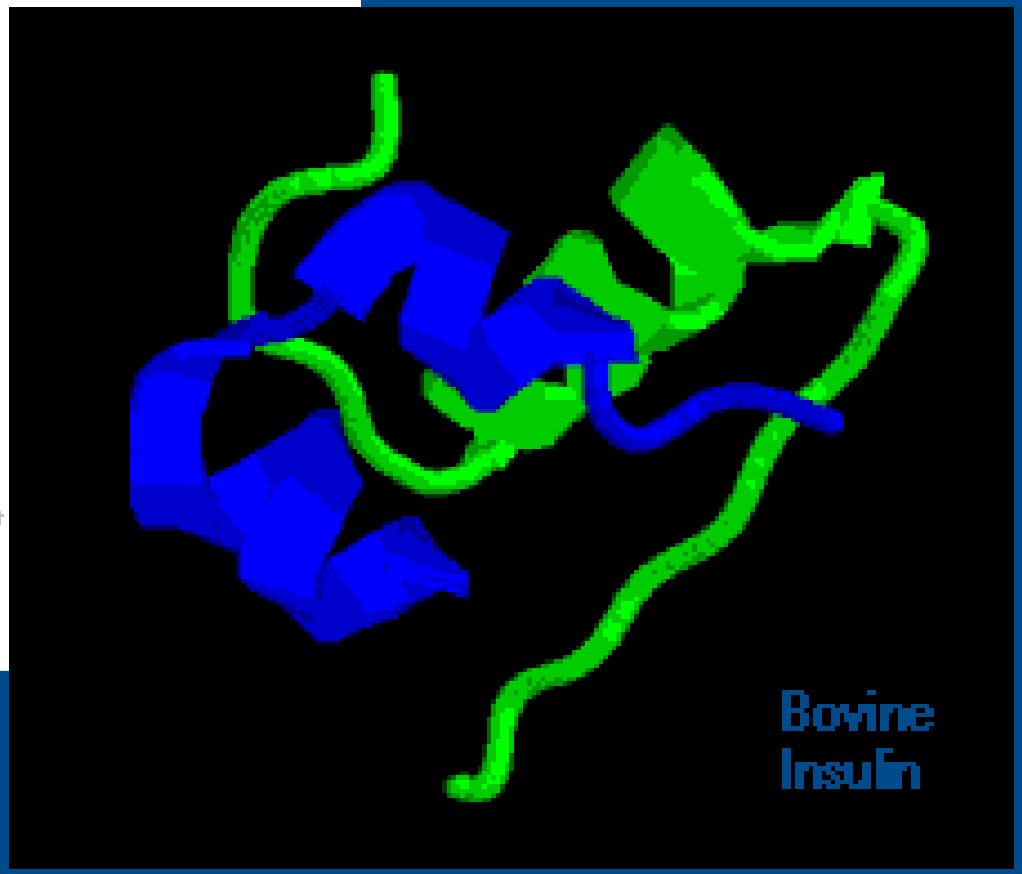


Overview-2

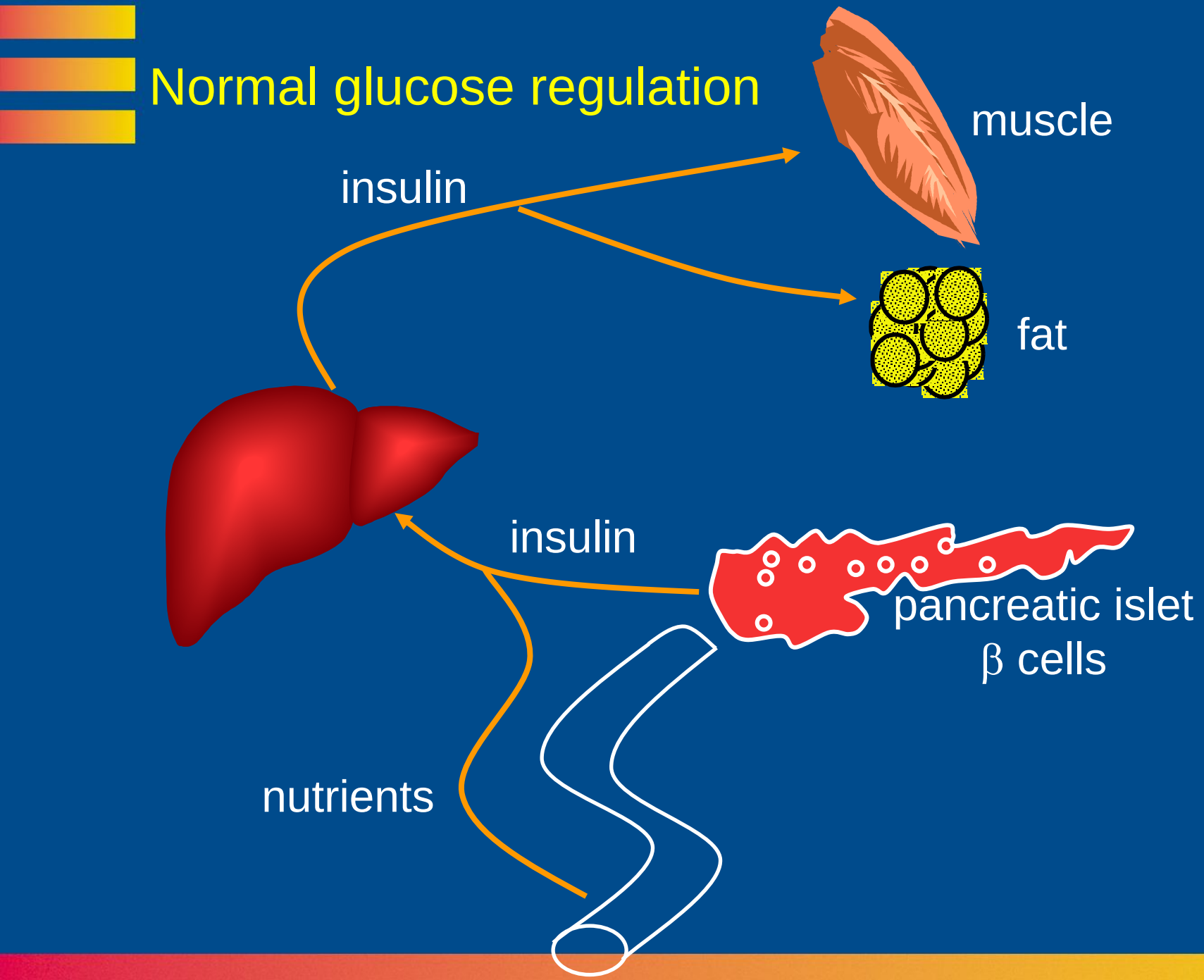
- Insulin is the major message to the various cells of the body that:-
  - The fed state has just been achieved
  - Anabolic functions may occur. i.e.,
    - Lipogenesis/Transport/Storage
    - Antagonize gluconeogenesis
    - Absorb glucose into fat and muscle and liver cells

Insulin

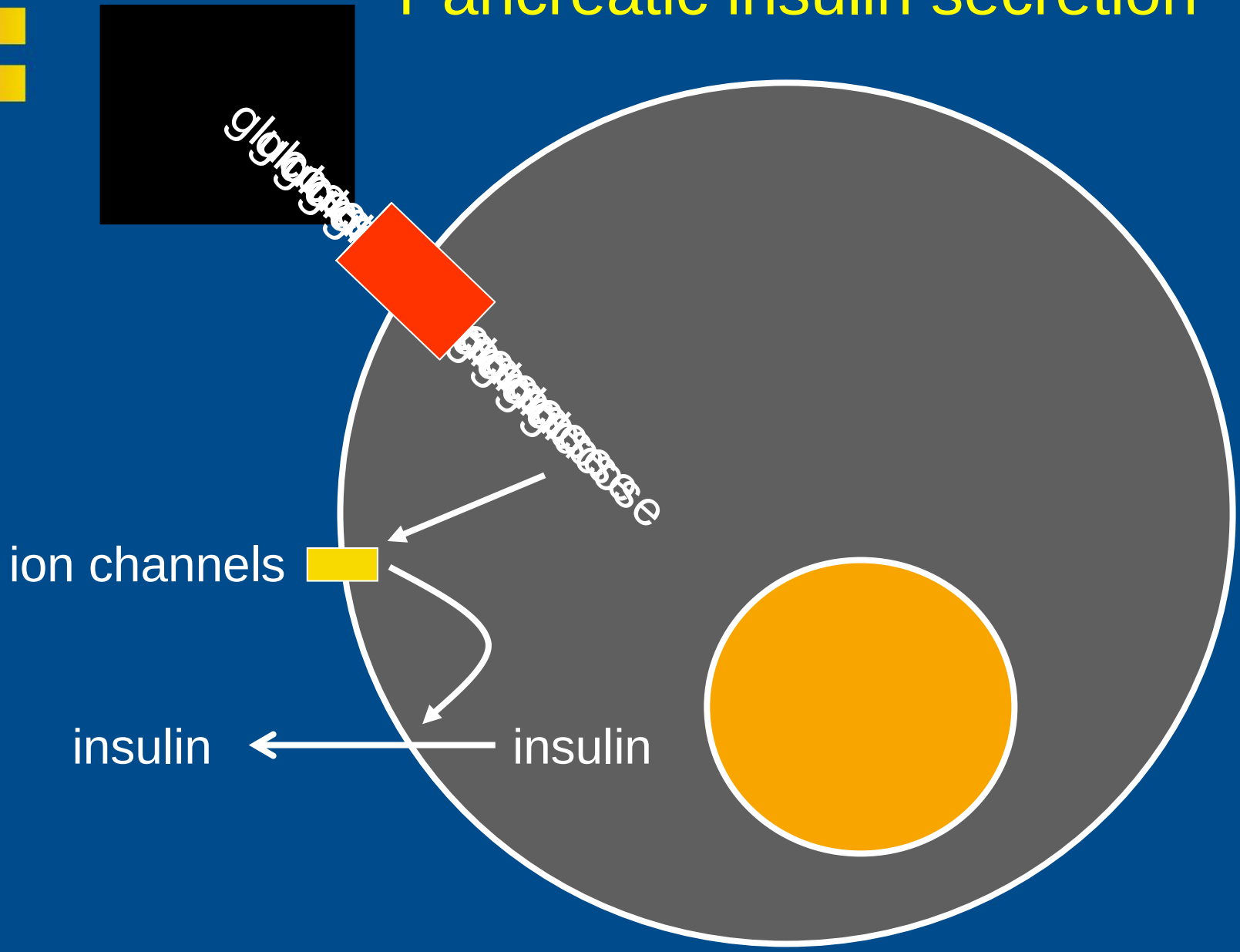

proinsulin
B cell
peptidases
insulin
free C peptide


Bovine
Insulin

Normal glucose regulation



Pancreatic insulin secretion



Insulin-2

from pancreatic islet cells
secretion requires glucose entry in cells

secretion triggered by
- hyperglycaemia
- vagal stimulation
- leucine / arginine
- free fatty acids & ketones
- sulphonylurea drugs

secretion inhibited by
- catecholamines
- neuropeptide Y
- somatoostatin
- diazoxide
- leptin

secretion enhanced by
- GIP
- glucagon like peptide
- vagal stimulation

Insulin-3

binds to cell-surface insulin receptor
activates a protein kinase
leading to downstream intracellular insulin signalling

intracellular actions of insulin stimulate
- nutrient uptake
- biosynthetic processes

glucose uptake enhanced by increasing glucose transporters on the cell surface

Insulin-4

- stimulates glucose uptake
  - esp by fat & muscle
  - increases membrane glucose transporters
- activates glycogen synthesis in muscle
  - ↑glycogen synthase activity
- activates lipogenesis
- phosphorylation of intracellular proteins
- increased DNA & RNA synthesis and cell division

