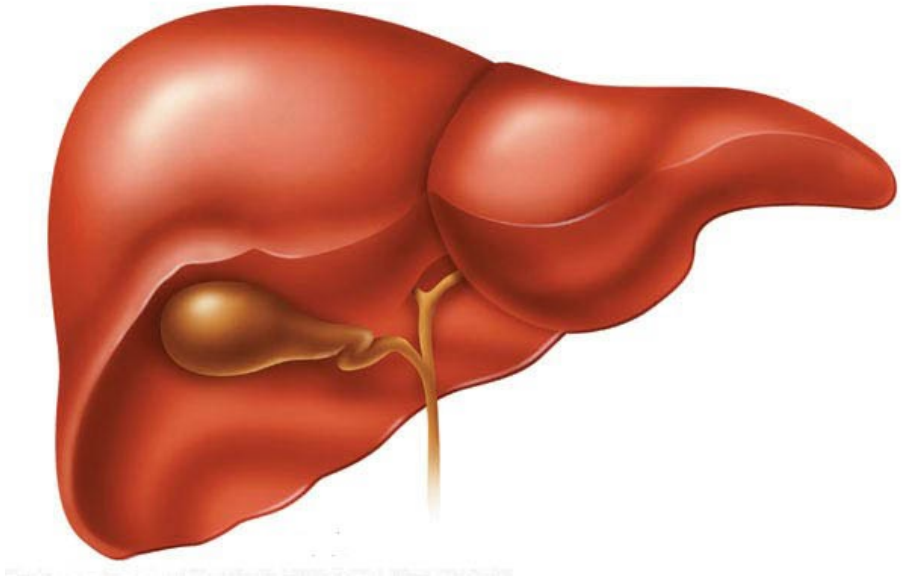
Pathophysiology of GIT II

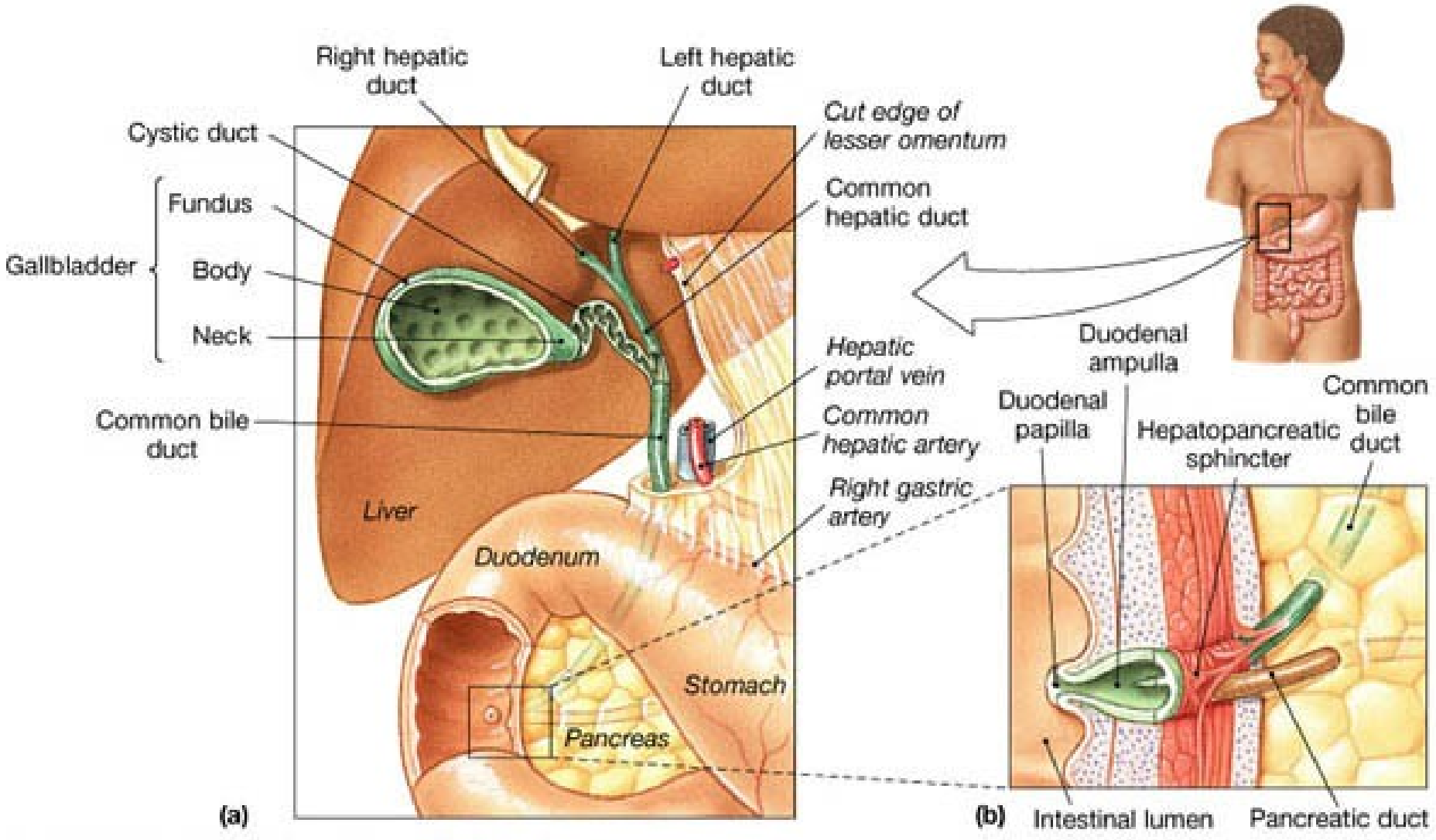
Exocrine pancreas

Liver

Biliary tract

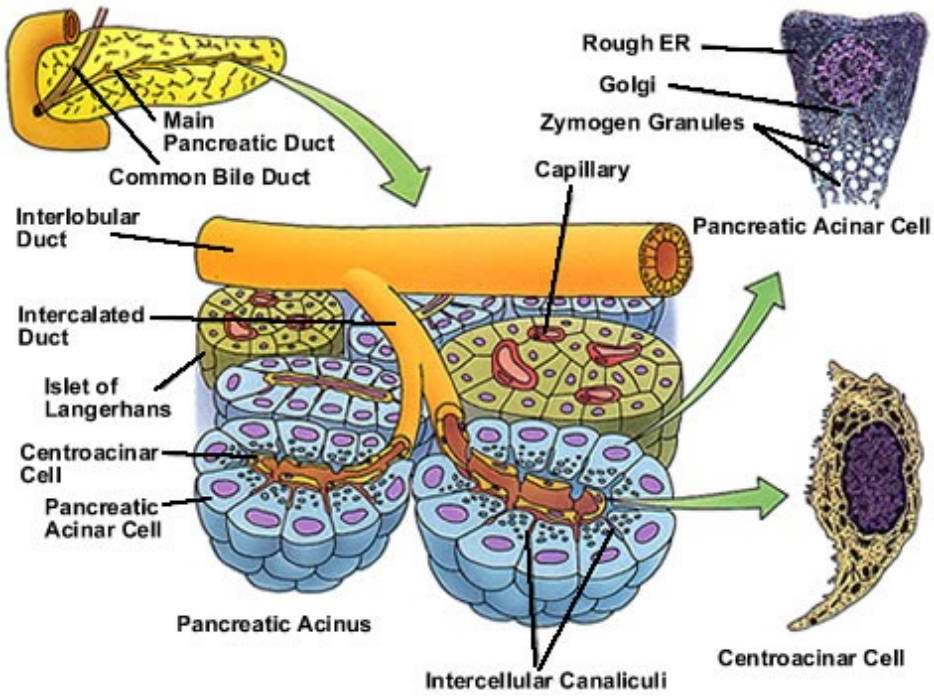


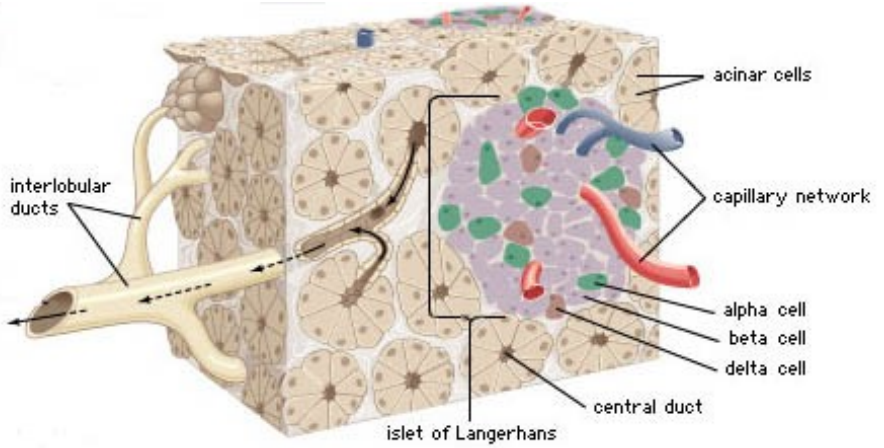
Pathophysiology of exocrine pancreas



Pancreas - secretion

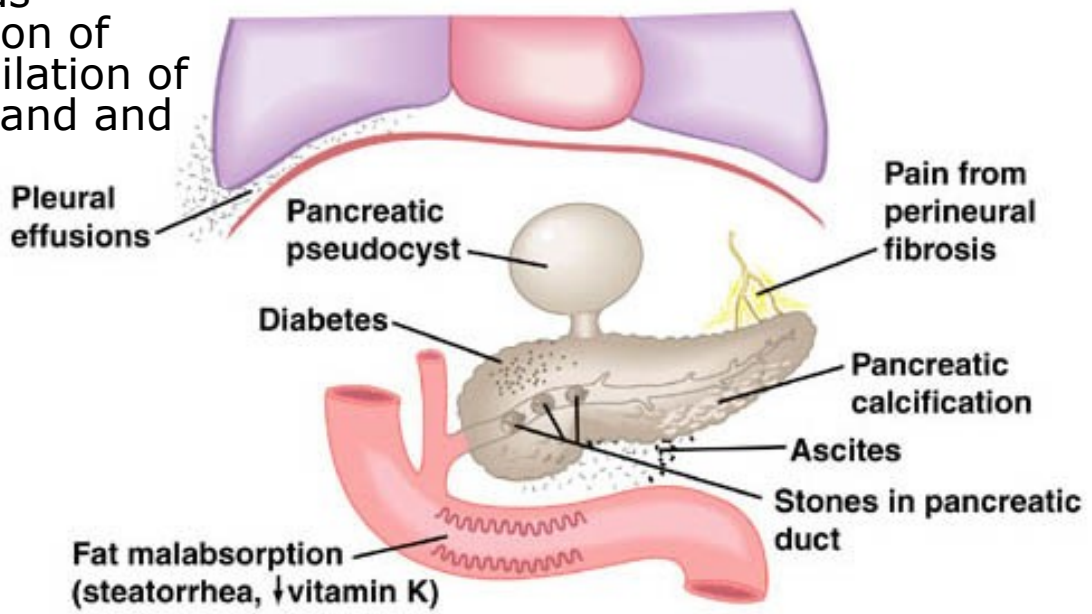
- endocrine part (2%)
  - insulin, glucagon, somatostatin, gastrin, pancreatic polypeptide, amylin
- exocrine part (85%) - acines
  - pancreatic juice (pH up to 8.3)
    - approx. 1-1.5l day
    - production stimulated by acetylcholine, CCK and secretin produced in duodenum
    - production inhibited by pancreatic polypeptide
    - composition
      - ions and water (← secretin)
        - Na, Cl, K and HCO_3^- (up to 150 mmol/l)
        - HCO_3^- necessary to neutralize acid content of stomach, for activation of pancreatic. enzymes and formation of micelle
      - enzymes (← CCK)
        - active - lipase, amylase, ribonuclease, deoxyribonuclease
        - inactive (activated by enterokinase in duodenum) - trypsinogen, chymotrypsinogen, prokarboxypeptidase, proelastase, phospholipase A_2
      - inhibitory trypsinu (α1-antitrypsin)
- disorder of secretion – insufficiency of exocrine pancreas
  - most often due to chron. pancreatitis
  - carcinoma of pancreas, cystic fibrosis, protein malnutrition





