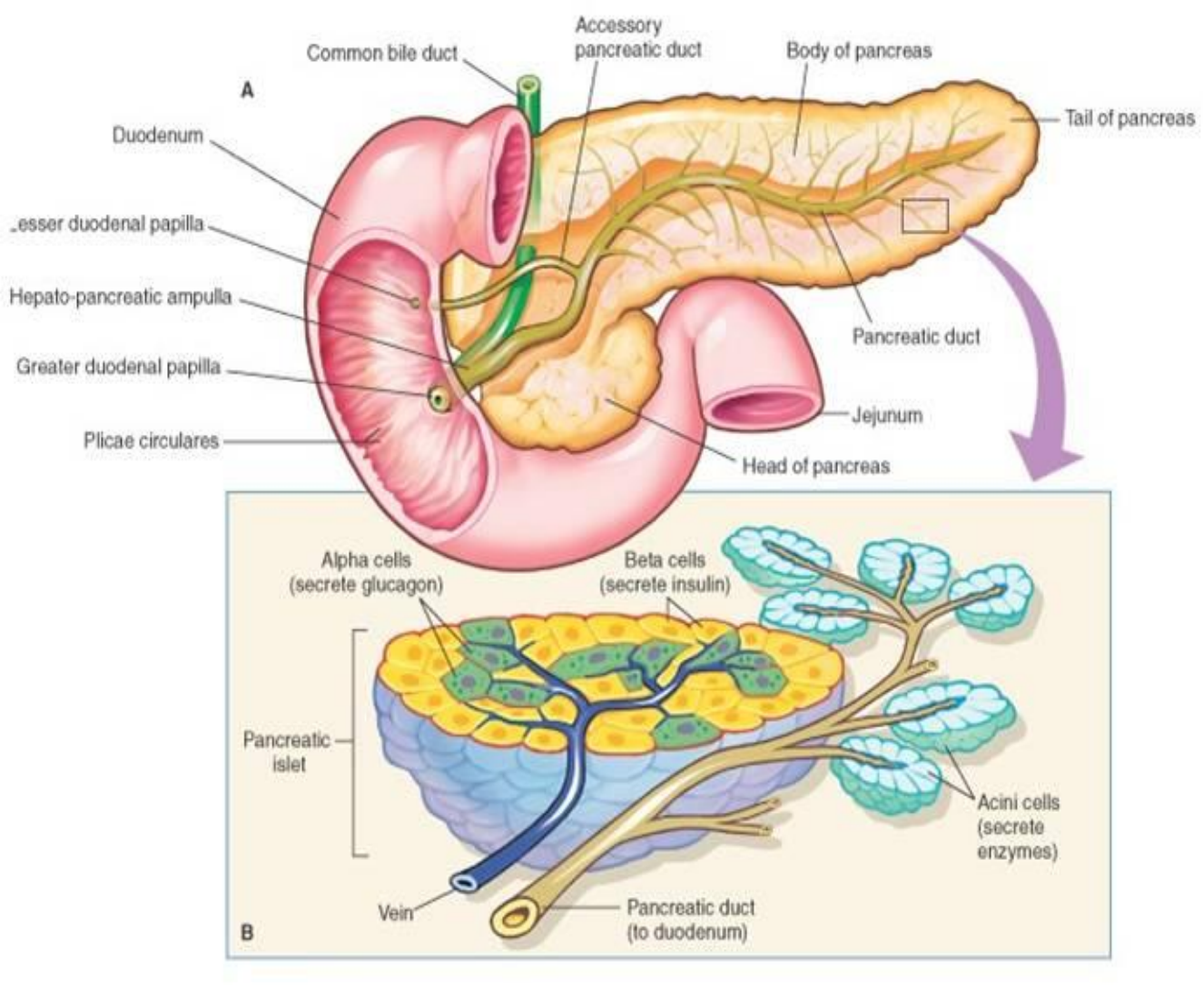
Diabetes Mellitus

Objectives

- Understand the structure of the pancreas and have a basic understanding of its function.
- The student should have an understanding of the pathogenesis and major histopathological changes seen in diabetes mellitus type 1 and type 2.
- The student should recognize the major complications of diabetes mellitus.


A
Common bile duct
Accessory pancreatic duct
Body of pancreas
Tail of pancreas
Duodenum
Lesser duodenal papilla
Hepato-pancreatic ampulla
Greater duodenal papilla
Plicae circulares
Pancreatic duct
Jejunum
Head of pancreas
Alpha cells (secrete glucagon)
Beta cells (secrete insulin)
Pancreatic islet
Acini cells (secrete enzymes)
Vein
Pancreatic duct (to duodenum)
B

THE ENDOCRINE PANCREAS

- ***islets of Langerhans*, contain four major and two minor cell types.**
- **The four main types are β, α, δ, and PP (pancreatic polypeptide) cells.**
- ***The β cell produces insulin***
- ***The α cell secretes glucagon* .**
- **δ cells contain somatostatin**
- ***PP cells contain a unique pancreatic polypeptide.***
- **The two rare cell types are *D1 cells* and *enterochromaffin cells.***

Diabetes Mellitus (DM)

- Sir William Osler defined diabetes mellitus as “a syndrome due to a disturbance in carbohydrate metabolism from various causes, in which sugar appears in the urine, associated with thirst, polyuria, wasting and imperfect oxidation of fats.”

Diabetes Mellitus (DM)

- Major health problem that affects increasing numbers of persons in the developed world.
- *Group of metabolic disorders sharing the common underlying feature of* ***hyperglycemia***
- Hyperglycemia in diabetes results from defects in insulin secretion, insulin action, or, most commonly, both.
- The chronic hyperglycemia may be associated with secondary damage in multiple organ systems, especially the kidneys, eyes, nerves, and blood vessels.

