

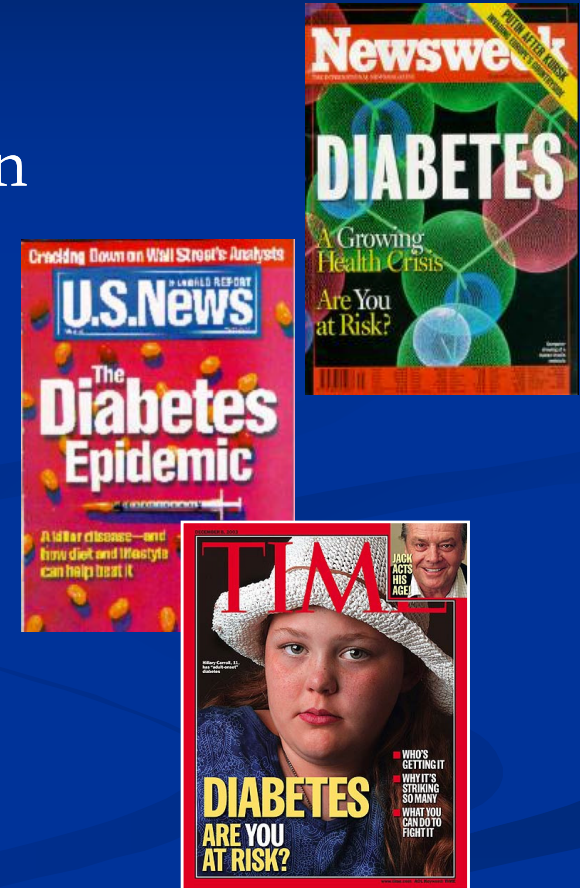
DIABETES MELLITUS

Definition, classification and pathogenesis

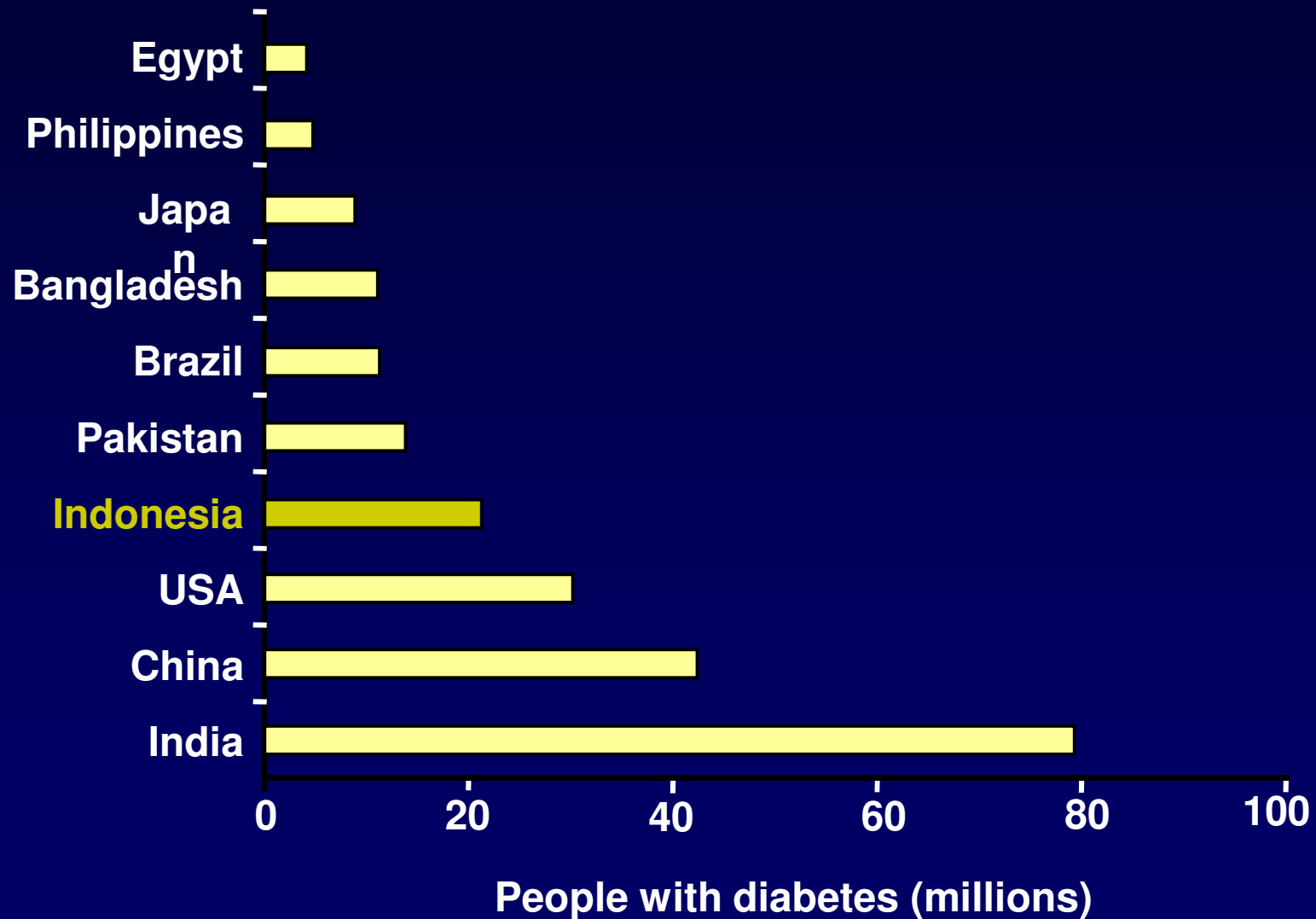
Diabetes Today: An Epidemic

- 20.8 million Americans have diabetes
- 1.5 million new cases in 2005 more than 3500 each day
- Complications of diabetes are a major cause of mortality and morbidity (2002 statistics)

90% of patients with diabetes are treated by primary care physicians



Countries with the highest numbers of estimated cases of diabetes for 2030



Definition of diabetes

Diabetes mellitus is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both.

