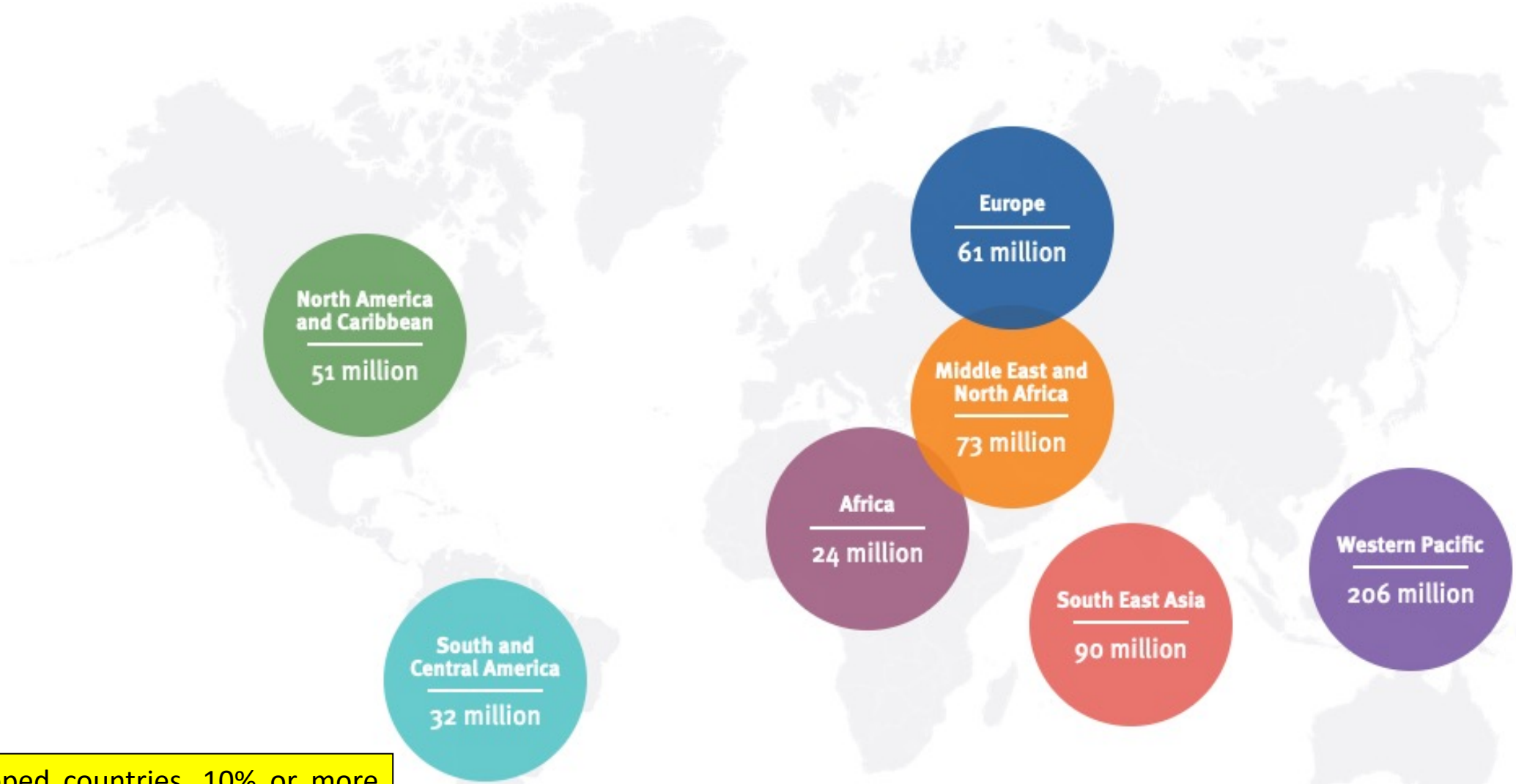
The Pancreas/Diabetes

Diabetes around the world in 2021



In developed countries, 10% or more of the total health budget is spent on the management of diabetes and its complications.

https://diabetesatlas.org/

Diabetes around the world in 2021:

537 million adults (20-79 years) are living with diabetes - 1 in 10. This number is predicted to rise to **643 million** by 2030 and **783 million** by 2045.

Over 3 in 4 adults with diabetes live in low- and middle-income countries.

Diabetes is responsible for **6.7 million** deaths in 2021 - 1 every 5 seconds.

Diabetes caused at least **USD 966 billion** dollars in health expenditure – a 316% increase over the last 15 years.

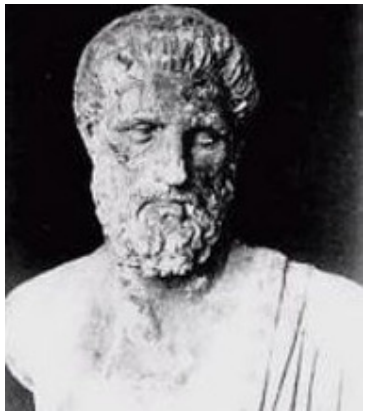
541 million adults have Impaired Glucose Tolerance (IGT), which places them at high risk of type 2 diabetes..

Diabetes Mellitus

- <u>Diabetes</u>
  - Greek for “siphon”, named for the excessive urination

- <u>mellitus</u>
  - Latin for “sweetened with honey”
  - Refers to the presence of sugar in the urine of patients having the disease
  - Remember: diabetes insipidus
  - caused by impaired renal reabsorption

A brief history of diabetes-1



- 1550 BC: The oldest description of diabetes as a polyuric state in ancient Egypt.

- 2nd century AD: Aretaeus of Cappadocia first used the term "diabetes",
- coming from Greek meaning "siphon" or "pass through".

  He characterized diabetes as "being a melting down of flesh and limbs into urine".

- 5th/6th century AD: Indian physicians, such as Susruta, recognized the sweet, honey-like taste of urine from polyuric patients, which attracted ants and insects. The descriptions of diabetes also recognized the distinction between two forms of diabetes, one in older, fatter people, and the other in thin people who rapidly succumbed to their illness.

- 17th century AD: Thomas Willis, physician to King Charles II, rediscovered sweetness in urine. He noted the importance of life style when he remarked that the prevalence of diabetes was increasing because of "good fellowship and gulling down chiefly of unalloyed wine".

- 1776: Matthew Dobson showed that urinary sweetness "glycosuria" was caused by sugar and was associated with a rise in blood sugar.

- End of 18th century: John Rollo, Scottish military surgeon, first used the term "diabetes mellitus" (honey) to distinguish the condition from "diabetes insipidus" (tasteless) and suggested to modify diet: low carbohydrates.

- 19th century: Claude Bernard, a French physiologist, discovered that: sugar was stored as glycogen in the liver

- 1869: Paul Langerhans discovered the pancreatic islets.

- 1889: Oskar Minkowski removed the pancreas from a dog and discovered that the animal developed severe and fatal diabetes.

- 1893: Edouard Laguesse showed islets were the endocrine tissue of the pancreas. It had long been thought of as a kidney disease.

- 1921: Frederick Banting, Charles Best, James Collip and J.J.R. Macleod, in Toronto, discovered insulin.

- 1922: First patients treated with improve pancreatic extract by physicians such as Elliot P. Joslin, who introduced systematic education in the US and Robin D. Lawrence who has diabetes himself and founded the British Diabetic Association (now Diabetes UK).

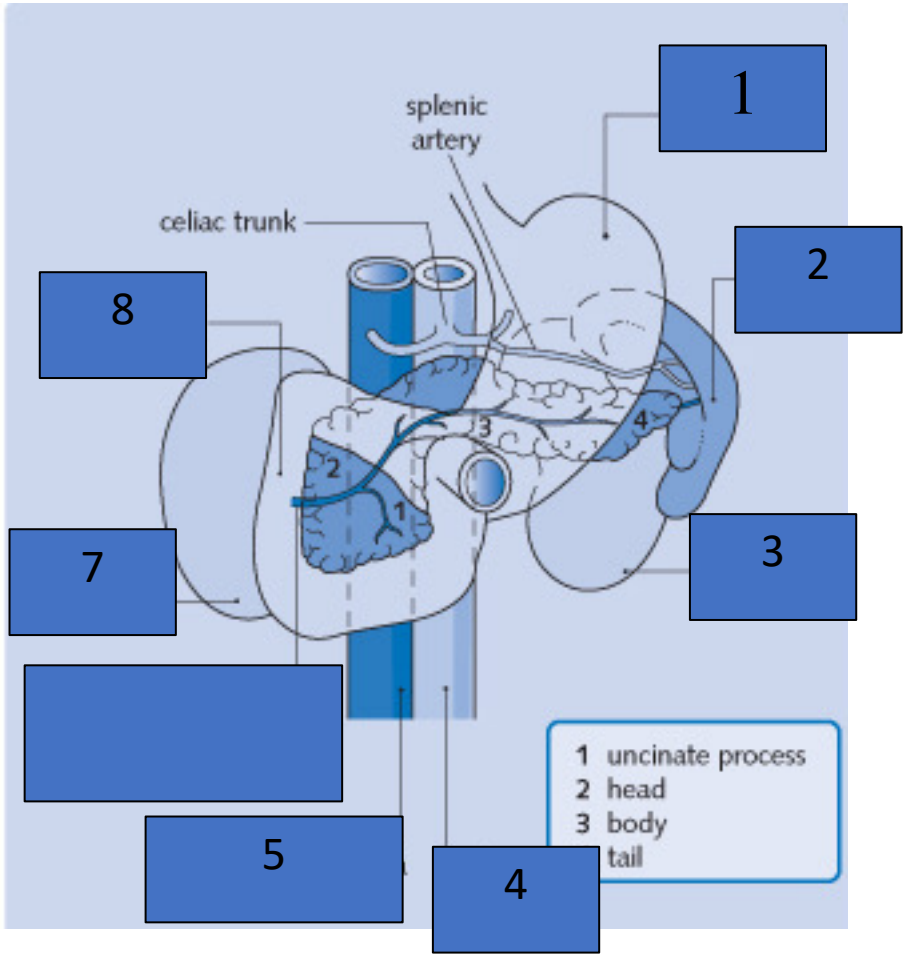
- 1955: Primary structure of insulin elucidated by Frederick Sanger: 51 aa Nobelprize in Chemistry 1958 (1980)

- 1969: Dorothy Hodgkin described the three dimensional structure of insulin using X-ray crystallography.

