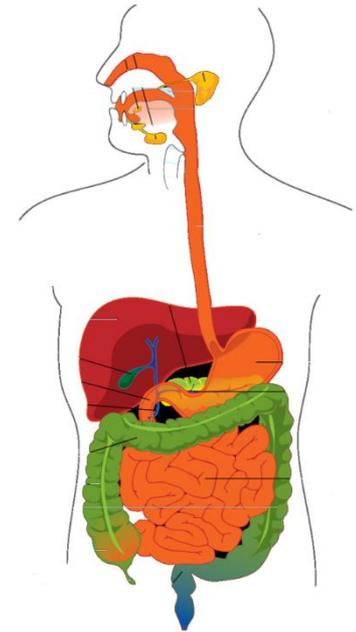


# DIGESTIVE SYSTEM III

- Microscopic anatomy of GIT-associated glands
- Overview of GIT embryonic development

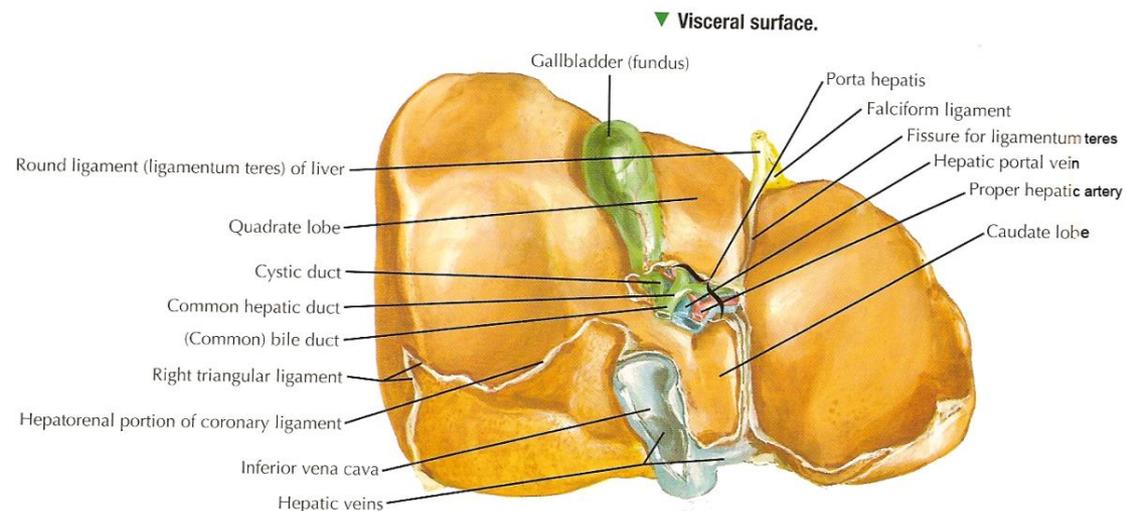
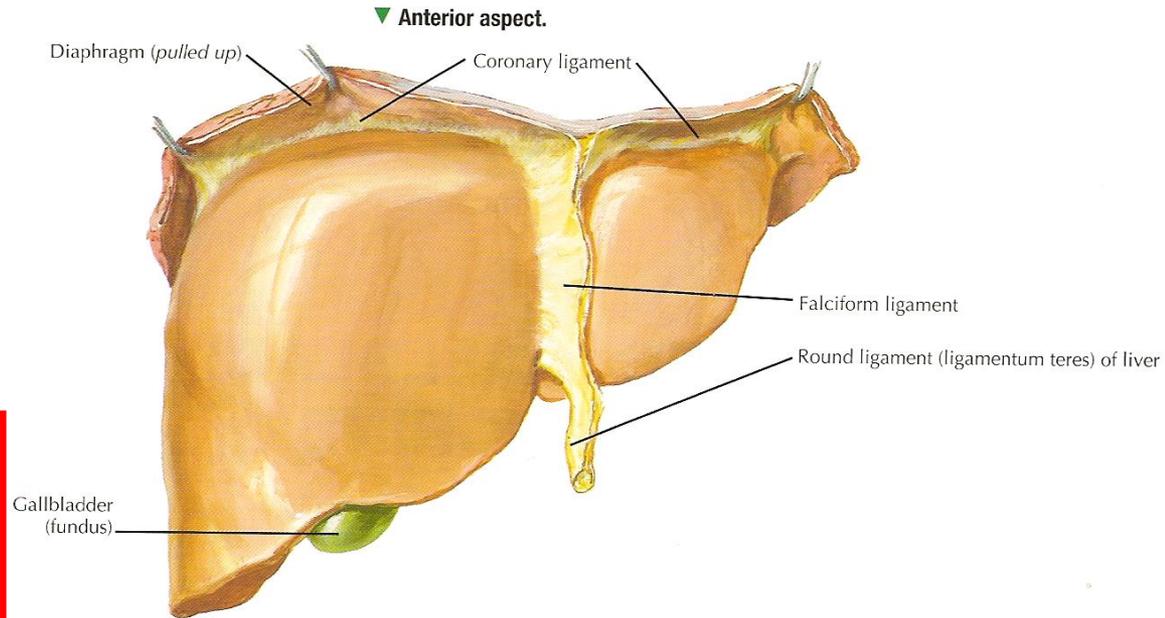


# LIVER (HEPAR)

- Liver parenchyma – biggest gland in human body
- C.t. capsule
- Nutritive and functional blood supply
- Endocrine and exocrine function
- Uniform histology of all four major anatomic lobules and segments:

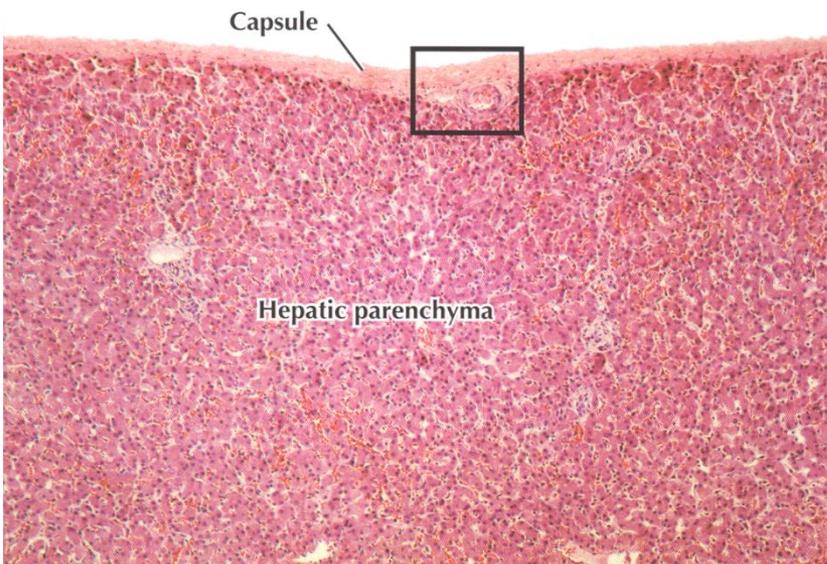
- Hepatocytes and other cell types
- C.t. stroma
- Blood and lymphatic vessels
- Sinusoids
- Innervation

- C.t. capsule
- Serosa

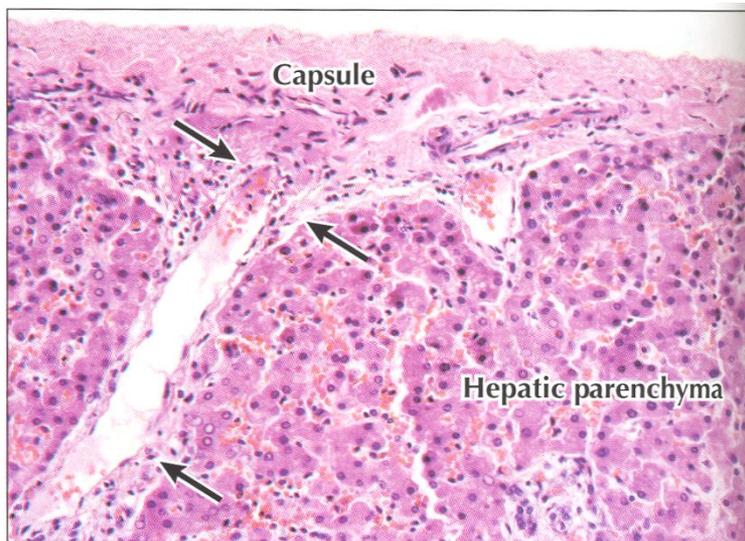
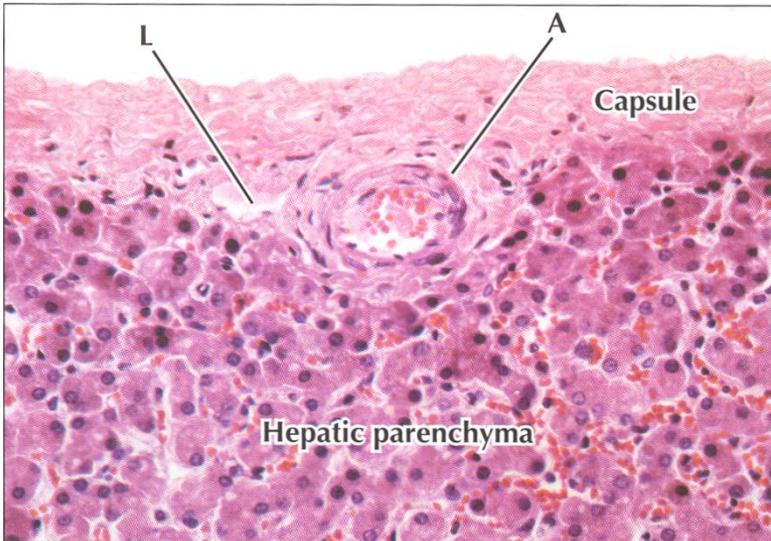


# LIVER (HEPAR)

## CAPSULA FIBROSA HEPATIS

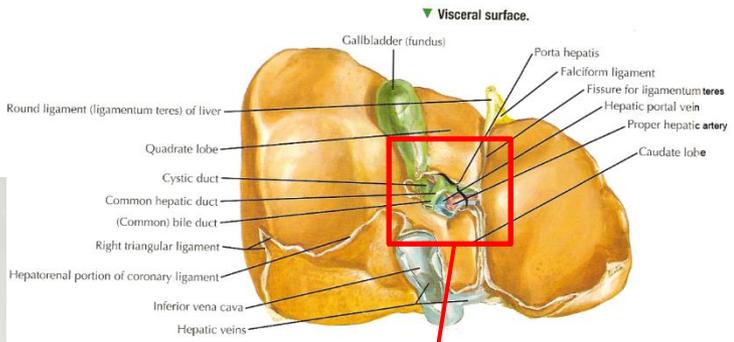
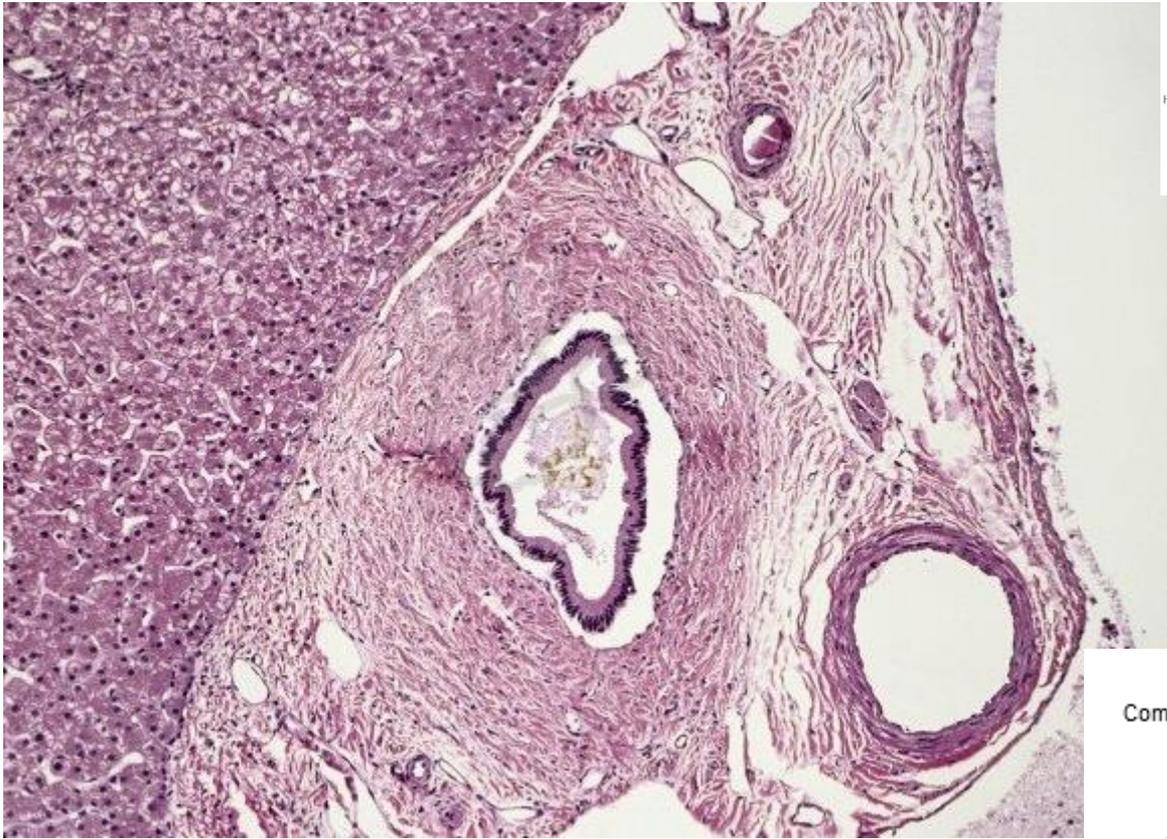


- Serous mesothelium
- Dense collagen c.t. – collagen and elastic fibers
- 70-100 $\mu$ m
- Porta hepatis

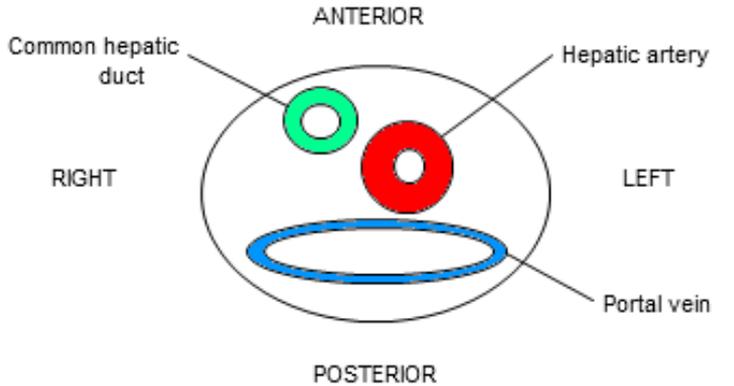


# LIVER (HEPAR)

## CAPSULA FIBROSA HEPATIS



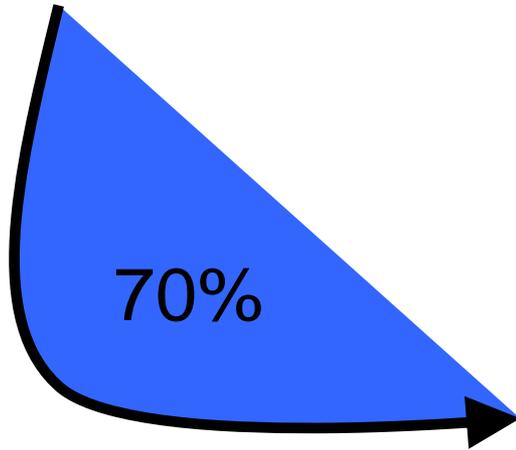
Porta hepatis



# LIVER VASCULARISATION

## FUNCTION

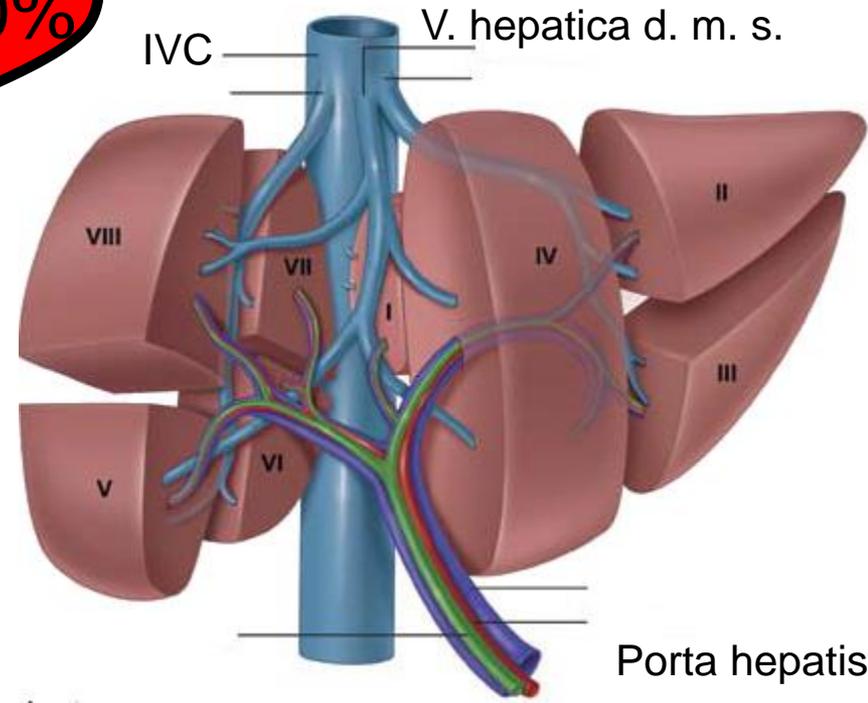
- capillary stream of stomach and intestine
- vena portae
- interlobular veins
- circumlobular venules



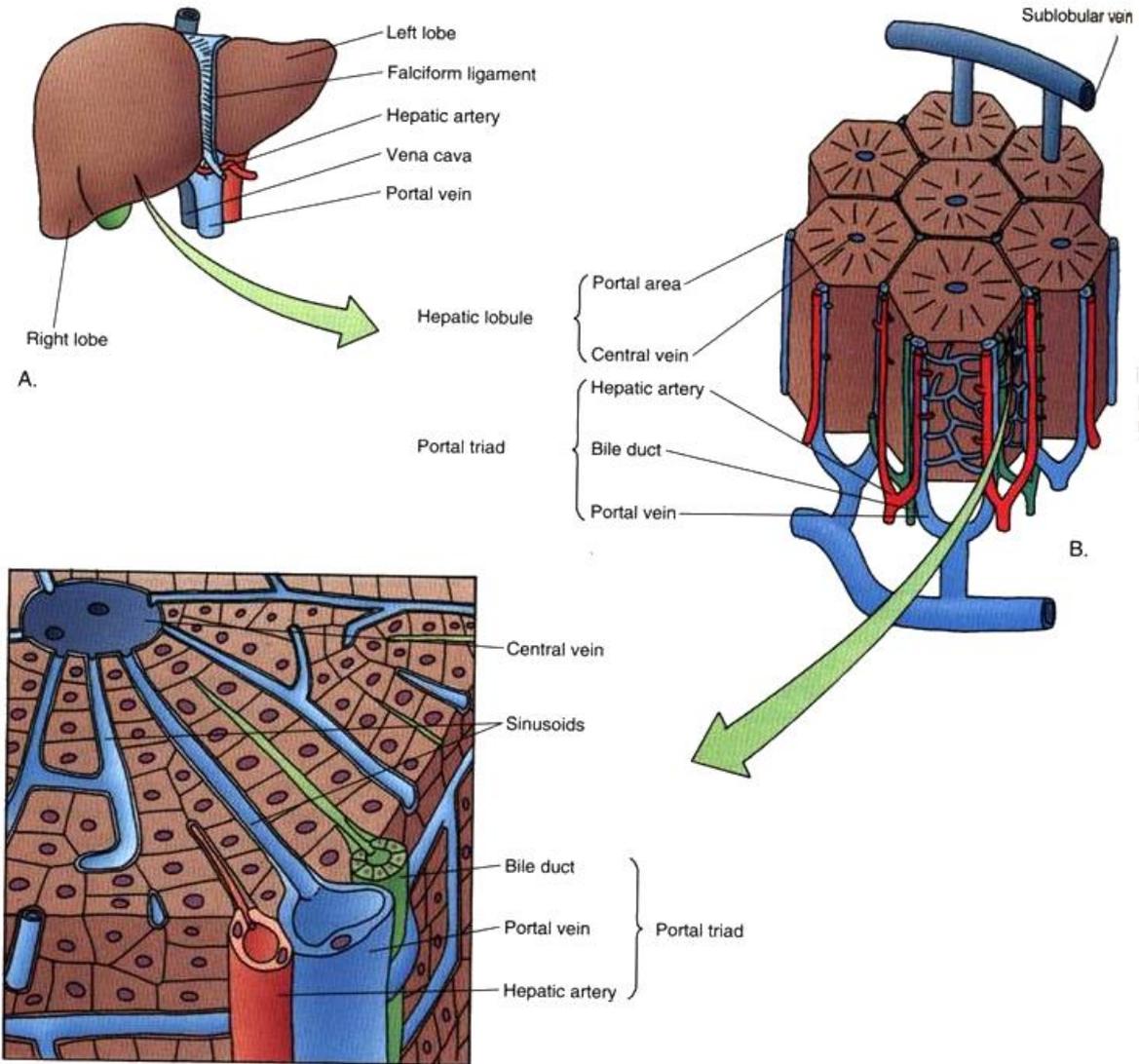
- **hepatic sinusoids**
- venae centrales hepatis
- venae sublobulares
- venae hepaticae
- vena cava inferior

## NUTRITIVE

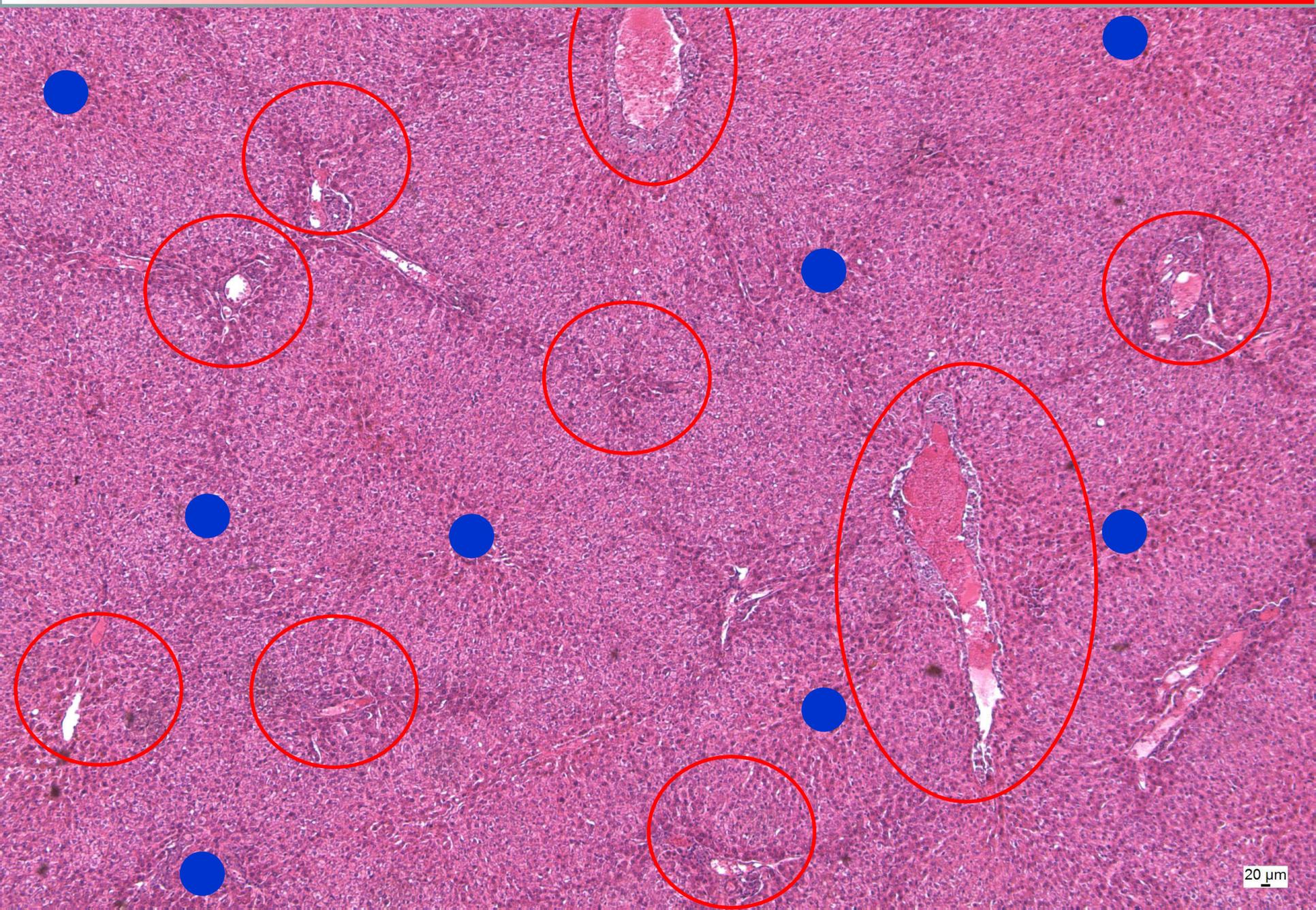
- aorta
- arteria hepatica
- segmental arteries
- interlobular arteries
- circumlobular arteriols



# LIVER VASCULARISATION



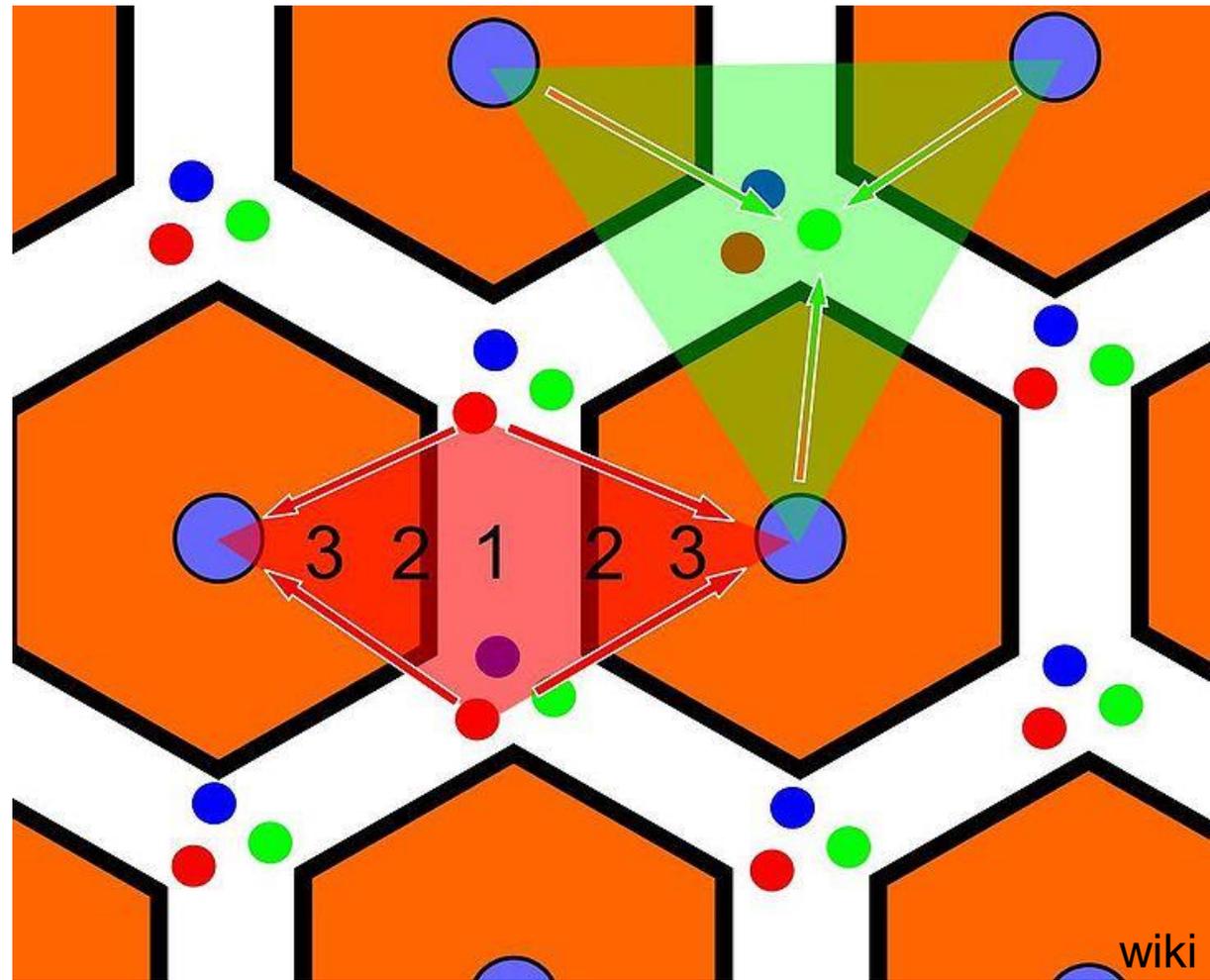
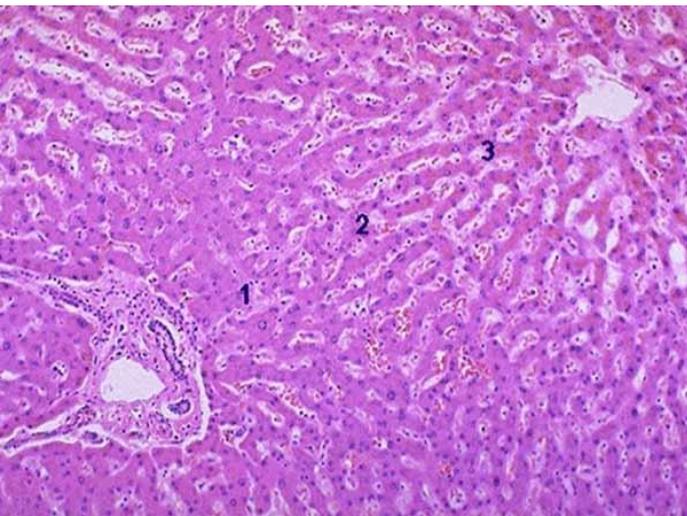
# MICROSCOPIC SEGMENTATION OF LIVER



# MICROSCOPIC SEGMENTATION OF LIVER

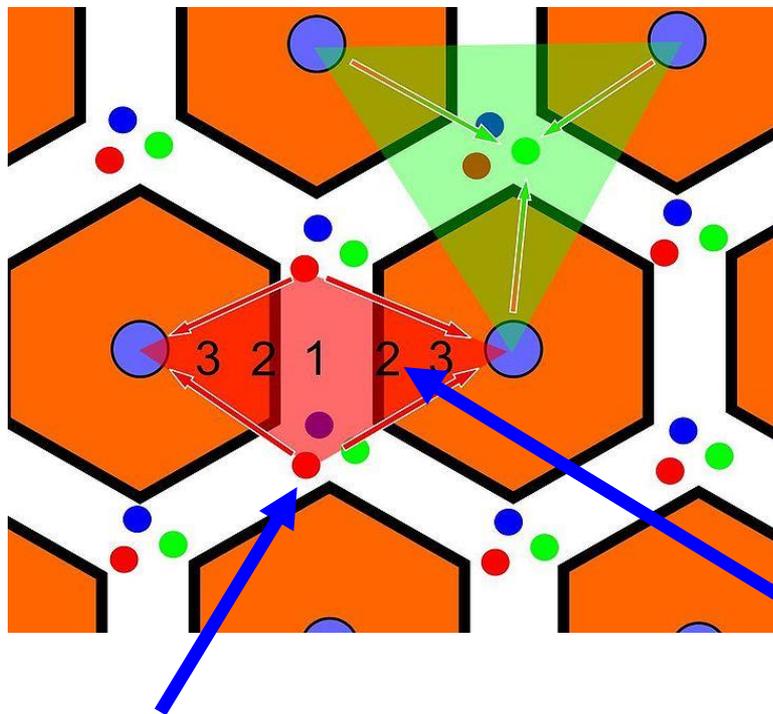
## Definitions:

- Histological – liver lobulus (**lobulus venae centralis**)
- Metabolic – **liver acinus**
  - metabolic zone 1 – 3
  - oxygenation of hepatocytes
- Functional (physiological historical) unit
  - **lobulus venae interlobularis** (portal acinus)





# MICROSCOPIC SEGMENTATION OF LIVER



Liver lobulus

venous drainage

Portal acinus

bile drainage

Liver acinus

metabolic divergence dependent on arterio-venous gradients

Zone I (periportal)	Zone III (perivenous)
oxidative processes	glycogen synthesis
beta-oxidation of fatty acids	glycolysis
catabolism of aminoacids	lipogenesis
gluconeogenesis	ketogenesis
production of urea	production of glutamine
synthesis of cholesterol	synthesis of bile acids
glycogenolysis	biotransformation
production of bile	

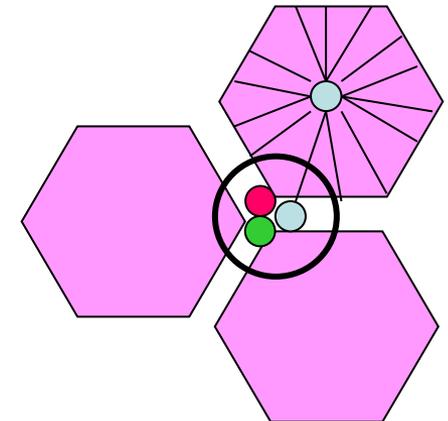
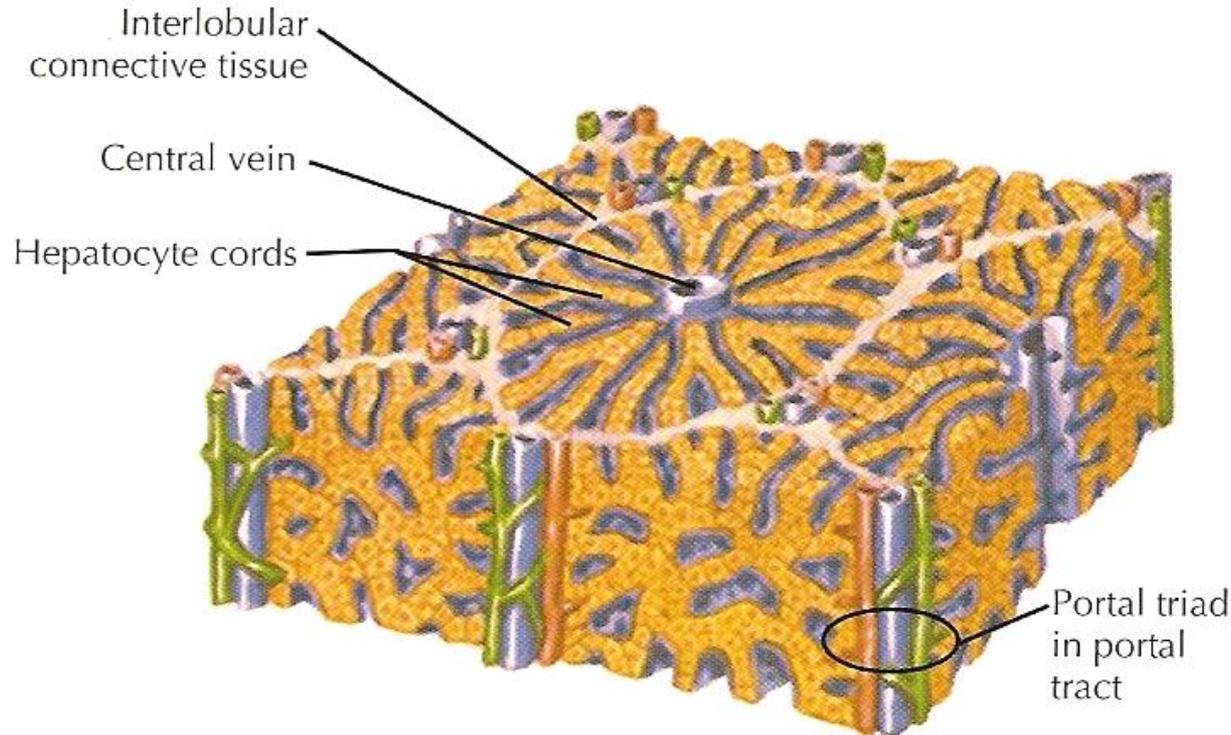
# LIVER LOBULUS

## Lobulus venae centralis



# LIVER LOBULUS

- Classical morphological unit
- Polygonal cells (hexagonal), 0.7 x 2mm
- Central vein
- Radial cords of hepatocytes
- Liver sinusoids
- Portal triad, portobilliary region

