

## Digestive system

1. Microscopic anatomy of esophagus, stomach, small and large intestine
2. **Microscopic anatomy of pancreas, liver, overview of GIT embryology**



1. Microscopic anatomy of liver and bile ducts

- Macro – a microscopic anatomy
- Definition and structure of liver lobulus
- Hepatocytes and other liver cells
- Intra- a extrahepatic bile ducts
- Gall bladder

2. Microscopic anatomy of pancreas

- Pancreatic acini and ducts
- Islets of Langerhans

3. Embryonic development of digestive system, liver and pancreas

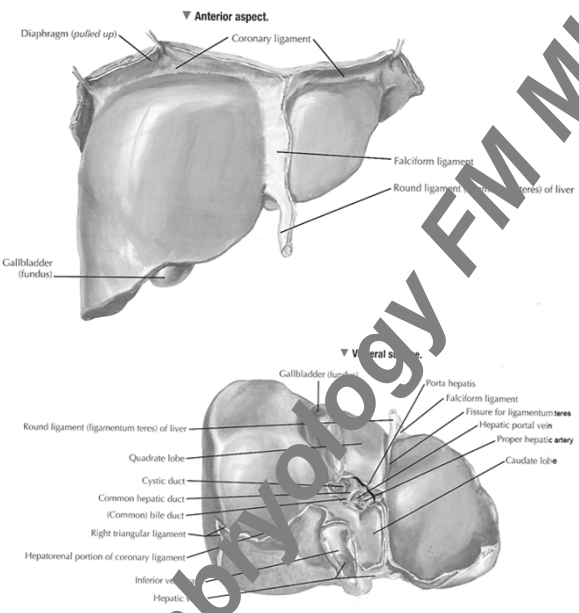
- Primitive gut derivatives
- Changes in morphology and localization during development
- Regeneration

## LIVER (HEPAR)

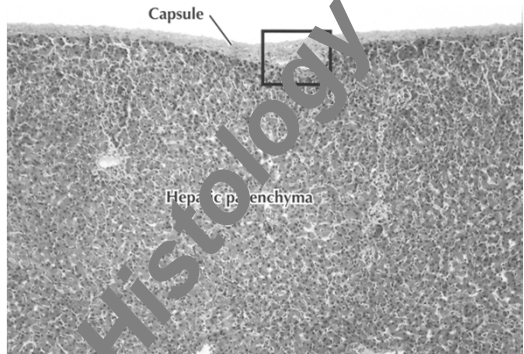
- Liver parenchyma – biggest gland in human body
- C.t. capsule
- Nutritive and functional blood supply
- Endocrine and exocrine function
- Uniform histology of all four major anatomic lobes and segments:

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

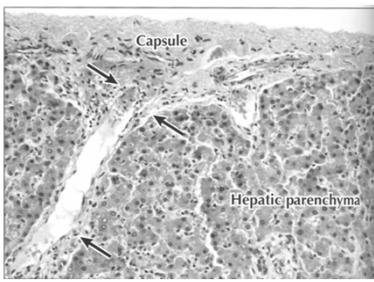
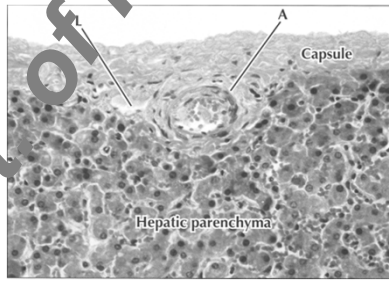
- C.t. capsule
- Serosa



## CAPSULA FIBROSA HEPATIS



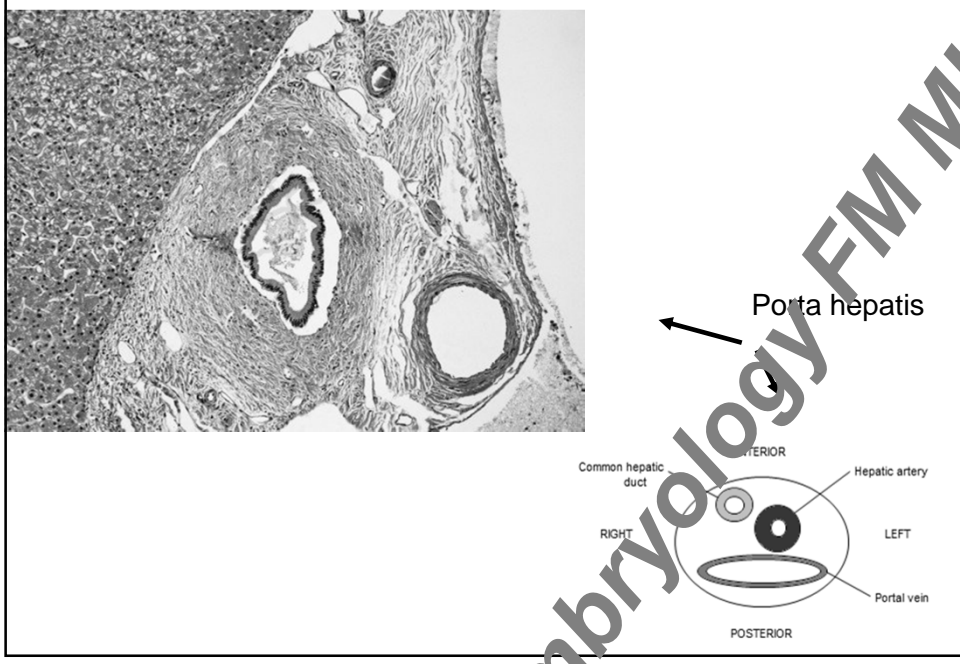
- Serous mesothelium
- C.t. – collagen and elastic fibers
- 70-100µm
- Porta hepatis



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CAPSULA FIBROSA HEPATIS



VASCULARISATION

FUNCTION

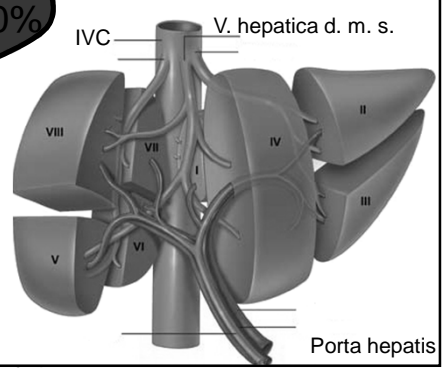
- capillary stream of stomach and intestine
- vena portae
- interlobular veins
- circumlobular venules

NUTRITIVE

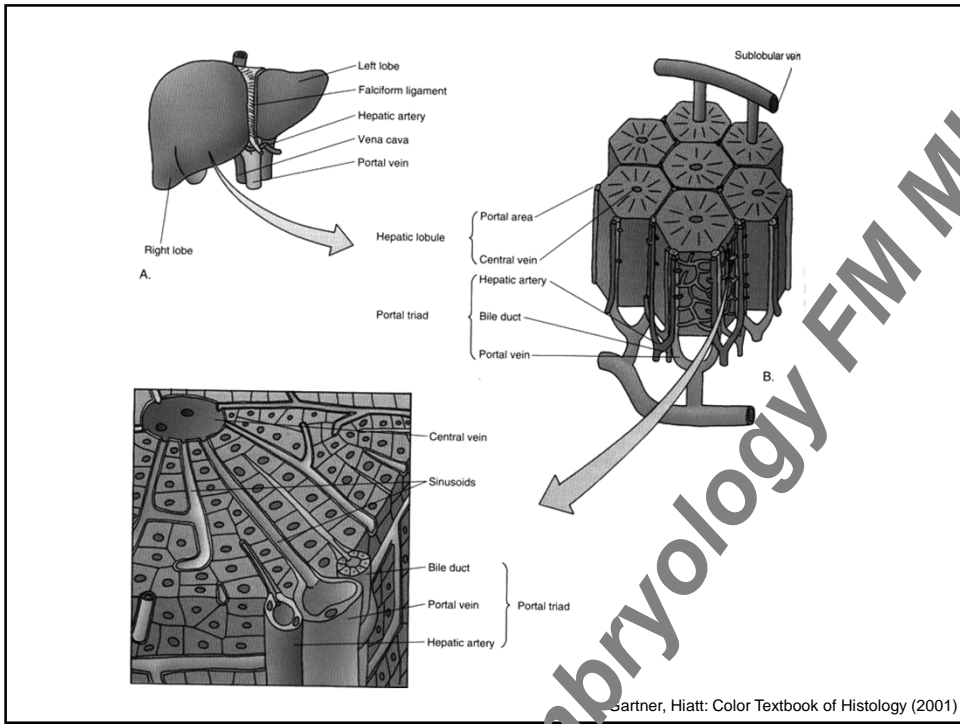
- aorta
- arteria hepatica
- segmental arteries
- interlobular arteries
- circumlobular arteriols



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

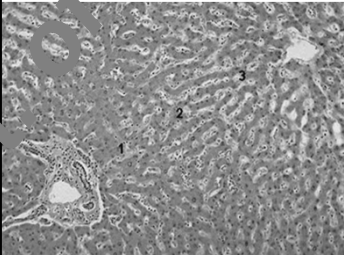
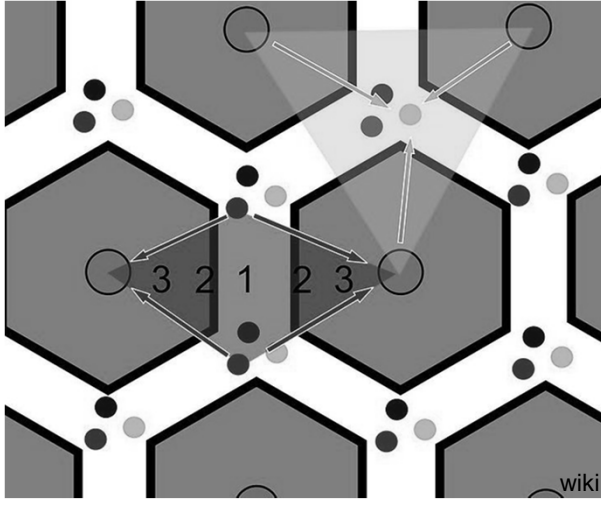


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### MICROSCOPIC SEGMENTATION OF LIVER

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

wiki

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**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	

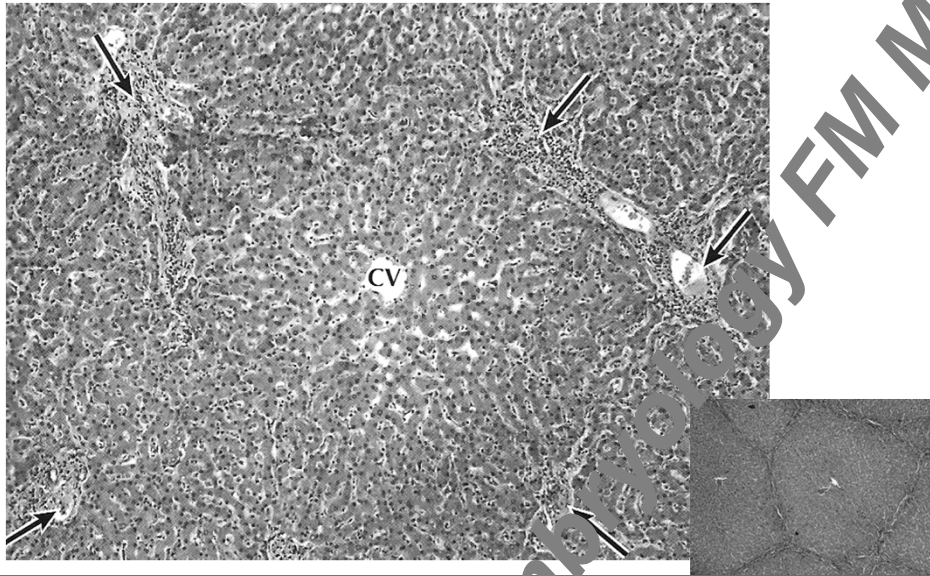
### CENTRAL VEIN LOBULUS Lobulus venae centralis

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

interlobular connective tissue  
Central vein  
hepatocyte cords  
Portal triad in portal tract

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LALCENTRAL VEIN LOBULUS  
Lobulus venae centralis

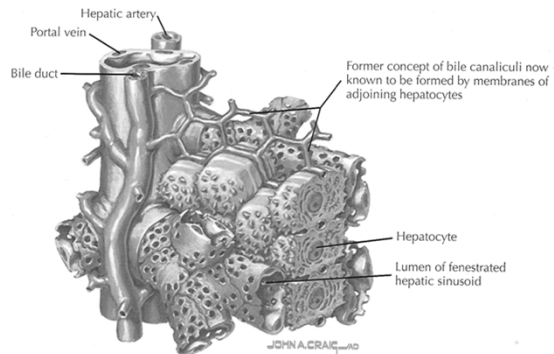


CENTRAL VEIN LOBULUS  
Portal triad

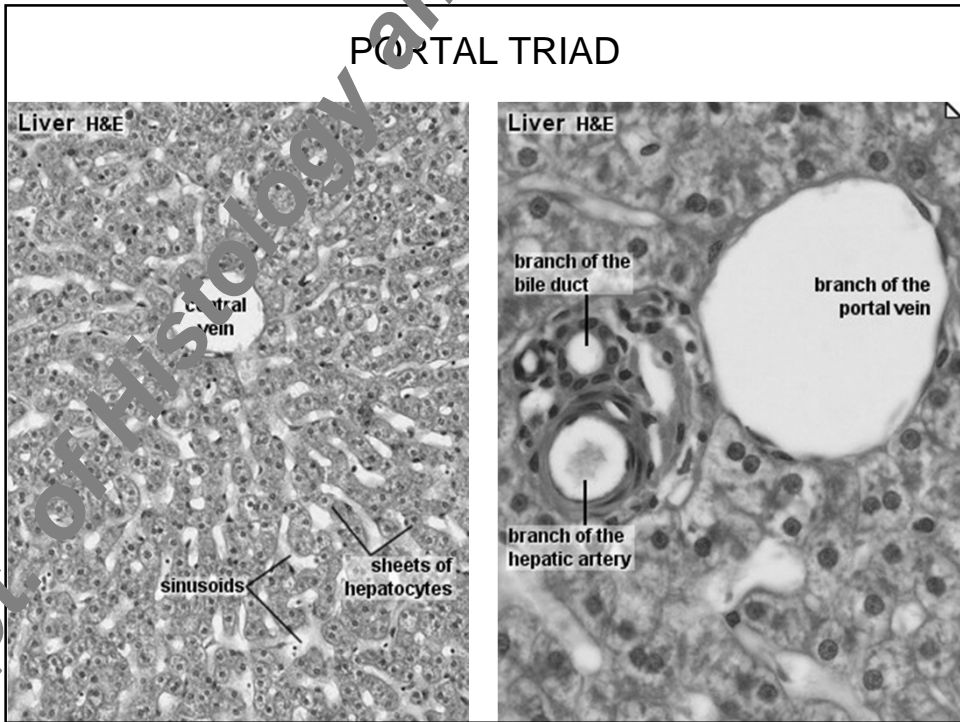
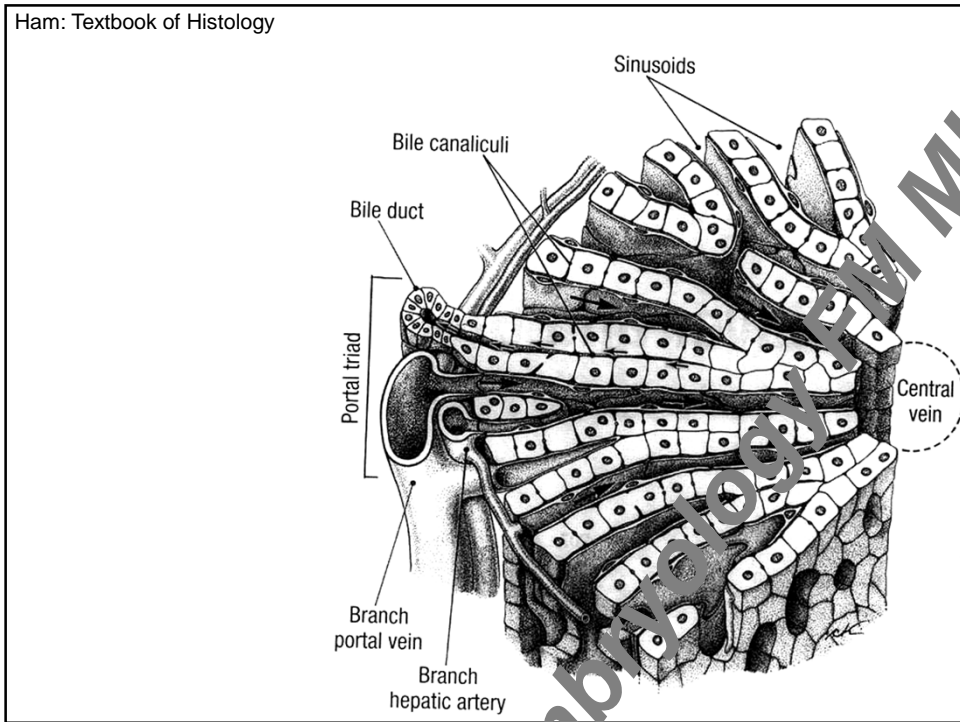
Contact of 3-4 neighboring lobules

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

Loose interstitial c.t.