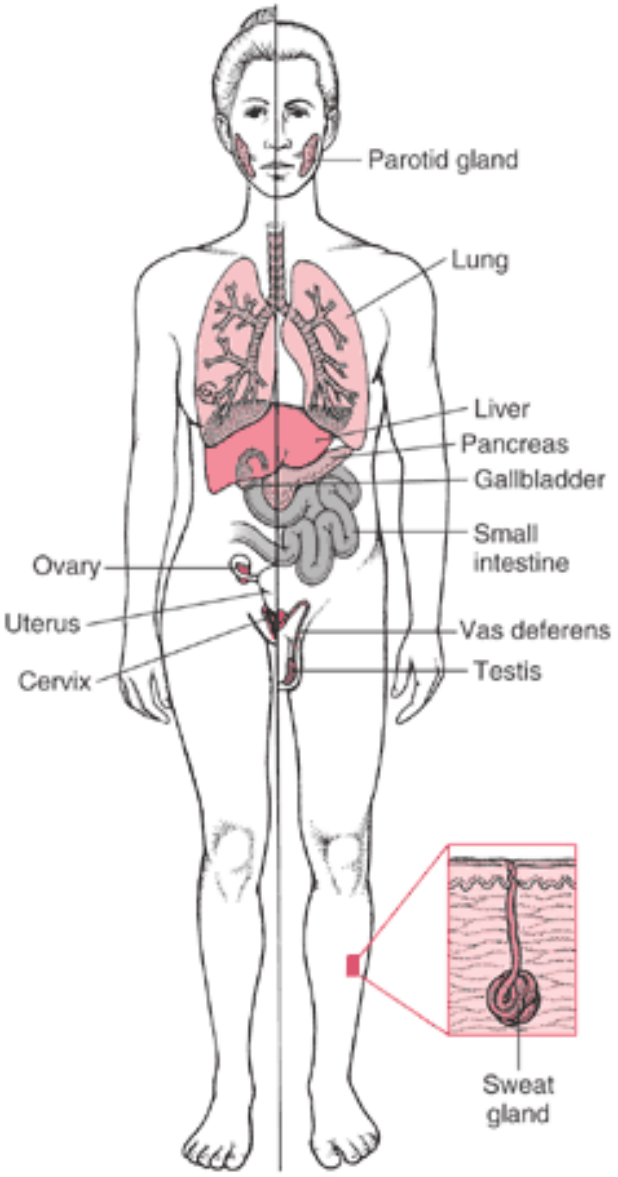
Chronic pancreatitis

- chronic inflammation of pancreas leading to progressive dysfunction of pancreatic acins, stenosis and dilation of ducts, fibrosis and atrophy of gland and calciphications in ducts
- etiology
  - hypertriglyceridemia
  - hypocalcaemia
  - chron. malnutrition
  - alcoholism
  - tropical form
  - hereditarily
  - cystic fibrosis
- consequences
  - absence of lipase
    - maldigestion and malabsorption of fats (→ steatorhea, diarrhea)
    - deficiency of lipid-soluble vitamins
  - absence of amylase and peptidases
    - mostly compensated by stomach and intestinal enzymes, malabsorption of sugars and AA thus clinically insignificant
  - hypocalcaemia and hyperphosphatemia (due to ↓ vit. D) → osteomalacia
  - deficit of vit. B12 (due to deficit of protease its release from dietary sources low) → anemia
  - pain
  - secondary diabetes mellitus (destruction of islets of Langerhans)
- complications
  - cysts, closure of ducts, leak of juice to peritoneal and pleural cavity



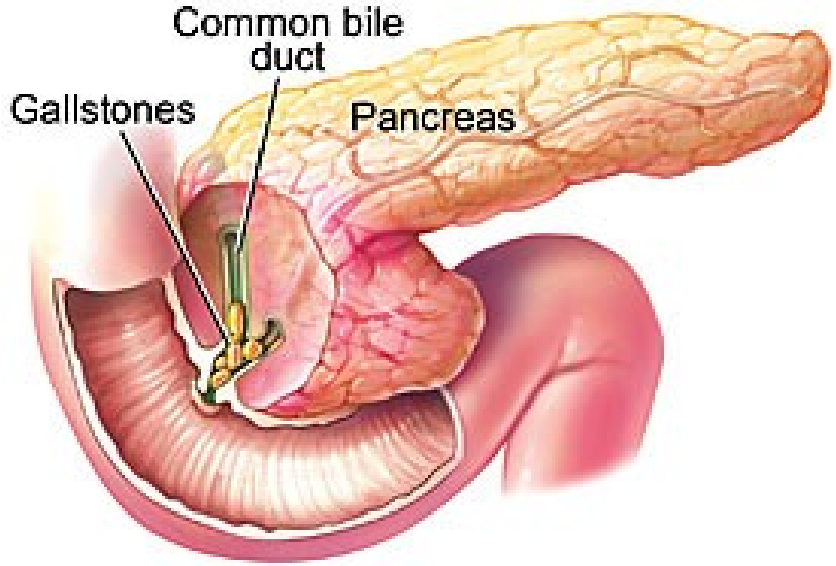
Cystic fibrosis (mucoviscidosis)

- monogenic (AR) disease due to mutation in gene encoding "cystic fibrosis transmembrane conductance regulator" (CFTR)
  - >600 known mutations in one of the 4 classes
    - I – defective protein (preterm stop of translation of CFTR mRNA)
    - II – increased degradation of protein in endopl. reticulum (incl. the most common mutation ΔF508 ~70%)
    - III – inactivated channel
    - IV – defect of transport
- function of CFTR
  - encodes a complex protein forming chloride channel
  - regulates other channels (e.g. Na)
- CF affects
  - epithelia of respiratory tract
    - viscous secret, limitation of respiration and coughing, terrain for infection (Pseudomonas aeruginosa) → chron. bronchitis, bronchiectasis, pneumonia
  - epithelia in pancreatic ducts
    - recycling of Cl involved in secretion of HCO_3^- into pancreatic juice → due to decreased bicarbonate too viscose protein secret blocking ducts(chron. pancreatitis)
  - sweat glands
    - decreased reabsorption of Cl (diagnostic sign - high Cl in sweat)
  - intestine
    - meconic ileus of newborns
  - liver and biliary tract
  - genitals



Acute pancreatitis

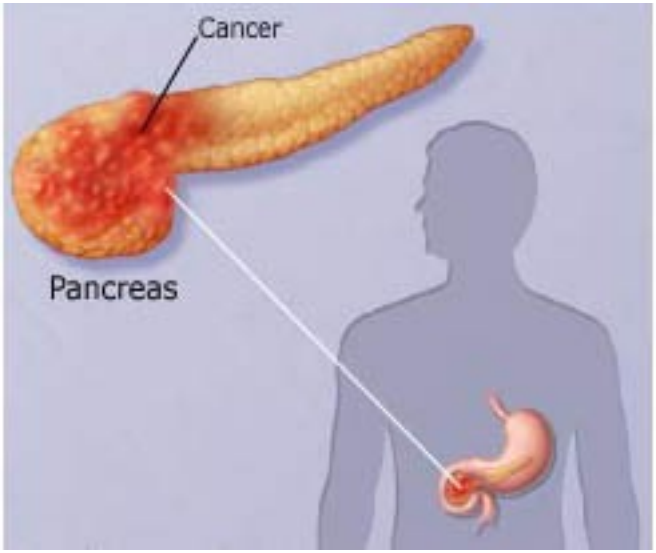
- acute destruction of pancreatic tissue and neighboring tissue due to autodigestion by pancreatic enzymes activated directly in the gland
- very serious and severe condition associated with high mortality
- symptoms
  - intensive pain
  - nausea and vomiting
  - fever
- etiology
  - biliary
    - blockade by bile stone in common duct
  - alcohol
    - relaxation of sphincter of Oddi
    - reflux of bile into pancreatic duct
  - abdominal trauma
  - infection
  - hypertriglyceridemia
  - hypercalcaemia
  - drugs



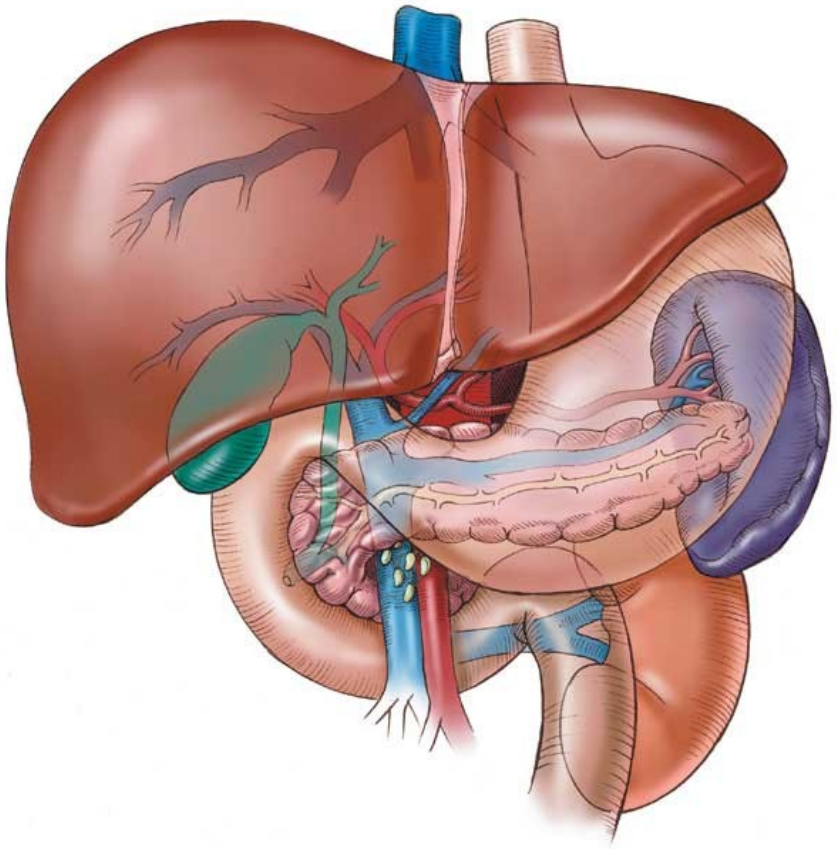
- pathogenesis
  - intracellular and extracellular activation of trypsinogen and subsequently of other enzymes
    - cathepsine B in low pH
  - autodigestion of gland
  - elastase digests elastin in vessel walls → hemorrhage into gland, leak of juice into circulation and damage of systemic circulation
  - lipolysis of pancreas by pancreatic lipase and phospholipase A2

Tumors of pancreas

- most commonly adenocarcinoma
  - ↑ risk
    - chron. pancreatitis
    - smokers
    - chron. alcoholism
  - typically head and body, less often caudal pancreas
  - signs
    - obstructive icterus (compression of biliary duct)
    - pancreatic insufficiency
    - thrombophlebitis
  - very poor prognosis
- tumors of endocrine pancreas
    - insulinoma (hypoglycemia)
    - gastrinoma (Zollinger-Ellison syndrome)
    - VIPoma (diarrhea, hypokalemia)
    - carcinoid

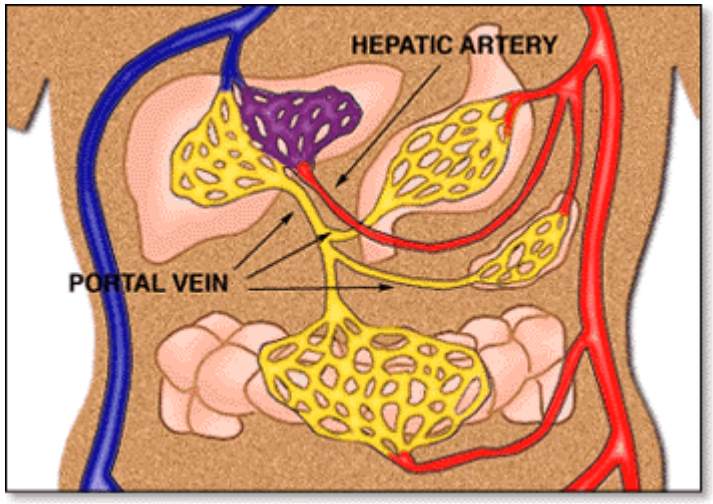


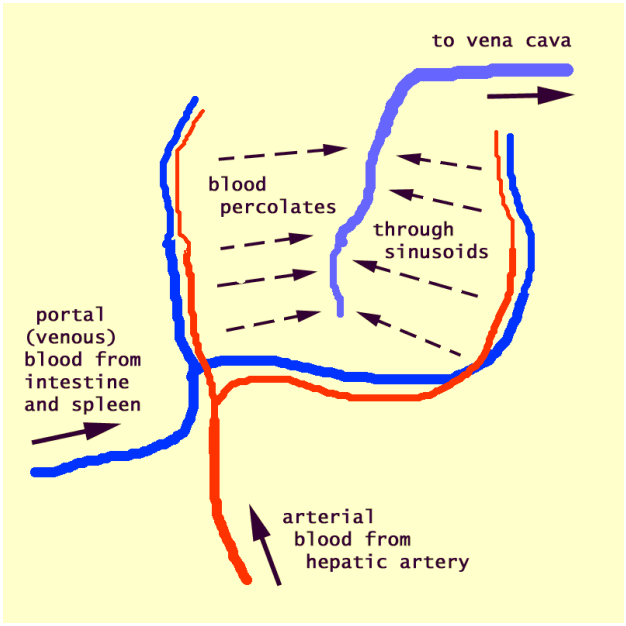
Anatomy and histology of liver



- liver (hepar) ~1.5kg
- 2 lobes (sin. and dx.) divided by ligament
- liver parenchyma has characteristic architecture
  - liver lobule is a basic morphologic unit
    - central vein lobule
    - peripheral portobiliar "trias"
  - liver acinus is basic functional unit
    - part of the tissue supplied by branches of one circumlobular vein
- function of liver
  - complex metabolic function
    - saccharides
      - glycogen synthesis, glycogen lysis, gluconeogenesis
    - lipids
      - clearance of lipoproteins, synthesis of cholesterol, synthesis of TAG
    - proteins
      - trans- and de-amination of AA, protein synthesis (albumin, clotting factors)
  - formation of bile
  - metabolisms of haem
  - biotransformation, detoxification
    - hormones, drugs, toxins, ammoniac from intestine
  - storage of vitamins and trace substances