Counter-regulatory hormones

released in response to hypoglycaemia

glucagon
- from pancreatic islet α cells
- acts on liver
- ↑ gluconeogenesis & glycogenolysis

adrenaline
- acts on liver muscle and fat cells
- ↑ glycogenolysis, lipolysis

cortisol
- acts on liver, muscle and fat
- ↑ gluconeogenesis, protein breakdown
- ↓ muscle glucose uptake

growth hormone
- from anterior pituitary
- ↑ lipolysis
- ↓ muscle glucose uptake

Endocrine causes of diabetes mellitus

no insulin production — common

insufficient insulin production — very common

tissue insensitivity to insulin — very common

increased circulating levels of counterregulatory hormones

- excessive growth hormone (acromegaly)
- excessive catecholamines (pheochromocytoma)
- excessive cortisol (Cushing's syndrome)

Very rare

Diagnosis of diabetes

high plasma glucose twice
OR
high plasma glucose + typical symptoms

Different types of diabetes

type 1
type 2
gestational diabetes
other types

Diabetes mellitus

Type 1 — autoimmune destruction of insulin producing pancreatic beta islet cells
UK prevalence 0.5% and rising

Type 2 — insulin resistant condition with inadequate insulin secretion
UK prevalence 4% (2% overt) and rising

Gestational diabetes

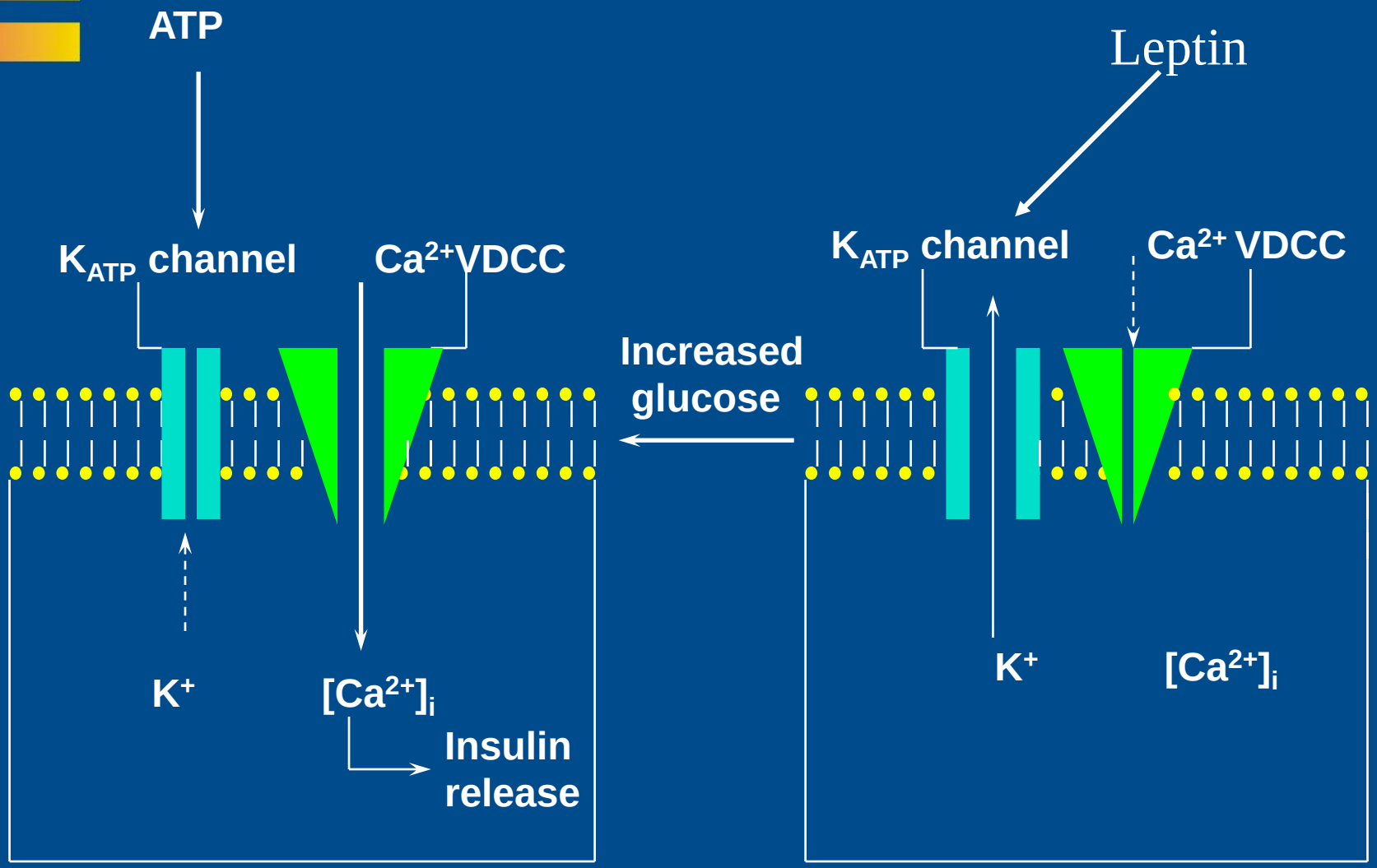
Other types

- pancreatic disease
- endocrine disease
- drug induced
- specific genetic disorders

Type 1 diabetes mellitus

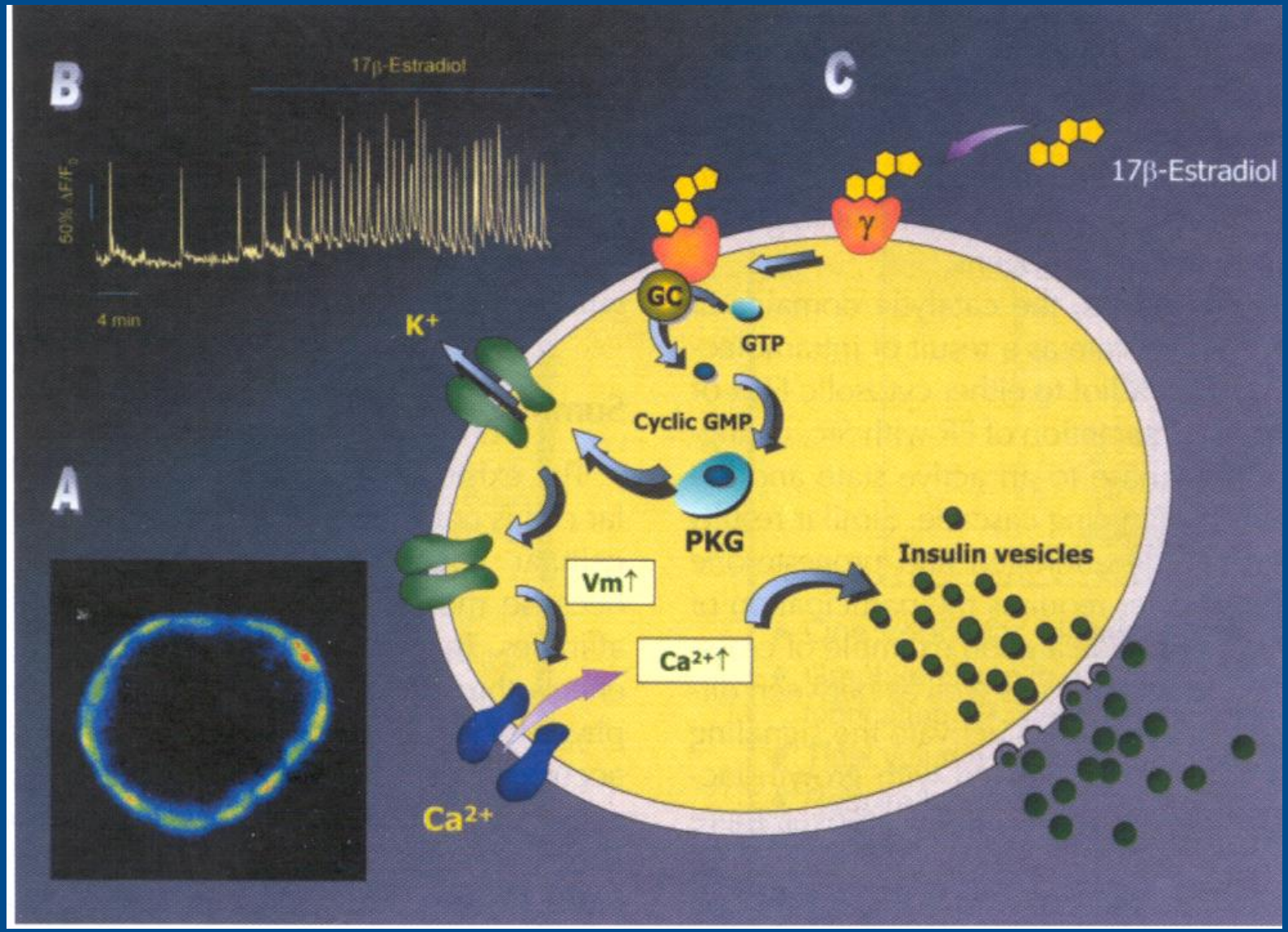
- usually autoimmune destruction of insulin-producing pancreatic islet β cells over months
- absolute insulin deficiency
- rapid presentation with
  thirst, polyuria, weight loss, blurred vision
  thrush, lethargy, dizziness
- usually thin and ketotic at presentation