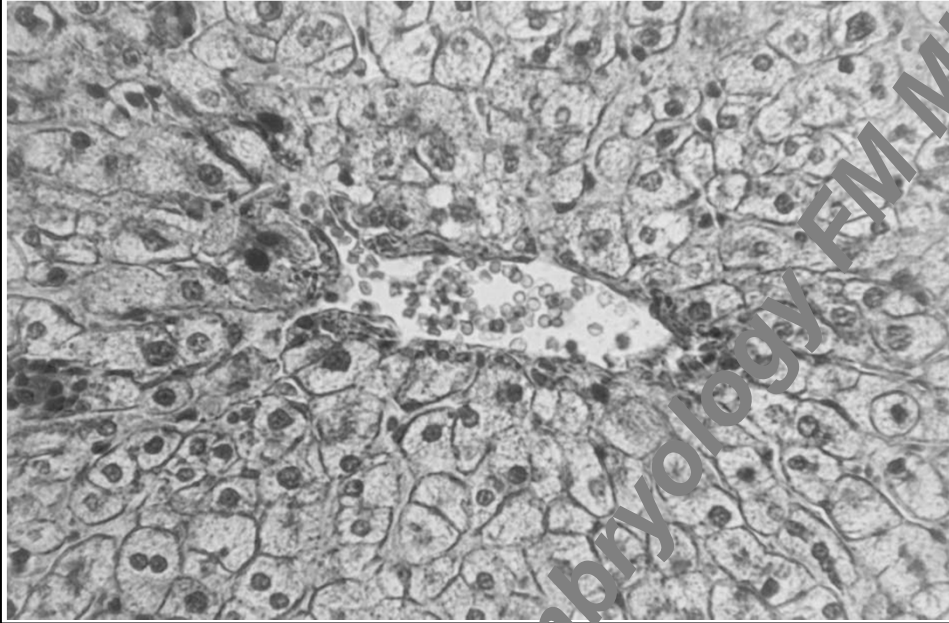


▲ Parts of hepatic lobule at portal triad (high magnification).

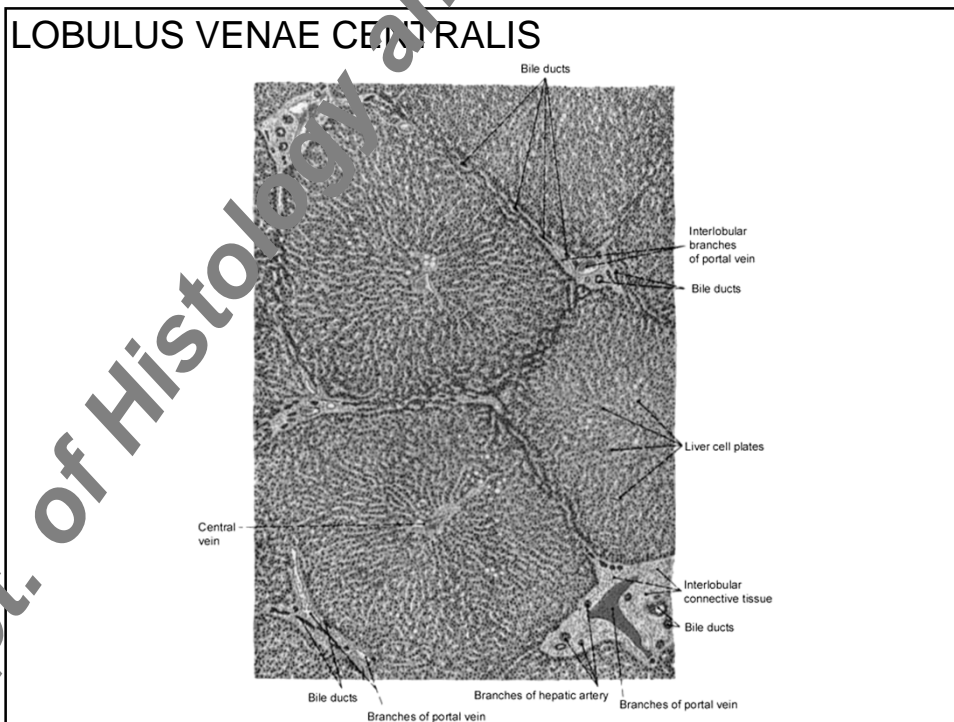


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### CENTRAL VEIN



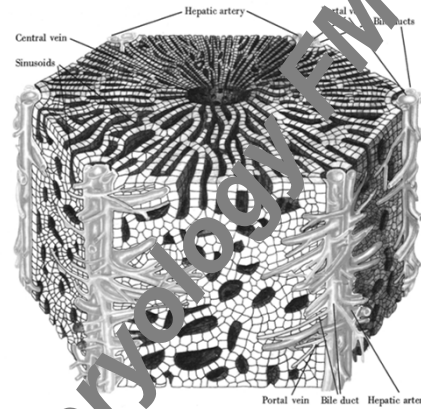
### LOBULUS VENAE CENTRALIS



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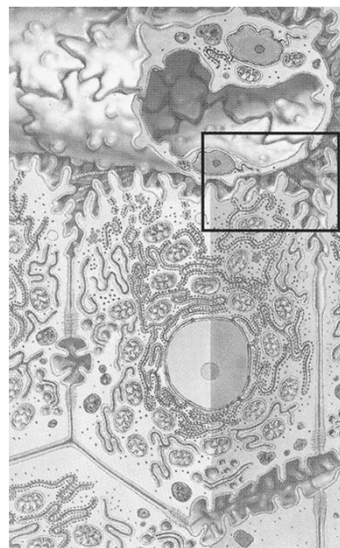
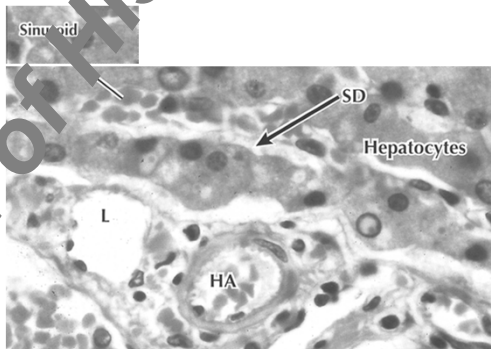
## LOBULUS VENAE CENTRALIS Hepatocytes and liver sinusoids

- 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 (Dissé) space
  - Reticular fibers, perisinusoidal fibroblasts
  - Dispersed Kupfer cells (monocyte-macrophage system)
  - Perisinusoidal cells of Ito
- Vena centralis – thin-walled vessel, draining blood from sinusoids

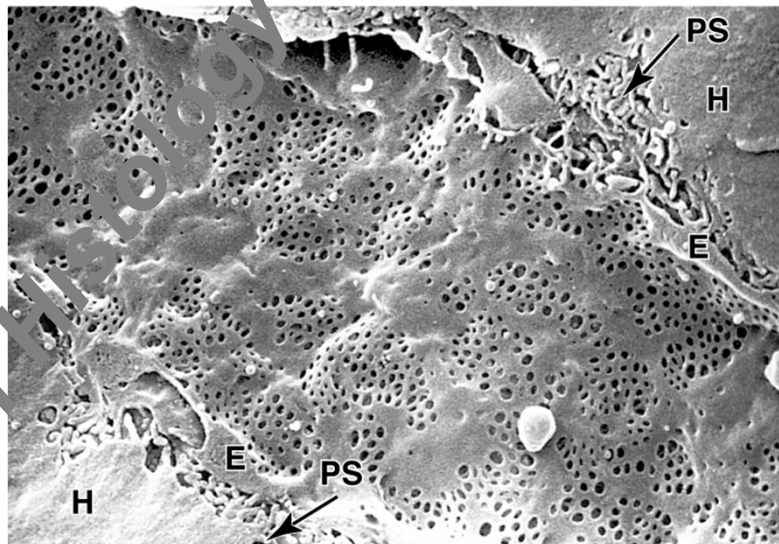
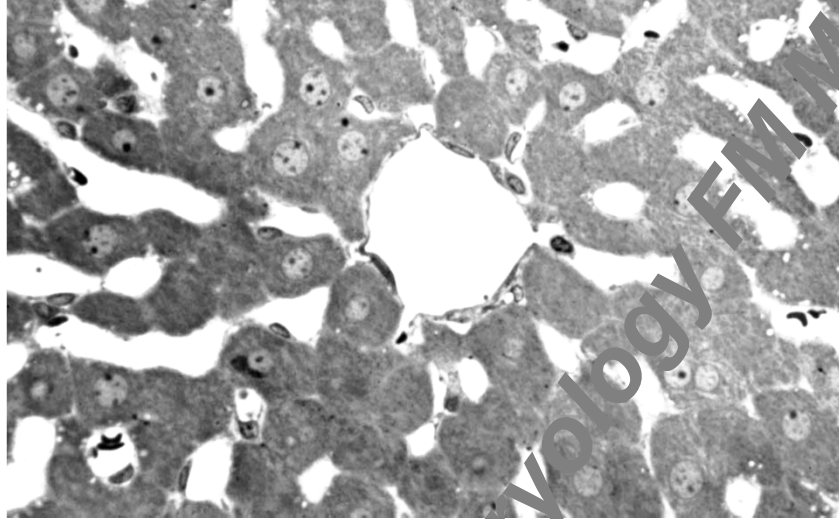


## LOBULUS VENAE CENTRALIS Hepatocytes and liver sinusoids

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



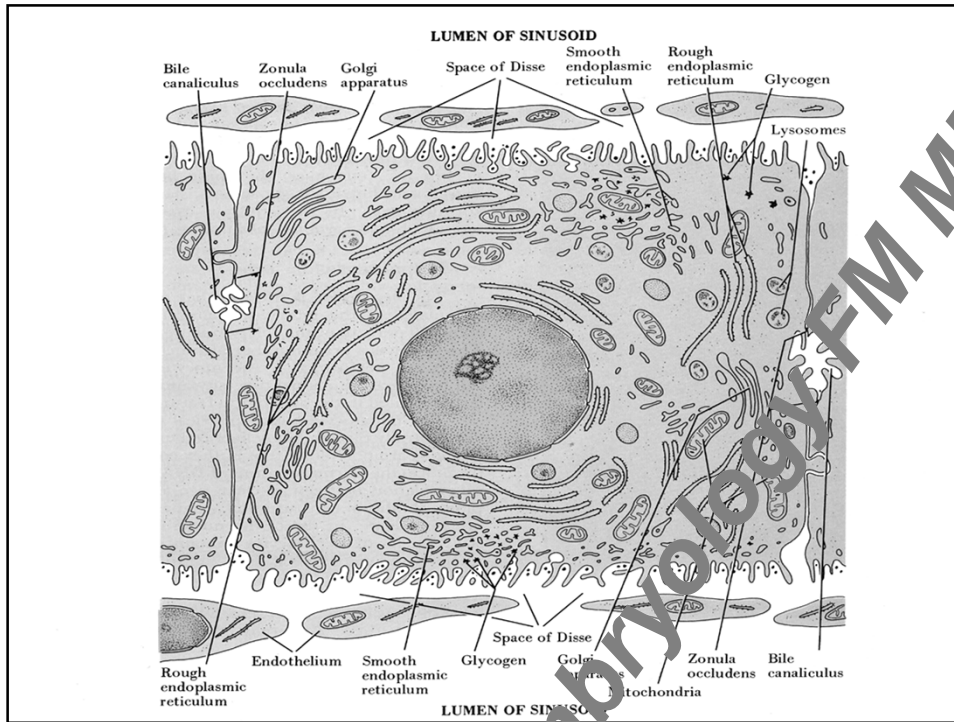
LIVER SINUSOIDS



INNER SURFACE OF LIVER SINUSOID – SEM

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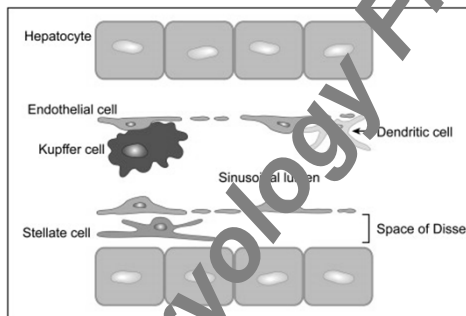
### KUPFFER CELLS

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

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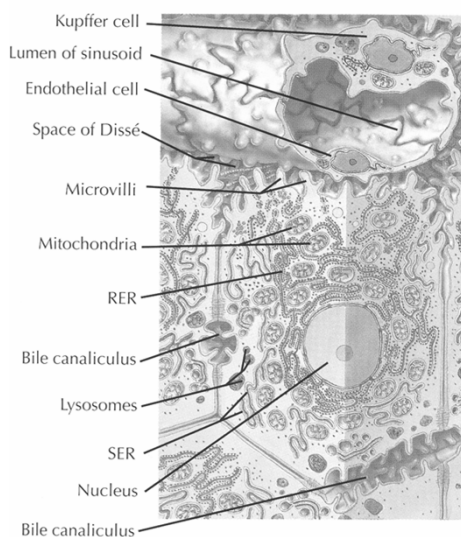
### CELLS OF ITO

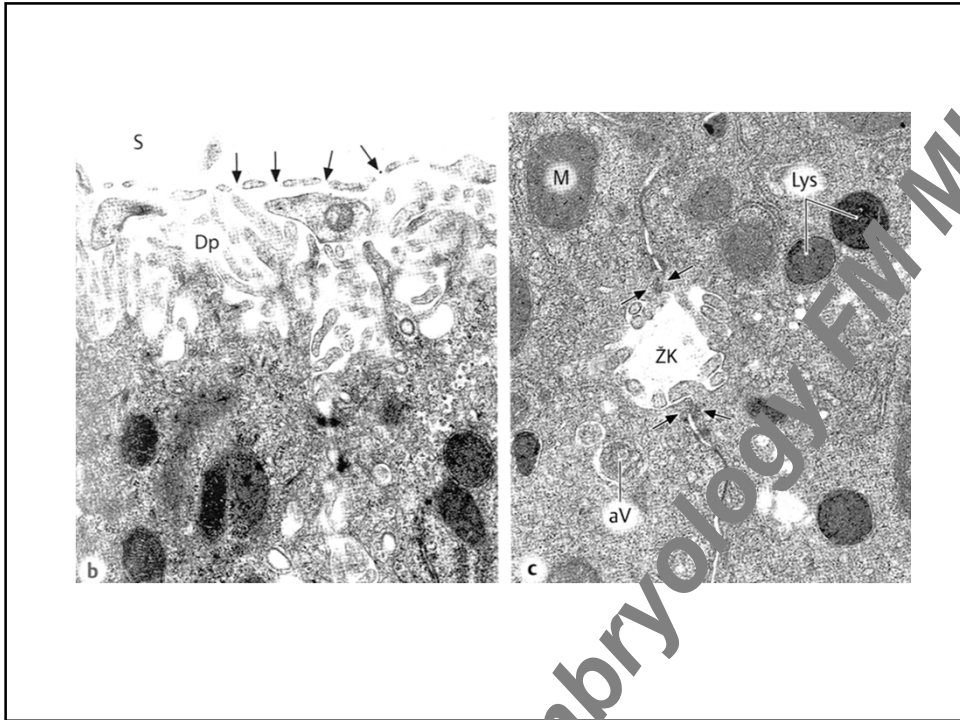
- Star-shape (stellate, perisinusoidal) cells
- Lipid droplets
- Deposition of vitamin A
- fine reticular c.t.
- Antigen presenting cells (lipid antigens)