Definition of diabetes

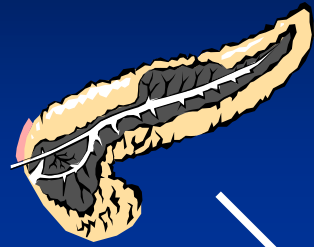
Chronic hyperglycaemia associated with long-term damage to:

- Eyes
- Kidneys
- Nerves
- Heart and blood vessels

CLASSIFICATION OF DIABETES MELLITUS

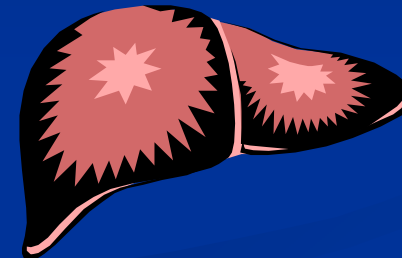
1. Type 1 diabetes (cell destruction, usually leading to absolute insulin deficiency)
2. Type 2 diabetes (ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance)
3. Other specific types of diabetes
4. Gestational diabetes mellitus (GDM)

Insulin and glucose disposal

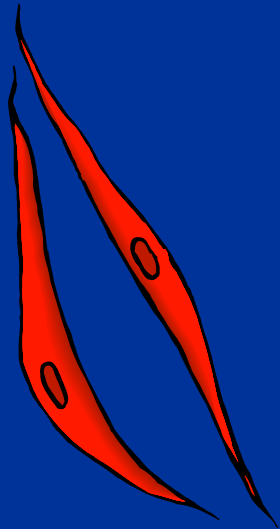


Insulin

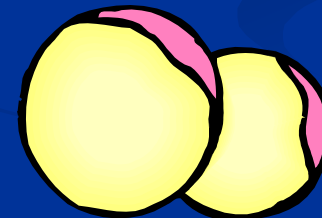
- ↓ Gluconeogenesis
- ↓ Glycogenolysis
- ↑ Glycogen synthesis



↓ Blood glucose



↑ Glycogen synthesis

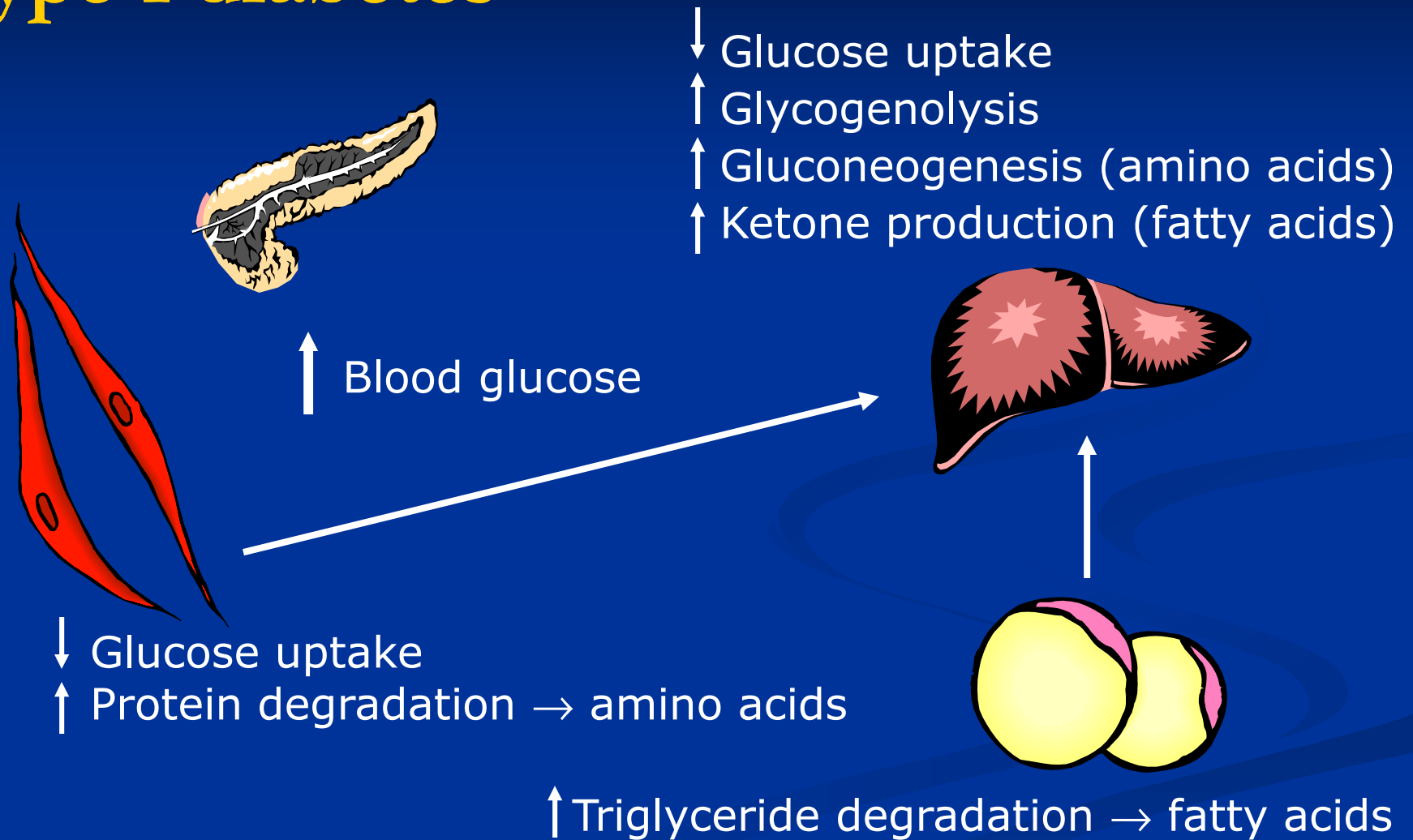


- ↑ Glucose uptake
- ↓ Free fatty acid release

Type 1 diabetes

- Insulin deficiency secondary to β -cell destruction usually by autoimmune process
- Insulin and C-peptide levels low
- May have islet cell autoantibodies, Autoantibodies to insulin, or antibodies to glutamic acid decarboxylase or tyrosine phosphatases.
- 20% risk of other autoimmune diseases
- Typically will present with DKA due to absolute lack of insulin