Insulin Secretion

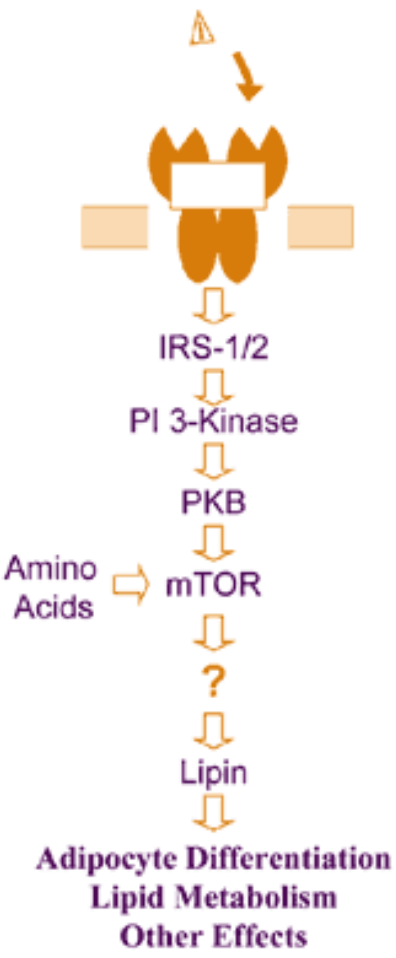


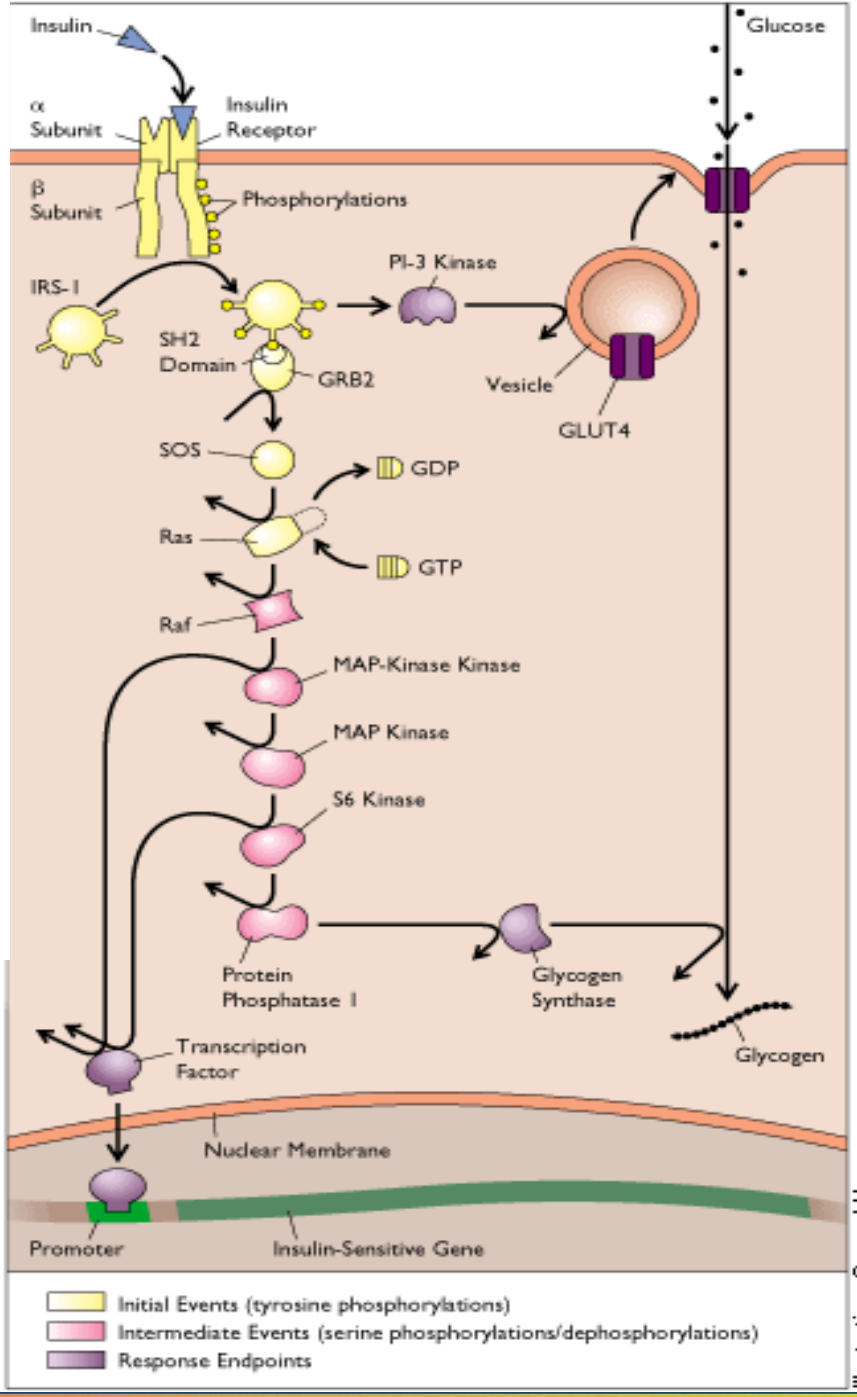
SUR-1/Kir6.2

Insulin Secretion - 2

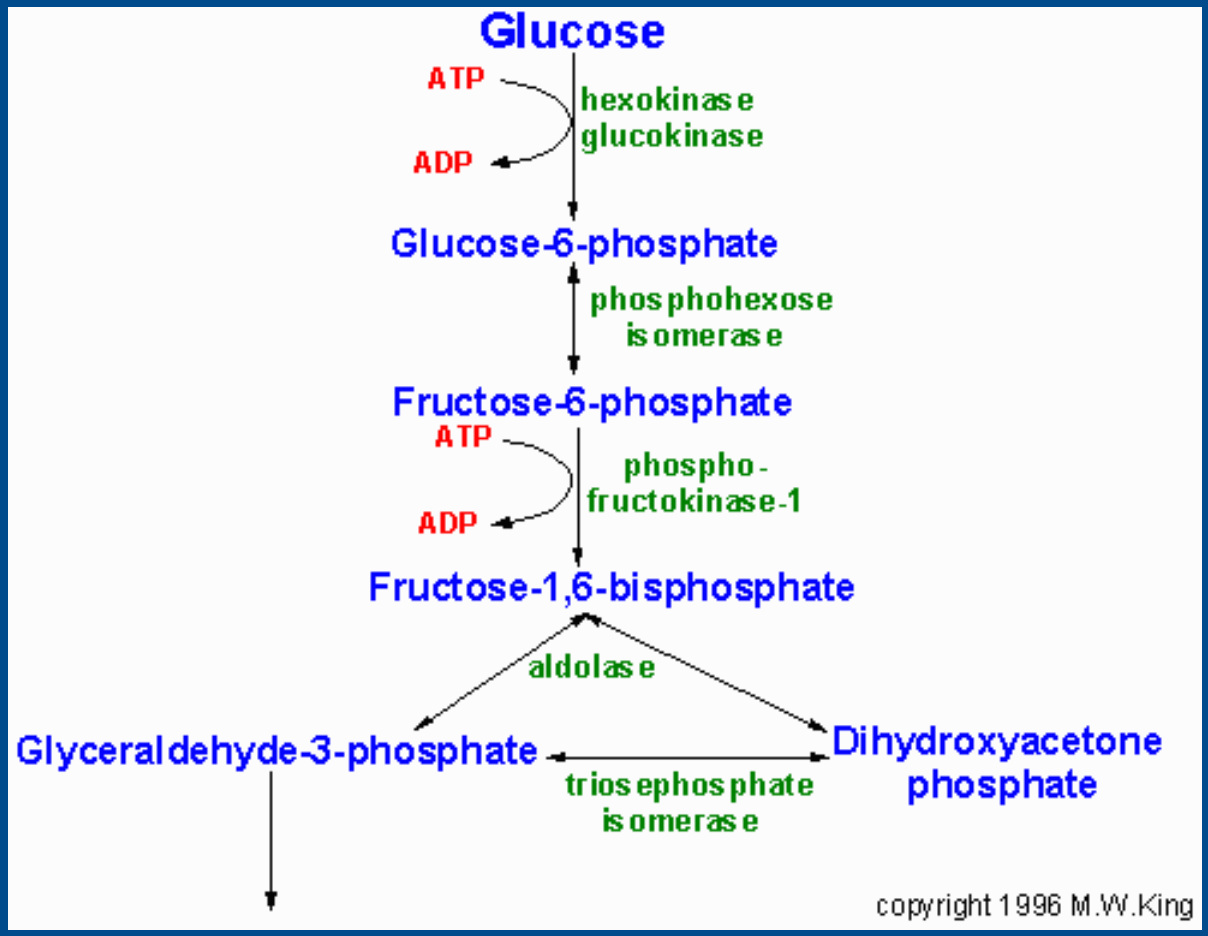


Insulin Action

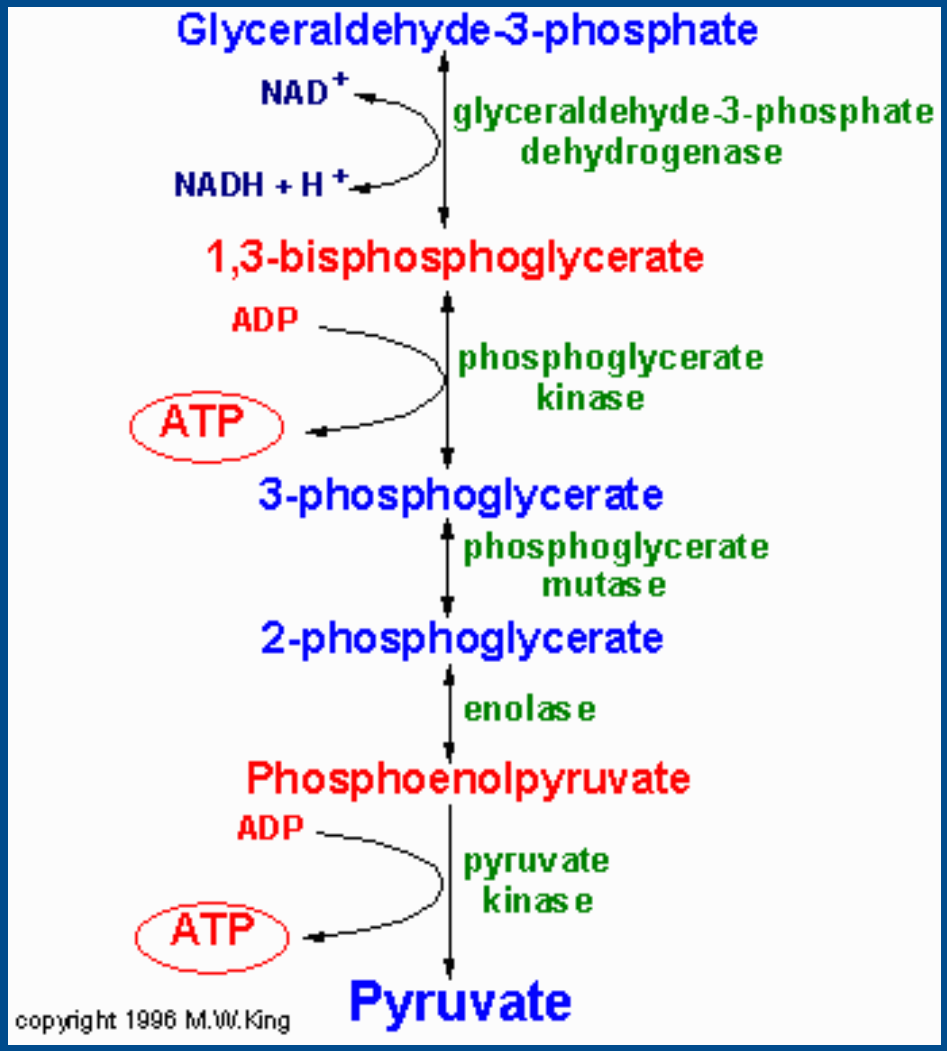