- *prediabetes*, is defined as elevated blood sugar that does not reach the criterion accepted for an outright diagnosis of diabetes, persons with prediabetes have an elevated risk for development of frank diabetes.

Diagnosis of DM

<u>Any one of three criteria:</u>

1- A random glucose concentration greater than 200 mg/dL, with classical signs and symptoms .

2- A fasting glucose concentration greater than 126 mg/dL on more than one occasion.

3- An abnormal oral glucose tolerance test (OGTT), in which the glucose concentration is greater than 200 mg/dL 2 hours after a standard carbohydrate load.

Classification of DM

1. Type 1 Diabetes
Beta cell destruction, usually leading to absolute insulin deficiency
2. Type 2 Diabetes
Combination of insulin resistance and beta cell dysfunction
3. Genetic Defects of Beta Cell Function
Maturity-onset diabetes of the young (MODY), caused by mutations in: Hepatocyte nuclear factor 4α gene (*HNF4A*)—MODY1 Glucokinase gene (*GCK*)—MODY2 Hepatocyte nuclear factor 1α gene (*HNF1A*)—MODY3 Pancreatic and duodenal homeobox 1 gene (*PDX1*)—MODY4 Hepatocyte nuclear factor 1β gene (*HNF1B*)—MODY5 Neurogenic differentiation factor 1 gene (*NEUROD1*)—MODY6
Maternally inherited diabetes and deafness (MIDD) due to mitochondrial DNA mutations (3243A→G)
Defects in proinsulin conversion
Insulin gene mutations
4. Genetic Defects in Insulin Action
Insulin receptor mutations
5. Exocrine Pancreatic Defects
Chronic pancreatitis
Pancreatectomy
Neoplasia
Cystic fibrosis
Hemochromatosis
Fibrocalculous pancreatopathy

6. Endocrinopathies
Growth hormone excess (acromegaly)
Cushing syndrome
Hyperthyroidism
Pheochromocytoma
Glucagonoma
7. Infections
Cytomegalovirus infection
Coxsackievirus B infection
Congenital rubella
8. Drugs
Glucocorticoids
Thyroid hormone
β-Adrenergic agonists
9. Genetic Syndromes Associated with Diabetes
Down syndrome
Klinefelter syndrome
Turner syndrome
10. Gestational Diabetes Mellitus
Diabetes associated with pregnancy

T1DM

- *Type 1 diabetes (T1D)* is characterized by an absolute deficiency of insulin secretion caused by pancreatic beta cell destruction, usually resulting from an autoimmune attack. Type 1 diabetes accounts for approximately 10% of all cases.

Type 2 DM

- *Type 2 diabetes (T2D)* is caused by a combination of peripheral resistance to insulin action and an inadequate compensatory response of insulin secretion by the pancreatic beta cells (*relative insulin deficiency*). Approximately 80% to 90% of patients have type 2 diabetes.

MODY

Maturity-onset diabetes of the young (MODY) :

- **Rare autosomal dominant form of inherited diabetes.**
- **Associated with a variety of gene defects that affect B-cell function, including glucokinase, an important sensor for glucose metabolism within the B-cell, and several mutations in genes that control the development and function of the B-cells.**
- **Mutations in these genes, however, do not account for the typical prevalent forms ofT2DM.**

Type 1 Diabetes Mellitus pathogenesis

- Autoimmune destruction of the B cells in the islets of Langerhans.
- The disease is characterized by:

- few if any functional B cells in the islets of Langerhans and
- Extremely limited or nonexistent insulin secretion.

- As a result, body fat rather than glucose is preferentially metabolized as a source of energy.
- In turn, oxidation of fat overproduces ketone bodies (acetoacetic acid and B-hydroxybutyric acid), which are released into the blood from the liver and lead to metabolic ketoacidosis.

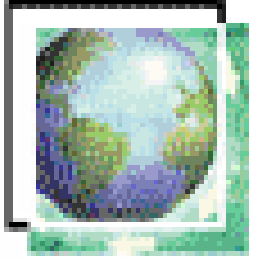
T1DM ,PATHOGENESIS

Represents interplay of genetic susceptibility , autoimmunity and environmental factors.

Type 1 Diabetes Mellitus

- Hyperglycemia results from unsuppressed hepatic glucose out-put and reduced glucose disposal in skeletal muscle and adipose tissue and leads to glucosuria and dehydration from loss of body water into the urine.

- If uncorrected, the progressive acidosis and dehydration ultimately lead to coma and death



Hyperglycemia
Glycosuria
Loss of calories
Ployuria
Hunger
Weight loss
Mobilization of fat and protein
Loss of electrolytes
Dehydration
Polyphagia
Acidosis
Polydipsia
Negative nitrogen balance
Hyperpnea
Coma and Death

