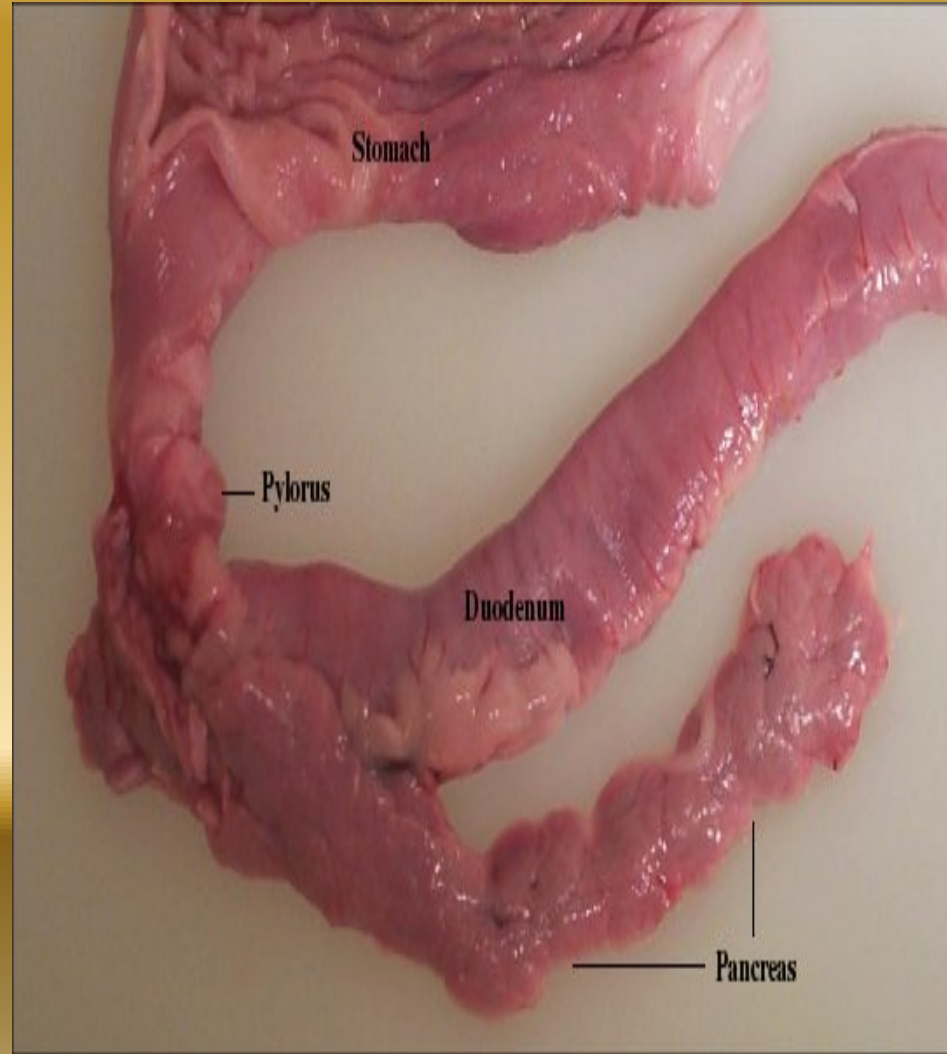


Diseases of pancreas

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The **pancreas** is a elongated organ, light tan or pinkish in color, that lies in close proximity to the duodenum. It is covered with a very thin connective tissue capsule which extends inward as septa, partitioning the gland into lobules.

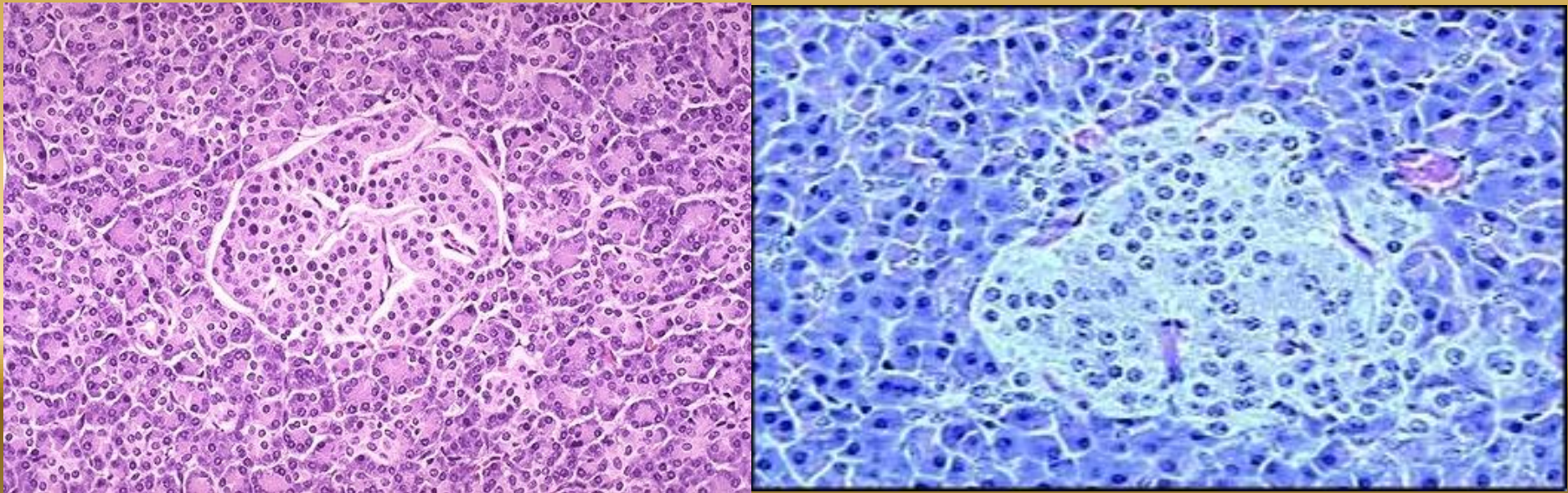


The pancreas is a mixed gland, having both an endocrine and an exocrine function.

As an endocrine gland, it secretes into the blood several important hormones, including insulin, glucagon, somatostatin, and pancreatic polypeptide.

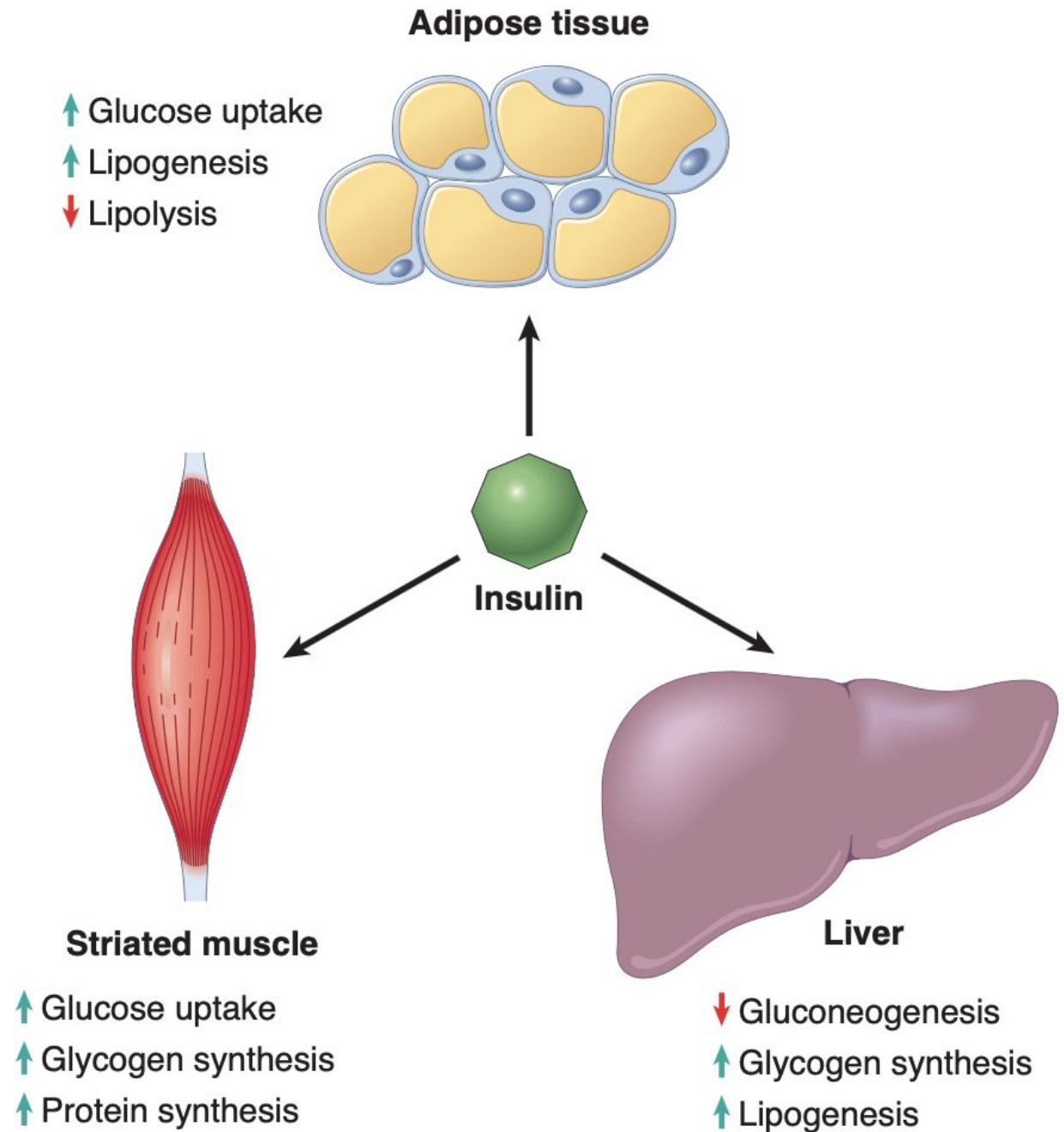
As an exocrine gland, it secretes pancreatic juice into the duodenum through the pancreatic duct.

- Embedded within this exocrine tissue are roughly one million small clusters of cells called the *Islets of Langerhans*, which are the endocrine cells



Here is a normal pancreatic islet of Langerhans surrounded by normal exocrine pancreatic acinar tissue. The islets contain alpha cells secreting glucagon, beta cells secreting insulin, and delta cells secreting somatostatin.

The function of insulin



Diabetes mellitus

Objective

1. What is the Definition of diabetes mellitus?
2. What is the classification of diabetes mellitus?
3. What is diagnostic approach of diabetes mellitus?
4. What are the short & long term pathological complications.

Diabetes mellitus

This is “a *group of metabolic disorders sharing the common underlying characteristic of hyperglycemia.*” with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.

Diabetes is an important disease because

- 1. It is common (affects 7% of the population).**
- 2. It increases the risk of atherosclerotic coronary artery and cerebrovascular diseases.**
- 3. It is a leading cause of**
 - a. Chronic renal failure**
 - b. Adult-onset blindness**
 - c. Non-traumatic lower extremity amputations (due to gangrene)**

Classification

Diabetes is divided into two broad classes:

- 1. *Type 1 diabetes (10%)***: characterized by an absolute deficiency of insulin secretion caused by pancreatic β -cell destruction, usually as a result of an autoimmune disease .
- 2. *Type 2 diabetes (80%)***: caused by a combination of peripheral resistance to insulin action and an inadequate secretion of insulin from the pancreatic β cells in response to elevated blood glucose levels.

Gestational diabetes: Is the third main form, and occurs when pregnant women without a previous history of diabetes develop high blood sugar levels.

Maturity onset diabetes of the young: (MODY) is an autosomal dominant inherited form of diabetes, due to one of several single-gene mutations causing defects in insulin production. It is significantly less common than the three main types.