### HEPATOCYTES

- Polygonal cells of liver parenchyma
- 20x30µm
- Irregular trabeculae 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 capillary
  - Blood pole - absorptive - sinusoidal - microvilli oriented to space of Dissé
  - Membranes with intercellular junctions

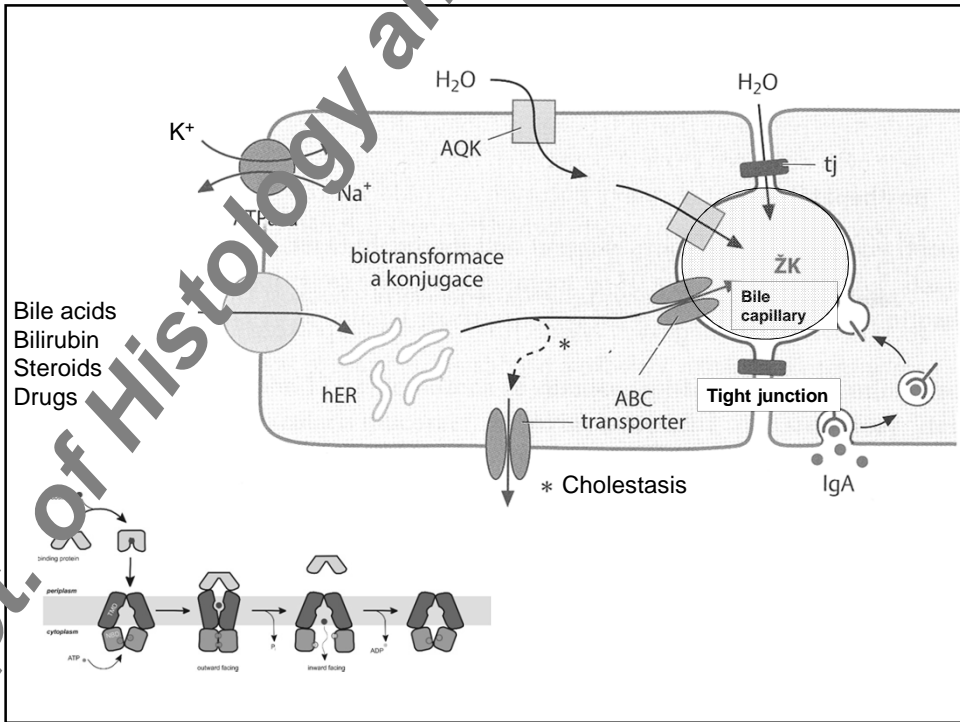
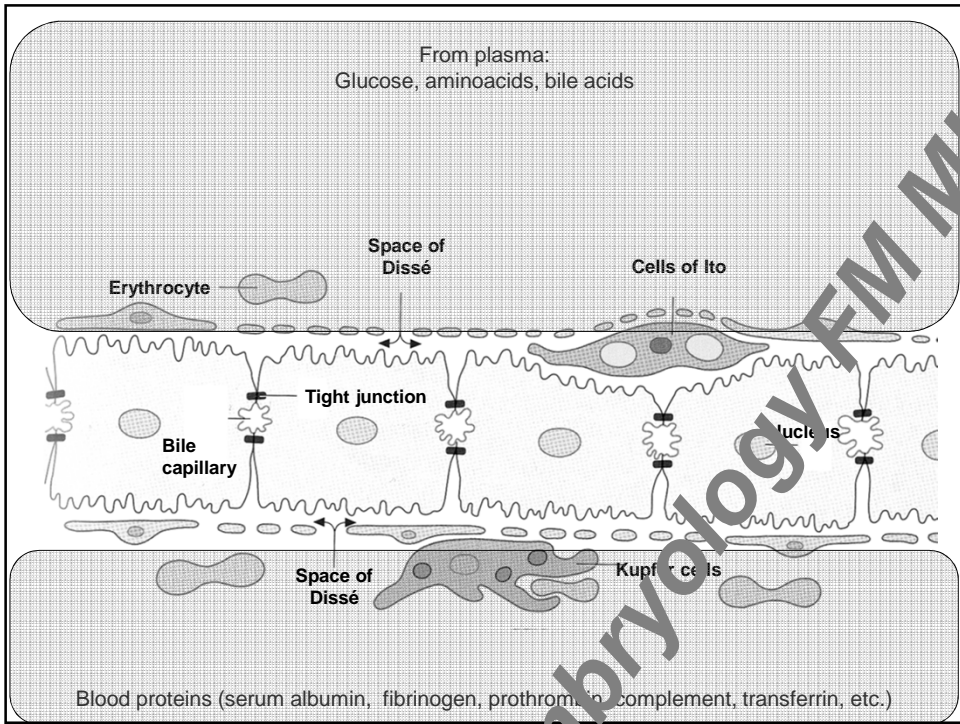




### HEPATOCTYTES

Long mitochondria with flat or tubular cristae  
 Apparent  $rER$ ,  $sER$  and Golgi  
 Glycogen, lipid droplets, lysosomes, peroxisomes

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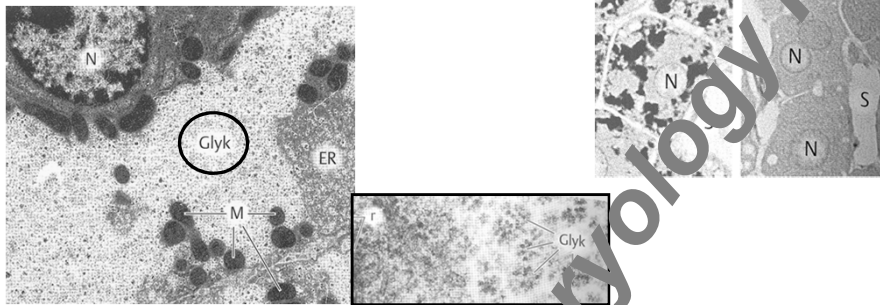


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## METABOLIC ACTIVITY OF HEPATOCYTES

- **Synthesis and metabolism:**

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



## METABOLIC ACTIVITY OF HEPATOCYTES

- **Detoxication:**

sER (steroids, barbiturates, polycyclic aromatic, lipid soluble compounds, etc., endo- and exotoxins)  
ROS

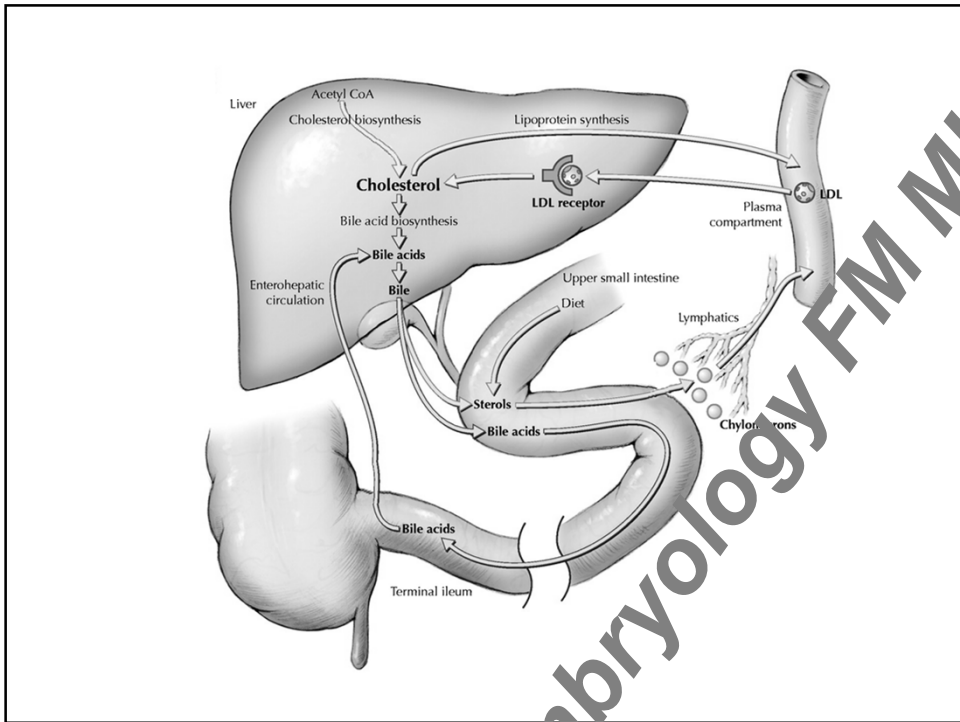
- Peribiliary located lysosomes (autophagy, degradation of endocytosed molecules)

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

- **Bile production:**

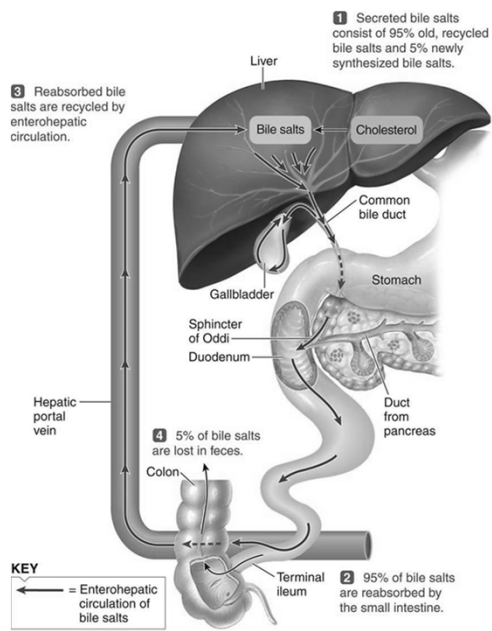
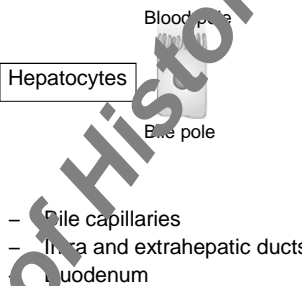
Recycling of bile acids (90%), 10% de novo synthesis, conjugation of toxic bilirubin and glucuronic acid to nontoxic complex bilirubin-glucuronid

rER



• **Enterohepatic circulation**

- Resorption in terminal ileum
- Vena portae
- Sinusoids



**KEY**  
 ← = Enterohepatic circulation of bile salts

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## INTRAHEPATIC AND EXTRAHEPATIC BILE DUCTS

### INTRAHEPATIC

- Bile capillaries (biliary canaliculi)**
- intercellular space between hepatocytes
  - 1-2µm
  - 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

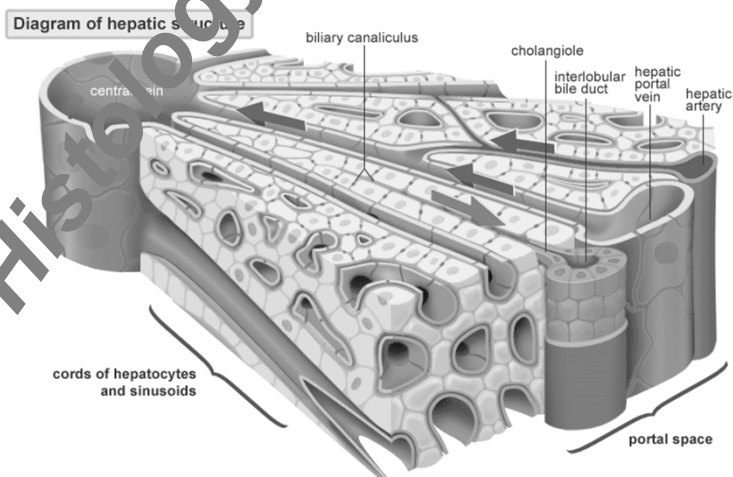
### EXTRAHEPATIC

**Ductus hepaticus, ductus cysticus, ductus choledochus**

- mucosa
- fibromuscular layer



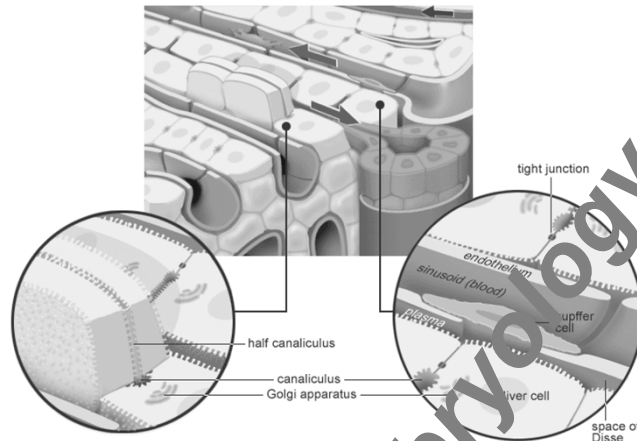
## INTRAHEPATIC BILE DUCTS



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### INTRAHEPATIC BILE DUCTS

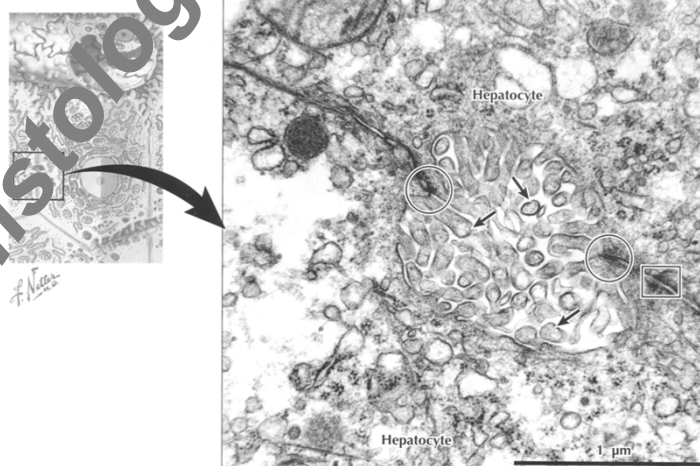
Hepatic structure (close-up)



[http://alexandria.healthlibrary.ca/documents/notes/bom/unit\\_4/unit%204%202007%20L-39%202008%20%20histology%20of%20the%20pancreas.xml](http://alexandria.healthlibrary.ca/documents/notes/bom/unit_4/unit%204%202007%20L-39%202008%20%20histology%20of%20the%20pancreas.xml)