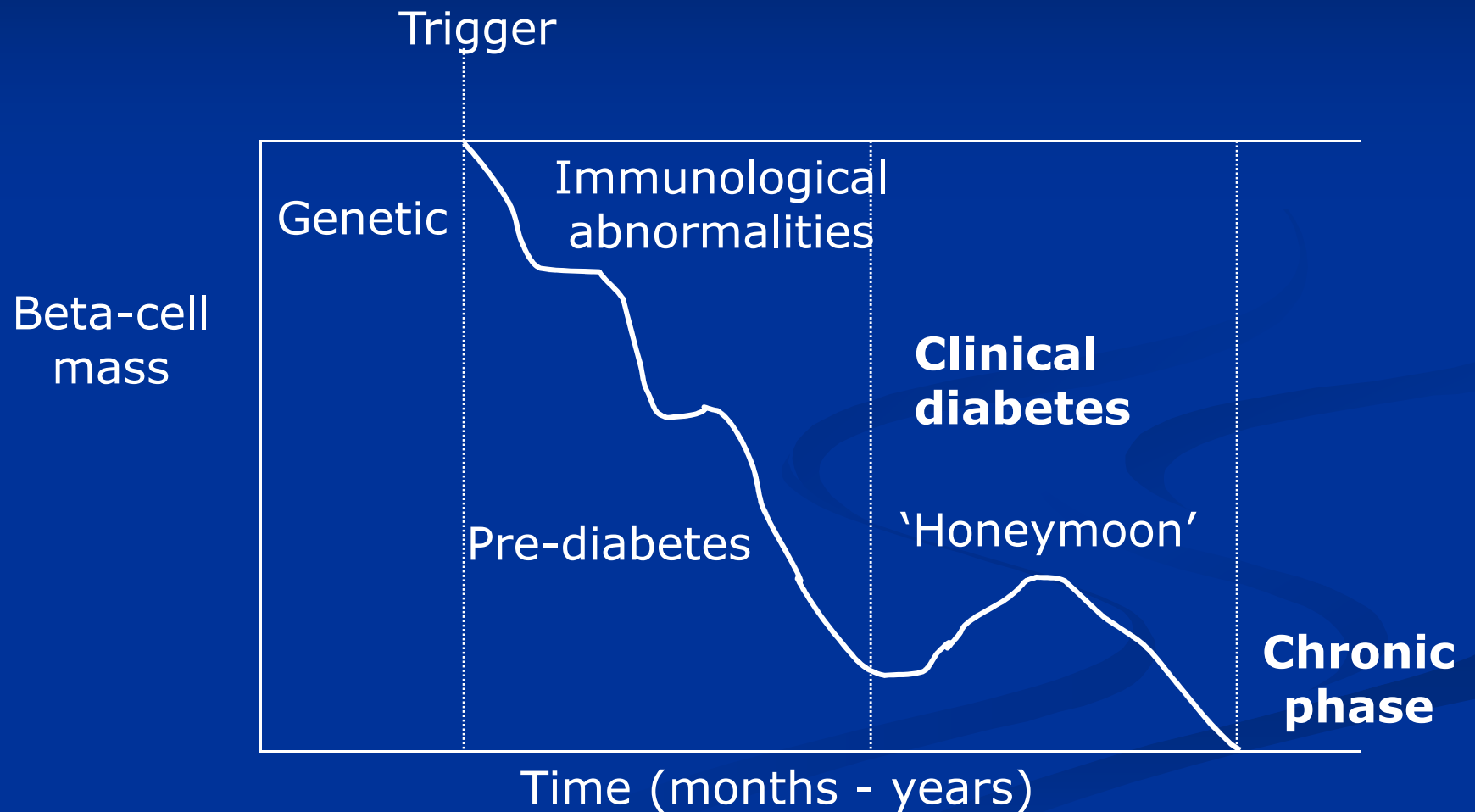
Insulin deficiency in type 1 diabetes



Pathogenesis of type 1 diabetes

- Genetic susceptibility
- Immune factors
 - other autoimmune disease
 - antigen-specific antibodies
- Environmental trigger
 - viruses
 - bovine serum albumin
 - nitrosamines: cured meats
 - chemicals: vacor (rat poison), streptozotin

Pathogenesis of type 1 diabetes

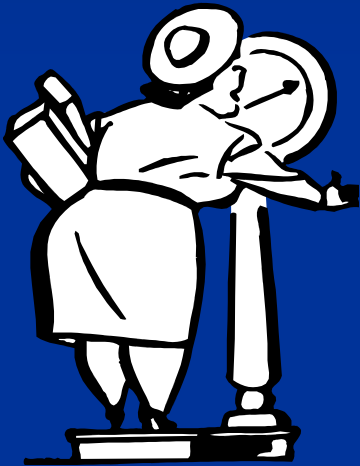


Idiopathic type 1 diabetes

Non-autoimmune type 1 diabetes

- No autoimmune markers
- Permanent insulinopenia
- Ketoacidosis
- People of African and Asian origin

Type 2 diabetes



- 90%-95% of people with diabetes
- Insulin insensitivity and relative insulin deficiency
- Obesity or overweight
- Complications often present at diagnosis

Pathogenesis of type 2 diabetes

- Multiple genes involved
- Hyperinsulinaemia
- Poor fetal nutrition → ↓ beta-cell formation
- Low birth weight/weight change
- “Thrifty gene”
- 7% beta-cell loss