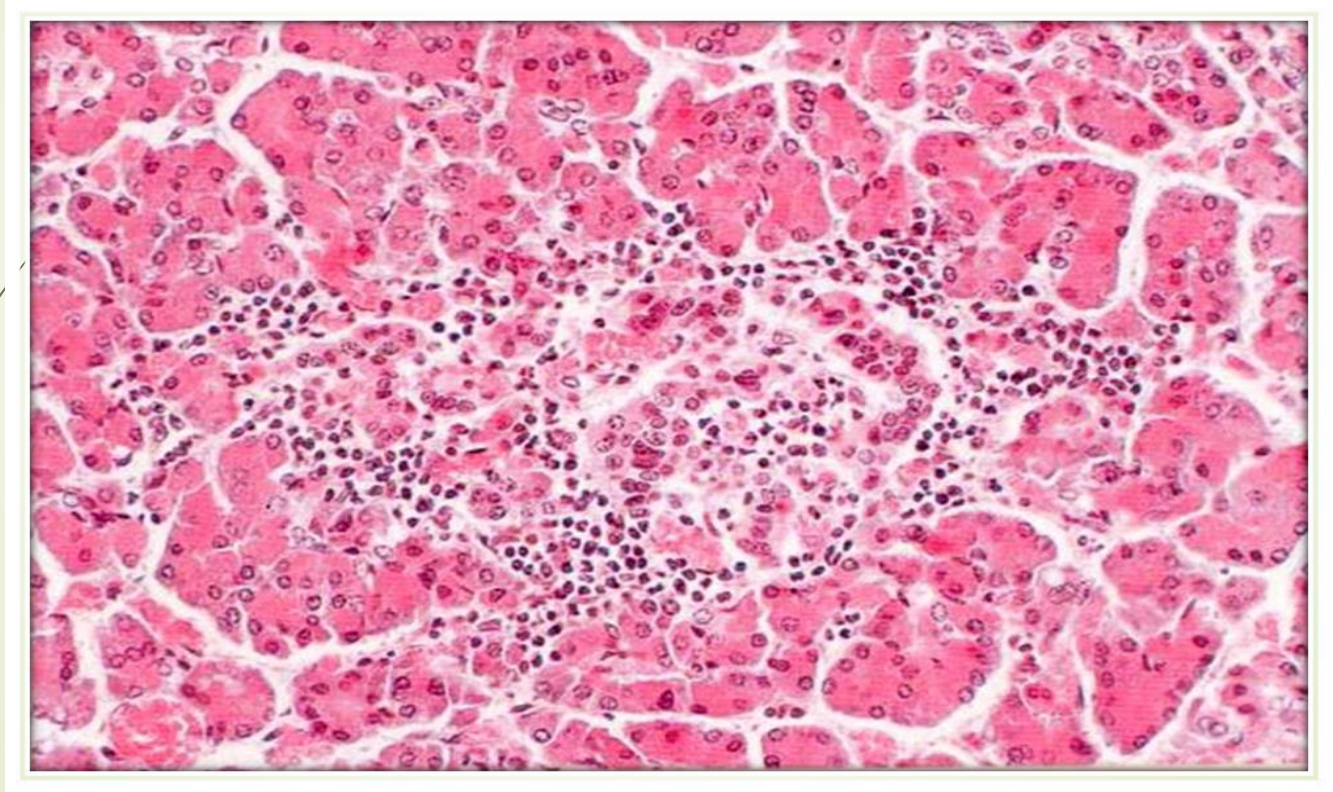
T1DM, EPIDEMIOLOGY

- The peak age of onset coincides with puberty.
- Some older patients may present with autoimmune B-cell destruction that has developed slowly over many years.

PATHOLOGY

- Lymphocytic infiltrate in the islets (insulitis), sometimes accompanied by a few macrophages and neutrophils
- As the disease becomes chronic, the B cells of the islets are progressively depleted of Beta cells
- Fibrosis of the islets is uncommon.
- In contrast to T2DM, deposition of **amyloid** in the islets of Langerhans is **absent** in T1DM.
- The exocrine pancreas in chronic T1DM often exhibits diffuse interlobular and interacinar fibrosis, accompanied by atrophy of the acinar cells.

Insulitis



Type 2 DM, Epidemiology

- Almost 10%of persons older than 65 years of age are affected, and 80% of patients with T2DM are overweight
- Heterogeneous disorder characterized by a combination of reduced tissue sensitivity to insulin and inadequate secretion of insulin from the pancreas.
- The disease usually develops in adults, with an increased prevalence in obese persons and in the elderly.