* MODY might be regarded
as the third type

TWO* Types of DM

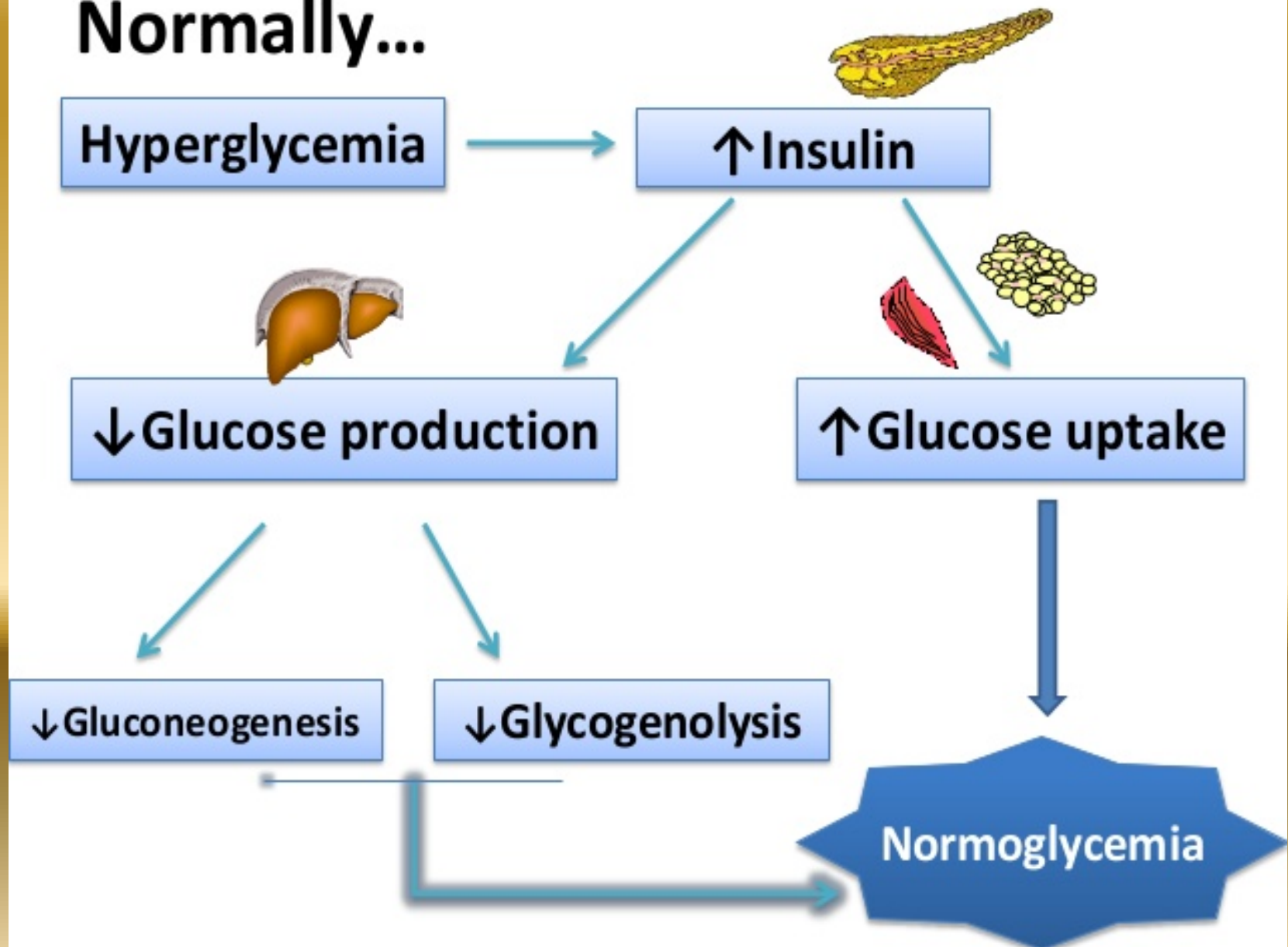
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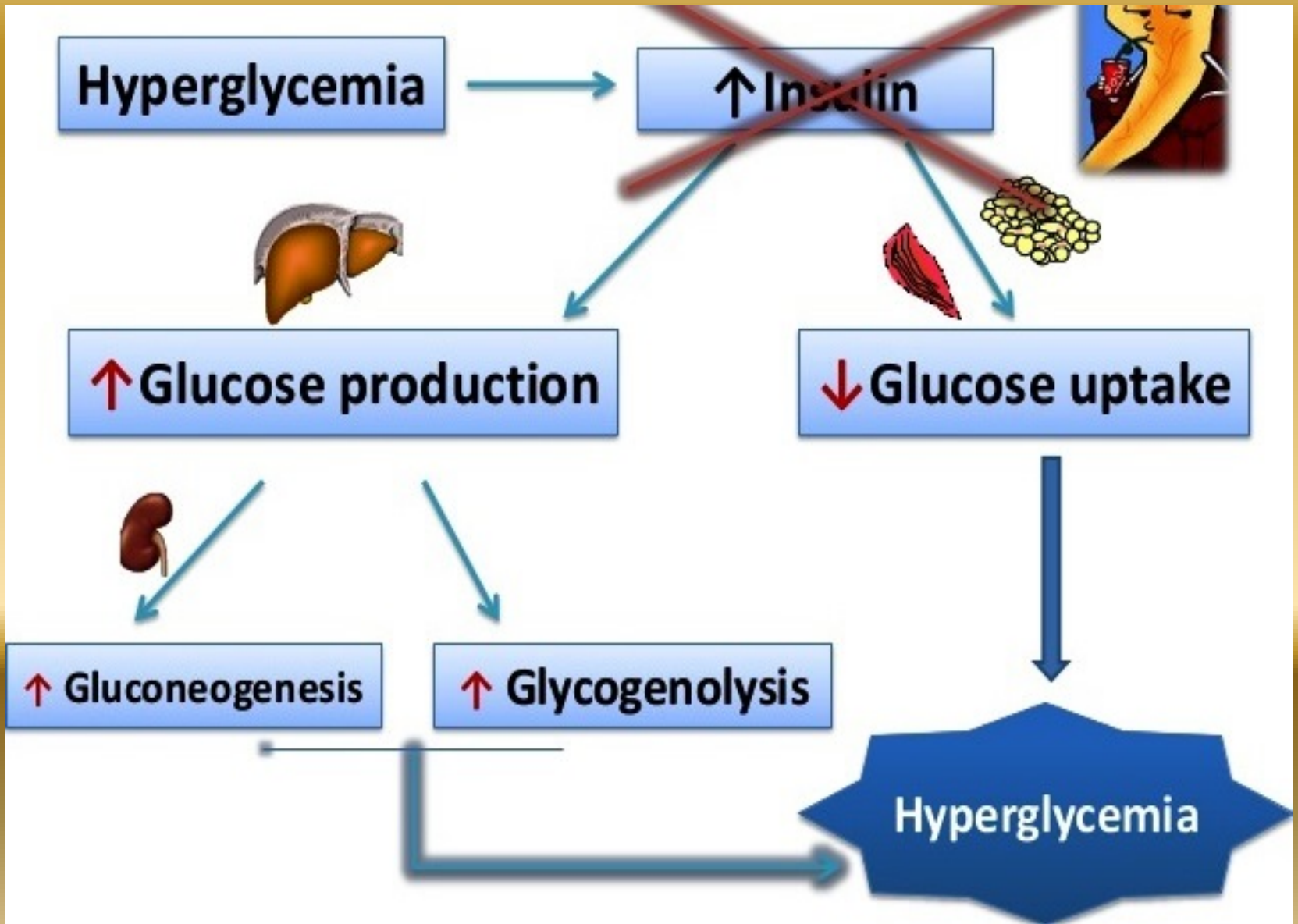
- 10%
- Genetic
- Autoimmune
- Childhood (juvenile) onset
- Antibodies to beta cells
- Beta cell depletion
- NON-OBESE patients

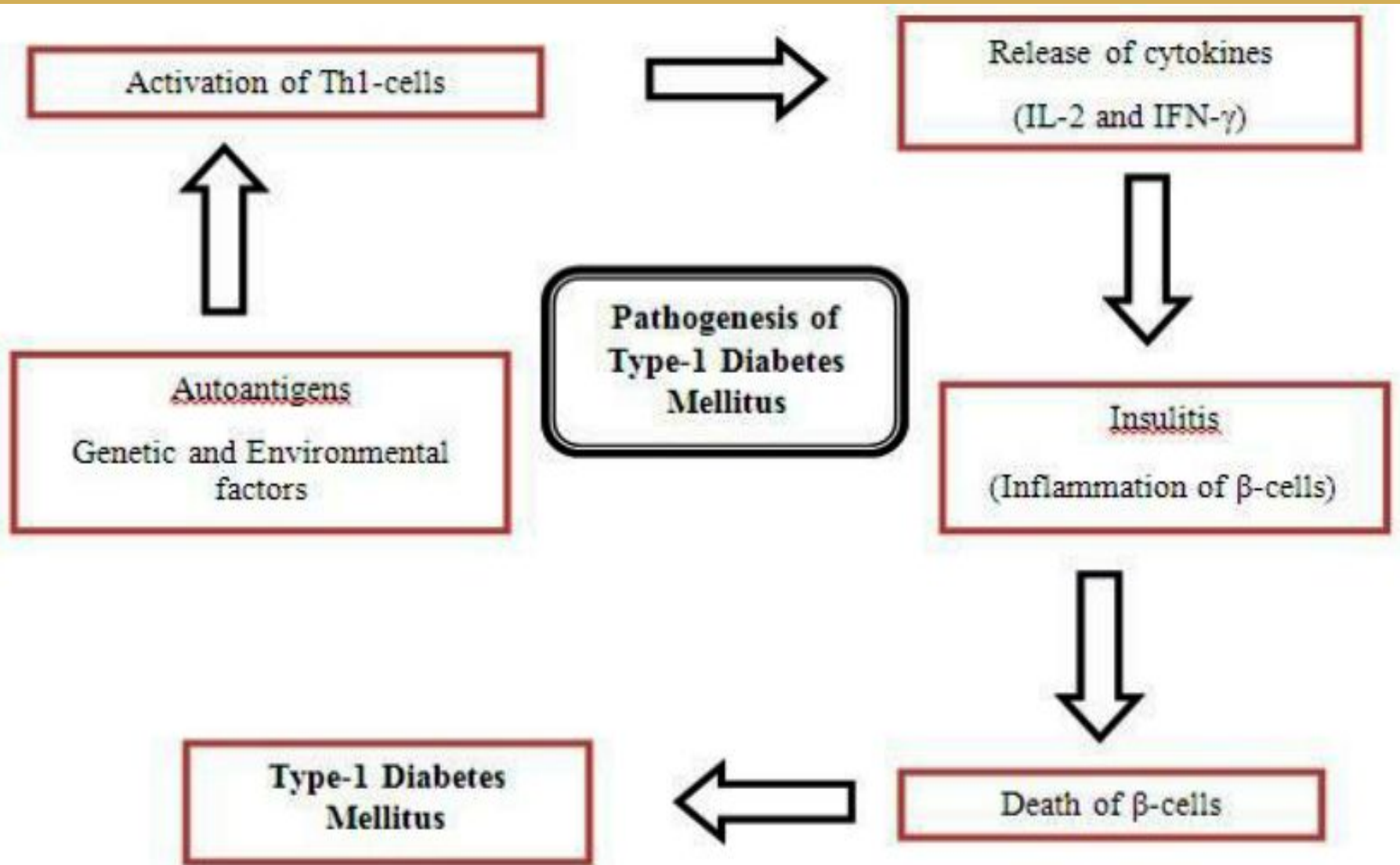
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- 80%
- Genetic, but diff. from Type 1
- NOT autoimmune
- Adult, or maturity onset, e.g., 40's, 50's
- Insulin may be low, BUT, peripheral resistance to insulin is the main factor
- OBESE patients