### INTRAHEPATIC BILE DUCTS

▼ The box indicates a bile canaliculus

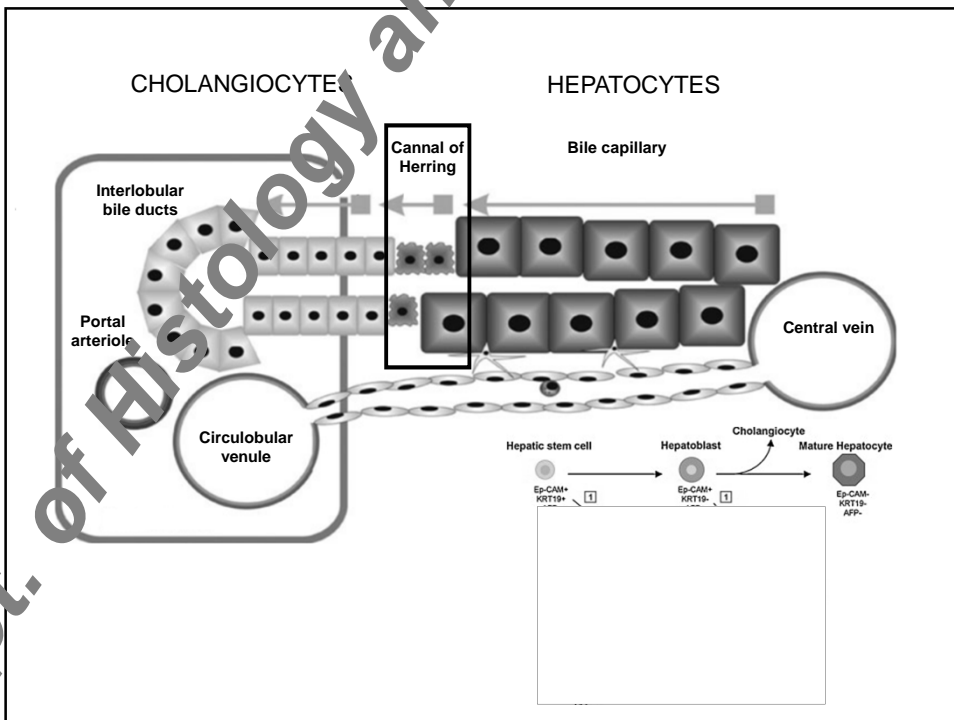
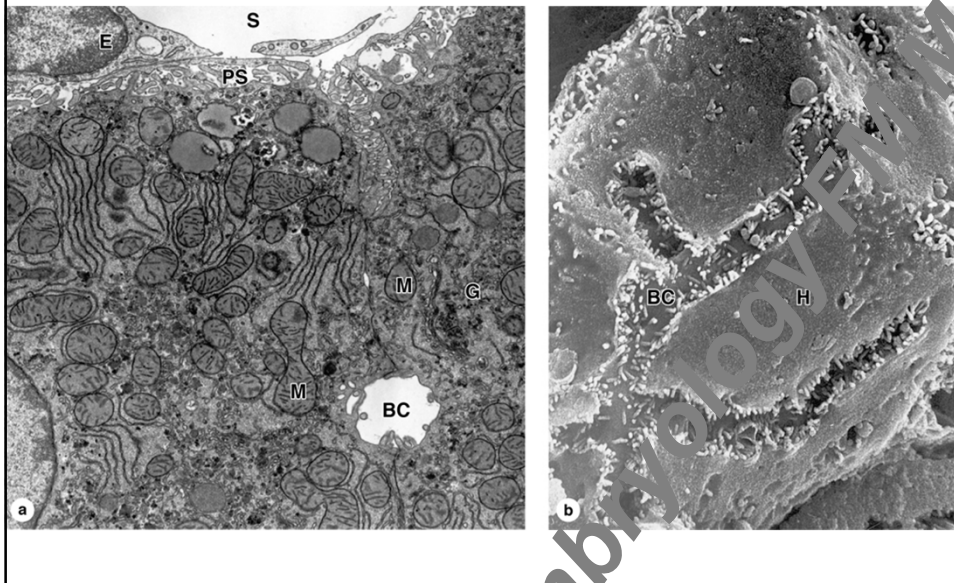


▲ EM of a bile canaliculus in transverse section. The lumen shows short stubby microvilli (arrows) of two hepatocytes. Desmosomes (rectangle) and tight junctions (circles) link cell membranes, which seals the canaliculus and prevents bile leakage to surrounding tissues. 47,000x.

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### INTRAHEPATIC BILE DUCTS TEM/SEM



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## EXTRAHEPATIC BILE DUCTS

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

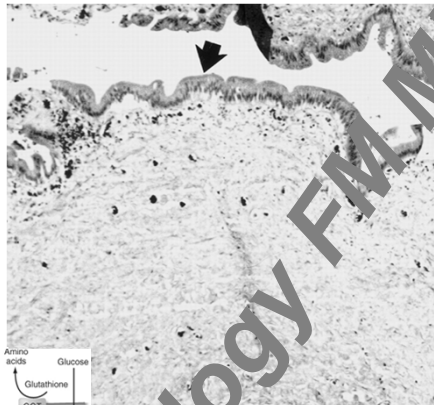
papilla duodeni major  
m. sphincter ampullae hepatoduodenalis (sphincter of Oddi)

### Mucosa

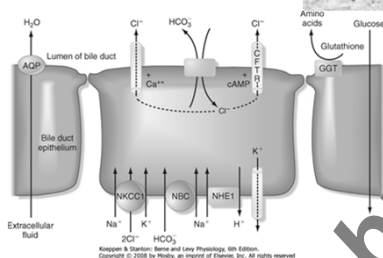
- lateral folds
- simple columnar epithelium (cholangiocytes)
- mucinous glands in c.t., goblet cells

### Fibromuscular layer

- dense network of collagen and elastic fibers
- leiomyocytes



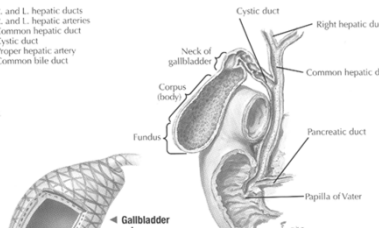
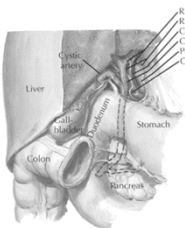
### Bile modification



## GALL BLADDER (VESICA FELLEA)

- Wall 1-2mm

- Mucous coat
- Muscle layer
- Serosa/adventitia



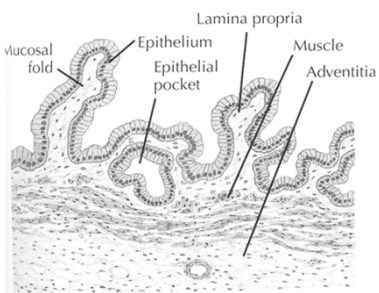
### Mucous coat

- mucosa folds
- 20-50 μm simple columnar epithelium with microvilli
- intercellular junctions
- lamina propria mucosae - loose collagen c.t. with mucinous tubuloalveolar 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)



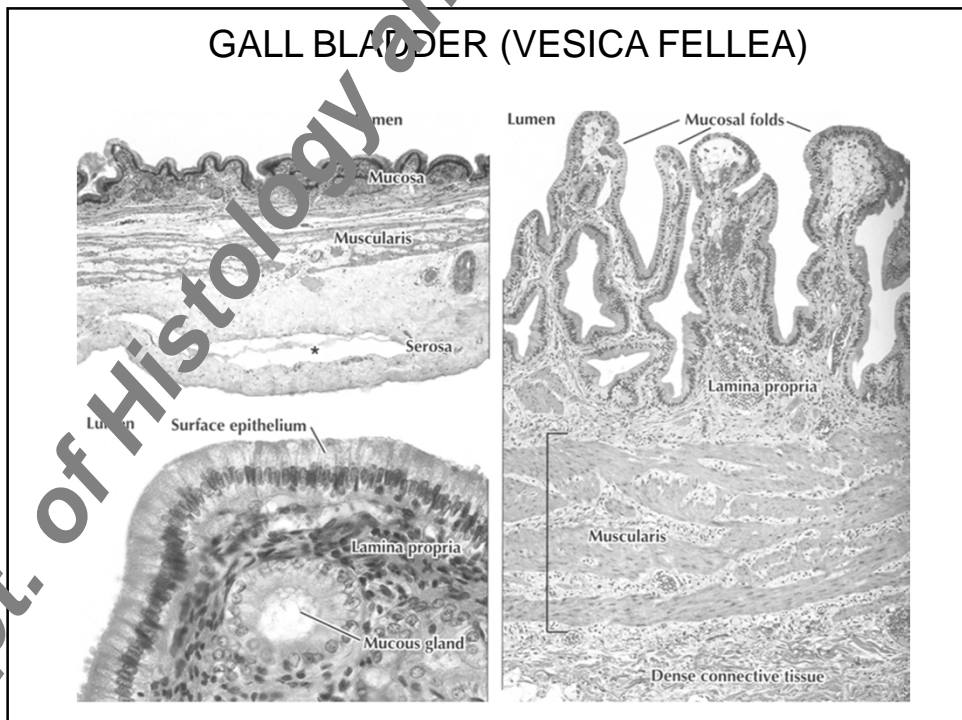
### Bile concentration

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

*Koppen & Stanton: Basic and Clinical Physiology, 10th Edition, Copyright © 2008 by Mosby, an imprint of Elsevier. All rights reserved.*

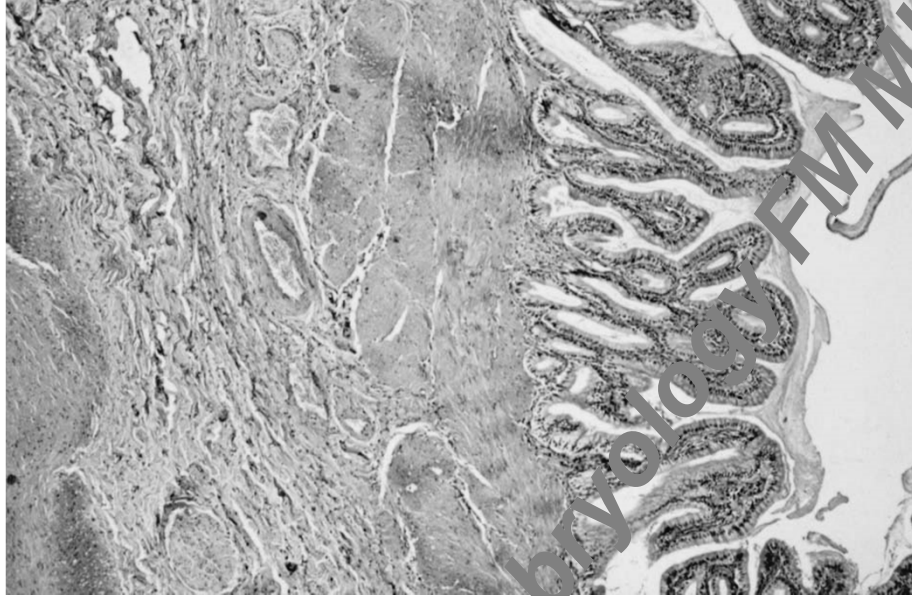
*Approximate Values for Major Components of Liver and Gallbladder Bile*

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	5.5 ↓
Cholesterol (mg/100 mL)	110	90 ↓
Bilirubin (mg/100 mL)	100	100 ↓

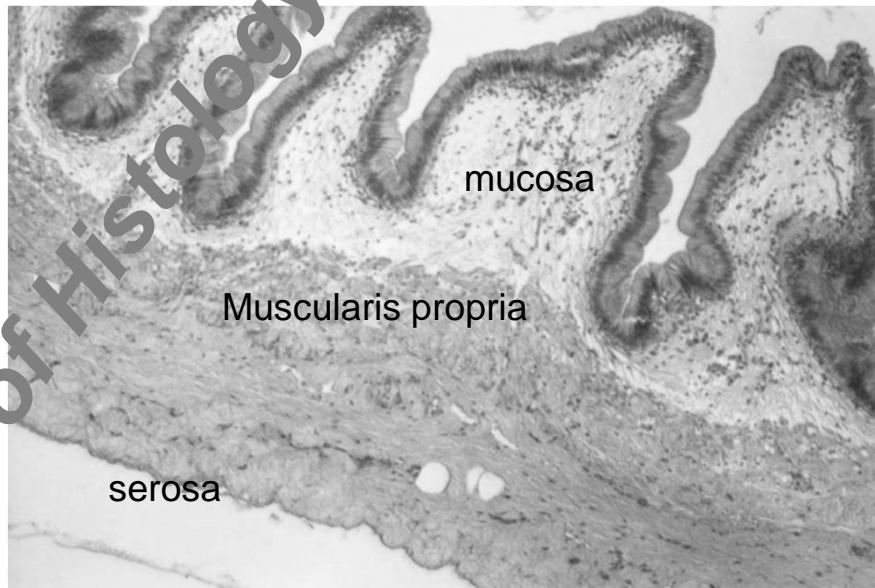


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GALL BLADDER (VESICA FELLEA)



GALL BLADDER (VESICA FELLEA)



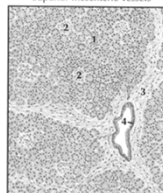
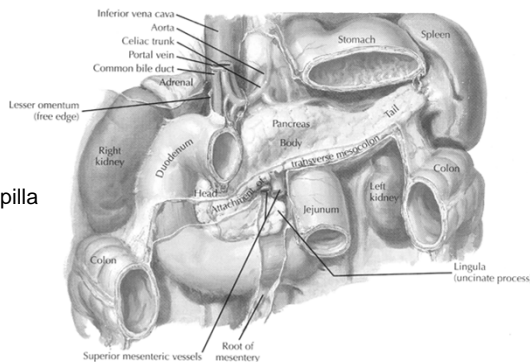
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### GALL BLADDER (VESICA FELLEA)

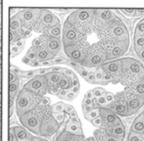


### PANCREAS

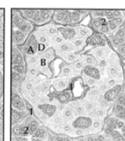
- Compound, serous, tubular acinar gland
- Exocrine and endocrine character
  - pancreatic acinus
  - Islets of Langerhans
- Major duct (Wirsung) opens to Vater papilla as a common bile and pancreatic duct
- Dense collagen c.t. capsule
- Septs - blood cells, innervation, and interlobular ducts



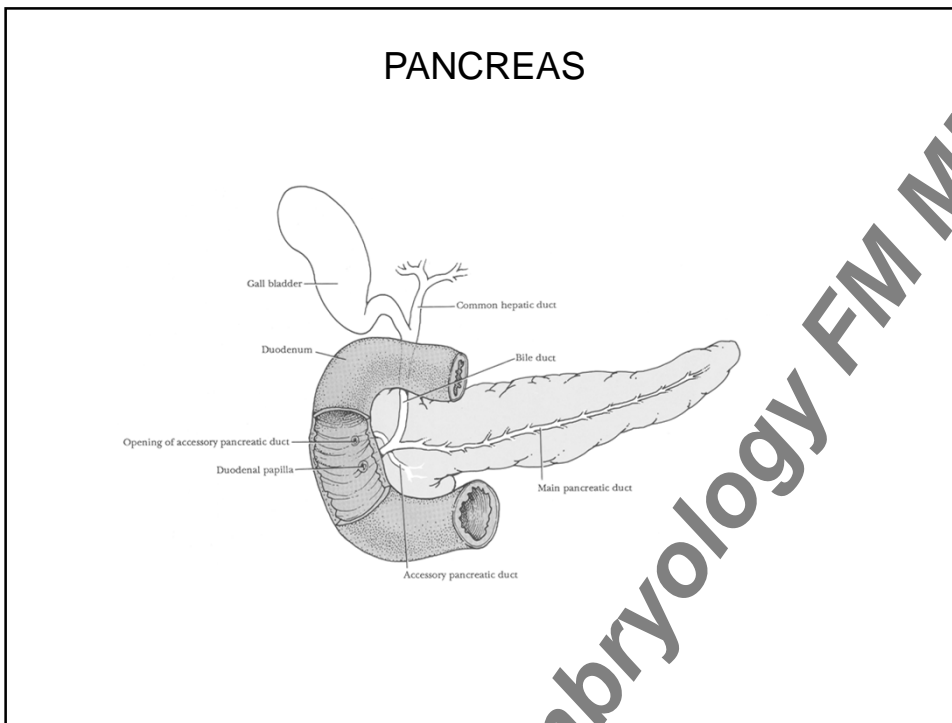
Low-power section of pancreas  
1. Acini, 2. islet, 3. interlobular septum, 4. interlobular duct