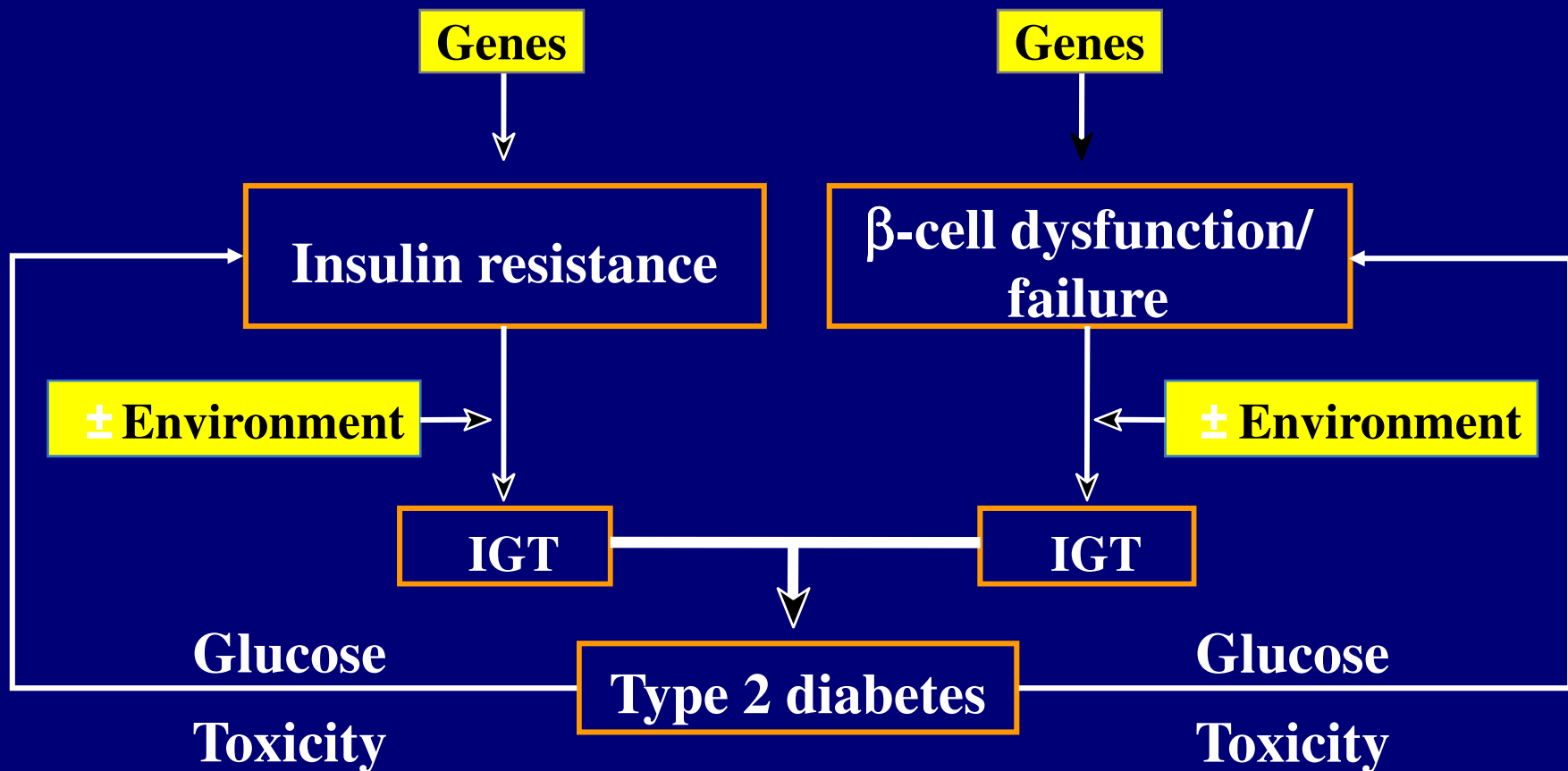
Epidemiology of type 2 diabetes

- Dramatic increase
- Aging population
- Disturbing trends parallel obesity epidemic
- Especially in adolescents and minority groups
- Increasing in young people

Risk factors for type 2 diabetes

- Age \geq 40 years
- First-degree relative with diabetes
- Member of high risk population
- History of impaired glucose tolerance, impaired fasting glucose
- Vascular disease
- History of gestational diabetes
- History of delivery of macrosomic baby