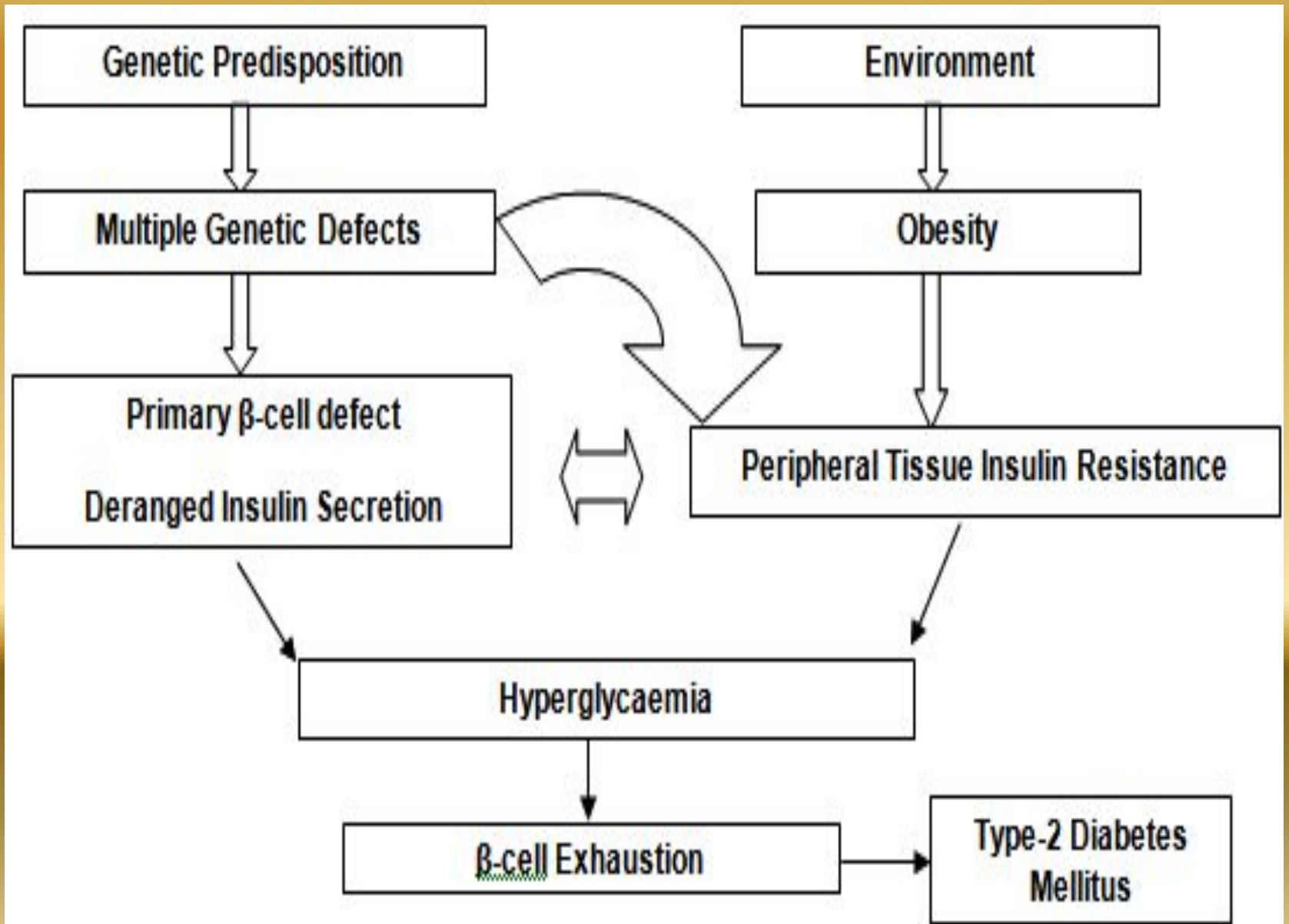
Normally...







Abbreviations: Th1, T helper cells; IL-2, Interleukin-2; IFN-γ, Interferon-gamma.



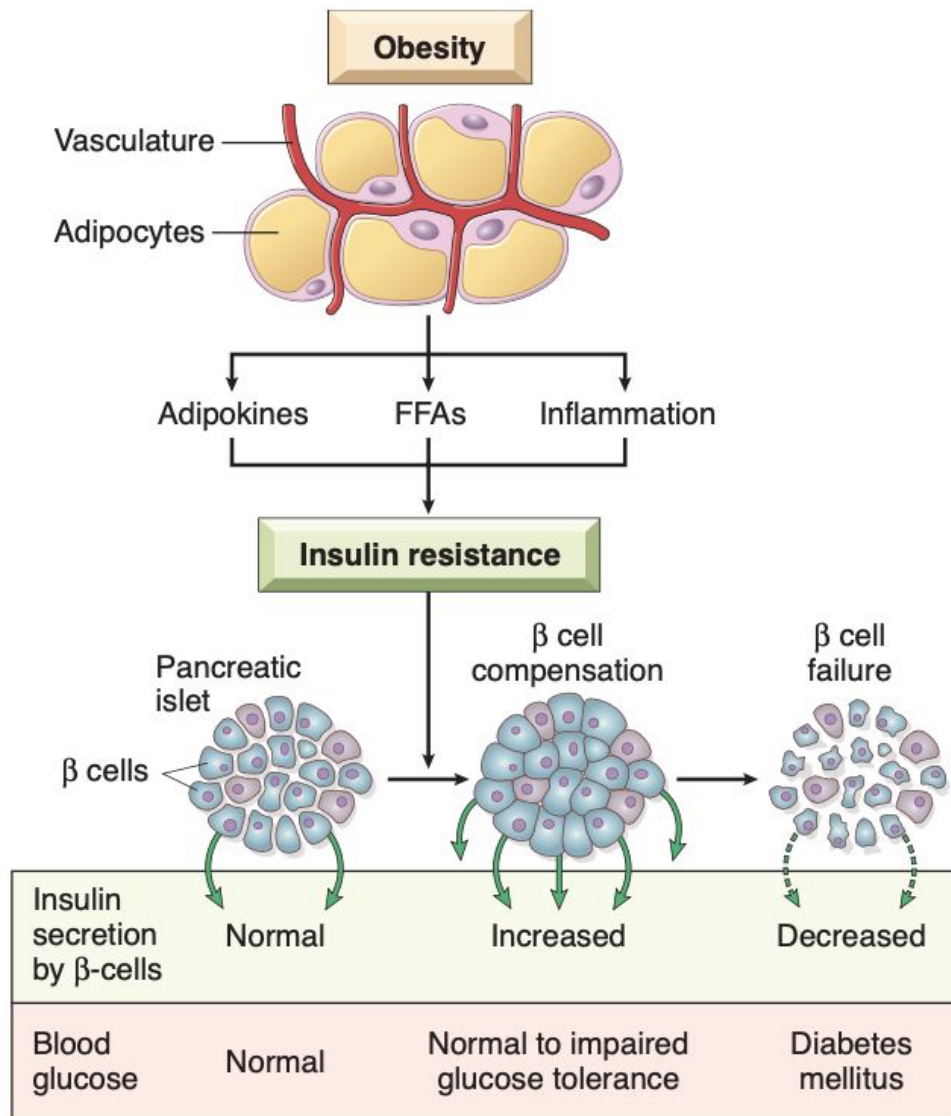
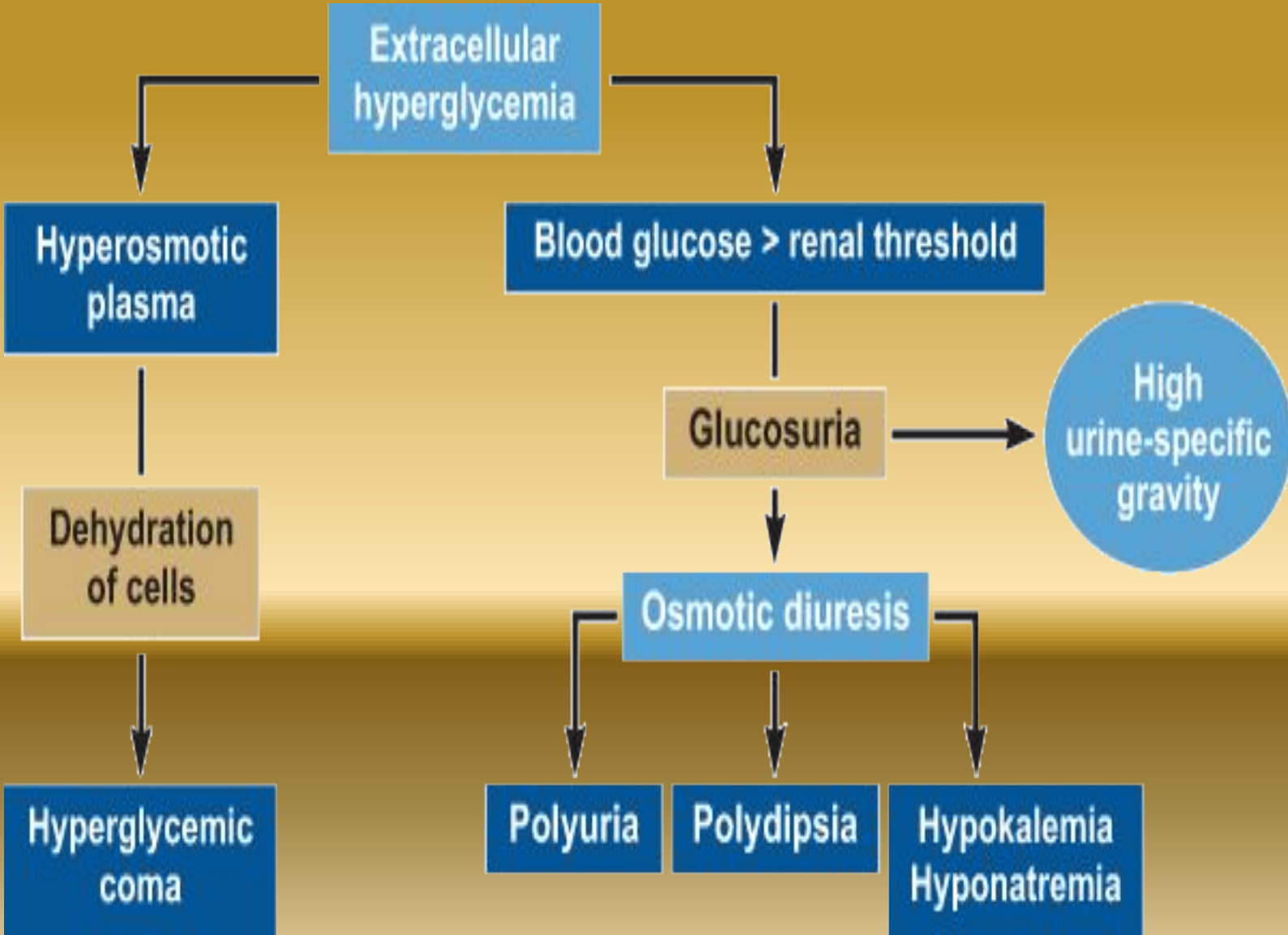
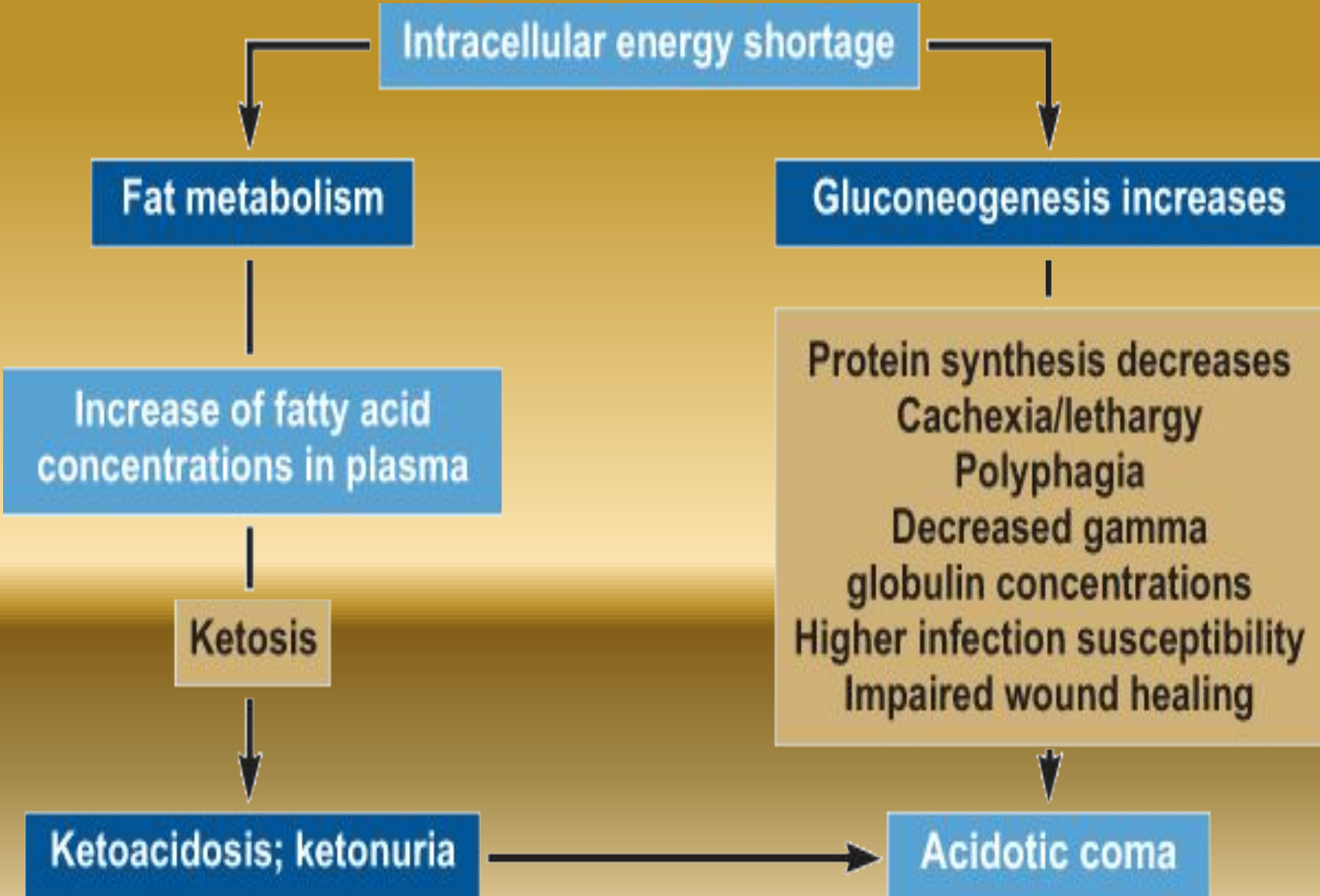


Fig. 20.23 Development of type 2 diabetes. Insulin resistance associated with obesity is induced by adipokines, free fatty acids, and chronic inflammation in adipose tissue. Pancreatic β cells compensate for insulin resistance by hypersecretion of insulin. However, at some point, β cell compensation is followed by β cell failure, and diabetes ensues. (Reproduced with permission from Kasuga M: *Insulin resistance and pancreatic β -cell failure*. J Clin Invest 116:1756, 2006.)