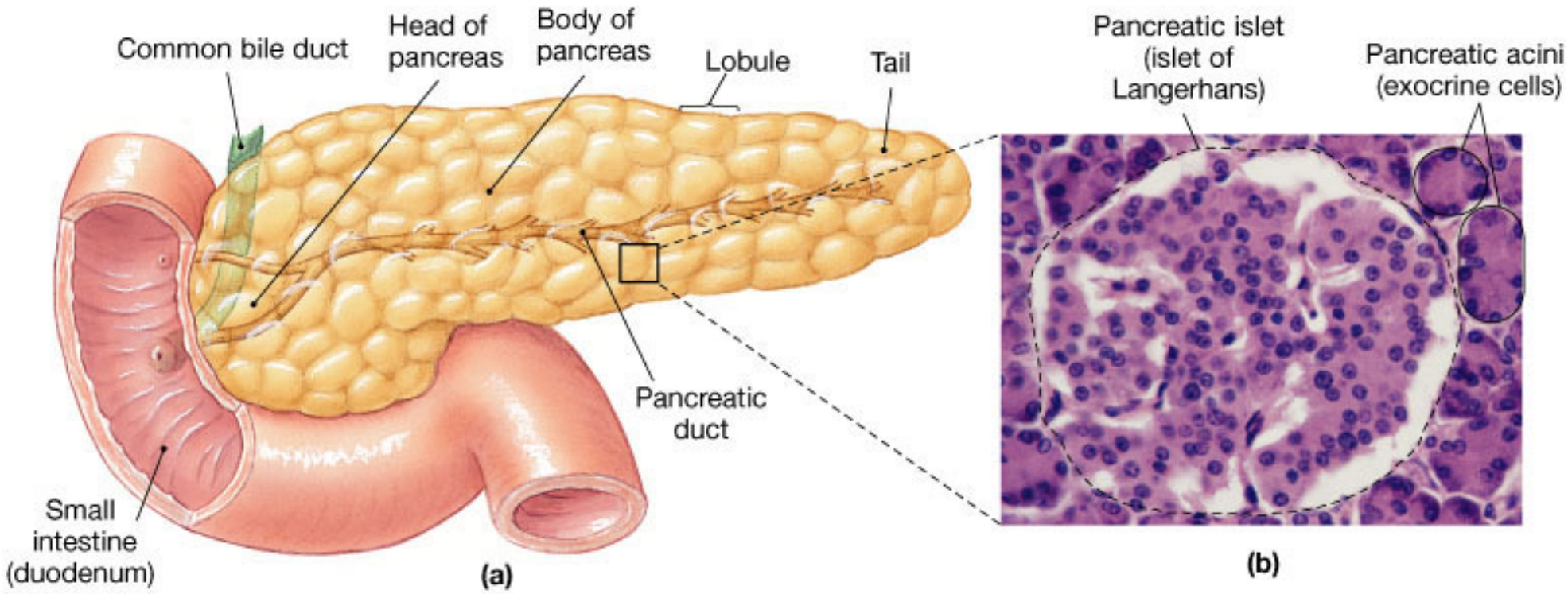
  also: Vitamin B12 and penicillin; Nobelprize in Chemistry 1964

- 2000: James Shapiro and colleagues establish the "Edmonton protocol" revitalizing efforts to cure type 1 diabetes by transplantation.