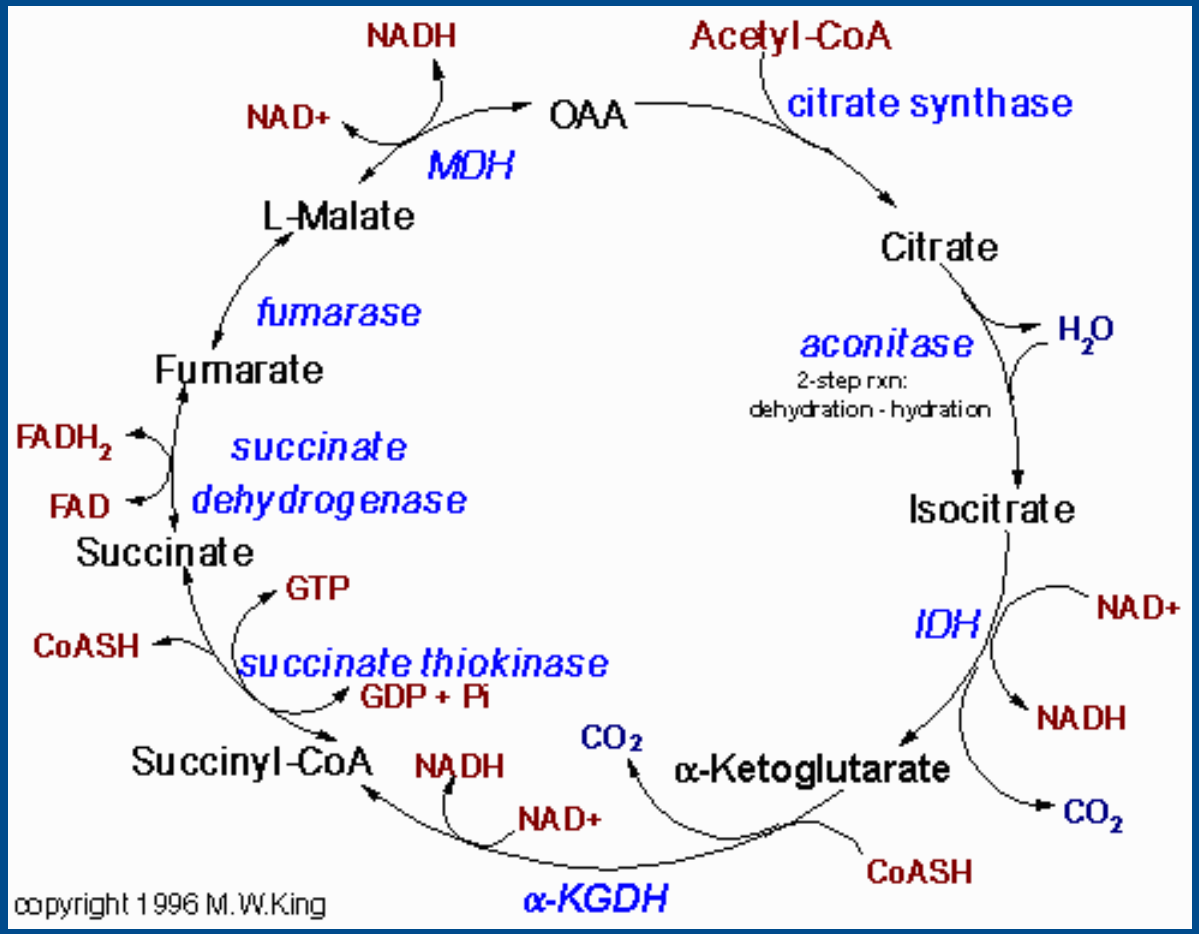
Glycolysis-1



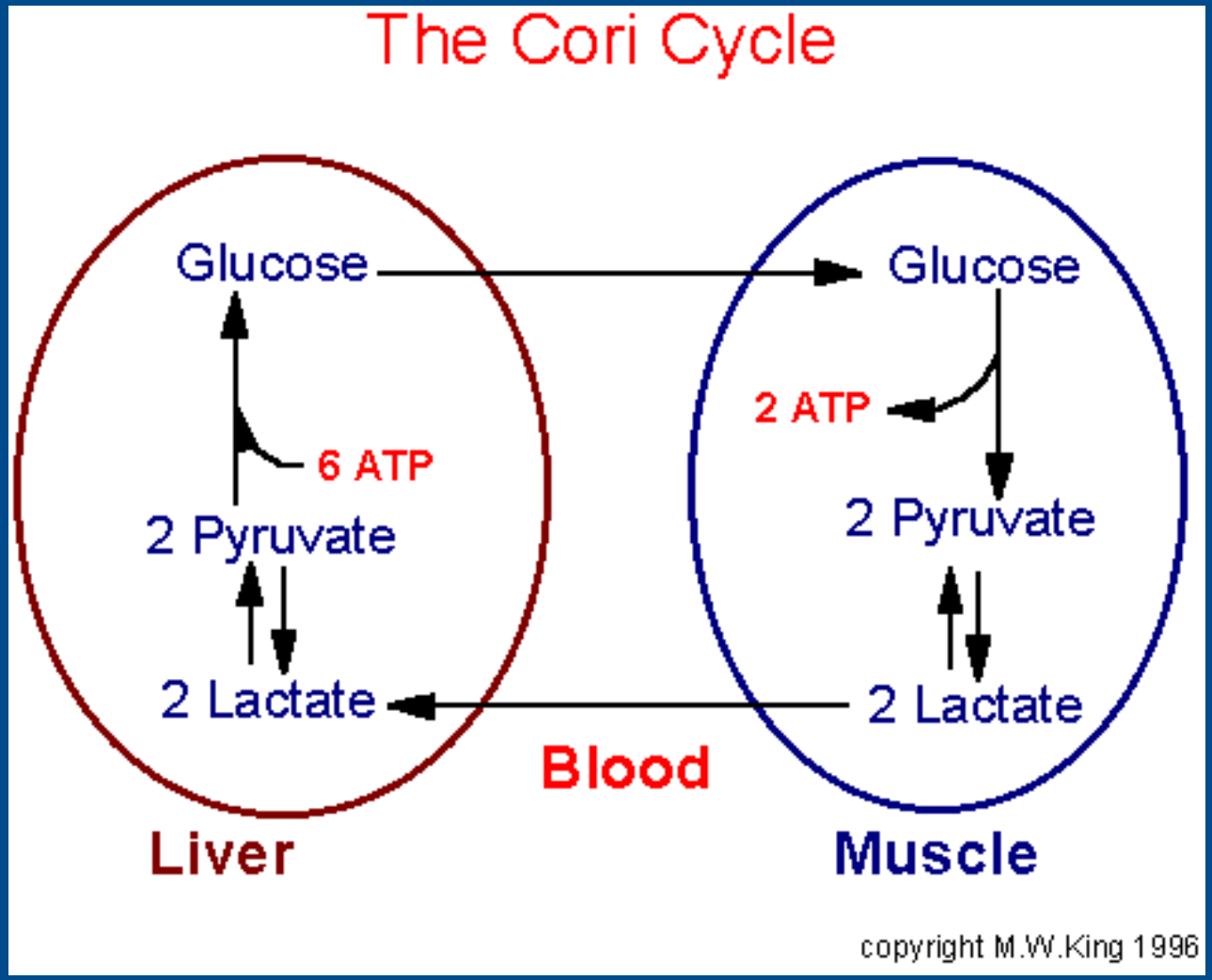
Glycolysis-2



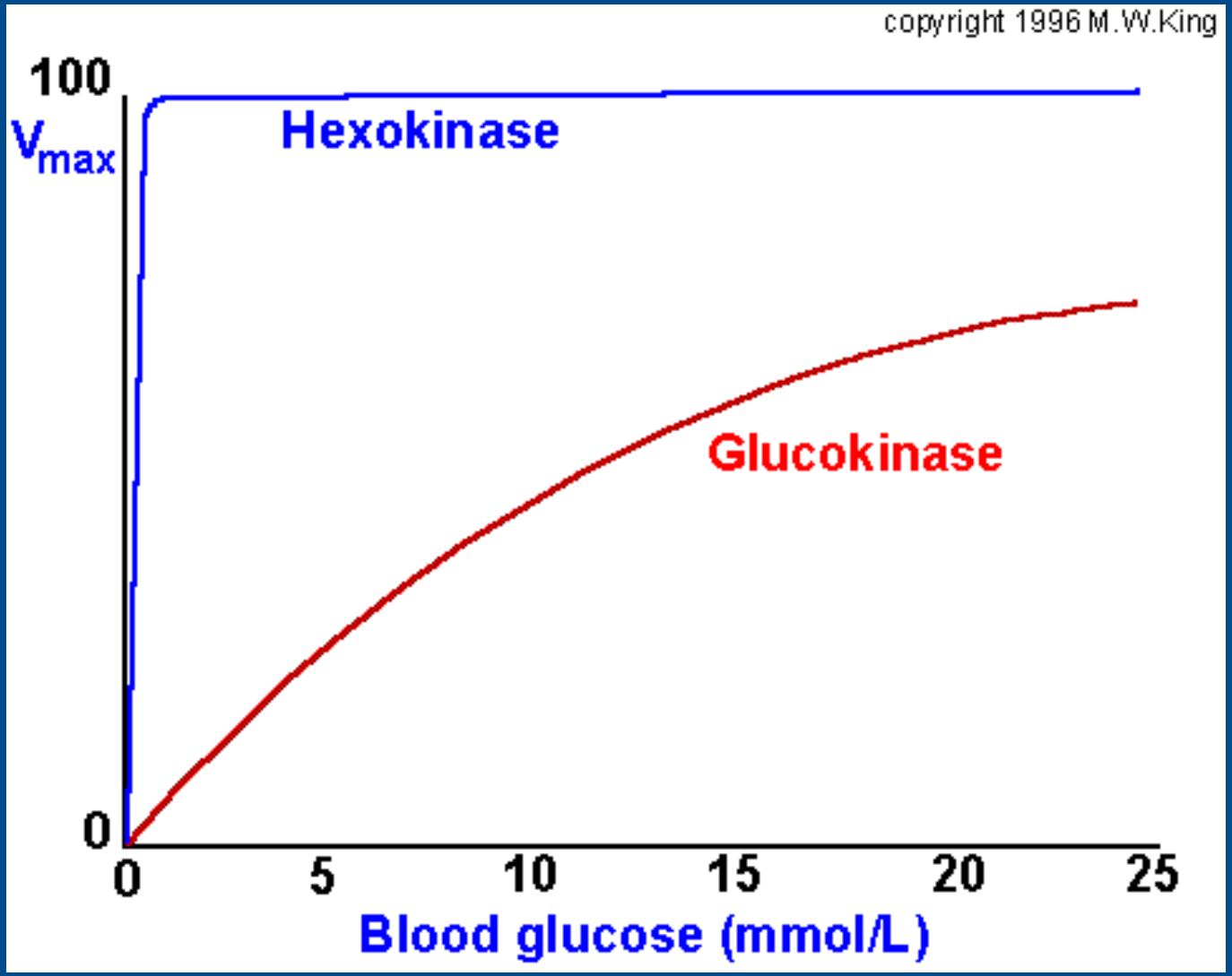
Mitochondrial Metabolism - The Tricarboxylic Acid Cycle (Krebs)