Type 2 Diabetes: Two Principal Defects

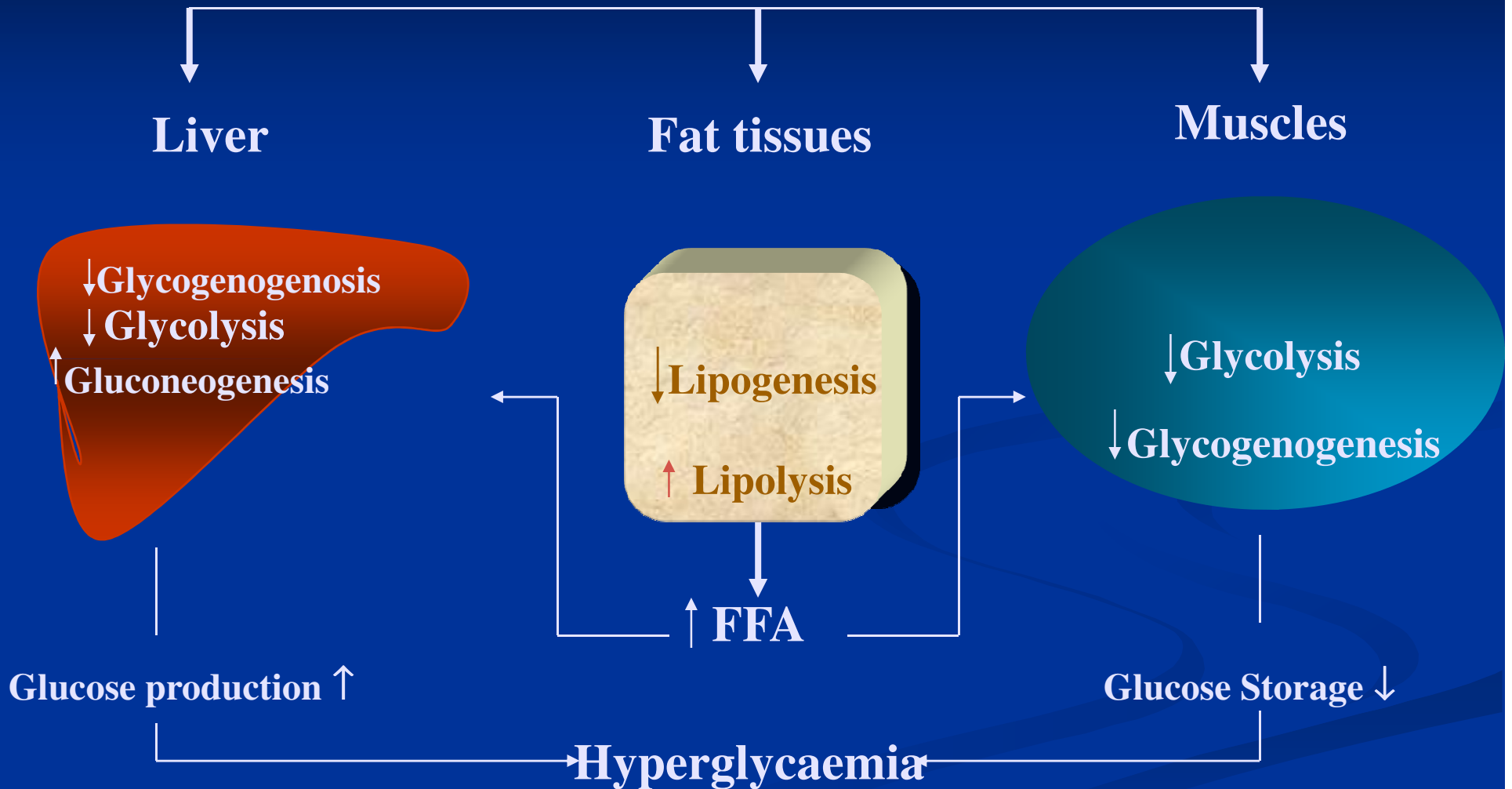


Reaven GM. *Physiol Rev.* 1995;75:473-486

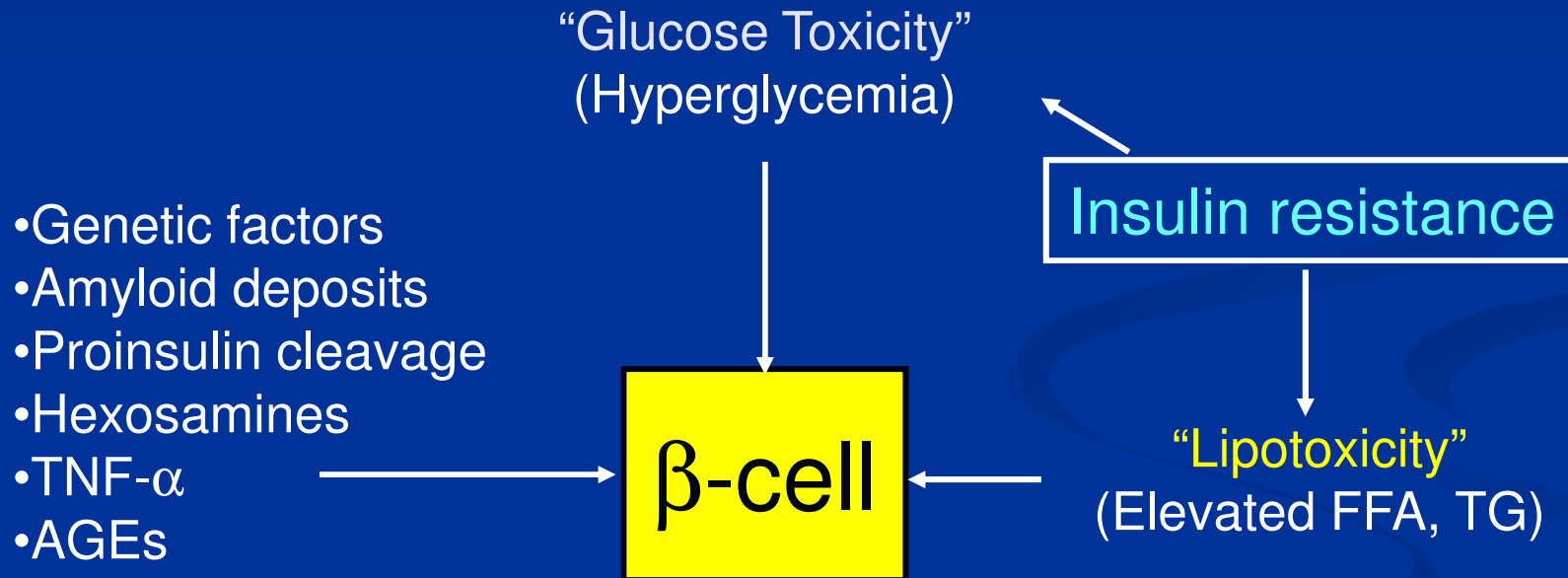
Reaven GM. *Diabetes/Metabol Rev.* 1993;9(Suppl 1):5S-12S;

Polonsky KS. *Exp Clin Endocrinol Diabetes.* 1999;107 Suppl 4:S124-S127.

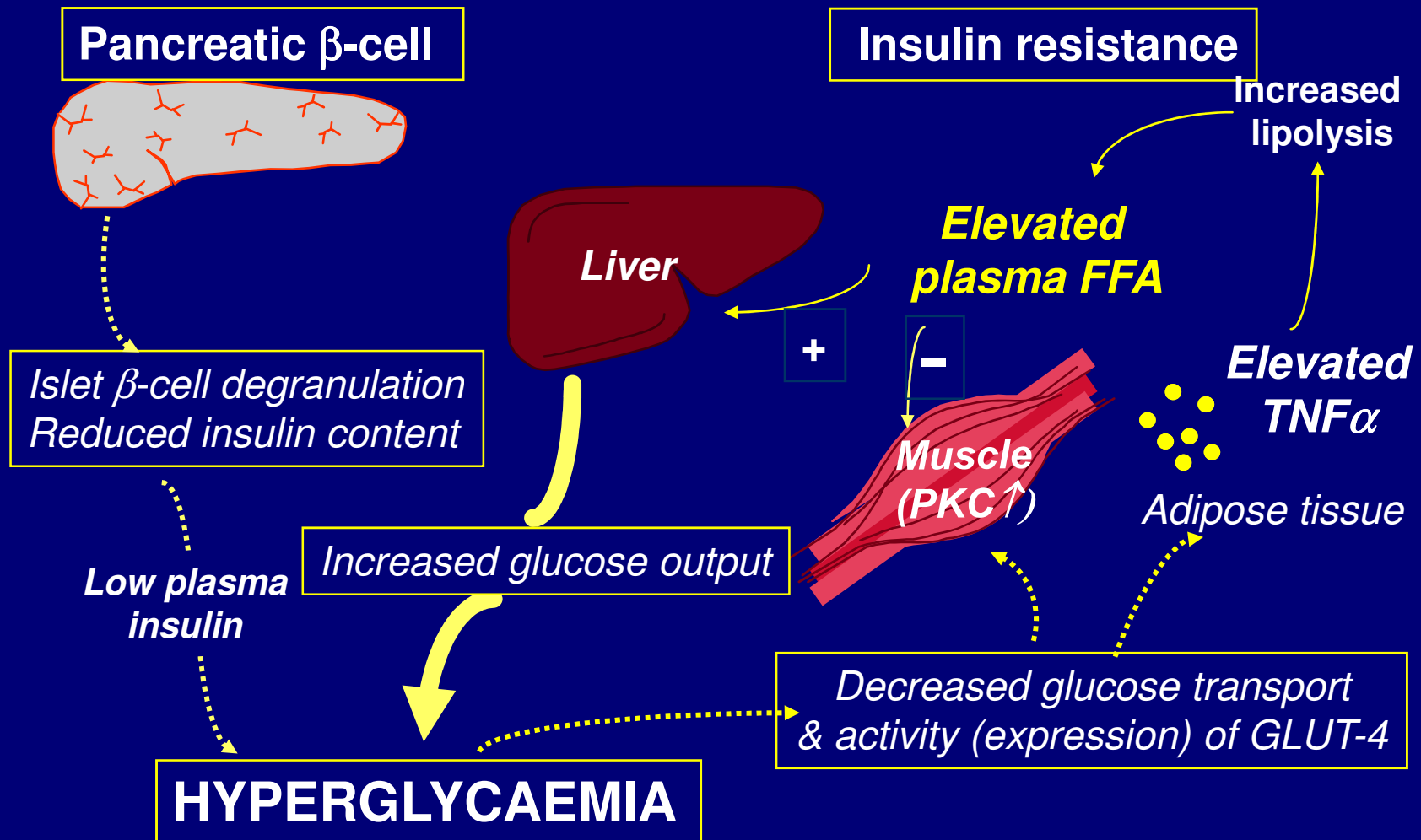
Insulin insensitivity in type 2 diabetes