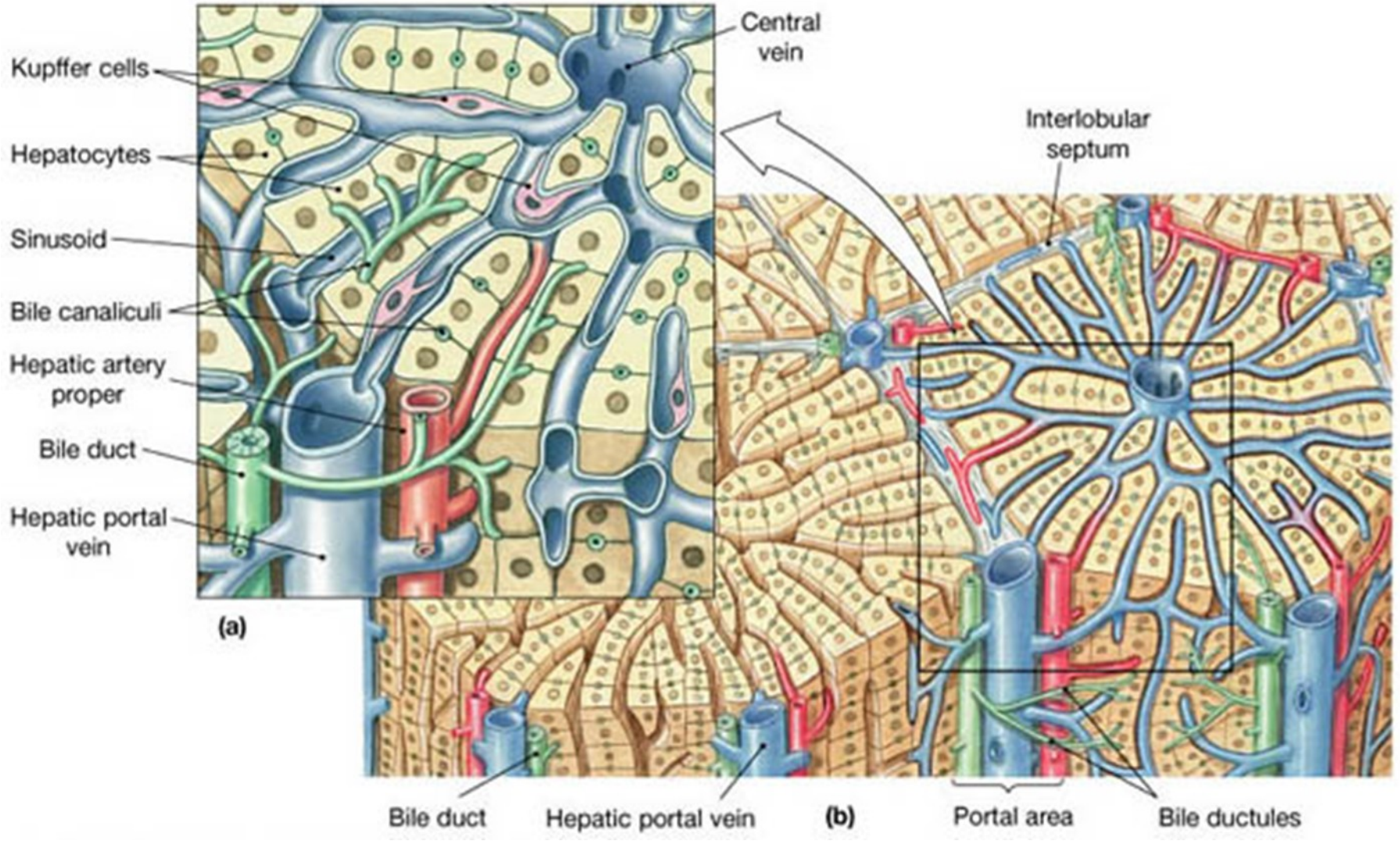
Liver blood supply



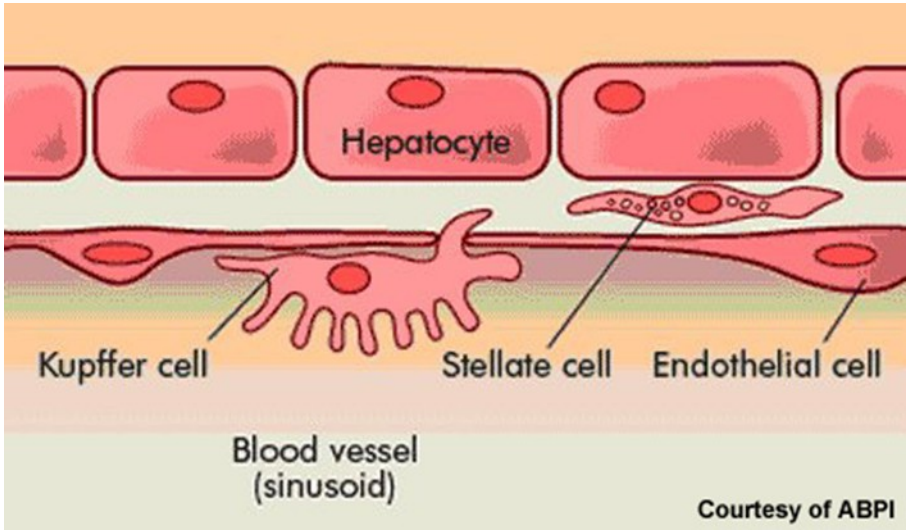


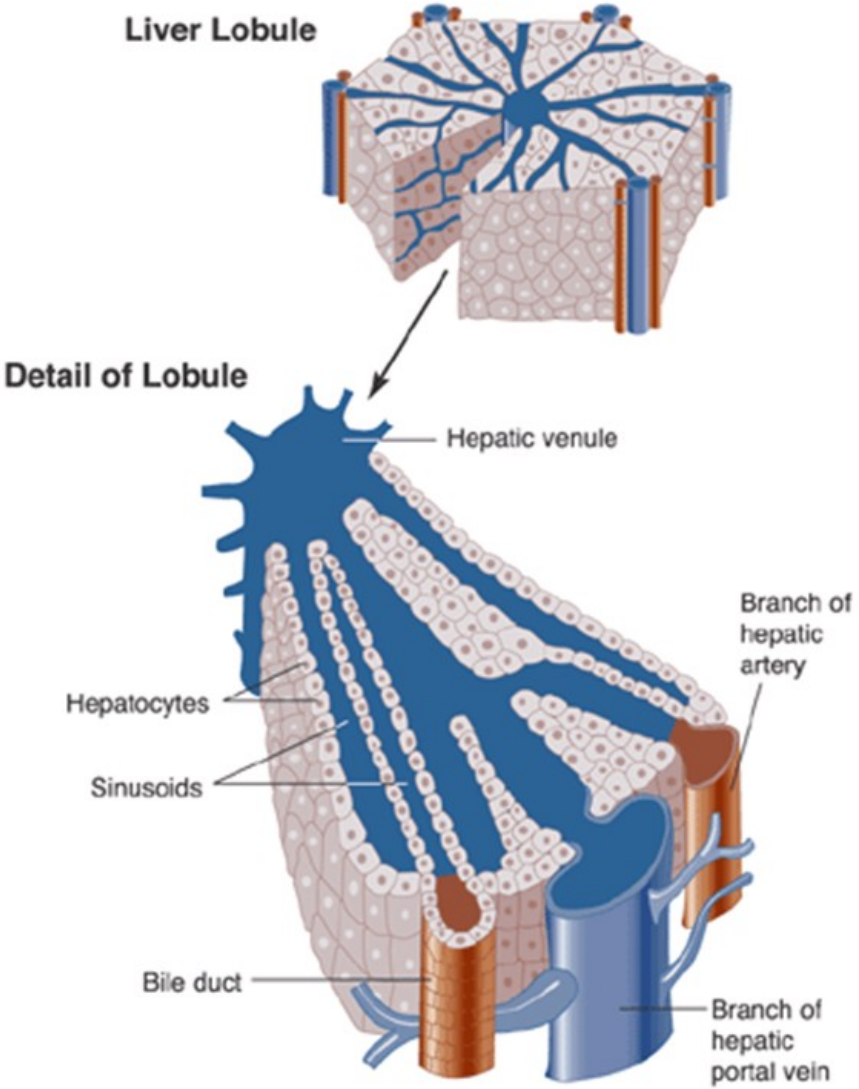
- v. portae (80% of blood supply)
  - drainage from splanchnic organs (= functional supply)
    - capillaries from stomach, intestine, pancreas and spleen connect in portal vein
    - its branches encircle liver lobules (v. interlobulares and circumlobulares)
    - they enter them as liver sinusoids
    - sinusoids join to form central vein
- a. hepatica (20% of supply)
  - branch of truncus coeliacus (= nutritional supply)
    - drain to sinusoid and then to the central vein
- v. hepatica
  - drainage from liver
    - central veins connect to right and left liver vein leading to lower vena cava