Complications



Complications



Main symptoms of Diabetes

blue = more common
in Type 1

Central

- Polydipsia
- Polyphagia
- Lethargy
- Stupor

Eyes

- Blurred vision

Breath

- Smell of acetone

Systemic

- Weight loss

Respiratory

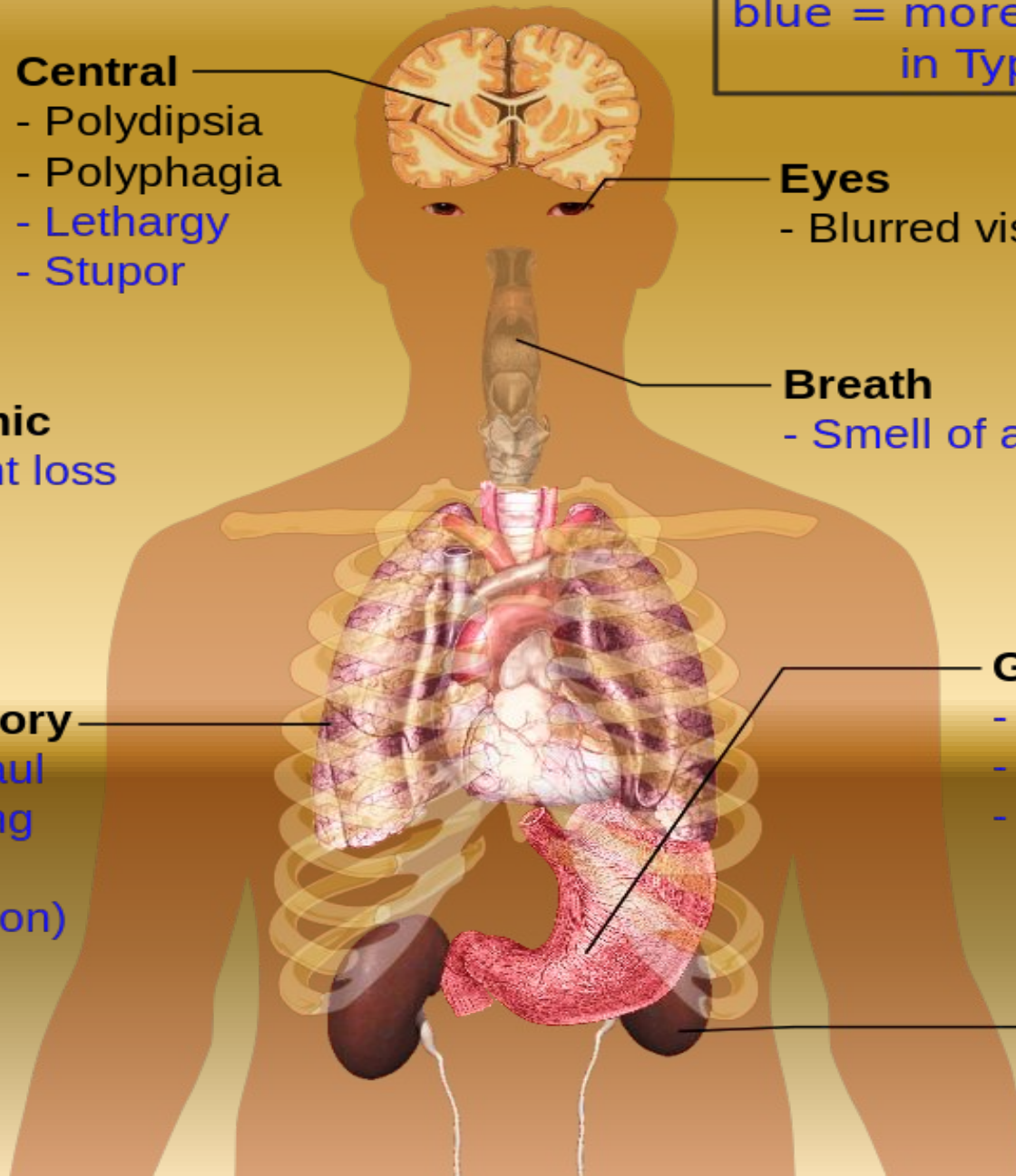
- Kussmaul breathing
(hyper-ventilation)

Gastric

- Nausea
- Vomiting
- Abdominal pain

Urinary

- Polyuria
- Glycosuria



LABORATORY:-

- **FPG level ≥ 7.0 mmol/l (126 mg/dl)**
- **RPG ≥ 11.1 mmol/l (200 mg/dl) two hours after a 75 g oral glucose load as in a glucose tolerance test**
- **Glycated hemoglobin (HbA1C) ≥ 48 mmol/mol (≥ 6.5 DCCT %).**

Morphology of Diabetes and Its Late Complications

- **Pancreas:** Findings are variable.

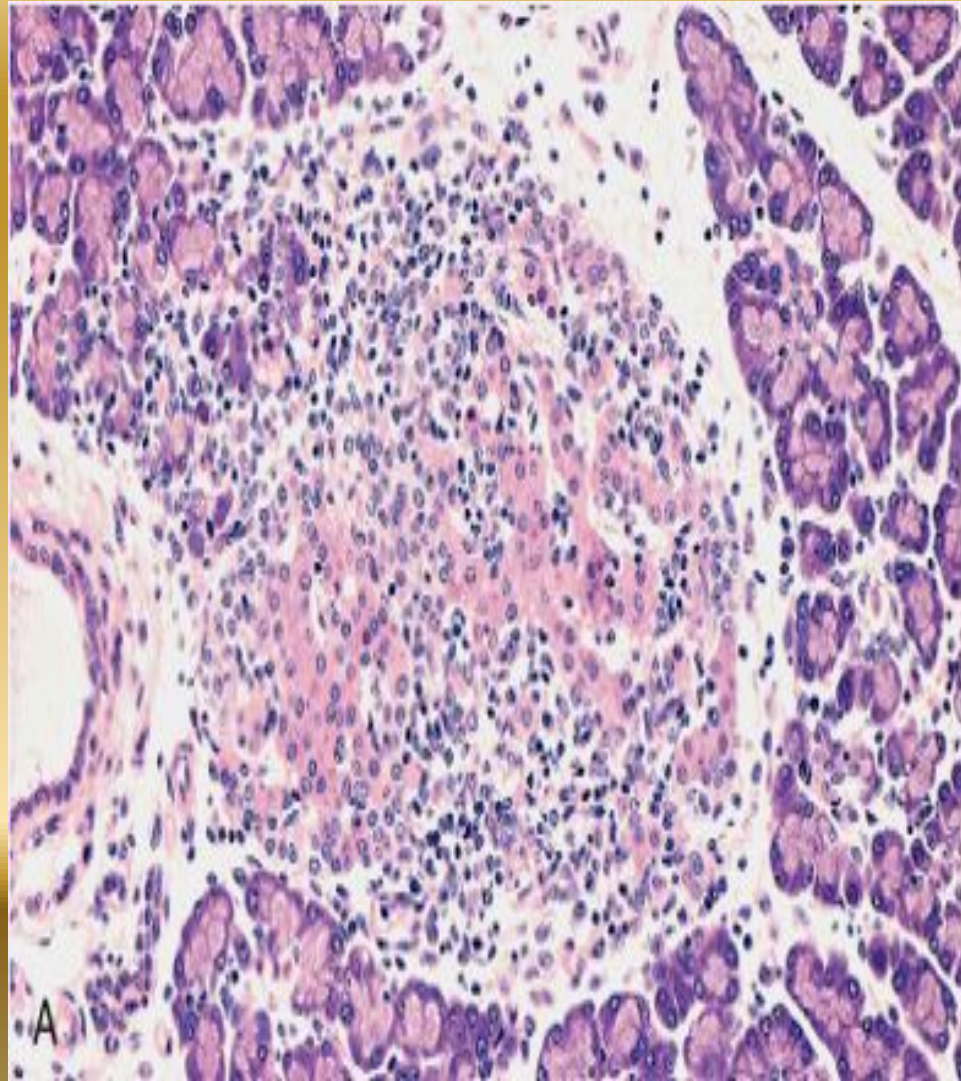
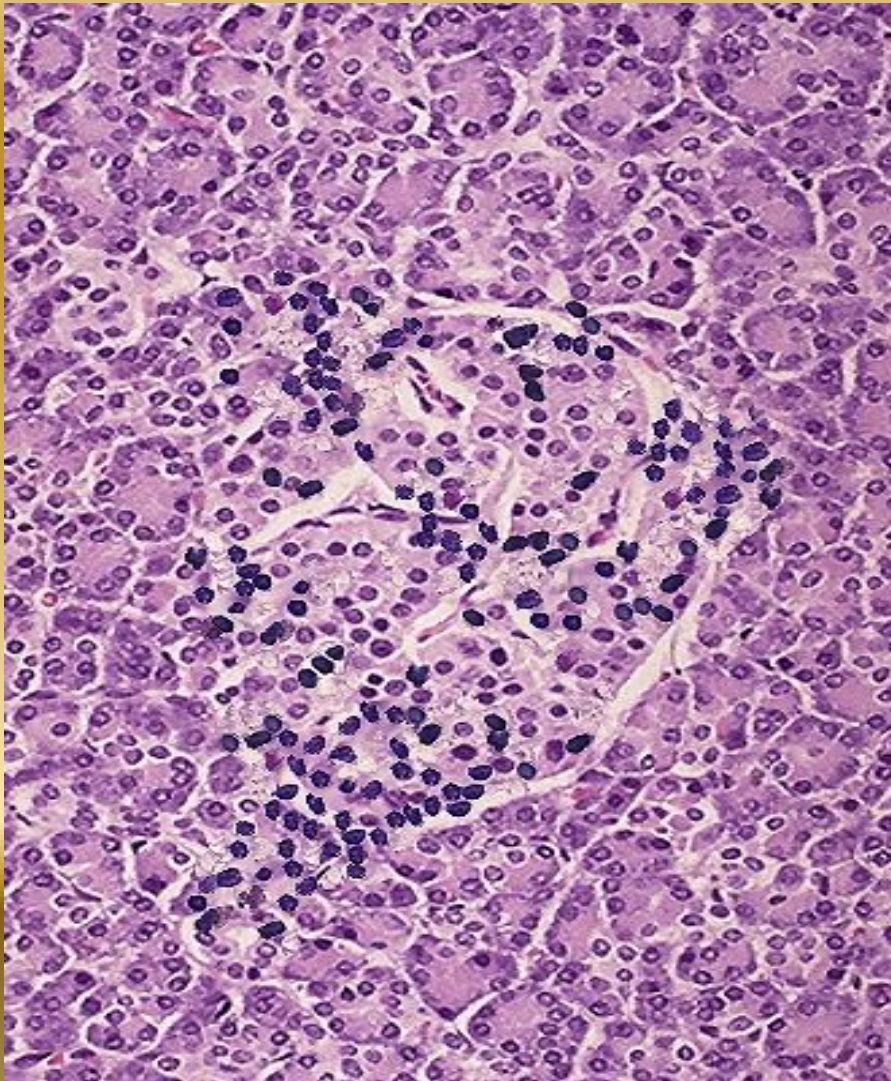
Type 1: Islet number and size are reduced and a lymphocytic infiltrate (insulitis) may be present.