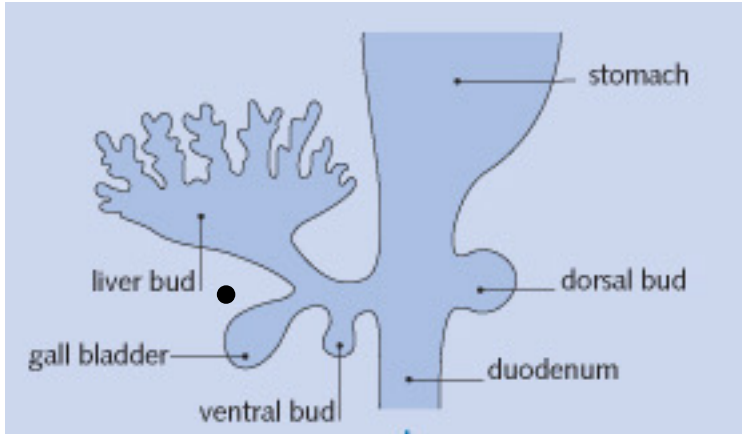
The Pancreas-anatomy



The Endocrine Pancreas

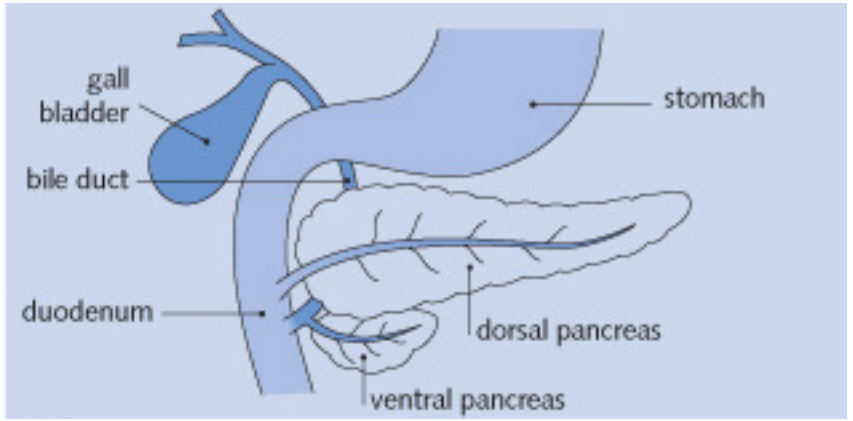


Embryological Development of the pancreas

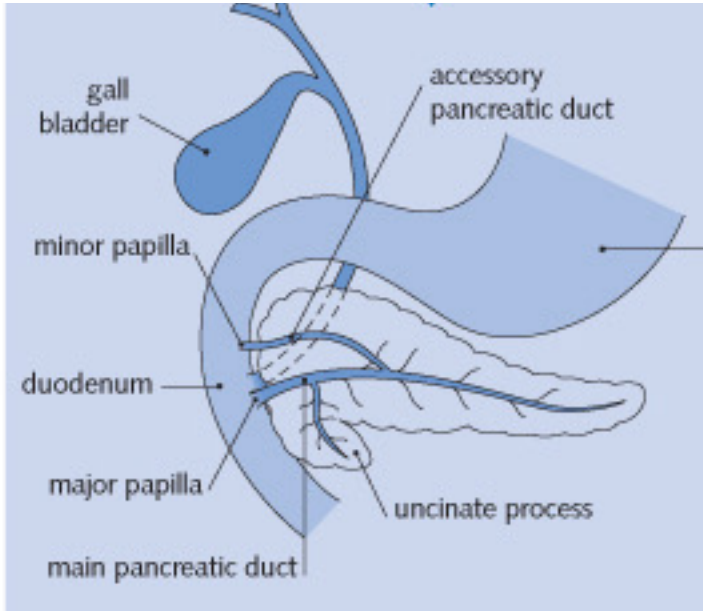


30 days gestation

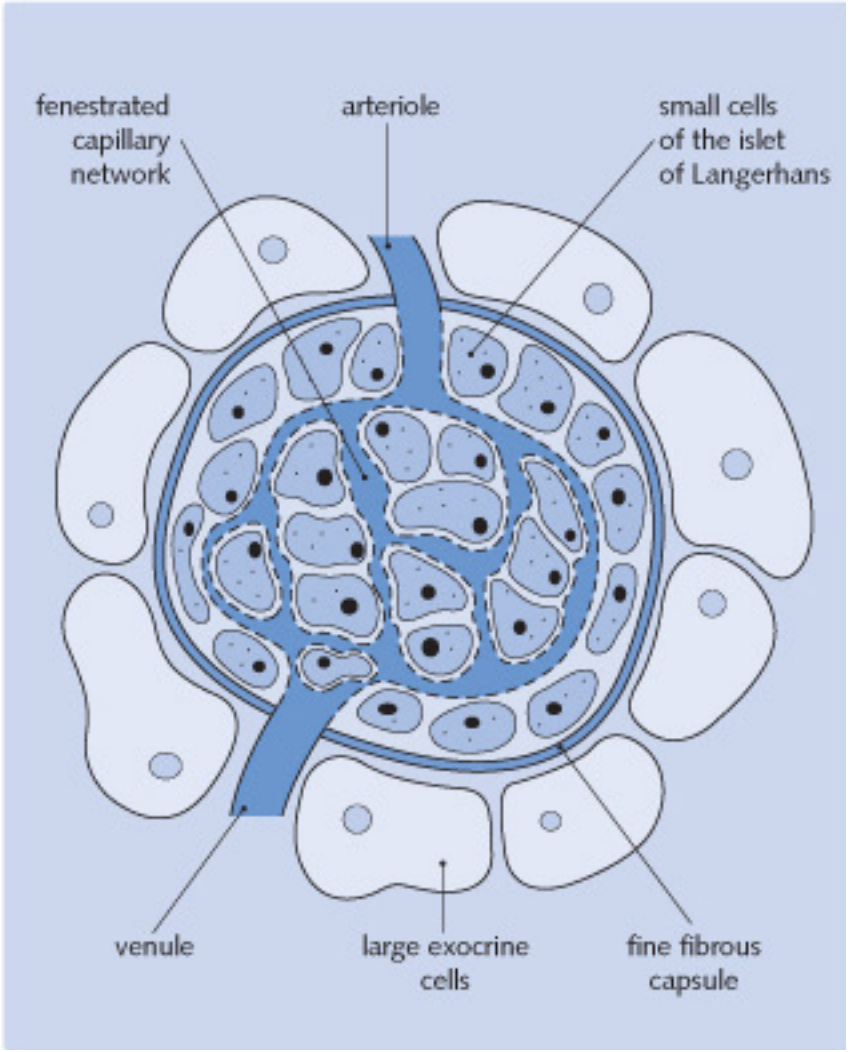
- 6 weeks gestation



7 weeks gestation

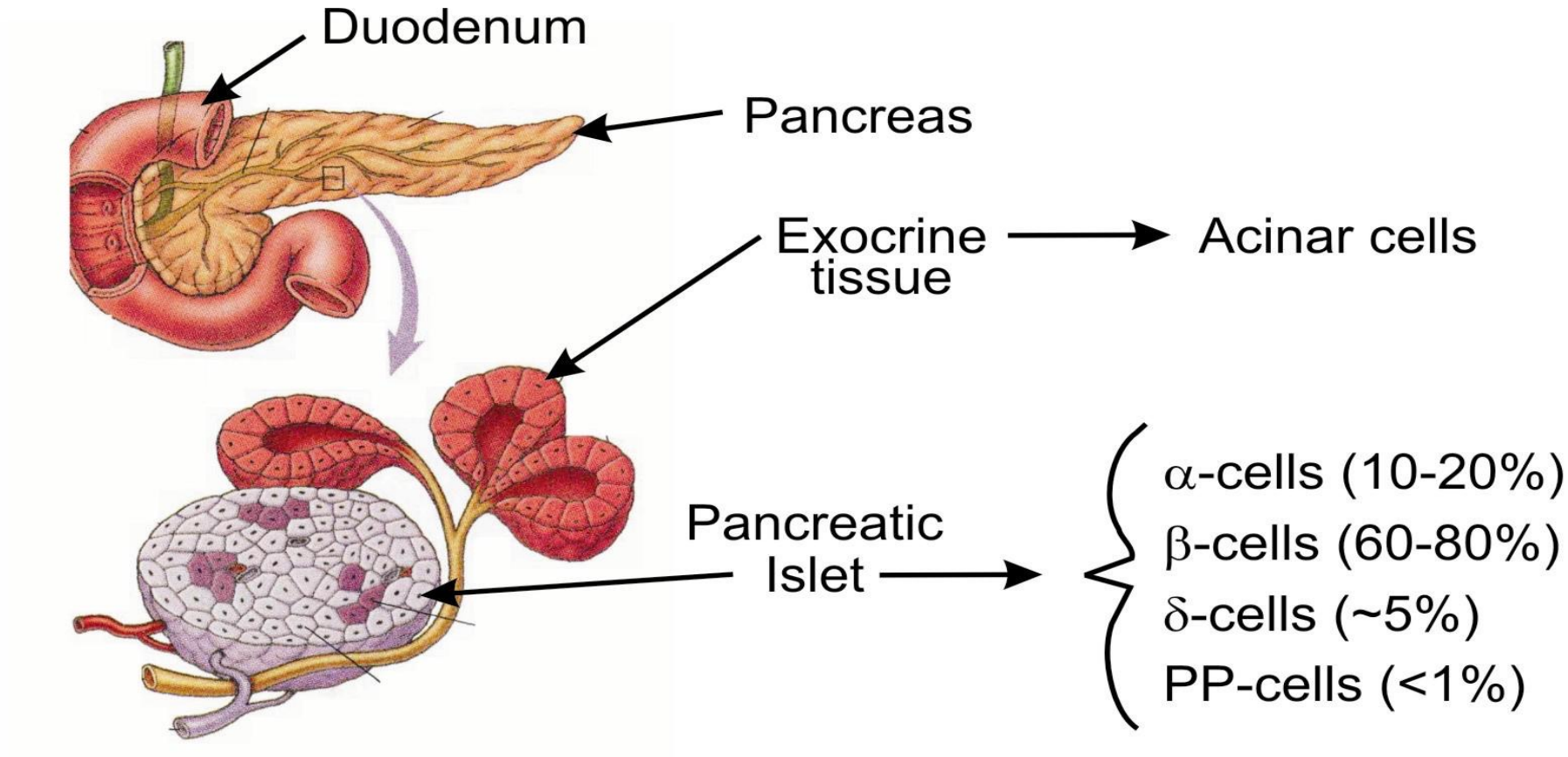


The pancreatic islets

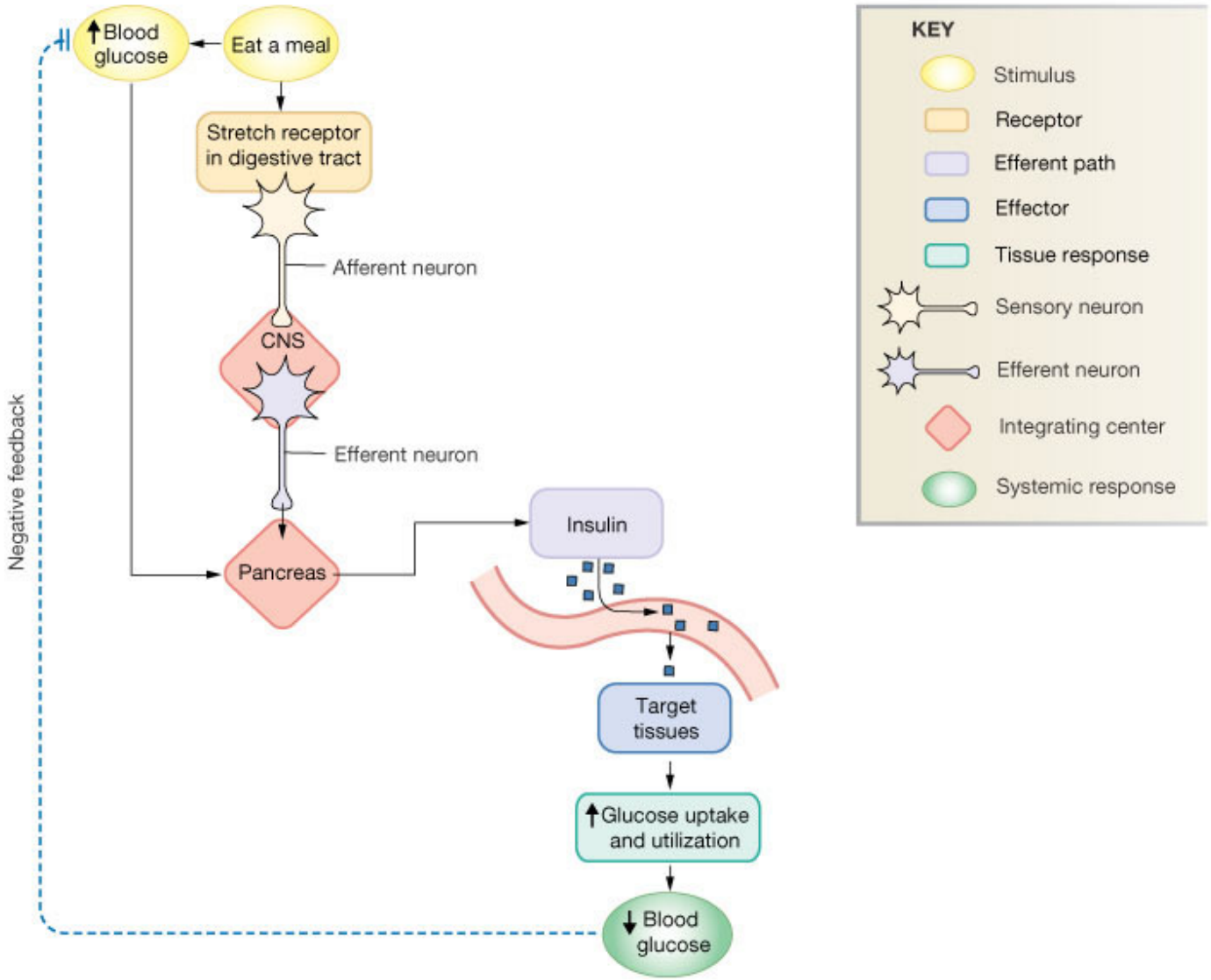


- Clusters of endocrine cells within the pancreas called Islets of Langerhans or pancreatic islets
  - α cells secrete glucagons
  - β cells secrete insulin
  - δ cells secrete somatostatin
  - PP cells secrete pancreatic polypeptide
  - β cells are the most numerous and located at the center of the islet while the other cells are located around the periphery

Pancreatic Islets within Pancreas



Endocrine Reflex Pathways: Overview



Glucose: Insulin and glucagon

- Insulin lowers blood glucose by increasing the rate of glucose uptake and utilization
- Glucagon raises blood glucose by increasing the rates of glycogen breakdown and glucose manufacture by the liver

Glucose: sources

- 1. food
- 2. Storage: glycogen
- 3. De novo synthesis: gluconeogenesis

Glucose uptake from food:

sodium-glucose-transporter 1: SGLT1

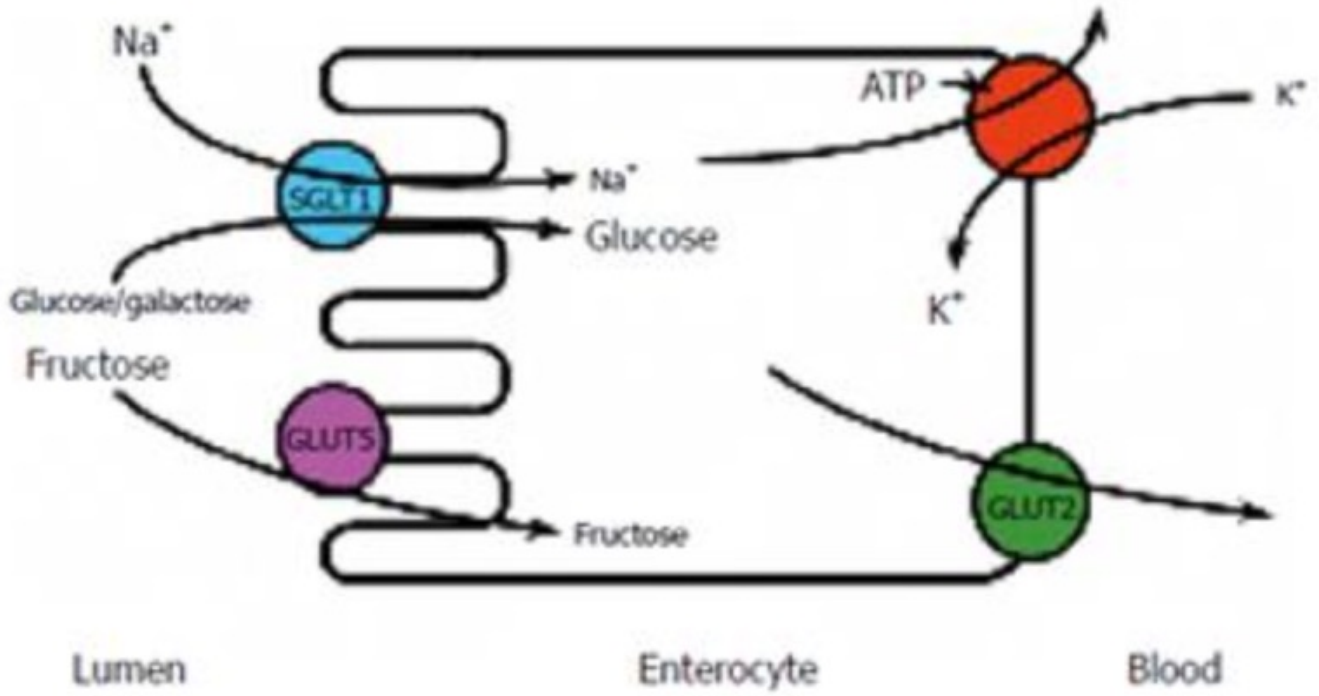
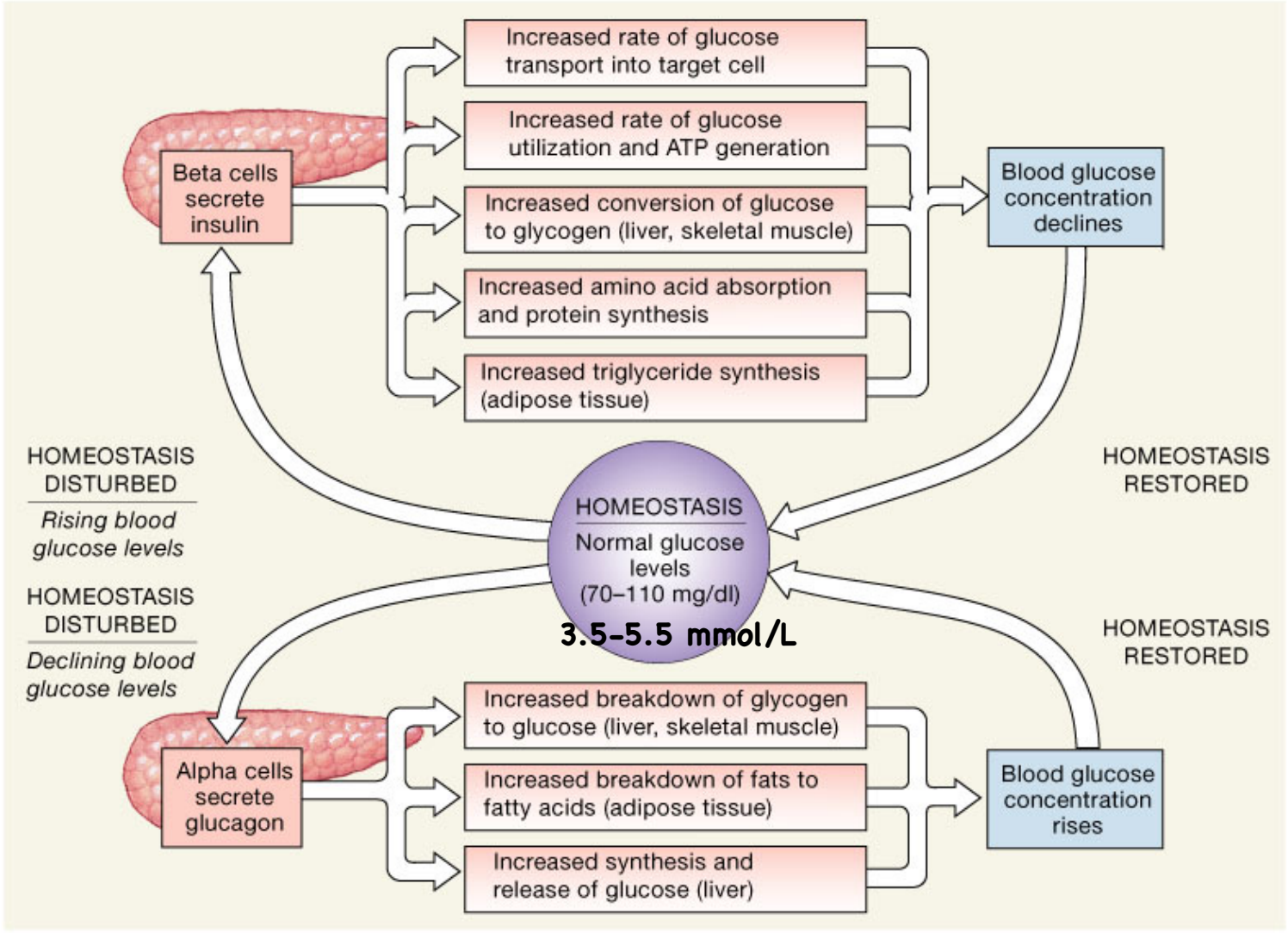


Figure 1 Classical model of intestinal sugar transport (from Wright, 1998). SGLT1 is the sodium dependent glucose/galactose transporter on the brush border membrane (BBM). The Na+K+-ATPase on the basolateral membrane (BLM) maintains the gradient necessary for the functioning of SGLT1. GLUT5 is a facilitative transporter on the BBM which transports fructose into the cell. GLUT2 on the BLM transports glucose, galactose and fructose out of the cell.