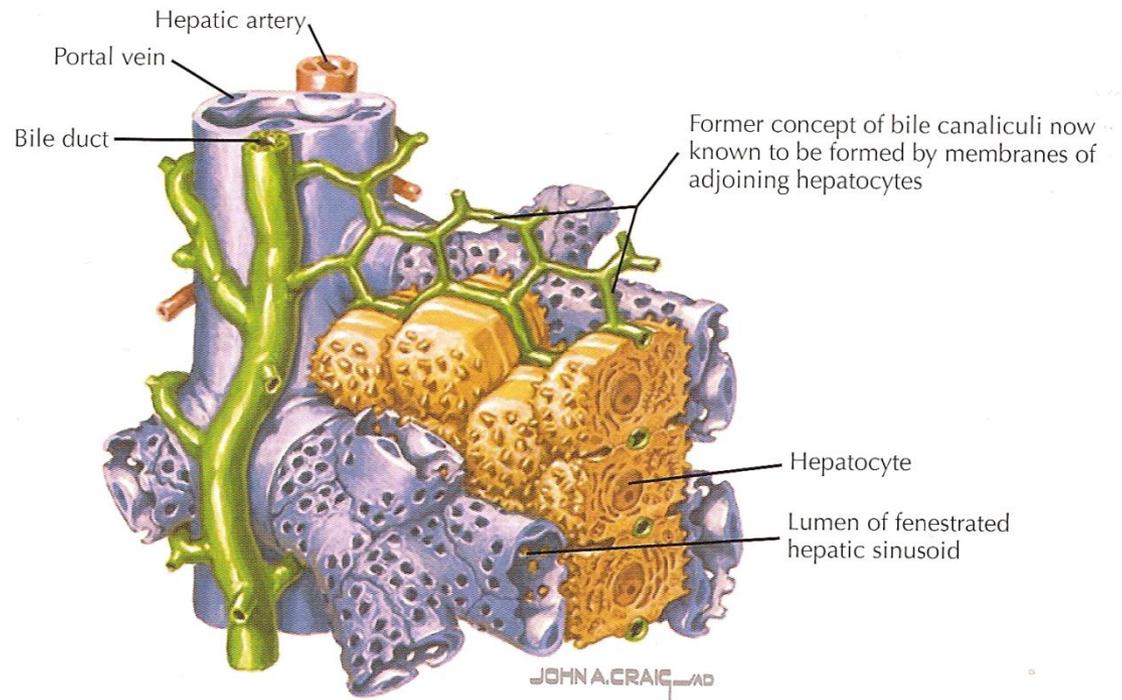


# LIVER LOBULUS – PORTAL TRIAD

## Contact of 3-4 neighboring lobuli

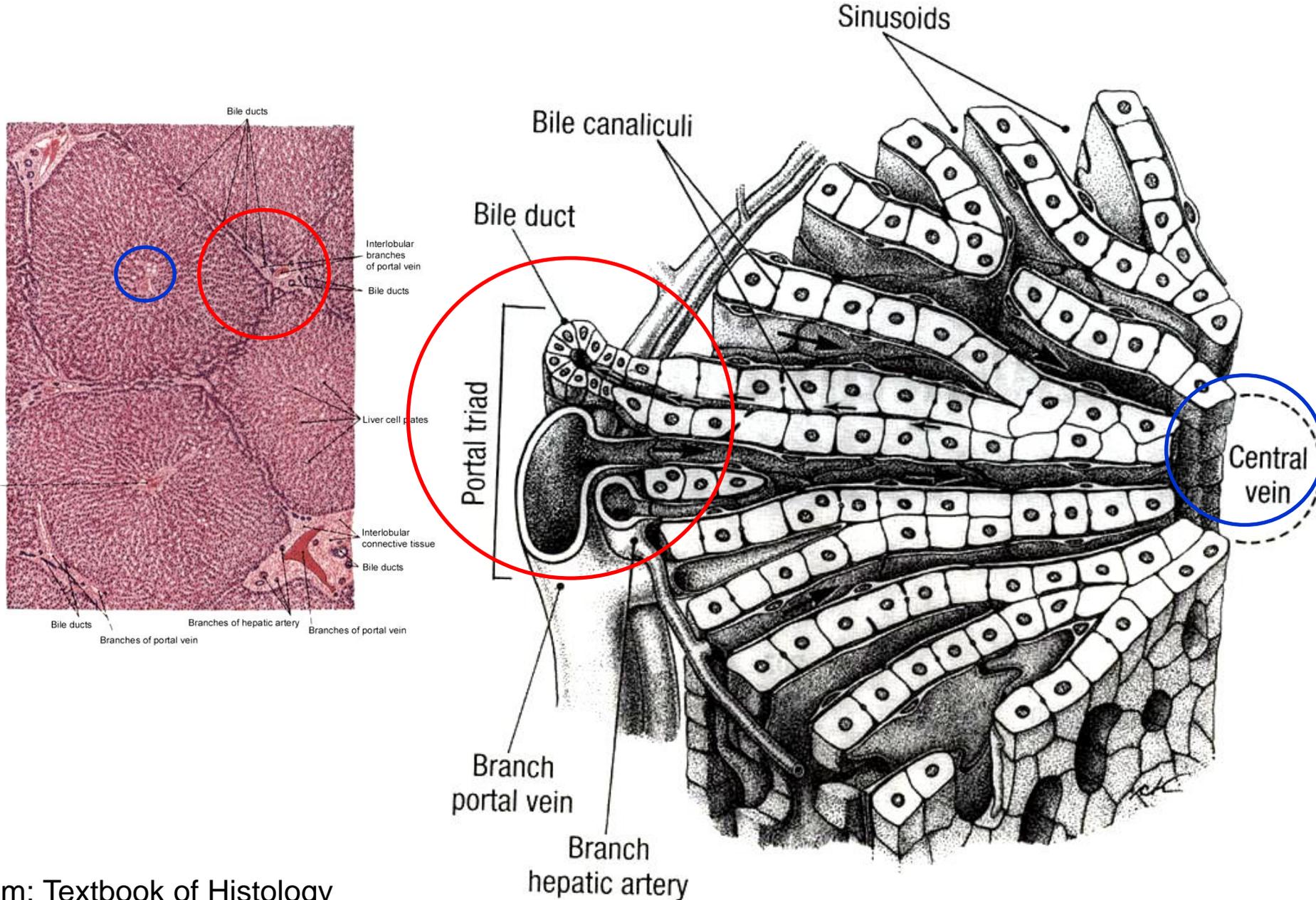
- Interlobular artery (*a. interlobularis*)
- Interlobular vein (*v. interlobularis*)
- Interlobular bile duct (*d. bilifer interlobularis*)
- Lymphatic vessels
- Innervation – *nervus vagus*

Loose interstitial c.t.



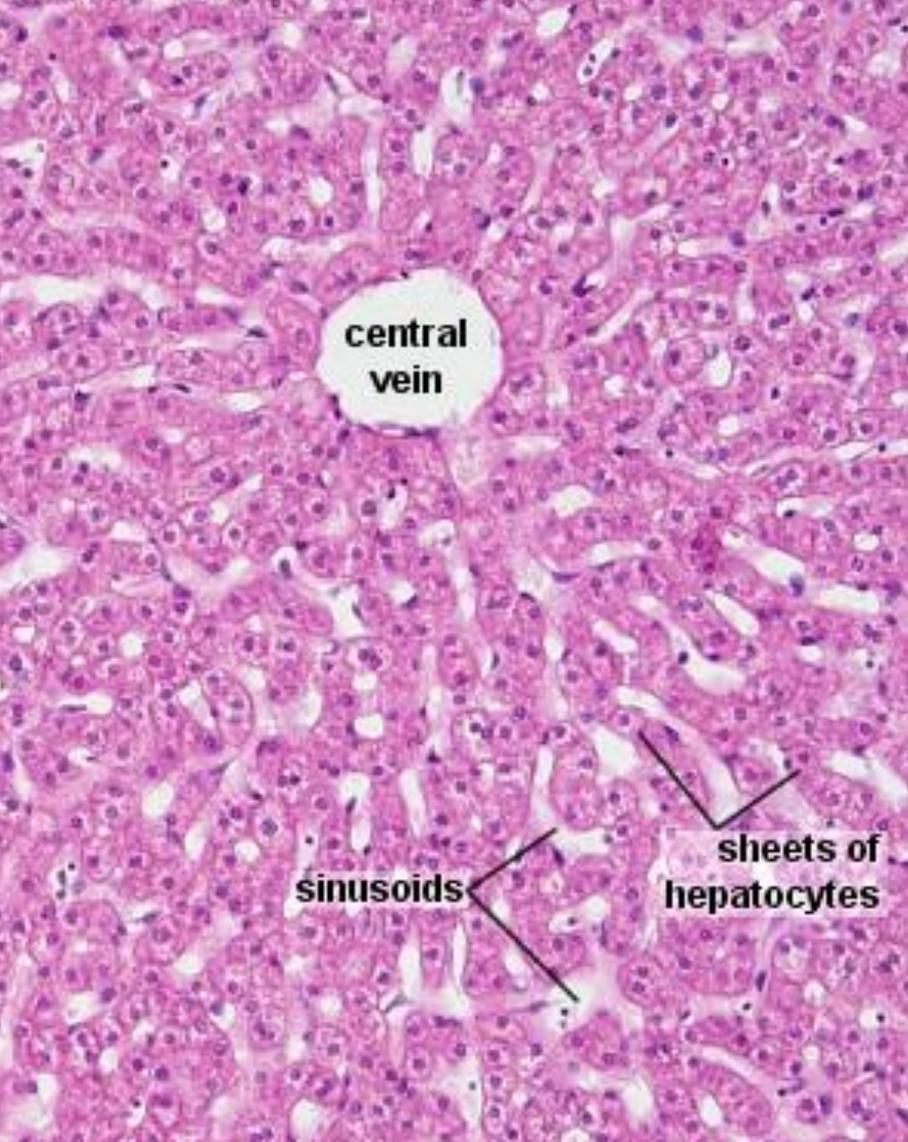
▲ Parts of hepatic lobule at portal triad (high magnification).

# LIVER LOBULUS – CENTRAL VEIN AND PORTAL TRIAD

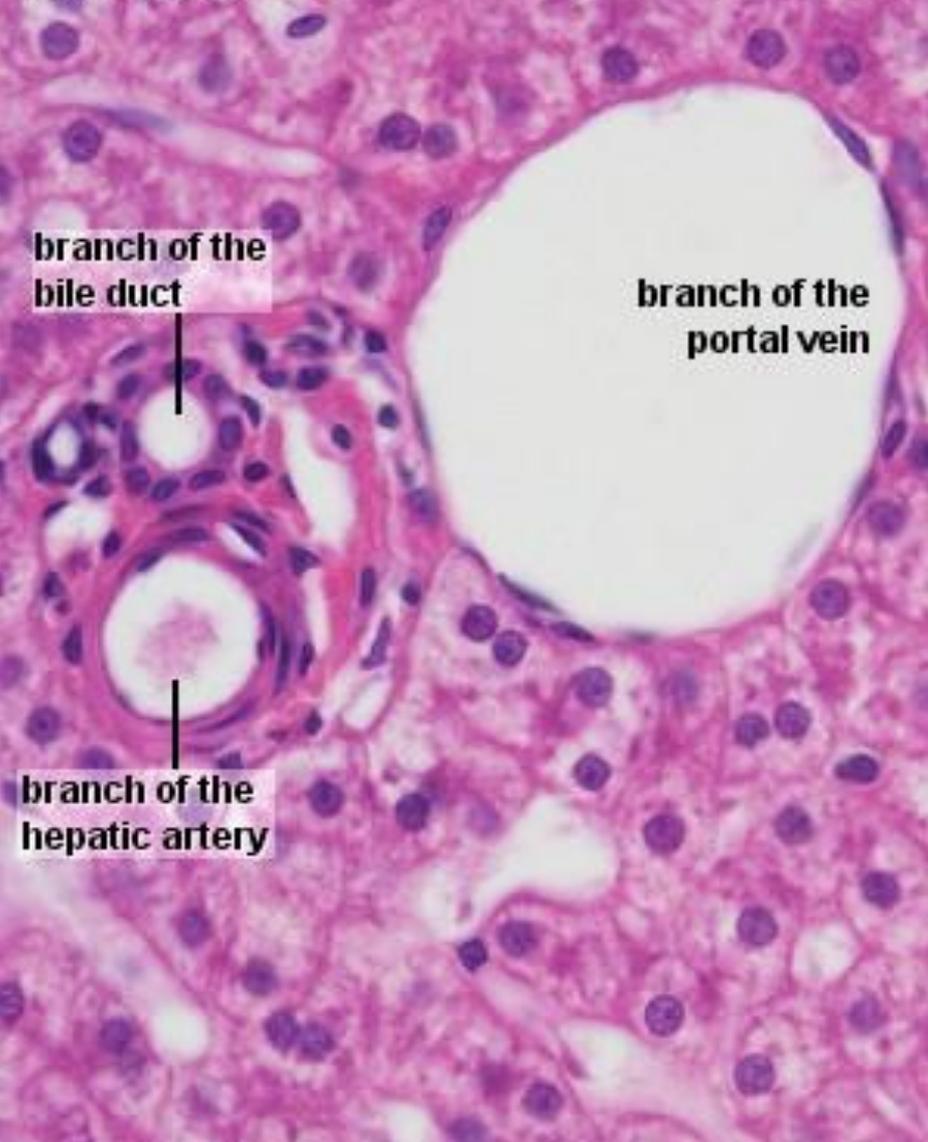


# LIVER LOBULUS – CENTRAL VEIN AND PORTAL TRIAD

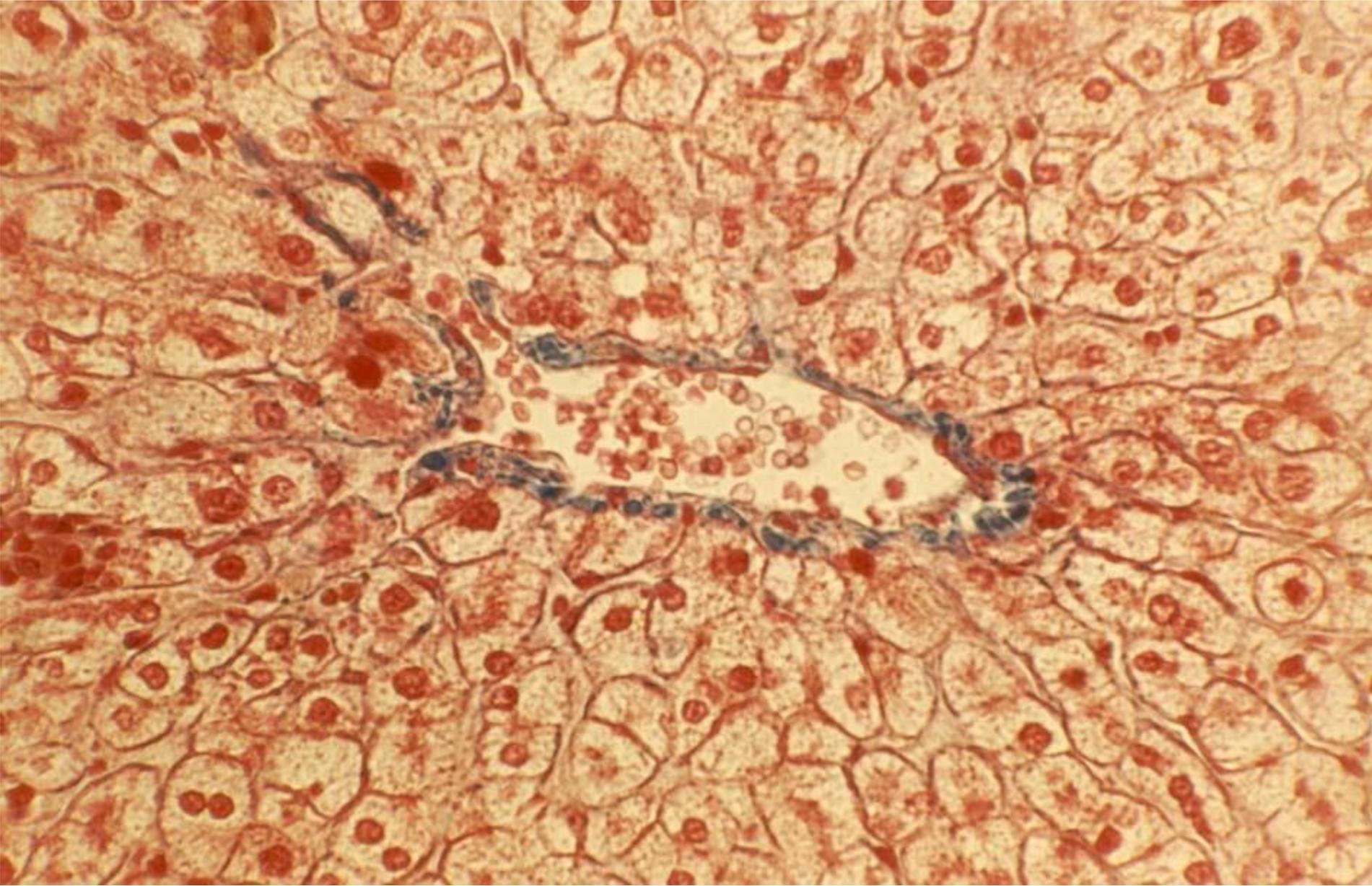
Liver H&E



Liver H&E

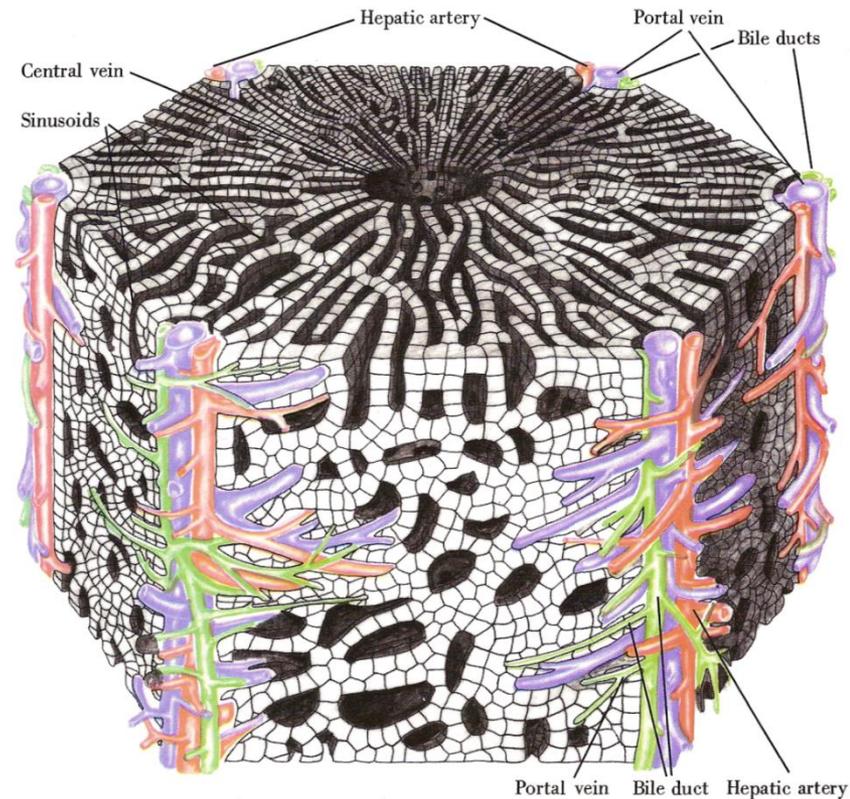


LIVER LOBULUS – CENTRAL VEIN



# LIVER PARENCHYMA – HEPATOCYTES AND LIVER SINUSOIDS

- **Hepatocytes** arranged to cords, width 1-2 cells, often anastomoses
- **Sinusoids**
  - 9-15 $\mu$ m
  - Anastomosing network of flat endothelial cells
  - Basal membrane absent - no diffusion barrier
  - **Fenestrations** - 100nm, diaphragm absent
  - Intercellular space
  - **Perisinusoidal space (of Disse)**
  - Reticular fibers
  - Dispersed **Kupffer cells** (monocyte-macrophage system)
  - **Perisinusoidal cells** of Ito
- **Vena centralis** – thin-walled vessel, draining blood from sinusoids

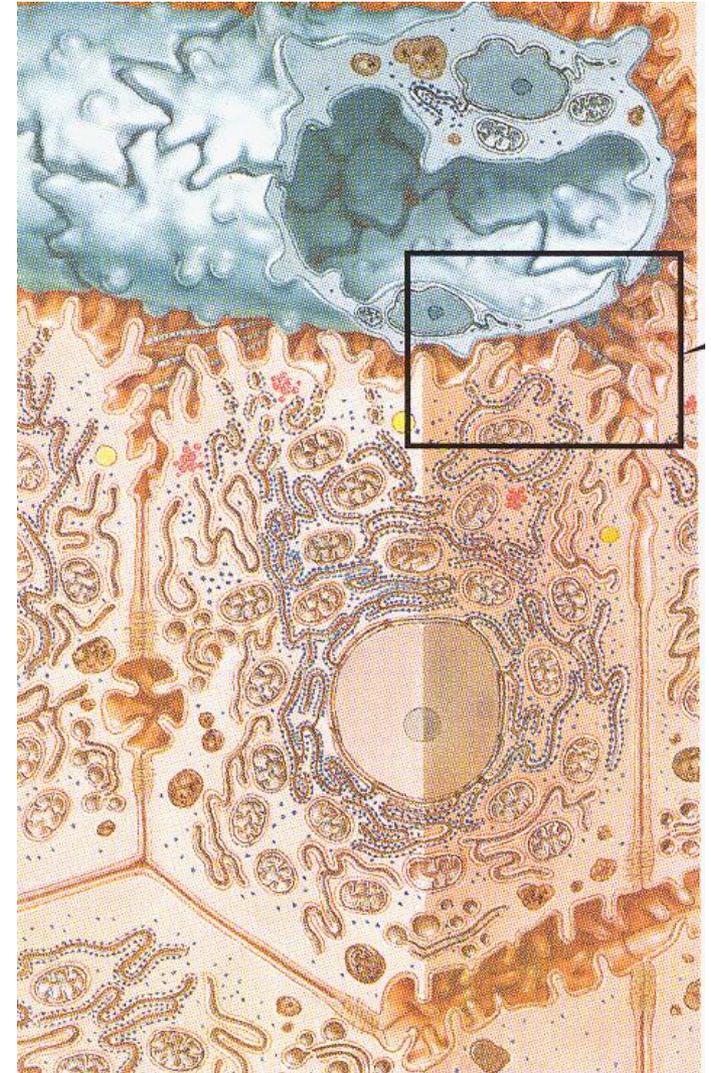
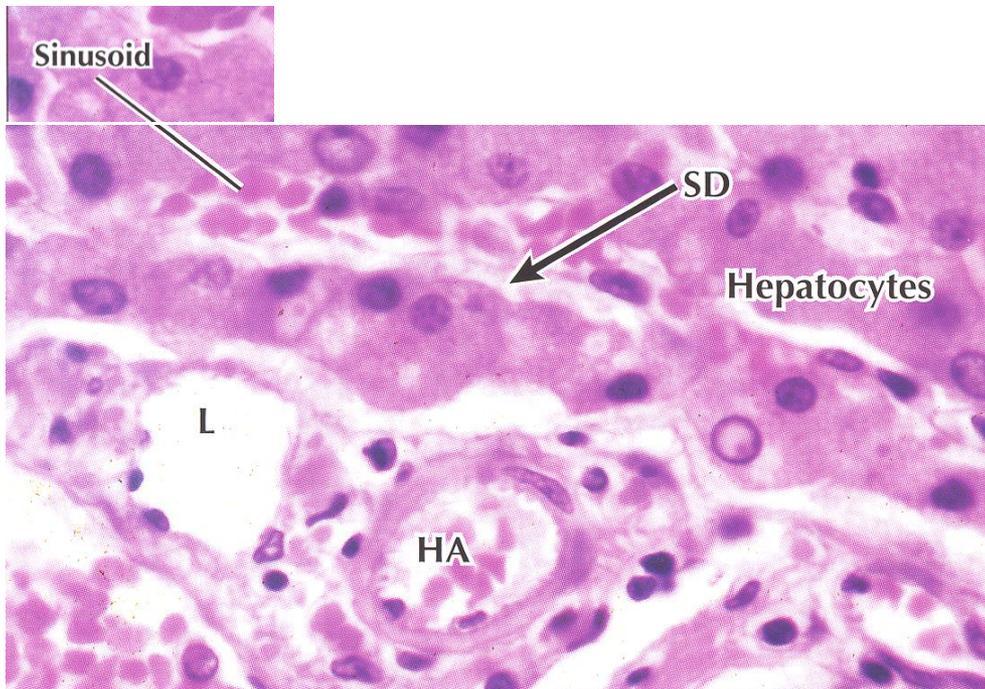




# LIVER PARENCHYMA – HEPATOCYTES AND LIVER SINUSOIDS

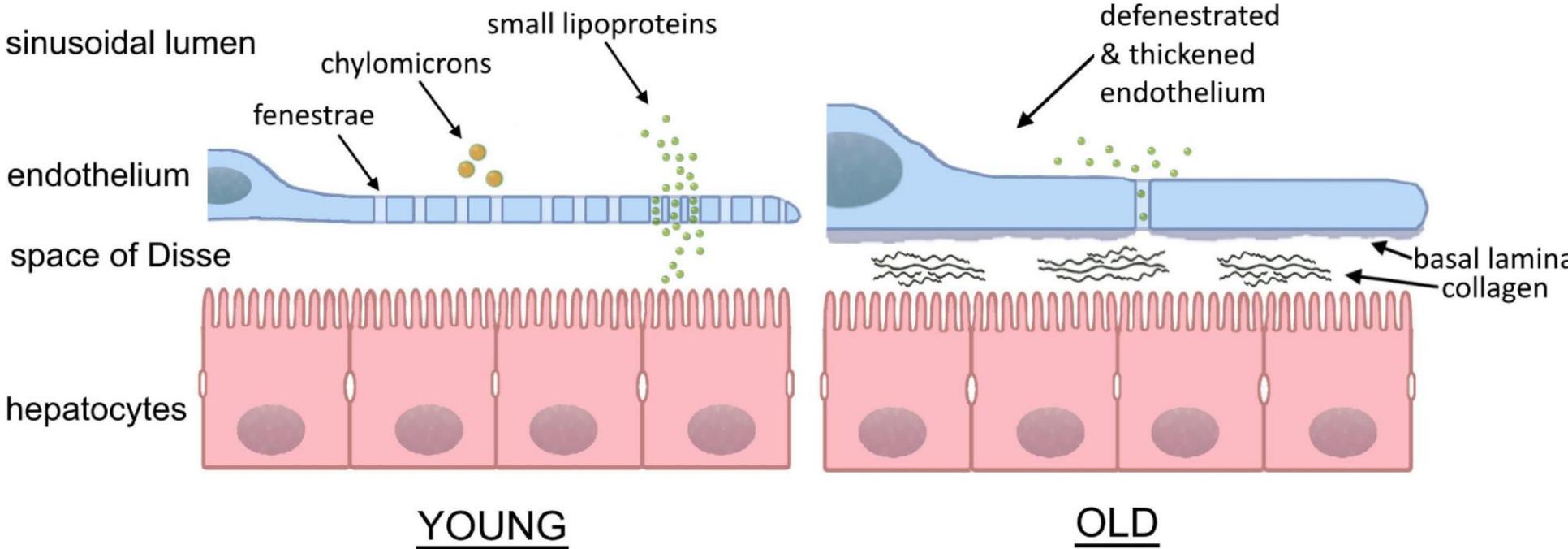
- **Space of Disse**

- Connection of space of Disse and sinusoidal lumen by fenestrated endothelium
- Hepatocytes in direct contact with plasma (microvilli)
- Cells of Ito

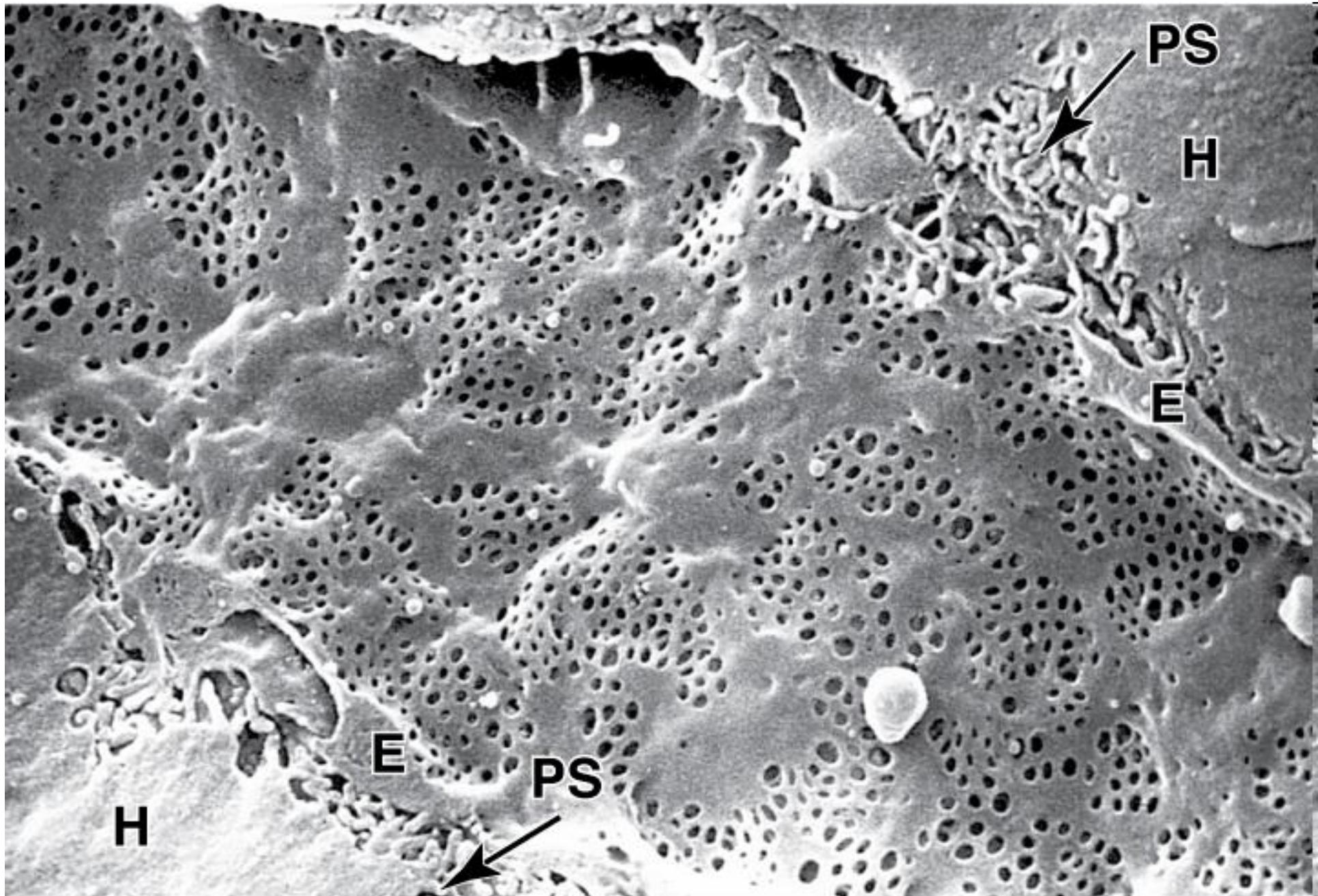


# LIVER SINUSOIDS

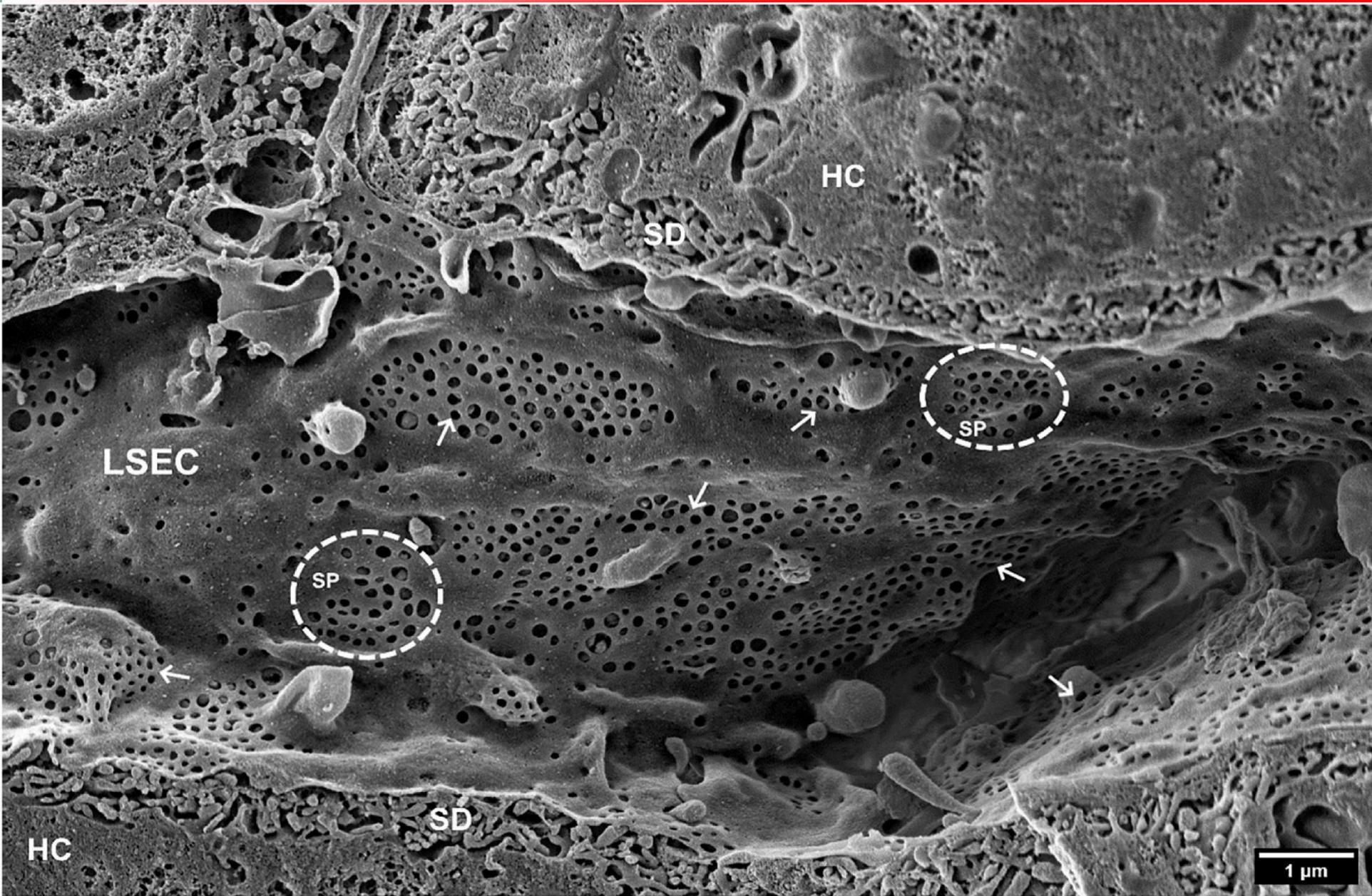
- Fenestrations are complex structures involved in selective transport
- They deteriorate with age compromising sinusoid functions