Leukocytic infiltration of the islets (insulitis) principally by T lymphocytes

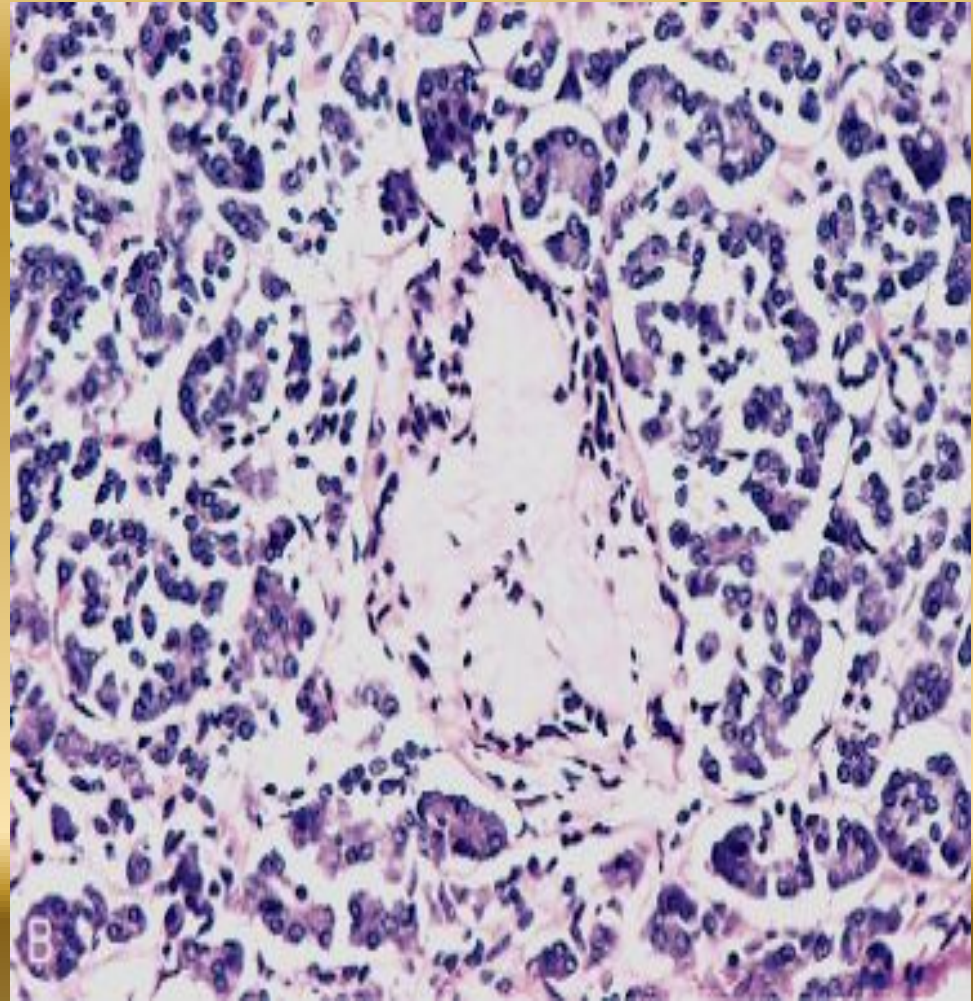
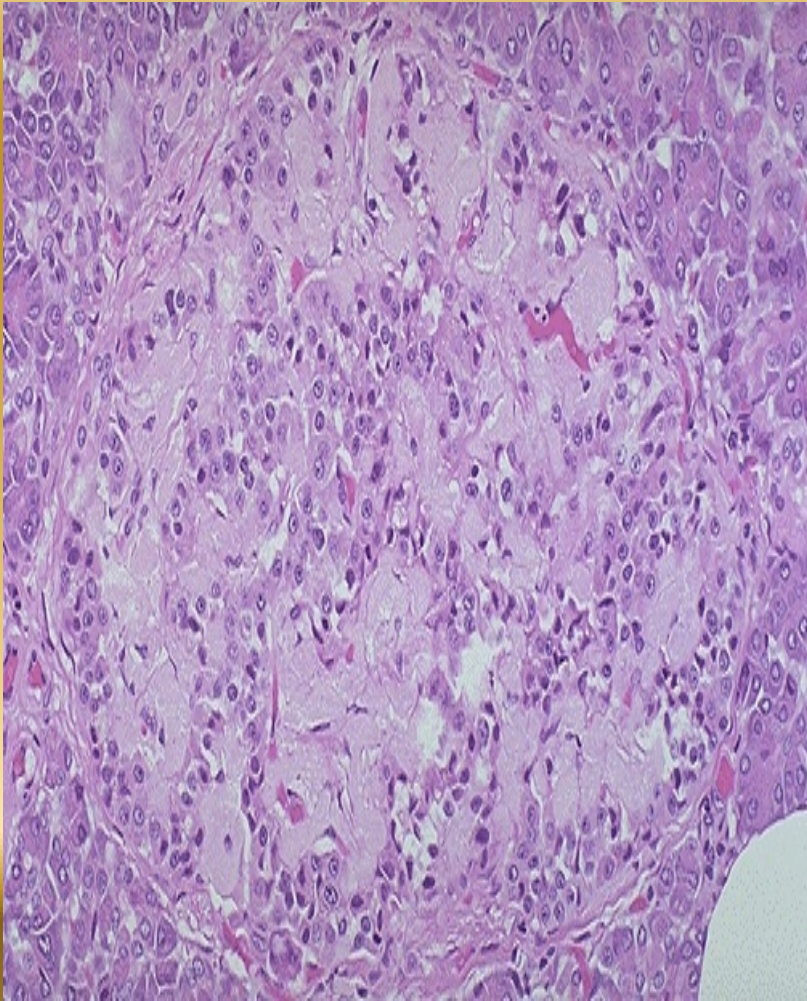
Type 2: Subtle reduction in islet cell mass may be accompanied by amyloid deposition.

Amyloid replacement of islets; which is seen in advanced stages

Insulitis



auto-immune disorder we see inflammatory changes against tissue with NO known external pathogen, in this case LYMPHOCYTES (T-Cells) attacking islets. Could this be called an Insulitis



This islet of Langerhans demonstrates pink hyalinization (with deposition of amyloid) in many of the islet cells. This change is common in the islets of patients with type II diabetes mellitus. This amyloid contains protein derivatives of amylin, or islet amyloid polypeptide. Amylin is secreted in small amounts at the same time as insulin and slows the rate of rise of glucose in the blood.

- **Diabetic macrovascular disease** is manifested as accelerated/ exacerbated atherosclerosis in the aorta and large and medium- sized arteries; hyaline arteriolosclerosis is more prevalent and severe
- **Diabetic microangiopathy** is reflected by diffuse basement membrane thickening, most evident in the capillaries of the skin, skeletal muscle, retina, renal glomeruli, and renal medulla. Such capillaries are more leaky than normal to plasma proteins. Basement membrane thickening can also affect nonvascular structures (e.g., renal tubules, Bowman capsule, peripheral nerves, and placenta).

- **Diabetic nephropathy:**

Glomerular involvement includes diffuse basement membrane thickening, mesangial sclerosis, nodular glomerulosclerosis (Kimmelstiel-Wilson lesion), and/or exudative lesions.

Vascular effects include renal artery atherosclerosis and arteriolosclerosis with hypertension.

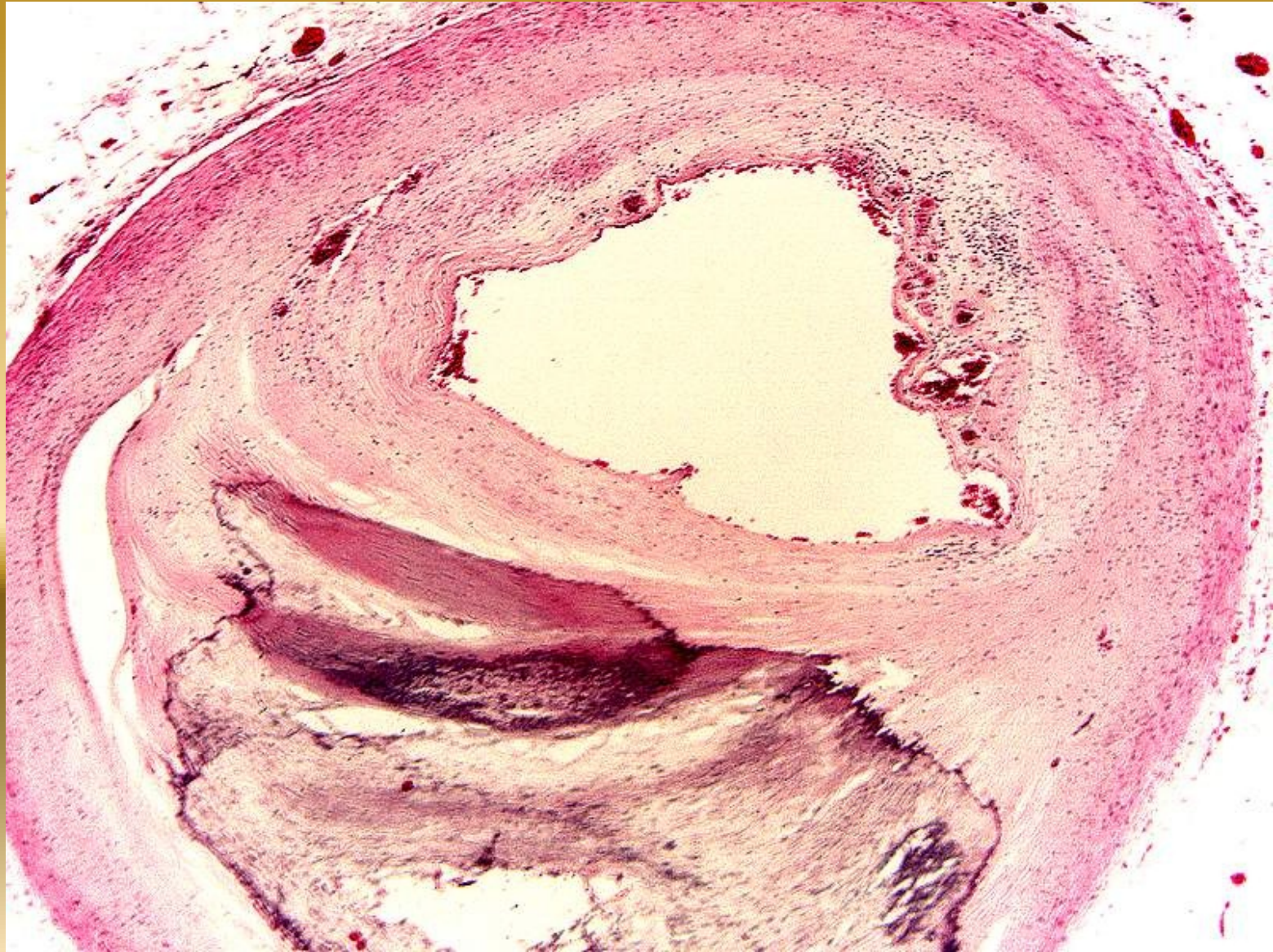
There is increased incidence of infections, including pyelonephritis and sometimes necrotizing papillitis.