The Regulation of Blood Glucose Concentration

Hypoglycemic:

insulin

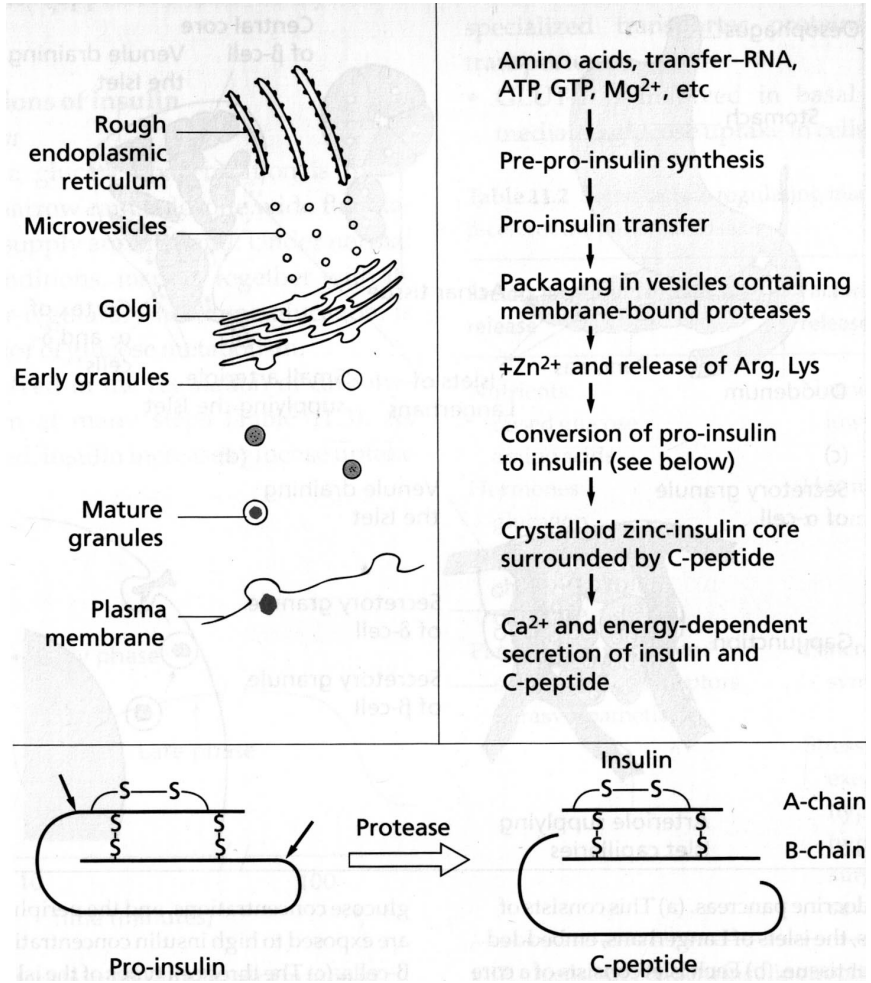


Hyperglycemic:

Glucagon
Growth hormone
Adrenalin
cortisol

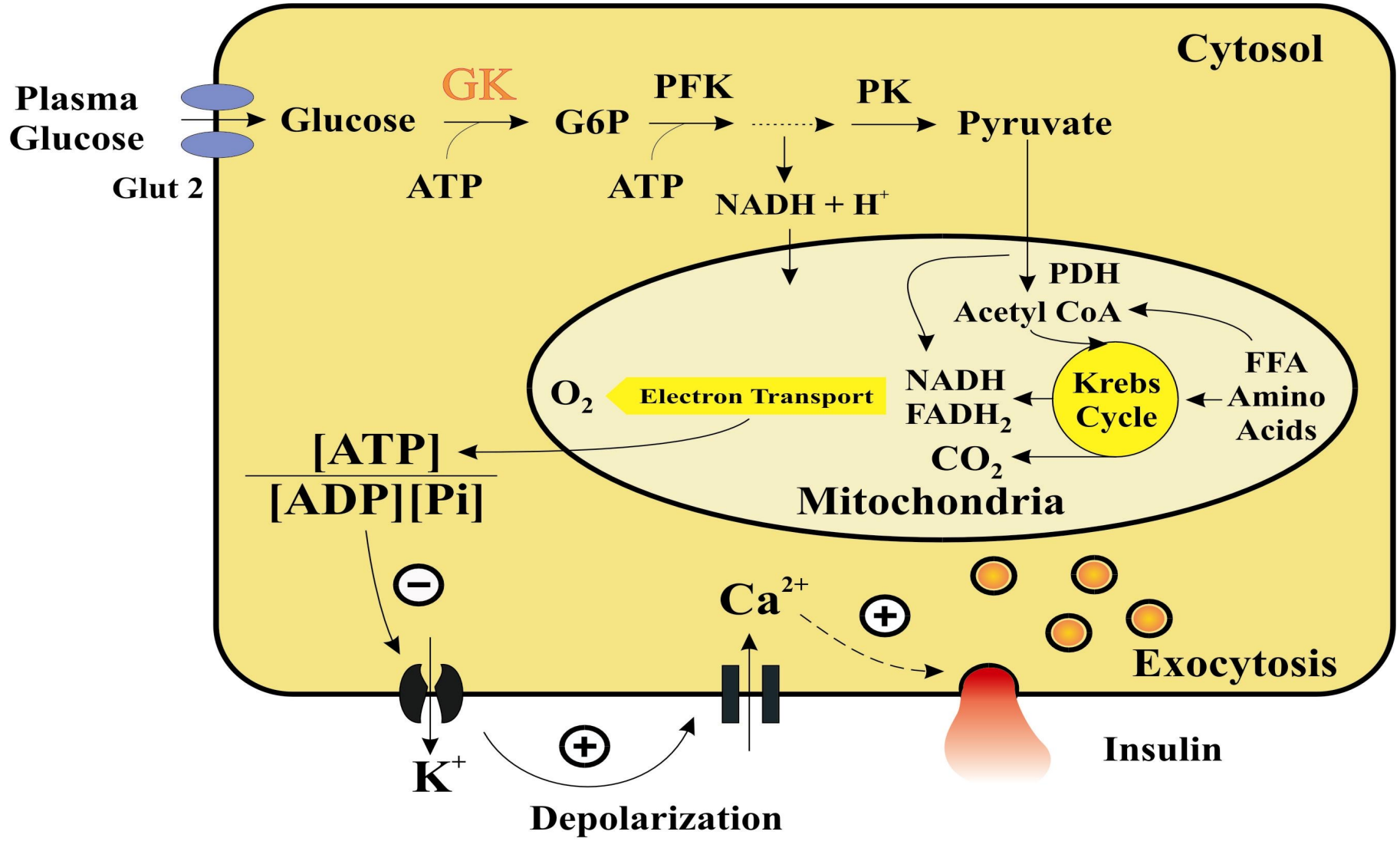
- Hyperglycemia: Fasting glucose concentrations > 7.8 mmol/L
- Hypoglycemia: Fasting glucose concentrations < 2.5 mmol/L

Insulin secretion



- protein synthesis in the rER yields preproinsulin which is transferred into the lumen of the ER
- hydrolysis yields proinsulin which is transferred to the Golgi about 20 min after initiation of protein synthesis
- in the Golgi soluble zinc-containing proinsulin hexamers are found
- proinsulin is enclosed in vesicles that carry specific proteases bound to the membrane
- within 0.5-2 hours, the specific proteases act on proinsulin to release the C-peptide and insulin within the granule
- when the cells are stimulated release occurs
- proinsulin: 86 amino acids
- insulin: 51 amino acids, 21 α chain, 30 β chain

Stimulus-secretion coupling



Factors regulating insulin release

Factors increasing insulin release	**Factors decreasing insulin release**
Nutrients:	**Nutrients:**
raised glucose	low glucose
amino acids, fatty acids, ketones	
Hormones:	**Hormones:**
glucagon	somatostatin
ACTH, TSH	
gastrin, secretin, cholecystokinin	
GIP, GLP-1	
Pancreatic innervation:	**Pancreatic innervation:**
sympathetic α receptors	sympathetic β receptors
parasympathetic	**Stress**
	exercise, hypoxia, hypothermia,
	surgery, severe burns

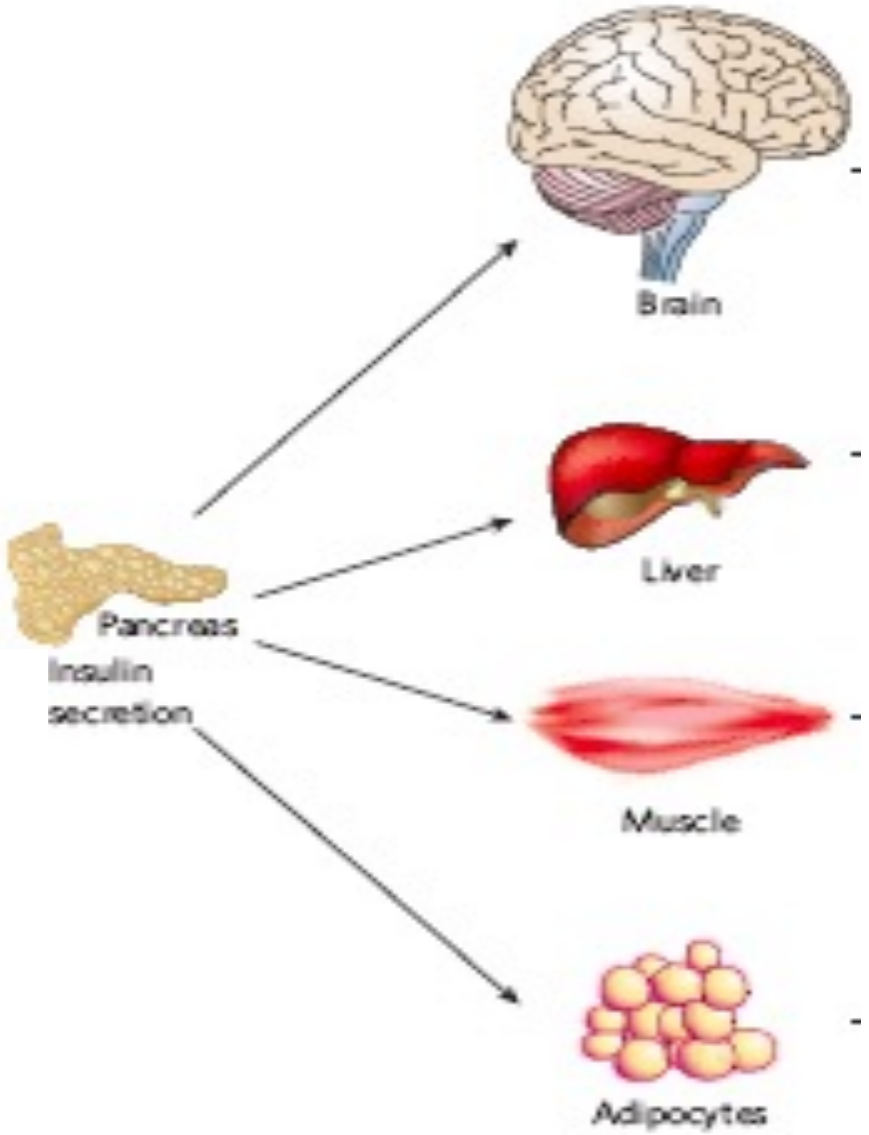
Insulin signals the “fed” state

- Has major anabolic actions on intermediate metabolism affecting glucose, lipid, and protein metabolism.