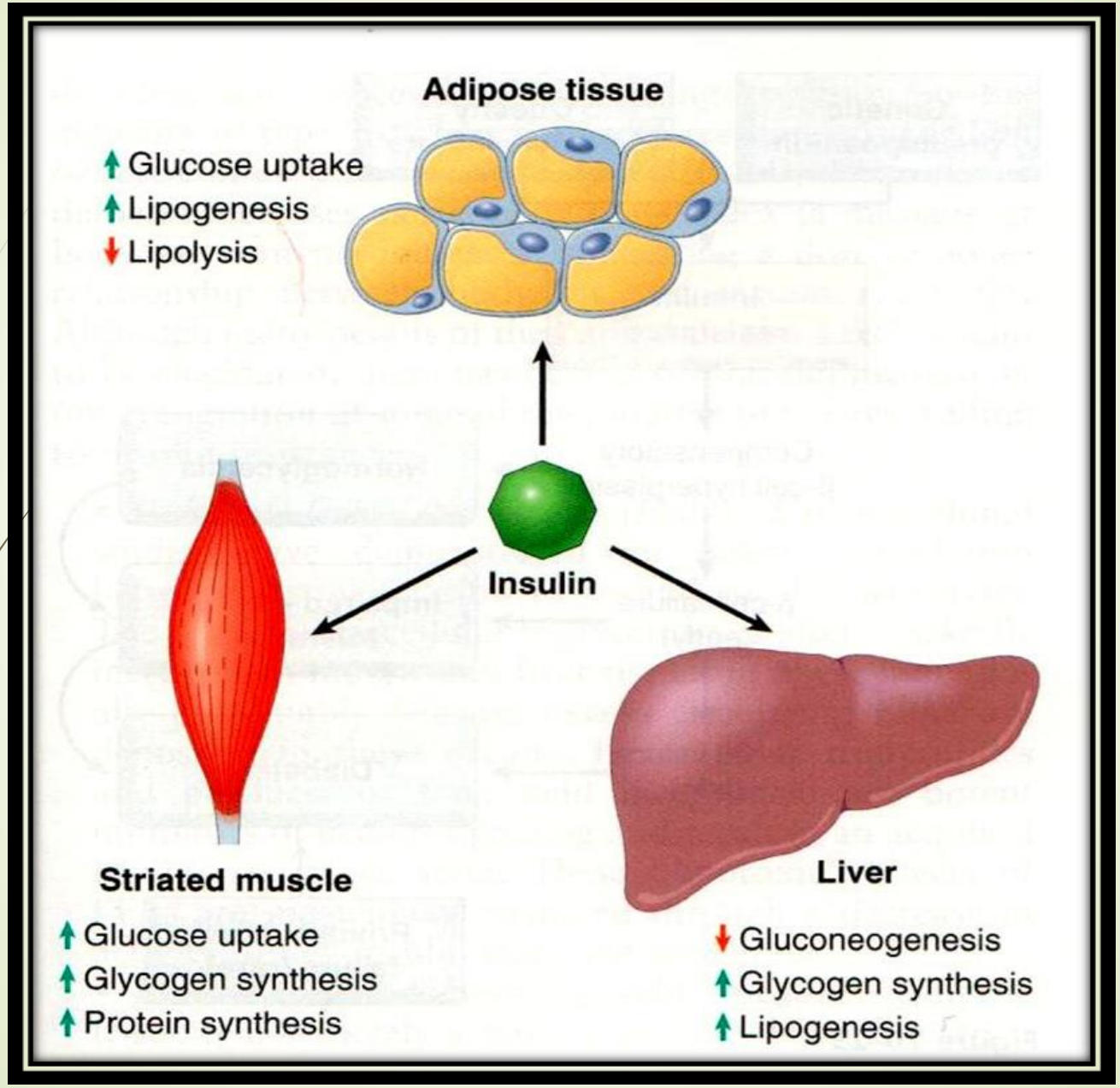
Type 2 DM, Epidemiology

- Recently, T2DM has been appearing in increasing numbers in younger adults and adolescents, owing to worsening obesity and lack of exercise in this age group.

- Hyperglycemia in T2DM is a failure of the B-cells to meet an increased demand for insulin in the body.