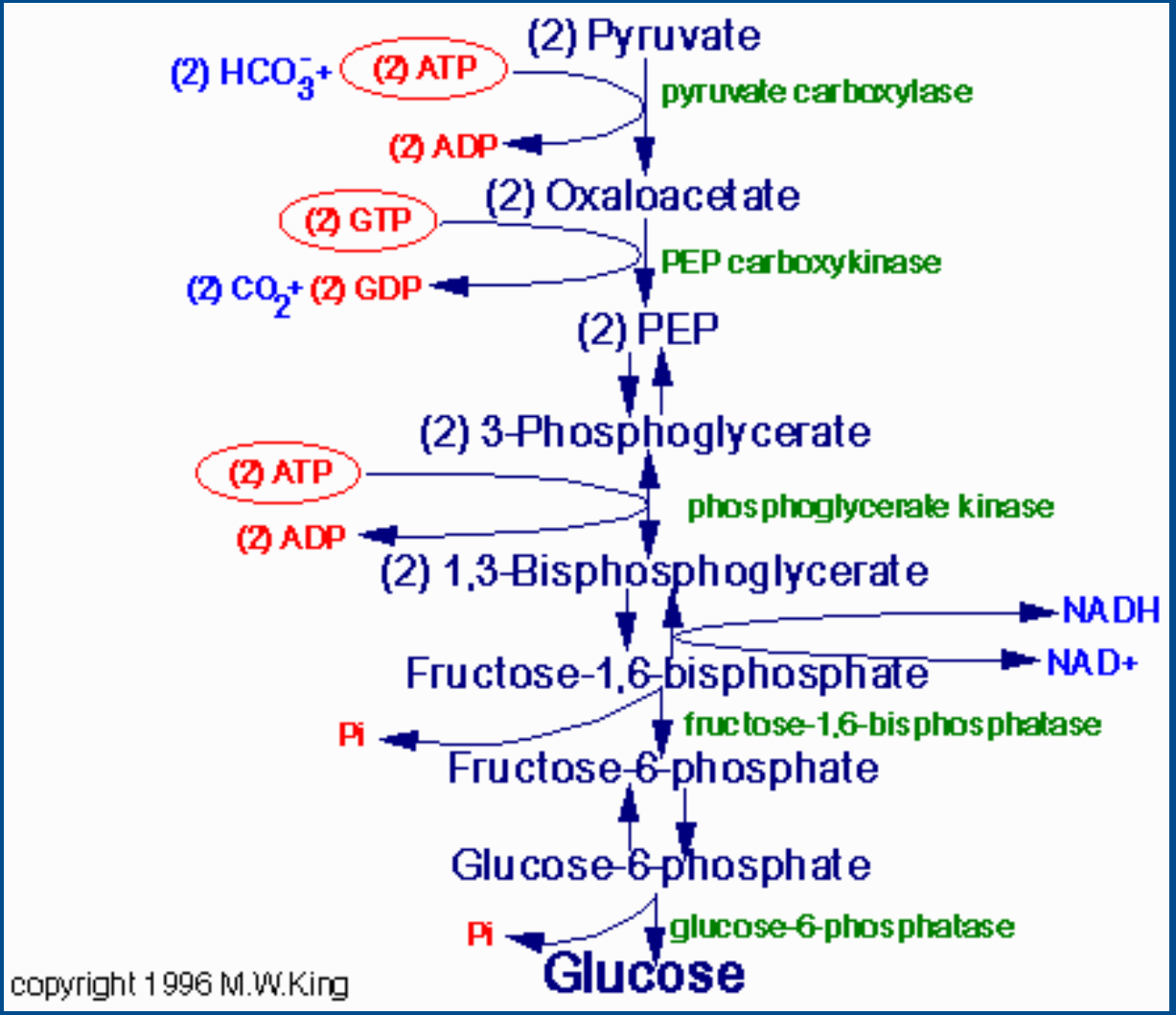
Liver and Muscle



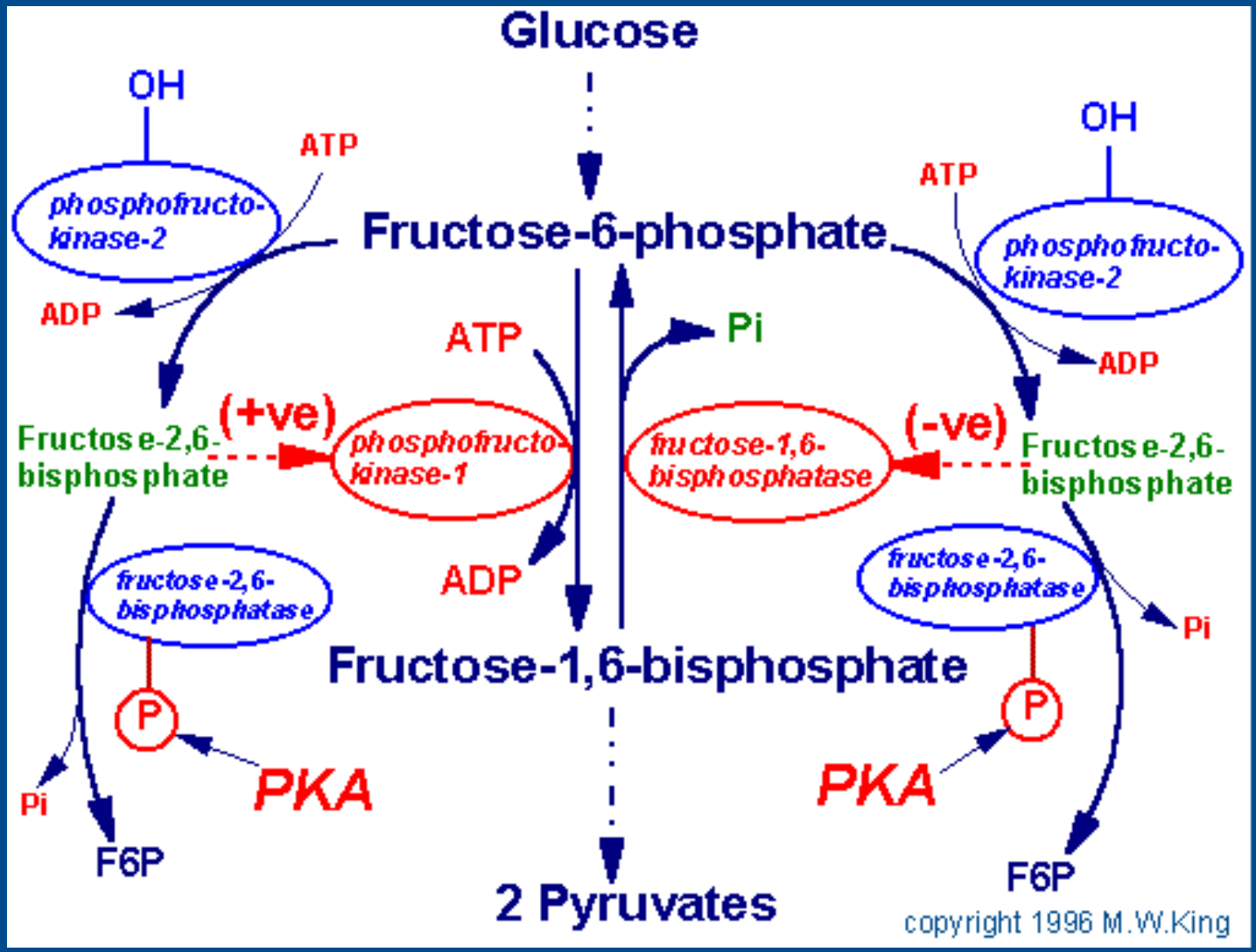
Hepatocyte – A Purveyor of Glucose



Gluconeogenesis-1

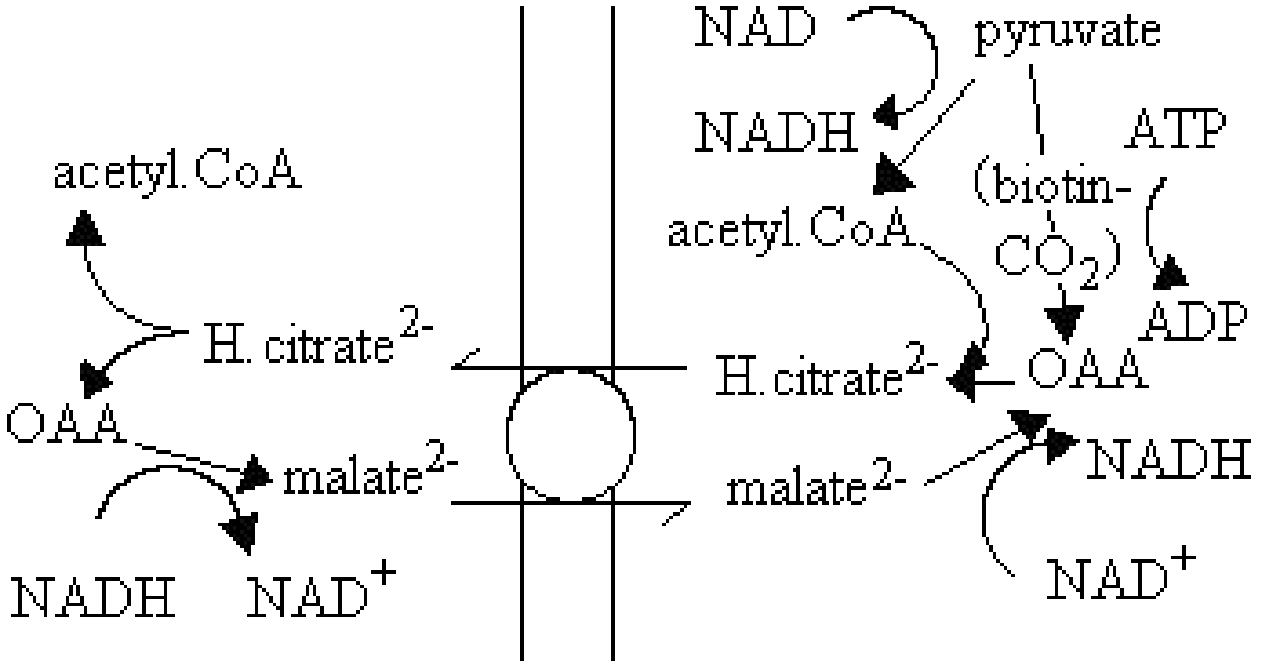


Gluconeogenesis-2

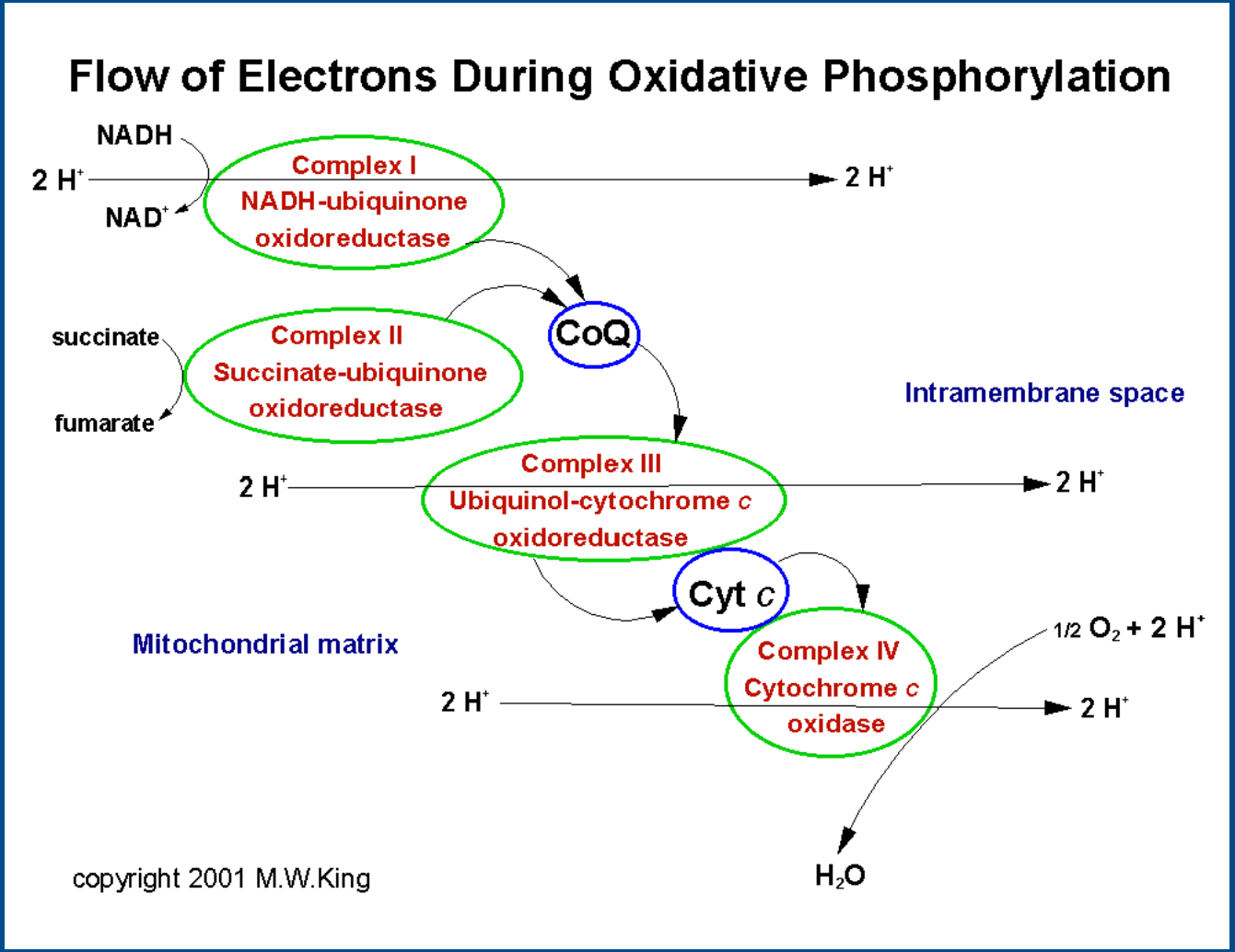


Lipogenesis (<= Insulin)