- 60% of the secreted insulin is removed by the liver

=> insulin concentrations reaching the liver are almost 3x higher than in the peripheral circulation

Metabolic effects of insulin on target cells



- may stimulate satiety (fullness)

- + glycogenesis (glucose to glycogen)
- -glycogenolysis (glycogen to glucose)
- -gluconeogenesis (amino acids to glucose)

- + glucose uptake
- + glycogenesis (glucose to glycogen)
- + glycolysis (glucose to energy)
- +amino acid uptake and protein synthesis
- -glycogenolysis (glycogen to glucose)
- -proteolysis

- + glucose uptake
- + lipogenesis (glucose to fatty acids)
- -lipolysis (fatty acids to energy)

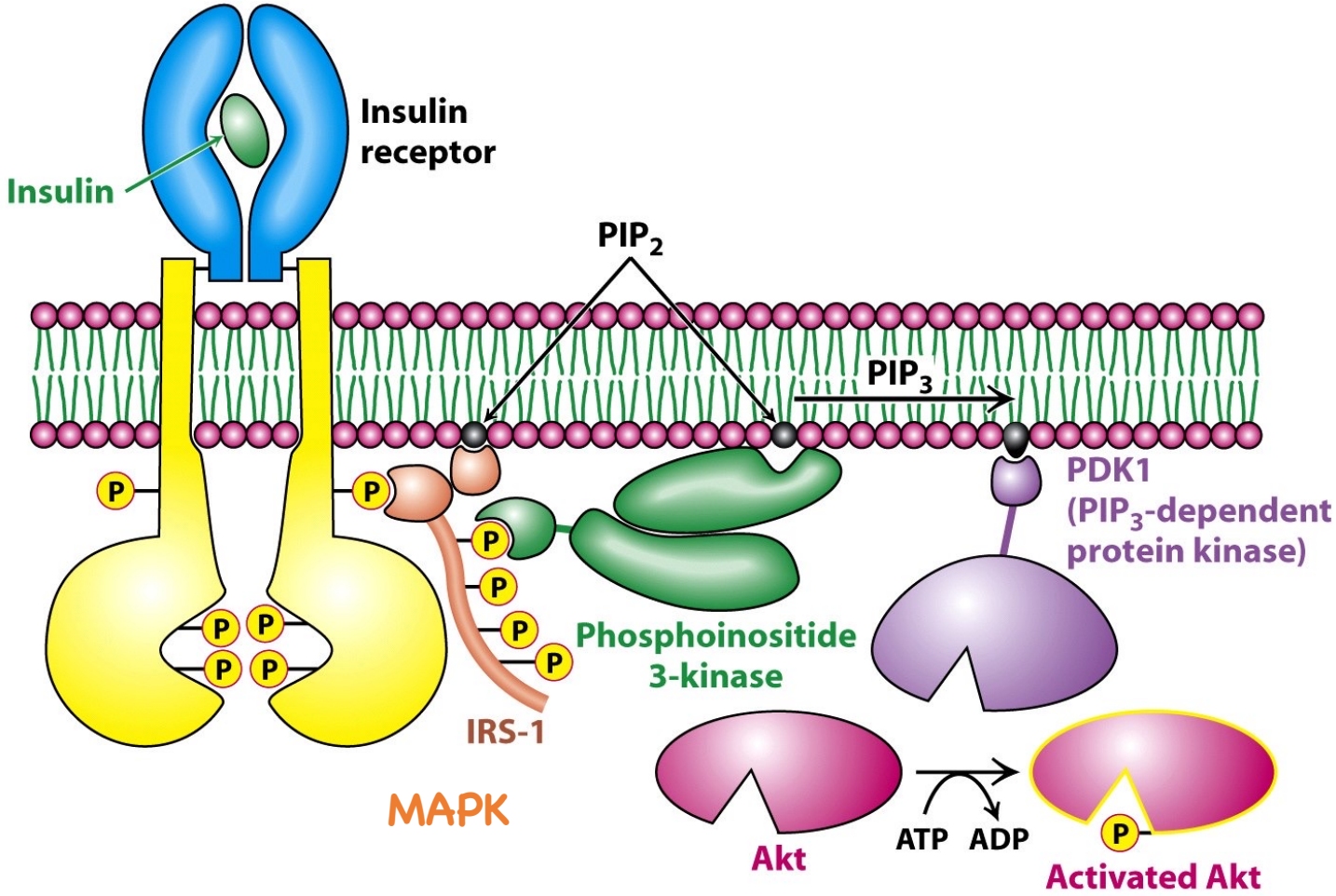
Metabolic effects of glucagon on target cells

Target cells	Action of glucagon
Muscle cells and many other cells	Stimulates glycogenolysis (glycogen → glucose)
	Inhibits glucose uptake
	Inhibits glycolysis (glucose → energy)
	Inhibits amino acid uptake and protein synthesis
Adipose cells	Stimulates lipolysis (fatty acids → energy)
Liver cells	Stimulates glycogenolysis (glycogen → glucose)
	Stimulates gluconeogenesis (amino acids → glucose)
	Stimulates ketogenesis (fatty acids → ketone bodies)

- Primary site of glucagon action is the liver.
- Glucagon binds to its receptors that are linked to adenylate cyclase.

Regulation of blood glucose concentration

- insulin facilitates absorption of food from the gut
- 90% of glucose is stored as lipids
- fatty acids, mobilized from adipose tissues under the control of a number of hormones (epinephrine, glucocorticoids, glucagon, growth hormone), provide a substrate for liver and muscle metabolism.
- Ketone bodies produced in the liver provide an energy source for muscle and brain during long periods of fasting.



Glucose transport

Glycogen synthesis

Lipogenesis+ Lipolysis -

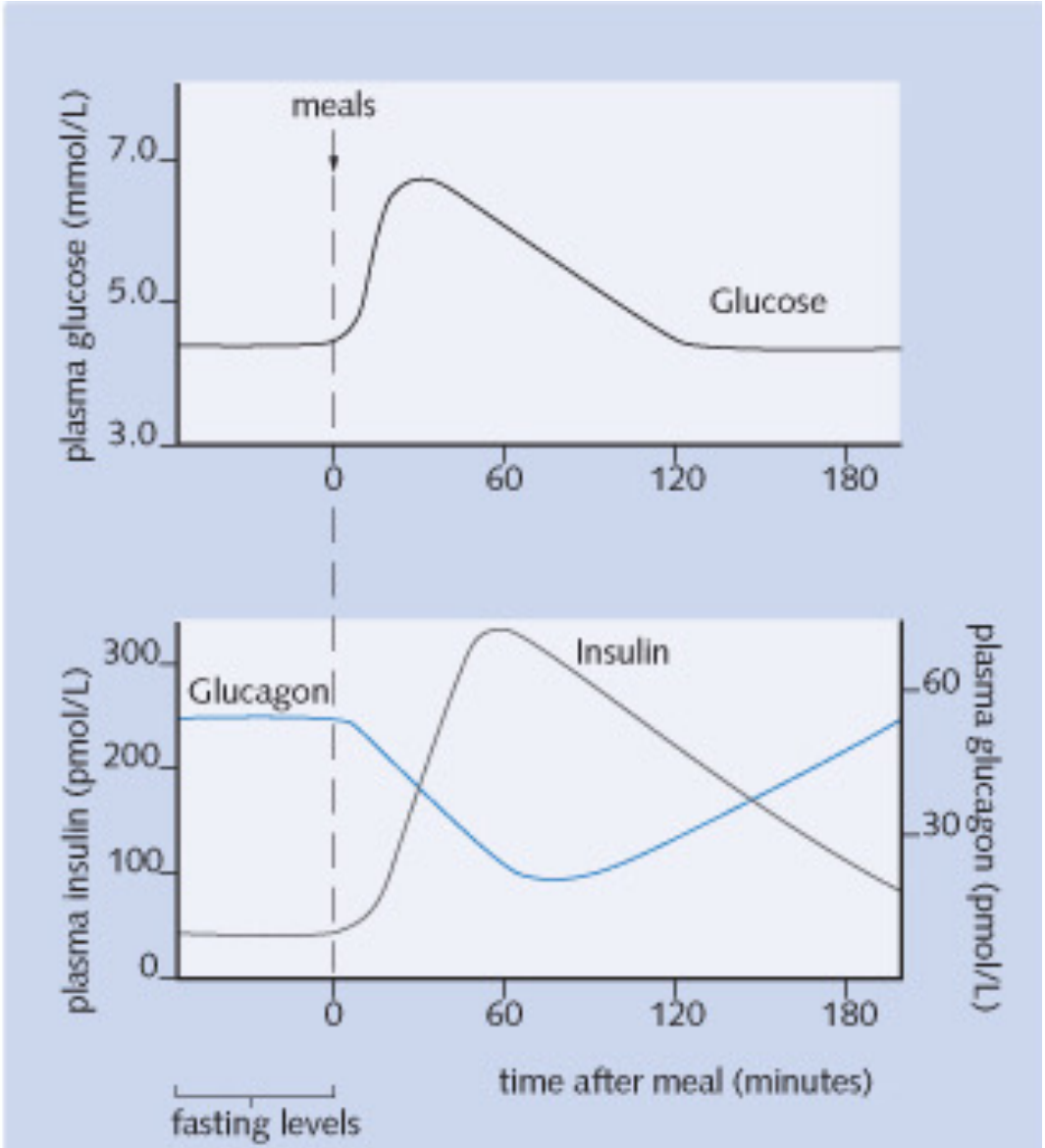
protein synthesis

gene expression

cellular growth

Responses that alter blood glucose levels

Responses that raise blood glucose	**Responses that lower blood glucose**
Ingestion of glucose in the diet	Increased uptake in cells
Gluconeogenesis (liver): irreversible conversion of amino acids to glucose	Metabolism to produce energy
Glycogenolysis (liver)-the irreversible breakdown of glycogen to release glucose	Glycogenesis-the reversible conversion of glucose to glycogen
	Lipogenesis, the irreversible conversion of glucose to fatty acids