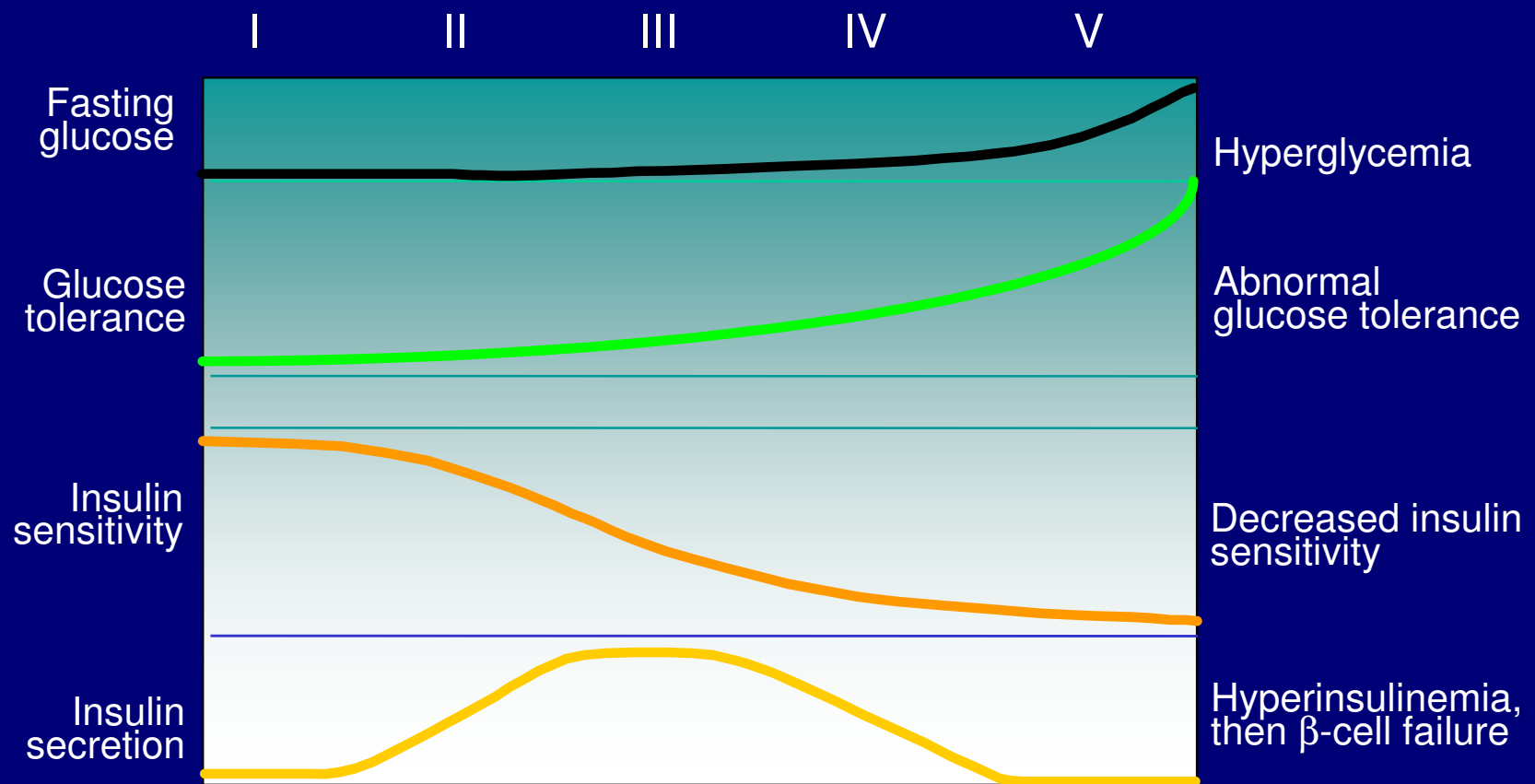
Possible Mechanisms for Decline of β -Cell Function



Insulin resistance and β -cell dysfunction produce hyperglycaemia in type 2 diabetes