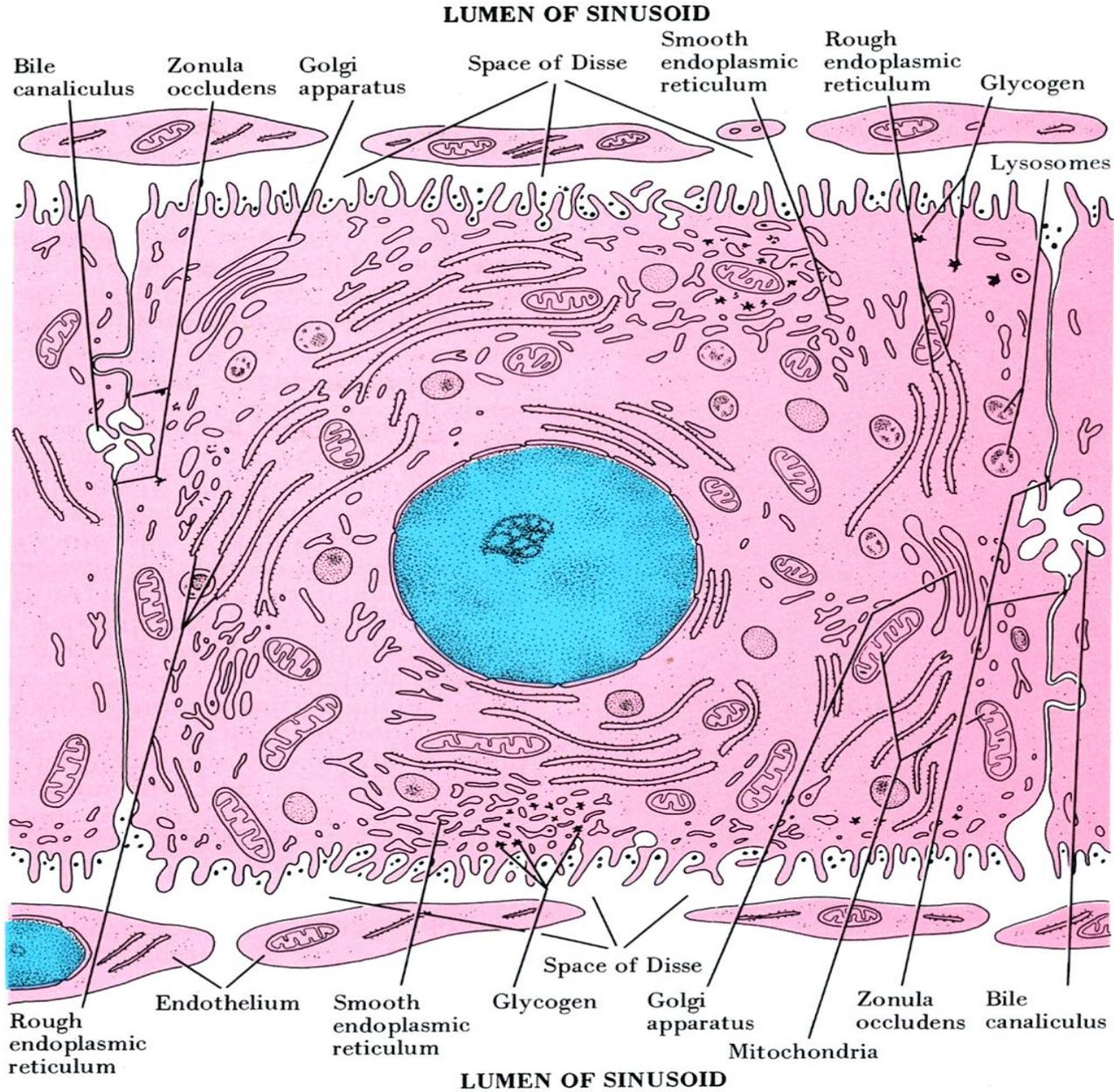
LIVER PARENCHYMA – LIVER SINUSOIDS



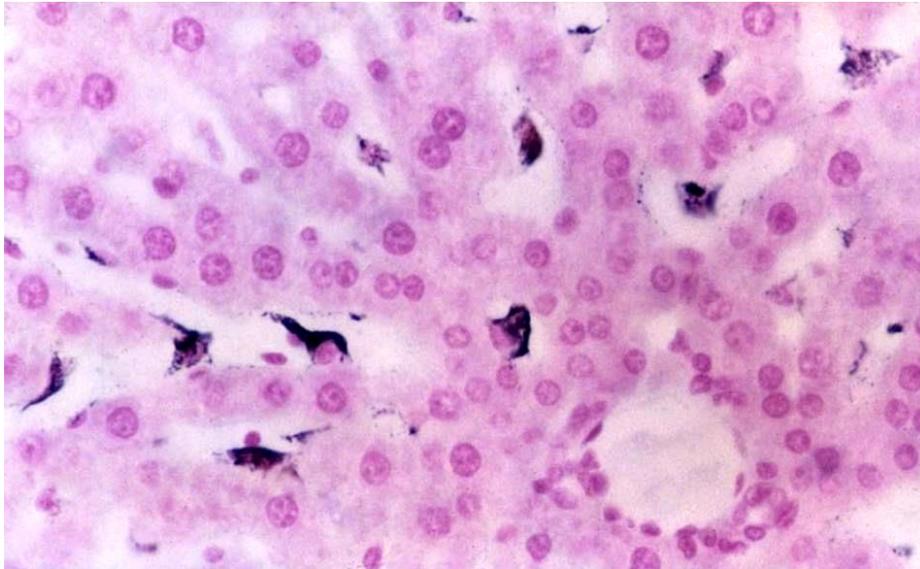
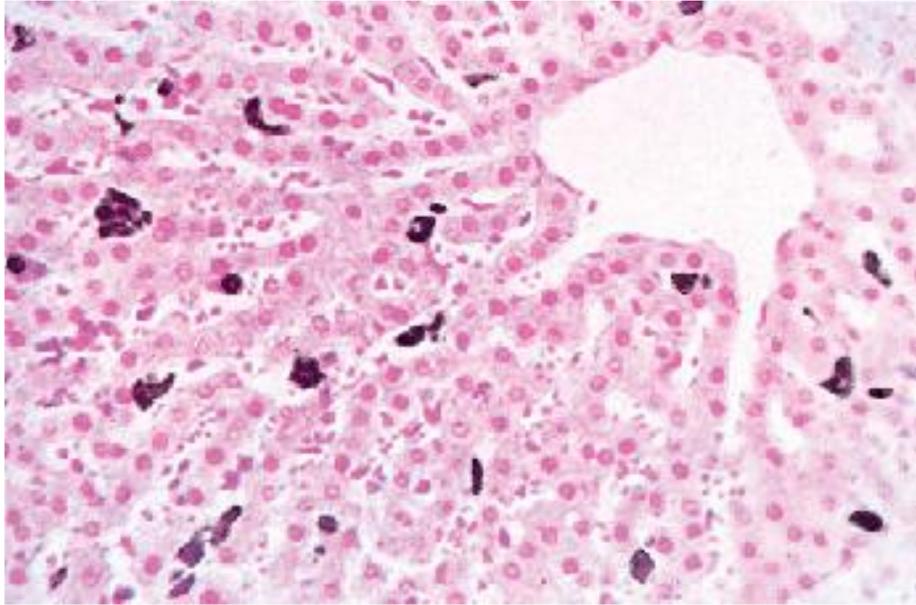
# JATERNÍ SINUSOIDY



# LIVER PARENCHYMA – HEPATOCYTES AND LIVER SINUSOIDS



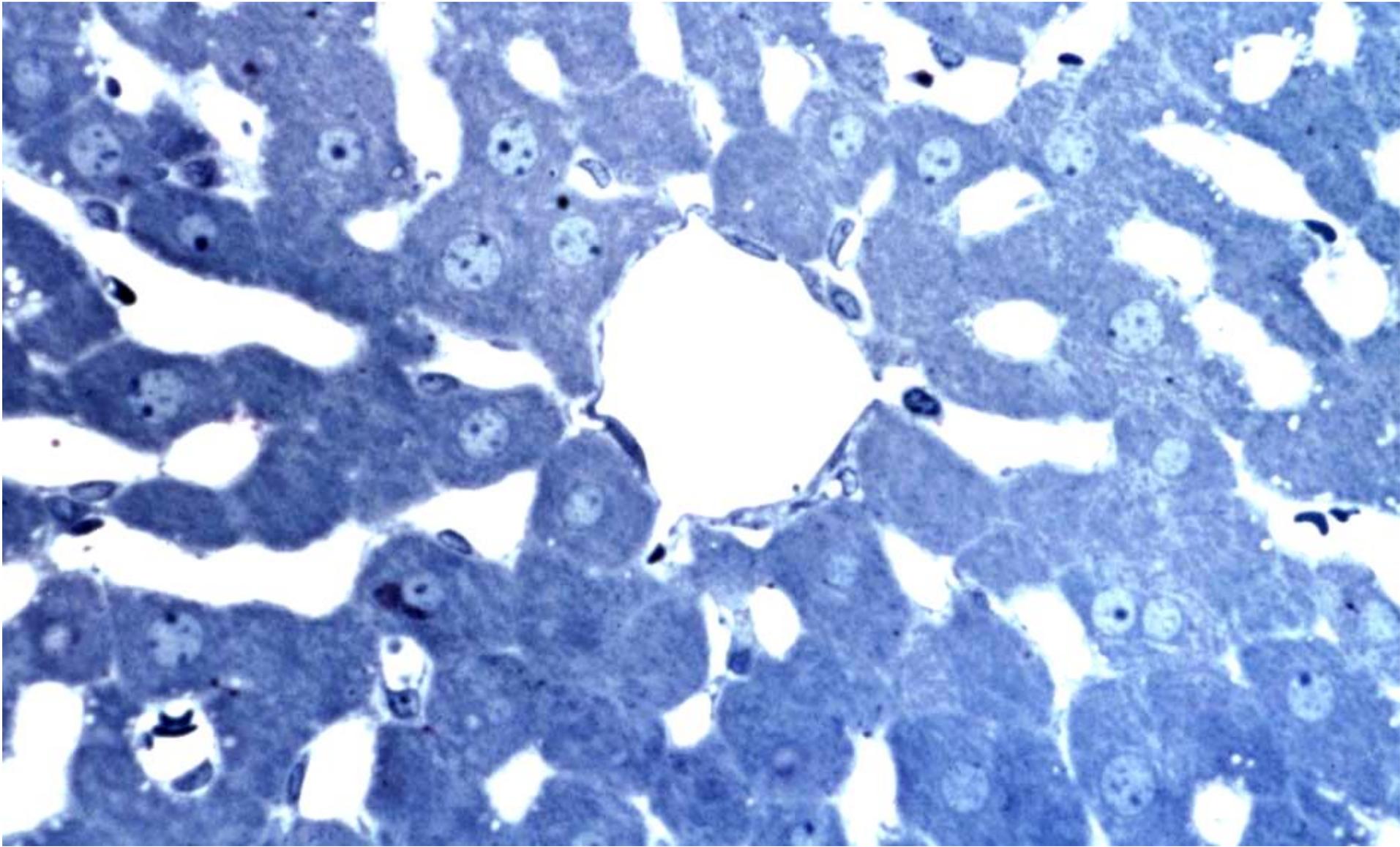
# LIVER PARENCHYMA – OTHER CELL TYPES



## KUPFFER CELLS

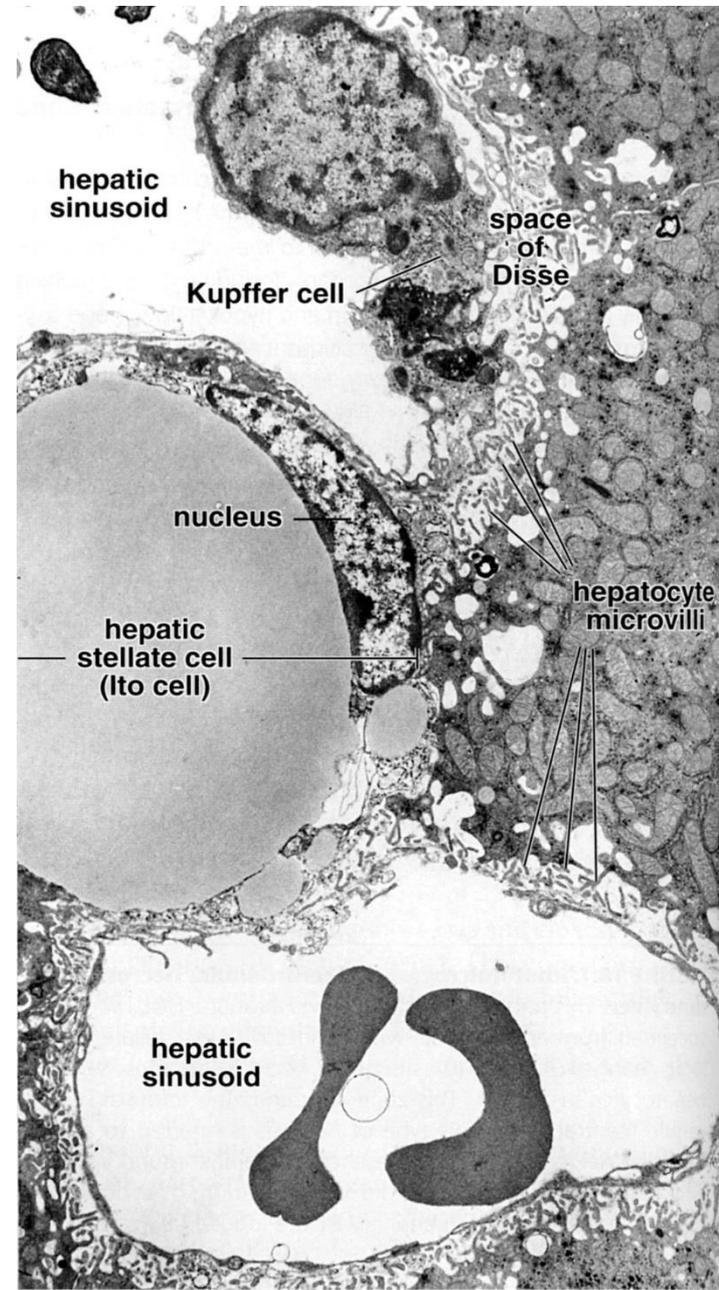
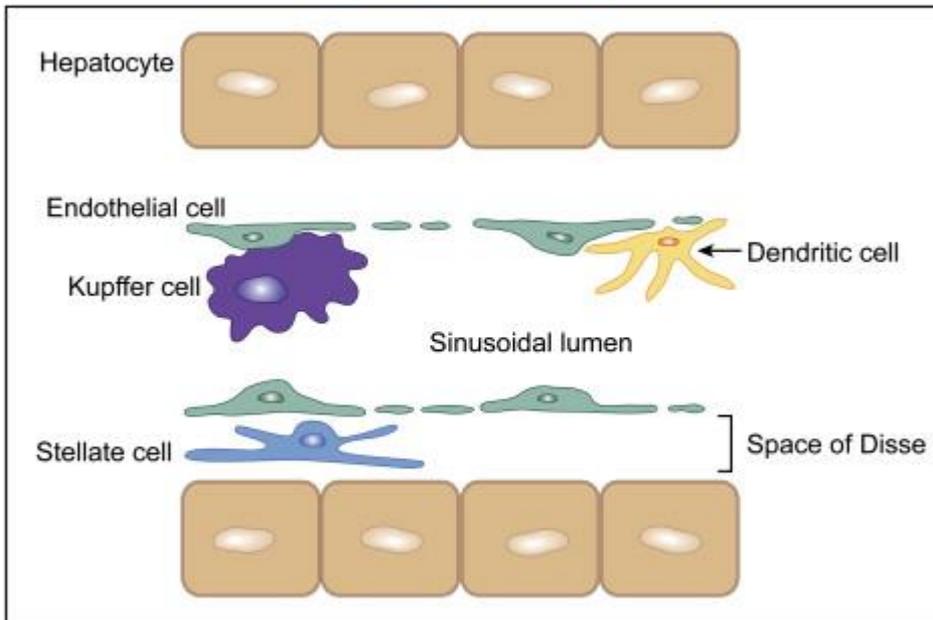
- Liver macrophages
- Mononuclear phagocyte system
- Phagocytosis of particles, damaged erythrocytes and pathogens

# LIVER PARENCHYMA – HEPATOCYTES AND LIVER SINUSOIDS



## CELLS OF ITO

- Star-shape (stellate, perisinusoidal) cells
- Lipid droplets
- Deposition of vitamin A
- Fine reticular c.t.
- Antigen presenting cells (lipid antigens)

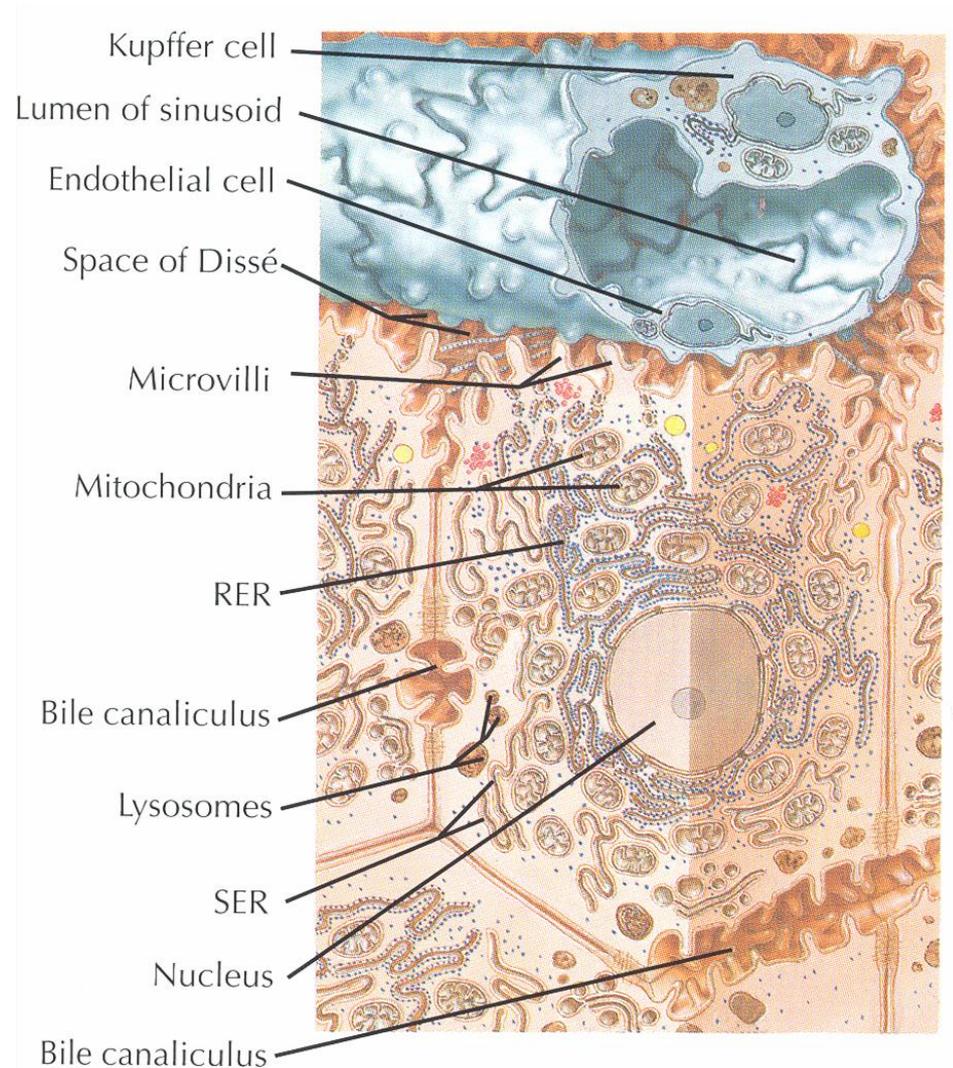




# HEPATOCYTES – ULTRASTRUCTURE

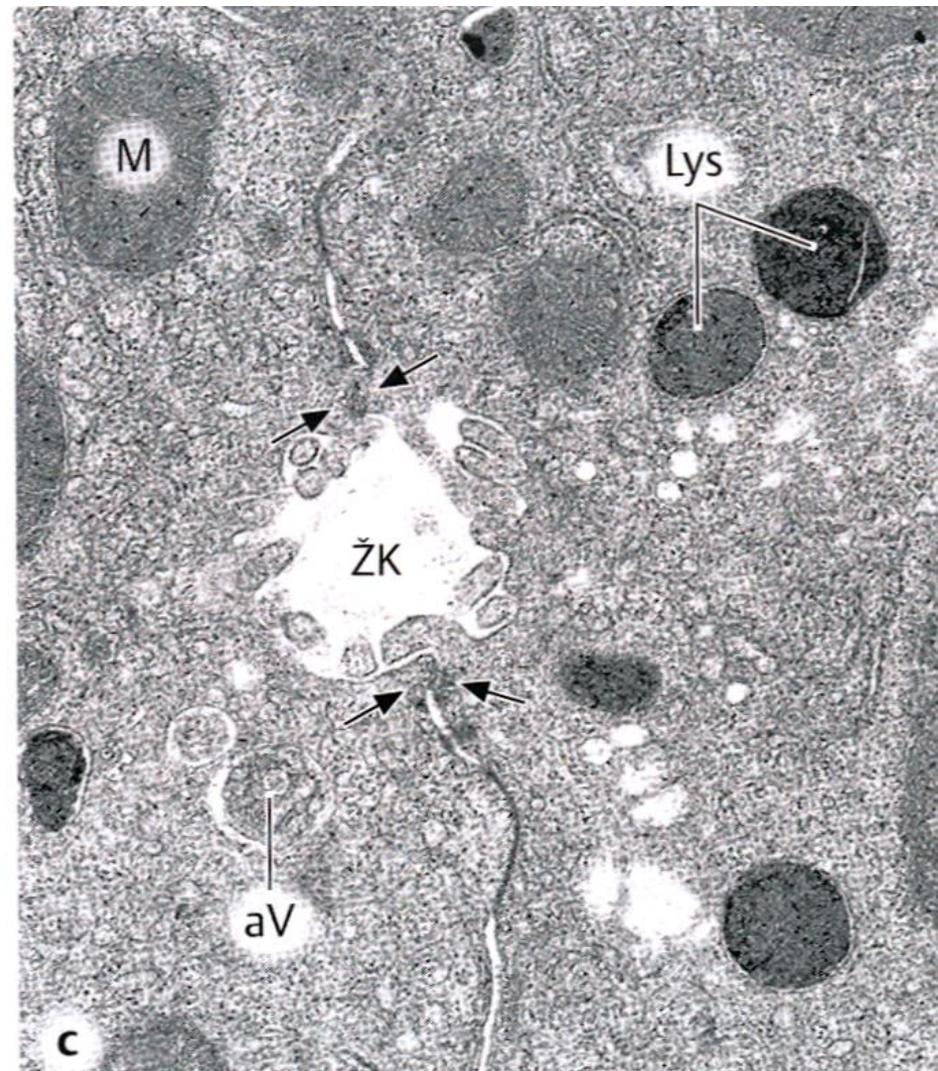
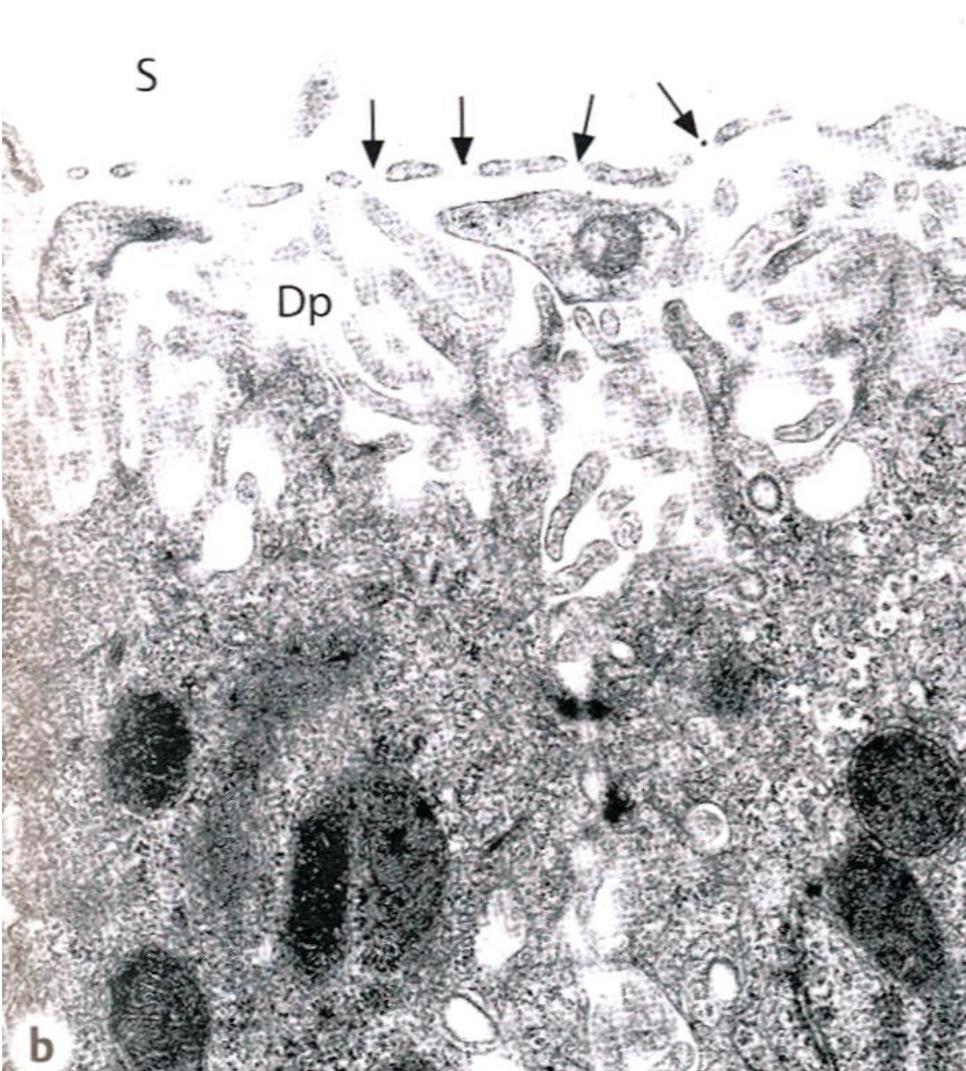
## HEPATOCYTES

- Polygonal cells of liver parenchyma
- 20x30µm
- Irregular trabecules between sinusoids
- Usually one central nucleus. Bi- and multi-nuclear cells common (20%)
- Nucleoli
- Lysosomes
- Glycogen
  
- Functional surfaces:
  - **Bile pole** – secretory – membranes of neighboring hepatocytes form bile canaliculi
  - **Blood pole** - absorptive - sinusoidal – microvilli oriented to space of Disse
  - Membranes with intercellular junctions

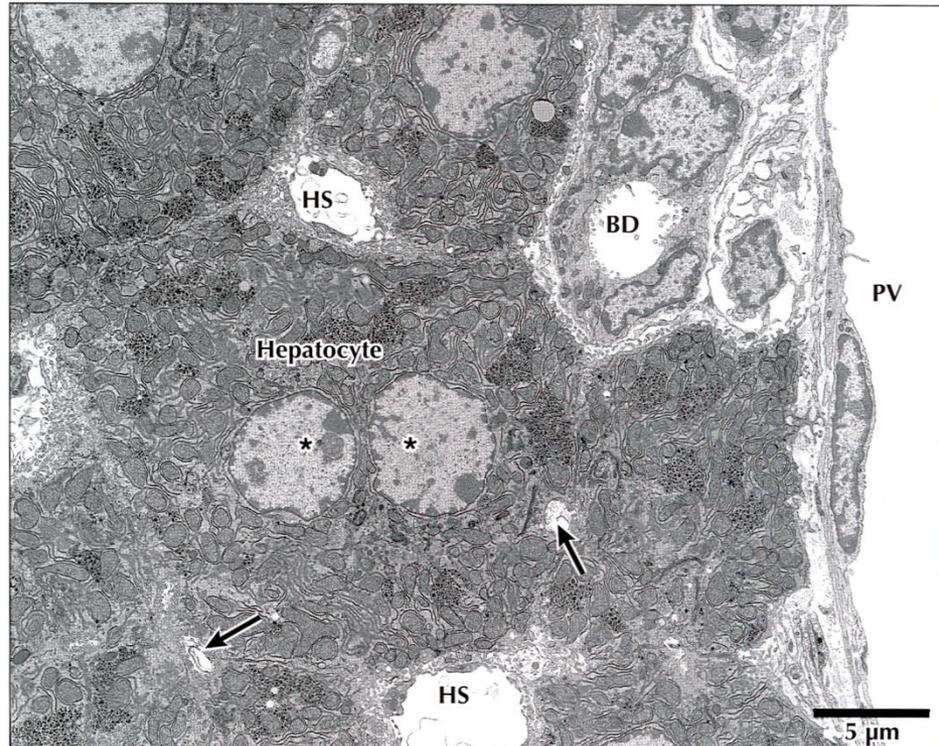


# HEPATOCYTES – ULTRASTRUCTURE

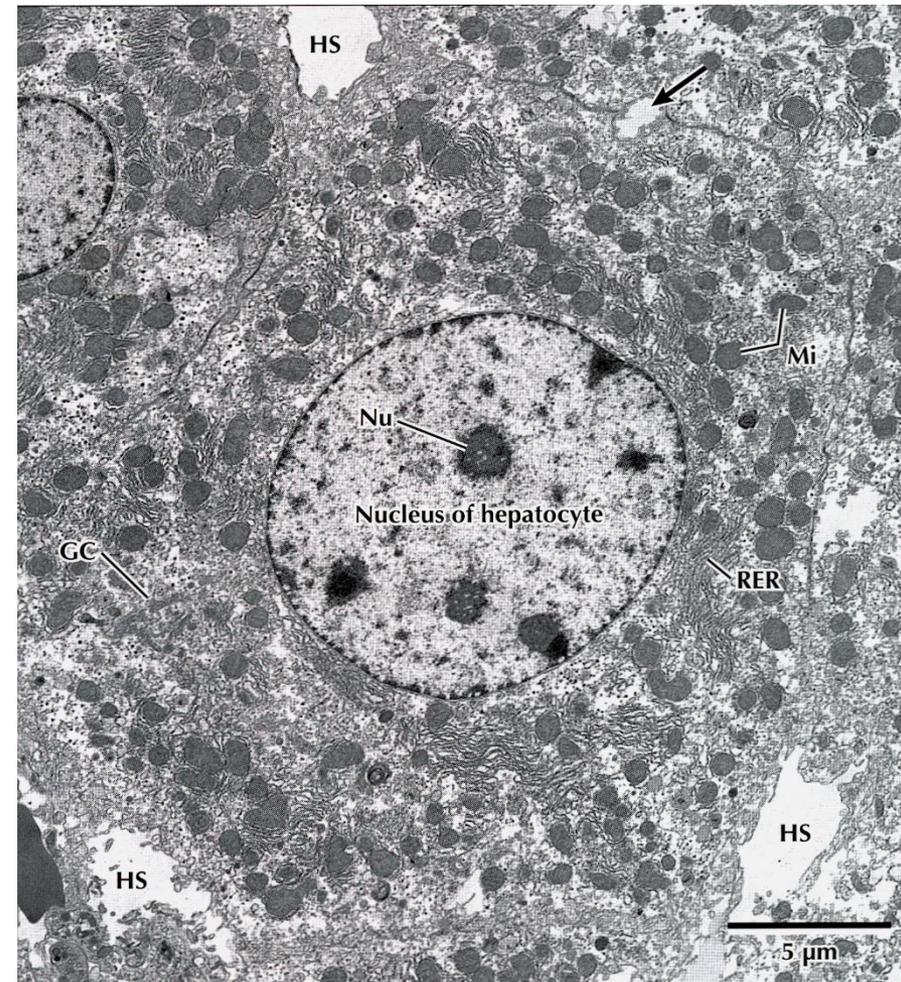
## BILIARY AND BLOOD POLES OF HEPATOCYTE



# HEPATOCTYTES – ULTRASTRUCTURE

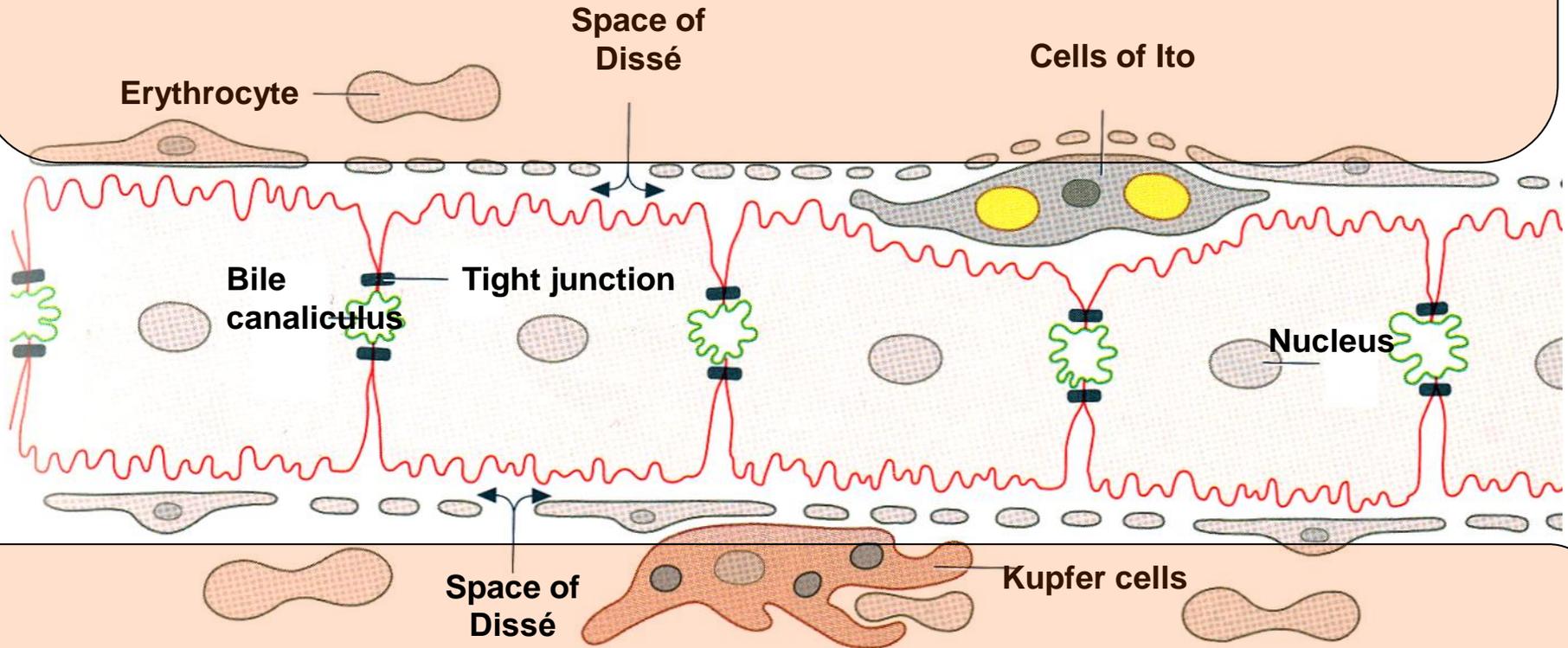


- Long mitochondria with flat or tubular cristae
- Apparent  $RER$ ,  $SER$  and Golgi
- Glycogen, lipid droplets, lysosomes, peroxisomes



# HEPATOCYTES – ULTRASTRUCTURE

From plasma:  
Glucose, aminoacids, bile acids

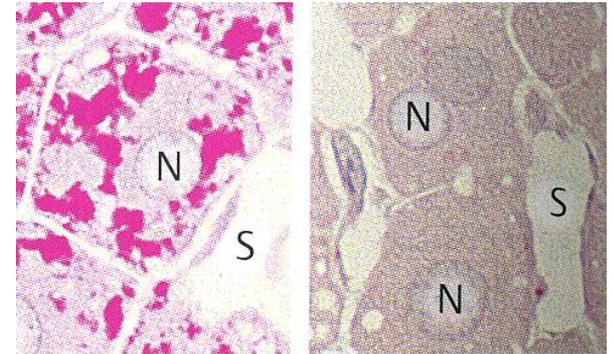
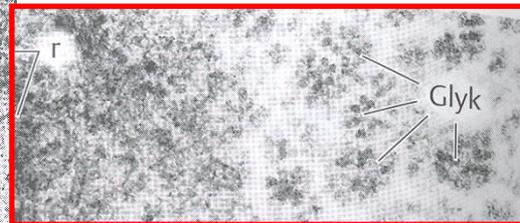
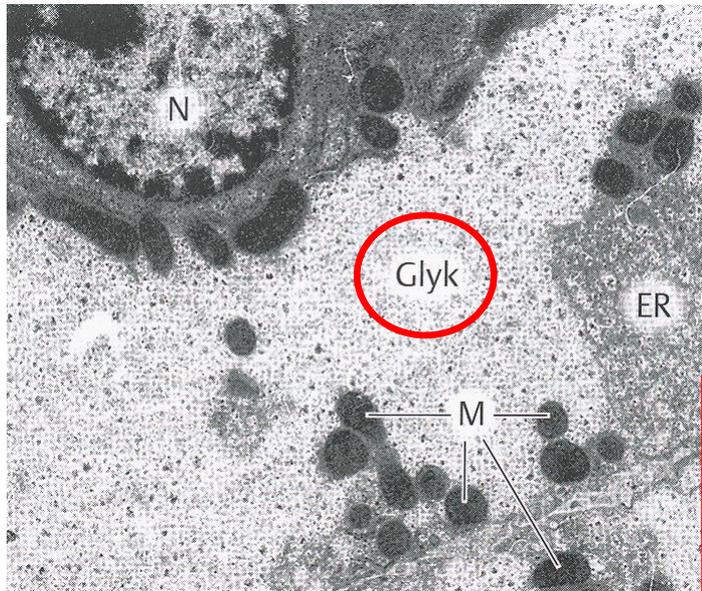


Blood proteins (serum albumin, fibrinogen, prothrombin, complement, transferrin, etc.)