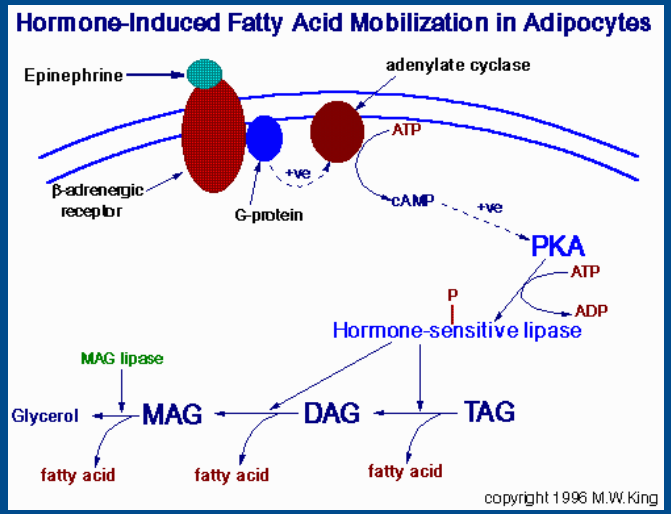
Lipogenesis



Electron Flow



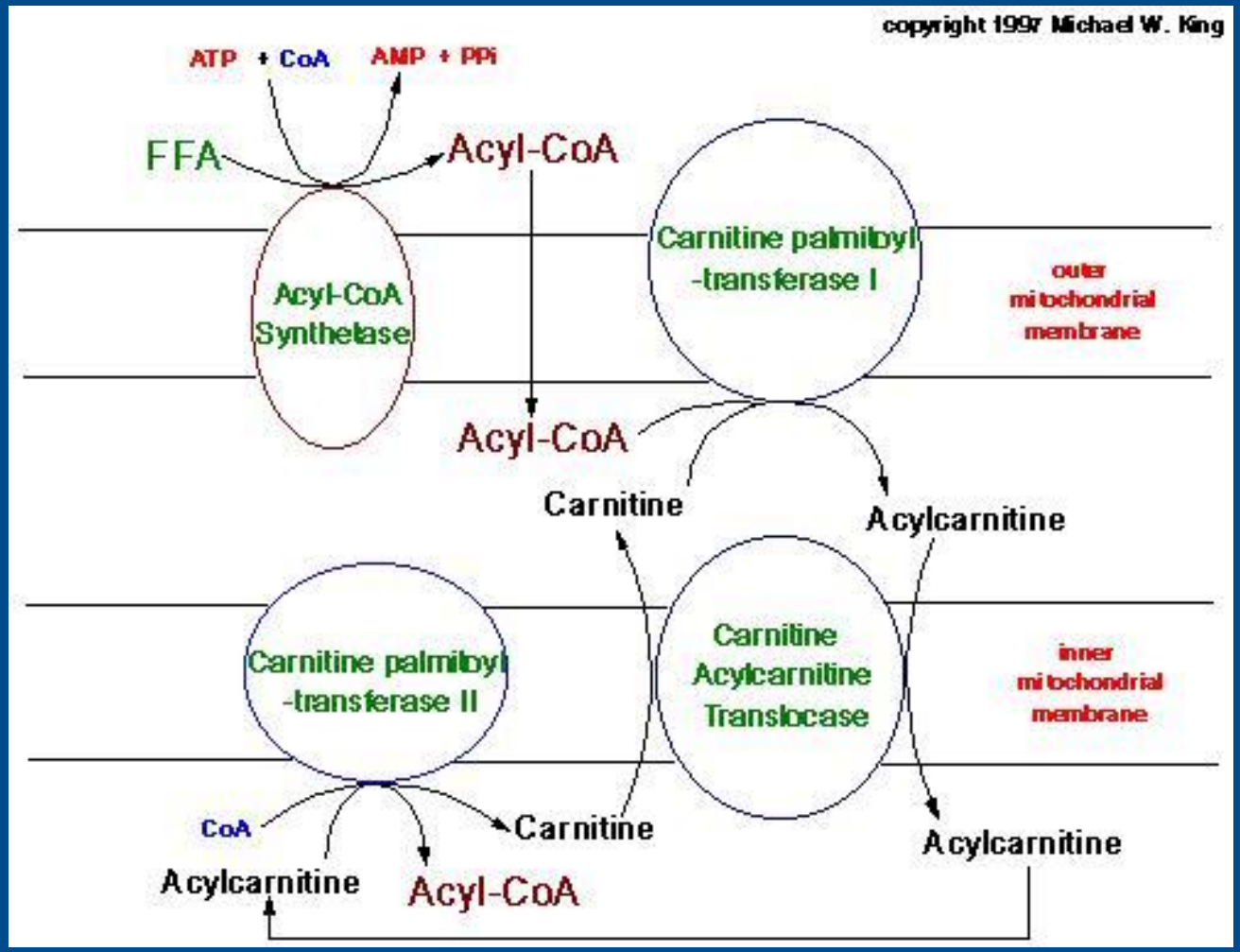
Insulinoprivic or *Counter-Regulatory* Lipolysis



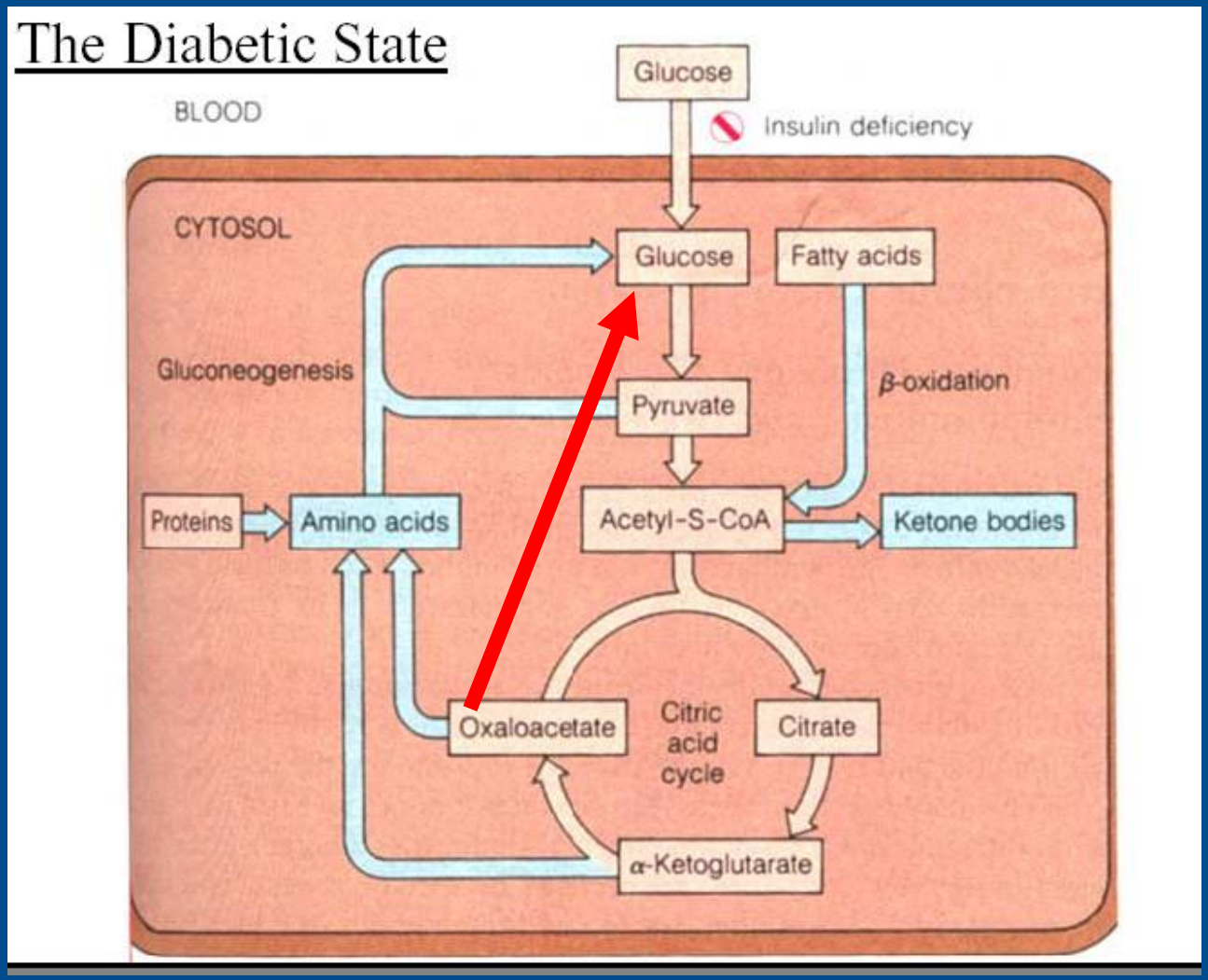
***ketoacyl-CoA-transferase*. [Liver? Inhibition by Glucagon?]**

Acetoacetate + Succinyl-CoA <------> Acetoacetyl-CoA + succinate

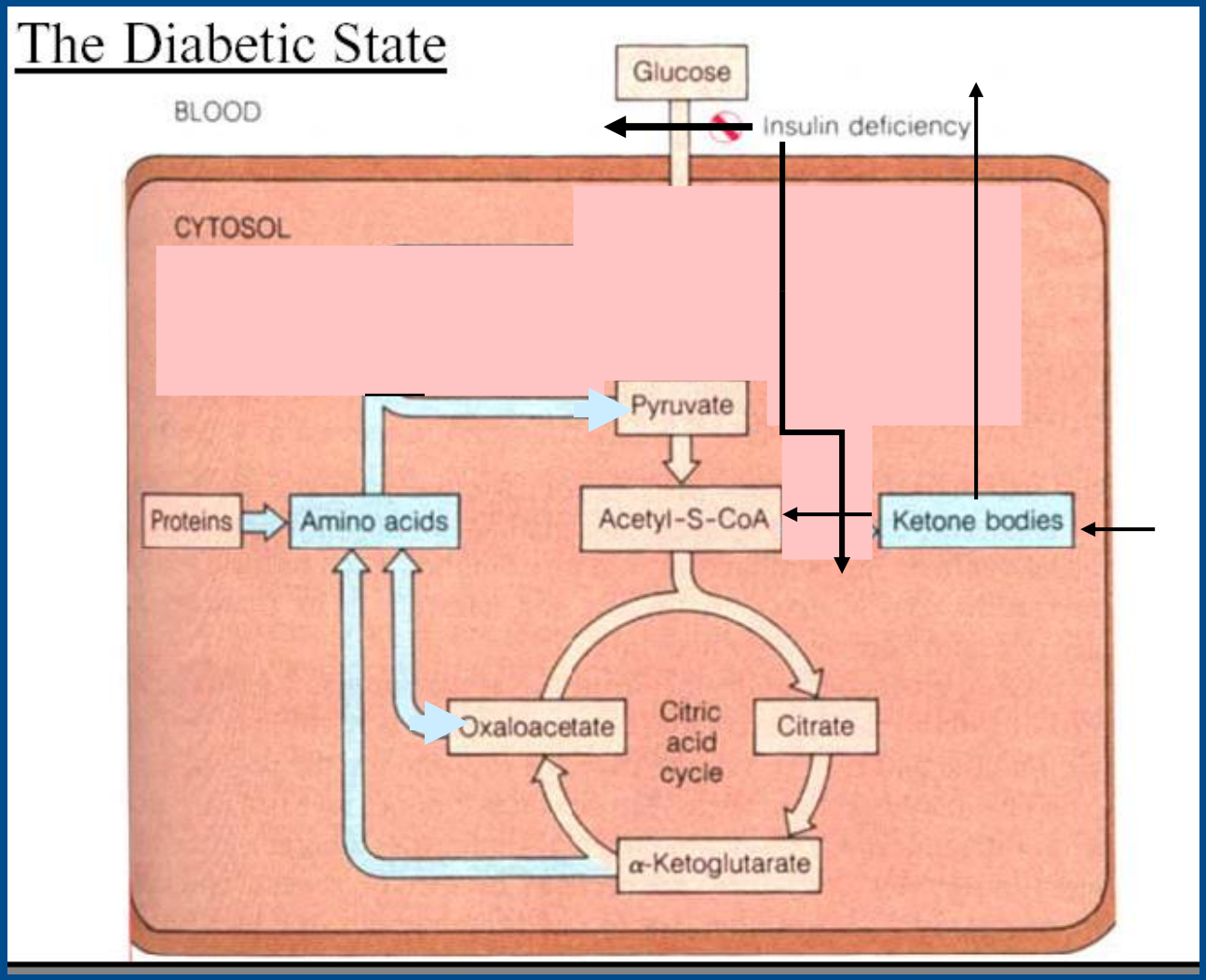
Lipolysis


copyright 1997 Michael W. King
ATP + CoA
AMP + PPi
FFA
Acyl-CoA
Acyl-CoA Synthetase
Carnitine palmitoyl -transferase I
outer mitochondrial membrane
Acyl-CoA
Carnitine
Acylcarnitine
Carnitine palmitoyl -transferase II
Carnitine Acylcarnitine Translocase
inner mitochondrial membrane
CoA
Carnitine
Acylcarnitine
Acyl-CoA
Acylcarnitine