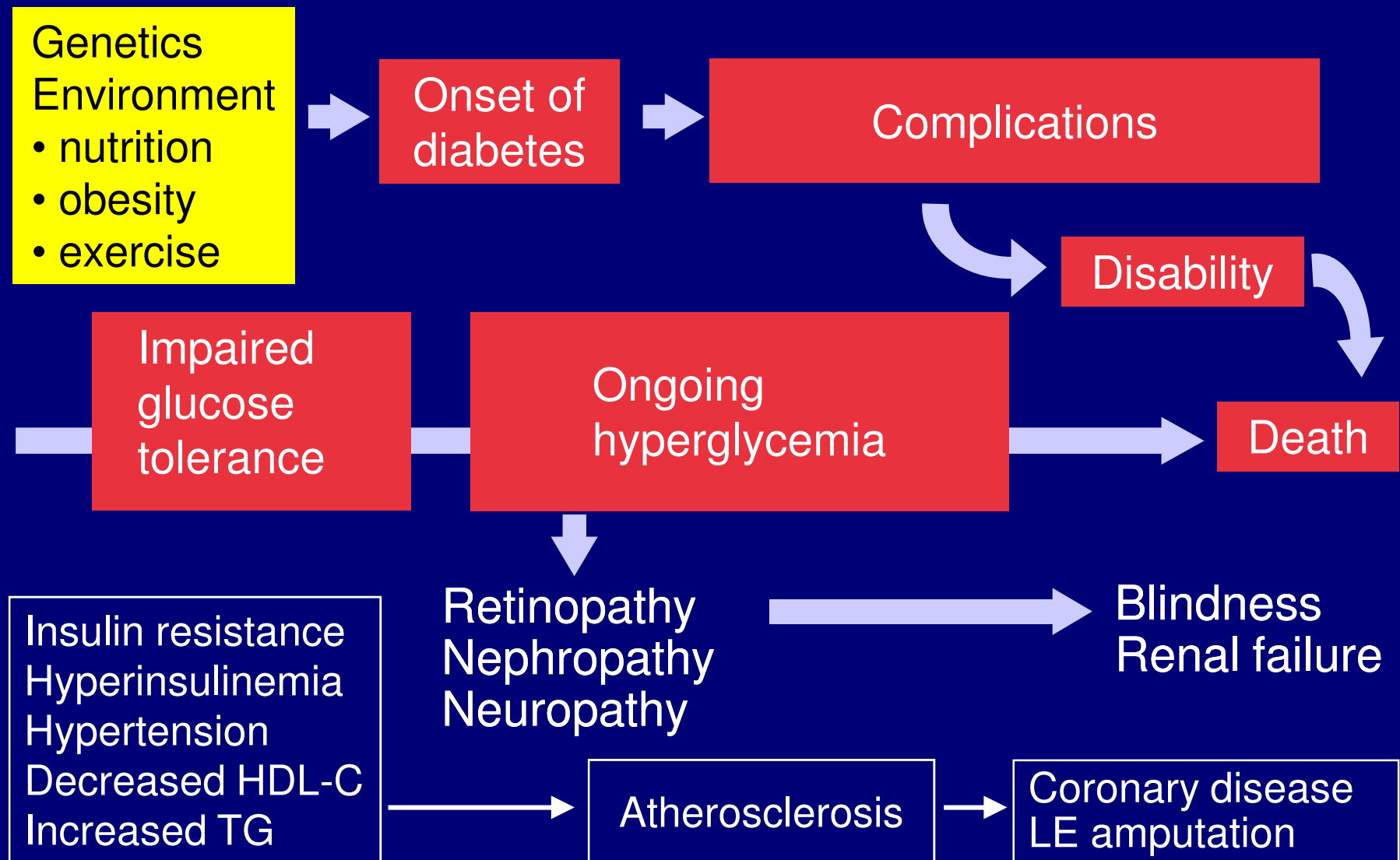


Development of type 2 diabetes



Normal → **IGT** → **Type 2 diabetes**

Natural History of Type 2 Diabetes



Pathophysiology

Impaired entry of glucose into the cells
Accumulation of glucose in the blood

Inability of the cells
utilize glucose

Cellular starvation

Stimulating hunger

Lipolysis and
proteolysis

Body weight

Plasma osmolarity \uparrow

Urinary loss of glucose \uparrow
Loss of water and Na

Dehydration of cells

Compensatory mechanism
Such as thirst

Common Symptoms

Classic symptoms

- increased hunger
- increased thirst
- frequent urination
- weight loss

Others symptoms

- fatigue
- tingling or numbness in hands and feet
- recurring infections
 - gums, skin, lung, urinary bladder
- slow healing
- blurred vision
- pruritus vulvae
- erectile dysfunction

ADA definition of hyperglycaemic states

Criteria for the diagnosis of diabetes

Symptoms of diabetes plus casual plasma glucose ≥ 200 mg/dl (11.1 mmol/l)

or

FPG

< 100 mg/dl (5.6 mmol/l)	-----· normal fasting glucose
100–125 mg/dl (5.6–6.9 mmol/l)	-----· impaired fasting glucose
≥ 126 mg/dl (7.0 mmol/l)	-----· diabetes