# HEPATOCTYTES – FUNCTIONS

- **Synthesis and metabolism**

- Proteosynthesis –  $R$ ER + Golgi (plasma proteins – albumins, prothrombin, fibrinogen)
- Metabolisms of lipids –  $S$ ER, peroxisomes (lipidic conversion of fatty acids and glucose, lipoprotein synthesis)
- Metabolism of glucose and saccharides - synthesis of glycogen, glycogenolysis and gluconeogenesis (insulin / glucagon)



# HEPATOCYTES – FUNCTIONS

- **Detoxication:**

- sER (steroids, barbiturates, polyaromatic, lipid soluble compounds, etc., endo- and exotoxins)

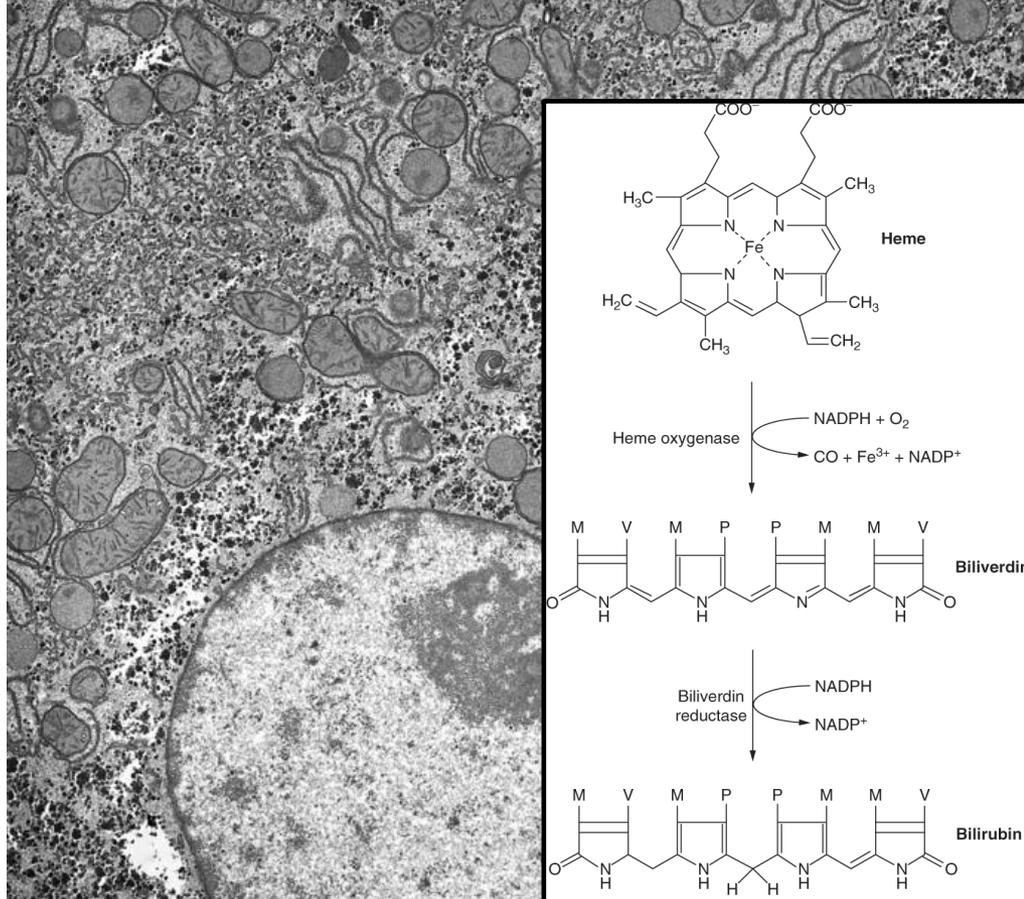
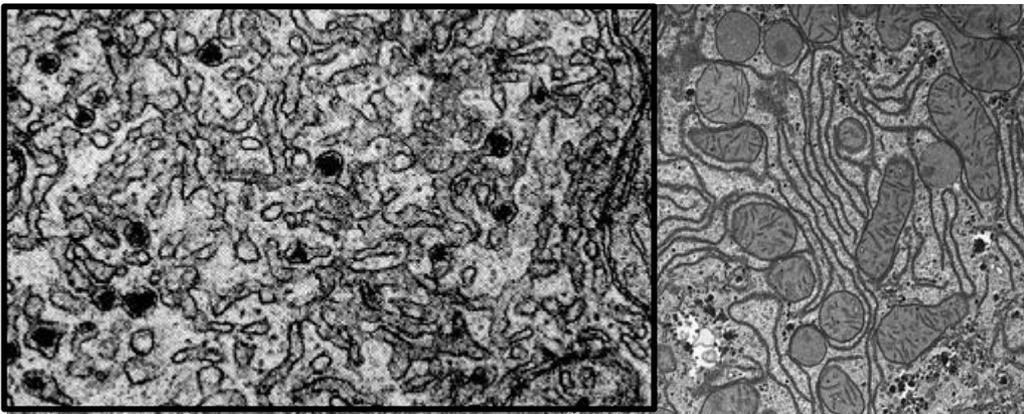
- ROS
- Peribilliary located lysosomes (autophagy, degradation of endocytosed molecules)

- **Metabolism and deposition of vitamins and trace elements**

- **Bile production:**

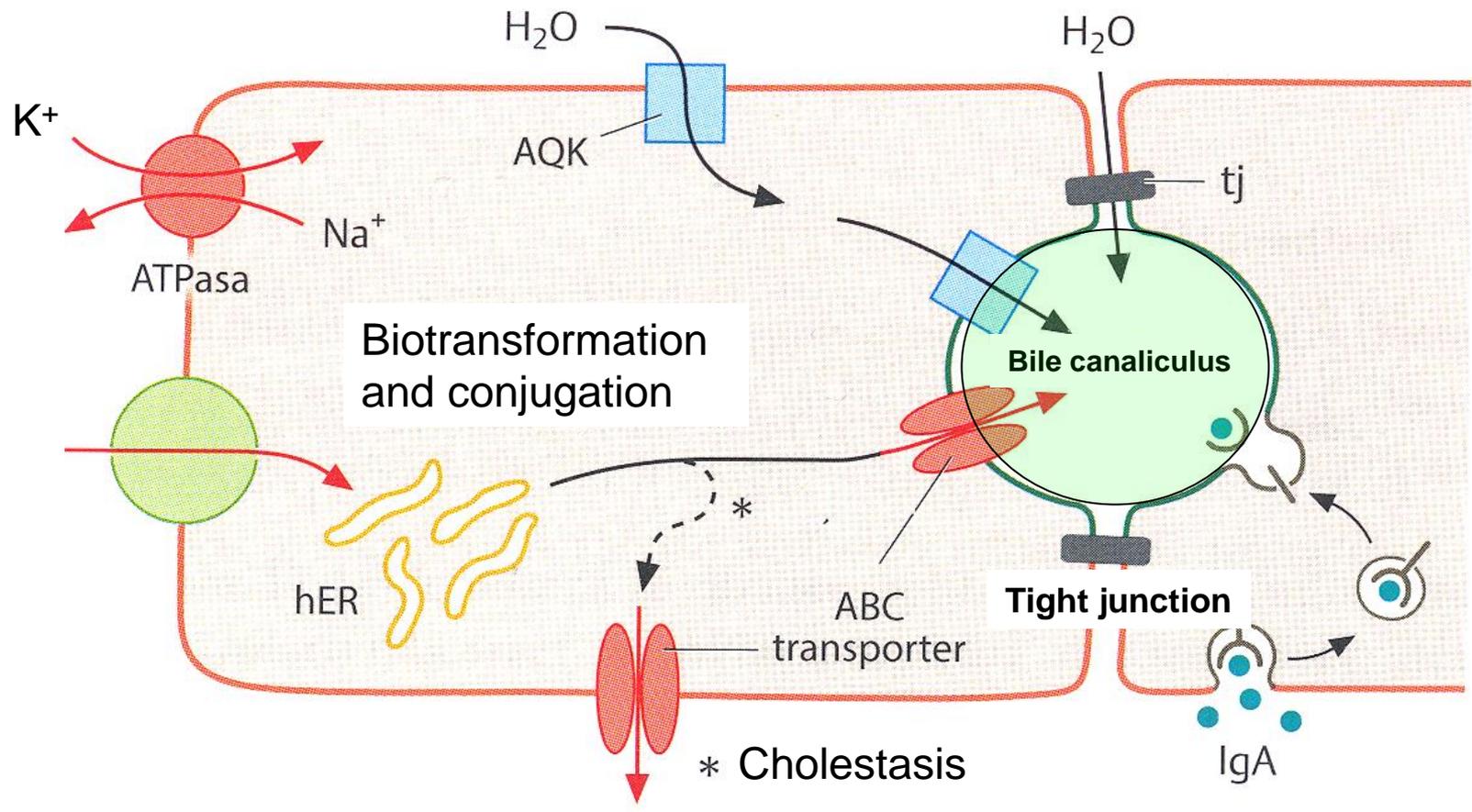
- Recycling of bile acids (90%), 10% de novo synthesis, conjugation of toxic bilirubin and glukuronic acid to nontoxic complex bilirubin-glucuronid

- sER



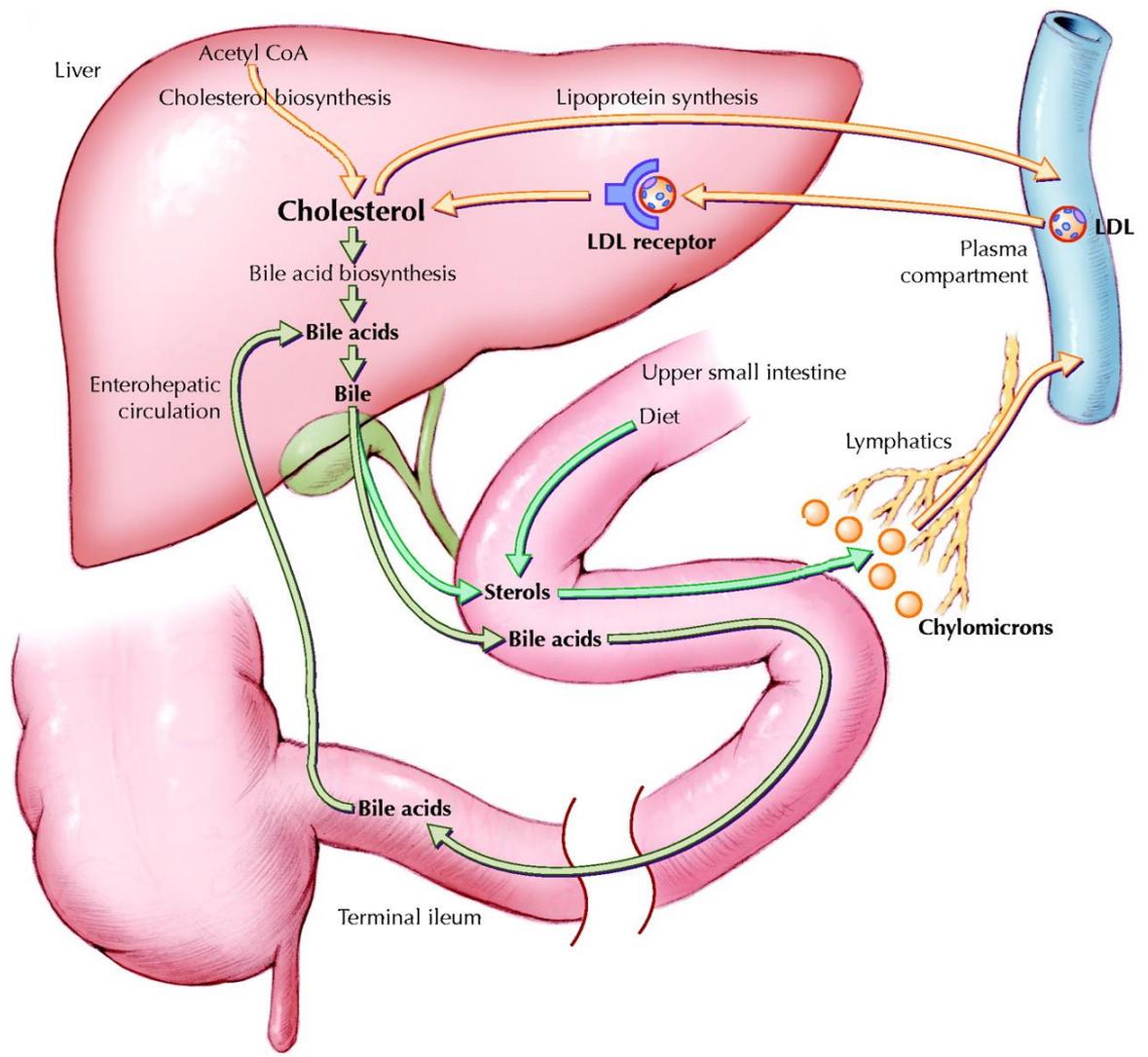
# HEPATOCYTES – FUNCTIONS

Bile acids  
Bilirubin  
Steroids  
Drugs



# HEPATOCYTES – FUNCTIONS

## ENTEROHEPATIC CIRCULATION





# HEPATOCTYTES – FUNCTIONS

## ENTEROHEPATIC CIRCULATION

- Resorption in terminal ileum
- Vena portae
- Sinusoids

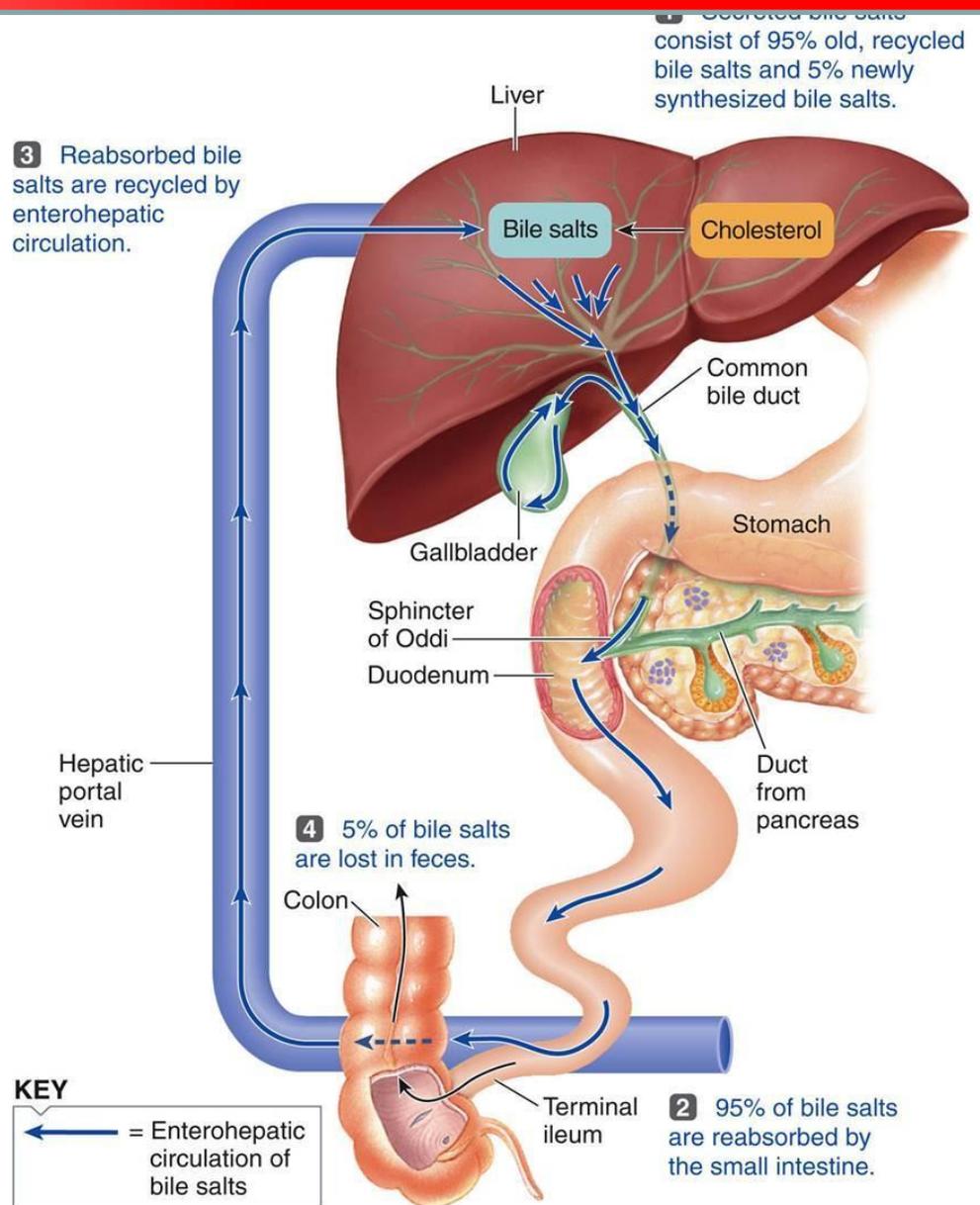
Hepatocytes

Blood pole



Bile pole

- Bile canaliculi
- Intra and extrahepatic ducts
- Duodenum



# BILE DUCTS

## INTRAHEPATIC

### Billiary canaliculli

- intercellular space between hepatocytes
- 1-2 $\mu$ m
- no true wall, formed by membranes of hepatocytes
- intercellular junctions

### Canals of Herring

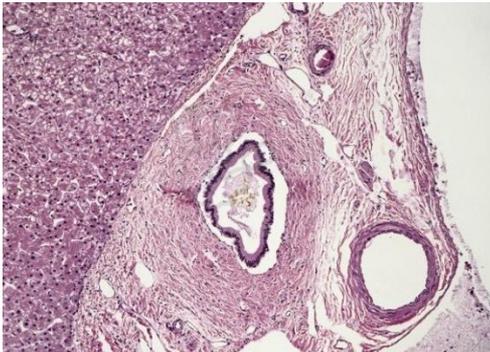
- simple squamous epithelium

### Interlobular bile ducts

- cholangiocytes
- cubic or low columnar epithelium + c.t.

### Lobar bile ducts

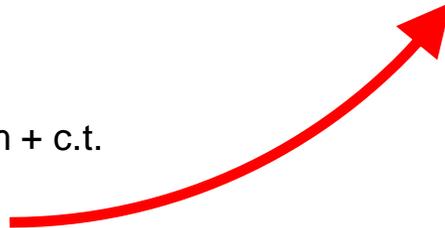
- ductus hepaticus dexter et sinister
- high simple columnar epithelium



## EXTRAHEPATIC

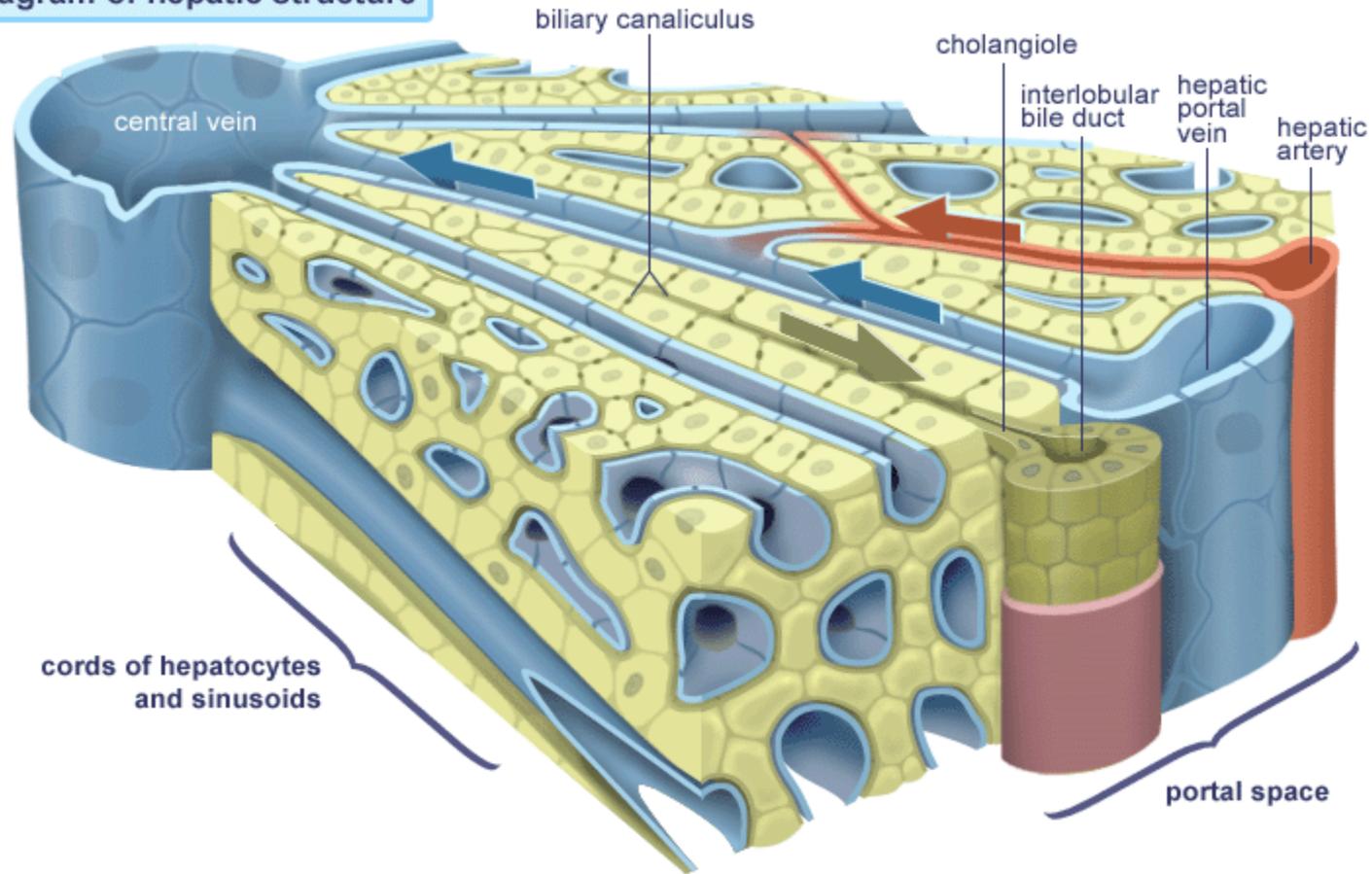
### Ductus hepaticus, ductus cysticus, ductus choledochus

- mucosa
- fibromuscular layer



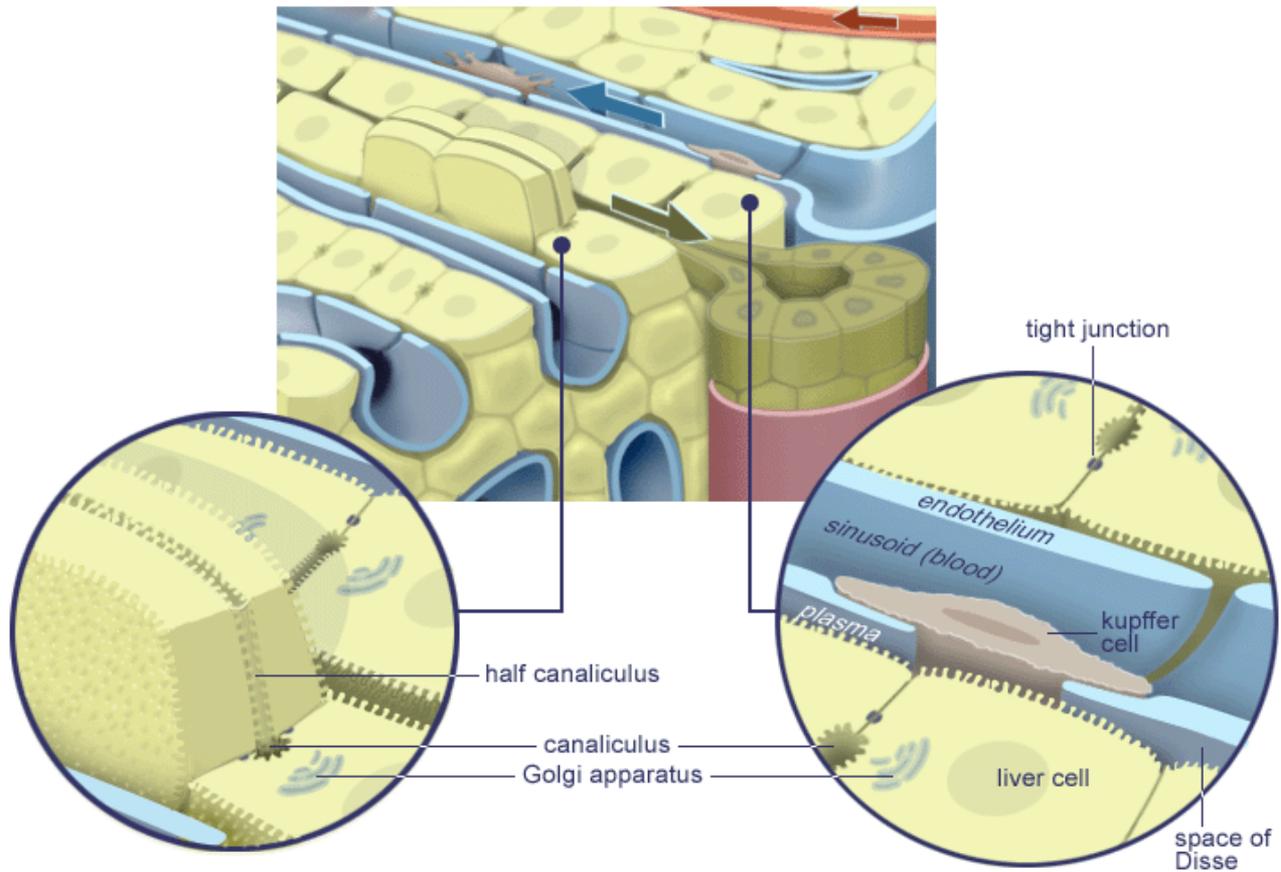
# INTRAHEPATIC BILE DUCTS

Diagram of hepatic structure



# INTRAHEPATIC BILE DUCTS

Hepatic structure (close-up)

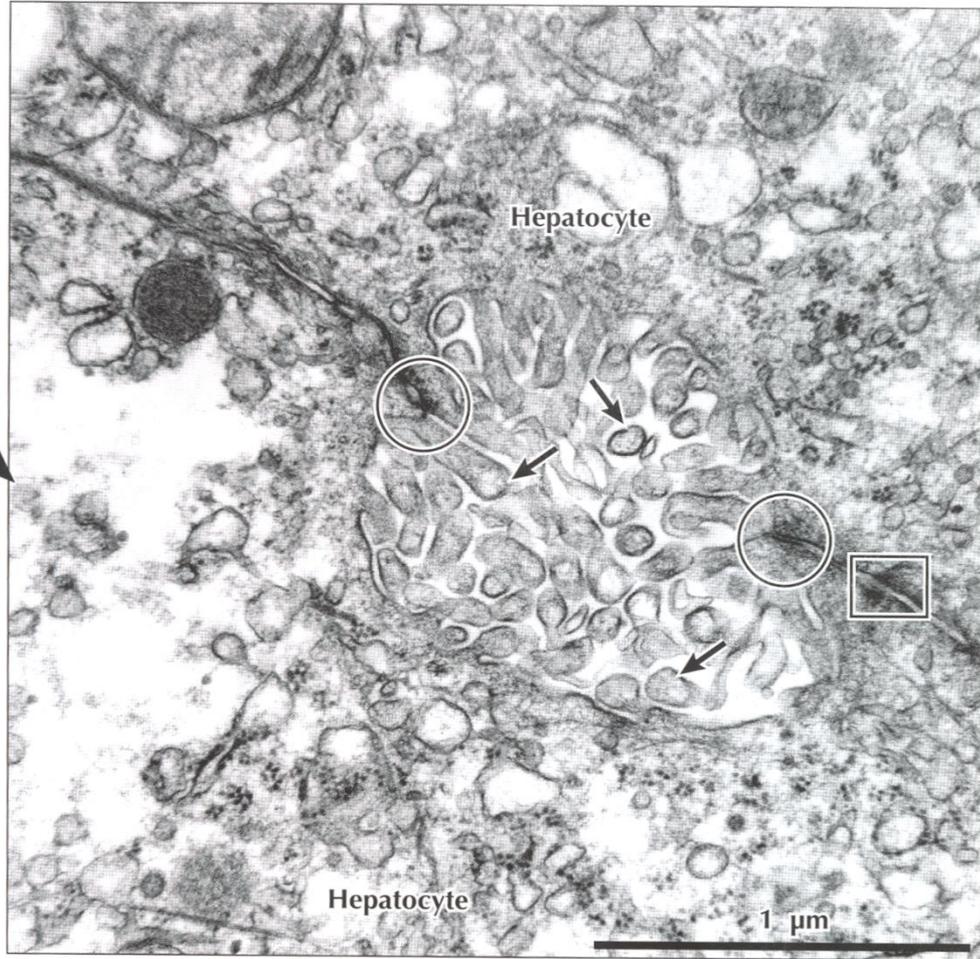


# INTRAHEPATIC BILE DUCTS

▼ The box indicates a bile canaliculus.

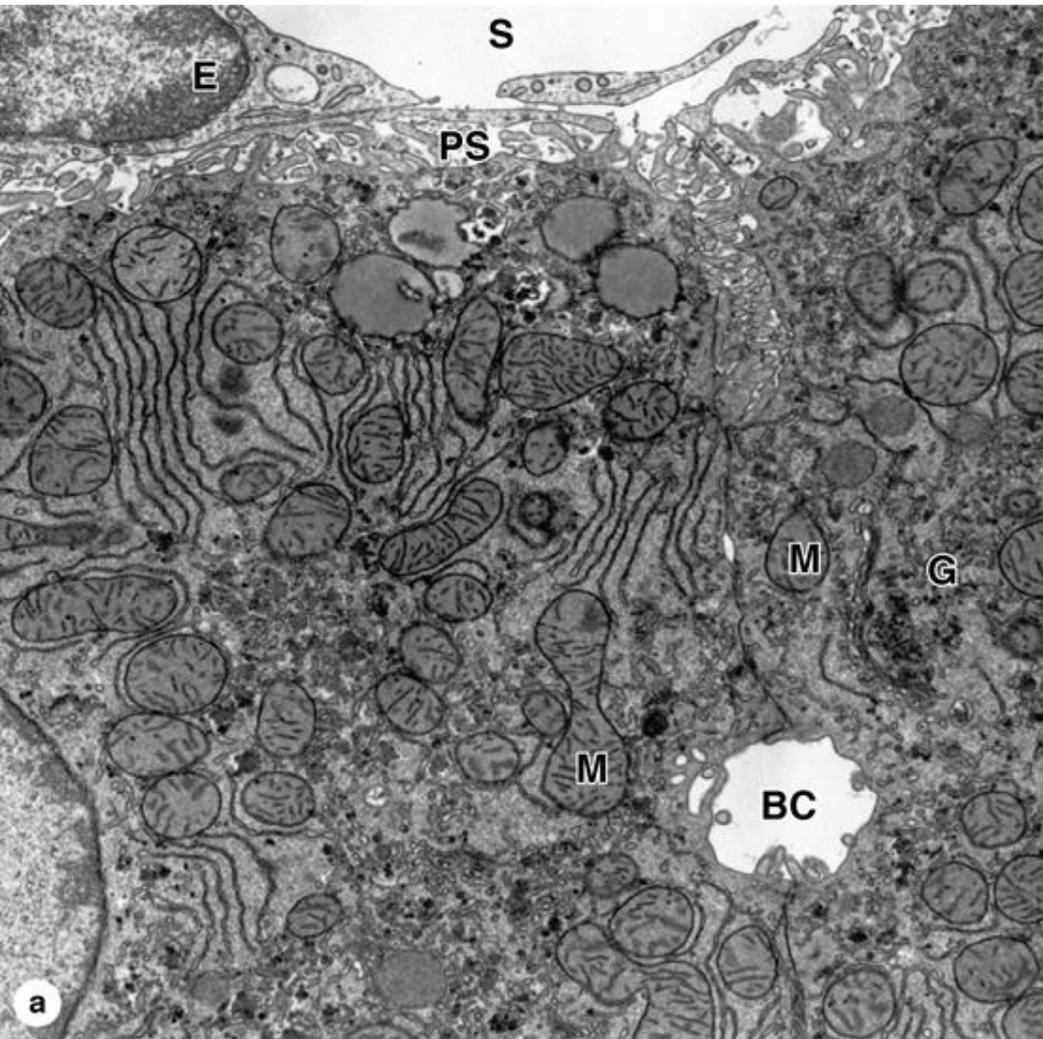


*F. Netter M.D.*



▲ EM of a bile canaliculus in transverse section. The lumen shows short stubby microvilli (arrows) of two hepatocytes. Desmosomes (rectangle) and tight junctions (circles) link cell membranes, which seals the canaliculus and prevents bile leakage to surrounding tissues. 47,000×

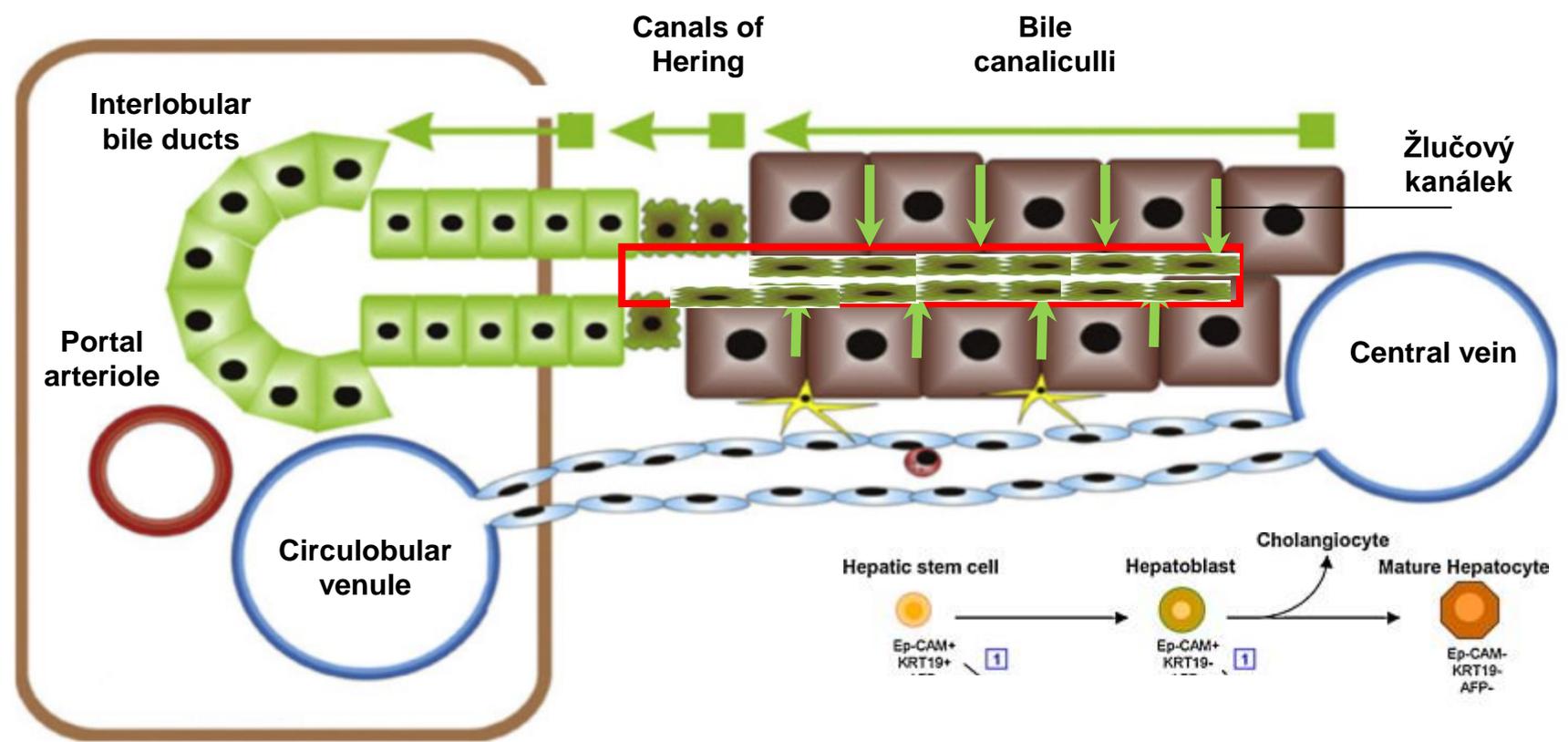
# INTRAHEPATIC BILE DUCTS



# INTRAHEPATIC BILE DUCTS

CHOLANGIOCYTES

HEPATOCTYTES



# EXTRAHEPATIC BILE DUCTS

d. hepaticus communis + d. cysticus → d. choledochus

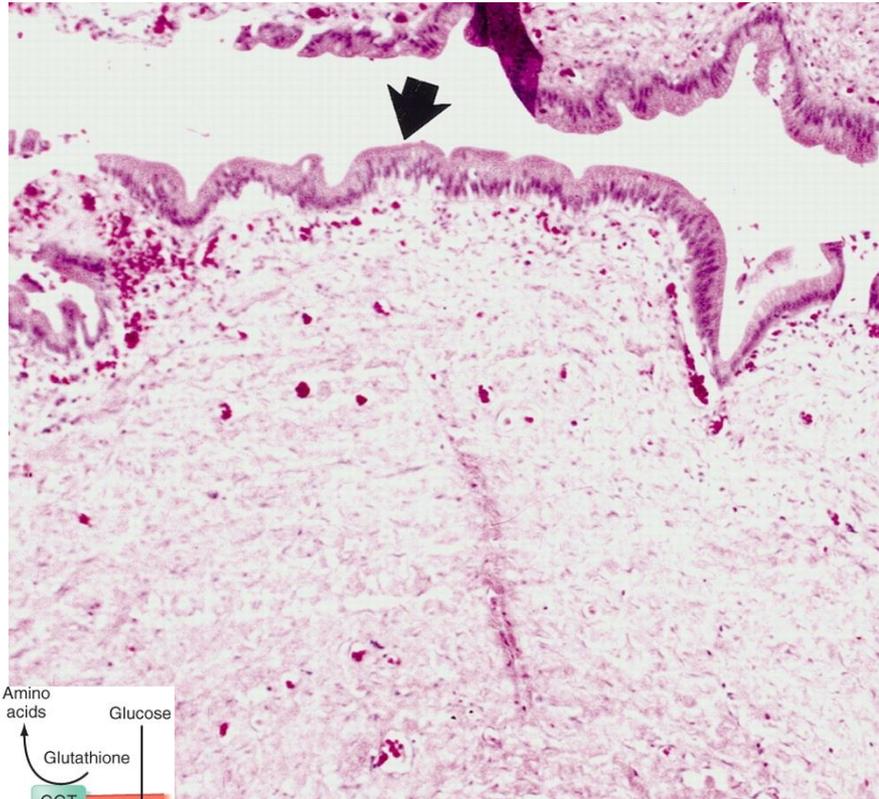
papilla duodeni major  
m. sphincter ampullae hepatoduodenalis (sphincter of Oddi)