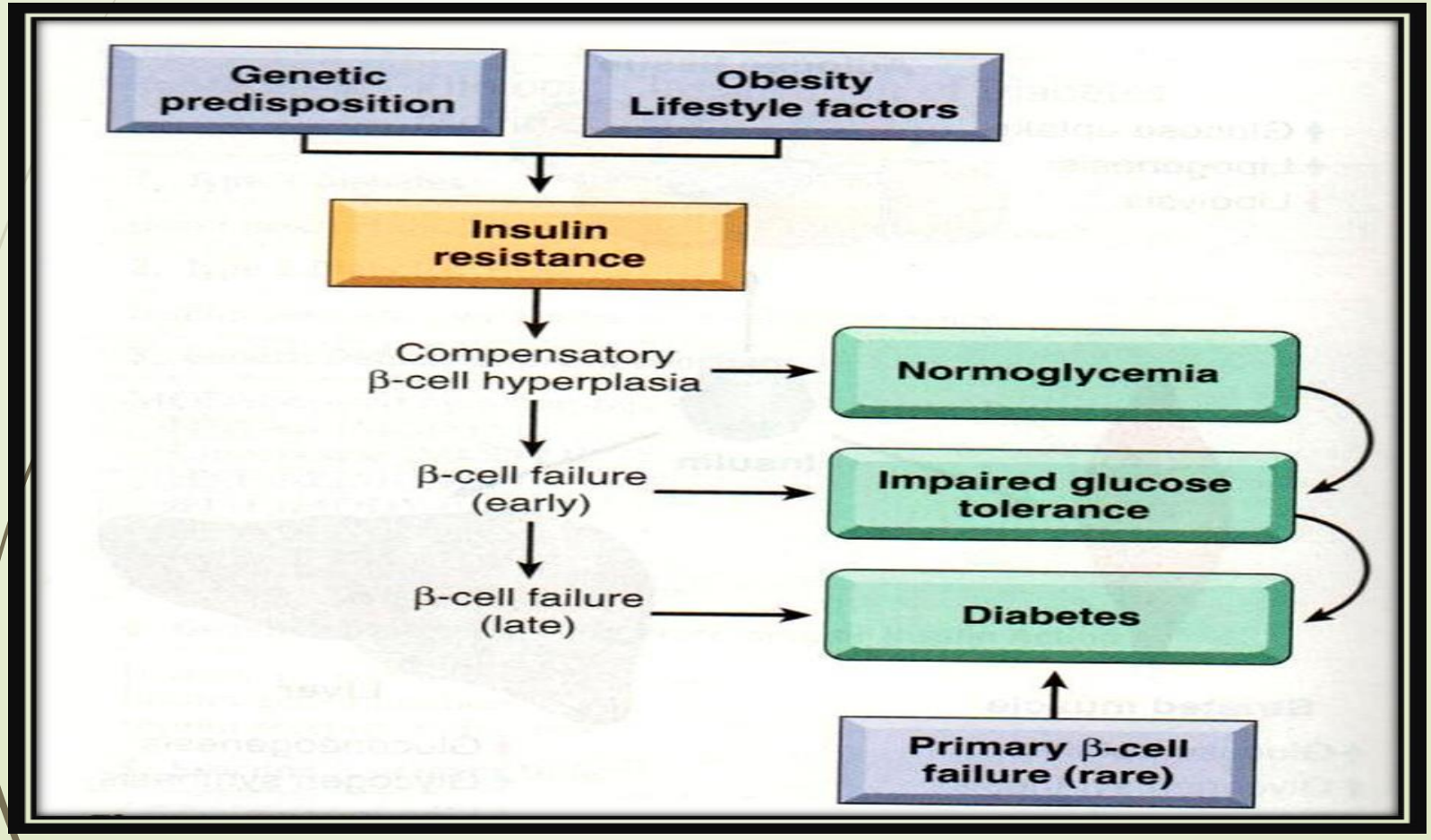
T2 DM, Pathogenesis

- Multi-factorial
- Sixty percent of patients have either a parent or a sibling with the disease.
- The inheritance pattern is complex and thought to be due to multiple interacting susceptibility genes.
- Constitutional factors such as obesity (which itself has strong genetic determinants),hypertension, and the amount of exercise influence the phenotypic expression of the disorder

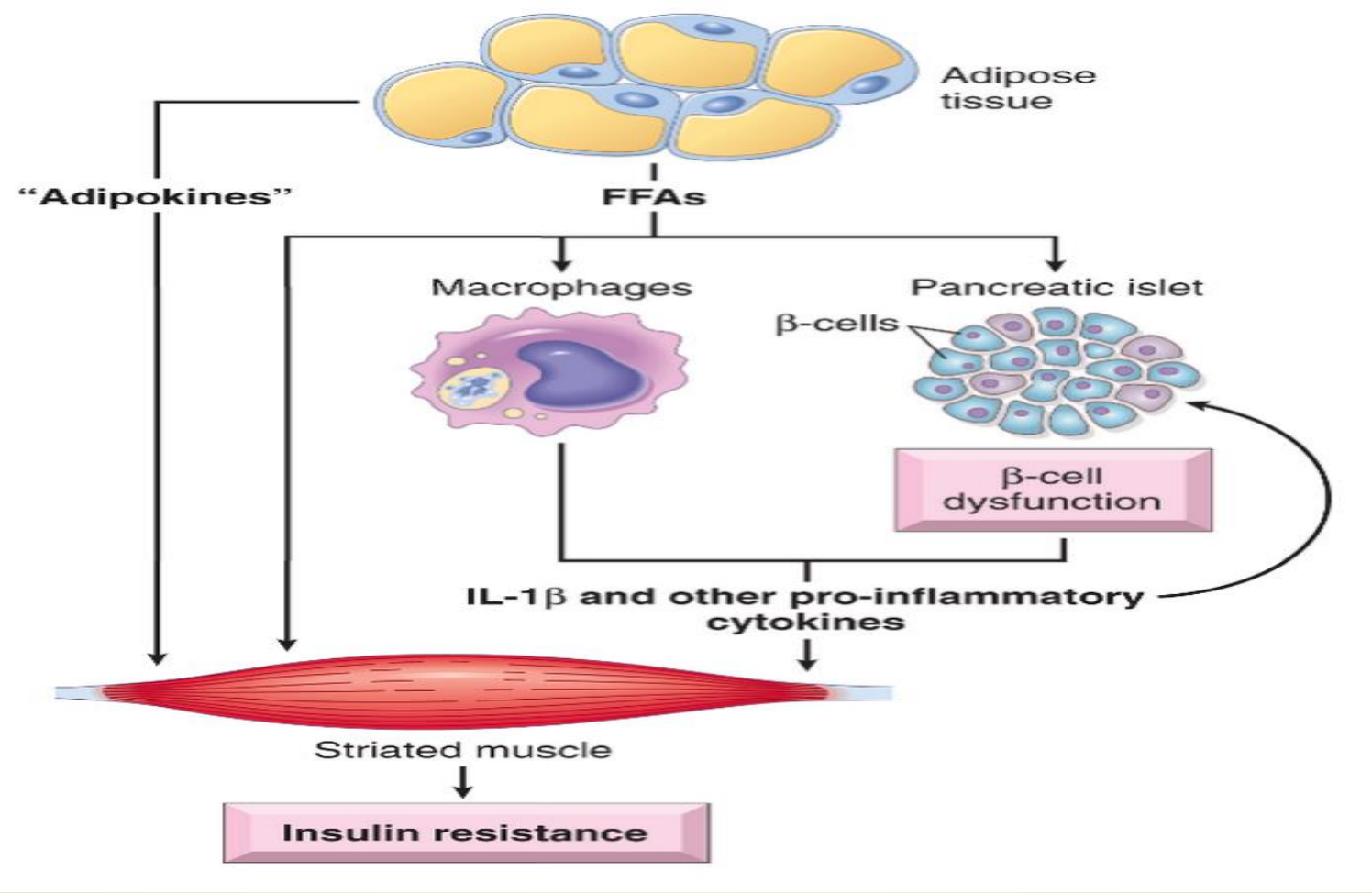

Adipose tissue
Glucose uptake
Lipogenesis
Lipolysis
Insulin
Striated muscle
Glucose uptake
Glycogen synthesis
Protein synthesis
Liver
Gluconeogenesis
Glycogen synthesis
Lipogenesis

- ***Insulin resistance*** **is defined as the failure of target tissues to respond normally to insulin. It leads to decreased uptake of glucose in muscle, reduced glycolysis and fatty acid oxidation in the liver, and an inability to suppress hepatic gluconeogenesis.**