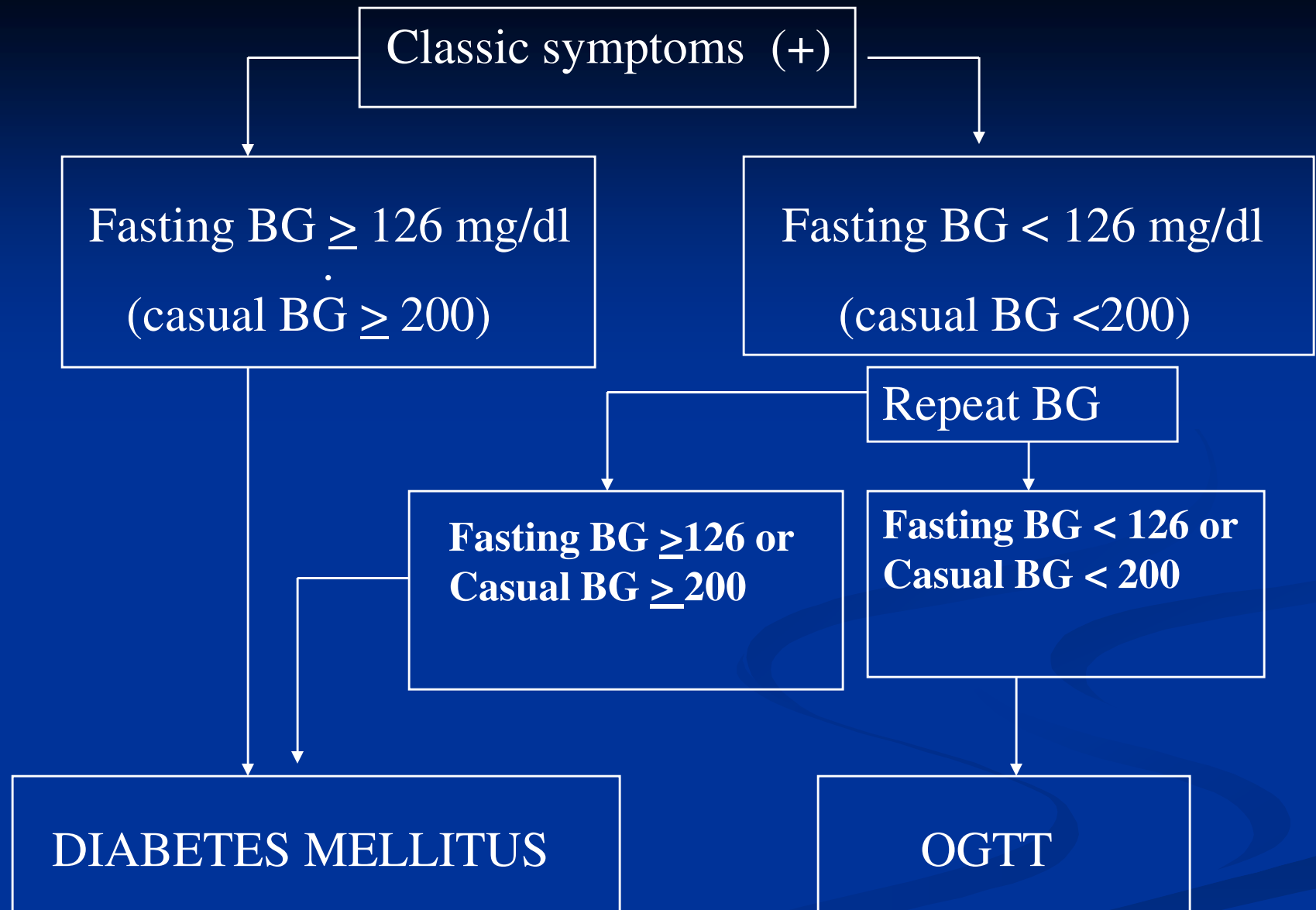
or

OGTT 2-h post-load glucose

< 140 mg/dl (7.8 mmol/l)	-----· normal glucose tolerance
140–199 mg/dl (7.8–11.1 mmol/l)	-----· impaired glucose tolerance
≥ 200 mg/dl (11.1 mmol/l)	-----· diabetes

ADA = American Diabetes Association

Adapted from American Diabetes Association. *Diabetes Care* 2004; 27:S5–S10.



Diagnosis of type 2 Diabetes Mellitus

Impaired glucose tolerance

Impaired fasting glucose

- Intermediate states
- Increased risk of developing diabetes
- Prevention strategies to prevent or delay progression
- Increased risk of cardiovascular disease

Uncertain diagnosis: Oral glucose tolerance test

- 75 g glucose load after 8 hours fasting
- Readings taken in fasting state and at 1 and 2 hours

Tests for differential diagnosis

- Urinary ketones
- Antibodies
- C-peptide

Other specific types of diabetes

A. Genetic defects of B-cell function

- Chromosome 12, HNF-1 (MODY3); Chromosome 7, glucokinase (MODY2); Chromosome 20, HNF-4 (MODY1); Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4); Chromosome 17, HNF-1 (MODY5); Chromosome 2, *NeuroD1* (MODY6); Mitochondrial DNA

B. Genetic defects in insulin action

- Type A insulin resistance; Leprechaunism; Rabson-Mendenhall syndrome; Lipoatrophic diabetes.

C. Diseases of the exocrine pancreas

- Pancreatitis; Trauma/pancreatectomy; Neoplasia; Cystic fibrosis; Hemochromatosis; Fibrocalculous pancreatopathy.

D. Endocrinopathies

- Acromegaly; Cushing's syndrome; Glucagonoma; Pheochromocytoma; Hyperthyroidism; Somatostatinoma; Aldosteronoma.

Other specific types of diabetes

E. Drug- or chemical-induced

- Vacor; Pentamidine; Nicotinic acid; Glucocorticoids; Thyroid hormone; Diazoxide; adrenergic agonists; Thiazides; Dilantin; Interferon.

F. Infections

- Congenital rubella; Cytomegalovirus.

G. Uncommon forms of immune-mediated diabetes

- “Stiff-man” syndrome; Anti-insulin receptor antibodies.

H. Other genetic syndromes sometimes associated with diabetes

- Down’s syndrome; Klinefelter’s syndrome; Turner’s syndrome; Wolfram’s syndrome; Friedreich’s ataxia; Huntington’s chorea; Laurence-Moon-Biedl syndrome; Myotonic dystrophy; Porphyria; Prader-Willi syndrome

Gestational diabetes mellitus (GDM)

- Gestational diabetes mellitus (GDM) is carbohydrate intolerance associated with hyperglycemia of variable severity with the onset or first recognition during pregnancy
- Return to normal glucose regulation after delivery is common
- Increased perinatal morbidity and mortality if untreated
 - Risk assessment for GDM should be undertaken at the first prenatal visit.
 - Women with clinical characteristics consistent with a high risk for GDM (those with marked obesity, personal history of GDM, glycosuria, or a strong family history of diabetes) should undergo glucose testing as soon as possible

Pathophysiology

- The pregnant woman undergoes a complex series of maternal hormonal actions (ie, a rise in blood glucose; the secondary secretion of pancreatic insulin, glucagon, somatomedins, and adrenal catecholamines).
- These hormones confer increasing tissue insulin resistance as their levels rise, the demand for increased insulin secretion with feeding escalates progressively during pregnancy.
- If the maternal pancreatic insulin response is inadequate, maternal and, then, fetal hyperglycemia results.
- This typically manifests as recurrent postprandial hyperglycemic episodes.

Gestational diabetes mellitus (GDM)

- Diagnostic criteria for the 100-g OGTT are as follows:
 - ≥ 95 mg/dl fasting, ≥ 180 mg/dl at 1 h, ≥ 155 mg/dl at 2 h, and ≥ 140 mg/dl at 3 h.
 - Two or more of the plasma glucose values must be met or exceeded for a positive diagnosis.
- The test should be done in the morning after an overnight fast of 8–14 h.