## Mucosa

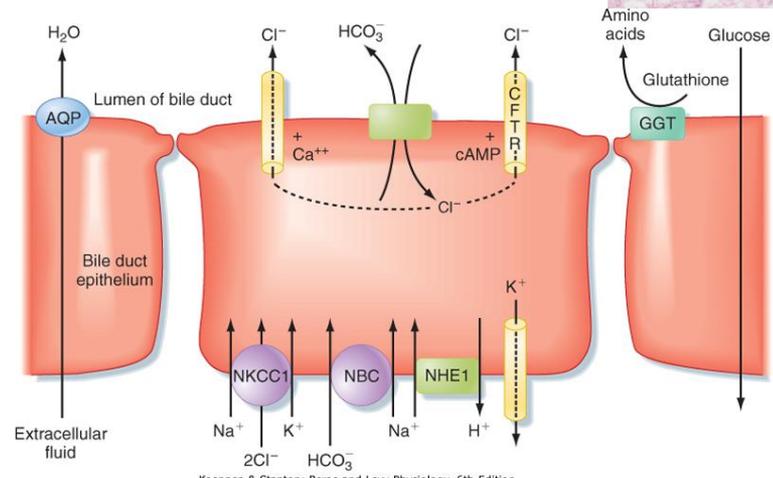
- lateral folds
- simple columnar epithelium (cholangiocytes)
- mucinous glands in c.t., goblet cells

## Fibromuscular layer

- dense network of collagen and elastic fibers
- leiomyocytes



## Bile modification



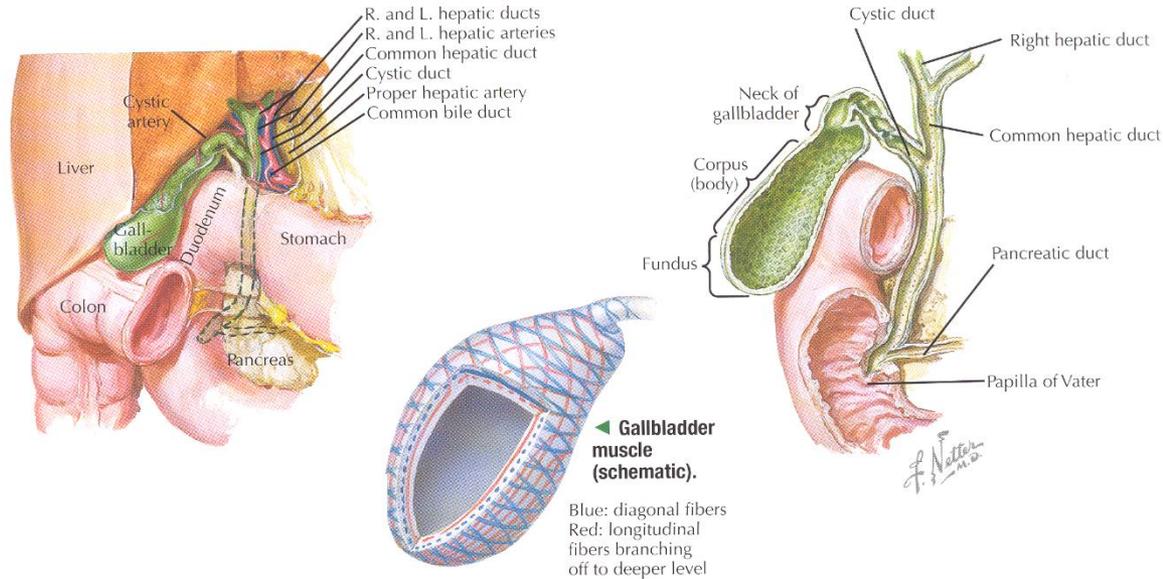
Koepfen & Stanton: Berne and Levy Physiology, 6th Edition.  
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# GALL BLADDER (VESICA FELLEA)

- Wall 1-2mm

- Mucous coat
- Muscle layer
- Serosa/adventitia



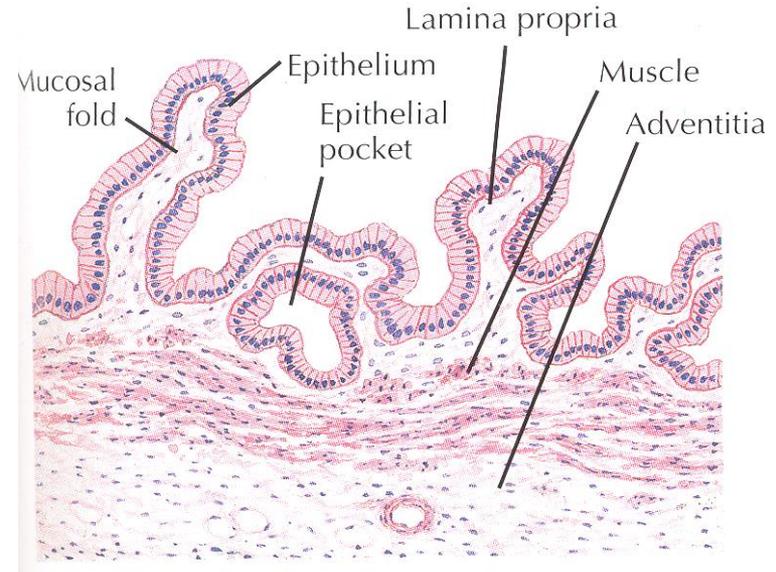
## Mucous coat

- mucosal folds
- 20-50 $\mu$ m simple columnar epithelium with microvilli
- intercellular junctions
- lamina propria mucosae - loose collagen c.t. with mucinous tuboalveolar glands
- lamina muscularis mucosae absent

## Muscular layer (Muscularis propria)

- 3D network of smooth muscle cells,
- elastic fibers

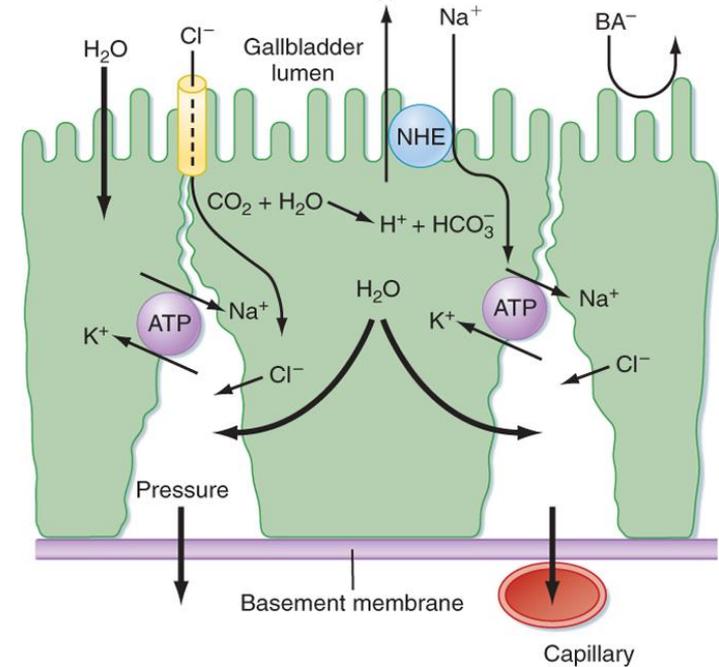
Large layer of **subserous** c.t. (l. propria serosae)



# GALL BLADDER (VESICA FELLEA)

## BILE CONCENTRATION

- Bile secretion by liver– ca 0,8-1l daily
- Gall bladder volume 15-60 ml
- Water resorption

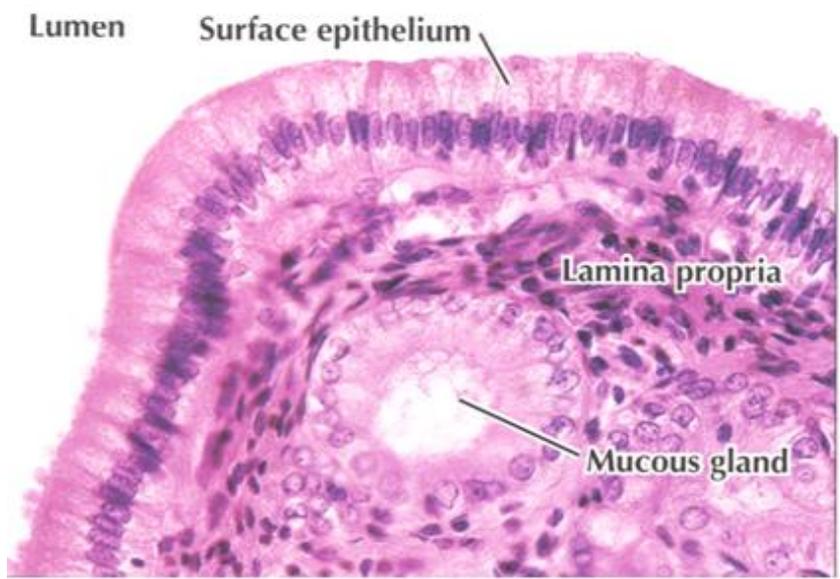
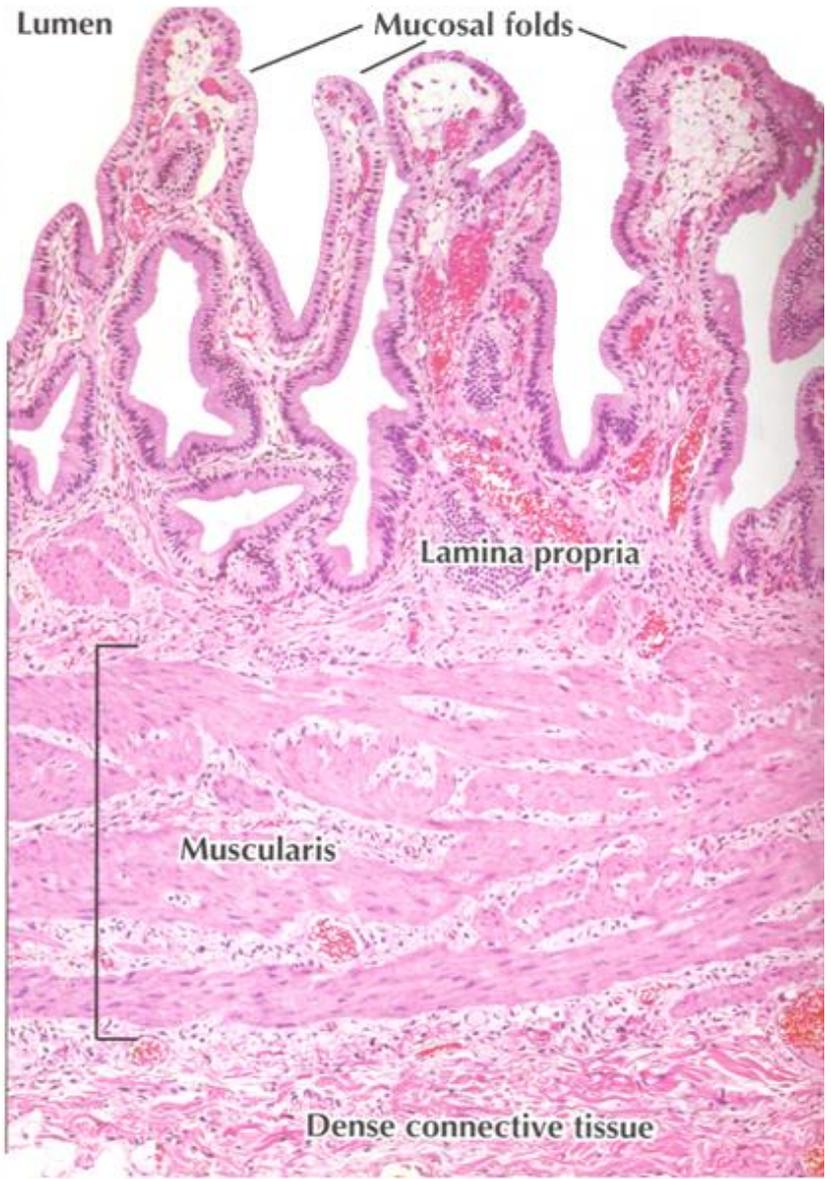
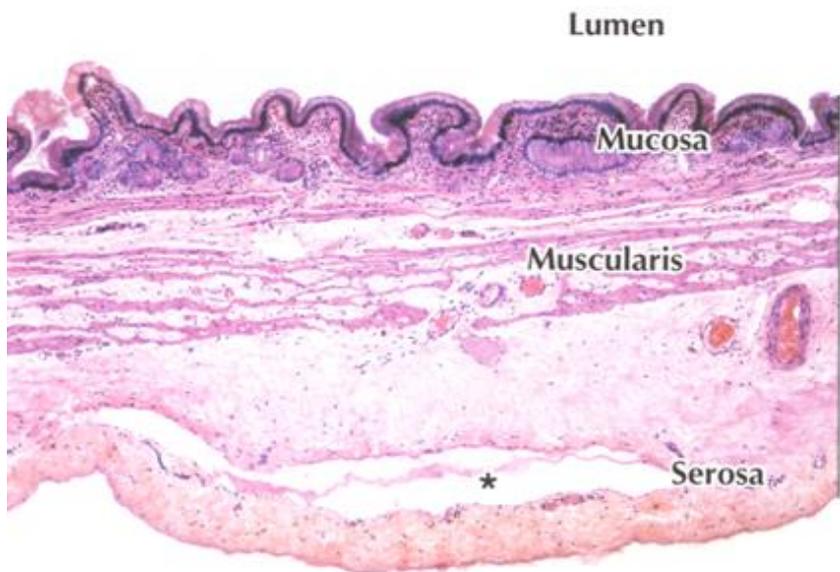


Koepfen & Stanton: Berne and Levy Physiology, 6th Edition.  
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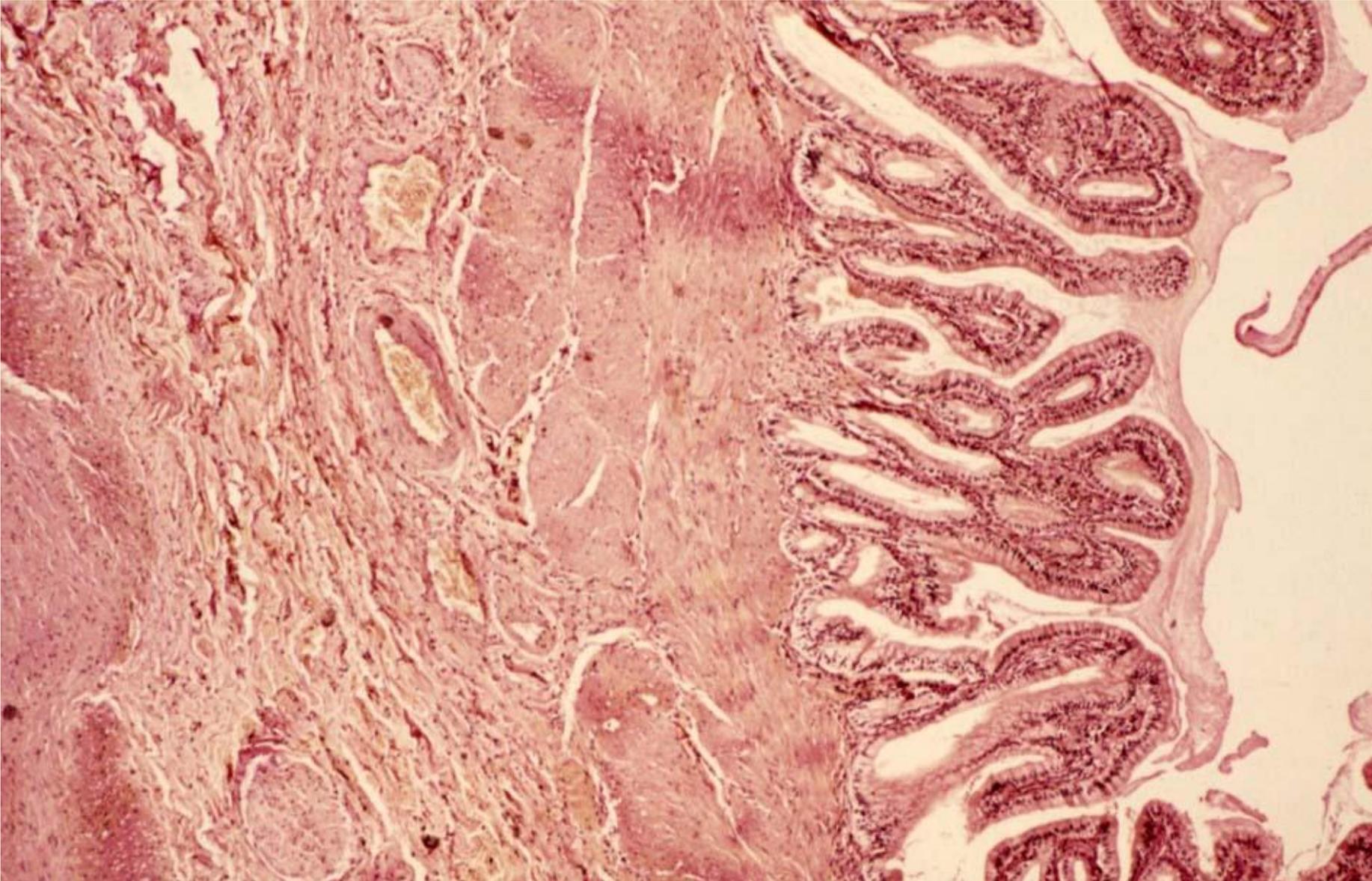
*Approximate Values for Major Components of Liver and Gallbladder Bile*

COMPONENT	LIVER BILE	GALLBLADDER BILE
Na <sup>+</sup> (mEq/L)	150	300 ↑
K <sup>+</sup> (mEq/L)	4.5	10 ↑
Ca <sup>++</sup> (mEq/L)	4	20 ↑
Cl <sup>-</sup> (mEq/L)	80	5 ↓
HCO <sub>3</sub> <sup>-</sup> (mEq/L)	25	12 ↓
Bile salts (mEq/L)	30	315 ↑
pH	7.4	6.5
Cholesterol (mg/100 mL)	110	600
Bilirubin (mg/100 mL)	100	1000

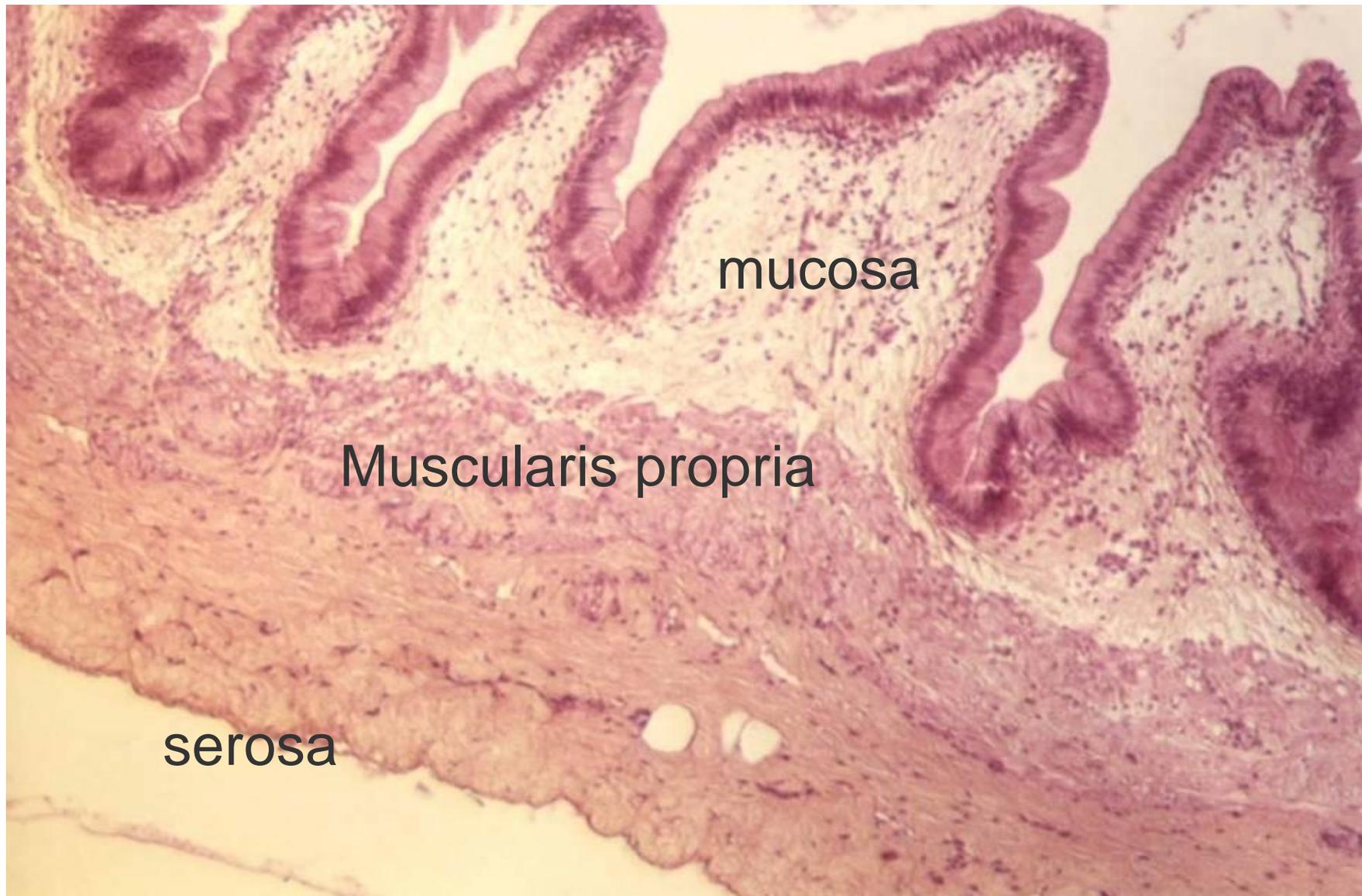
# GALL BLADDER (VESICA FELLEA)



# GALL BLADDER (VESICA FELLEA)



# GALL BLADDER (VESICA FELLEA)

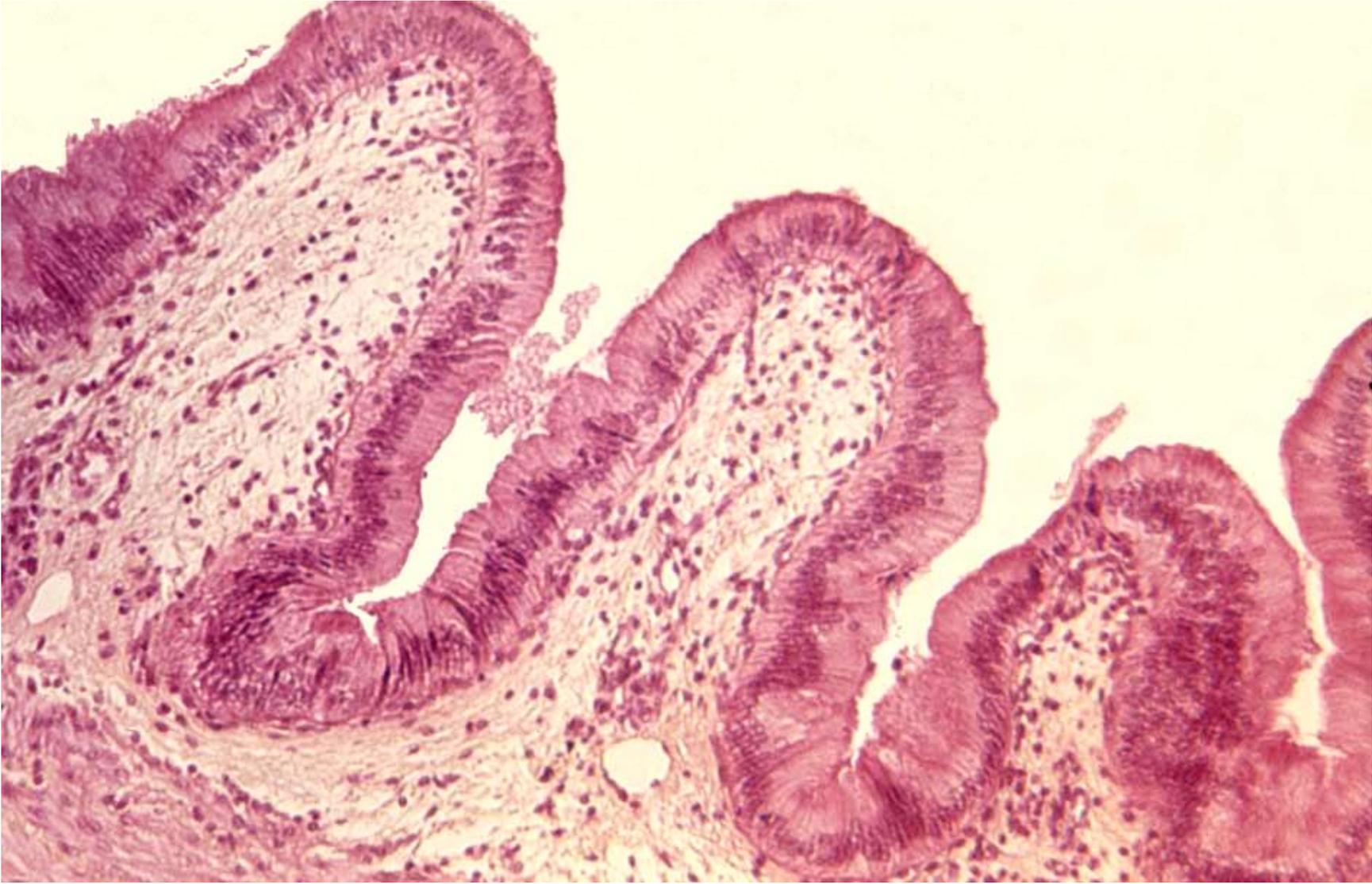


mucosa

Muscularis propria

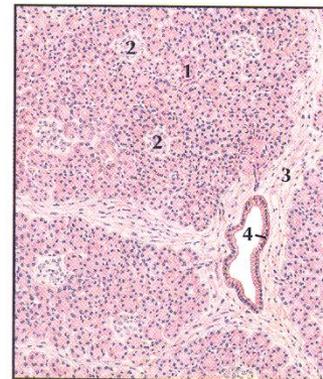
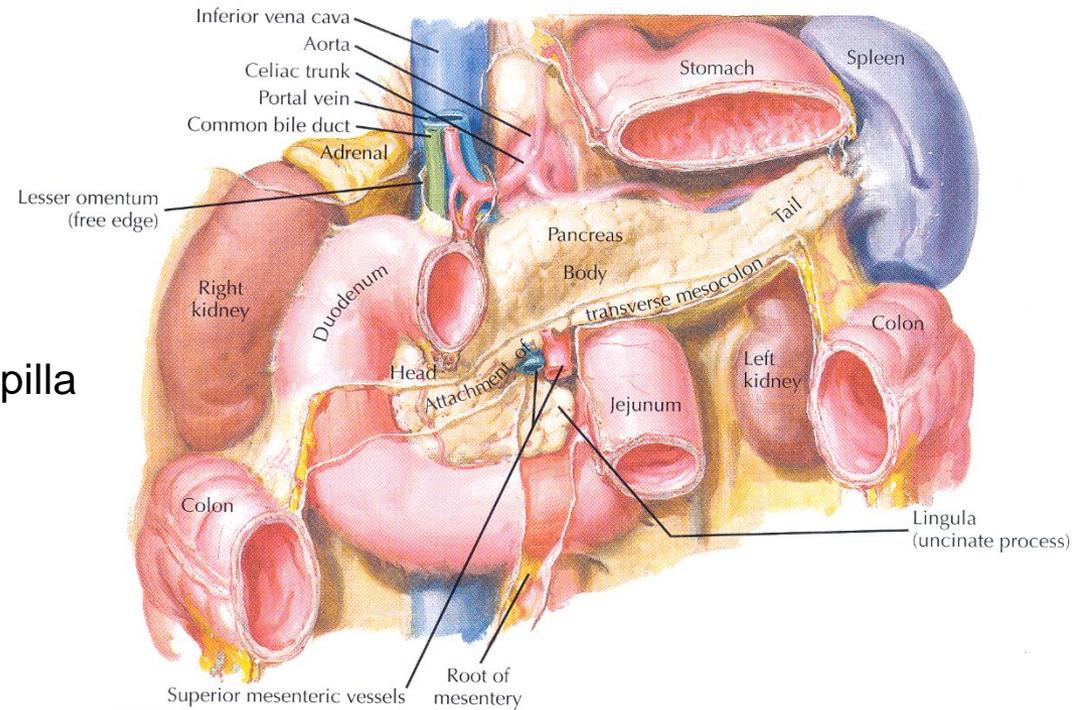
serosa

# GALL BLADDER (VESICA FELLEA)

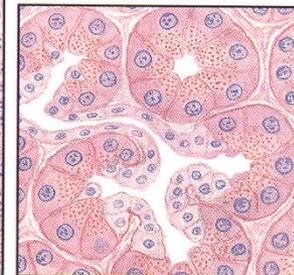


# PANCREAS

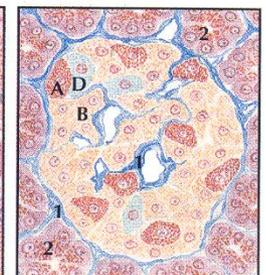
- Compound, serous, tuboalveolar gland
- Exocrine and endocrine character
  - pancreatic acinus
  - Islets of Langerhans
- Major duct (Wirsungi) opens to Vater papilla as a common bile and pancreatic duct
- Dense collagen c.t. capsule
- Septs – blood cells, innervation, and interlobular ducts



Low-power section of pancreas  
 1. Acini, 2. islet, 3. interlobular septum, 4. interlobular duct

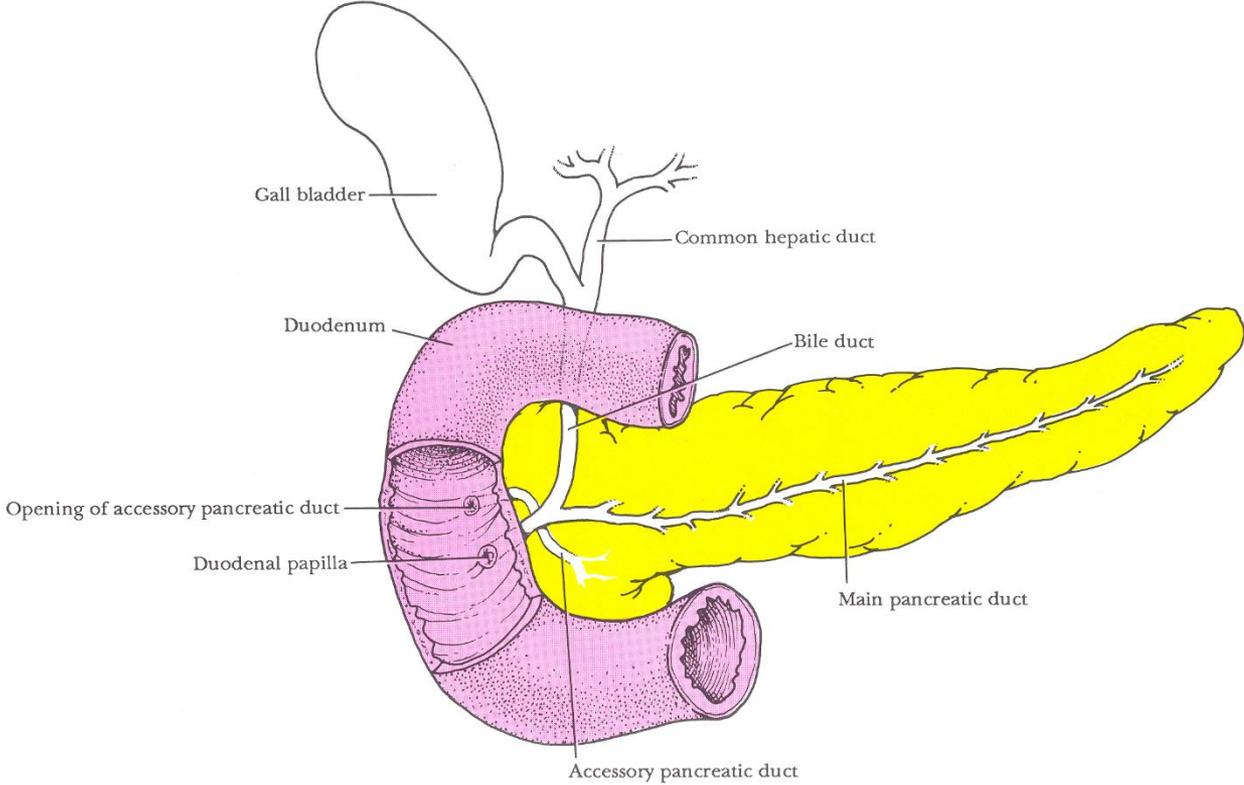


High magnification: acini, intercalated duct and zymogen granules



Pancreatic islet: A, B, and D cells. 1. Reticulum, 2. acini

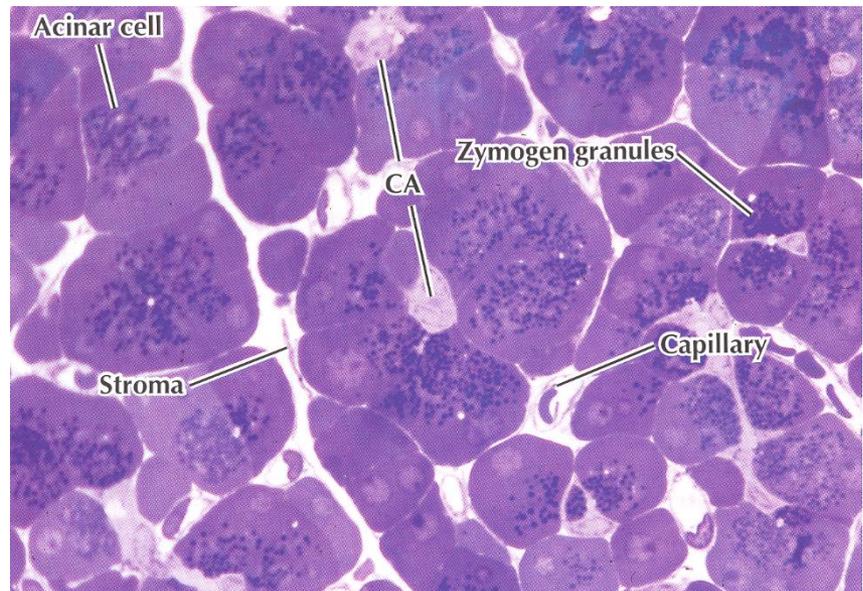
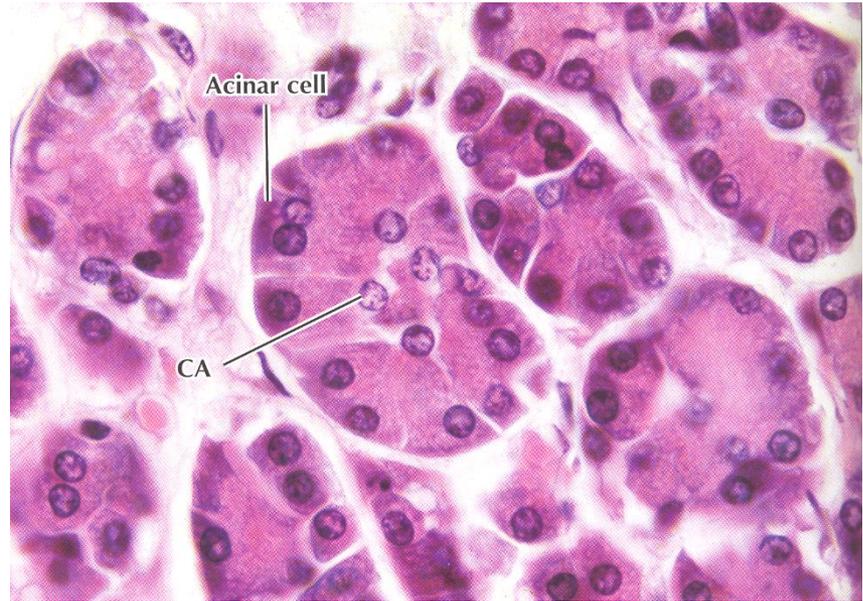
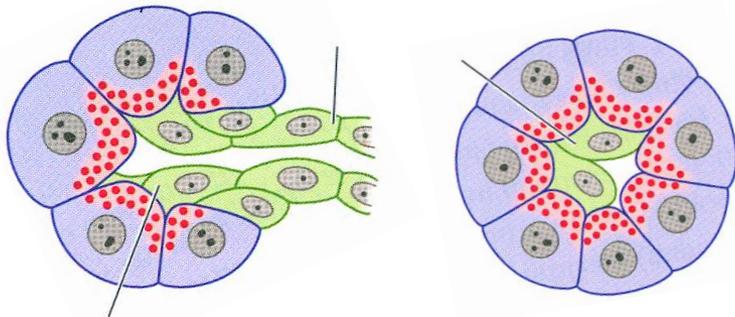
# PANCREAS