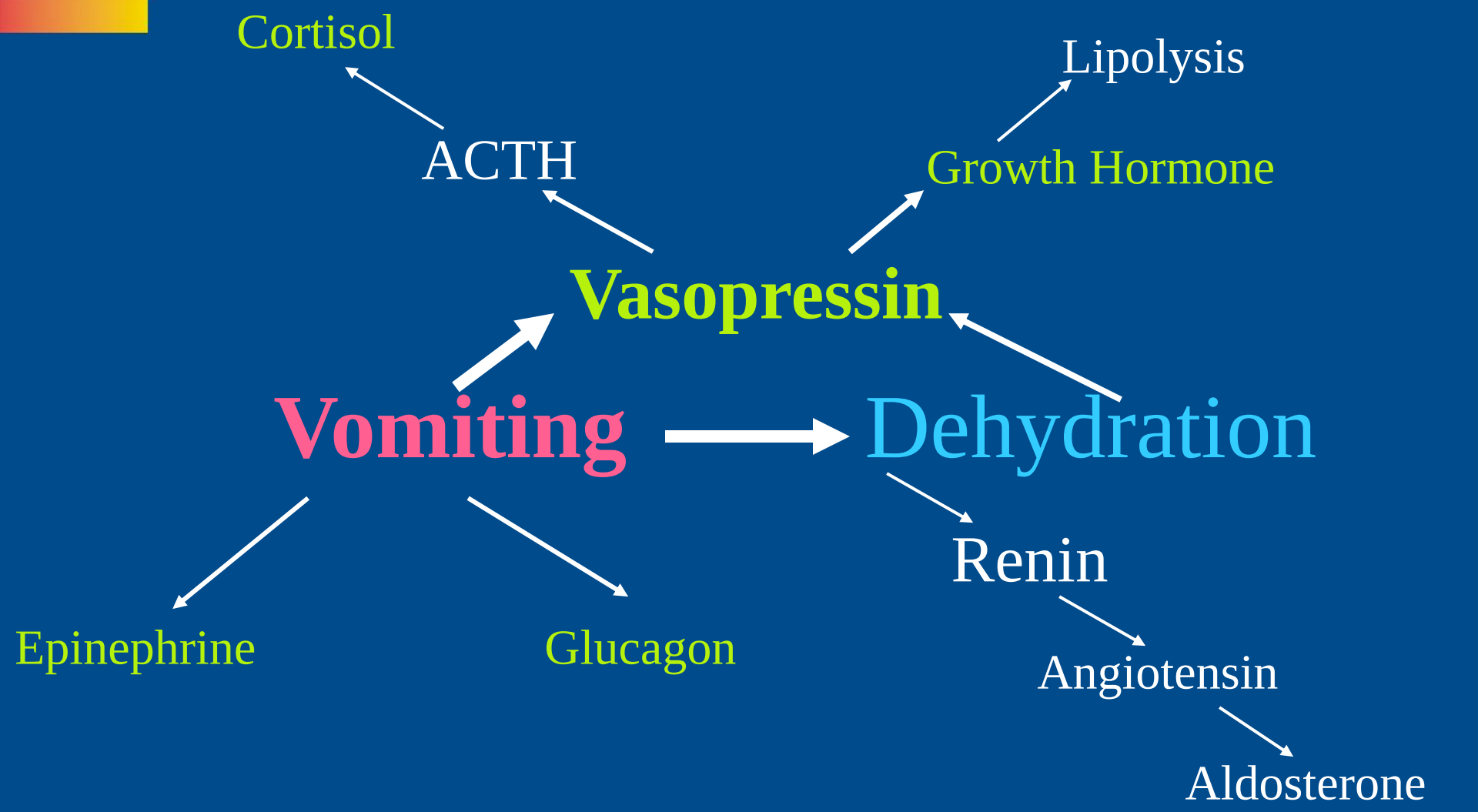
Diabetic Pathophysiology - Liver



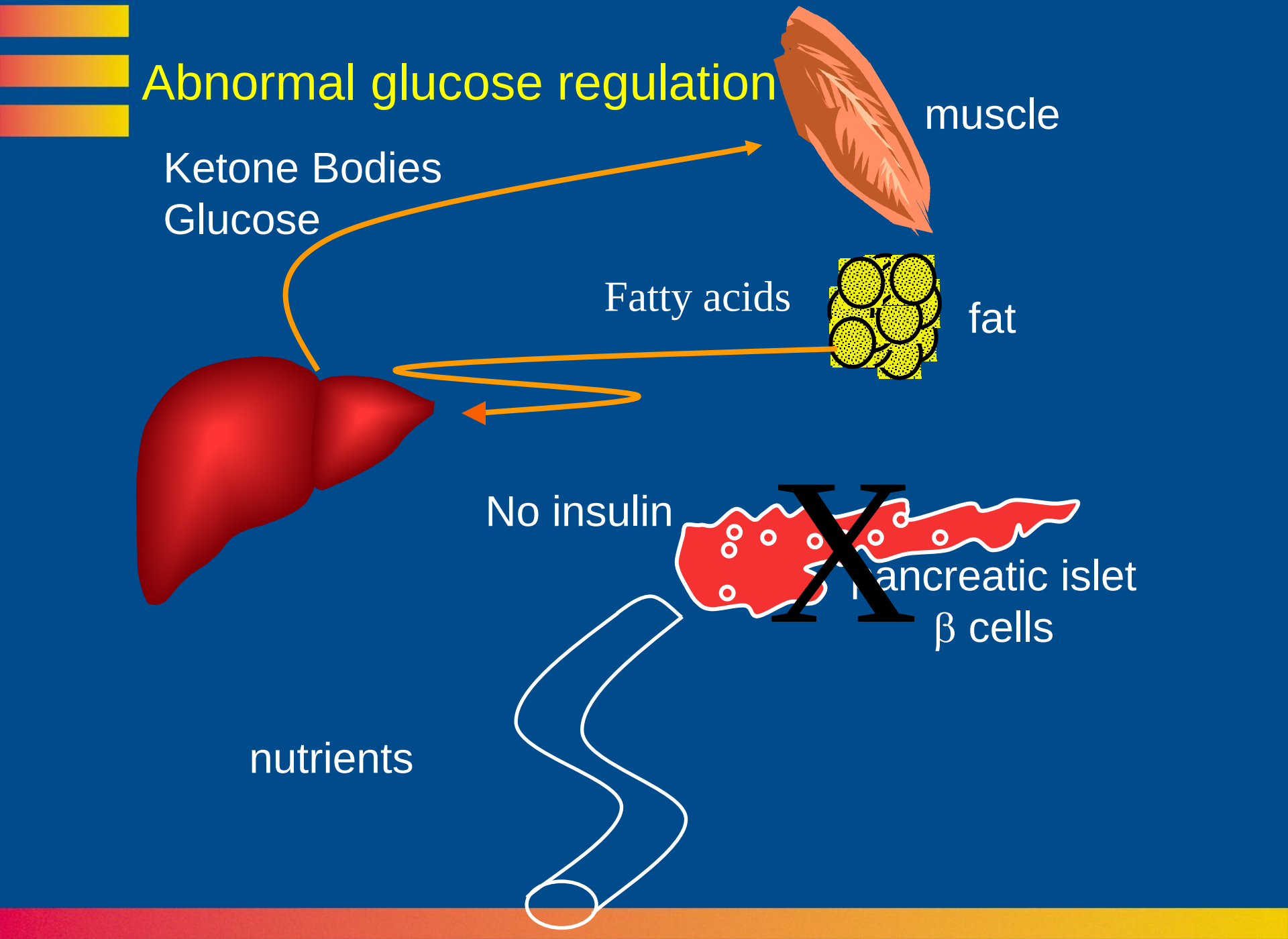
Diabetic Pathophysiology - Muscle



Diabetic KetoAcidosis (DKA)



Abnormal glucose regulation



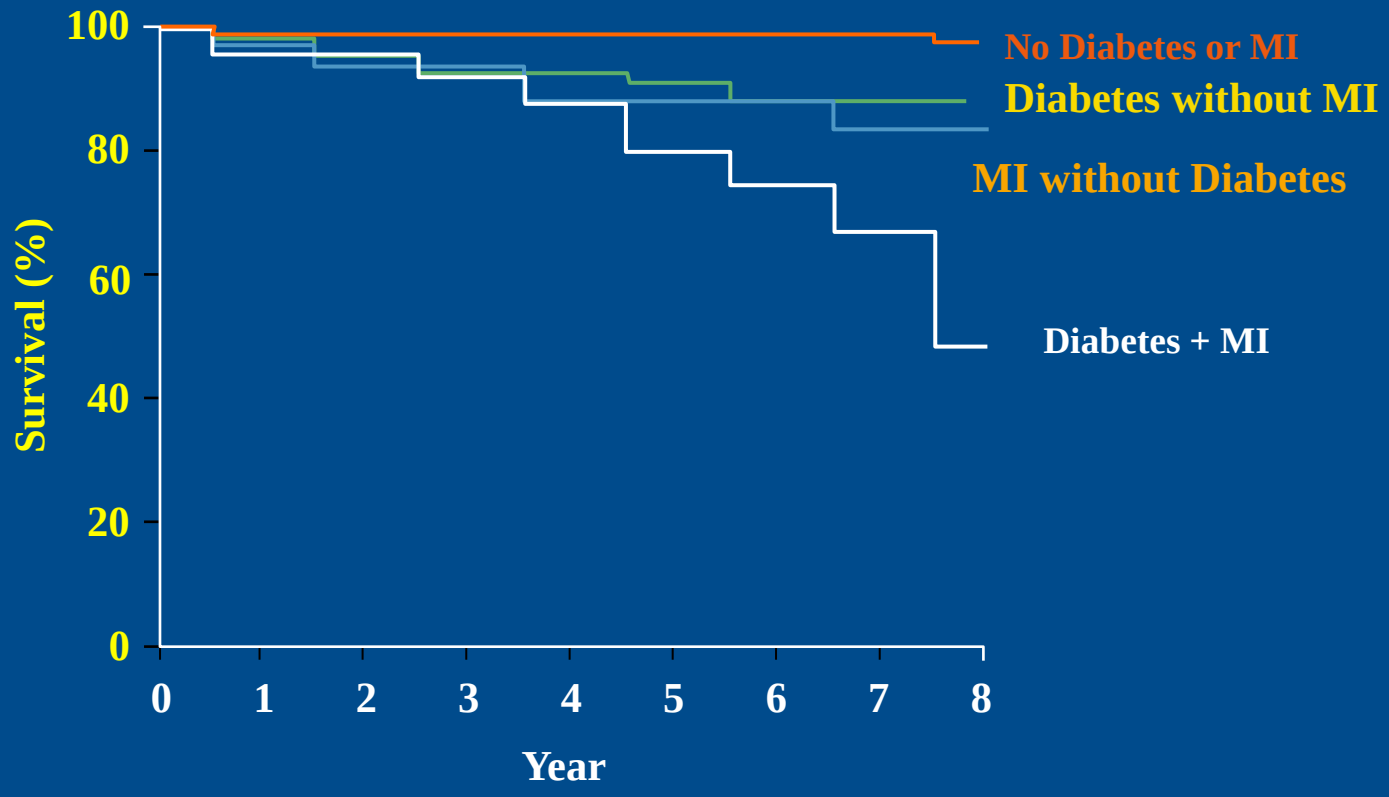
What is the selective advantage of type 2 diabetes mellitus?