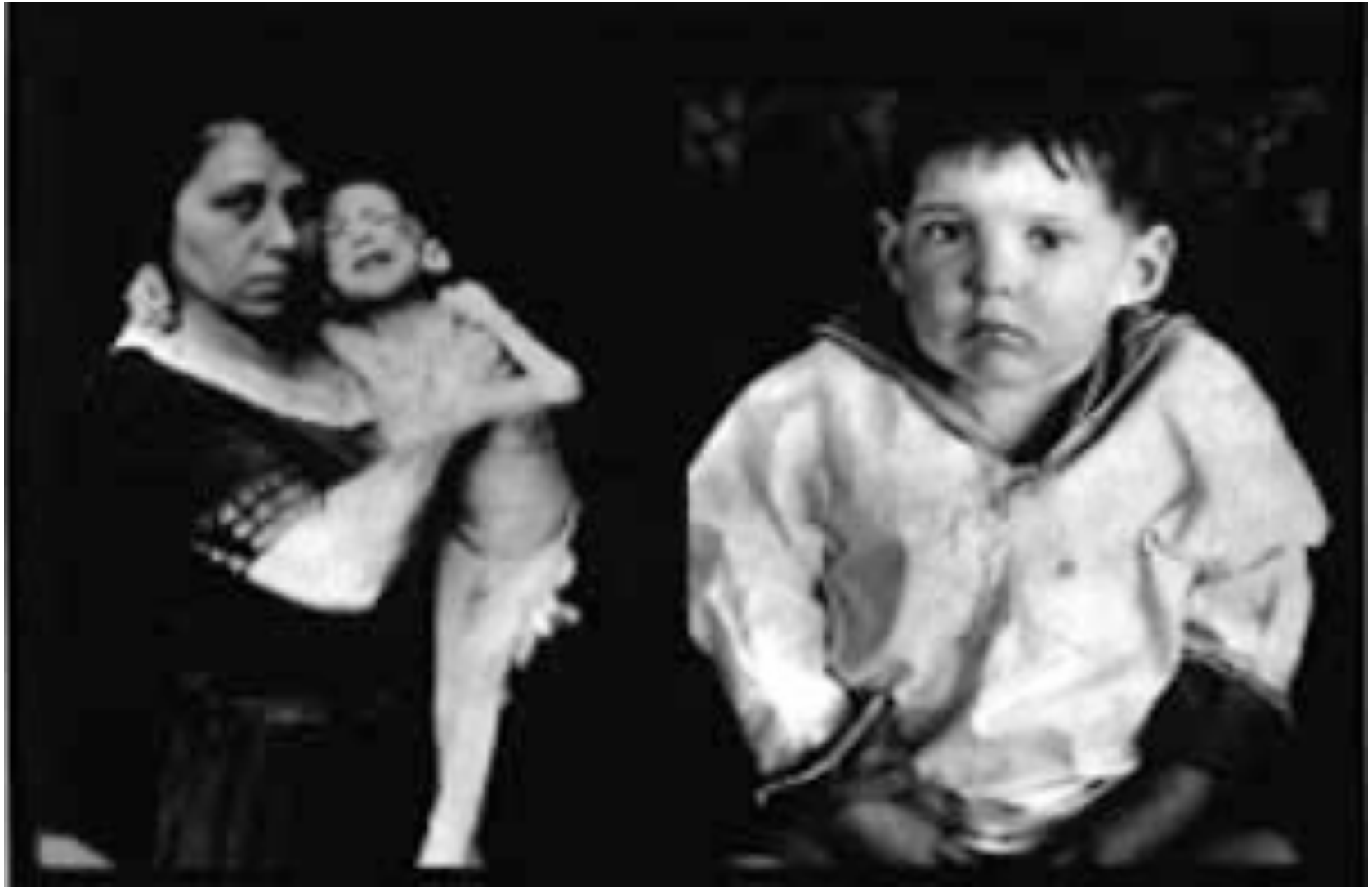


NB Basal secretion of insulin occurs during fasting because body cells require insulin in order to take up and utilize blood glucose

2 Types of Diabetes Mellitus

- Insulin-dependent diabetes mellitus (IDDM), Type I
- Non-insulin-dependent diabetes mellitus (NIDDM), Type II

Type I Diabetes



Presenting features of type I Diabetes

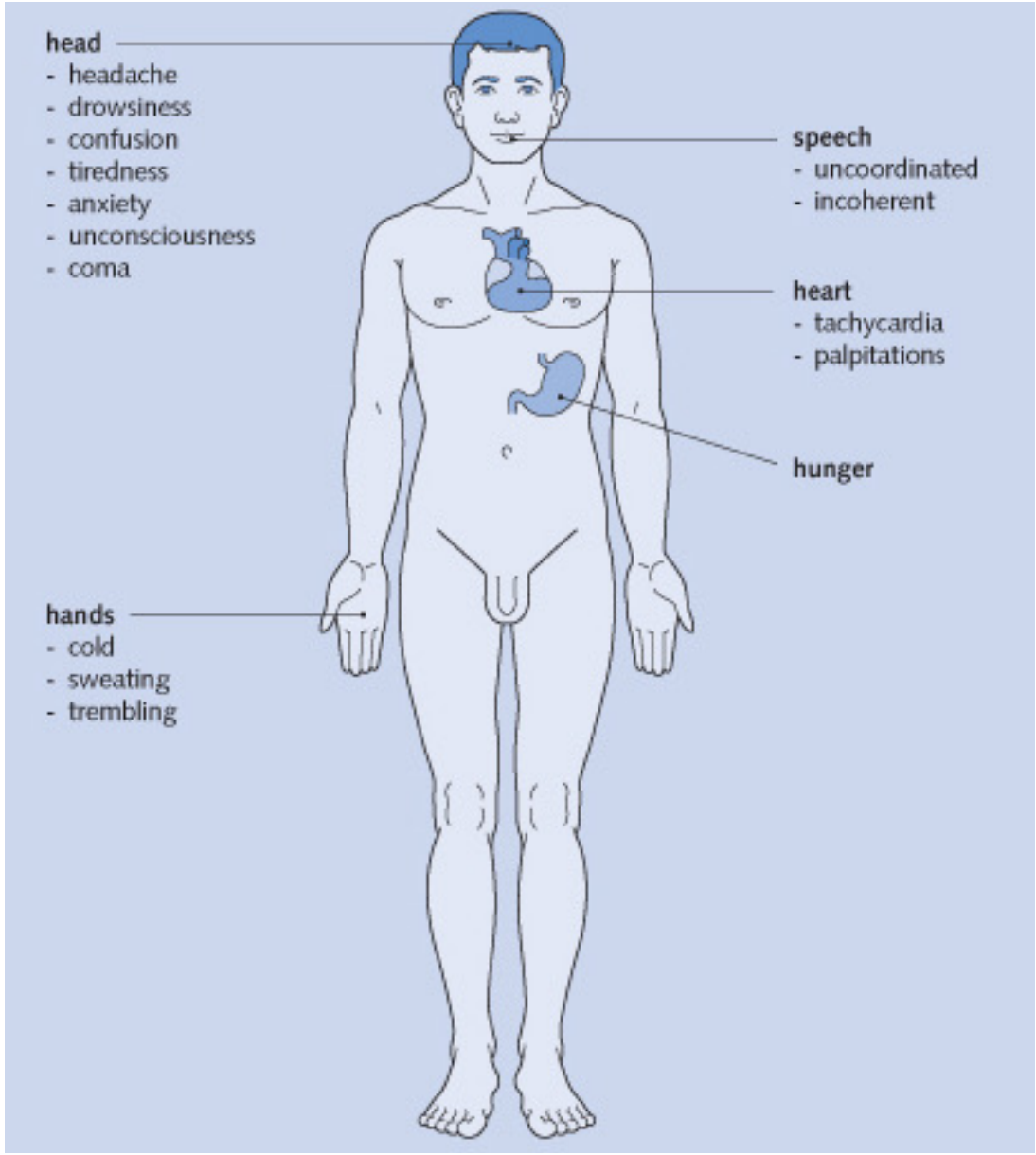
- Symptoms relating to osmotic effect of the hyperglycemia
  - Increased thirst and polydipsia
  - Polyuria and nocturia
  - Blurred vision
  - Drowsiness and dehydration

- Cutaneous candidal infections
  - Vulva (pruritus vulva)
  - Foreskin (balanitis)

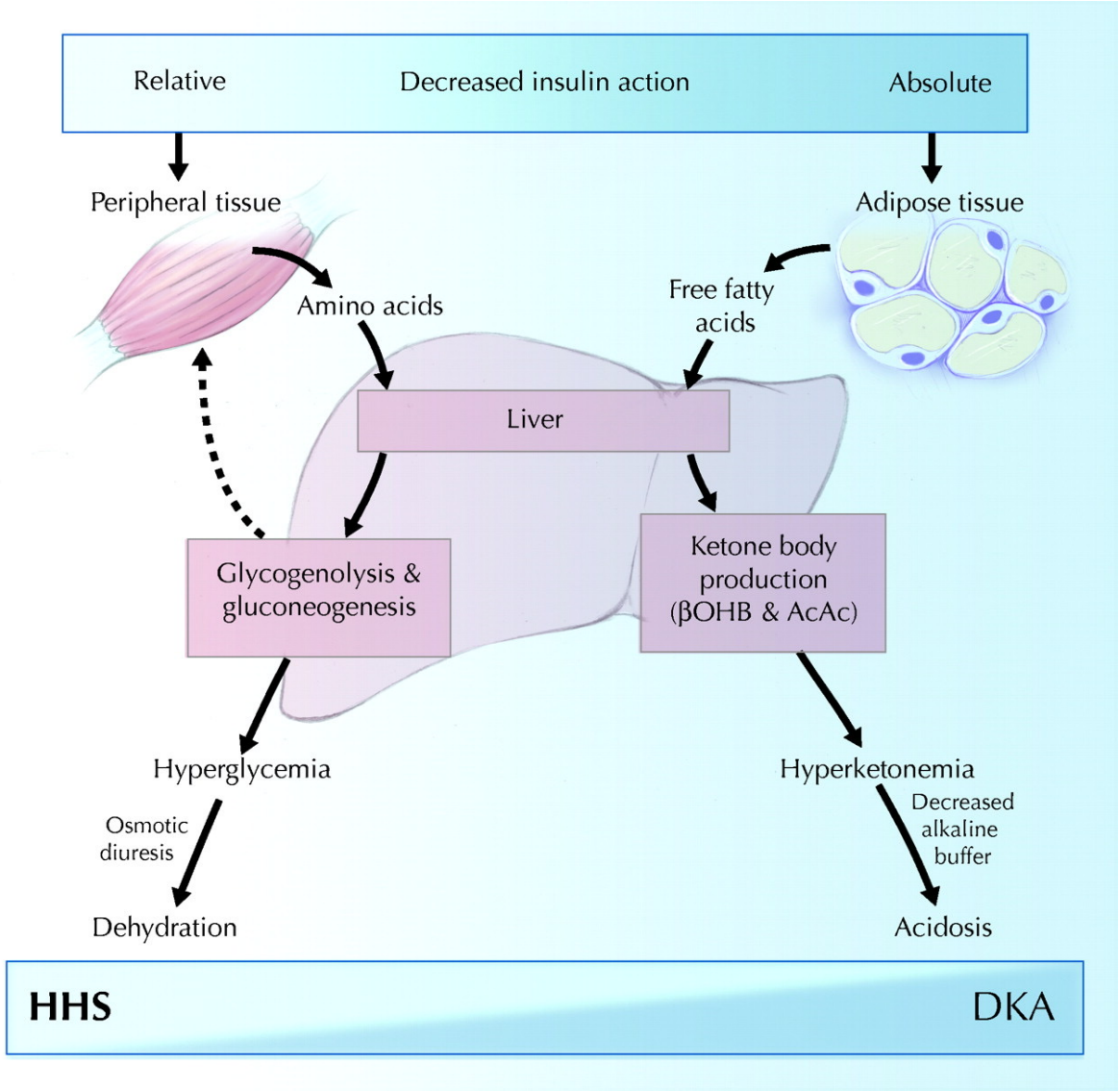
- Symptoms relating to the inability to transport fuel substrates
  - Extreme fatigue
  - Muscle wasting through protein breakdown
  - Weight loss

- Diabetic ketoacidosis

Symptoms of hypoglycemia



Ketoacidosis (Type I)



- ketone bodies metabolic acidosis-lipolysis

Therapy:

- IV insulin 12-20 u bolus
- .05 to 0.1 u/kg/hr
- Intravenous fluid - 0.9% normal saline
- glucose approx. 200 add dextrose
- potassium electrolytes as needed

hyperglycemic hyperosmolar state diabetic ketoacidosis

Jean-Louis Chiasson et al. CMAJ 2003;168:859-866

Symptoms of ketoacidosis

Type I Diabetes (Juvenile diabetes)

Autoimmune destruction of the insulin producing b-cells

The body cells fail to take up glucose.
Plasma glucose rises, overflows into the urine taking with it water, and increasing the urine volume.
The liver then produces ketones, which eventually acidify the blood.
The brain cannot function in an acid medium.