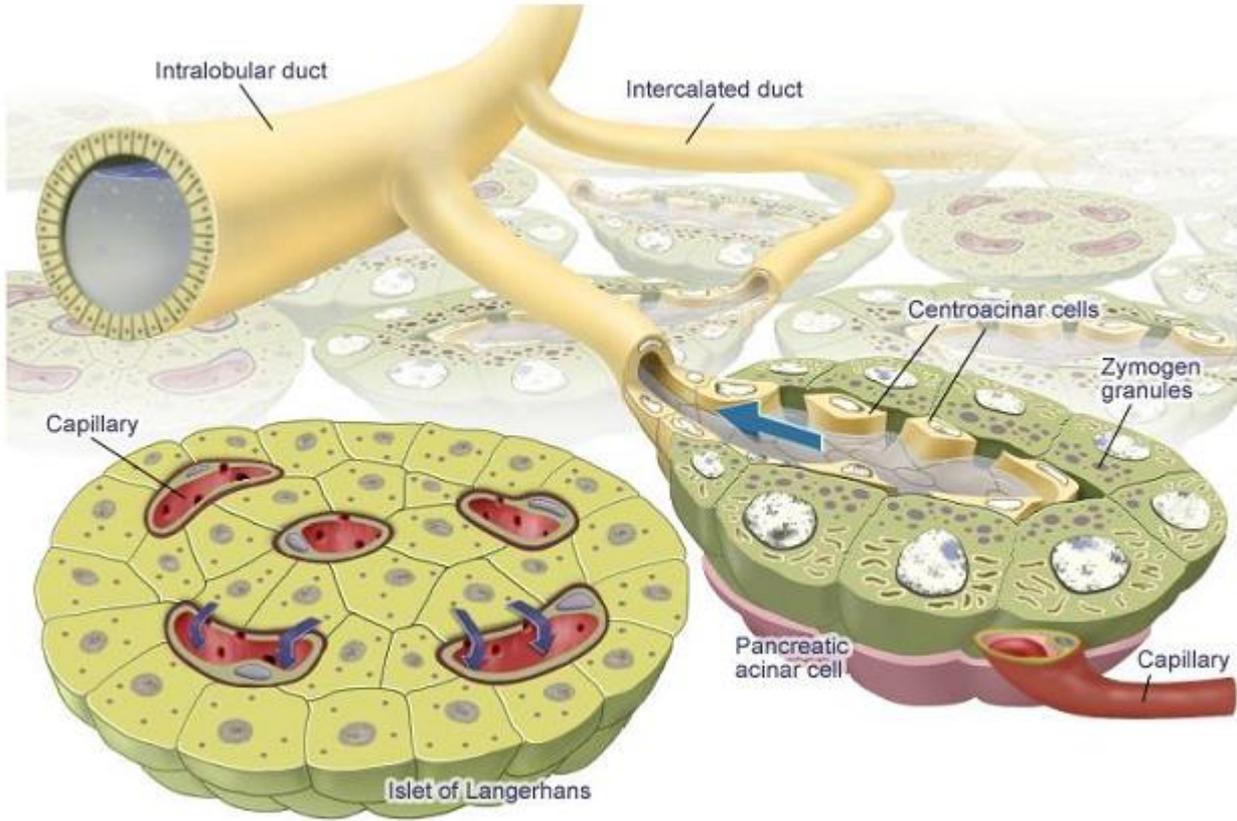


# PANCREAS – PANCREATIC ACINUS

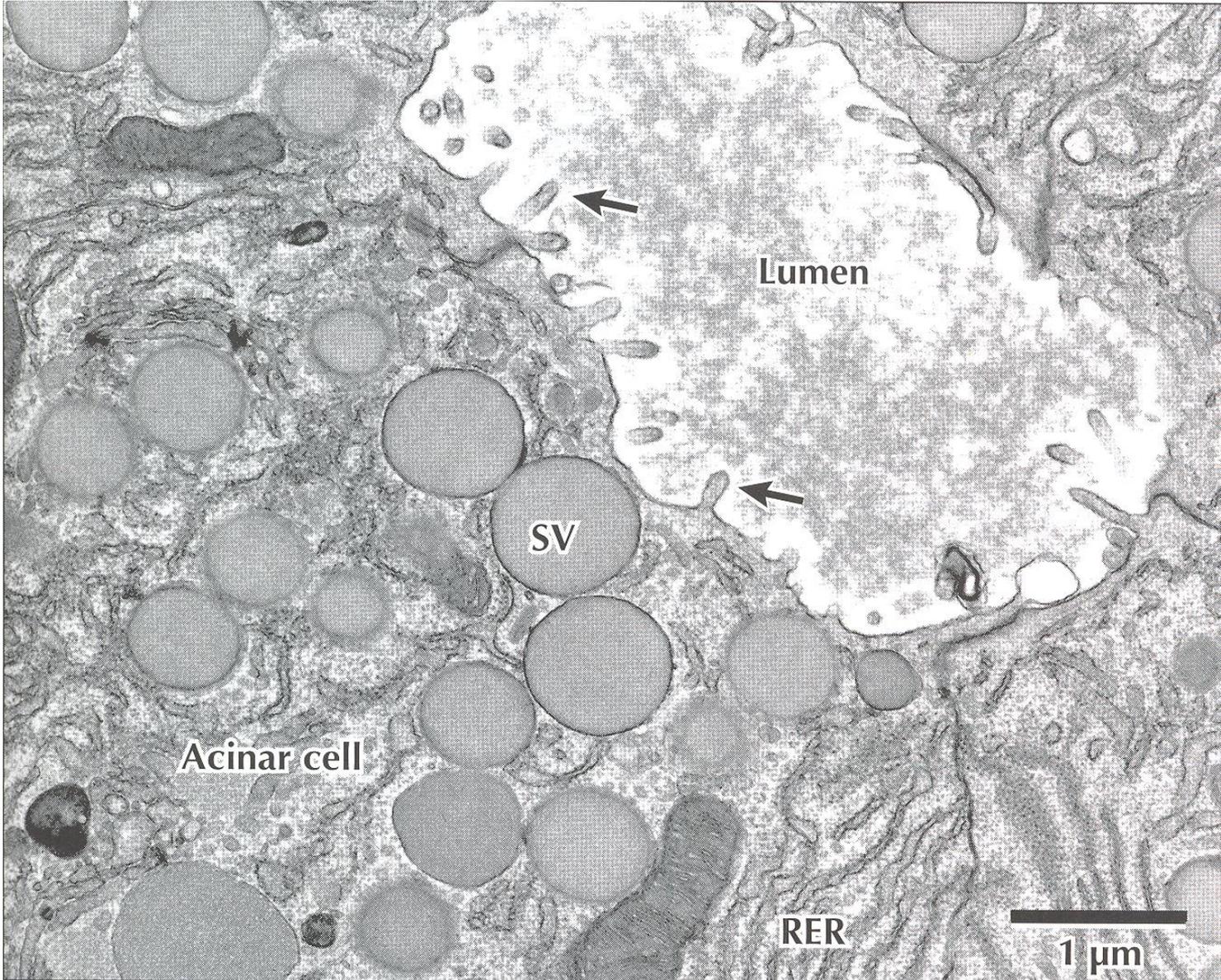
- Pyramidal epithelial cells
- Pancreatic digestive enzymes
- intercalated ducts
  
- Serous acinar cells
  - Polarized secretory cells
  - Basophilic
  - Apex – Golgi and zymogenic granules
  - Microvilli
  - Intercellular junctions
  
- Centroacinar cells
  - Centrally located nucleus, squamous character
  - Continuous with intercalated ducts



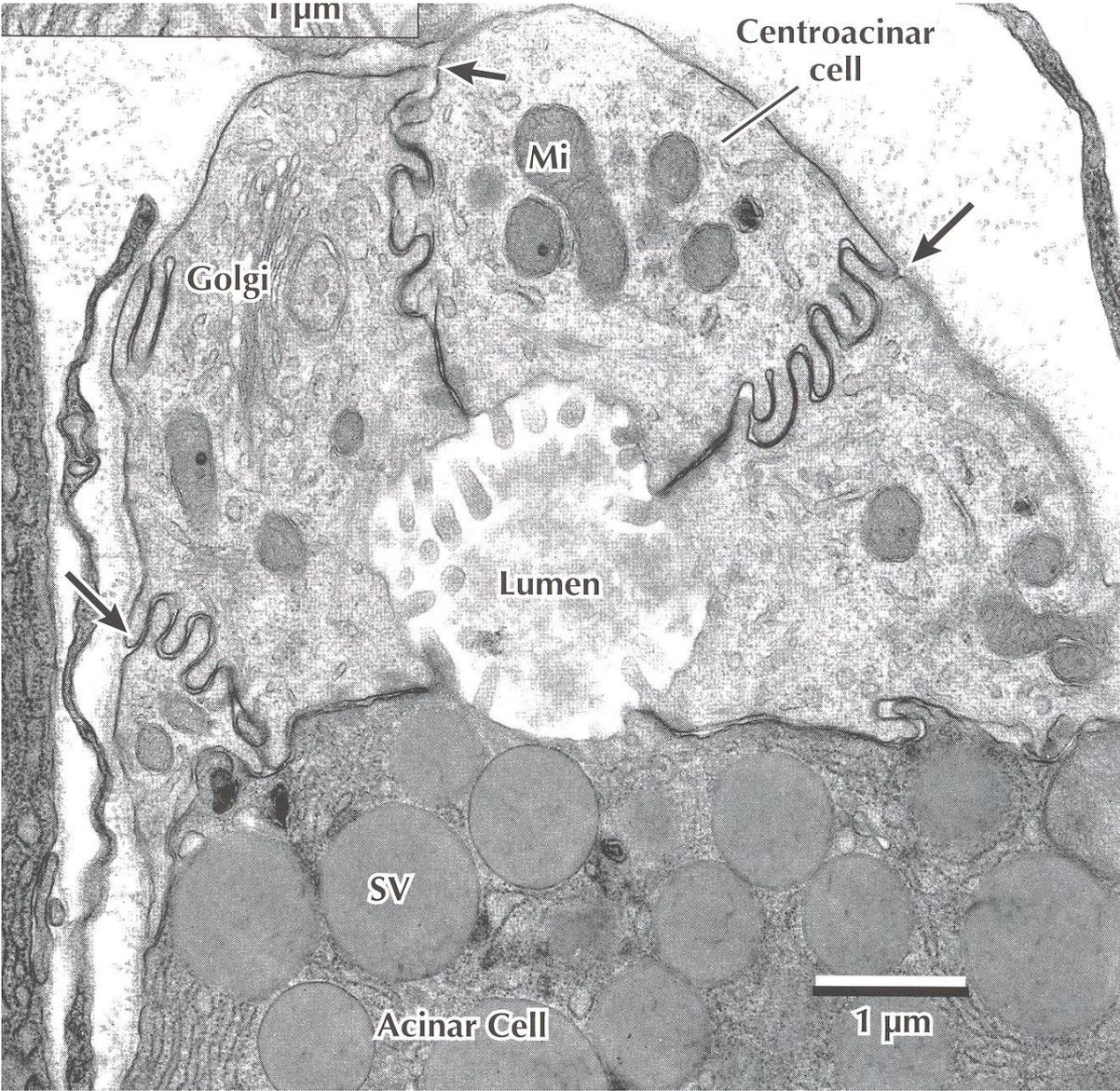
# PANCREAS – PANCREATIC ACINUS



# PANCREAS – PANCREATIC ACINUS

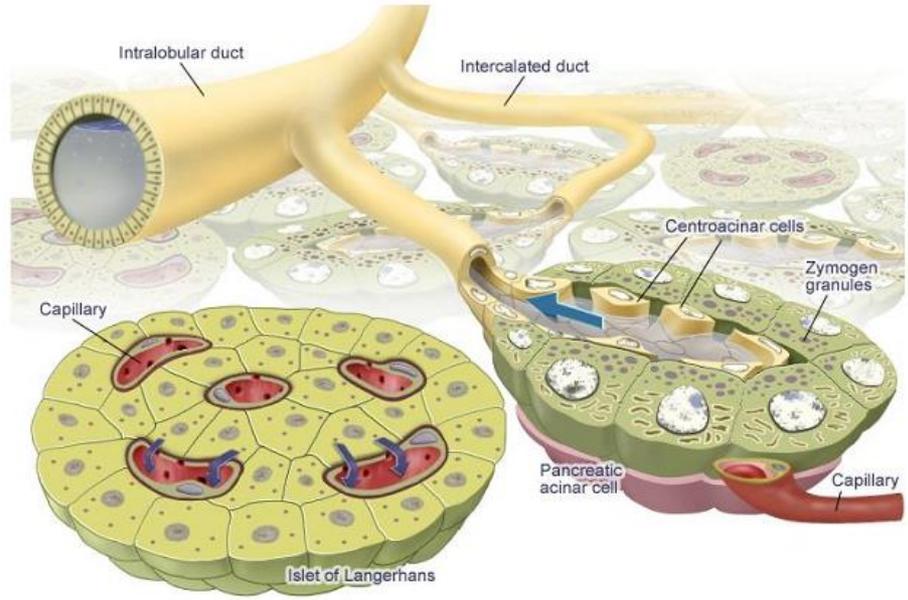
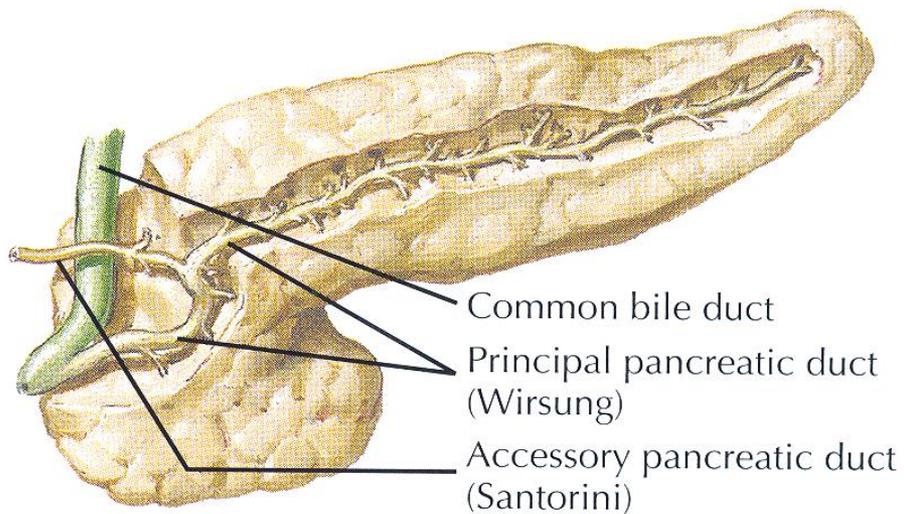


# PANCREAS – PANCREATIC ACINUS



# PANCREAS – PANCREATIC DUCTS

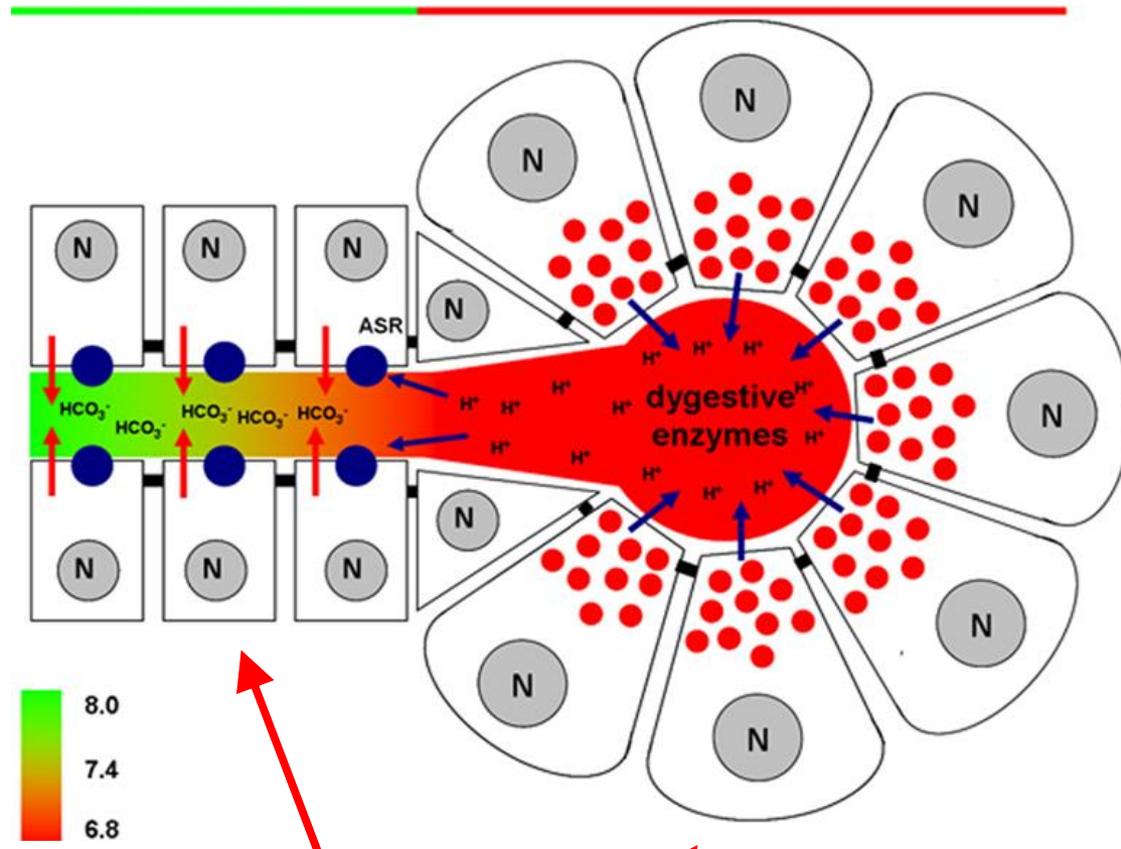
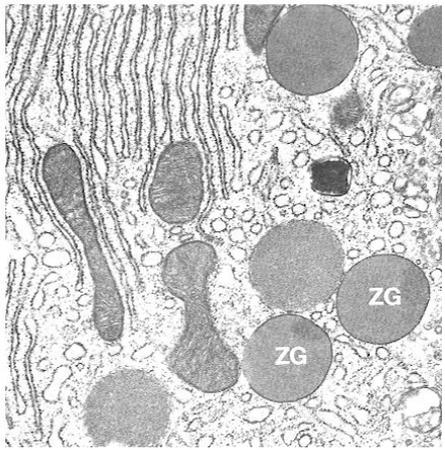
- Centroacinar cells
- Intercalated ducts
  - simple squamous epithelium + basal membrane
- Intralobular and interlobular ducts
  - simple cubic – low columnar epithelium
- Major pancreatic ducts
  - D. pancreaticus major – Wirsungi and D. pancreaticus accessorius - Santorini
  - bilayered columnar epithelium and dense collagen c.t.
  - intramural mucinous tubular glands, goblet cells, EC cells



# PANCREAS – EXOCRINE FUNCTION

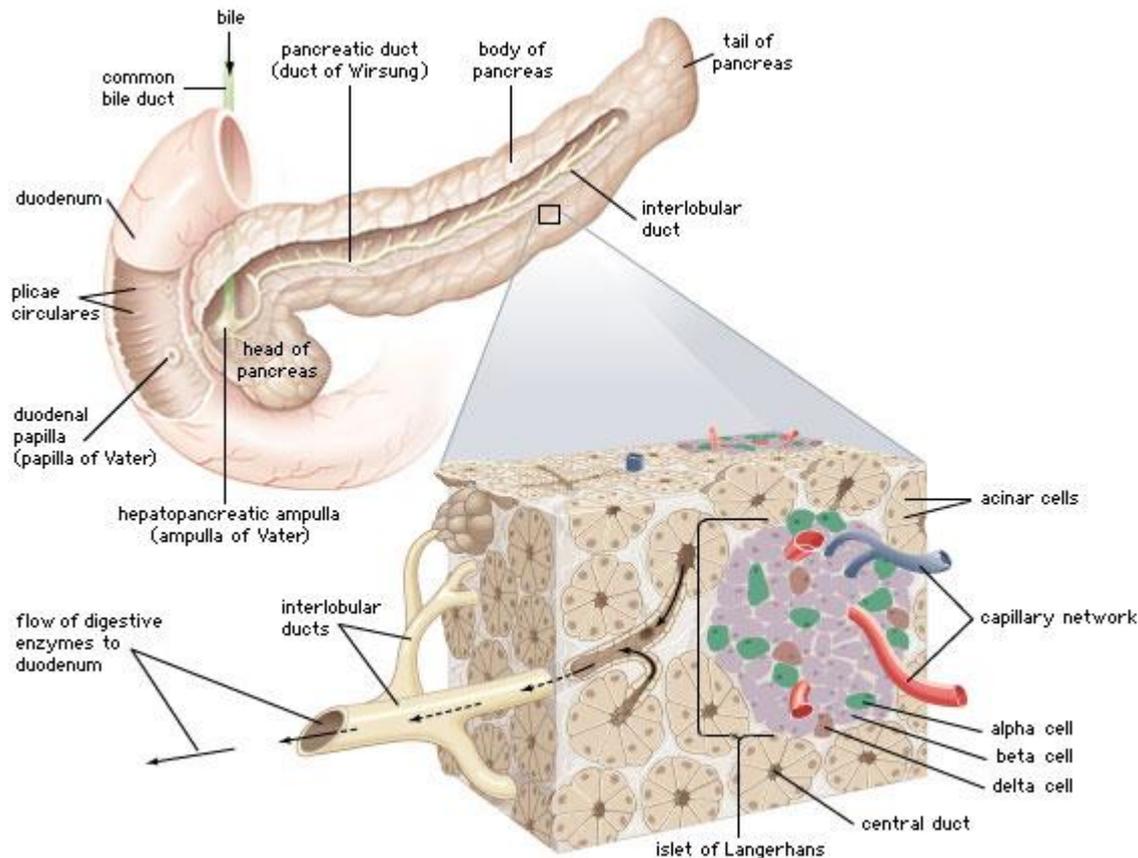
- ca 1000-2000 ml daily
- alkalic pH (8.8),  $\text{HCO}_3^-$  (intercalated duct epithelium)
- mucin (epithelium of large ducts)

- Hydrolases
  - Trypsinogen
  - Chymotrypsinogen
  - Proelastases
  - Carboxypeptidases
  - Pancreatic lipase
  - Amylases
  - ...



Hormonal regulation (secretin, cholecystikinin) + parasymphatikus

# PANCREAS – ENDOCRINE FUNCTION



## Glucagon

- Glycogen consumption in tissues and muscles
- Increase of blood glucose

## Insulin

- Increase of membrane permeability for glucose
- Glucose oxidation in tissues
- Decrease of blood glucose
- Synthesis of glucan in muscles and liver

## Pancreatic polypeptide

- Autoregulation of pancreatic secretion

## Somatostatin

- Inhibition of GIT hormones

# PANCREAS – ISLETS OF LANGERHANS

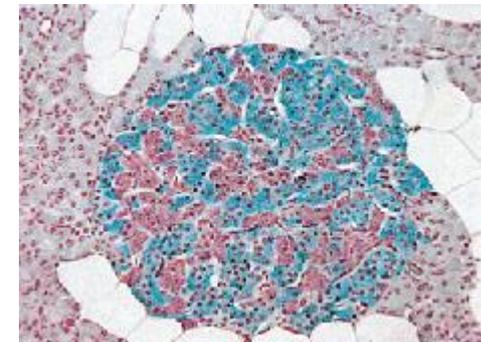
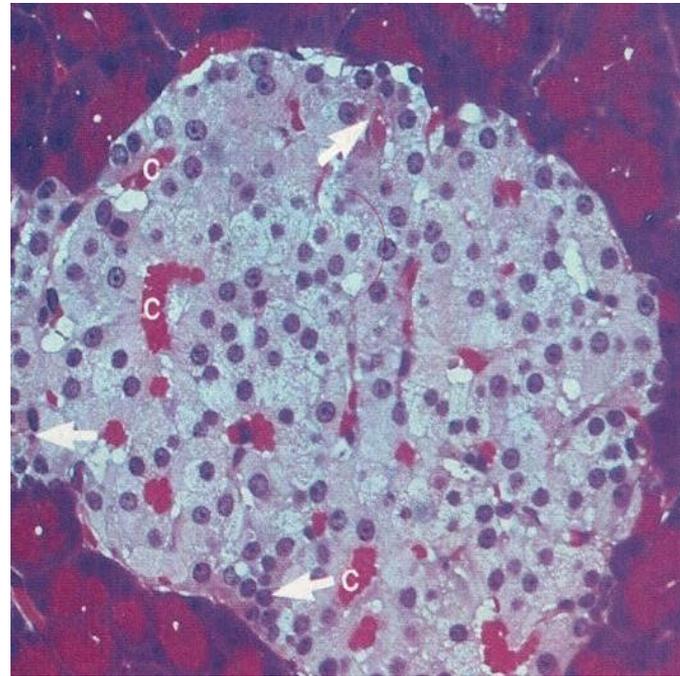
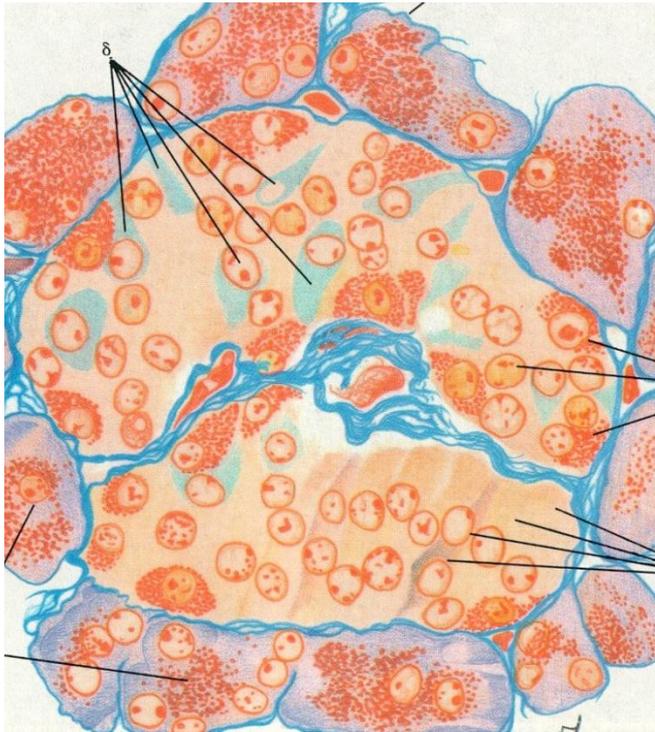
- Clusters of pale cells
- ca  $1,5 \times 10^6$
- Thin c.t. capsule
- Cords of epithelial cells
- Sinusoids
- General characteristics of APUD cells
- A, B, D, PP cells