High magnification: acini, intercalated duct and zymogen granules



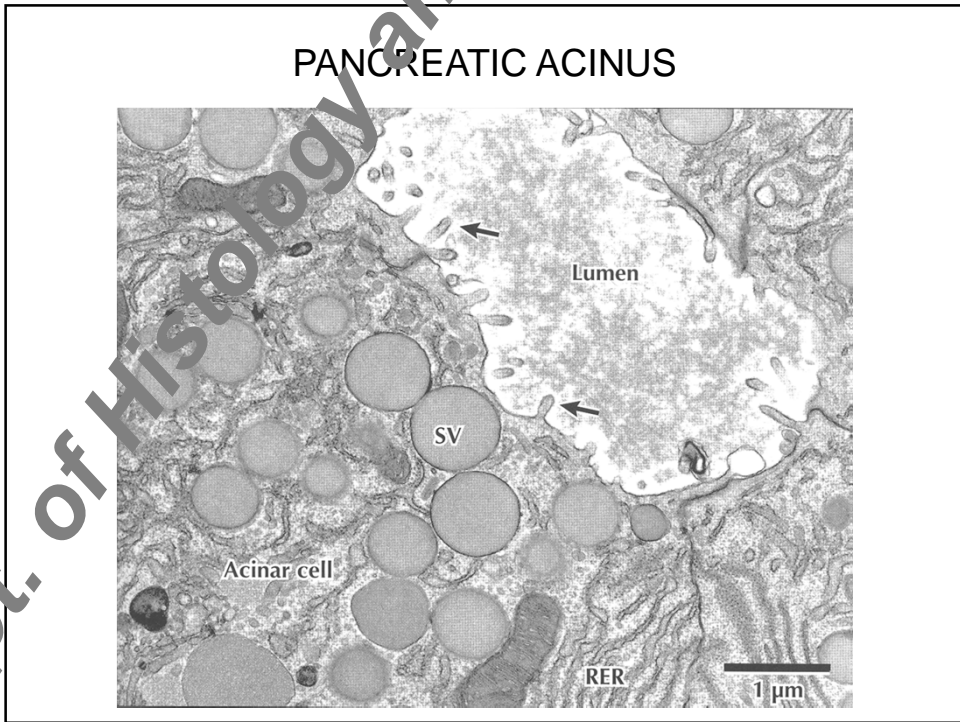
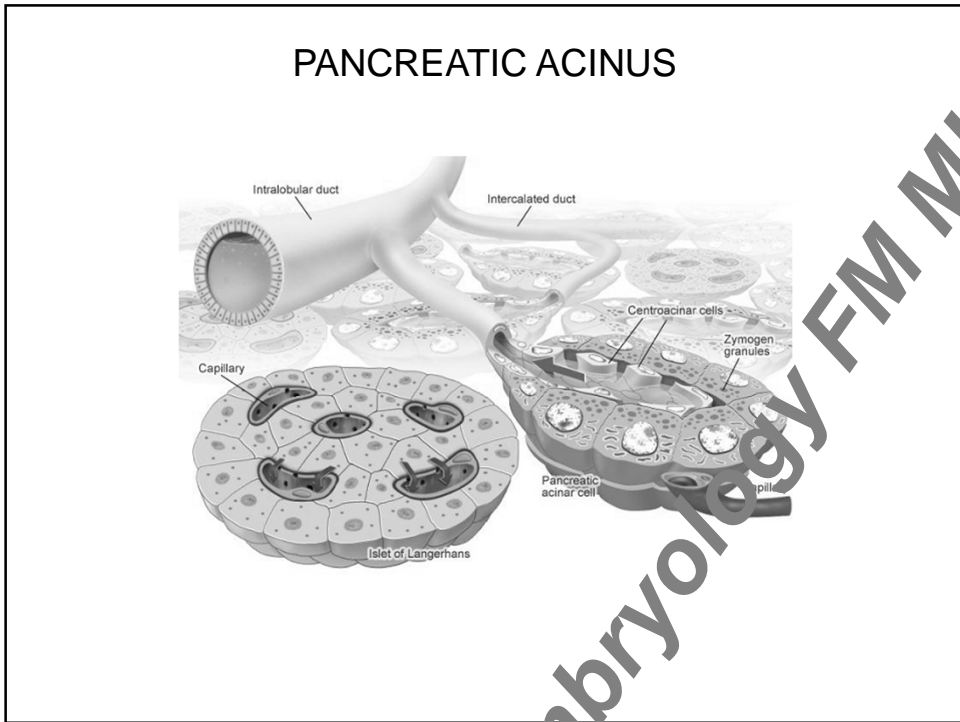
Pancreatic islet: A, B, and D cells. 1. Reticulum, 2. acini



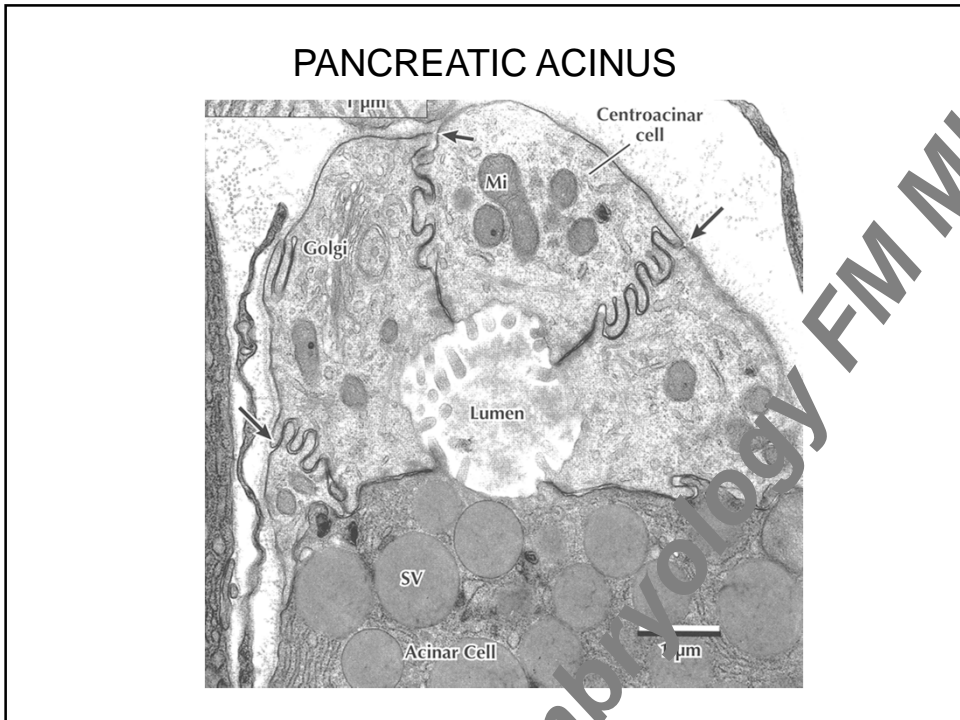
### PANCREATIC ACINUS

- 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

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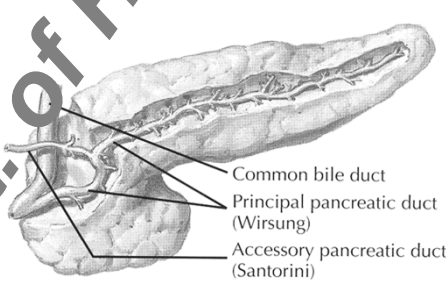
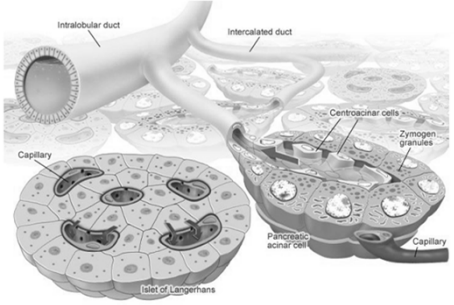


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### PANCREATIC DUCTS

- 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

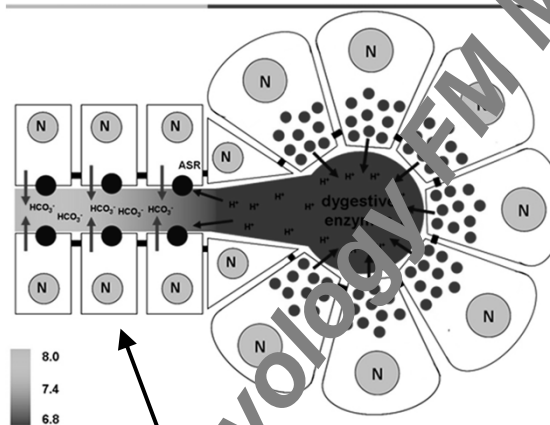
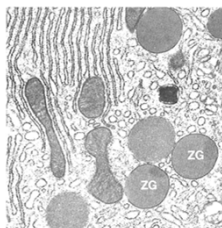
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## EXOCRINE FUNCTION OF PANCREAS

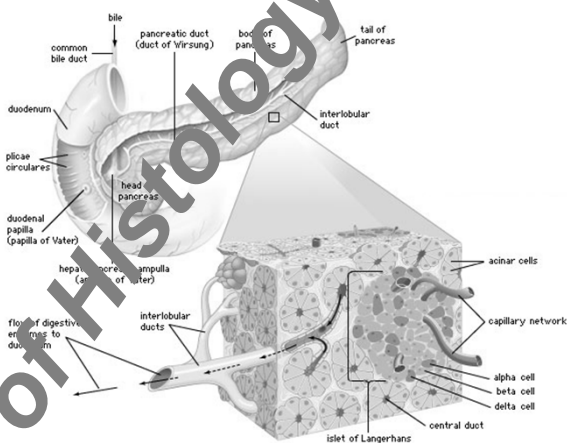
- ca 1000-2000 ml daily
- alkalic pH (8.8),  $\text{HCO}_3^-$  (intercalated duct epithelium)
- mucin (epithelium of large ducts)

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



Hormonal regulation (secretin, cholecystokinin) + parasymphatikus

## ENDOCRINE FUNCTION OF PANCREAS



### 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

### ISLETS OF LANGERHANS

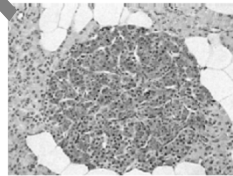
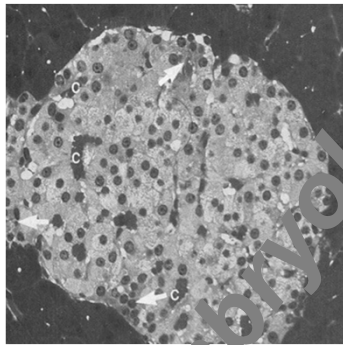
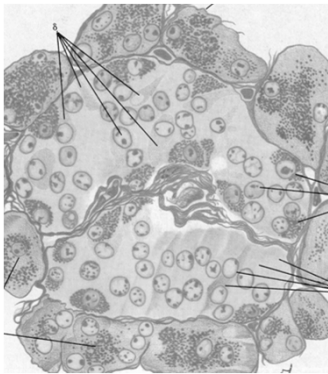
- Clusters of pale cells
- ca  $1,5 \times 10^6$
- Thin c.t. capsule
- Cords of epithelial cells
- Sinusoids
- General characteristics of APUD cells
- A, B, D, PP cells

A cells: 20%, glucagon

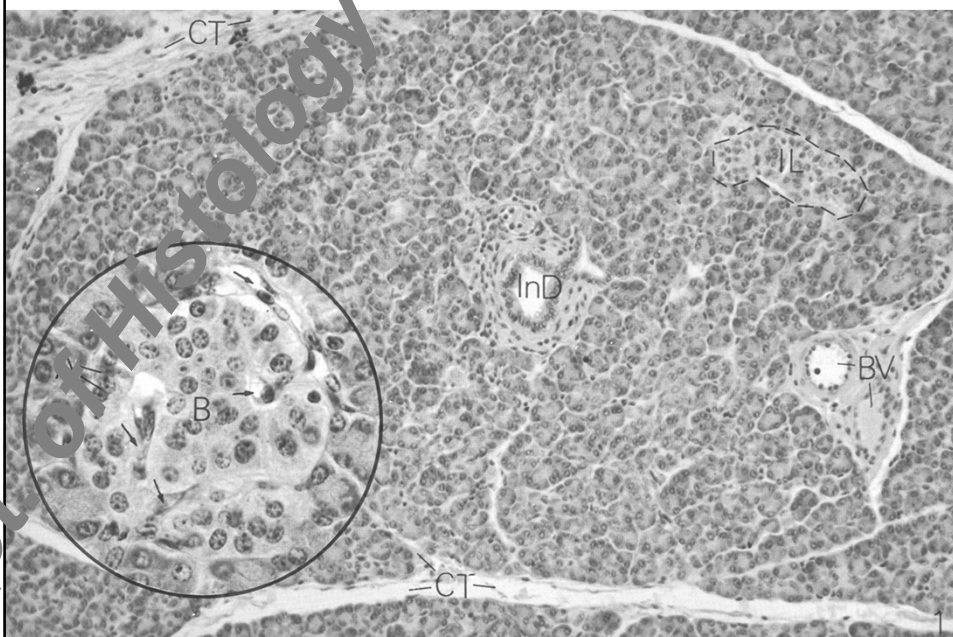
B cells: 60-70%, insulin

D cells: minor, somatostatin

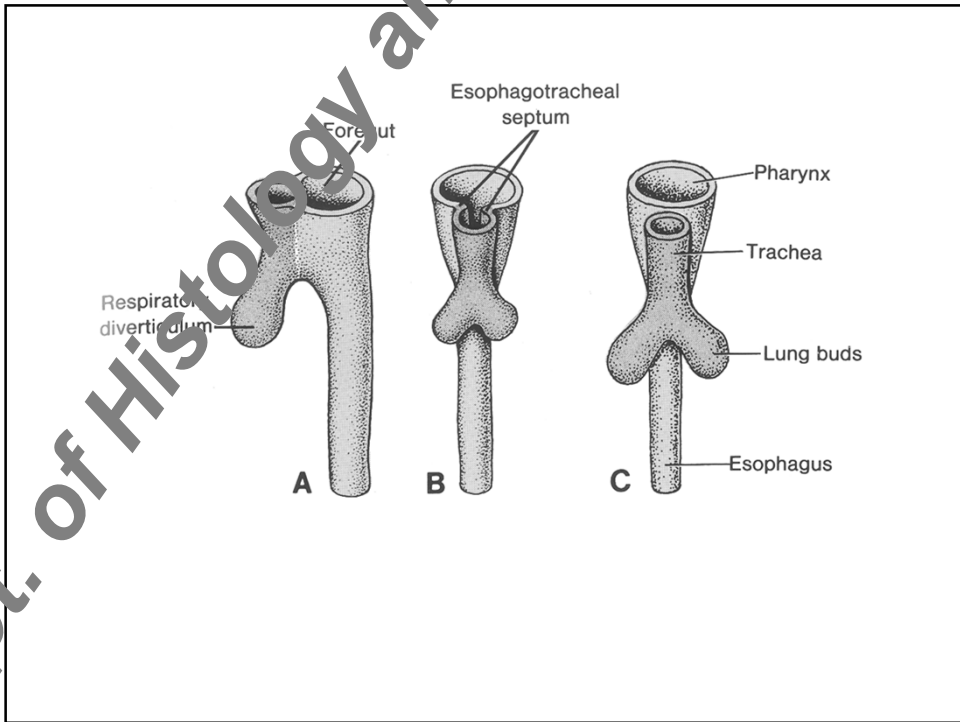
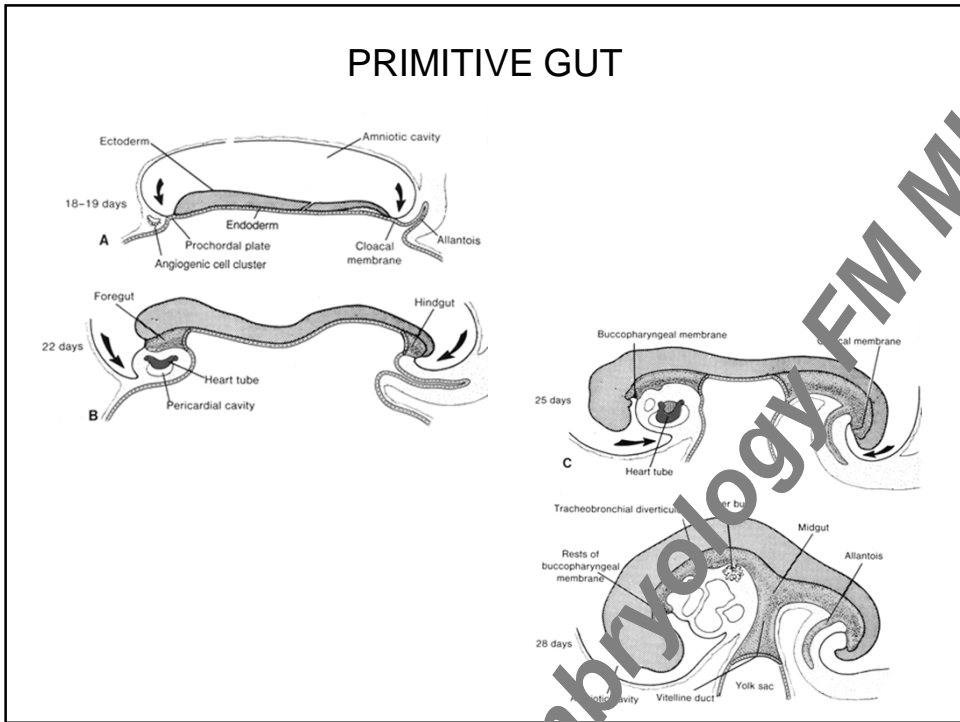
PP cells: minor, pancreatic polypeptide