- **Diabetic ocular complications** take the form of retinopathy, cataracts, or glaucoma
- **Diabetic neuropathy** is a combination of direct neural injury as well as microvascular ischemia

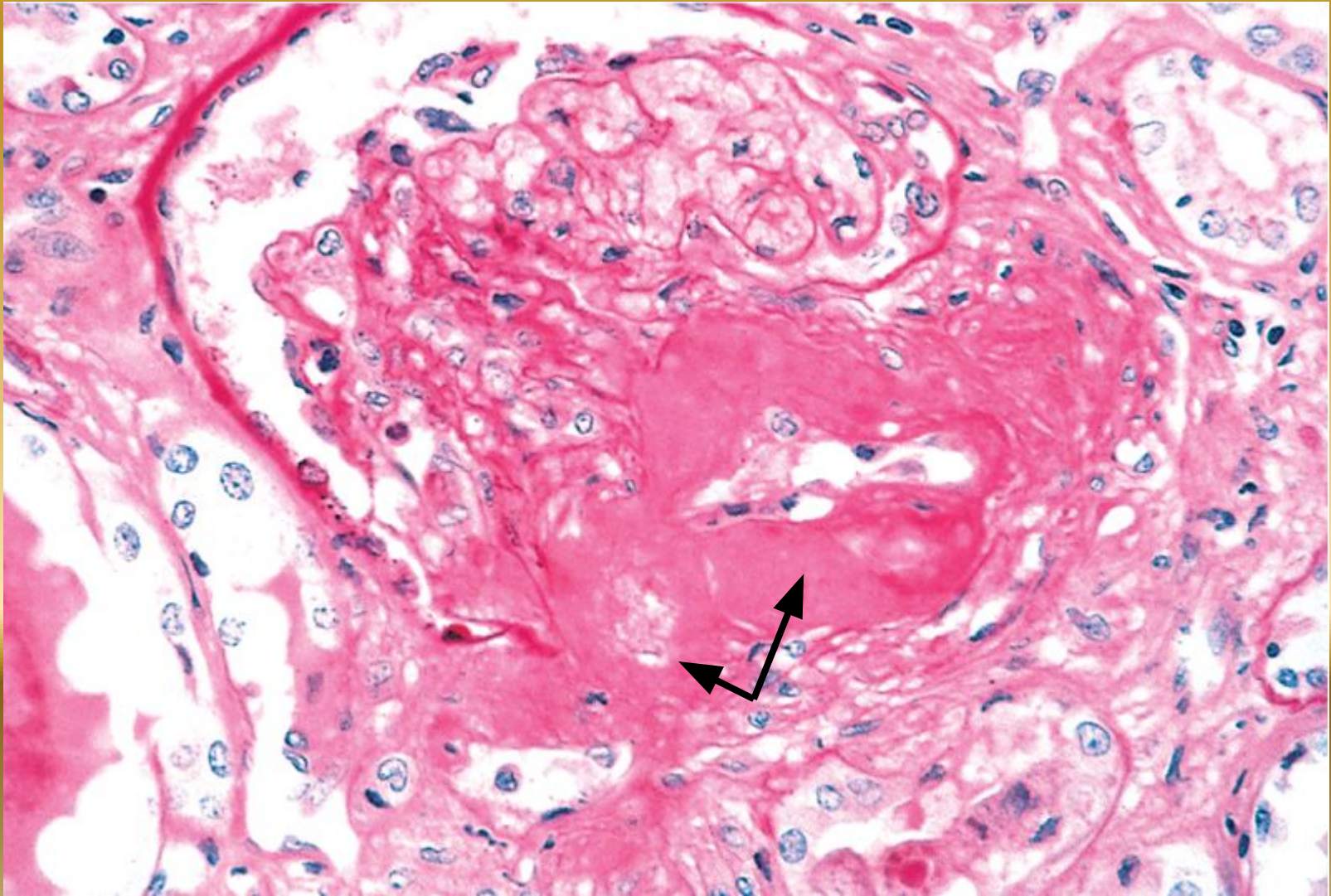
ATHEROSCLEROSIS



ATHEROSCLEROSIS



Severe renal hyaline arteriosclerosis



Note a markedly thickened, tortuous afferent arteriole. The amorphous nature of the thickened vascular wall is evident (arrow). (PAS stain)

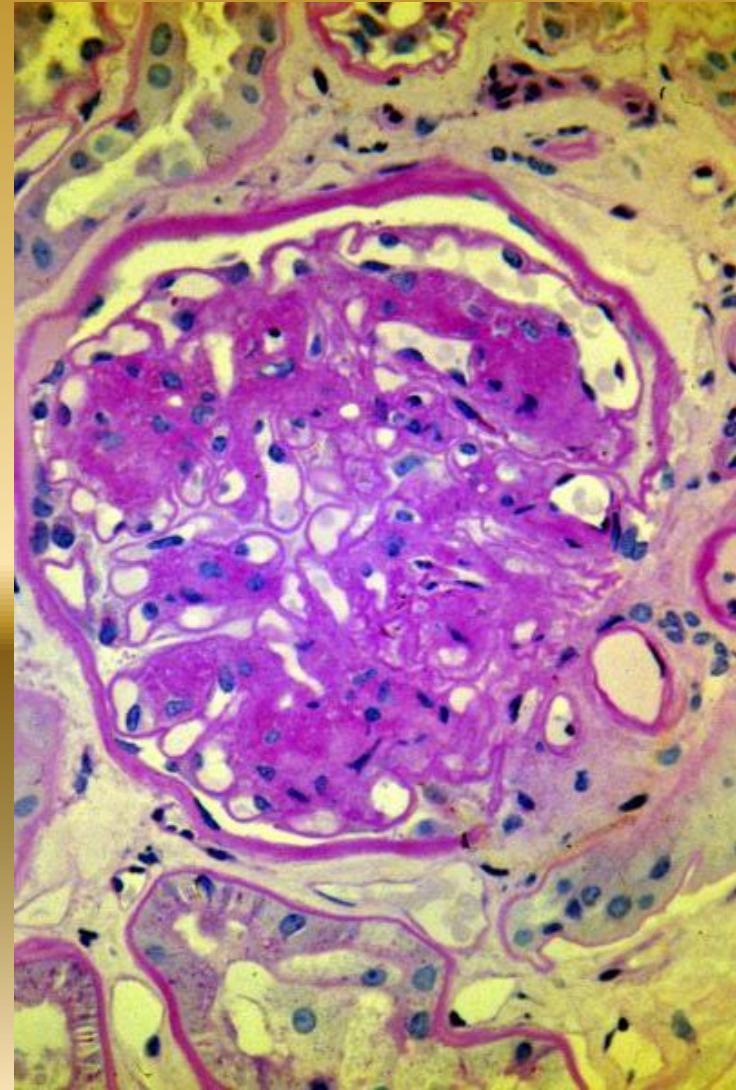
NEPHROPATHY



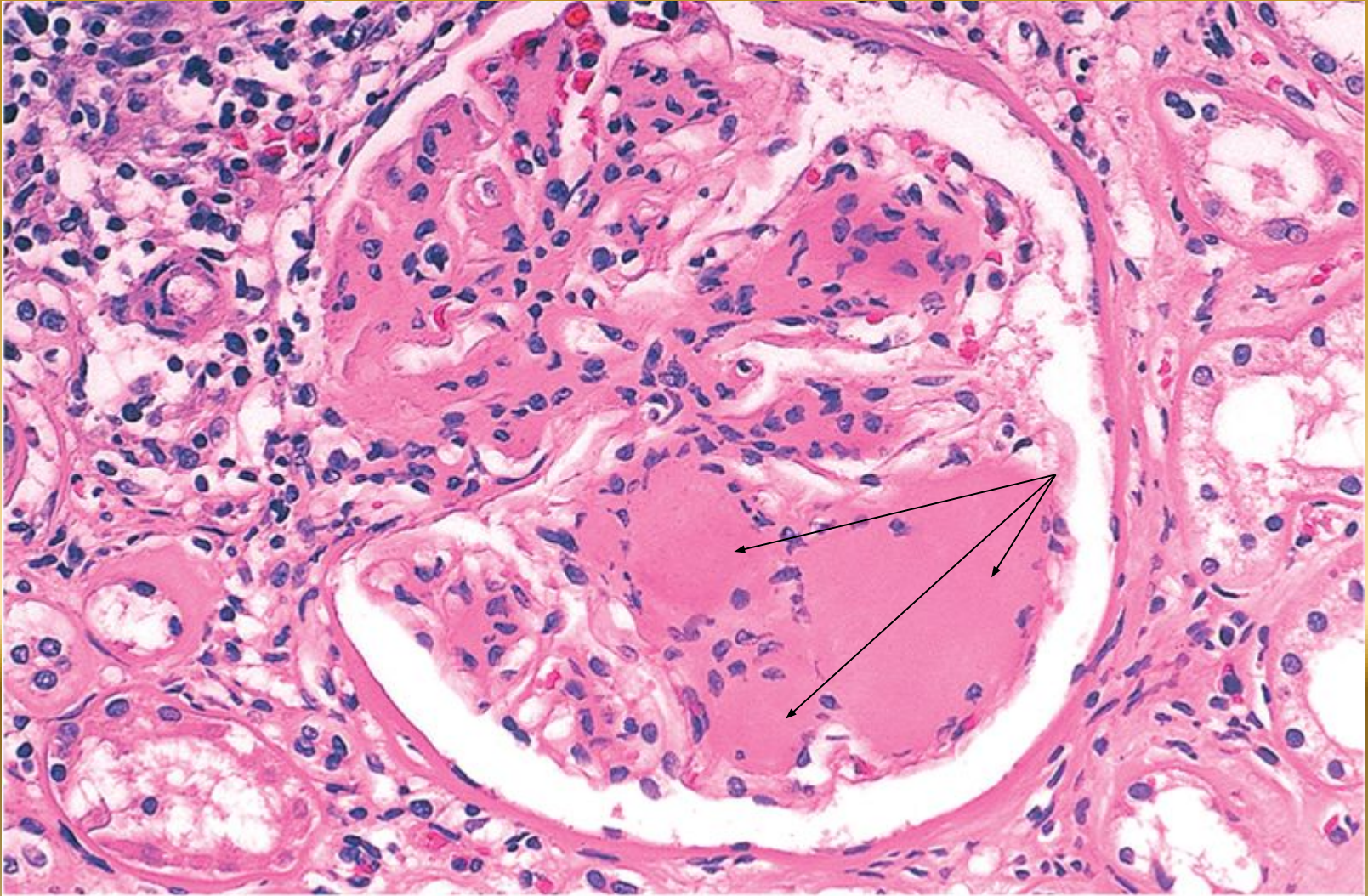
**Kimmelstiel-
Wilson (KW)**
Kidneys

Is.....

“Nodular”
glomerulosclerosis

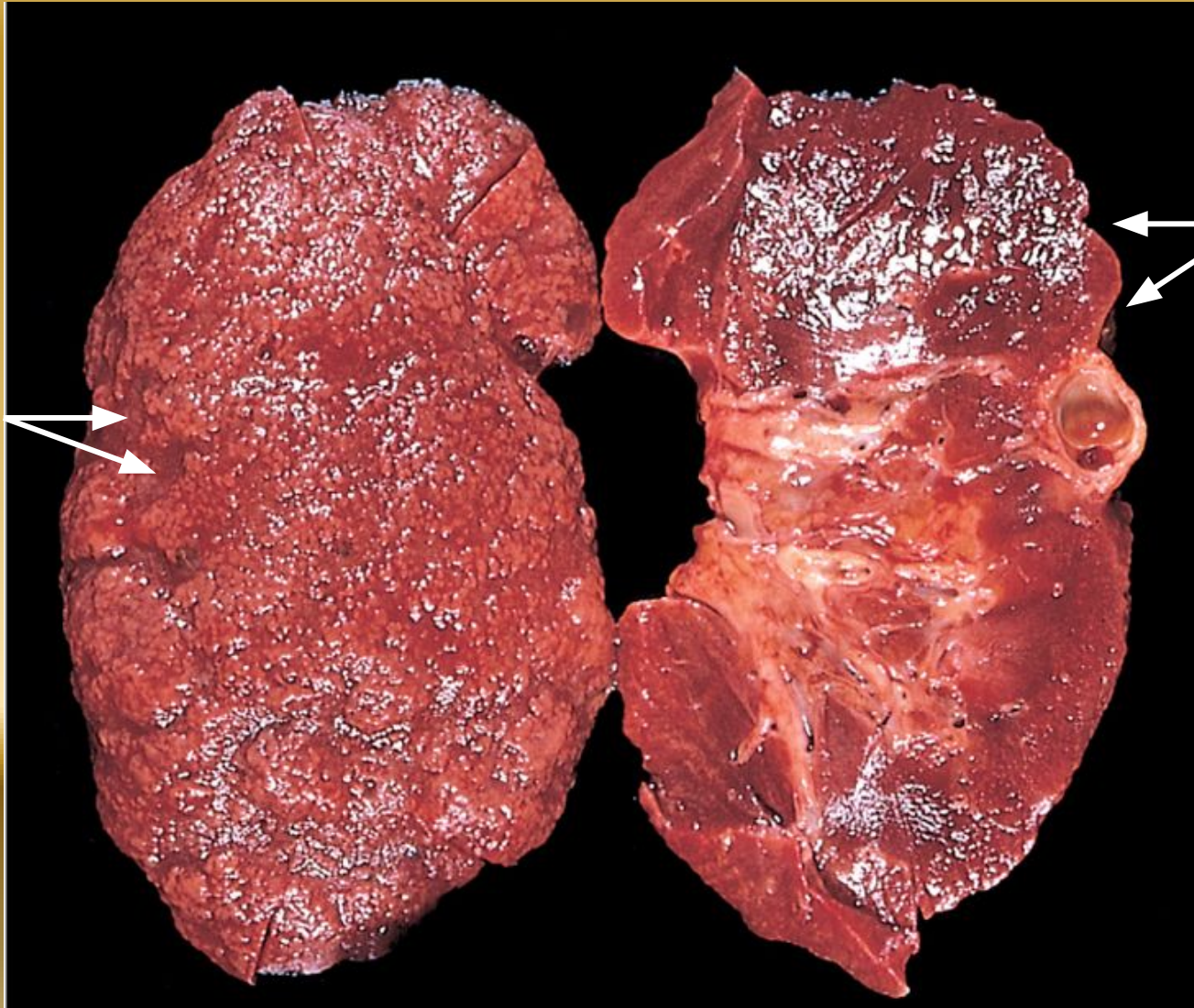


Nodular glomerulosclerosis (Kimmelstiel-Wilson lesion)



This is seen in persons with long-standing diabetes. It is characterized by rounded, pinkish deposits of situated in the periphery of the glomerulus.