A cells: 20%, glucagon

B cells: 60-70%, insulin

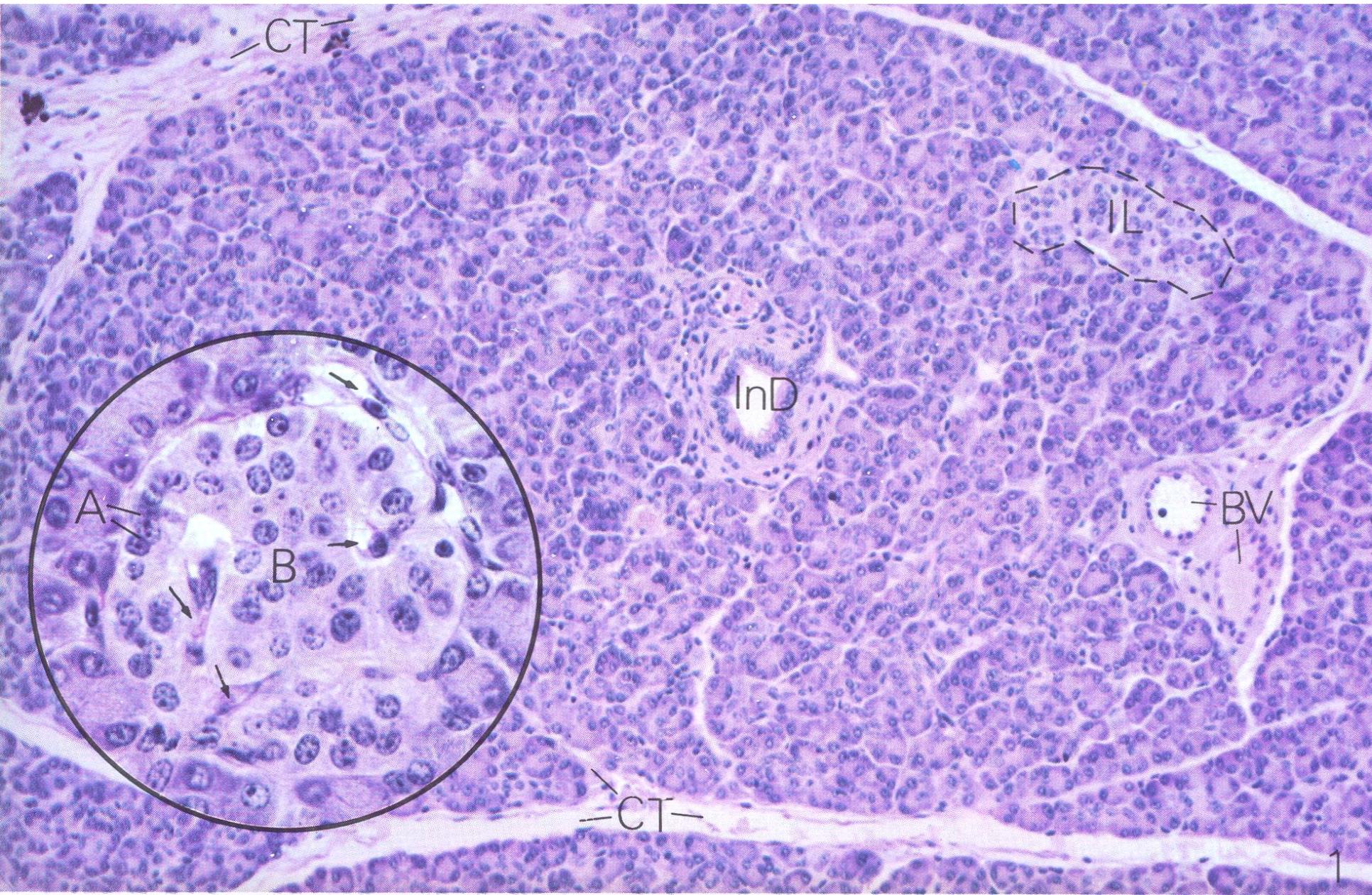
D cells: minor, somatostatin

PP cells: minor, pancreatic polypeptide



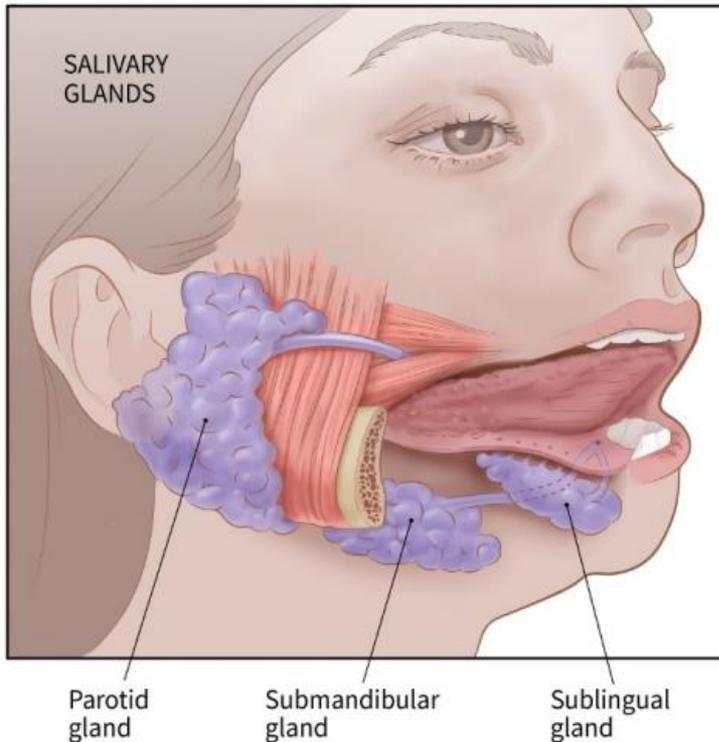


# PANCREAS – ISLETS OF LANGERHANS

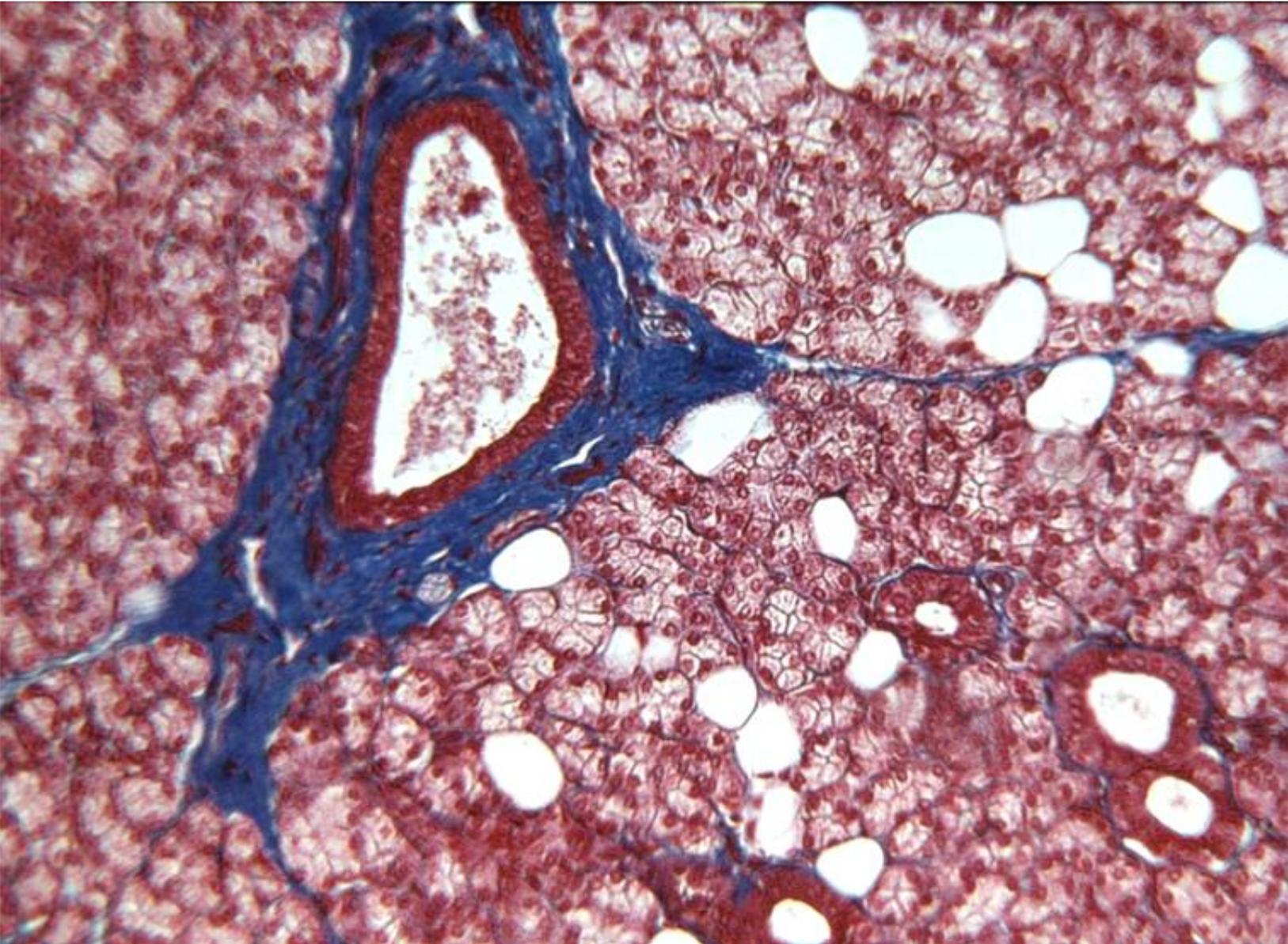


# SALIVARY GLANDS

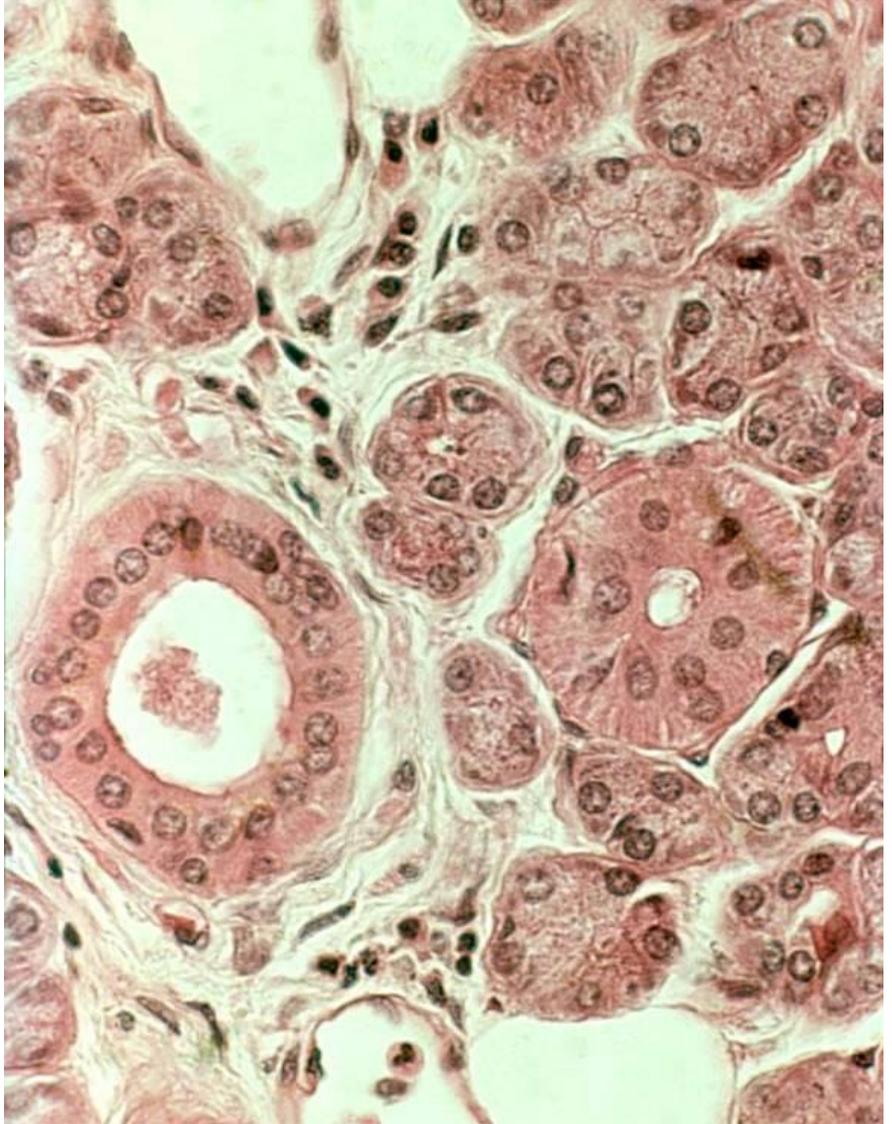
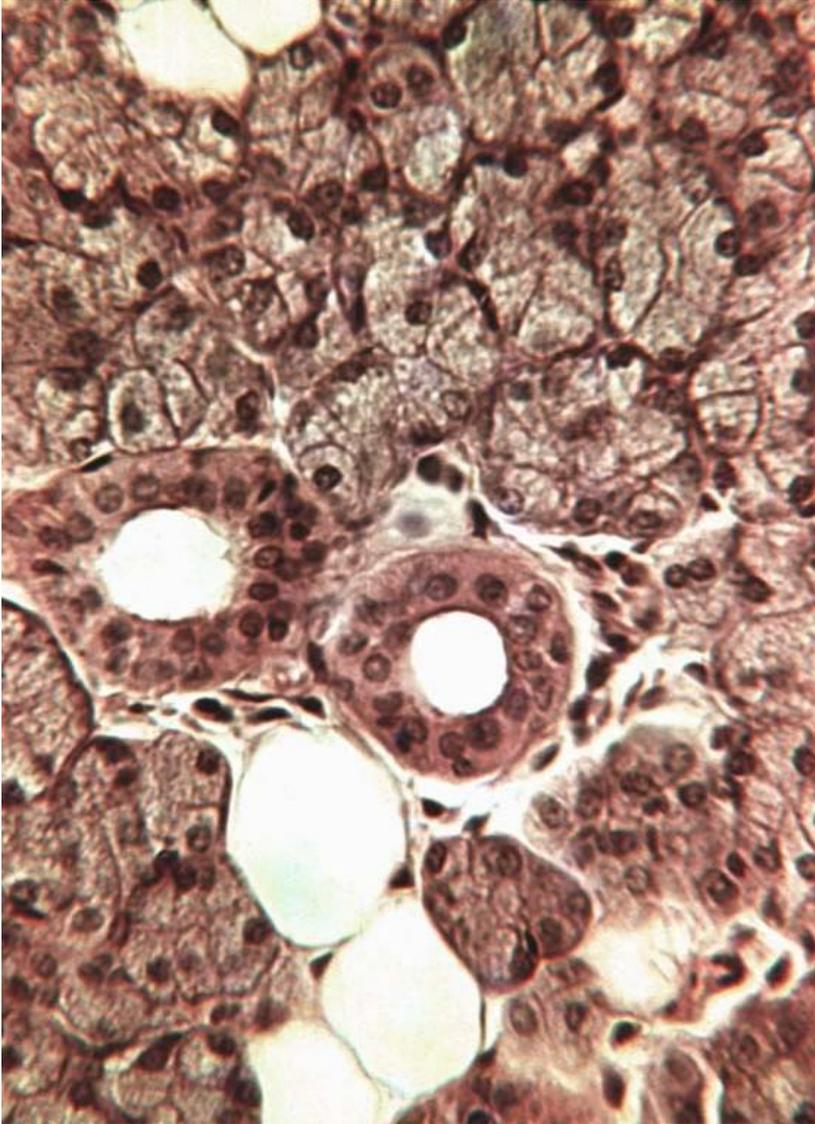
- **small** (gl. labiales, buccales, retromolares, palatinae, gl. lingualis anterior, gl. Ebneri, gl. Weberi)
- **large** (gl. parotis, gl. submandibularis, gl. sublingualis)



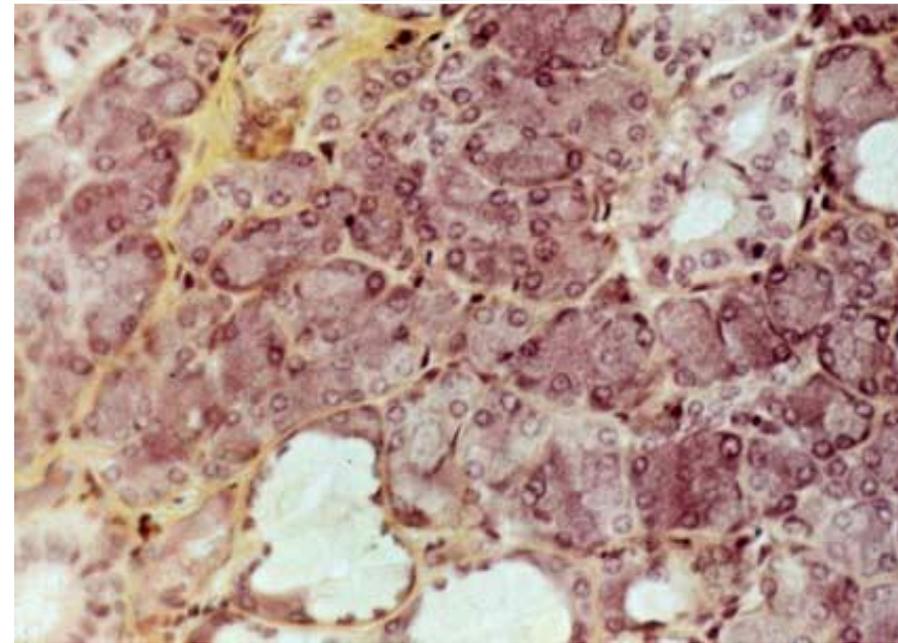
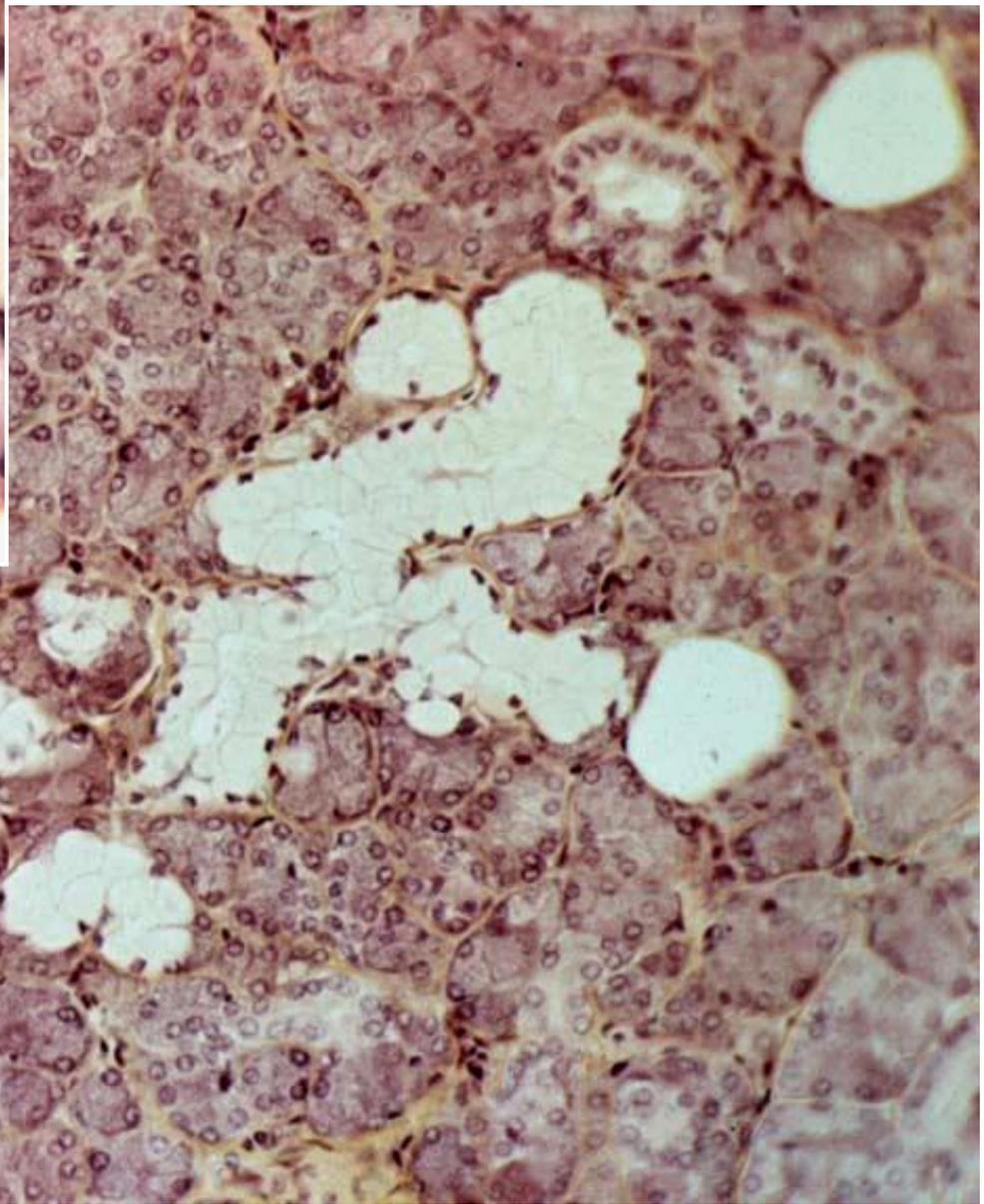
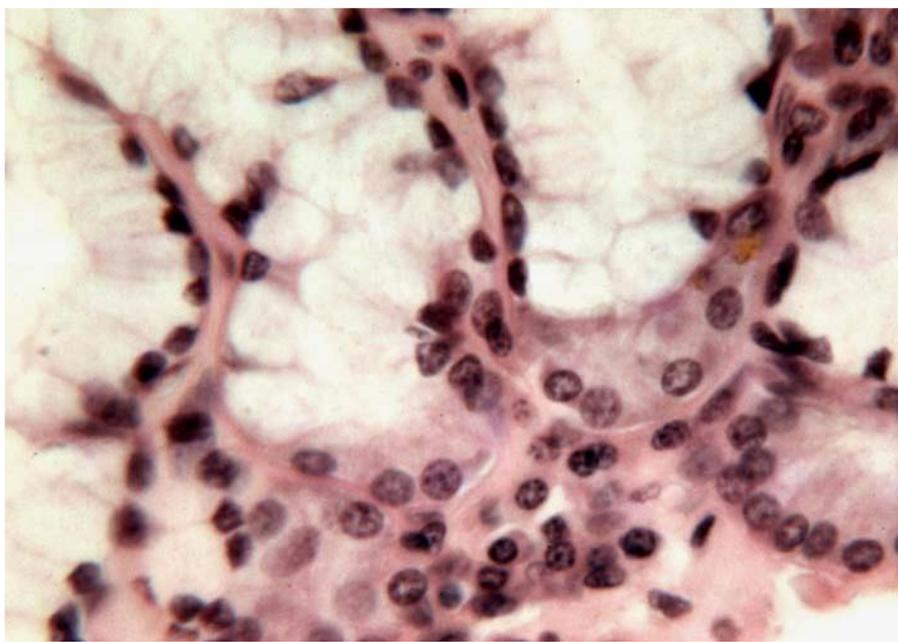
# SALIVARY GLANDS – GL. PAROTIS



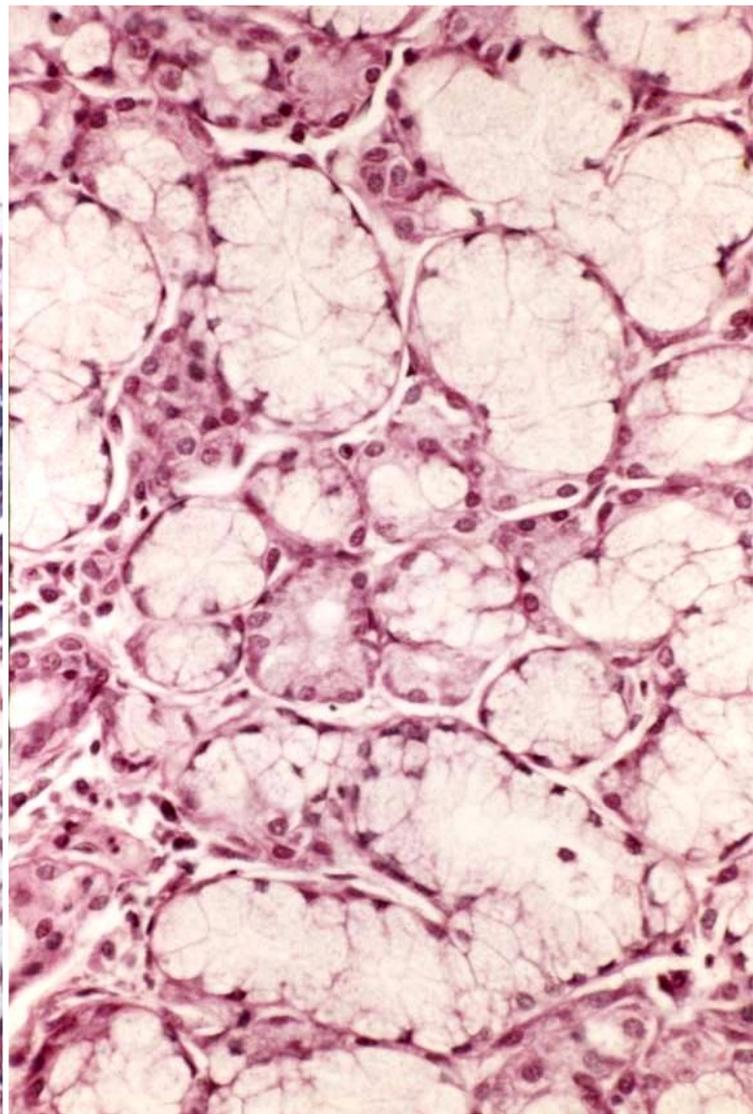
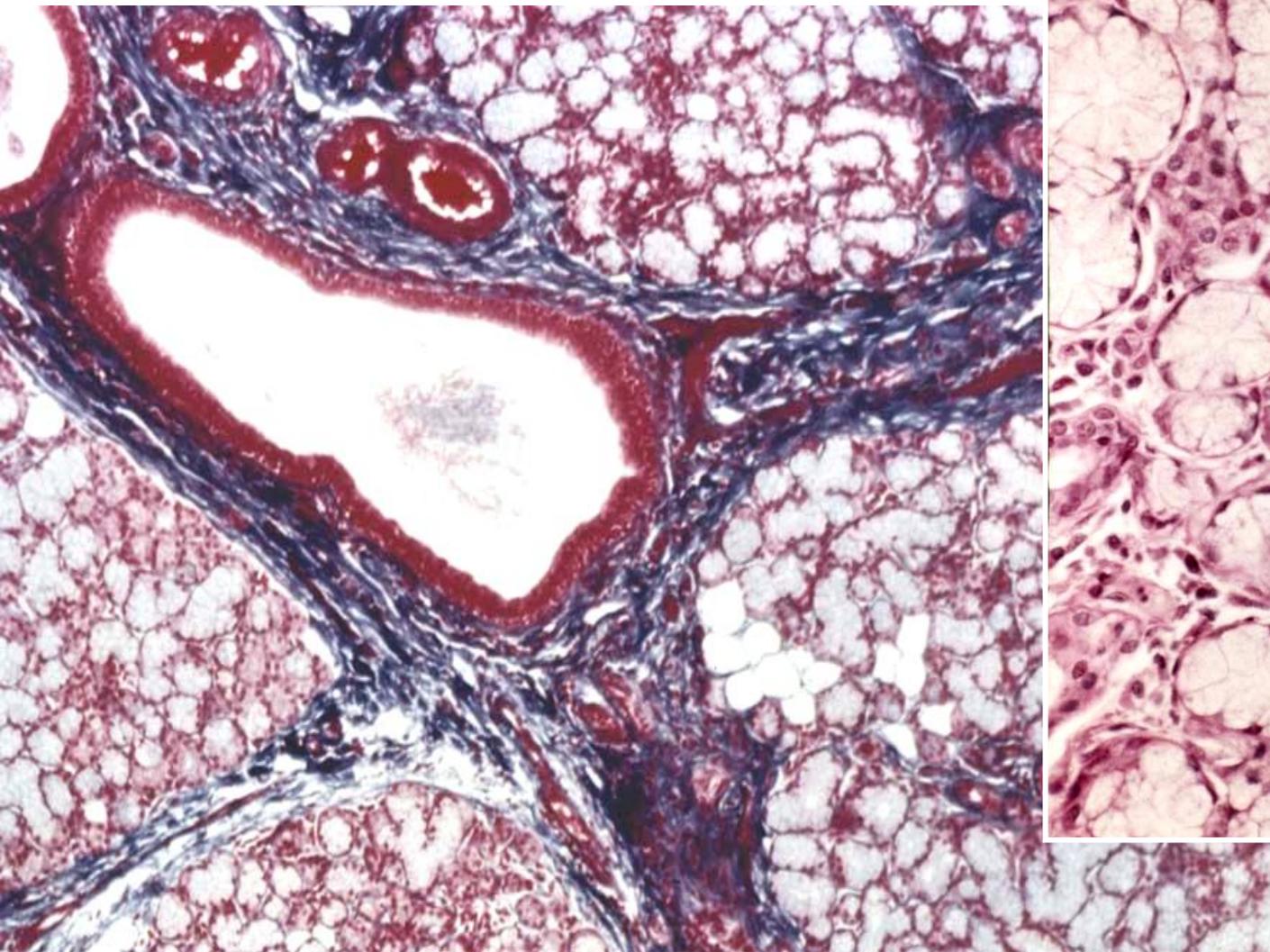
# SALIVARY GLANDS – GL. PAROTIS



# SALIVARY GLANDS – GL. SUBMANDIBULARIS



# SALIVARY GLANDS – GL. SUBLINGUALIS



# DEVELOPMENT OF LIVER, PANCREAS AND LARGE SALIVARY GLANDS

# PRIMITIVE GUT

since 4th week

- oropharyngeal membrane (stomodeum-foregut)
- cloacal membrane (hind gut-proctodeum)

## Foregut

- primitive pharynx (→ and its derivatives)
- lower respiratory passages (→ laryngotracheal div.)
- **liver and bile passages** (→ hepatic div.)
- **pancreas** (→ pancreatic div.)

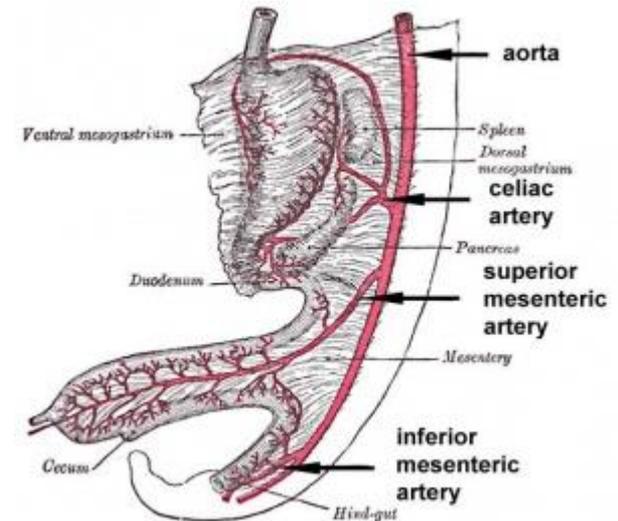
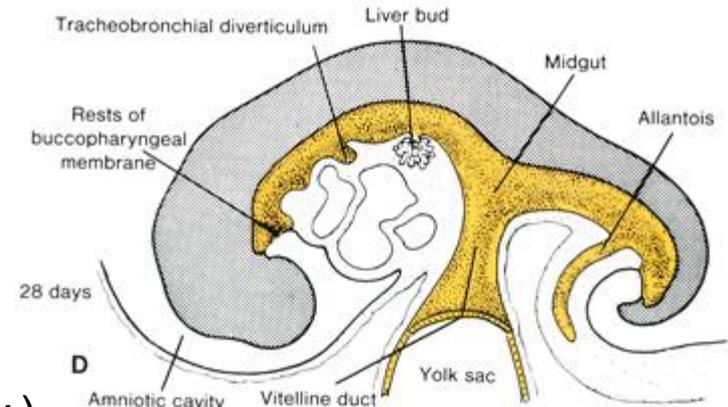
- oesophagus and stomach
- proximal duodenum

## Midgut

- distal duodenum, ileum, jejunum
- caecum, appendix, colon ascendens, colon transversum (1/2-2/3)

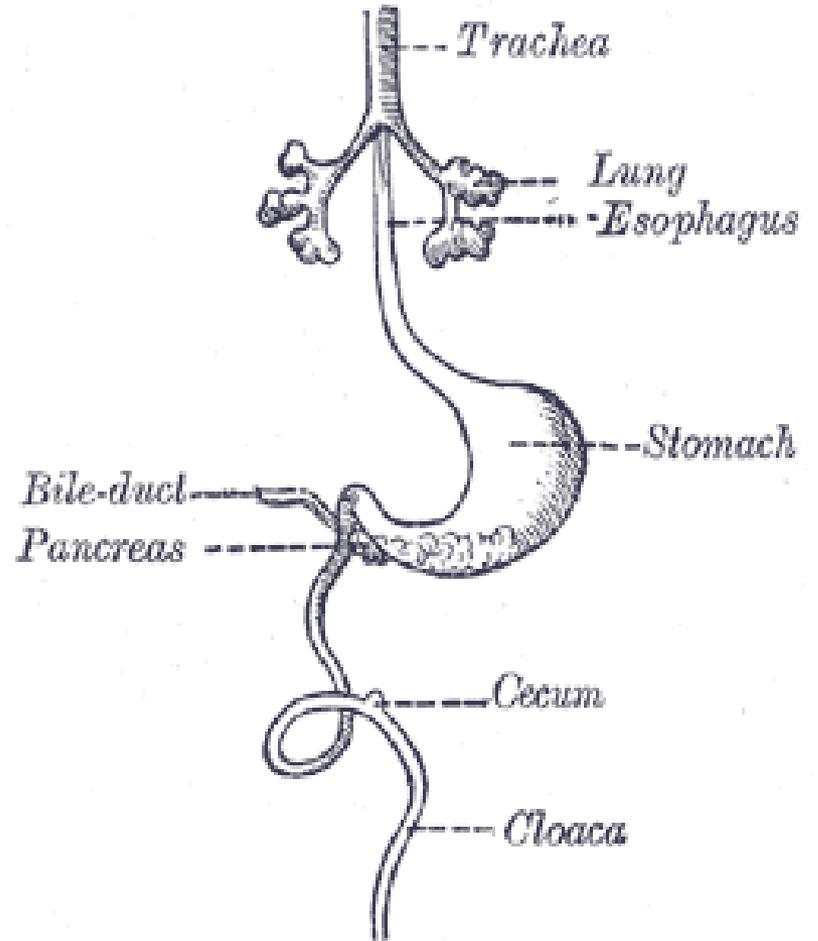
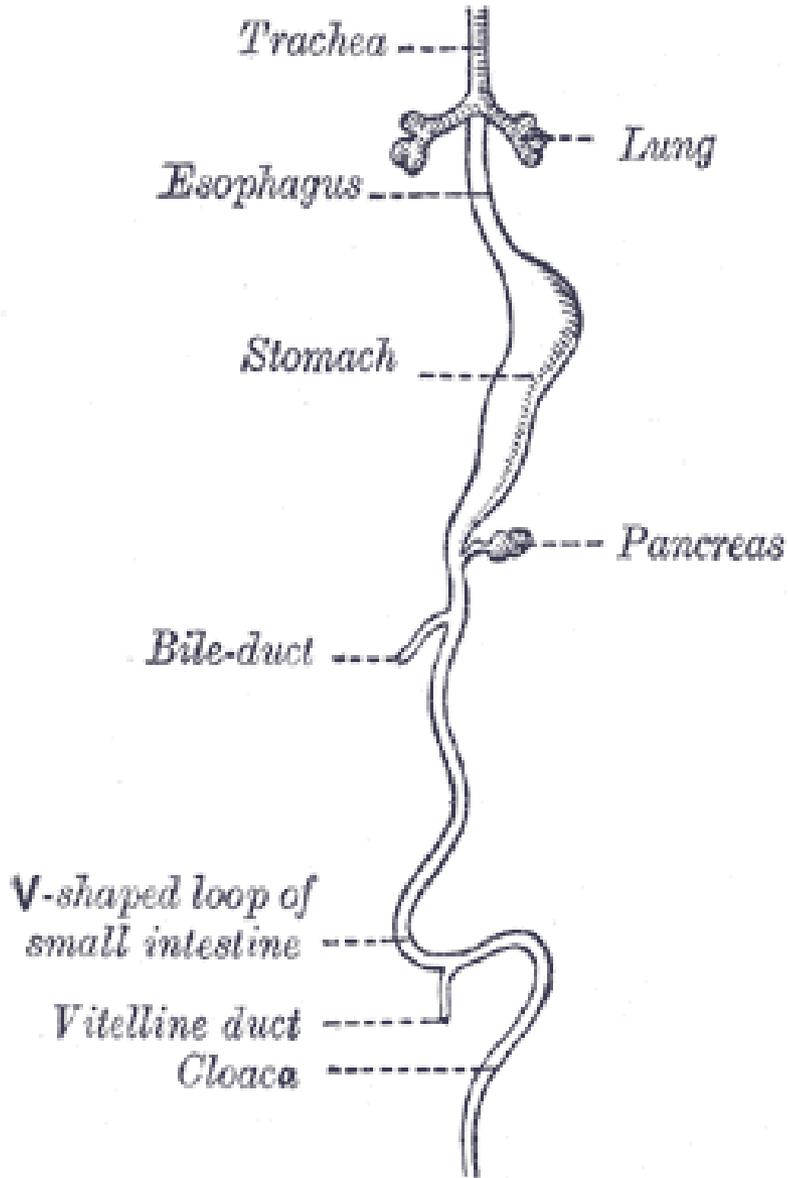
## Hindgut

- colon transversum (1/3-1/2), colon descendens, colon sigmoideum
- rectum, anal canal
- part of urinary system (derivatives of sinus urogenitalis)





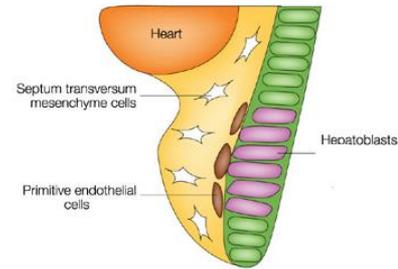
# DEVELOPMENT OF DIGESTIVE TUBE



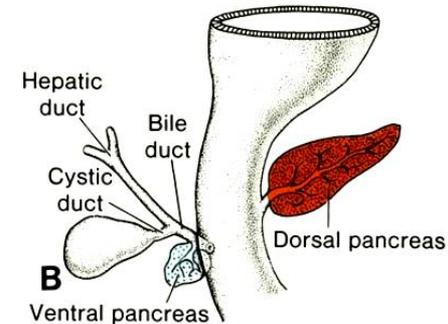
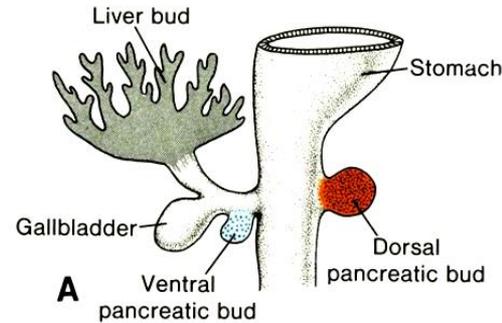
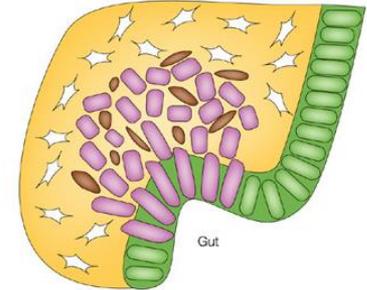
# EMBRYONIC DEVELOPMENT OF LIVER

- Diverticulum of embryonic duodenum - **liver diverticulum**
- **Pars hepatica** (parenchyma + ductus hepaticus) and **pars cystica** (ductus cysticus + gall bladder) form d. choledochus
- Rapidly proliferating cells penetrate septum transversum (mesodermal plate between pericardial cavity and yolk sac) and growth into ventral mesentery
- liver cords – parenchyma
- Interactions between cells of liver cords and vv. omphalomesentericae induce development **liver sinusoids**
- C.t. , Kupffer and hematopoietic cells – from mesoderm of septum transversum
- Surface mesoderm differentiate into visceral peritoneum

a Post-specification  
11-13-somite stage

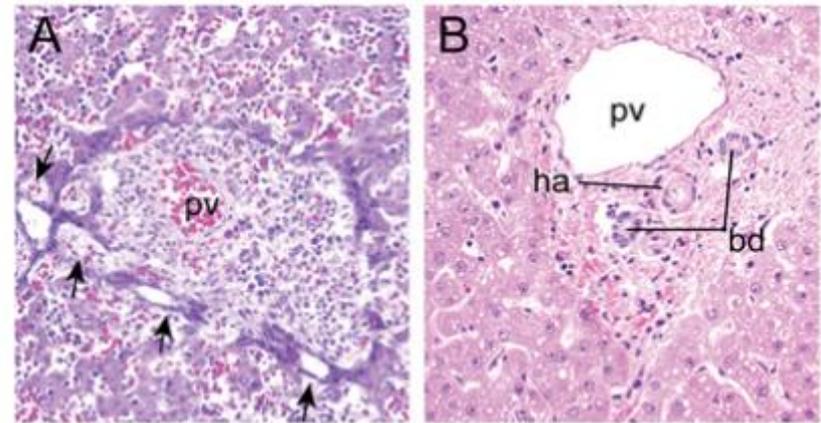
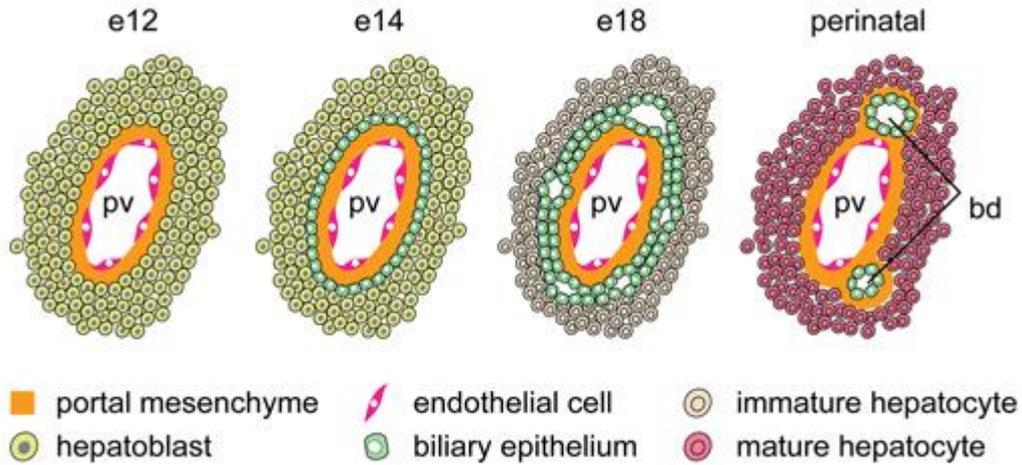


b Liver-bud stage  
18-25-somite stage



- 10th week
  - 10% of body volume
  - hematopoiesis
- 12th week
  - bile production