Morphology of liver - lobule

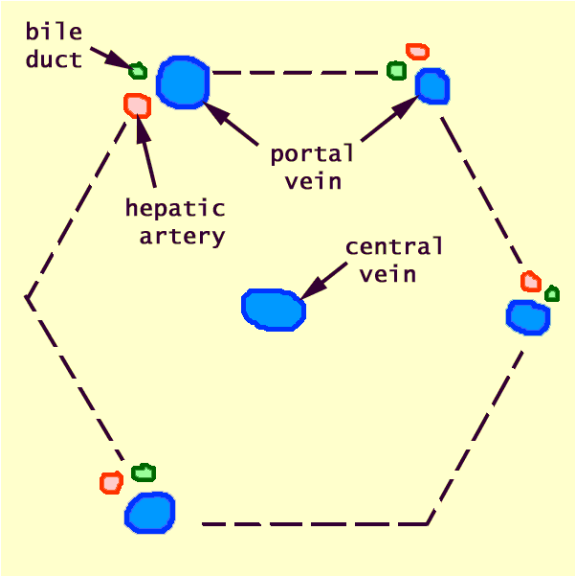


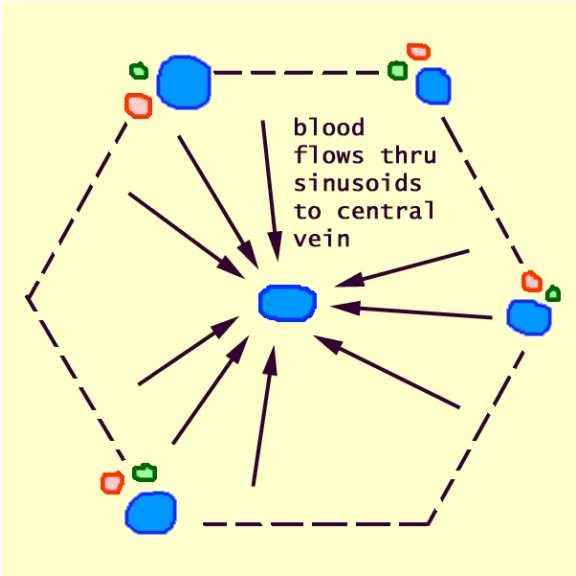
Details of liver architecture

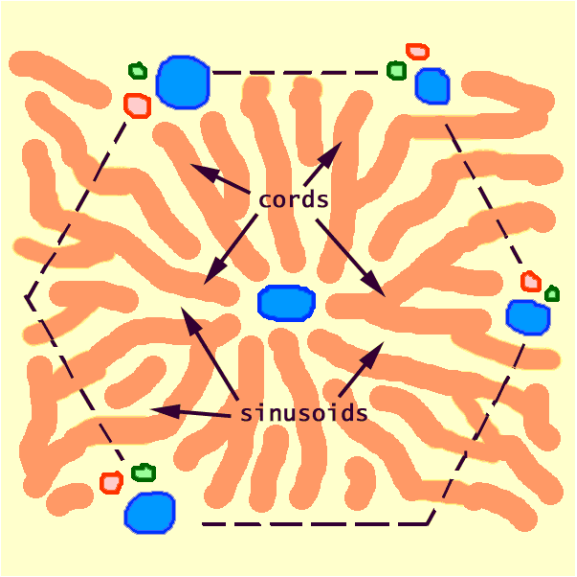


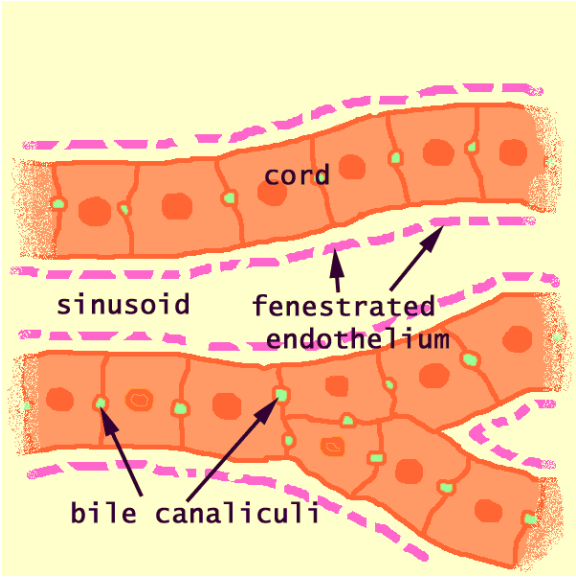


Liver lobule schematically

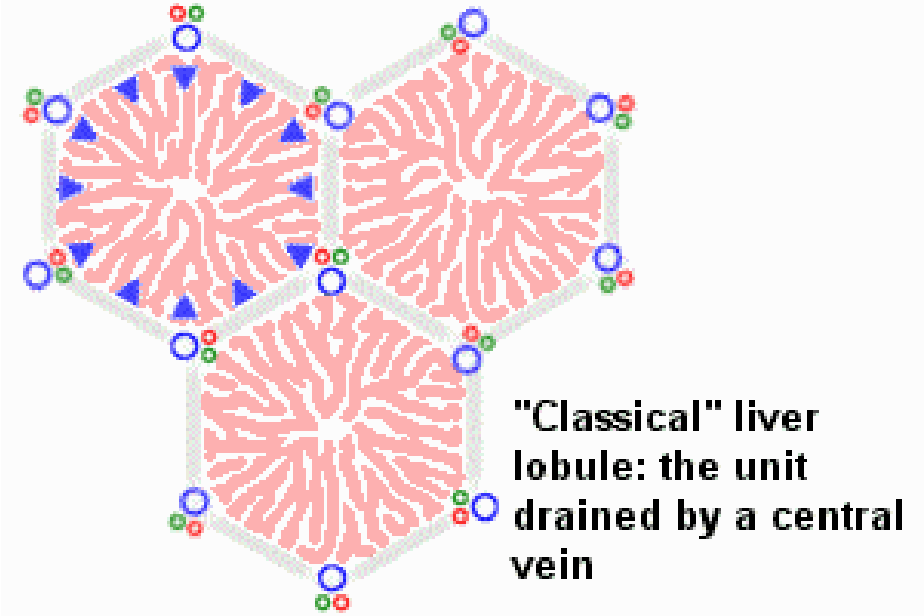




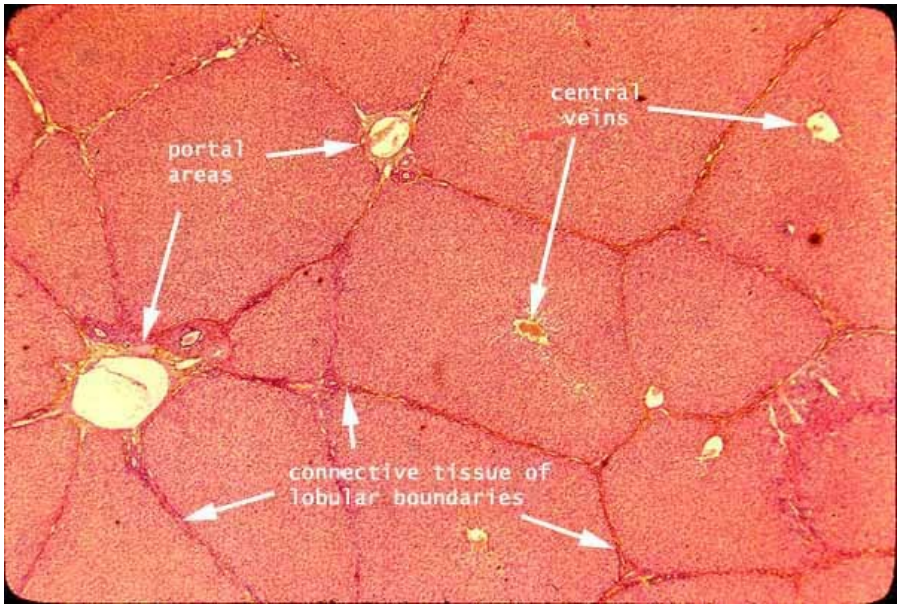




Liver lobule vs. acinus

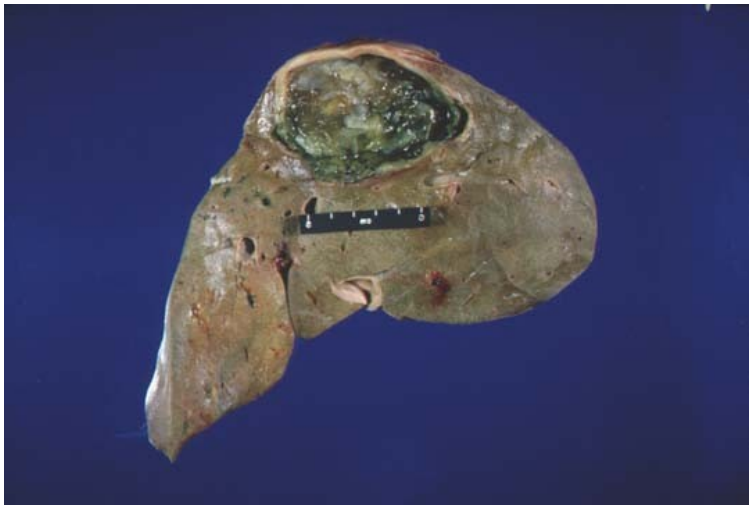


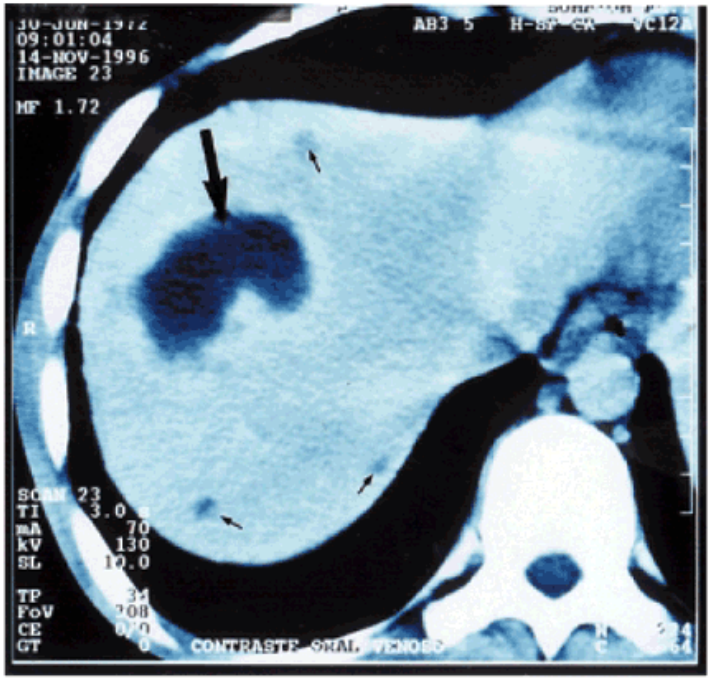
"Classical" liver lobule: the unit drained by a central vein



Etiology of liver damage

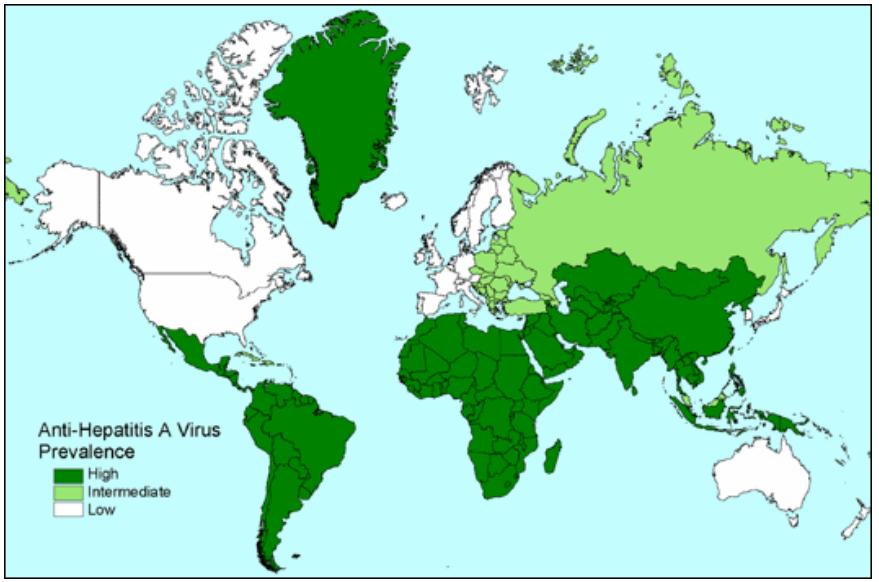
- infection
  - viral
    - hepatitis viruses (HAV, HBV, HCV, …)
    - inf. mononucleosis (EBV)
  - bacterial
    - leptospirosis
  - parasite
    - Echinococcus
      - globally, Europe - Mediterranean
    - Schistosomiasis (= bilharzias)
      - Africa, J. America, Caribbean, SE Asia
    - malaria
- toxic
  - alcohol
  - faloidin (Amanita faloides)
  - drugs (e.g. paracetamol)
  - chemicals
- autoimmune
  - autoimmune hepatitis
  - prim. biliary cirrhosis
- metabolic disorders
  - common - NAFLD/NASH
  - rare
    - heredit. hemochromatosis
    - Wilson disease
    - porphyria
    - glycogenosis
- tumors
  - primary (hepatocellular carcinoma)
  - metastases