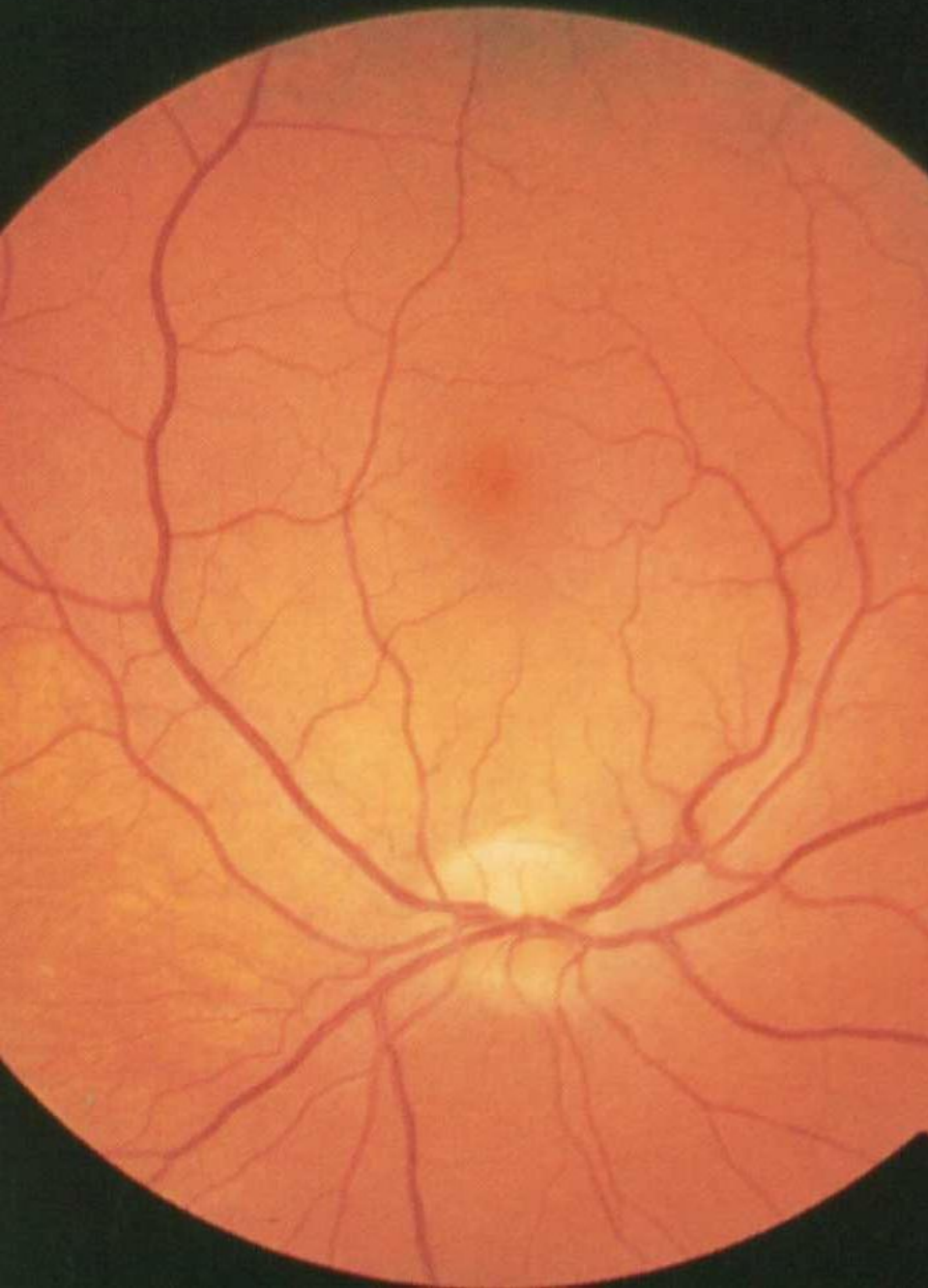
Pyelonephritis, Nephrosclerosis



The kidney has been bisected to demonstrate both diffuse granular transformation of the surface (left) and marked thinning of the cortical tissue (right). Additional features include some irregular depressions (arrows), the result of pyelonephritis, and an incidental cortical cyst (far right).

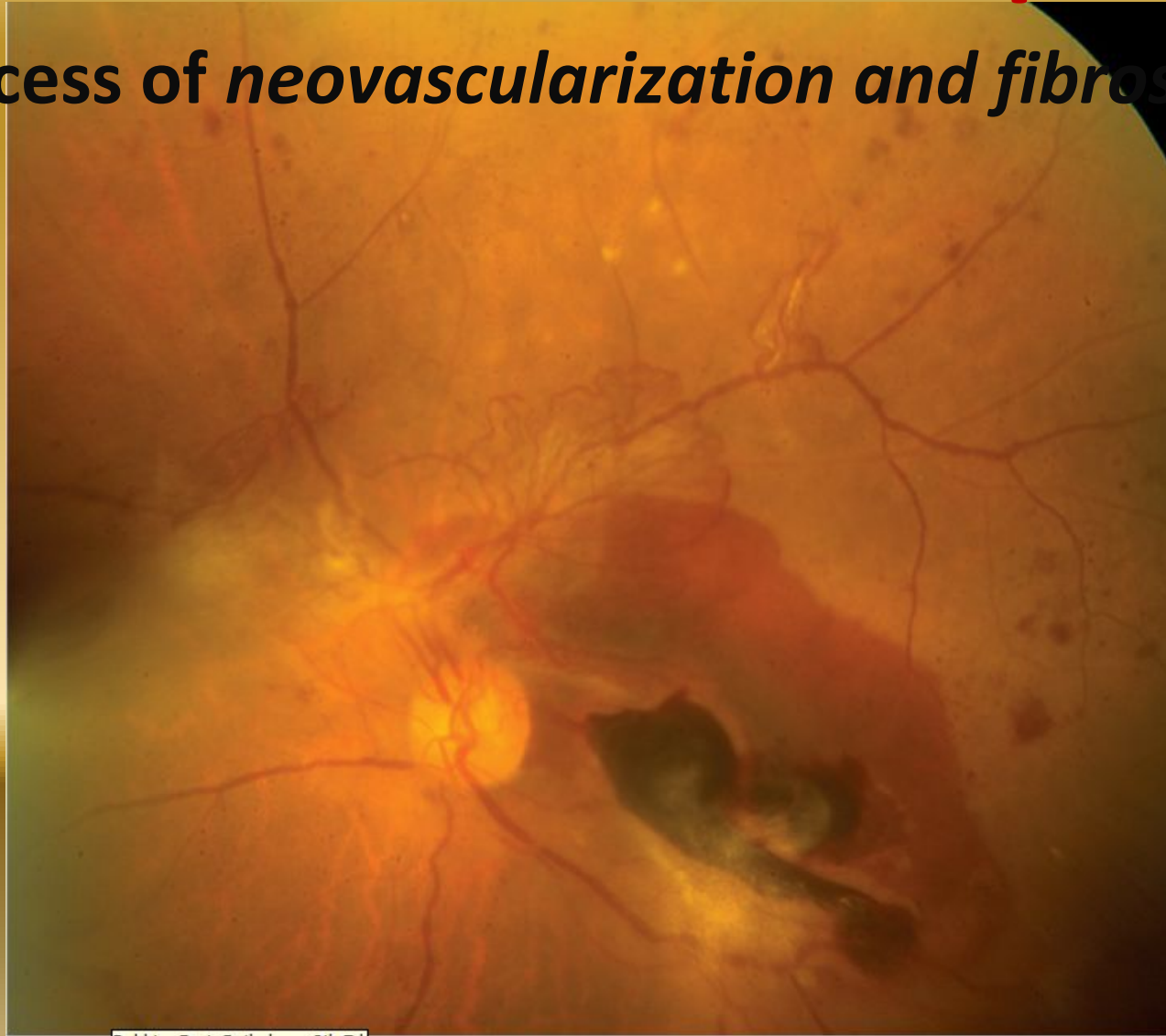
Proliferative retinopathy

**Shows microaneurysms,
areas of hemorrhage,
cotton wool spots, hard
exudates, venous beading,
neovascularization, retinal
detachment, vitreous
detachment, pre retinal
hemorrhage**



Non Proliferative retinopathy

a process of *neovascularization and fibrosis*.



This demonstrates advanced proliferative retinopathy with retinal hemorrhages, exudates, neovascularization, and tractional retinal detachment in the lower right corner.

Non-proliferative
diabetic retinopathy



Aneurysm

Hard
exudate

Hemorrhage

Proliferative
diabetic retinopathy



Growth of abnormal
blood vessels

Clinical Features of Diabetes

Type 1 diabetes can occur at any age.

polyuria , Intense thirst (polydipsia) develops, with increased appetite (polyphagia), weight loss and muscle weakness.

Diabetic ketoacidosis occurs

Type 2 diabetics are usually older than 40 years and typically obese; they can also present with polyuria and polydipsia but are most often discovered by routine blood glucose screening.

Ketoacidosis is uncommon due to persistent insulin production that minimizes ketone body production. Non-ketotic hyperosmolar coma can occur in compromised individuals who become dehydrated secondary to osmotic diuresis and inadequate water intake.

Complications of long-standing diabetes:

Cardiovascular events (e.g., myocardial infarction, renal vascular insufficiency, and stroke) are the most common causes of death.

Diabetic nephropathy is a leading cause in the United States of end-stage renal disease

Diabetic retinopathy develops in 60% to 80% of patients within 15 to 20 years of diagnosis. The fundamental lesion is neovascularization attributable to hypoxia-induced over-expression of VEGF in the retina.

Diabetic neuropathy typically presents with extremity distal symmetric polyneuropathy, affecting both sensory and motor function. Autonomic neuropathy can produce bladder, bowel, or sexual dysfunction, and diabetic mononeuropathy can manifest with sudden cranial nerve palsy or foot or hand drop.

Enhanced susceptibility to infections is attributable to compromised tissue perfusion, diminished neutrophil function, and impaired macrophage cytokine production.

INFECTIONS in Dm

- SKIN
- TUBERCULOSIS
- PNEUMONIA
- PYELONEPHRITIS
- CANDIDA

Pancreatic endocrine neoplasm

Pancreatic endocrine neoplasm (*islet cell tumors*)

Pancreatic endocrine neoplasms

- Are rare in comparison with tumors of the exocrine pancreas
- Accounting for only 2% of all pancreatic neoplasms.
- These are most common in adults .
- May be single or multiple, and benign or malignant.
- They tend to be functional.

*Unequivocal criteria for malignancy include **metastases, vascular invasion, and local infiltration***

Insulinomas (β -cell tumors)

Most common of pancreatic endocrine neoplasms; they are generally benign but may produce sufficient insulin to induce hypoglycemia.