Therapy:

1920 Insulin

Pathogenesis

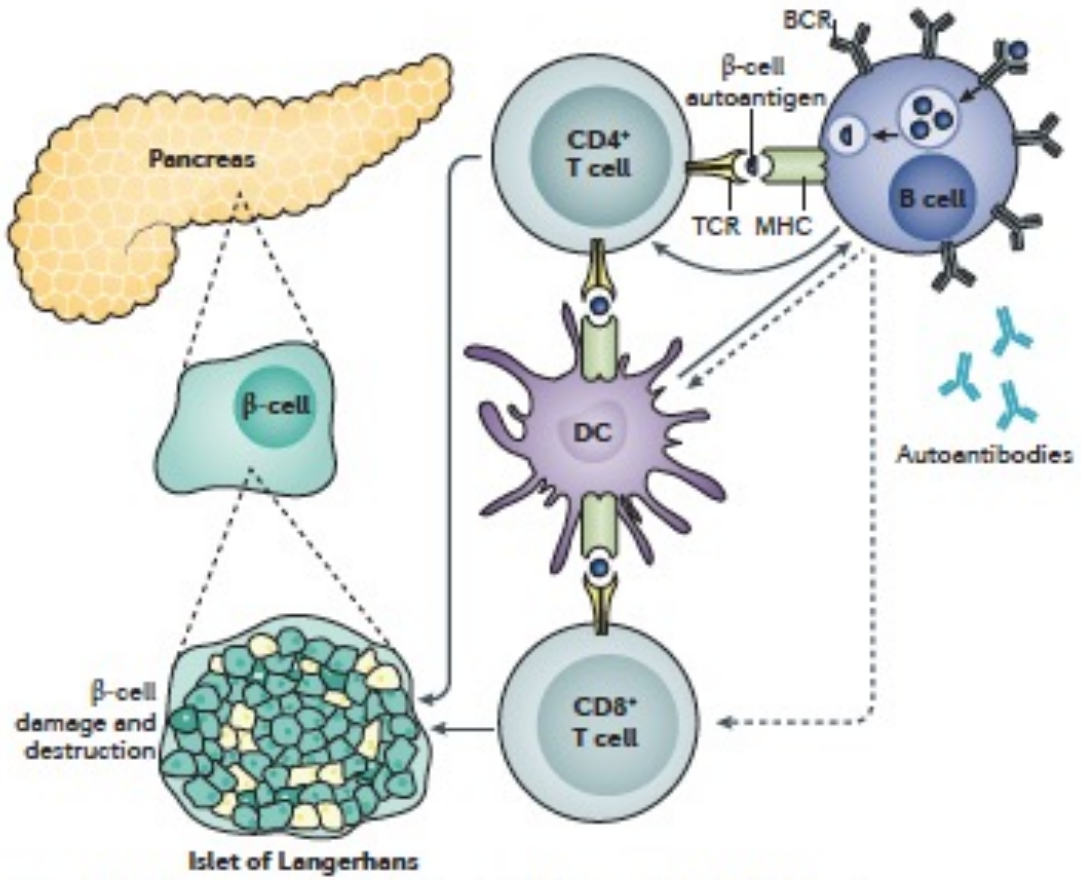


Figure 4 | **Pathogenesis of T1DM.** Type 1 diabetes mellitus (T1DM) is an immune-mediated disease. Activated B cells interact with CD4+ and CD8+ T cells, as well as dendritic cells (DCs). Antigen presentation by B cells and DCs drives the activation of β-cell-specific T cells. In addition, the exposure of B cells to β-cell autoantigens leads to the production of islet-targeting autoantibodies, which serve as biomarkers of asymptomatic disease. Dashed arrows indicate the potential interactions between B cells and CD8+ T cells and between B cells and DCs. BCR, B cell receptor; TCR, T cell receptor.

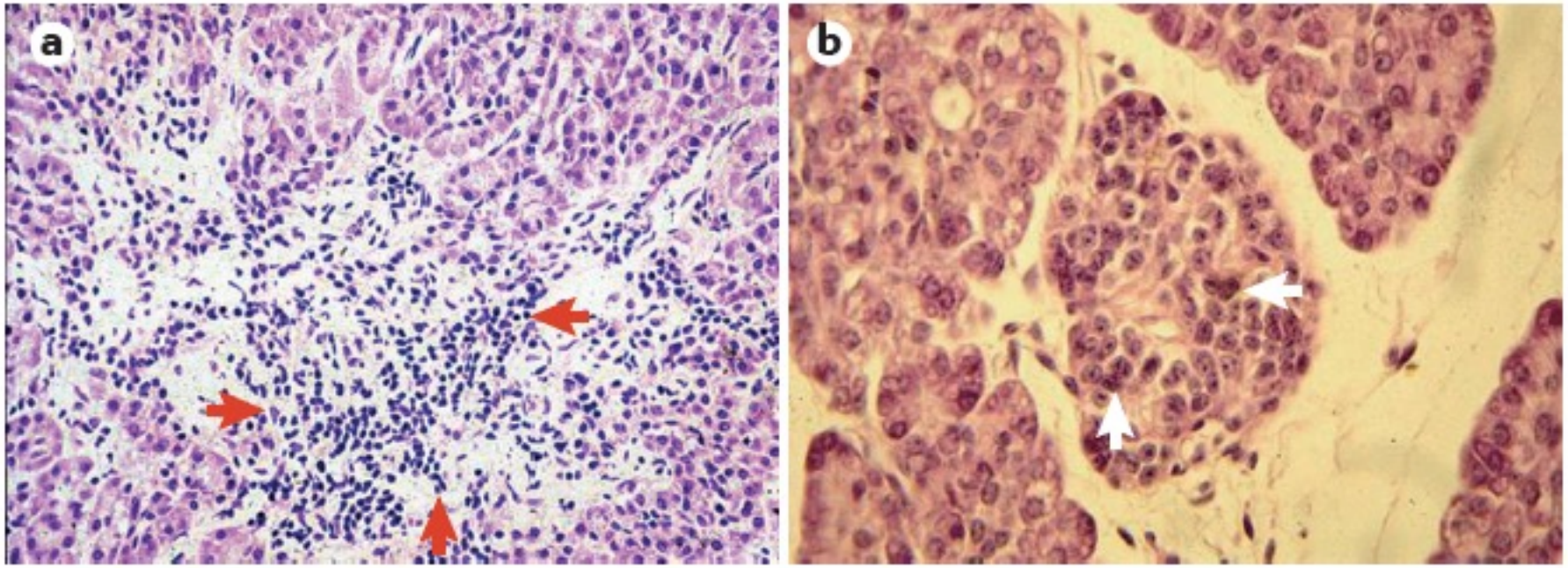
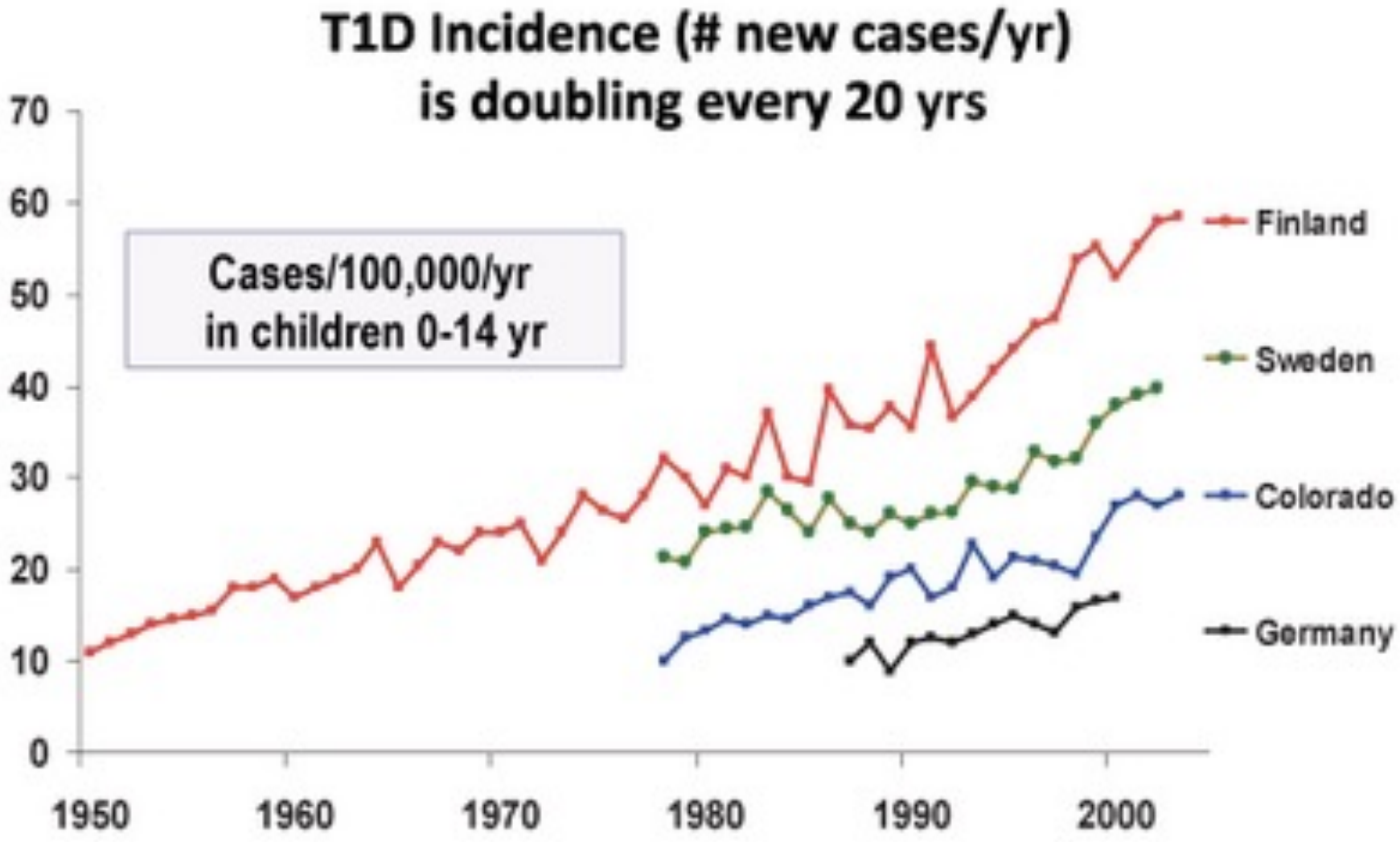


Figure 5 | **Pancreatic inflammation and insulitis in T1DM.** Histological examination of pancreas tissue after symptom onset (diabetic ketoacidosis) shows very severe insulitis with massive mononuclear cell infiltration in and around the pancreatic islets in one patient (part **a**; red arrows; magnification ×125) and less-severe insulitis only involving dendritic cells in another patient (part **b**; white arrows; magnification ×250). Biopsies were obtained from individuals who carried the *HLA-DR3/4* genotype and succumbed to brain oedema <1 week after symptom onset. Adapted with permission from REF. 108, Springer.