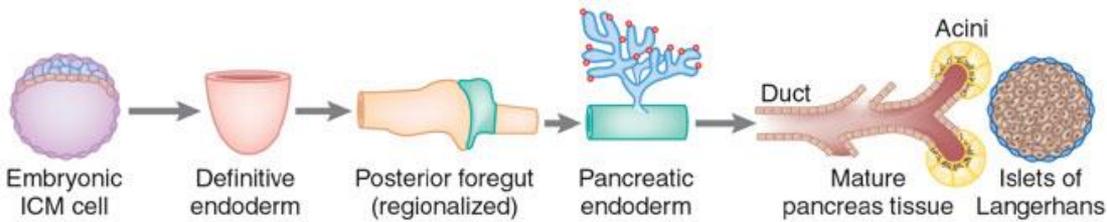
# EMBRYONIC DEVELOPMENT OF LIVER



fetal liver

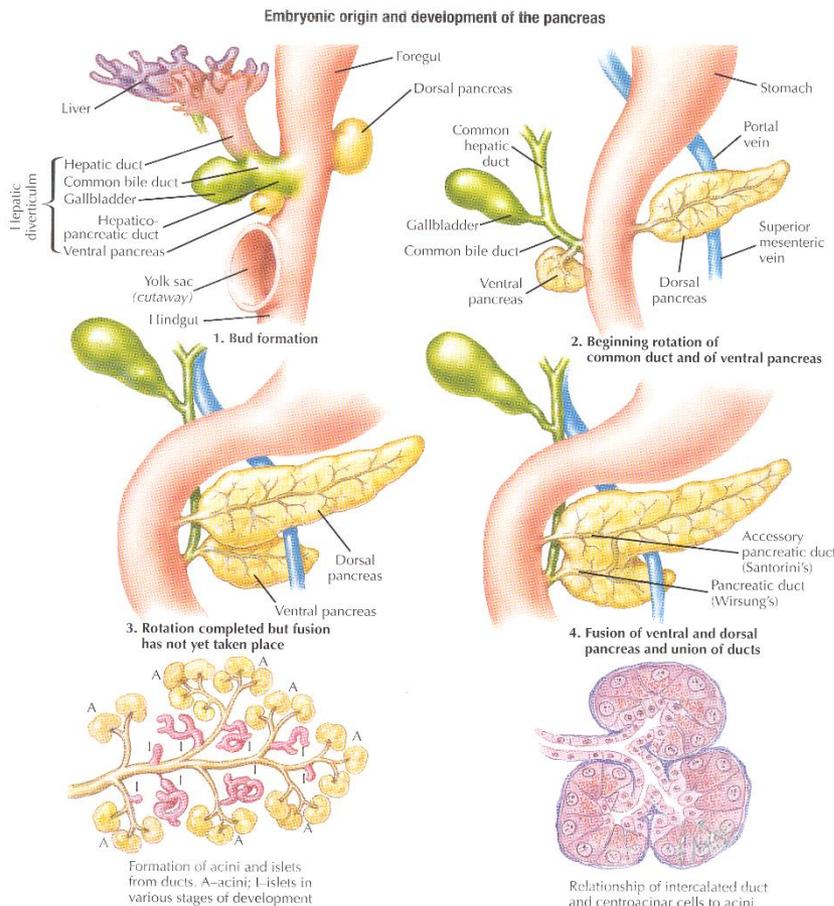
adult liver

# EMBRYONIC DEVELOPMENT OF PANCREAS



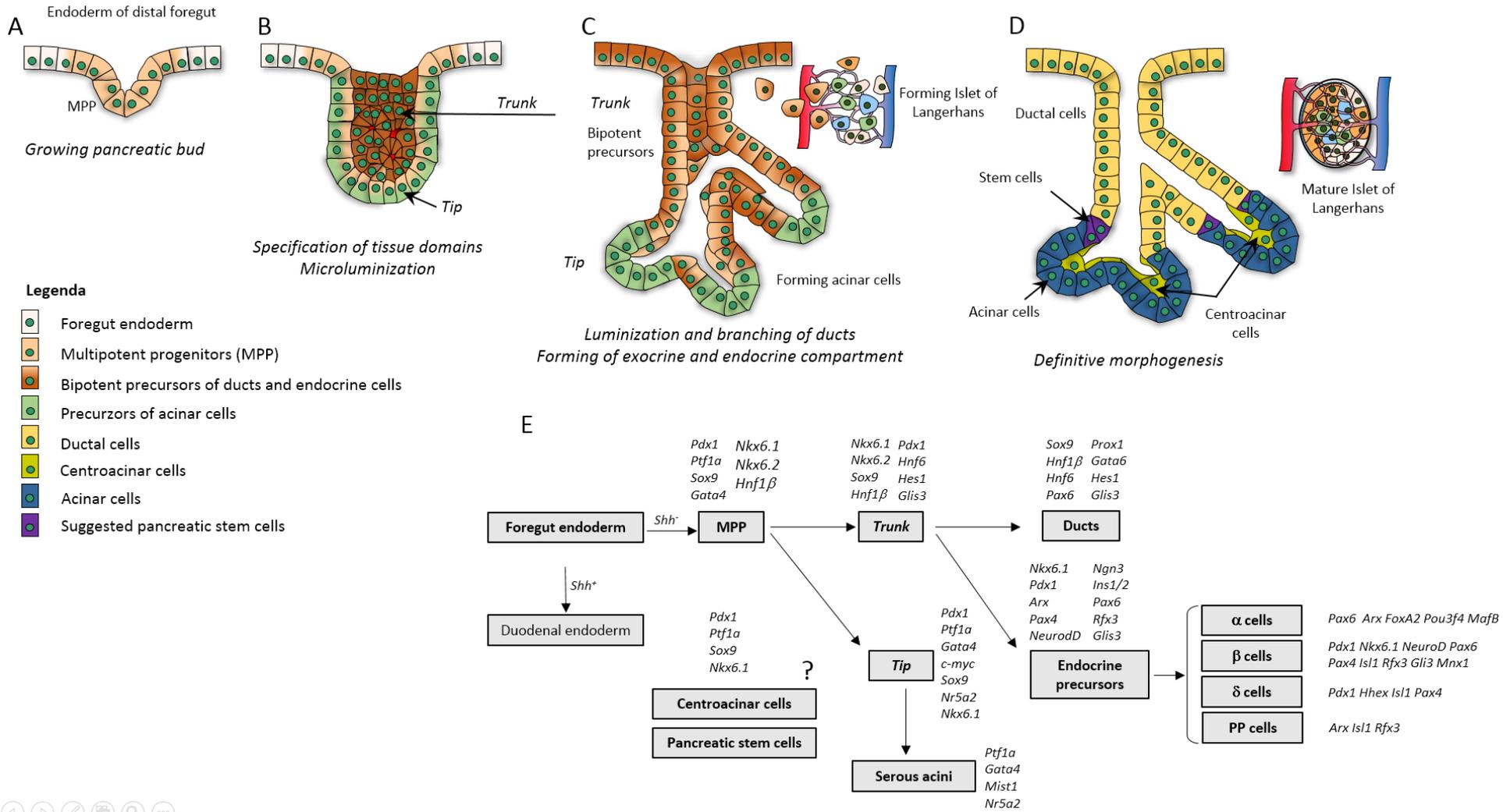
|-5th week of development: two endodermal diverticles

- dorsal and ventral duodenal diverticle (= pancreas dorsale et ventrale)



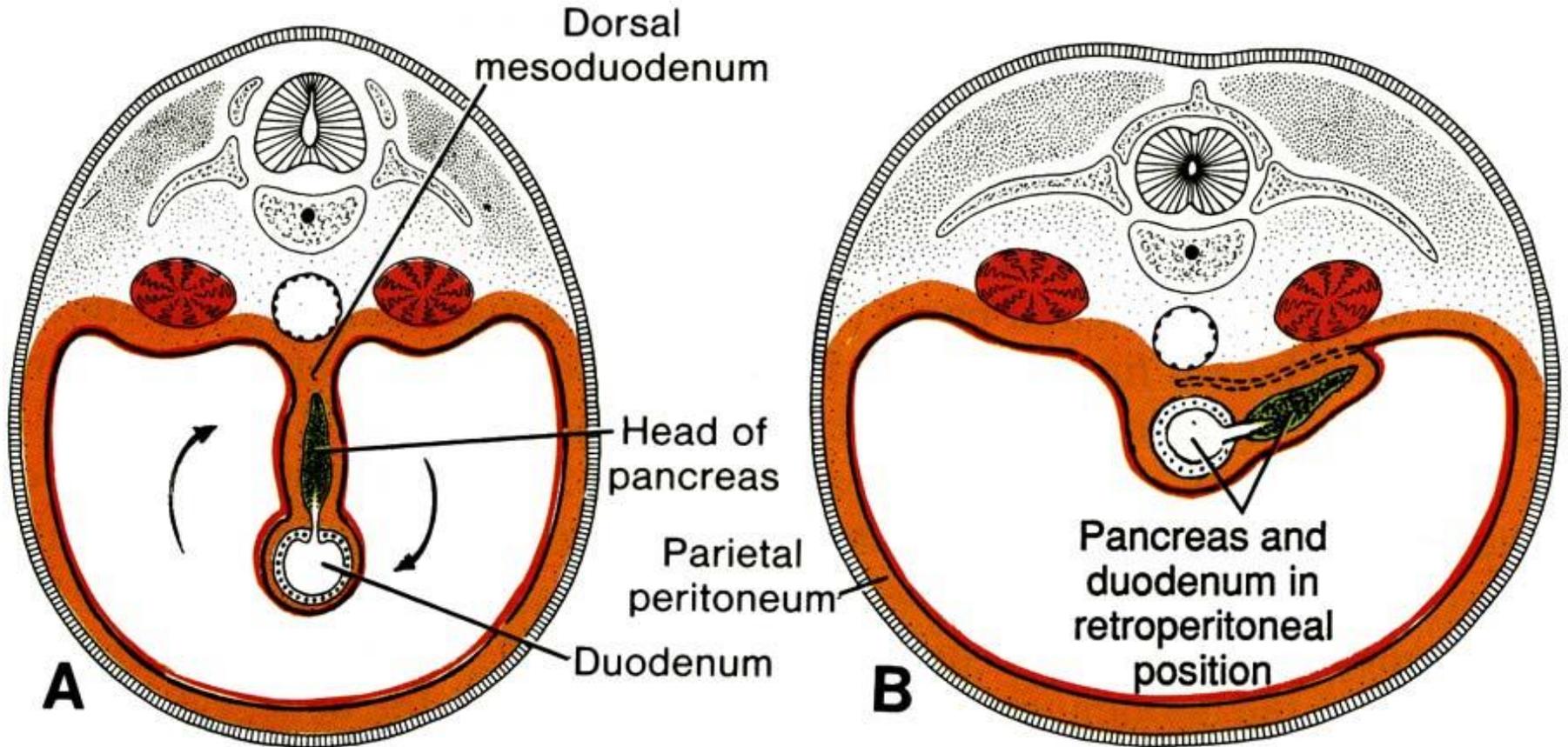
- after rotation of duodenal loop both diverticula fuse
- development of ducts:
  - ventral duct fuses with dorsal duct and divides it to proximal and distal part
  - proximal part of dorsal duct obliterates
  - ventral duct and distal part of dorsal duct form ductus pancreaticus major
  - if the proximal part of dorsal part persists, it will form ductus pancreaticus accessorius
- ductal system develops first, secretory acini follow
- cells that are not part of ductal structures differentiate into Islets of Langerhans
- since 4th month in utero - secretory activity

# HISTOGENESIS OF PANCREAS



# ANATOMIC LOCALIZATION OF PANCREAS

- Pancreas is secondary retroperitoneal



# DEVELOPMENT OF LARGE SALIVARY GLANDS

## **Gl. parotis**

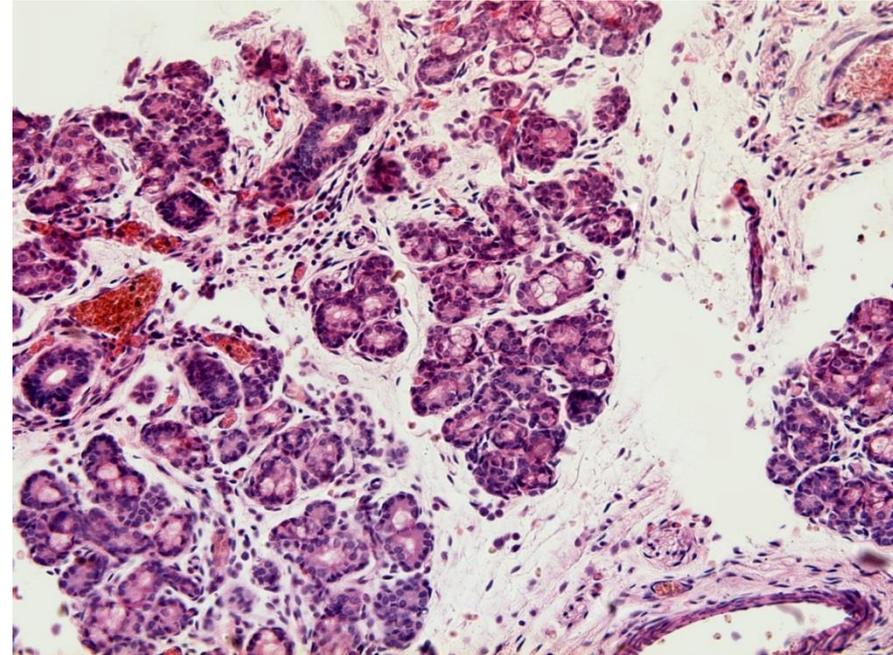
- develops first (6<sup>th</sup> week)
- ectodermal buds from corners of stomodeum
- proliferation and branching of solid cords
- luminization and development of acini (10<sup>th</sup> week)
- vaso - mesenchym

## **Gl. submandibularis**

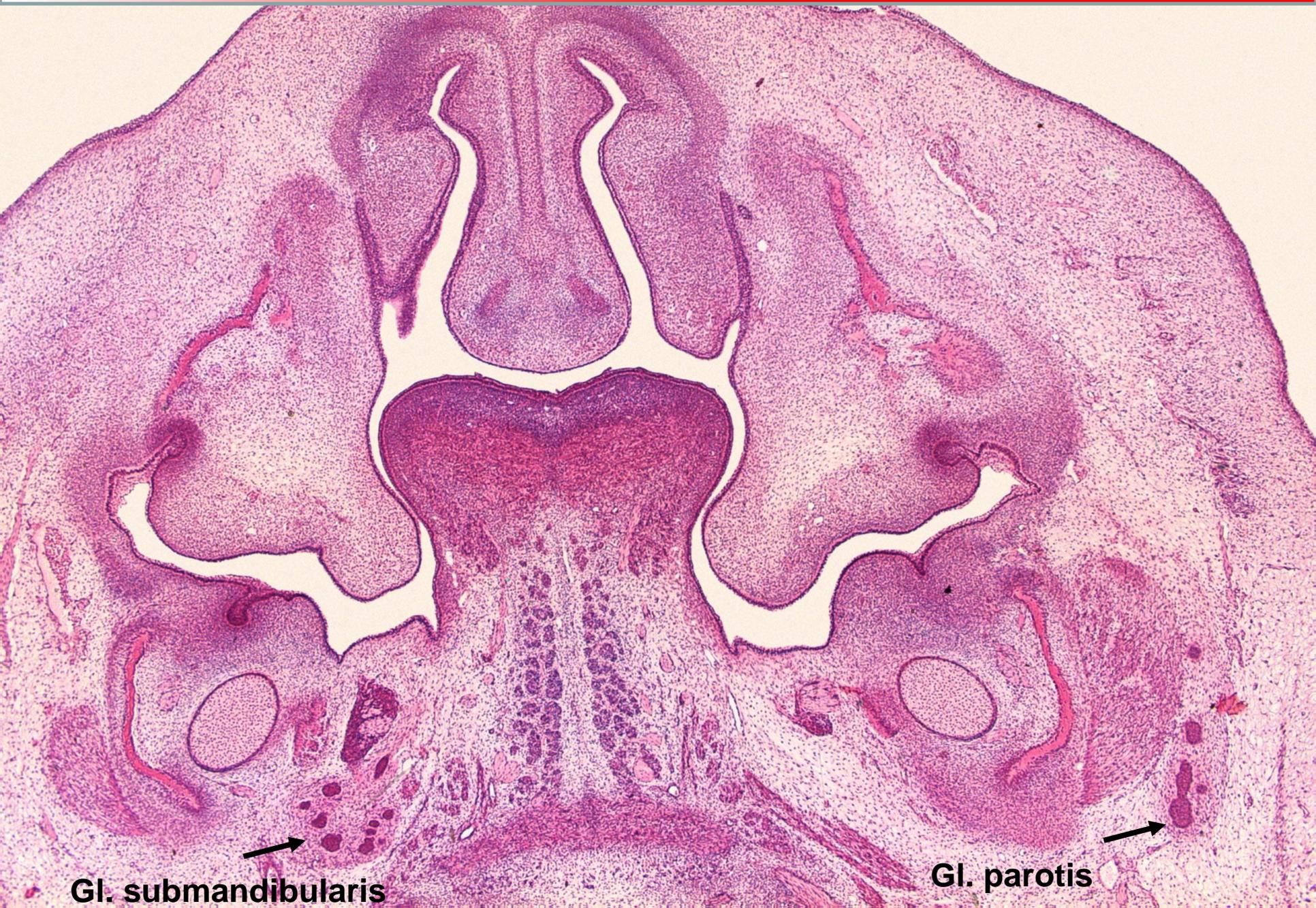
- end of 6<sup>th</sup> week
- endodermal buds from floor of stomodeum
- proliferation and branching of solid cords together with tongue development
- luminization and development of acini (12<sup>th</sup> week)
- connective tissue– mesenchym
- growths even post natally

## **Gl. sublingualis**

- 8<sup>th</sup> week
- multiple endodermal buds in paralingual groove
- proliferation and branching of solid cords
- luminization and development of glandular parenchyma
- connective tissue – mesenchym
- 10-12 independent ducts



# DEVELOPMENT OF LARGE SALIVARY GLANDS

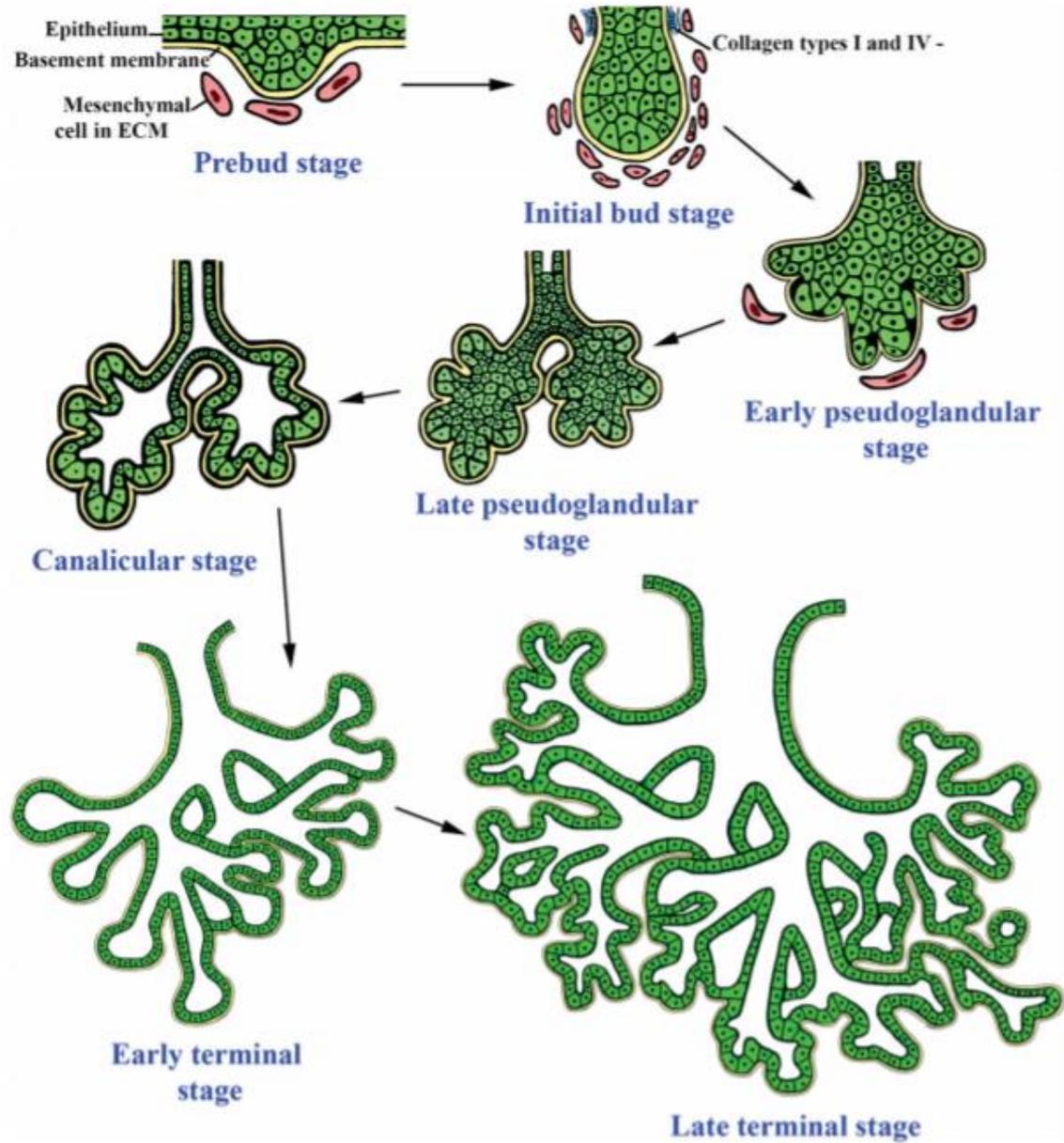


**Gl. submandibularis**

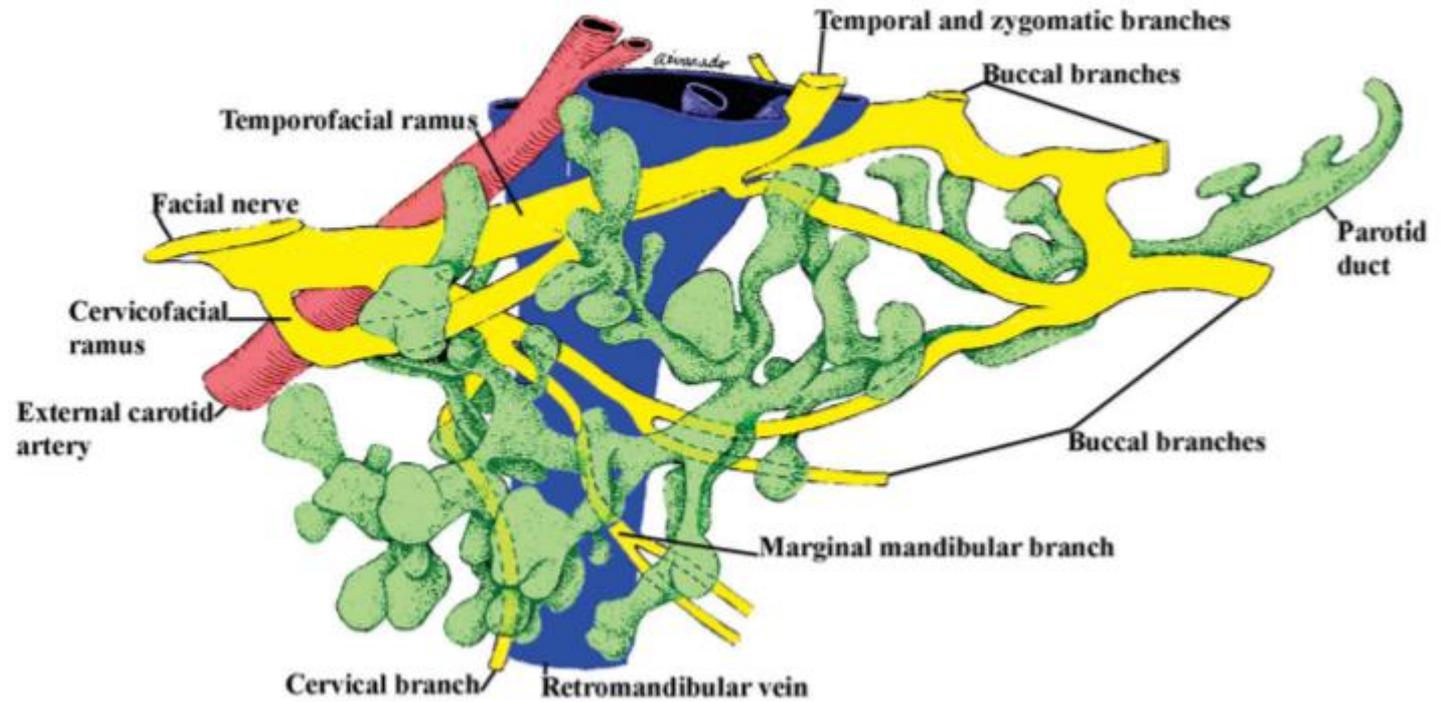
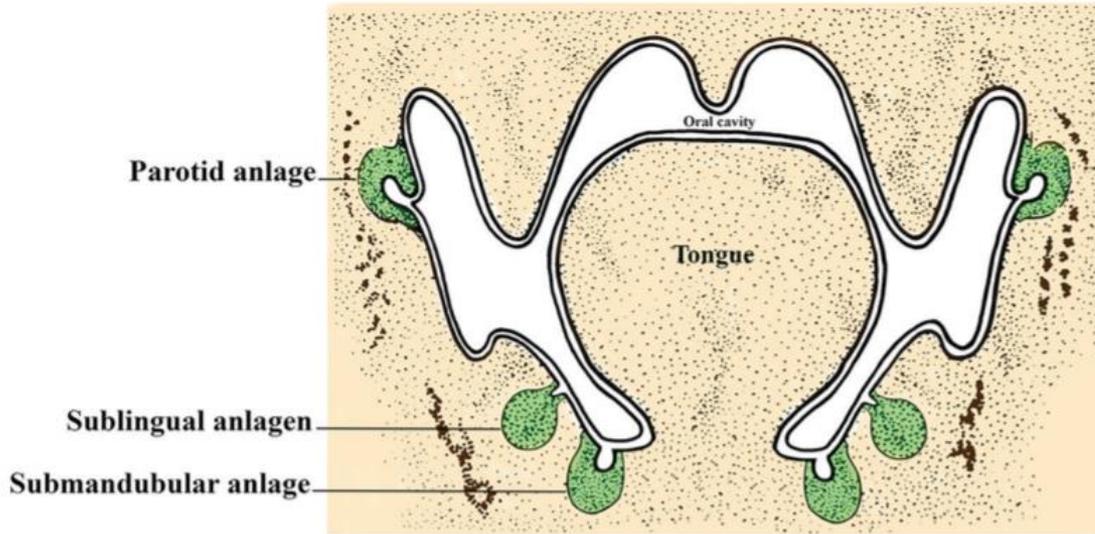
**Gl. parotis**



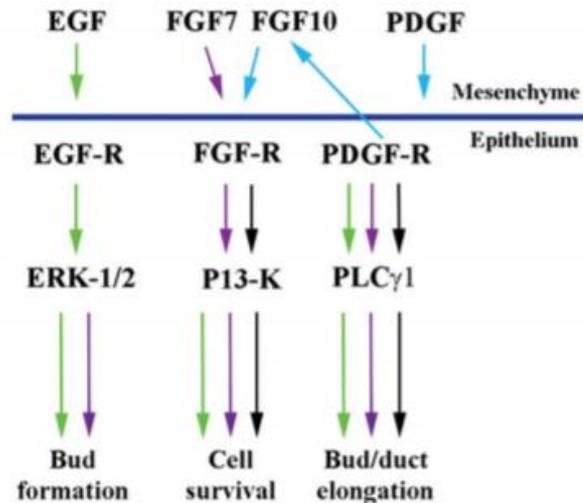
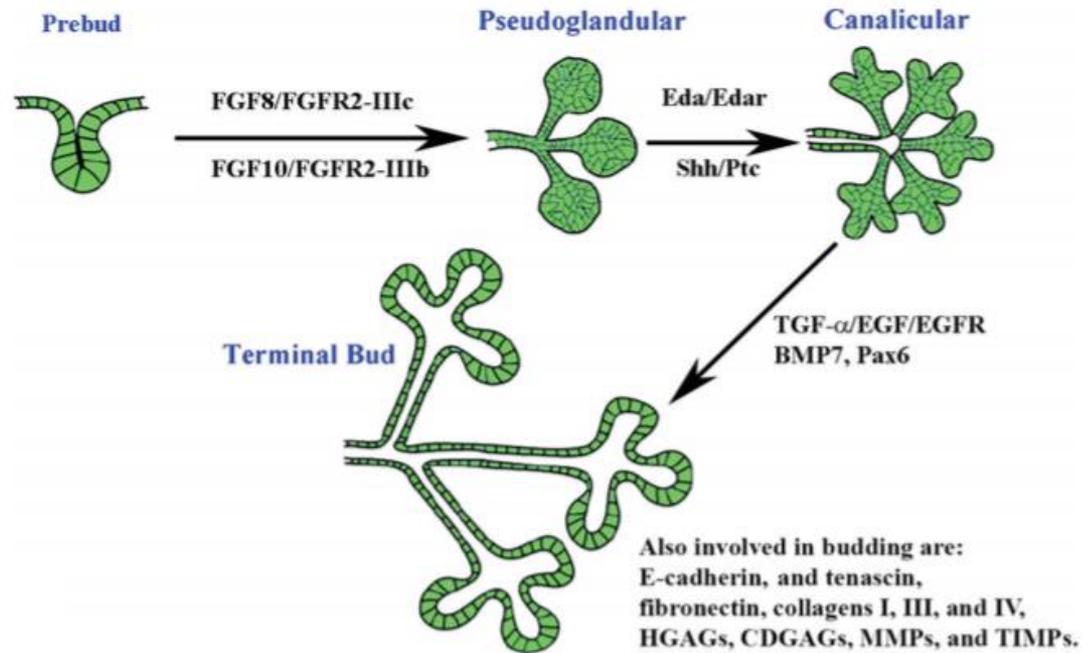
# DEVELOPMENT OF LARGE SALIVARY GLANDS



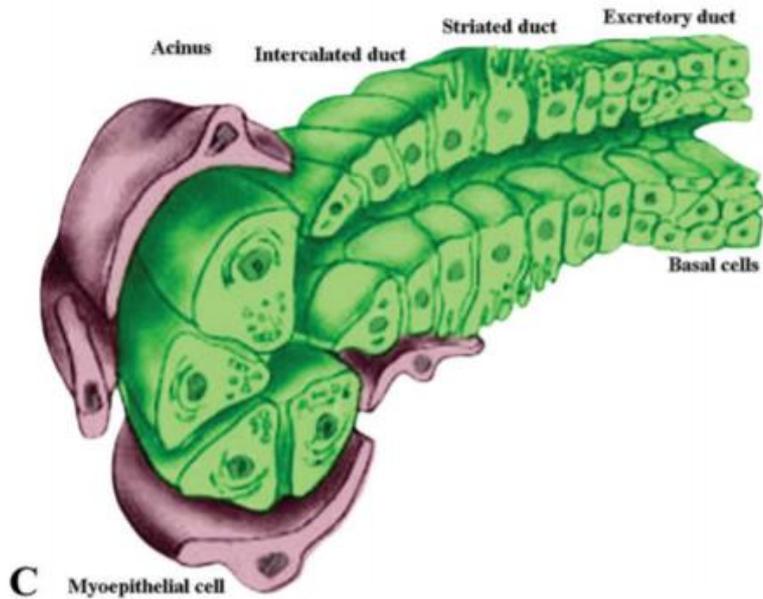
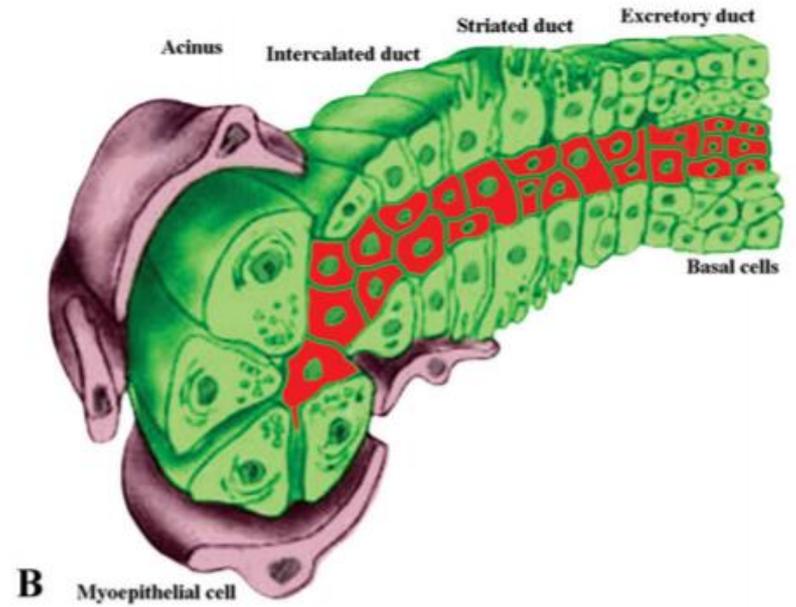
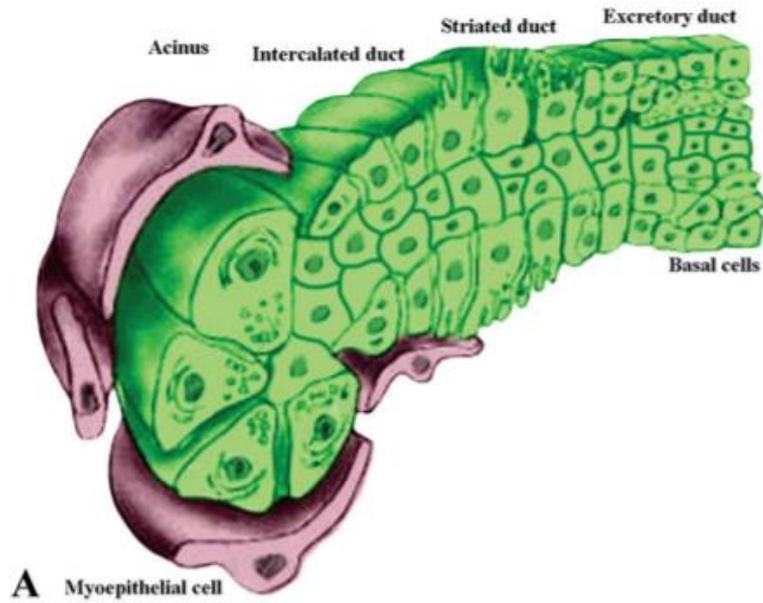
# DEVELOPMENT OF LARGE SALIVARY GLANDS



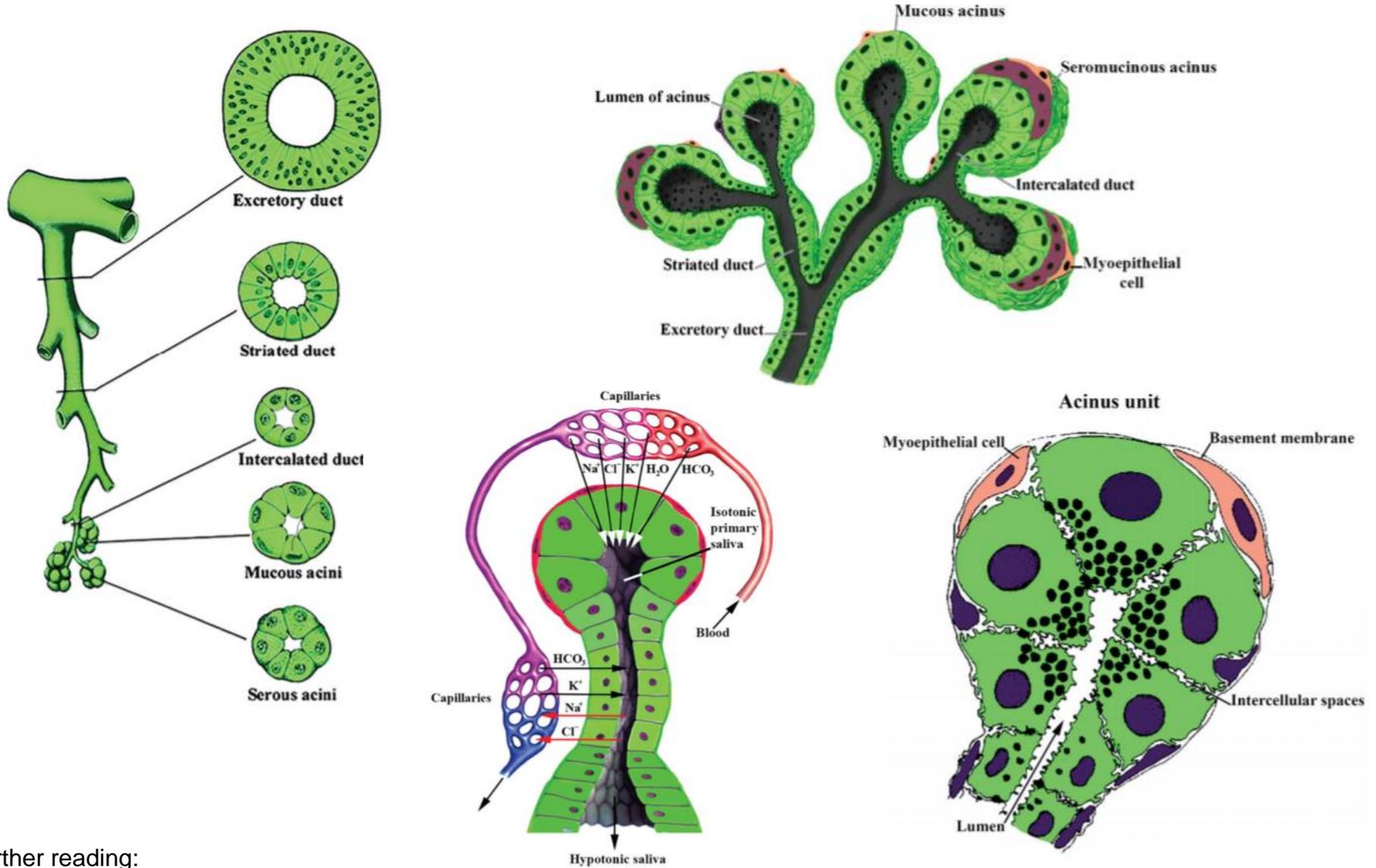
# DEVELOPMENT OF LARGE SALIVARY GLANDS



# DEVELOPMENT OF LARGE SALIVARY GLANDS



# DEVELOPMENT OF LARGE SALIVARY GLANDS



Further reading:

**The Embryology of the Salivary Glands: An Update**

P.M. Som and I. Miletich

Neurographics 2015 July/August; 5(4):167–177; [www.neurographics.org](http://www.neurographics.org)

# Thank you for attention

**Question? Comments?**

[pvanhara@med.muni.cz](mailto:pvanhara@med.muni.cz)

<http://www.histology.med.muni.cz>