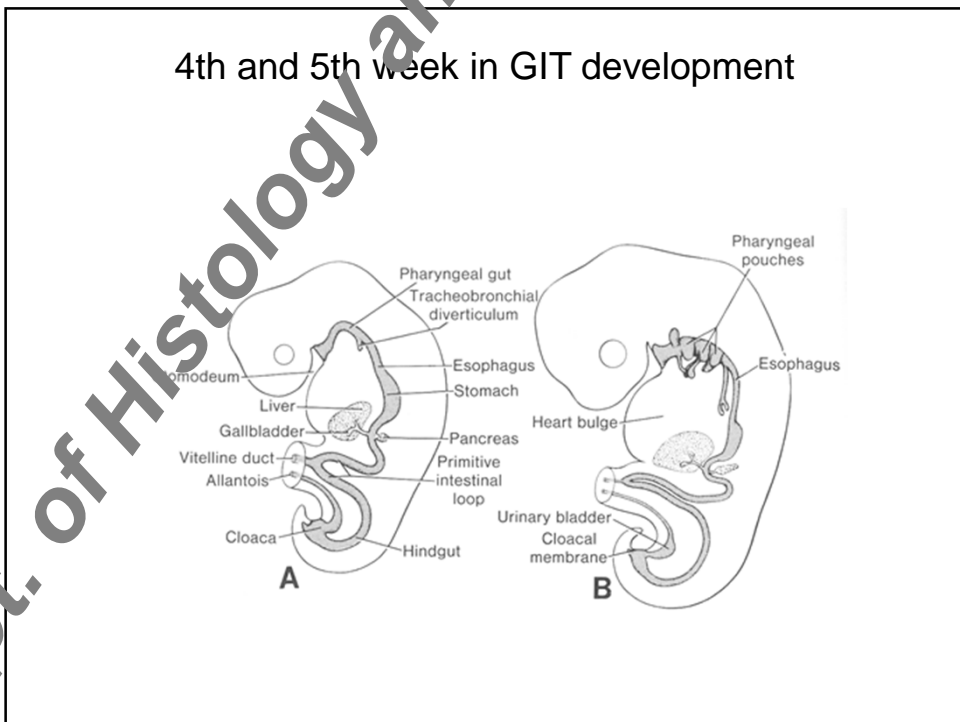
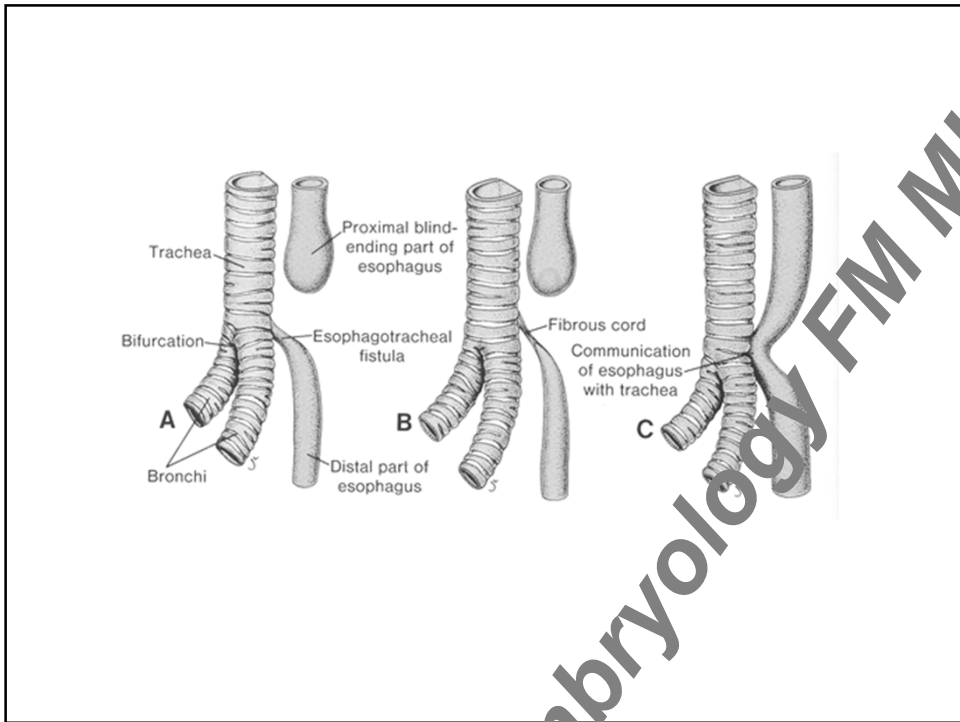
### ISLETS OF LANGERHANS

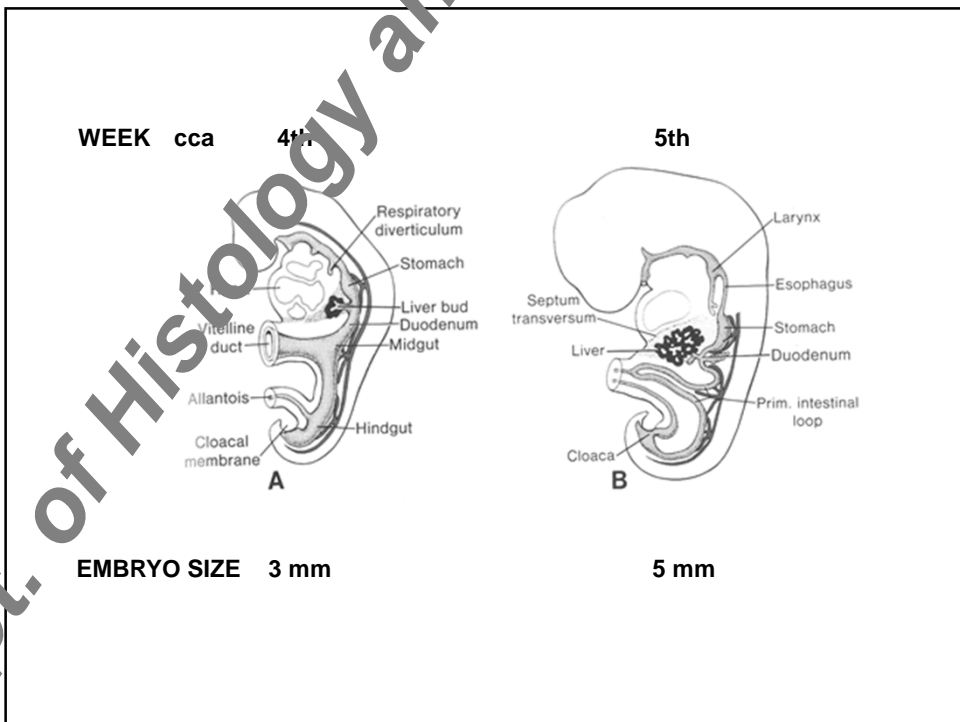
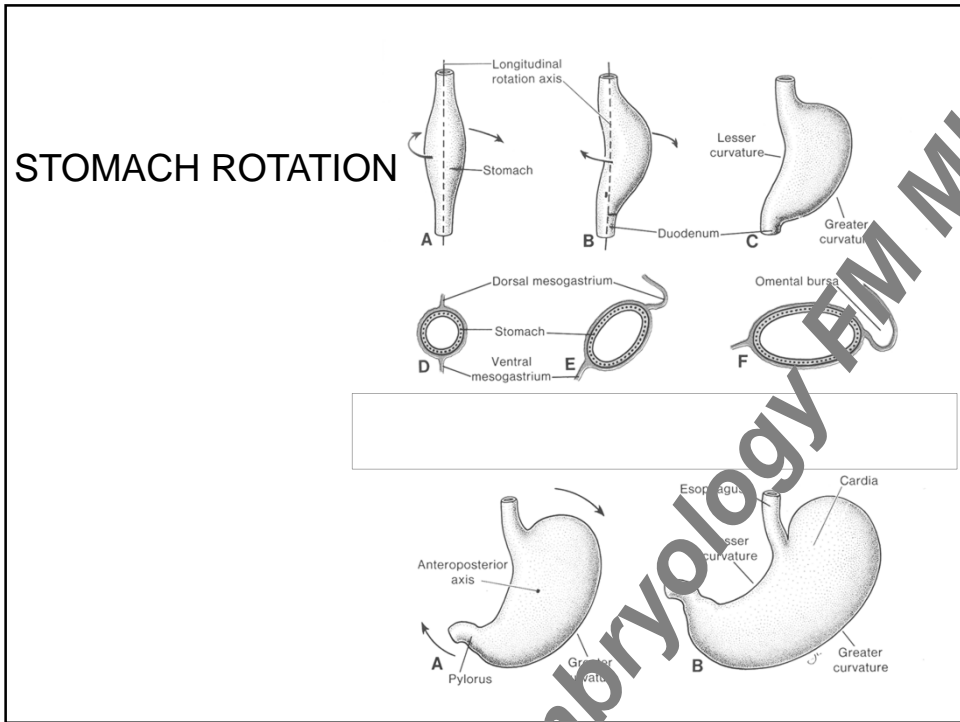


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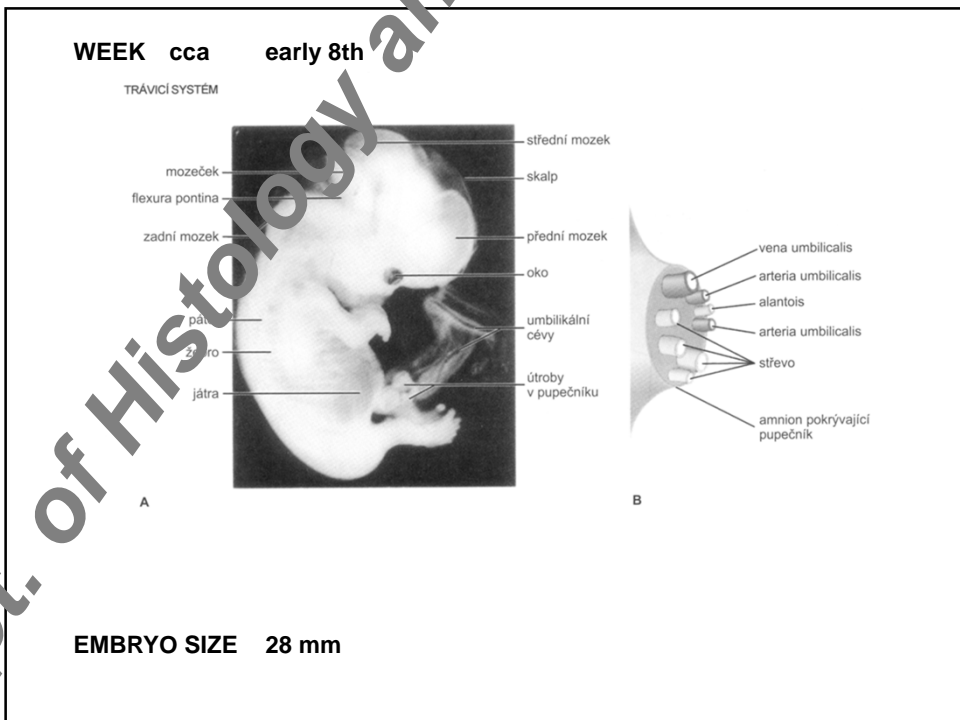
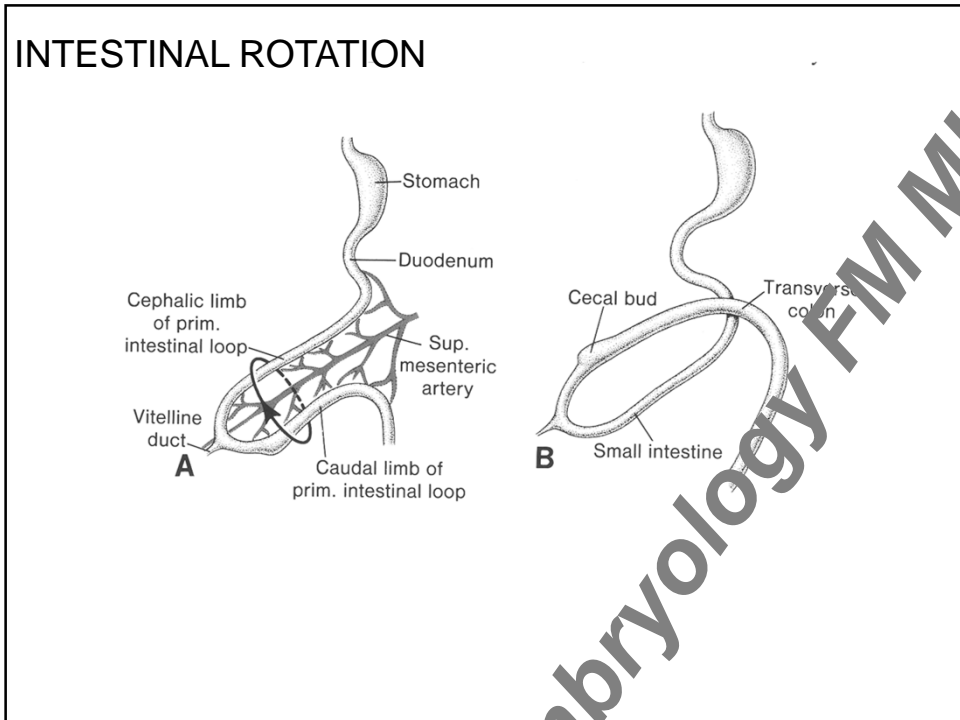