T2 DM, PATHOGENESIS

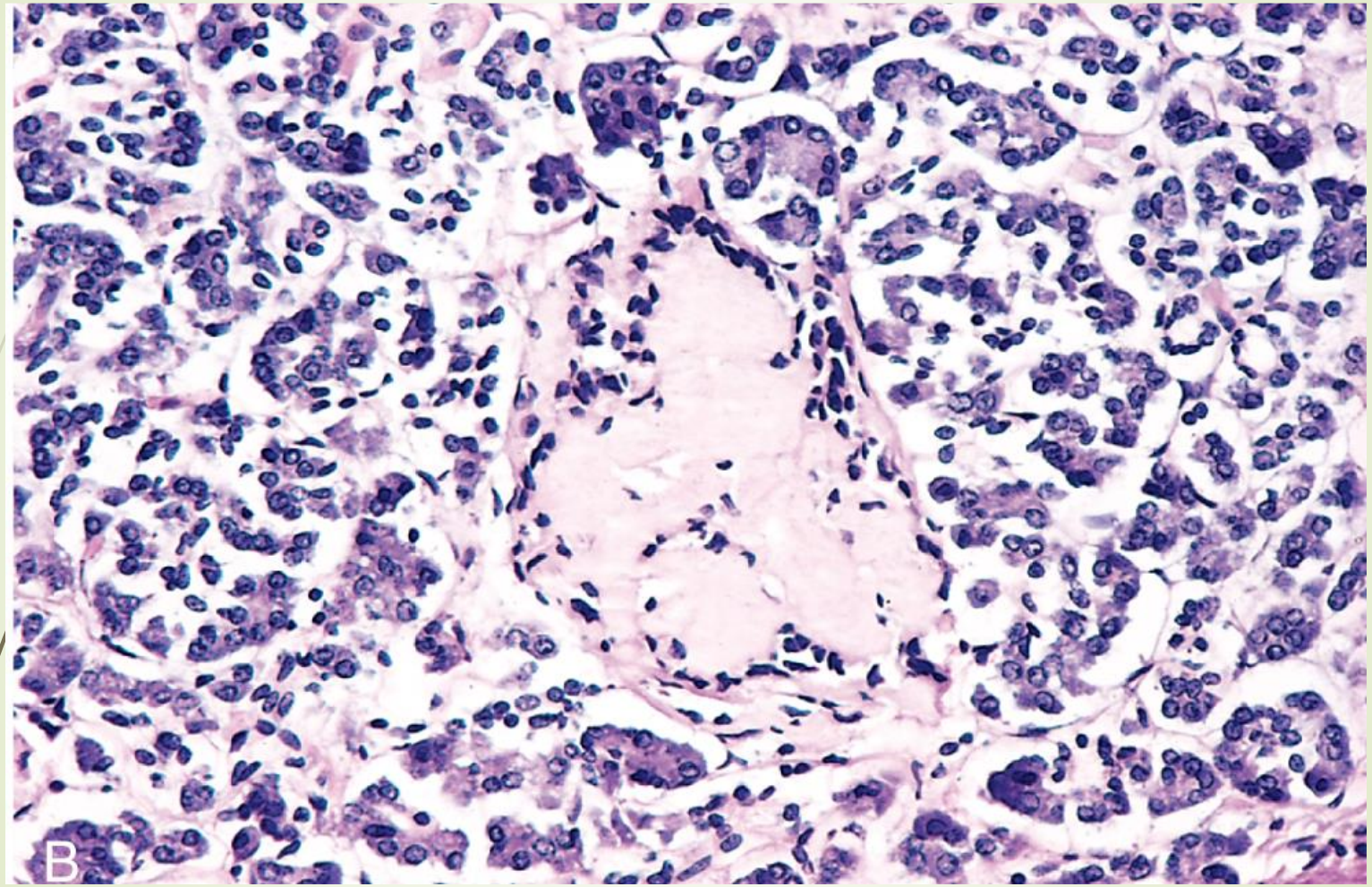


Obesity and diabetes



T2 DM , Pathology

- No consistent reduction in the number of B-cells
- No morphologic lesions of B- cells
- In some islets, fibrous tissue accumulates, sometimes to such a degree that they are obliterated.
- Islet amyloid is often present particularly in patients over 60 years of age.


B

The two main diseases that result in diabetes mellitus

Type 1 diabetes	Type 2 diabetes
Onset age <40 years	Onset age >40 years
Thin patient	Obese patient
Affects 1 in 250 of population in the UK	Affects 1 in 25 of population in the UK
Liable to ketoacidotic coma	Liable to hyperosmolar non-ketotic coma
Always requires insulin for therapy	Does not always require insulin for therapy
Concordance rate for monozygotic twins 40%	Concordance rate for monozygotic twins 90%
Genetic link with class II MHC antigens	No genetic link with class II MHC antigens
Islet cell antibodies present	Islet cell antibodies absent
Insulitis present	Insulitis absent
B cells destroyed in pancreas	B cells not destroyed in pancreas
Islet amyloid absent	Islet amyloid present

MHC = major histocompatibility complex.

Complications of Diabetes

- The most significant complications of diabetes are vascular abnormalities, renal damage, and lesions affecting the peripheral nerves and eyes
- Although the 2 major types of diabetes have different pathogenesis and clinical presentations, the long term systemic complications are the same.