Type 2 Diabetes

a horizontally challenging condition

Type 2 Diabetes is a CV Risk Factor

Diabetes and Prior MI Predict Mortality Equally



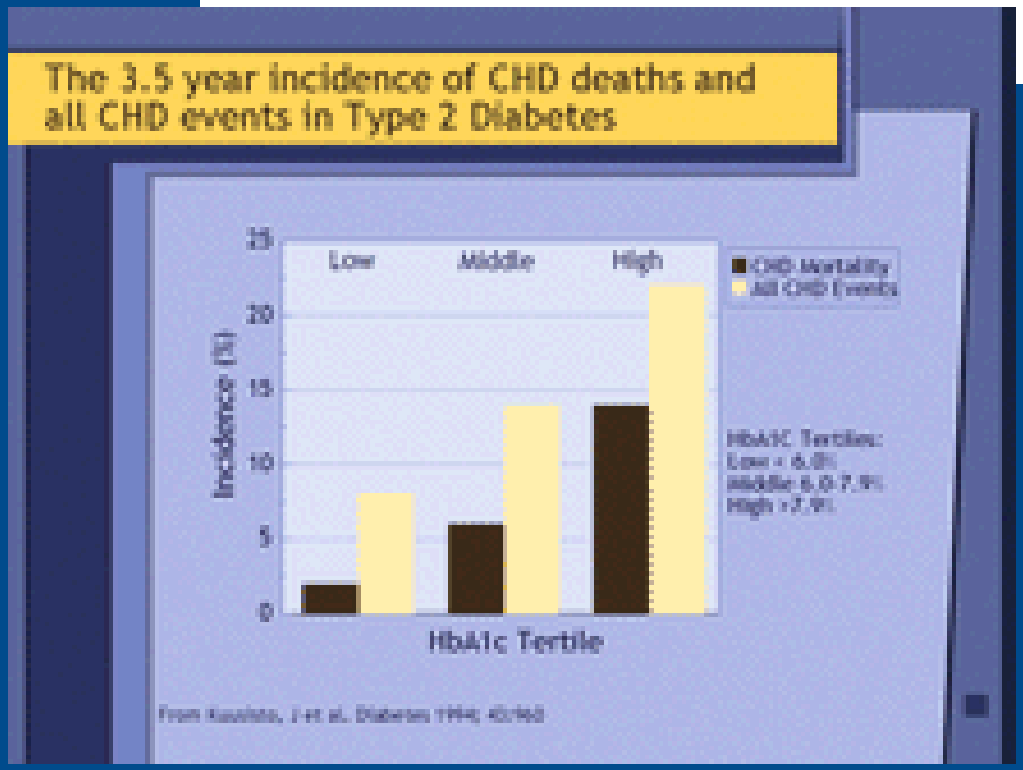
Haffner SM, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;339:229-34.

Cardiovascular Mortality **in Diabetes**

TABLE 2
Hyperglycemia as predictor of cardiovascular mortality in type 2 diabetes: a 15-year follow-up from the time of diagnosis-
The Kuopio 2 Study

	All-cause Mortality Odds Ratio	Cardiovascular Mortality Odds ratio
Men	5.0, P < 0.001	6.2, P < 0.001
Women	5.2, P < 0.001	11.2, P < 0.001

Diabetes Care 1998 Nov;21(11):1861-9



(**Diabetes 1994 Aug;43(8):960-7**)
In a Finnish 3.5 year study at Kuopio 1 (Figure 2), coronary heart disease deaths and events are shown to increase by tertile of hemoglobin A1c. "In NIDDM subjects, only glycated hemoglobin A1c (GHbA1c) at baseline ($P < 0.01$) and duration of diabetes ($P < 0.05$) predicted CHD death ($n = 15$) and all CHD events ($n = 33$)." Moreover the HbA1c correlation was still seen across long and short periods of disease duration

UMDS

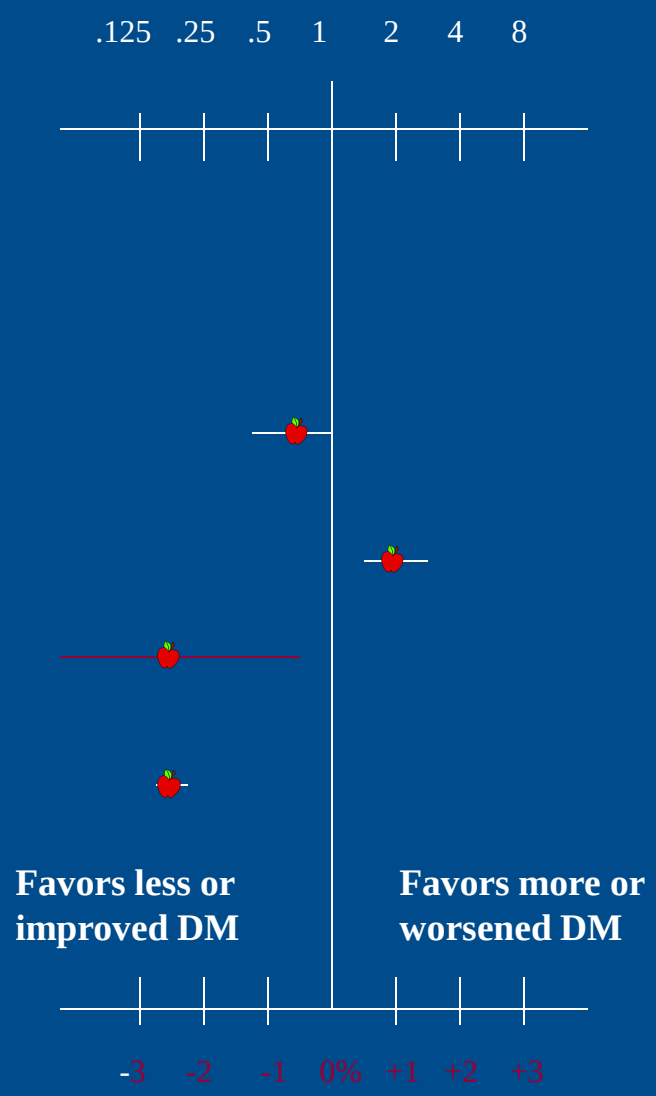
Dr. Harry Keen (1968)

"It is, of course, possible to formulate three standard hypotheses to explain the relationship - that A causes B, that B causes A, or that both A and B are caused by C. We have chosen to examine what is perhaps the most likely and potentially the most useful of these explanations - that hyperglycemia contributes causally to the development of the arterial lesions. It is a useful explanation because there is long experience and knowledge of methods aimed at lowering the blood sugar: the possibility of intervening in the progress of a disease process is one which stimulates both the interest of the doctor and the co-operation of the patient." (Keen H, Jarrett, RJ, Chlouverakis C, Boyns DR, The effect of treatment of moderate hyperglycemia on the incidence of arterial disease. *Postgrad. Med.J*. [1968] **44**:960)

Effects of Atherogenic Interventions on Incidence or Control of Diabetes

drug	CV death*	OR/A1c Δ
pravastatin	↓	0.695
smoking	↑	1.96
ramipril	↓	-2.3%
Estrogen*	↓	-2.4%

*Change Carotid Artery Intimal Medial Thickness



Adam Morley sees his GP urgently

Dm1-onset

18 years old works with his father; delivery service
White North European

Since on holiday 2 weeks ago
always thirsty
always tired
ratty with family
dizzy after meals

Kylie Middleton calls her GP out

16 years old single mother
White North European

5 episodes of thrush infection in 3 weeks
dry mouth
depressed fed up
losing weight

tummy pain for 12 hours
now vomiting
feeling breathless

Geoffrey Barwick sees his GP

Dm1-LADA

55 years old solicitor
White North European

3 stones in weight loss over one year
having to get up at night 4 times to pass urine
calf cramps

“now that I’m here, difficulty keeping it up”

Barry Bramley is on the coronary care unit

Dm2-HASHD

53 years old builder
has been admitted with a suspected heart attack
White North European

nurses check his blood glucose: 21 mmol/L

Henrietta Allerton goes to Eye Casualty

Dm2- amaurosis fugax

73 year old Jamaican, retired nurse

notices sudden total loss of vision in the right eye

urinalysis shows protein and glucose
venous plasma glucose 14 mmol/L

Reverend Patrick Fitzcolton rings his GP

Dm-secondary

62 years old

recently developed polymyalgia rheumatica
has been taking steroid prednisolone 60mg daily

since starting these has needed to drink 20 pints/day
sermons have shortened as needs toilet every 40 minutes
misty vision

Mohammed Rawal sees the practice nurse

Dm2-FHx

28 year old Pakistani, taxi driver
his mother, father and 2 of his 3 brothers have diabetes

a customer (medical student) recommended he be checked out

blood glucose 17 mmol/L

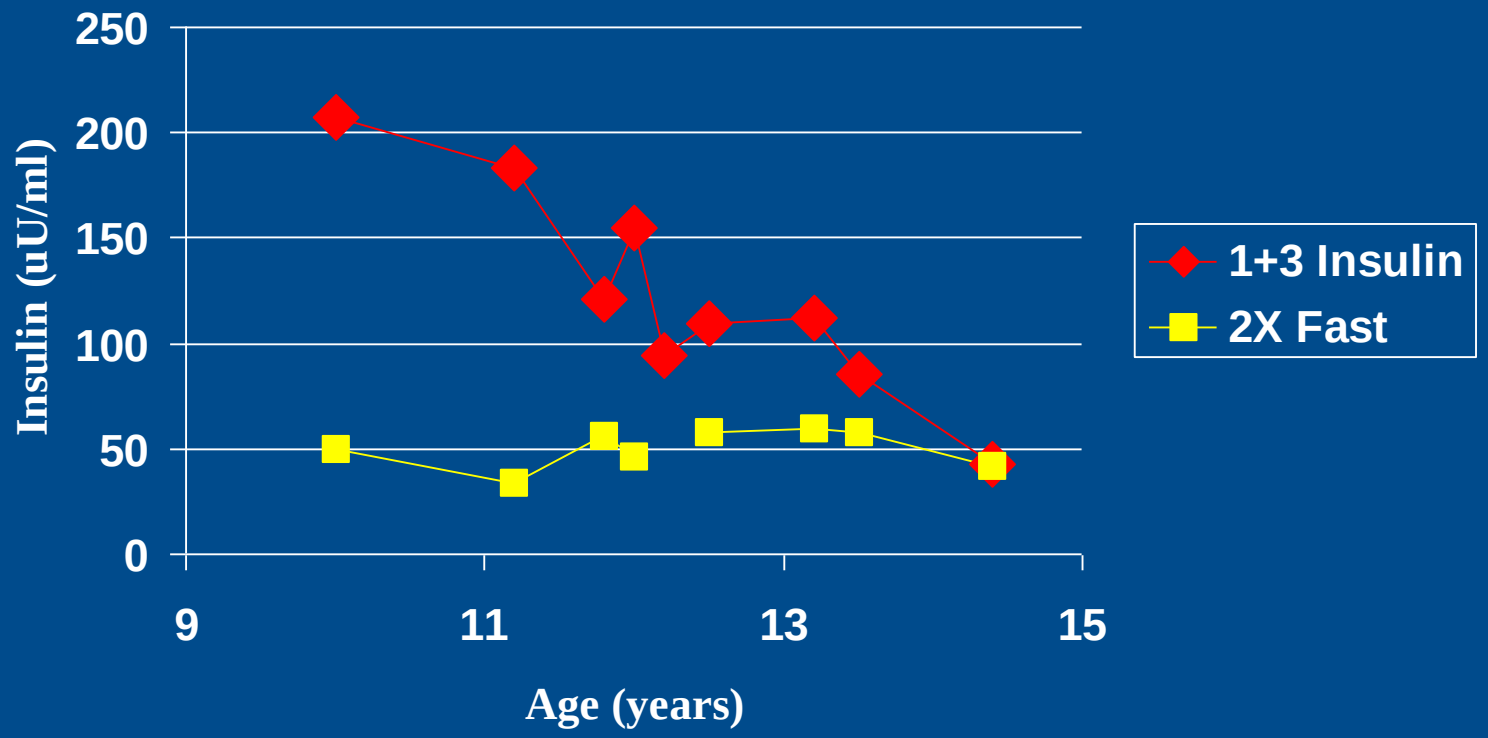
Farhana Safraz attends the lipid clinic

31 year old Pakistani
has hypercholesterolaemia and hypertension
venous plasma glucose 11 mmol/L

75g oral glucose tolerance test:

fasting	7.3 mmol/L
2 hour	12.6 mmol/L

Insulin Secretion (IVGTT) in Obese Child (BMI 30 to 35) Progressing to Diabetes: Type 1 + Type 2 with Elevated Fasting Insulin



So many interesting questions,
So little time….