- 1. Occur with blood glucose levels below 50 mg/dL of serum;*
- 2. Consist principally of central nervous system manifestations such as confusion, stupor, and loss of consciousness*
- 3. Precipitated by fasting or exercise and are promptly relieved by feeding or parenteral administration of glucose.*

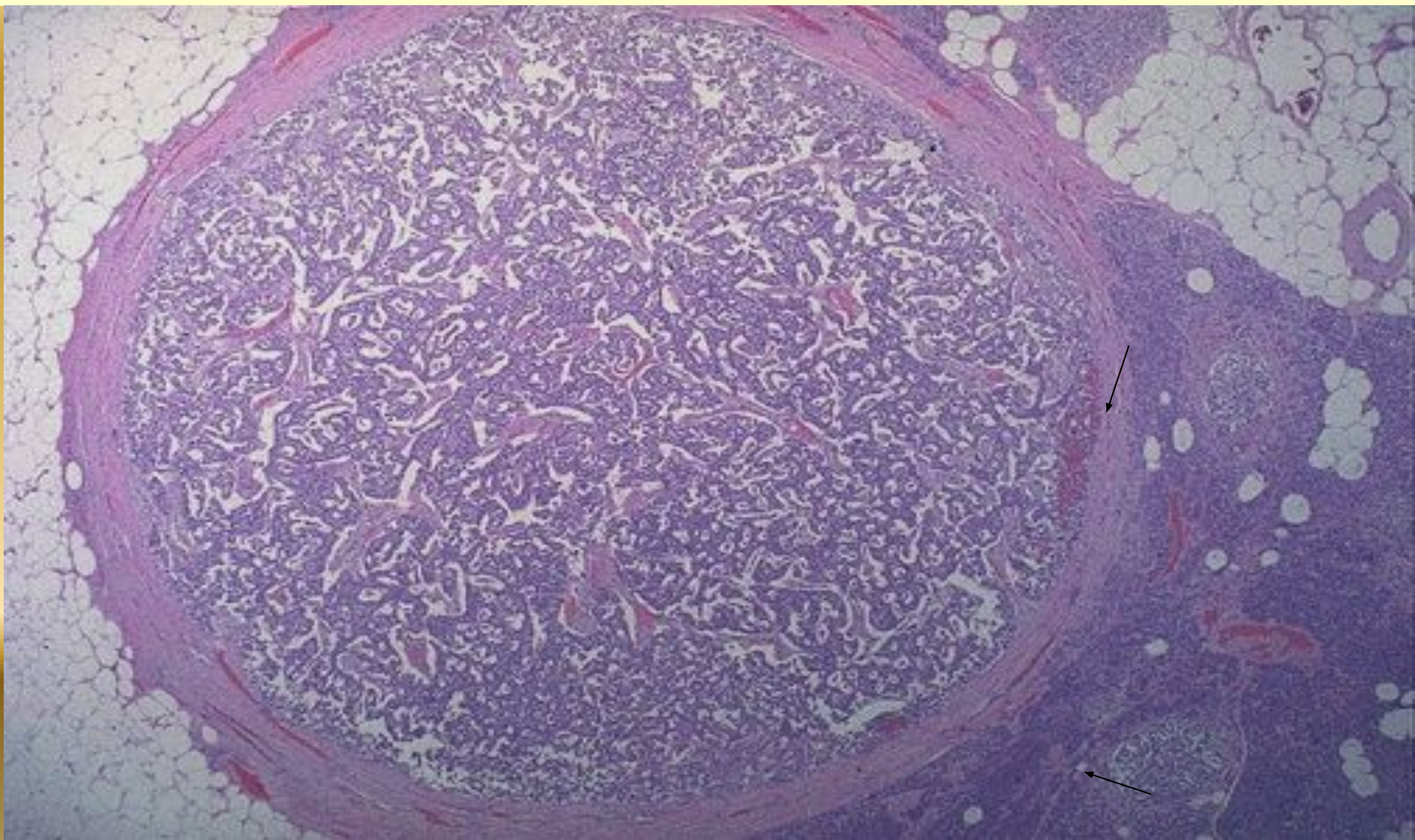
Approximately 90% of insulinomas are benign,
While 60% to 90% of other functioning and nonfunctioning pancreatic endocrine neoplasms are malignant

Gross features

These are mostly solitary lesions, & usually small (<2 cm in diameter), They tend to be encapsulated, pale to red-brown nodules located anywhere in the pancreas.

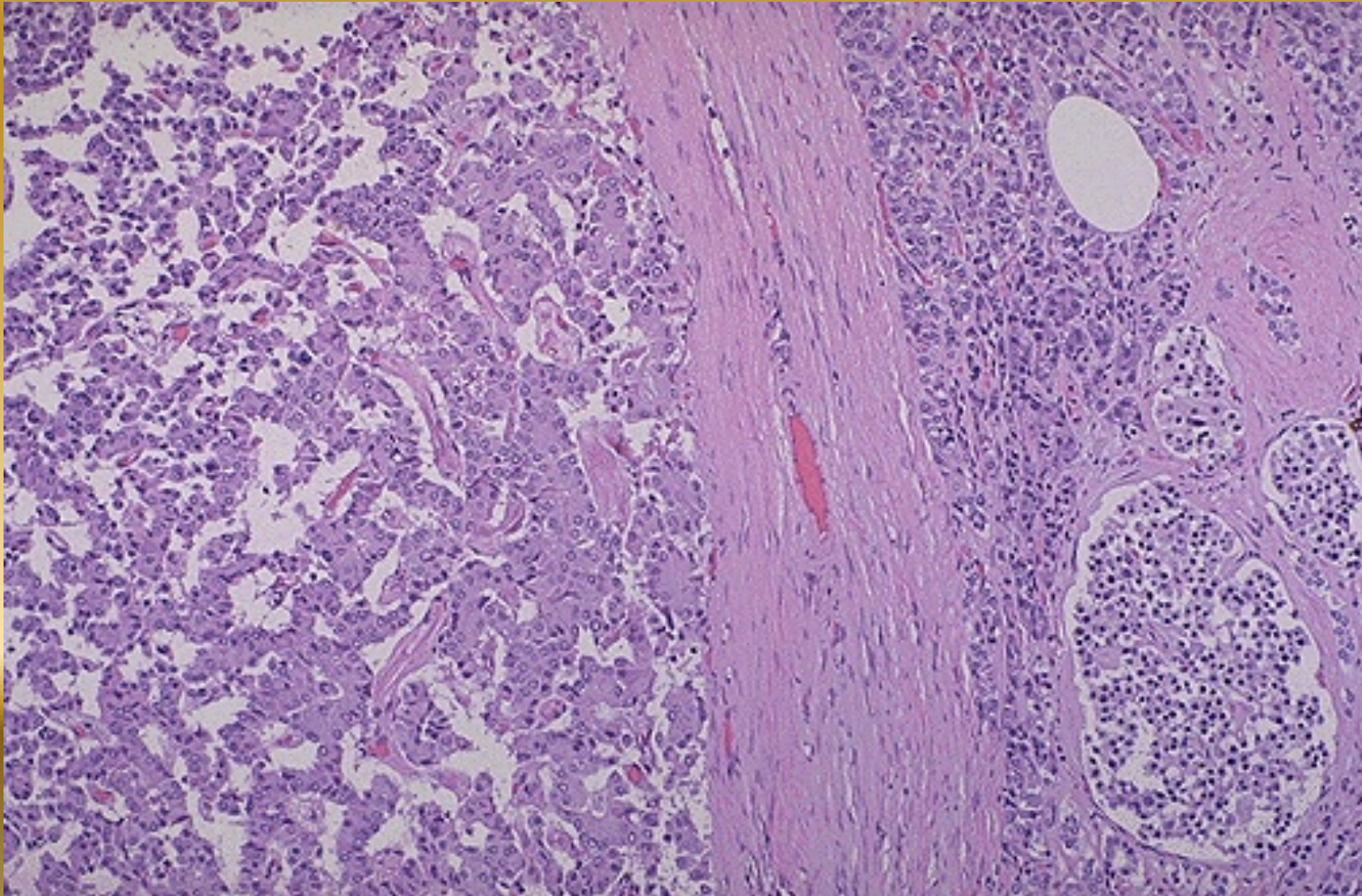


Islet cell adenoma



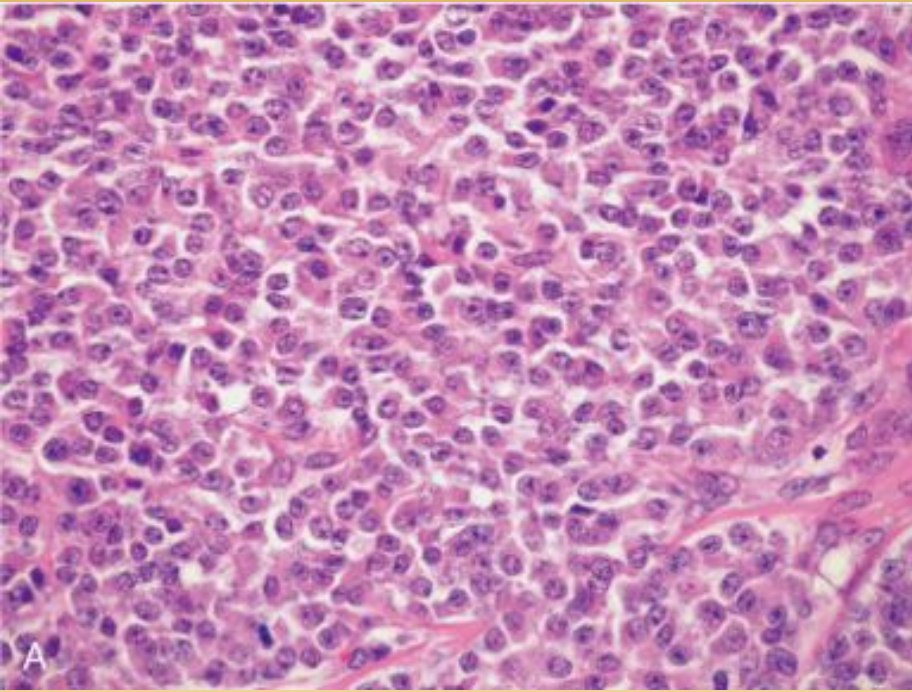
This tumor is separated from the pancreas by a thin collagenous capsule. A few normal islets are seen in the pancreas at the right (arrows) for comparison.

Islet cell adenoma

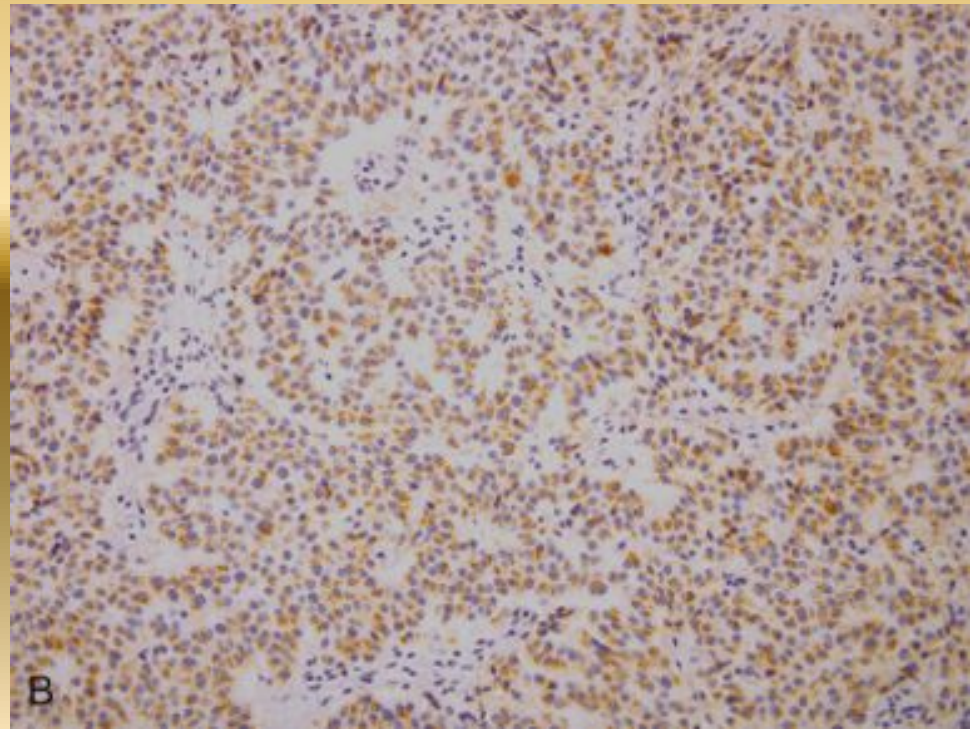


Higher magnification of the previous photo. The islet cell adenoma at the left contrasts with the normal pancreas with islets at the right. Some of these adenomas function. Those that produce insulin may lead to hypoglycemia. Those that produce gastrin may lead to multiple gastric and duodenal ulcerations (Zollinger-Ellison syndrome).

Pancreatic endocrine tumor ("islet cell tumor") (insulinoma)



A, The neoplastic cells are monotonous and demonstrate minimal pleomorphism or mitotic activity (H&E stain). B, Immunoreactivity for insulin confirms the neoplasm is an insulinoma. Clinically, the patient had episodic hypoglycemia.



Gastrinomas:- are associated with hypersecretion of gastrin. These tumors may be pancreatic, duodenal or peripancreatic ("gastrinoma triangle").

Zollinger and Ellison were the first to report the *association of pancreatic islet cell lesions with hypersecretion of gastric acid and severe peptic ulceration (Zollinger-Ellison syndrome).*

Over half of gastrinomas are locally invasive or have already metastasized at the time of diagnosis. In 25% of the cases, gastrinomas form a member of MEN-1 syndrome.

In Zollinger-Ellison syndrome, hypergastrinemia stimulates extreme gastric acid secretion, which in turn leads to multiple duodenal and gastric ulcers. In addition, ulcers may also occur in the jejunum.

Thank you