Complications of Diabetes

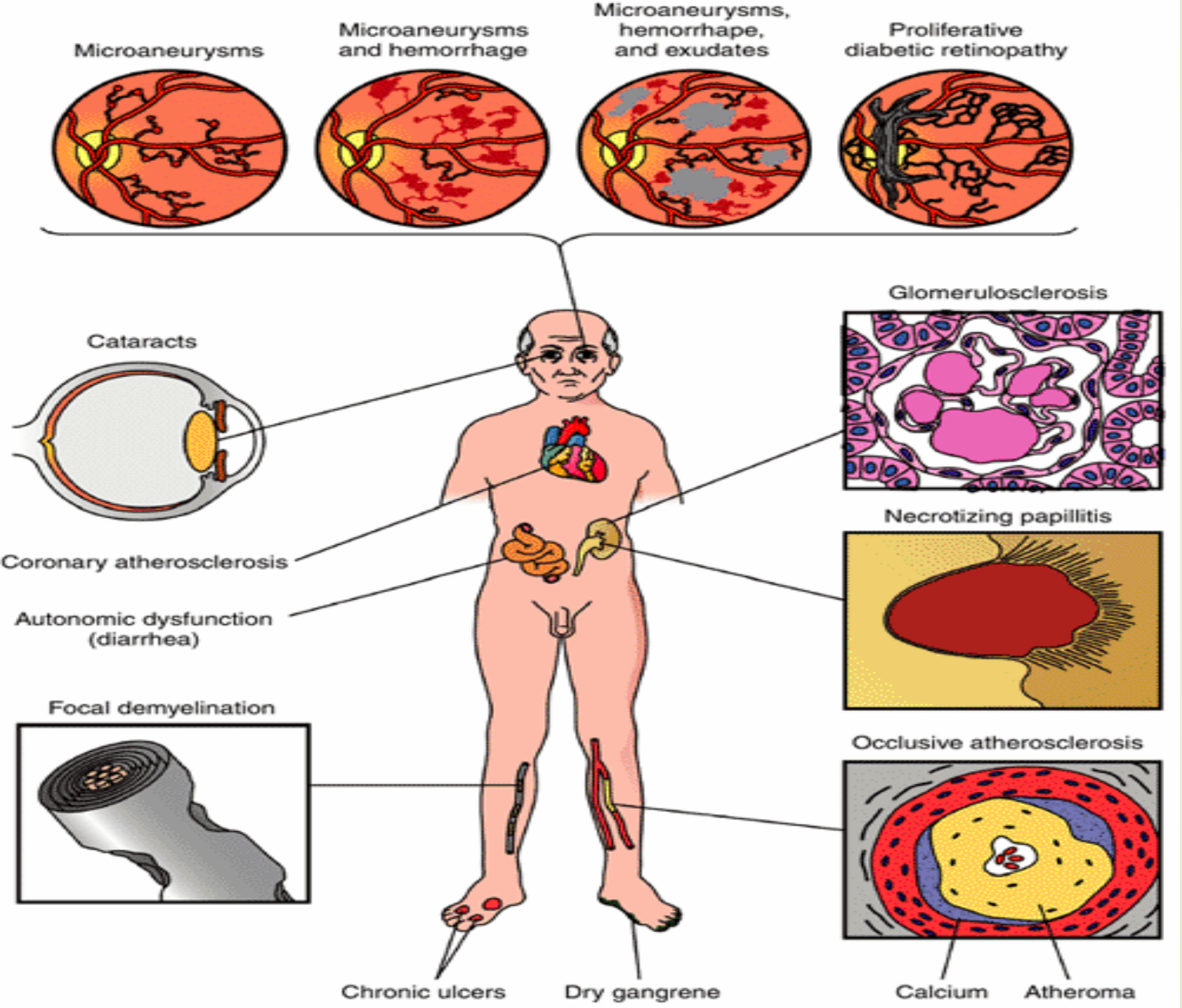
Diabetic Microvascular Disease:

- Responsible for Many of the Complications of Diabetes, Including Renal Failure and Blindness (diabetic microangiopathy)
- Arteriolosclerosis and capillary basement membrane thickening are characteristic vascular changes in diabetes.
- The frequent occurrence of hypertension contributes to the development of the arteriolar lesions.
- Aggregation of platelets in smaller blood vessels and impaired fibrinolytic mechanisms have also been suggested as playing a role in the pathogenesis of diabetic microvascular disease.