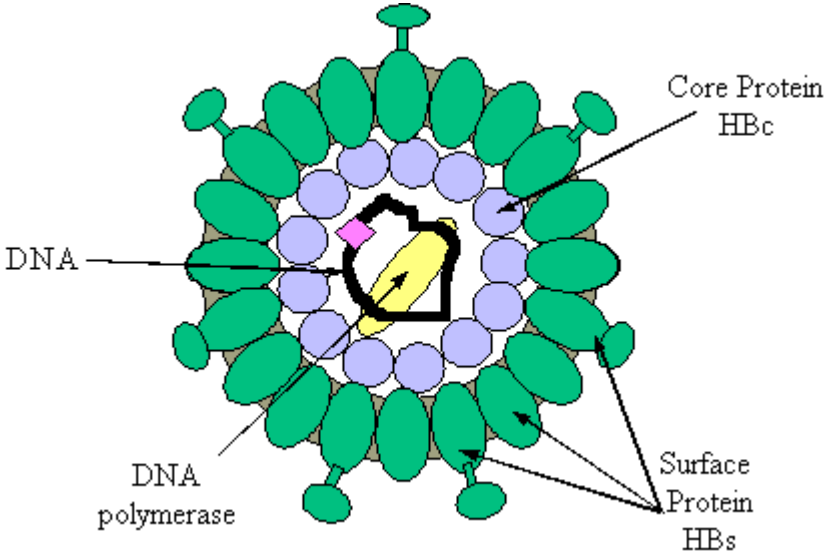




Liver infection - hepatitis

- time course
  - acute
    - ussually without residual damage
    - fulminant form leading to liver failure
  - chronic
    - only persistent infection (carriers)
    - necrosis of parenchyma and progression to cirrhosis
- viral hepatitis
  - hepatitis A (HAV – RNA virus)
    - only acute time course
    - virus directly cytotoxic
    - epidemic
    - fecal-oral transmission (vaccination)
  - hepatitis B (HBV – DNA virus)
    - blood borne (parenteral) and STD
    - time course
      - virus is not directly cytotoxic, damage is the results of the reaction of immune system
      - mostly acutely without residual damage
      - in 10% of cases progresses to chronicity
        - either solely HBsAg positive carriers
        - or active process leading to fibrosis and cirrhosis)
  - hepatitis C (HCV – RNA virus)
    - blood born (parenteral) and STD
    - acute phase typically asymptomatic
    - more than 80% cases progress to chronicity – can lead to cirrhosis

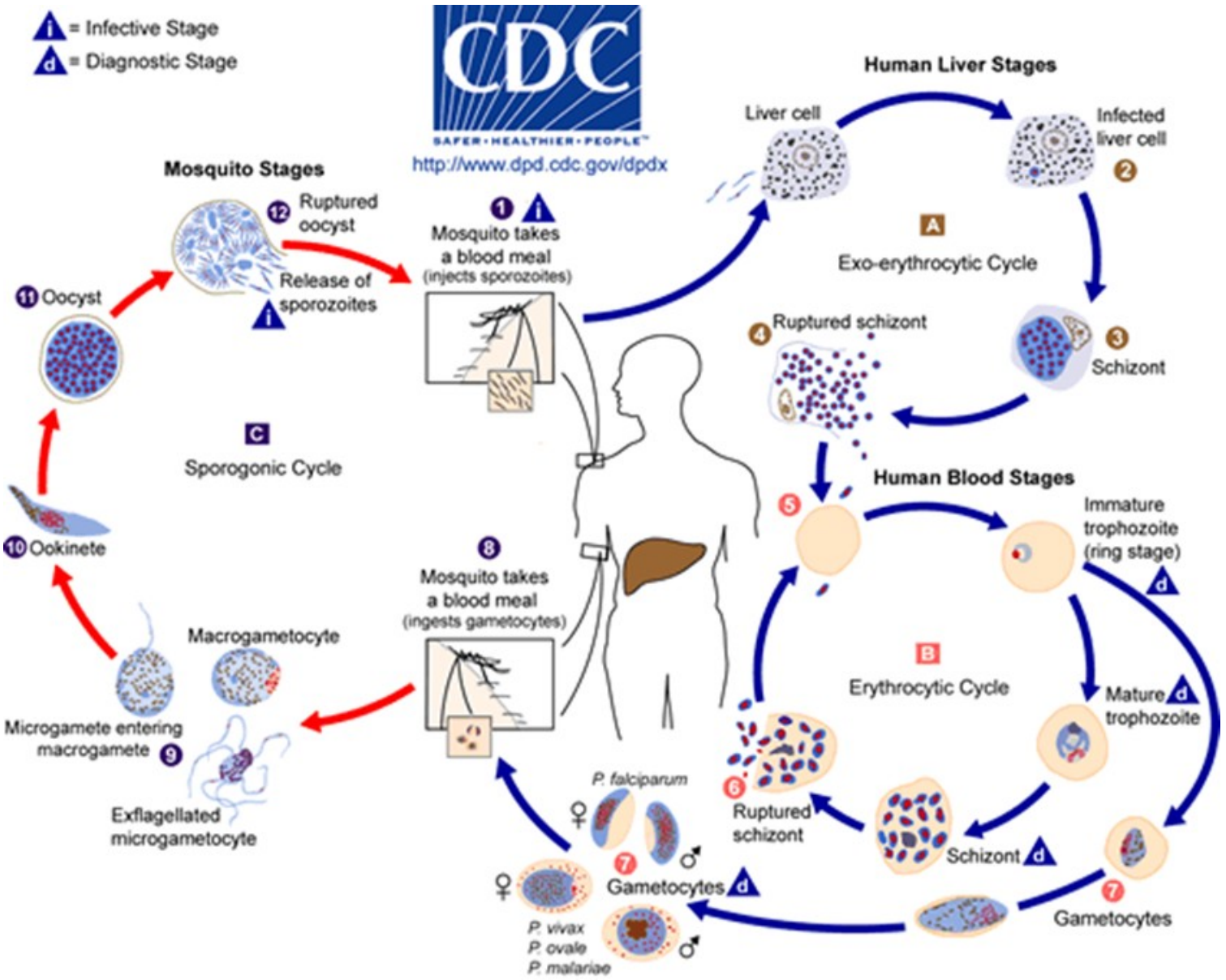




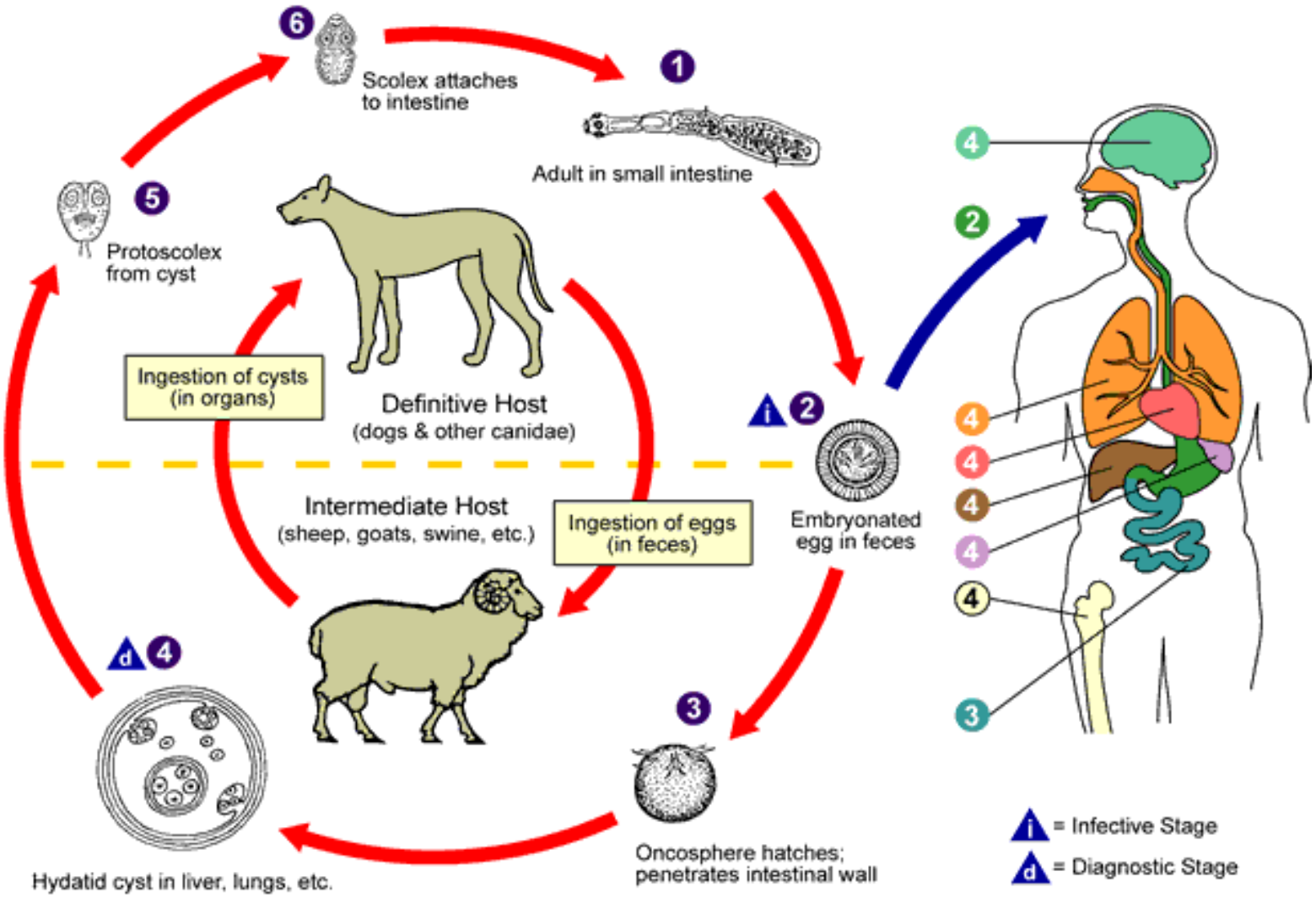
Hepatitis Viruses

Virus Family	Hepatitis A Picornavirus	Hepatitis E Calicivirus	Hepatitis B Hepadnavirus	Hepatitis C Flavivirus	Delta virus Satellite virus (only in combination with HBV)
Commonality	All generate conditions of illness in the liver				
Symptoms (acute)	All the same – malaise, dark urine, anorexia, nausea, vomiting, jaundice				
Transmission	Enteric (food and water)		Sex, blood and close contact		
Chronic condition	No	No	Yes	Yes	Yes
Virus genome	+ss RNA	+ss RNA	DNA with reverse transcriptase activity	+ss RNA	-ss RNA
Virus antigens	HA Ag	HEV ORF2 proteins	HBsAg HBcAg HBeAg	Many – core E1 E2 NS3	Delta antigen
Incubation	1 month (15 – 50 d)		4 months (45 – 160 d)	2 months (15 – 150 d)	1 – 2 months
Current therapeutics	No specific treatment	No specific treatment	Interferon alpha, Lamivudine, Adefovir, Etecavir	Interferon alpha + ribavirin, Pegylated Interferon	Follow HBV therapy
Vaccines available?	Yes Havrix (GSK) Vacta (Merck)	No	Yes Engerix-B (rHBsAg) GSK Recombivax B (Merck)	No	Can be prevented by vaccination against HBV