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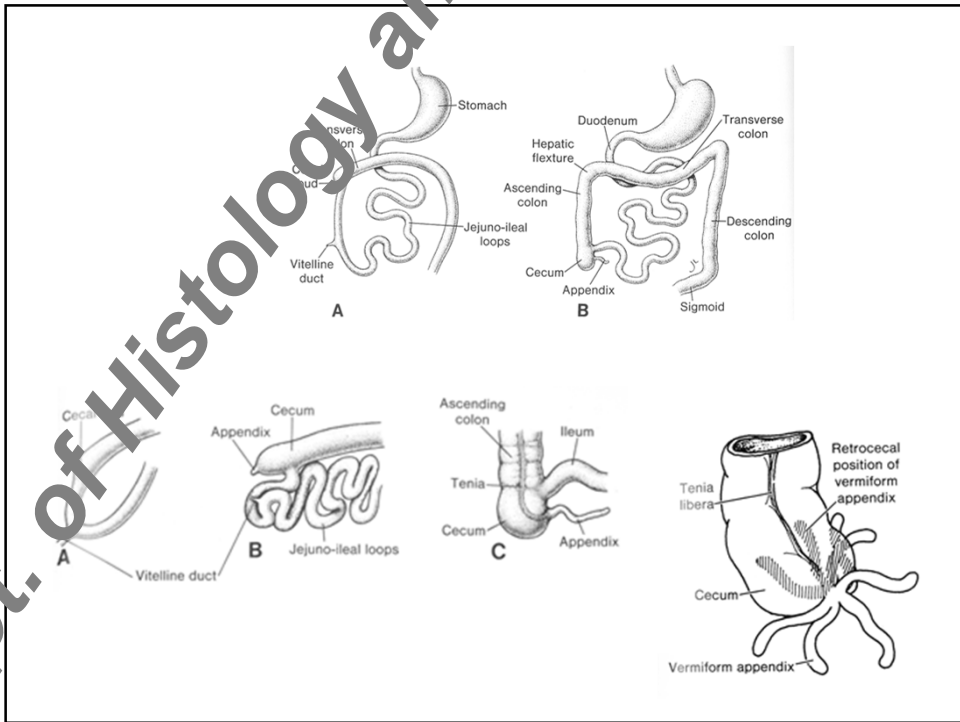
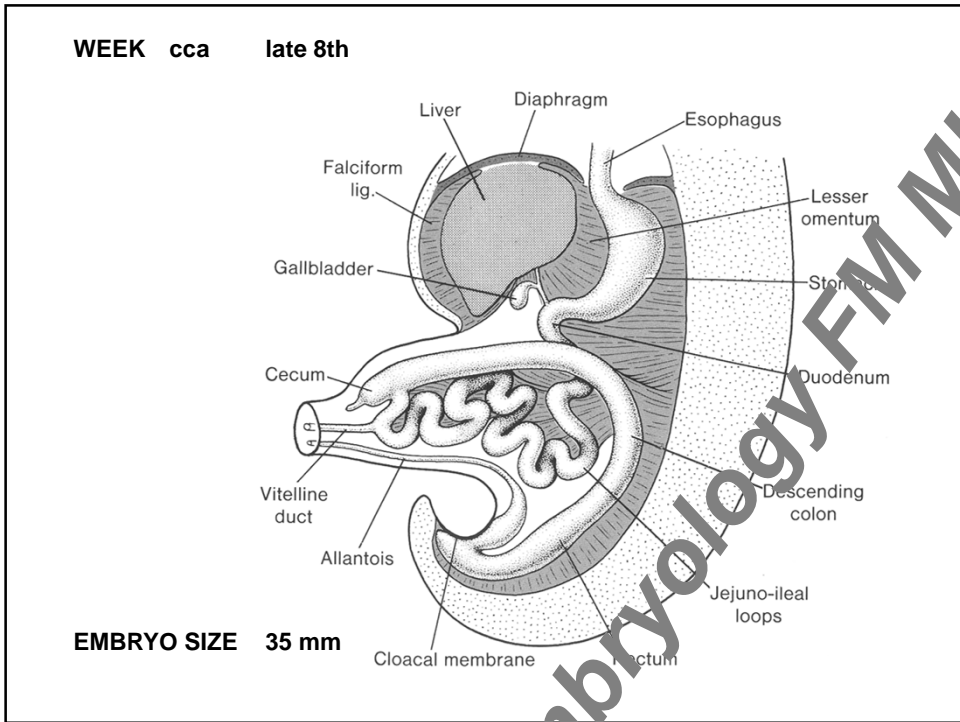




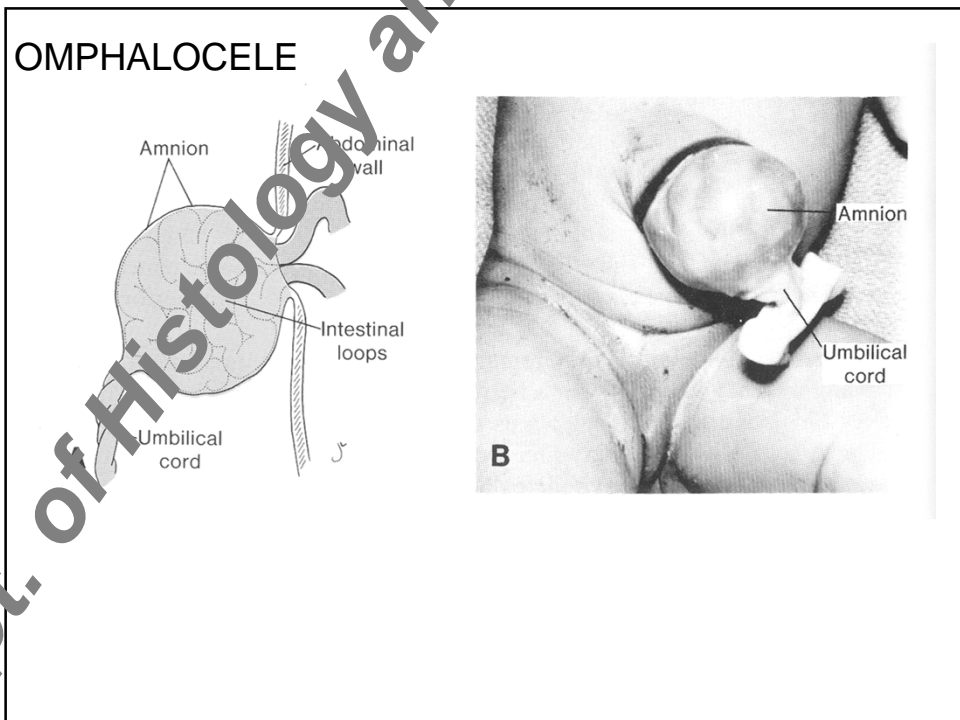
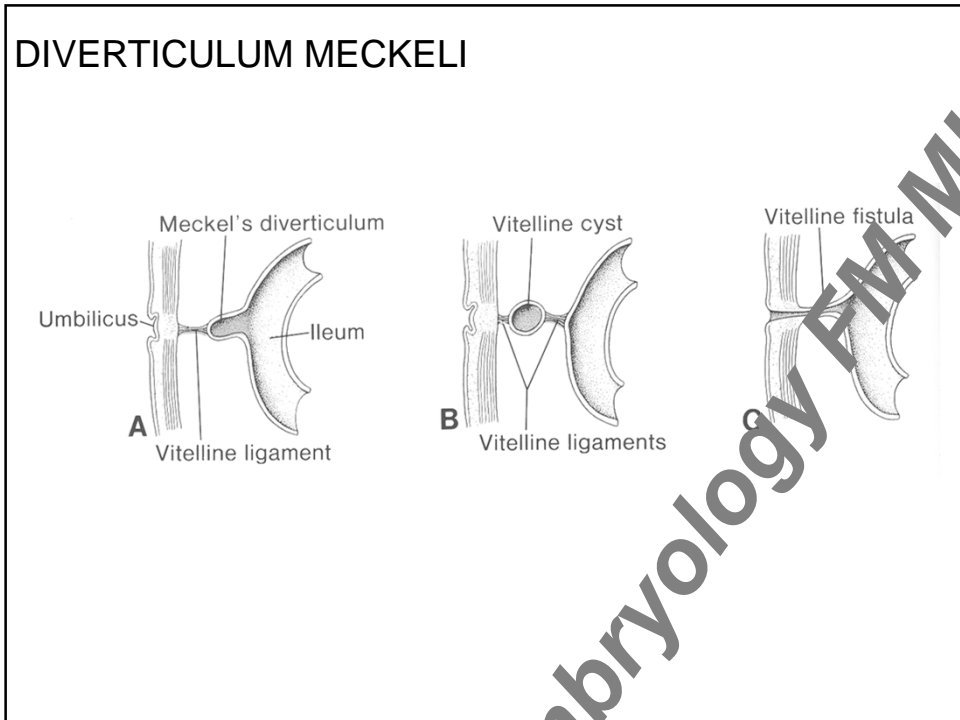
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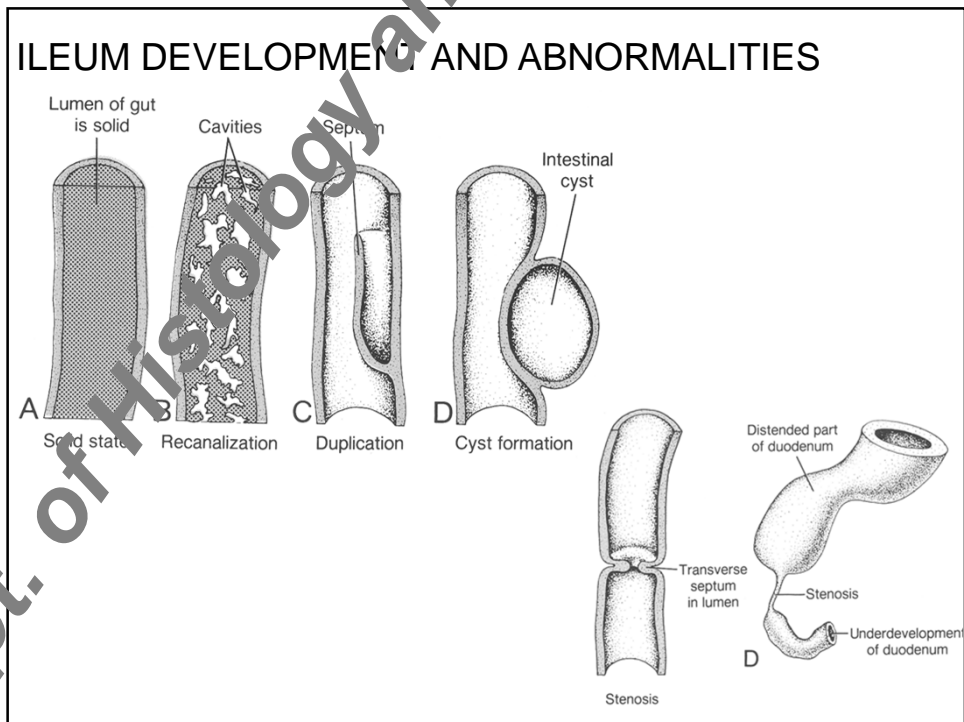
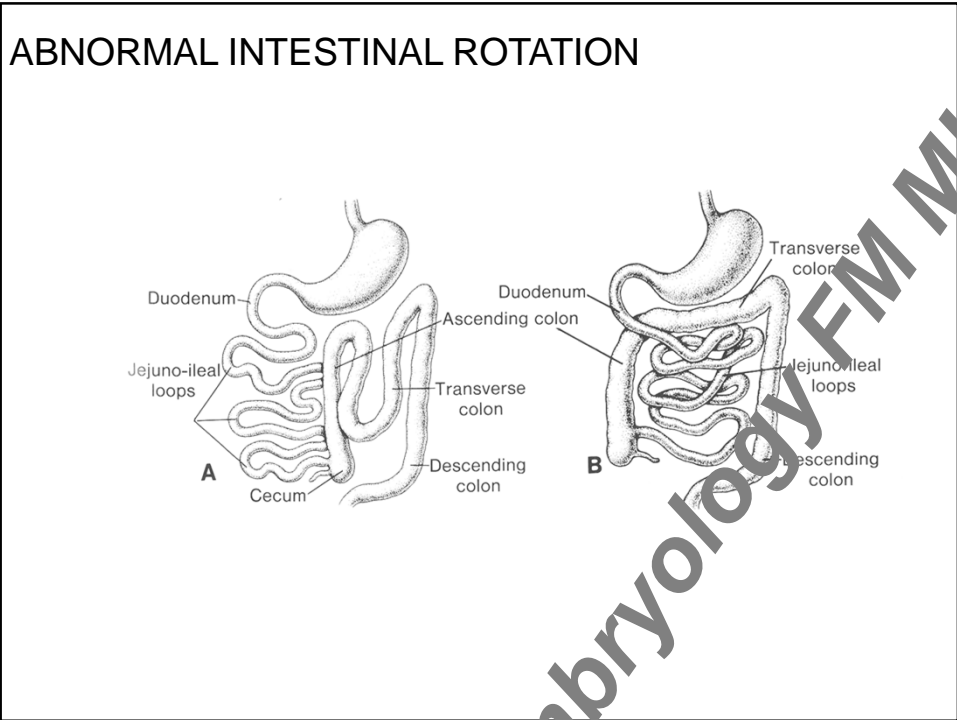


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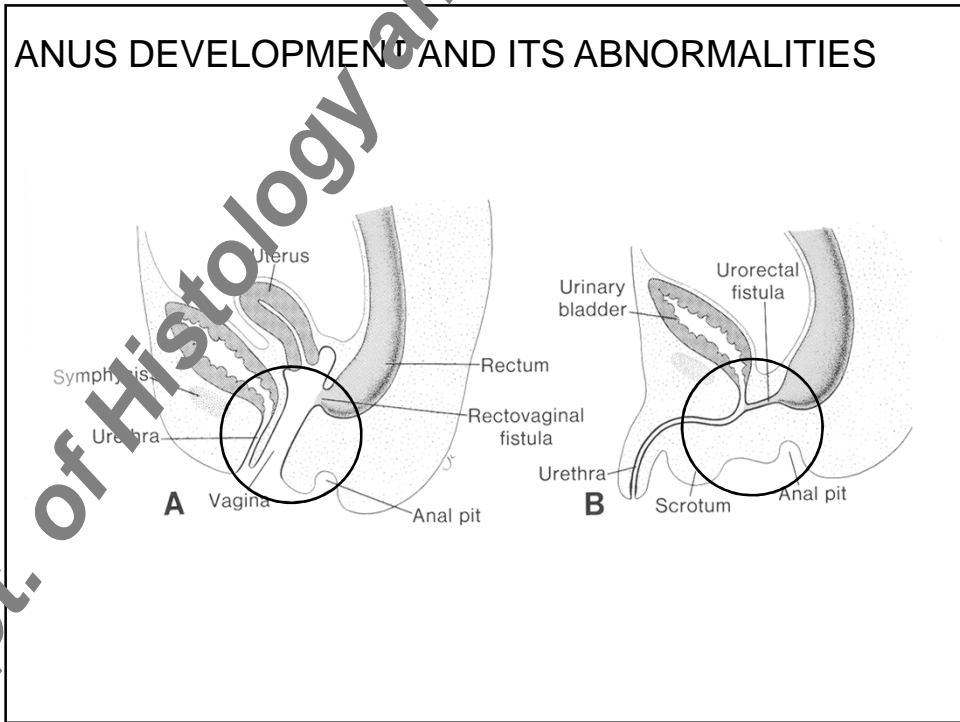
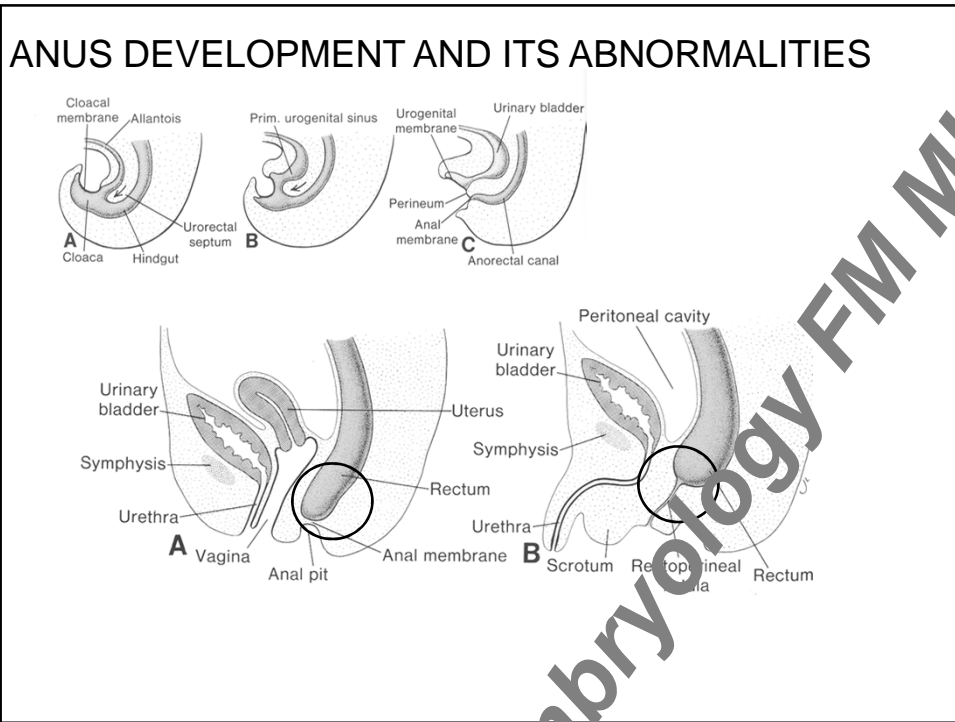