Complications of Diabetes

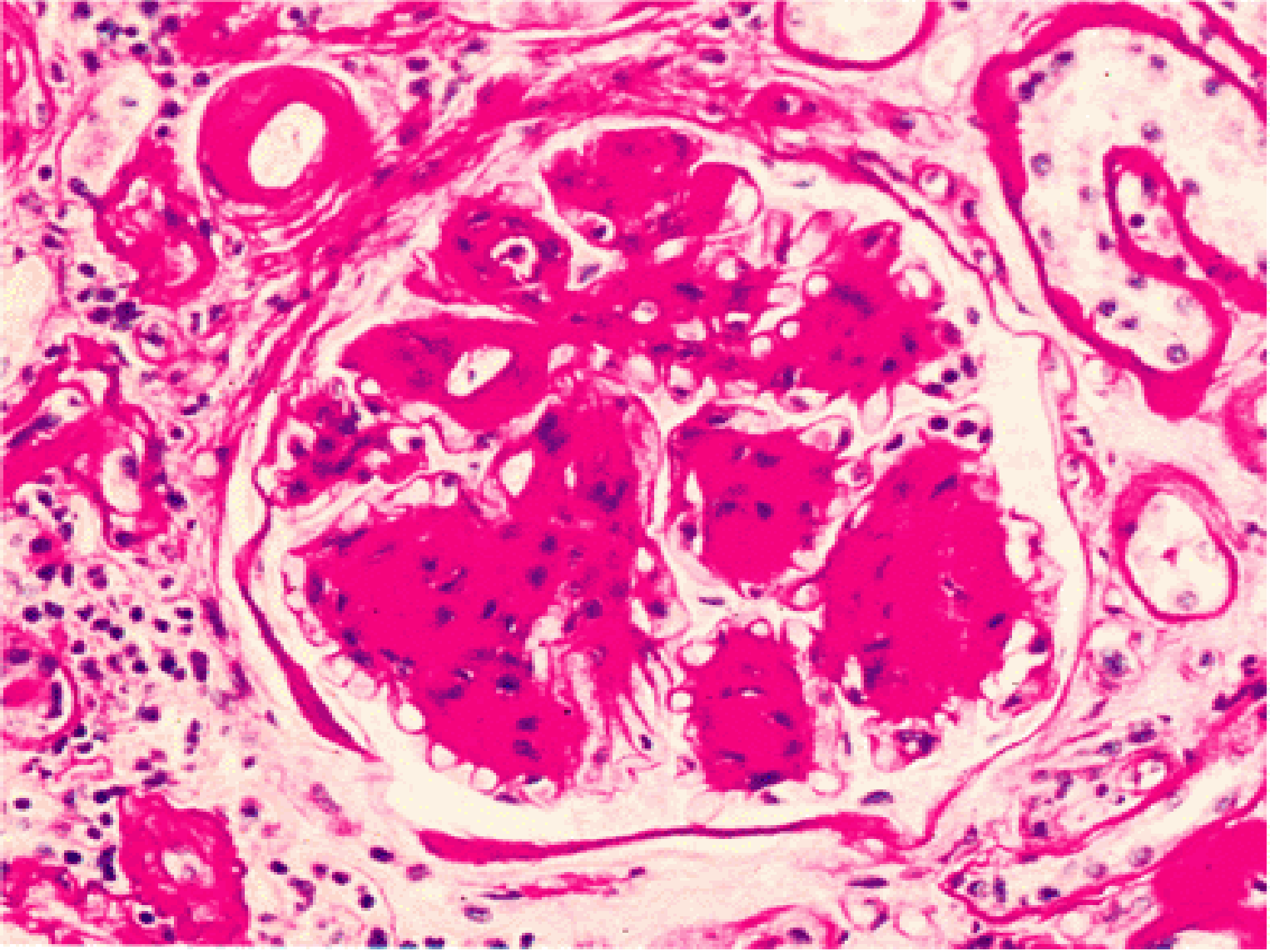
Diabetic Microvascular Disease:

- The effects of microvascular disease on tissue perfusion and wound healing are profound
- Reduce blood flow to the heart, which is already compromised by coronary atherosclerosis.
- Healing of chronic ulcers that develop from trauma and infection of the feet in diabetic patients is commonly defective (gangrene)


Microaneurysms
Microaneurysms and hemorrhage
Microaneurysms, hemorrhape, and exudates
Proliferative diabetic retinopathy
Glomerulosclerosis
Cataracts
Necrotizing papillitis
Coronary atherosclerosis
Autonomic dysfunction (diarrhea)
Focal demyelination
Occlusive atherosclerosis
Chronic ulcers
Dry gangrene
Calcium
Atheroma

Diabetic Nephropathy

- 30% to 40% of T1DM ultimately develop renal failure. A somewhat smaller proportion (up to 20%) of patients with T2DM are similarly affected
- Diabetic nephropathy accounts for one third of all new cases of renal failure.
- The prevalence of diabetic nephropathy increases with the severity and duration of the hyperglycemia.
- The glomeruli in the diabetic kidney exhibit a unique lesion termed Kimmelstiel-Wilson disease or nodular glomerulosclerosis
- Vascular changes: atherosclerosis and arteriolsclersosi
- Parynchyma :pyelonephritis and necrotizing papilitis.



Diabetic Retinopathy

- The most devastating ophthalmic complication of diabetes
- The most important cause of blindness in the Unites States in persons under the age of 60 years.
- The risk is higher in T1DM than in T2DM.

Diabetic retinopathy

- **<u>Non-proliferative changes:</u>**
- Thickening of capillary basement membrane(microangioathy) with microaneurysms
- Retinal hemorrhages(bots)
- Retinal edema and exudate (cotton wool sopts)
- Proliferative changes: neovascularization and fibrosis leads to retinal detachment and blindness.

Diabetic Neuropathy

- Characterized by pain and abnormal sensations in the extremities.
- The most common and distressing complications of diabetes.
- Microvasculopathy involving the small blood vessels of nerves contributes to the disorder.
- Affects Sensory and Autonomic Innervations, Peripheral sensory impairment, and autonomic nerve dysfunction.

Diabetic Neuropathy

- Changes in the nerves are complex, and abnormalities in axons, the myelin sheath, and Schwann cells have all been found.
- Peripheral neuropathy can leads to foot ulcers.

Infections

- Bacterial and Fungal Infections Occur in Diabetic Hyperglycemia if Poorly Controlled
- Renal papillary necrosis may be a devastating complication of bladder infection.
- Mucormycosis: A dangerous infectious complication of poorly controlled diabetes is often fatal fungal infection tends to originate in the nasopharynx or paranasal sinuses and spreads rapidly to the orbit and brain.

Gestational diabetes

- Diabetes Occurring During Pregnancy
- May Put both Mother and Fetus at risk
- Develops in only a few percent of seemingly healthy women during pregnancy.
- It may continue after parturition in a small proportion of these patients.
- These women highly susceptible to overt T2DM later in life.