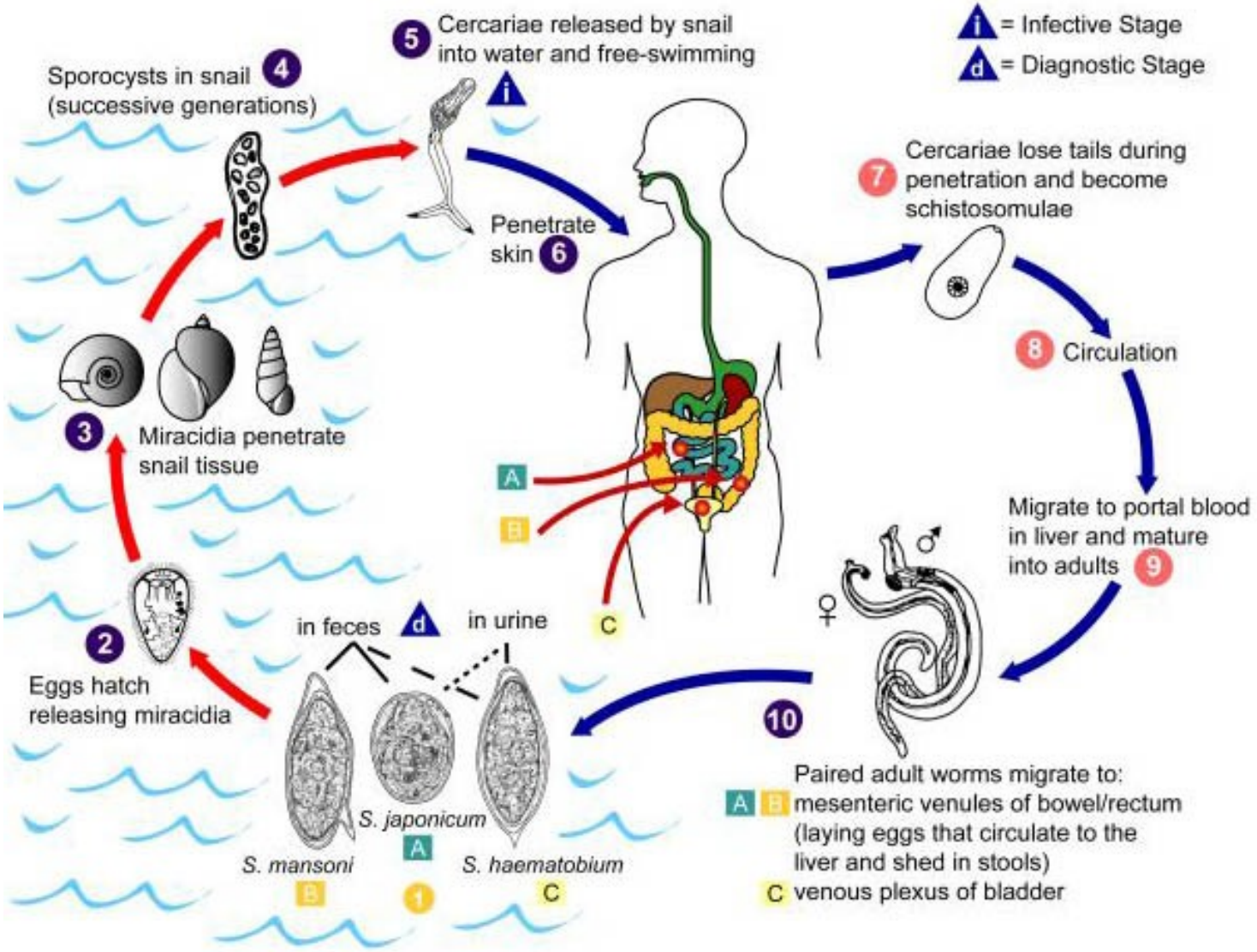
Cycle of *Plasmodium*



Cycle of *Echinococcus granulosus*

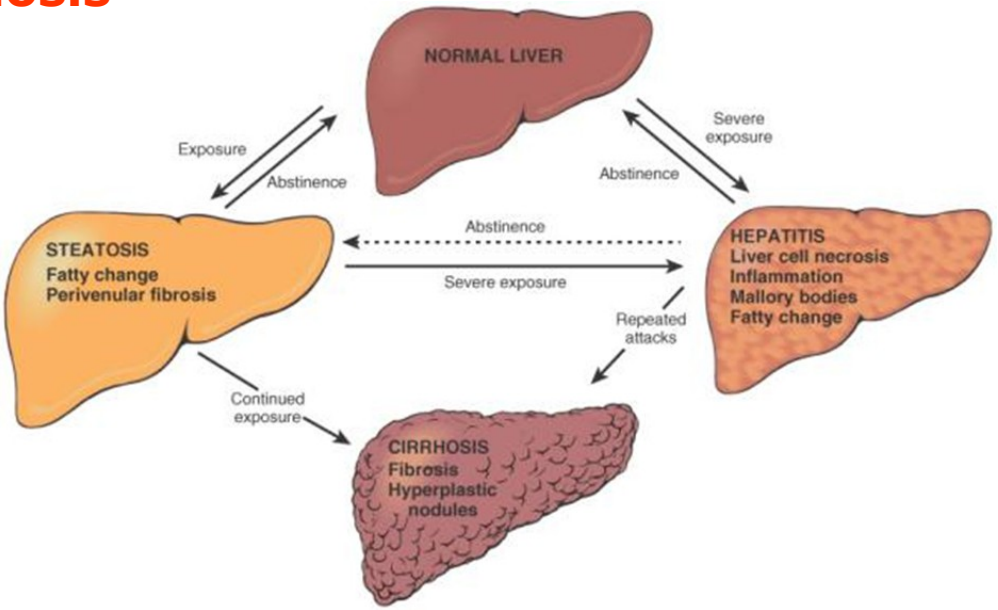


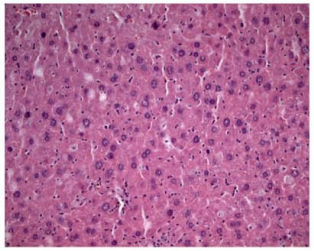
Cycle of *Schistosoma mansoni*



Reaction of liver to damage

- liver can react the same way to various etiologies of damage
  - mild damage change metabolic activity of hepatocyte, which become to cumulate fat (= **steatosis**)
  - steatosis with lab. signs of inflammation is called **steatohepatitis**
  - more severe damage leads to cell death, however liver has a considerable ability to regenerate
  - long-term damage leads to production of connective tissue in periportal areas (= **fibrosis**)
  - combination of intensive necrosis, fibrosis and regeneration significantly altering lobular architecture is called **cirrhosis**





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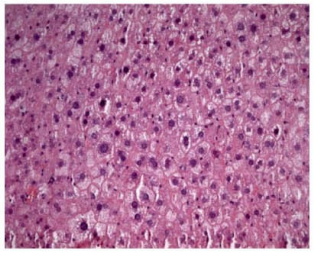

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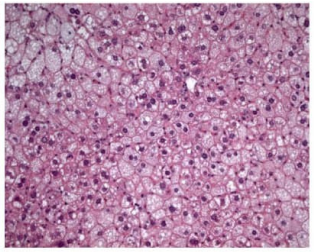

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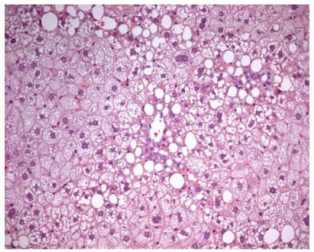
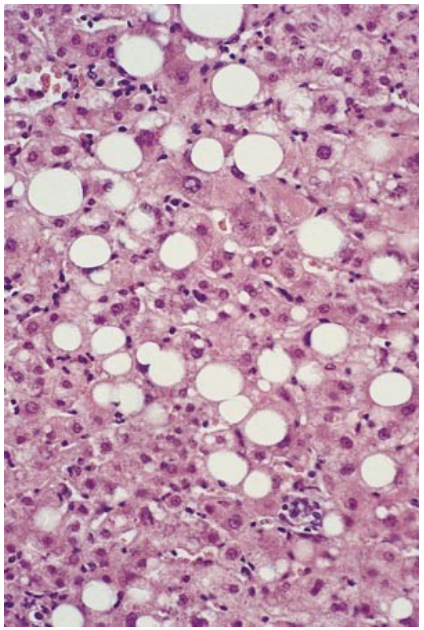
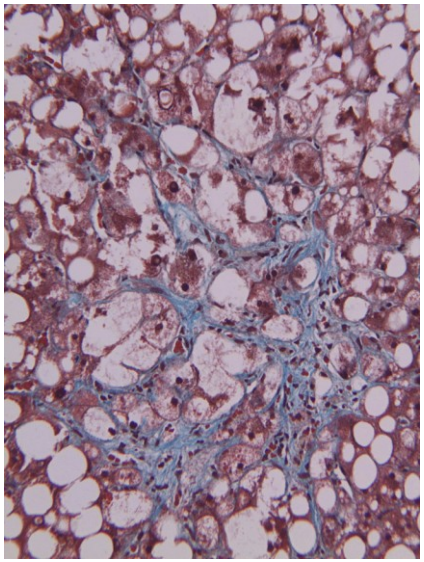


Initial (reversible) liver damage

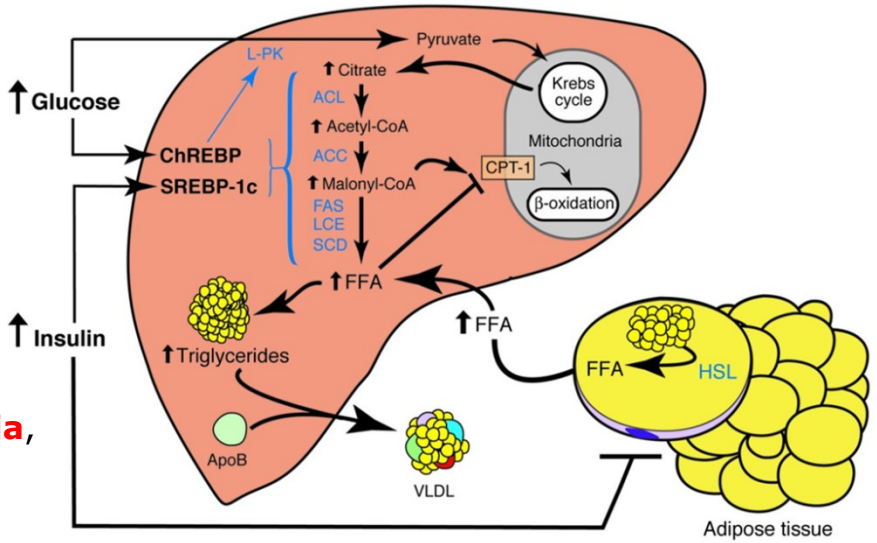
- **steatosis (S)**
  - normally fat content (TAG) in hepatocytes <5%
    - histologically microvesicular or macrovesicular
  - causes
    - excessive dietary intake or lipolysis in adipose tissue
    - increased endogenous synthesis
    - decreased catabolism in liver
    - combination
  - steatosis itself is not harmful for liver (sometimes is even considered protective mechanisms), however it represents substrate for increased lipid peroxidation
- **steatohepatitis (SH)**
  - together with S also necrosis, inflammation and fibrosis
  - more serious than simple S (which is reversible when causing factor ceases)
  - it can reverse to normal or progress to fibrosis or cirrhosis
  - transition of S to SH enhanced by other factors such as oxidative stress, endotoxin, immune system, nutrition etc.
- etiology S a SH
  - alcoholic
    - energetic content of alcohol
    - alteration of intermediary metabolism
      - inhibition of β-oxidation
      - ↑ NADH and acetyl-CoA (↑ synthesis FFA)
  - non-alcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH)
    - component of insulin resistance syndrome
      - ↑ lipolysis in adipose tissue – ↑ uptake of FFA by liver
      - ↑ peroxidation of lipids and ox. stress for hepatocytes
      - hypeinsulinemia stimulates synthesis of FFA and TAG





NAFLD and NASH

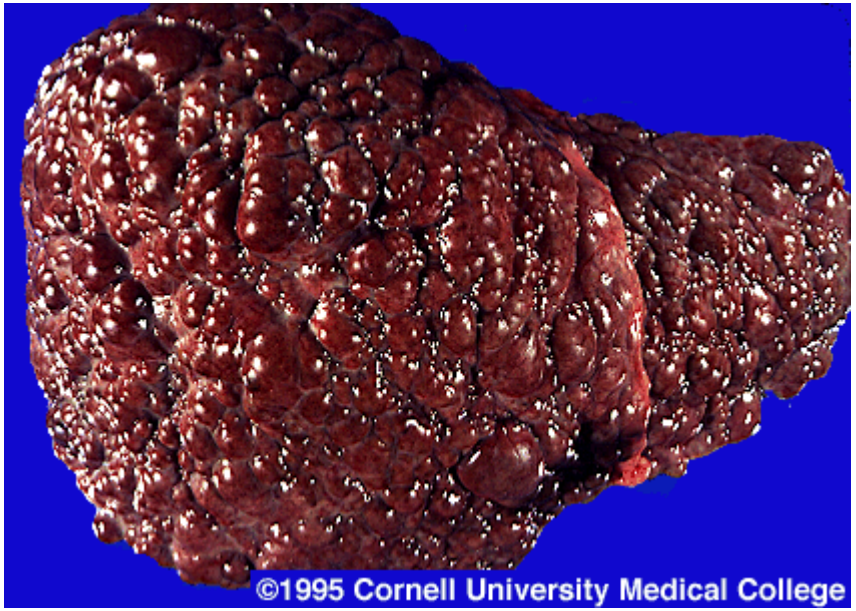
- prevalence ~20 - 30% in industrialised countries (associated with **OBESITY**!!!)
- can be difficult to dissect non-alcoholic from alcoholic damage in countries where alcohol consumption is socially accepted and common
  - definition of non-alcoholic etiology: daily intake <10g/day in men (i.e. ~140g ethanol per week) and (~70g ethanol in women)
- pathogenesis of NAFLD/NASH = metabolic alterations resulting in hepatic triglyceride accumulation in **insulin-resistant states**
  - insulin resistance is manifested by **hyperinsulinemia**, increased hepatic glucose production, and decreased glucose disposal
  - in adipocytes, hyperinsulinemia increases hormone-sensitive lipase (HSL) activity, resulting in elevated rates of triglyceride lipolysis and **enhanced FFA flux to the liver**
    - FFAs can either be oxidized in the mitochondria to form ATP or esterified to produce triglycerides for storage or incorporation into VLDL particles
  - in liver, hyperinsulinemia induces SREBP-1c and ChREBP expression, leading to the transcriptional activation of all lipogenic genes and the enzymatic machinery necessary for the **conversion of excess glucose to fatty acids**
  - a consequence of increased fatty acid synthesis is increased production of malonyl-CoA, which inhibits CPT-1, the protein responsible for fatty acid transport into the mitochondria
  - thus, in the setting of insulin resistance, FFAs entering the liver from the periphery, as well as those derived from de novo lipogenesis, will be preferentially esterified to triglycerides.
    - ACL, ATP citrate lyase; CPT-1, carnitine palmitoyl transferase-1; FAS, fatty acid synthase; LCE, long-chain fatty acyl elongase