T1D Incidence (# new cases/yr)
is doubling every 20 yrs
Cases/100,000/yr
in children 0-14 yr
70
60
50
40
30
20
10
0
1950
1960
1970
1980
1990
2000
Finland
Sweden
Colorado
Germany

Aetiology of Type I diabetes

- An environmental factor triggers a selective autoimmune destruction of the β-cells of the pancreas in a genetically predisposed individual

- Genetic risk
  - HLA region allele combinations important to T cell tolerance
  - Class II HLA region in MHC: HLA-DR, HLA-DQ
  - Other loci: modify the vulnerability of b-cell to inflammatory mediators

- Putative environmental triggers:
  - Chemicals: N-nitro compounds
  - Viruses: mumps, rubella, cytomegalovirus, enteroviruses
  - Increased hygiene
  - Vaccination
  - Stress
  - Perinatal factors: maternal rubella, blood group incompatibility, maternal age, birth weight, gestational age, birth order
  - Food components: milk and wheat protein, Vitamin D deficiency

The 'Hygiene hypothesis' and the sharp gradient in the incidence of autoimmune and allergic diseases between Russian Karelia and Finland

ANITA KONDRASHOVA,[1] TAPIO SEISKARI,[1,2] JORMA ILONEN,[3,4] MIKAEL KNIP,[5,6,7,8] and HEIKKI HYÖTY[1,2]

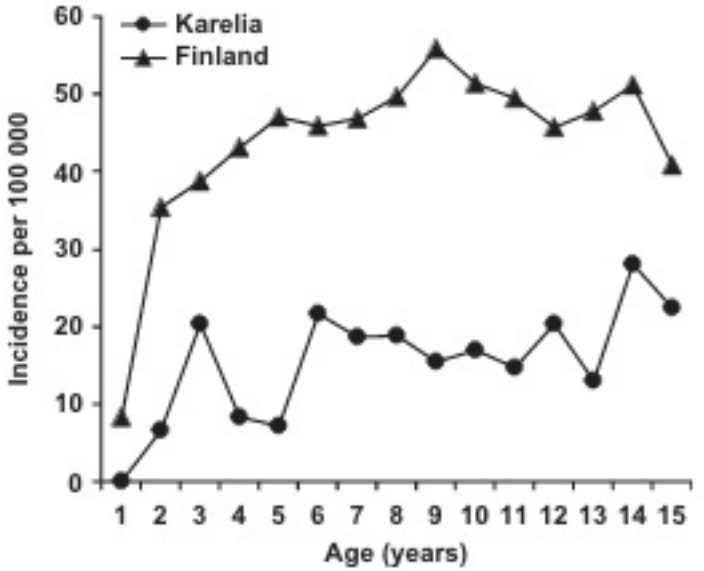
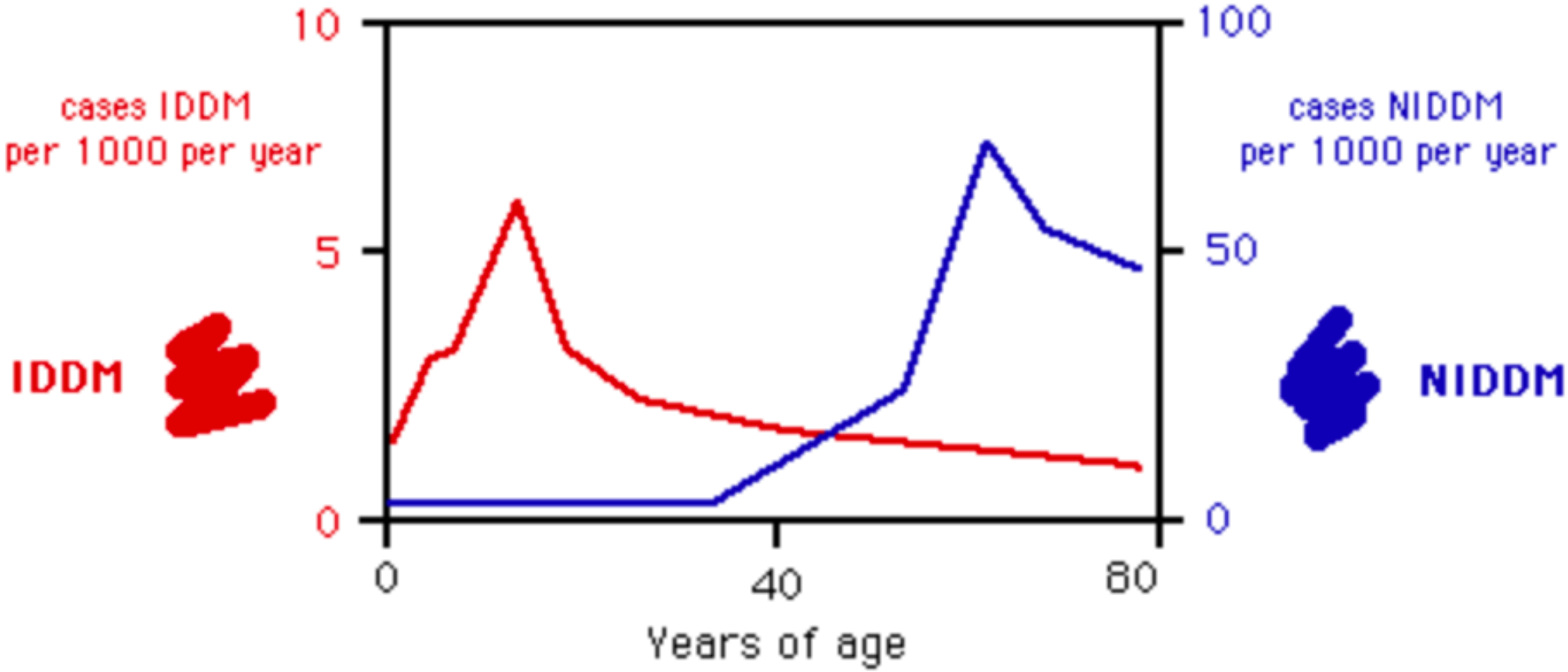
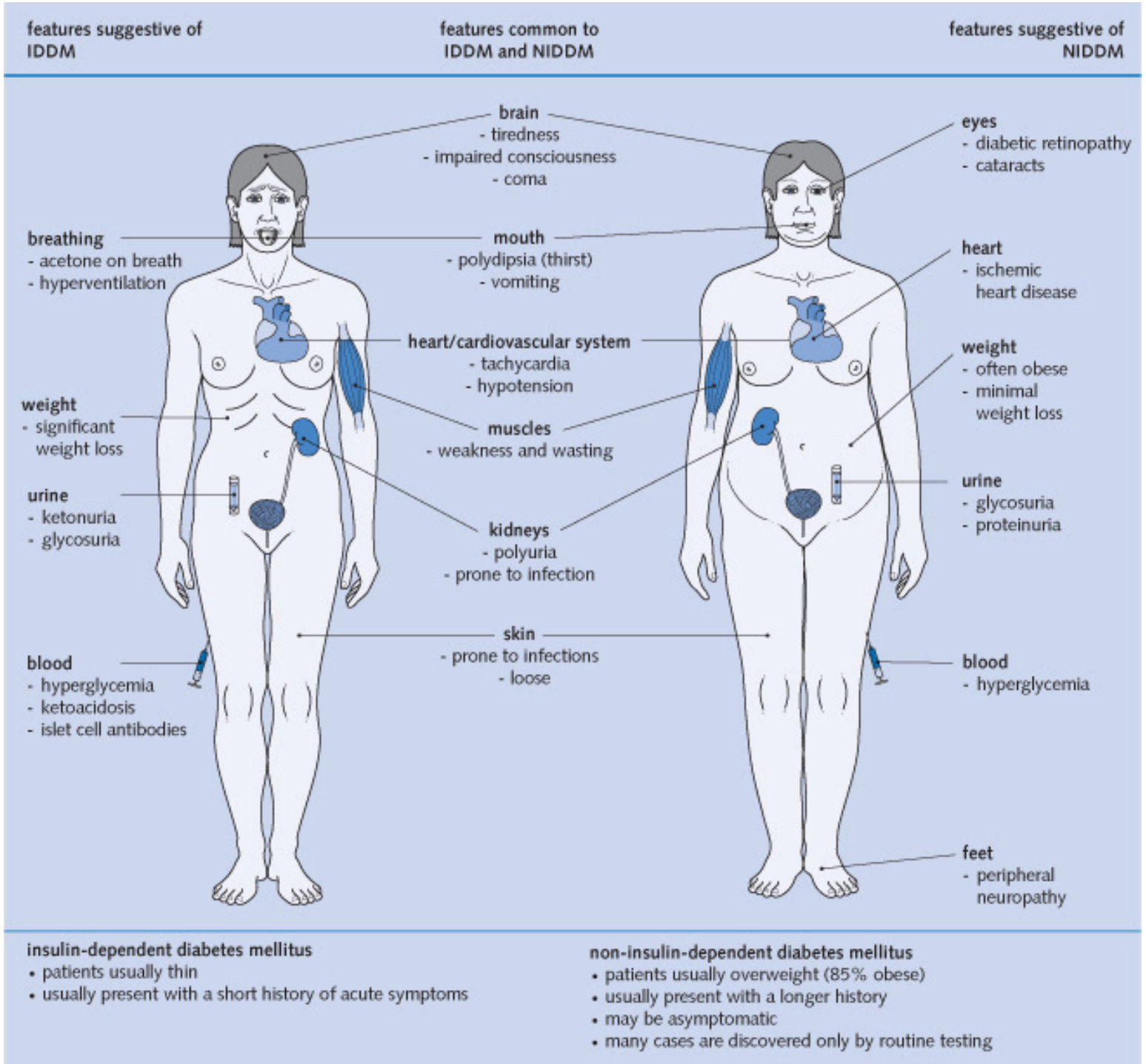


Fig. 2. Annual incidence of type 1 diabetes by age in 0–14-year-old children in Russian Karelia (circles) and Finland (triangles) during the years 1990–99.

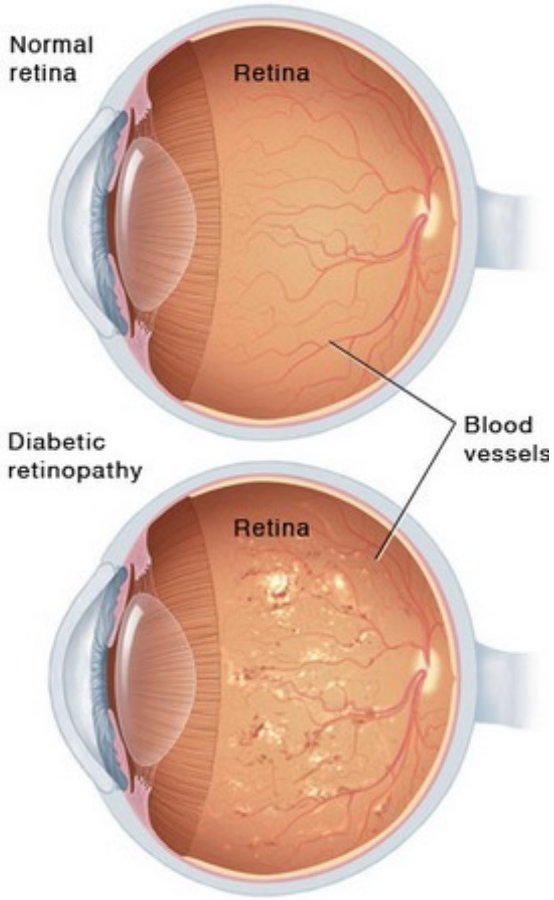
Incidence of IDDM and NIDDM with age




features suggestive of IDDM
features common to IDDM and NIDDM
features suggestive of NIDDM
brain
- tiredness
- impaired consciousness
- coma
eyes
- diabetic retinopathy
- cataracts
breathing
- acetone on breath
- hyperventilation
mouth
- polydipsia (thirst)
- vomiting
heart
- ischemic heart disease
heart/cardiovascular system
- tachycardia
- hypotension
weight
- often obese
- minimal weight loss
weight
- significant weight loss
muscles
- weakness and wasting
urine
- ketonuria
- glycosuria
urine
- glycosuria
- proteinuria
kidneys
- polyuria
- prone to infection
skin
- prone to infections
- loose
blood
- hyperglycemia
- ketoacidosis
- islet cell antibodies
blood
- hyperglycemia
feet
- peripheral neuropathy
insulin-dependent diabetes mellitus
• patients usually thin
• usually present with a short history of acute symptoms
non-insulin-dependent diabetes mellitus
• patients usually overweight (85% obese)
• usually present with a longer history
• may be asymptomatic
• many cases are discovered only by routine testing

Complications of Diabetes

- Chronic microvascular complications
  - Eyes: retinopathy
  - Kidney
  - Nerves
- Macrovascular complications
  - Myocardial infarction
  - Stroke
  - Peripheral vascular disease



Chronic complications of Diabetes

- Retinopathy: most common cause of blindness in people of working age
- Nephropathy: 16% of all patients needing renal replacement therapy have diabetes
- Erectile dysfunction: may affect up to 50% of men with long-standing diabetes
- Macrovascular disease: 2-3 fold increased risk of coronary heart disease and stroke
- Foot problems: 15% of people with diabetes develop foot ulcers; 5-15% of people with diabetic foot ulcers need amputations