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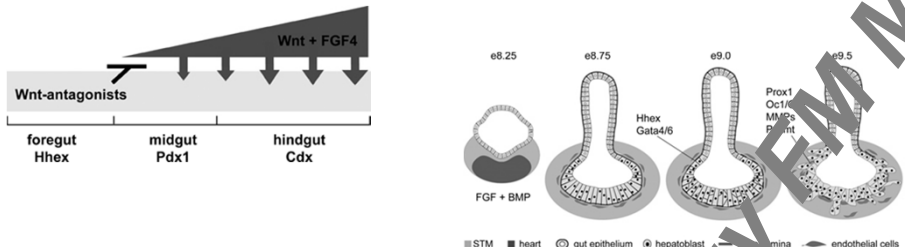
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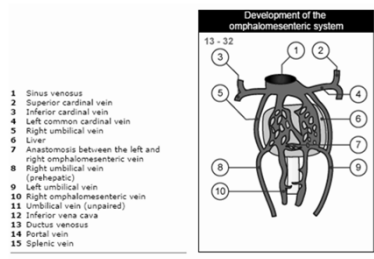
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## EMBRYONIC DEVELOPMENT OF LIVER

- Differentiation of endoderm and formation primitive gut
- Growth factors of mesoderm determine identity of individual parts

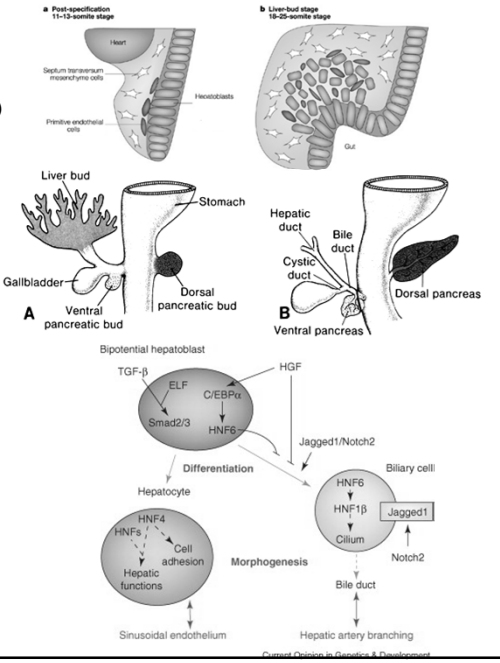


- Interactions with mesoderm of septum transversum and vv. omphalomesentericae

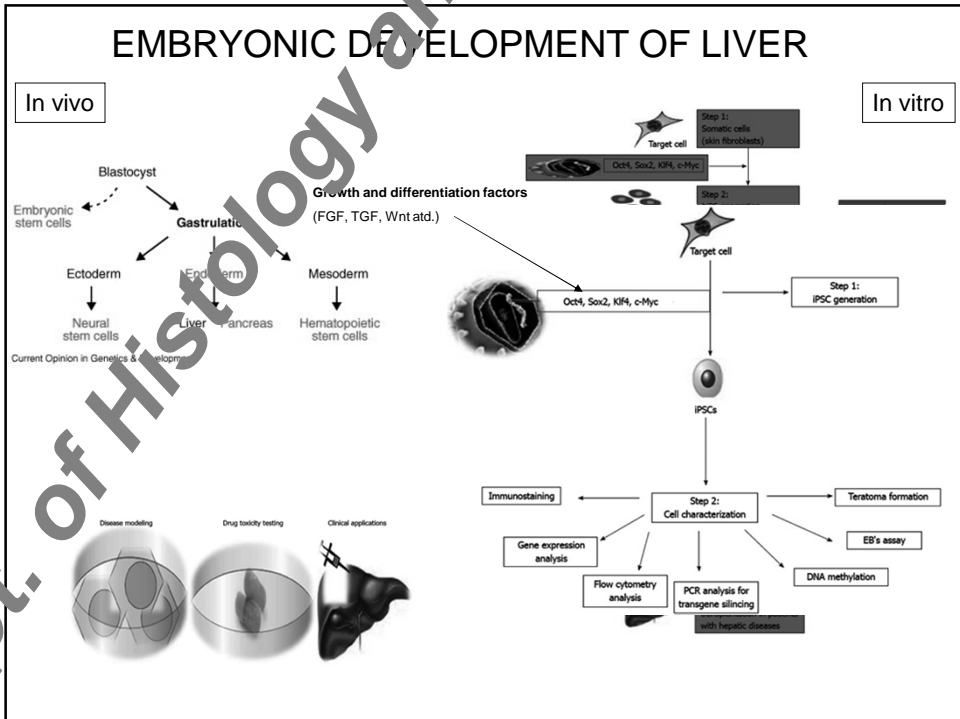
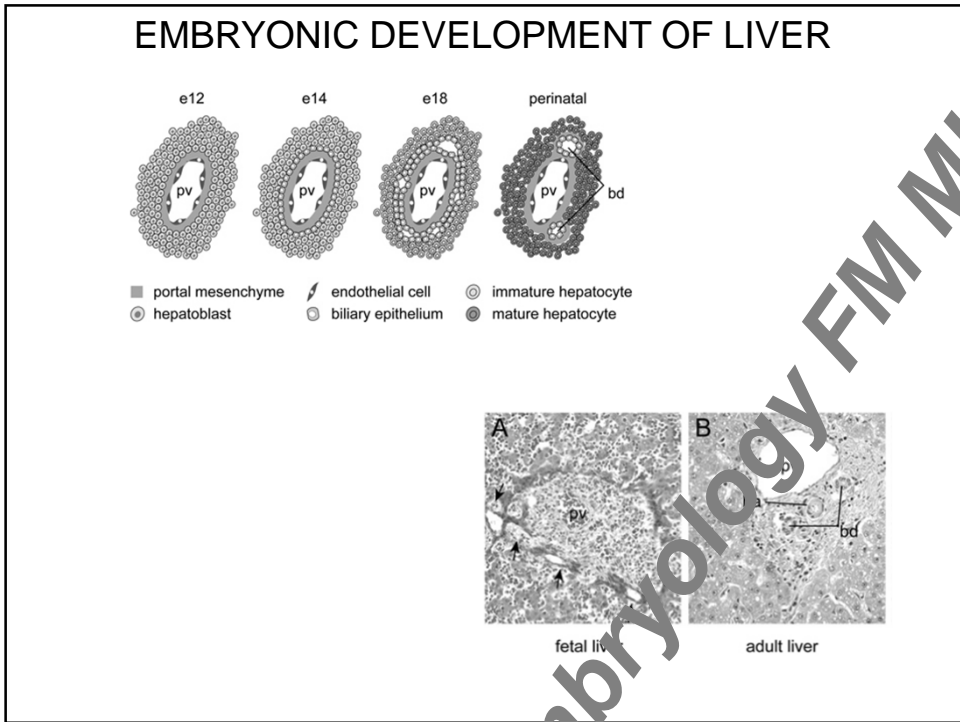


## EMBRYONIC DEVELOPMENT OF LIVER

- 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 (meso-epithelial plate between pericardial cavity and work sac) and growth into ventral mesentery
- liver cords - parenchyma
- Interactions between cells of liver cords and vv. omphalomesentericae induce development **liver sinusoids**
- Kupffer and hematopoietic cells - from mesoderm of septum transversum
- Surface mesoderm differentiate into visceral peritoneum
- 10th week
  - 10% of body volume
  - hematopoiesis
- 12th week
  - bile production



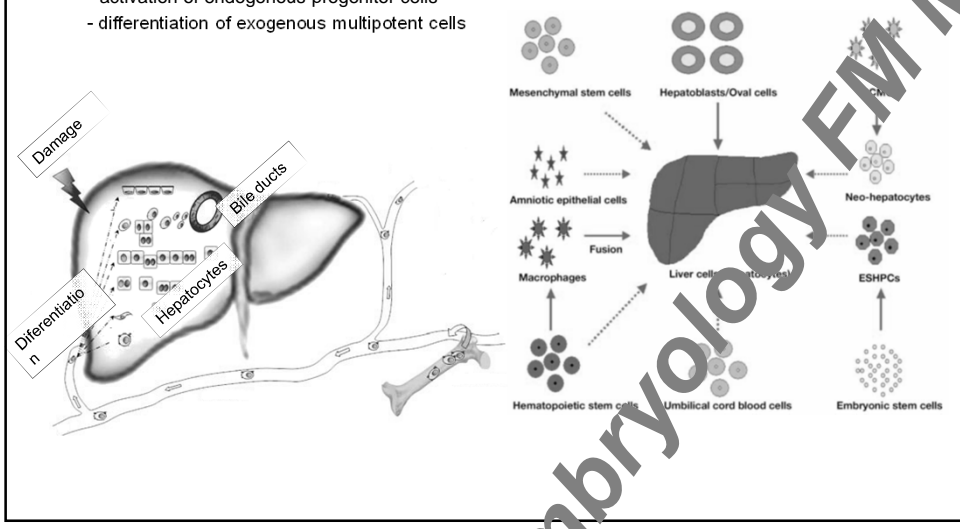
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## REGENERATION OF LIVER TISSUE

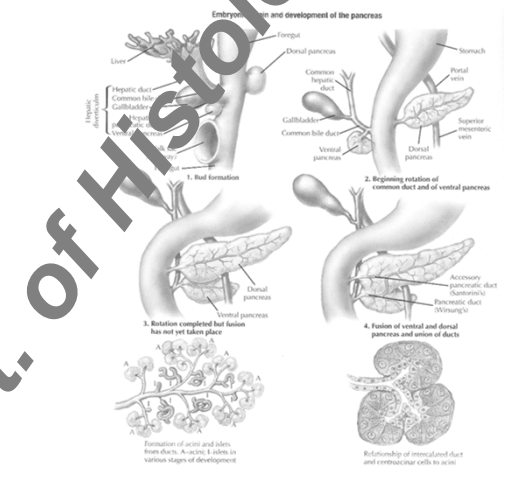
- complex physiological response to damage of liver tissue
- induction of proliferation and growth of liver parenchyma
  - hepatocyte proliferation
  - activation of endogenous progenitor cells
  - differentiation of exogenous multipotent cells



## EMBRYONIC DEVELOPMENT OF PANCREAS

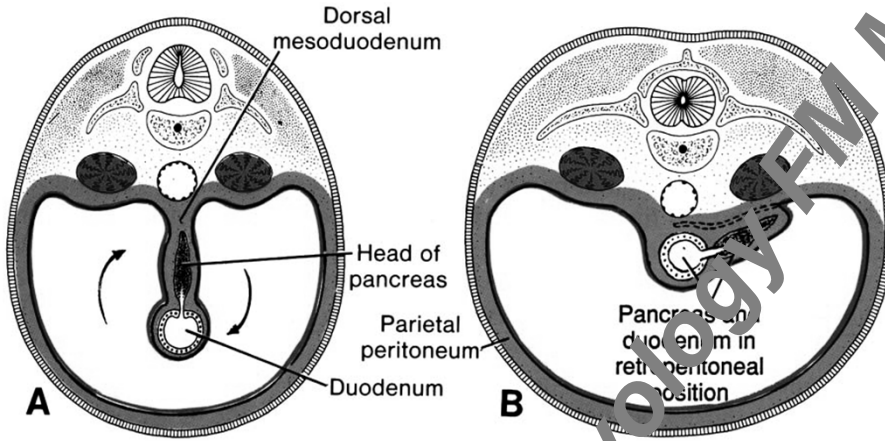


- 6th week of development
- two endodermal diverticula
- dorsal and ventral duodenal diverticulum (= pancreas dorsale et ventrale)
- after rotation of duodenal curve both diverticula fuse
- ducts persist (ventral - major and dorsal - accessorius)
- first ductal system develops
- the secretory acini follow
- cells that are not part of ductal structures differentiate into Islets of Langerhans
- since 4th month in utero - secretory activity



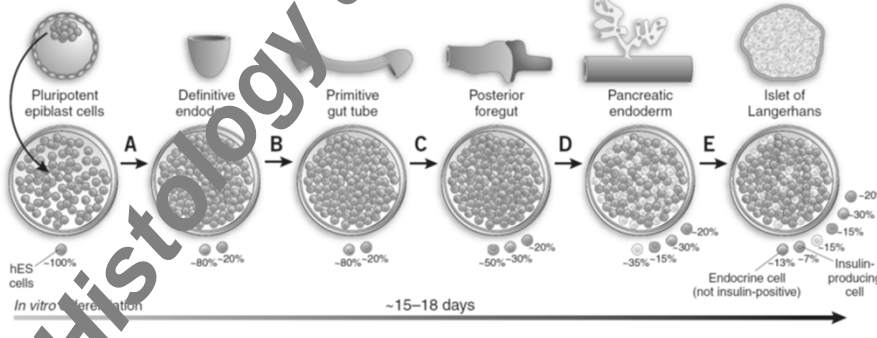
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### EMBRYONIC DEVELOPMENT OF PANCREAS

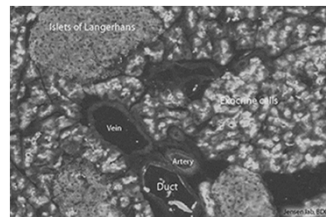


Human pancreas development

12-13 weeks



- A - hESC → endoderm
- B - primitive gut
- C - foregut
- D - pancreatic precursors
- E - Insulin producing β-buňky



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## Summary of GIT II

- Microscopic anatomy of liver: endocrine and exocrine function of liver, vascularization, liver lobulus and its definition, liver cells, ultrastructure and function of hepatocytes, organization of intra- and extra-hepatic passages
- Microscopic anatomy of pancreas: endocrine and exocrine function, pancreatic acinus and its ducts, ultrastructure and function of acinar cells, Islets of Langerhans and their structure, cell types of Islet of Langerhans and their function
- Embryonic development and morphogenesis of digestive tube, liver and pancreas, primitive gut and its derivatives, esophagus, stomach, intestine. Flexion of embryo and rotation, liver and pancreatic diverticulum, differentiation of individual cell types.

### Study materials SEE IS FOR DETAILS

- Sadler: Langman's Medical Embryology, 2000
- Ovalle&Nahirney: Netter's Essential Histology, 2008
- Klika&Vacek: Histologie, 1974
- Ross&Pawlina: Histology (a text and atlas), 2011
- Ross&Romrell: Histology (a text and atlas), 1989
- Berman: Color Atlas of Basic Histology



### Ústav histologie & embryologie LF MU, [www.med.muni.cz/histology](http://www.med.muni.cz/histology)

#### LESSONS, LECTURES AND PRACTICALS

- Čech S., Horký D., Sedláčková M.: Přehled embryologie člověka, Brno, LF MU, 2011
- Horký D., Čech S.: Mikroskopická anatomie, Brno, LF MU, 2011
- Lullmann-Rauch J.: Histologie, Grada 2012
- Ehrmannová, Hušek P., et al. Hepatologie, Grada 2010

StemBook

<http://www.stembook.org/>

**Thank you for attention**

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