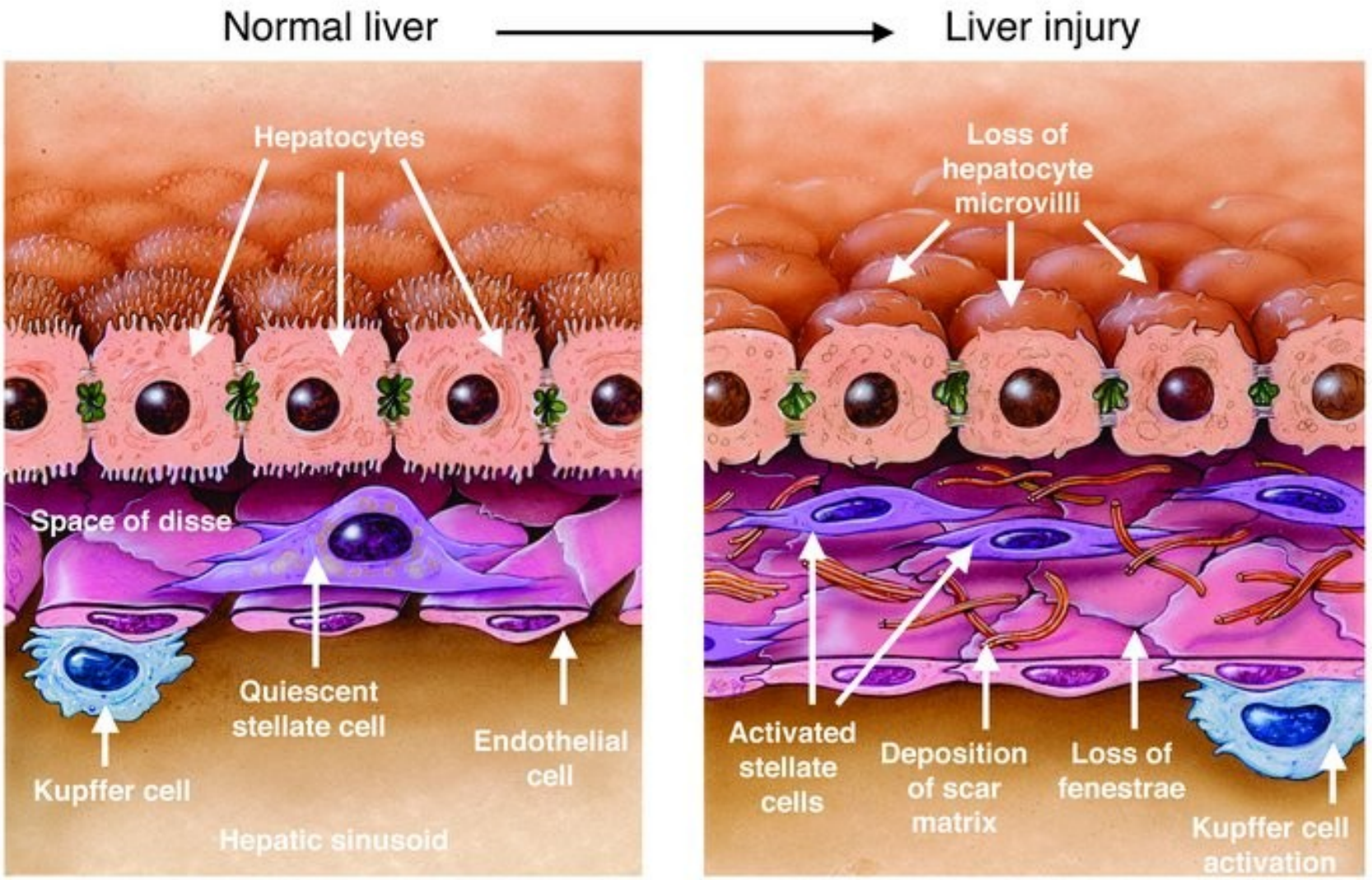
- NAFLD represent good terrain for lipid peroxidation due to oxidative stress
  - ↑ox. stress in ins. resistance (↑ resistin, TNFa, IL-6 and other pro-inflammatory adipokines)
- products of lipid peroxidation – malondialdehyd (MDA) or 4-hydroxynonenal (HNE) – stimulate Kuppfer and HSC to fibroproduction and chemotaxis of neutrophils

Advanced (irreversible) liver damage

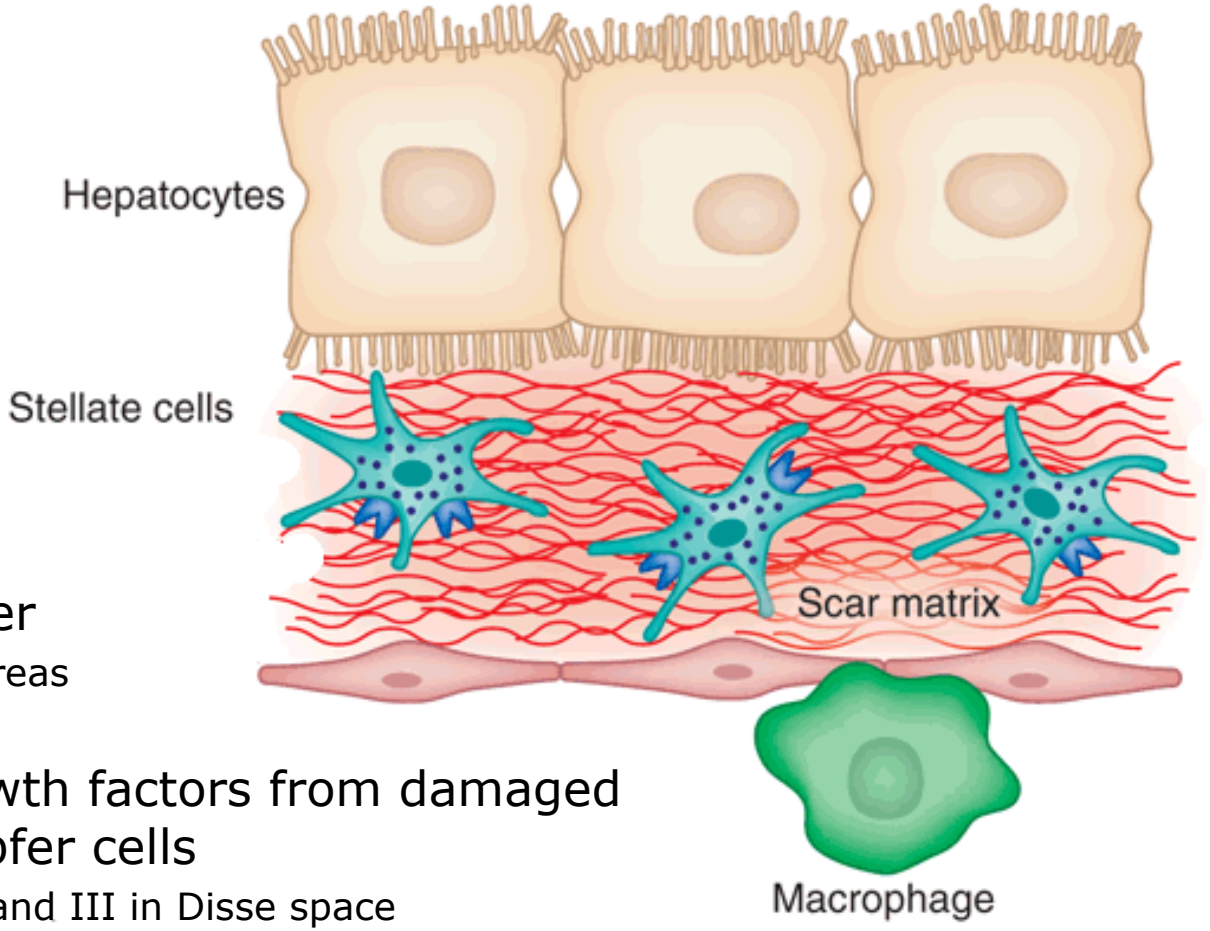
- result of chronic damage of hepatocytes
  - infection, alcohol, toxic substances, accumulation of metals (Cu, Fe), drugs, …
- **fibrosis (F)** = increased content of connective tissue
  - damaged hepatocyte activate Kuppfer cells which release paracrine factors (PDGF and TGF-β)
  - activation of hepatic stellate cells (HSC)
    - regulation of blood flow through sinusoids (↑ resistance)
    - synthesis of connective tissue (collagen, laminin, …)
    - release of photolytic enzymes (matrix-metaloproteinases)
  - alteration of morphology of sinusoids (loss of fenestrations of endothelia), accumulation of extracel. matrix
- **cirrhosis (C)**
    - histologically micronodular or macronodular
  - irreversible change of architecture (lobules, vessels, collagen)
  - fibrosis + necrosis + nodular regeneration
  - loss of functional parenchyma
  - portal hypertension and liver failure
  - ↑ risk of carcinoma
- general symptoms of advanced liver diseases
  - weakness, weight loss
  - jaundice
  - bleeding (deficit of clotting factors)
  - edema, ascites (hypoalbumiemia)
  - prolonged action of hormones
    - gynecomastia in men
    - spider nevi
  - liver encephalopathy (ammonia)



Role of HSC in l. fibrosis on hepatic sinusoidal cells

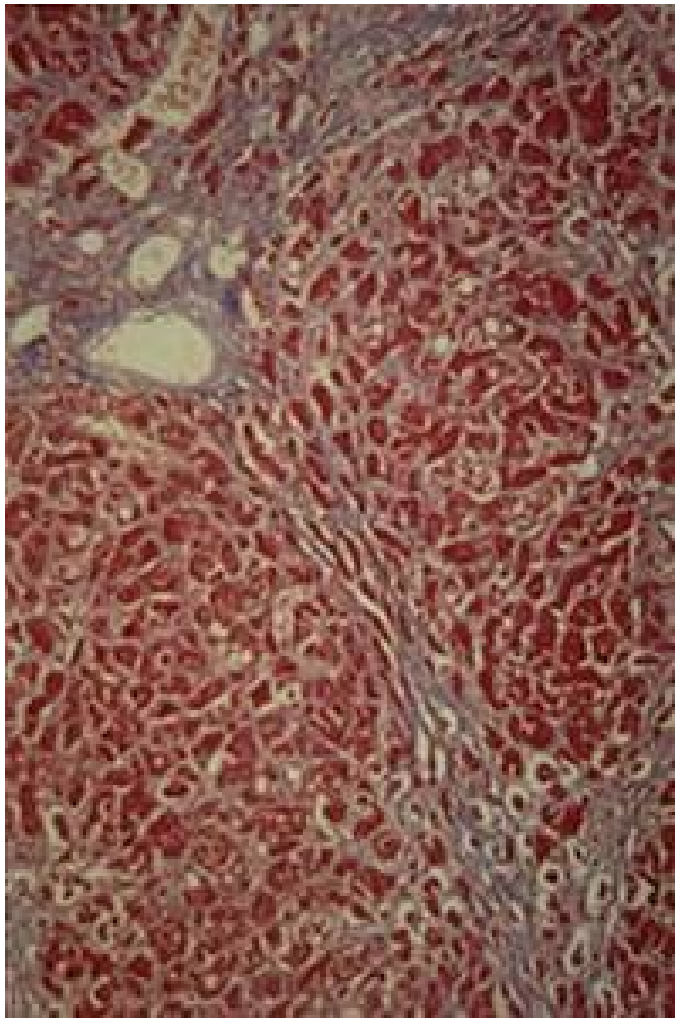


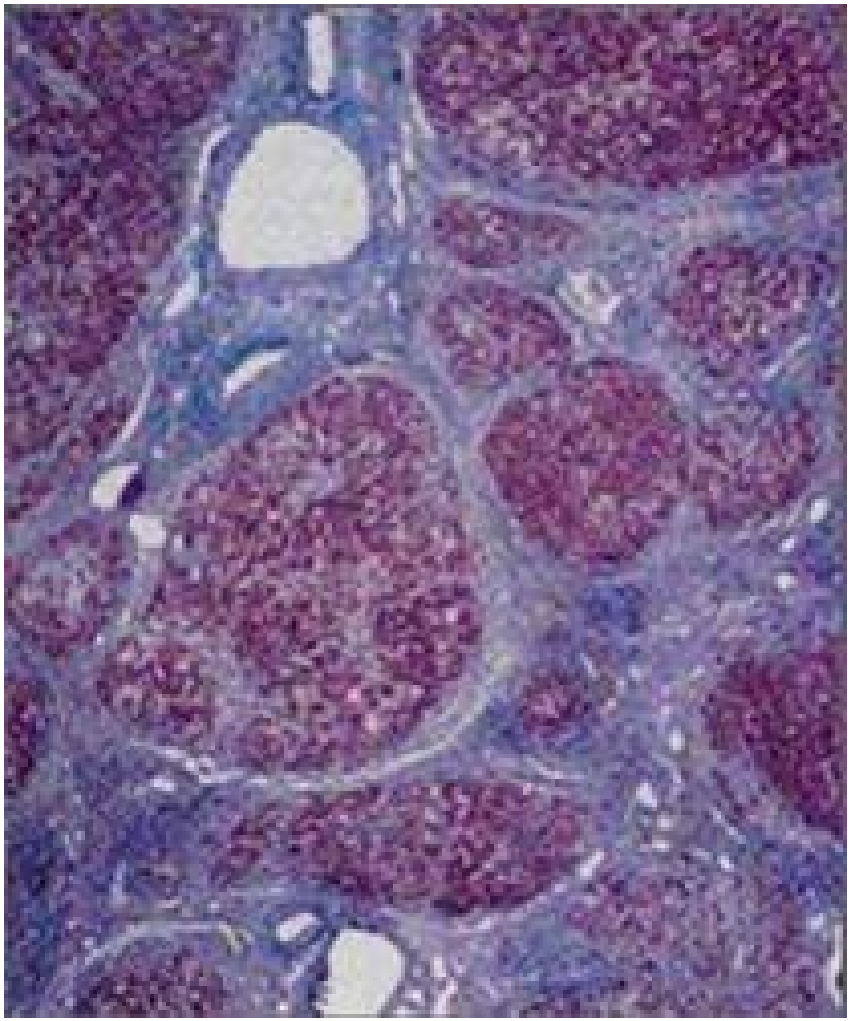
Activation of HSC in cirrhosis



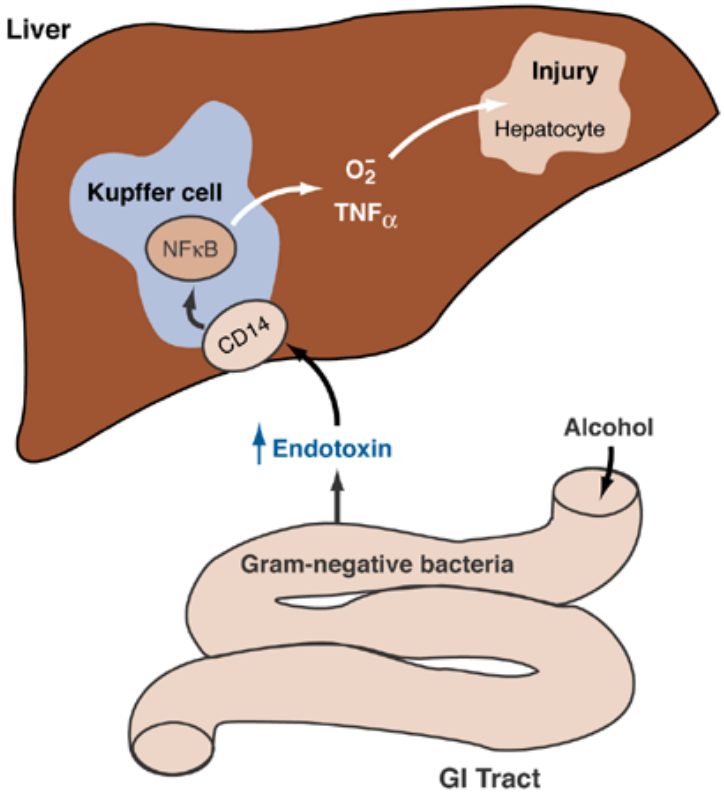
- collagen in normal liver
  - I and III in periportal areas
  - IV in Disse space
- HCS activated by growth factors from damaged hepatocytes and Kuppfer cells
  - synthesis of collagen I and III in Disse space
  - loss of microvilli of hepatocytes
  - loss of fenestration of sinusoids (= capilarisation of sinusoids)
- regeneration of remaining hepatocytes - nodules

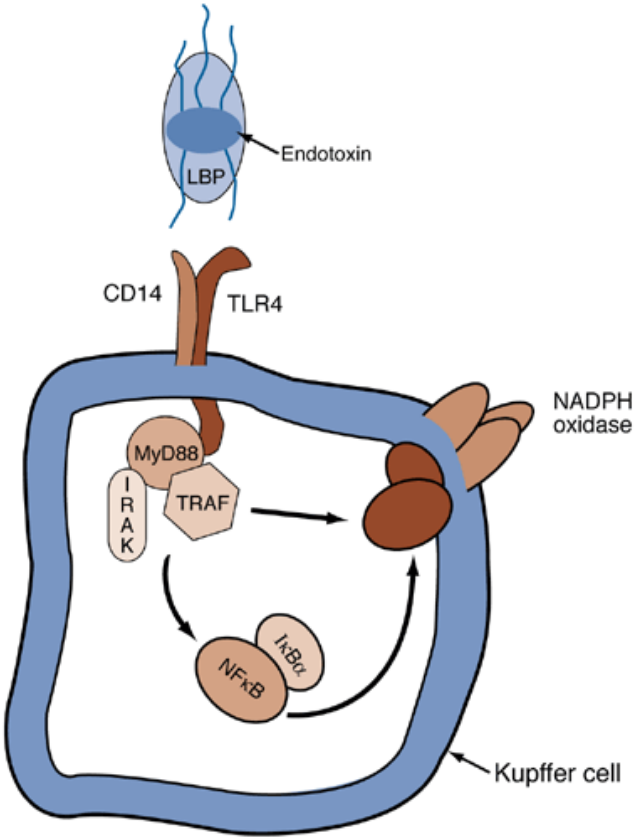
Histology – F vs. C



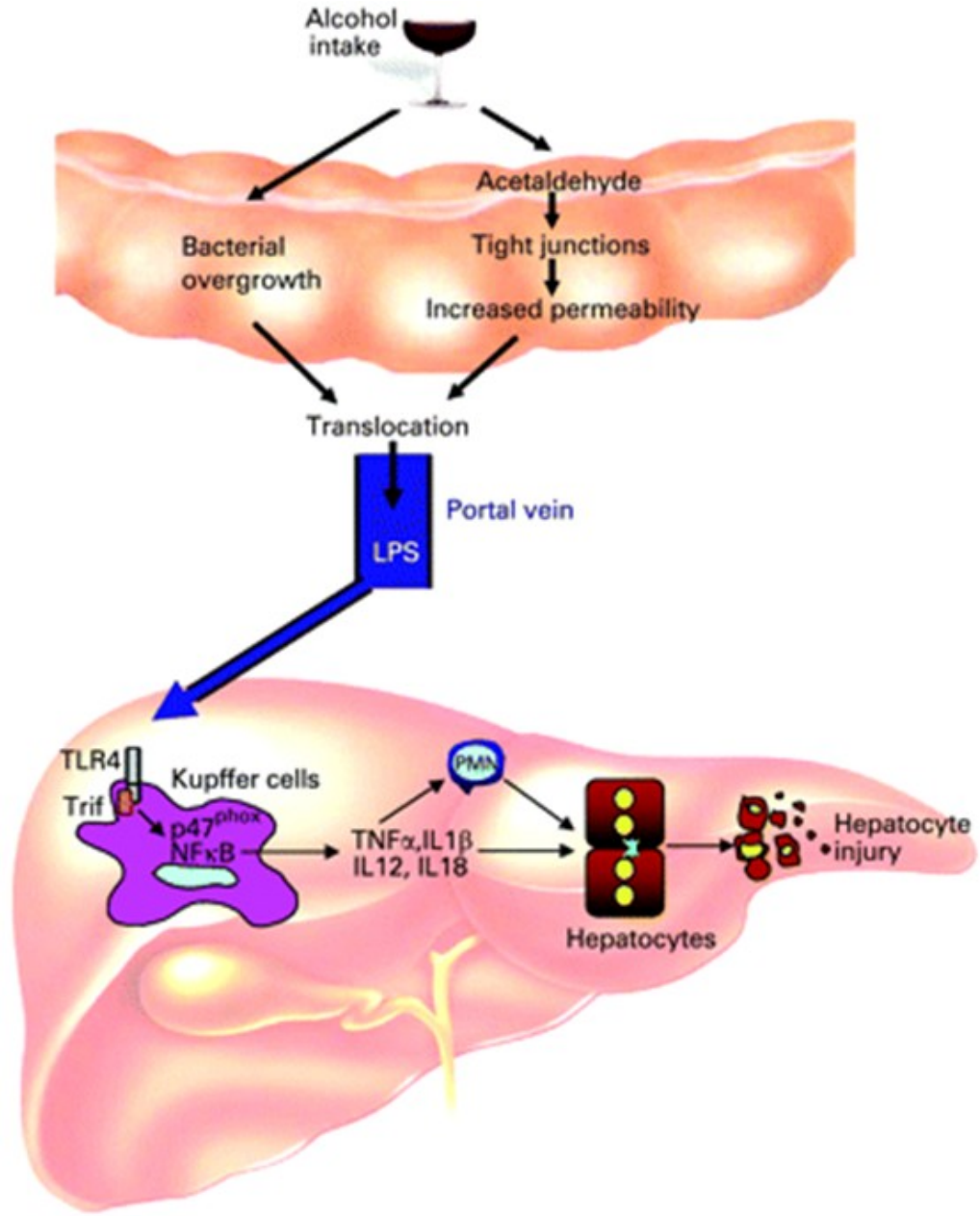


Alcohol and liver - endotoxin



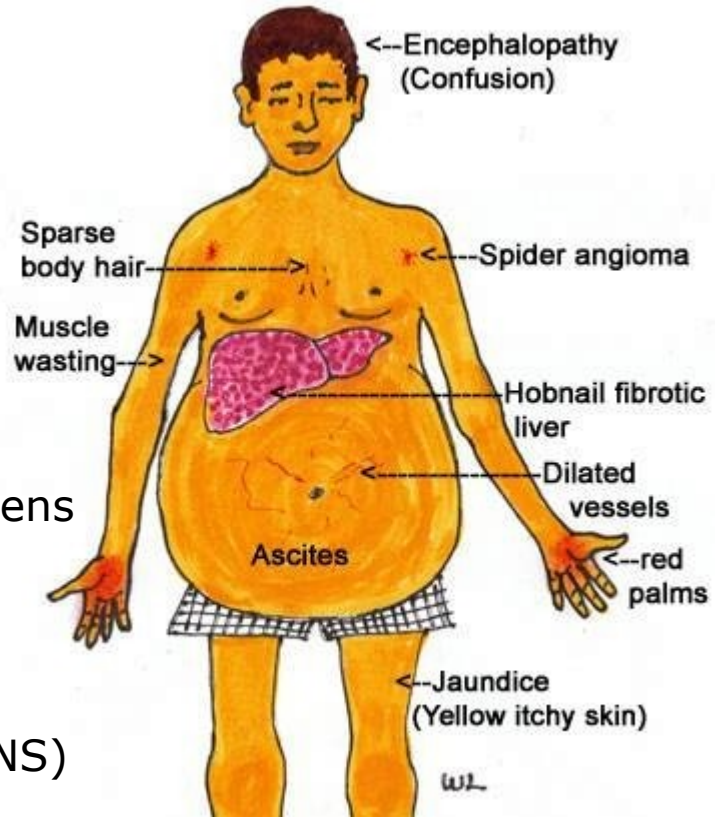


- alcohol increases permeability for endotoxin from intestine to circulation
  - endotoxin is a part of the G-negative bacteria wall
- endotoxin (via receptors CD14 and TLR4) activates Kuppfer cells (specialized macrophages along liver sinusoids) to production of cytokines (NFkB) and superoxide (NADPH oxidase)

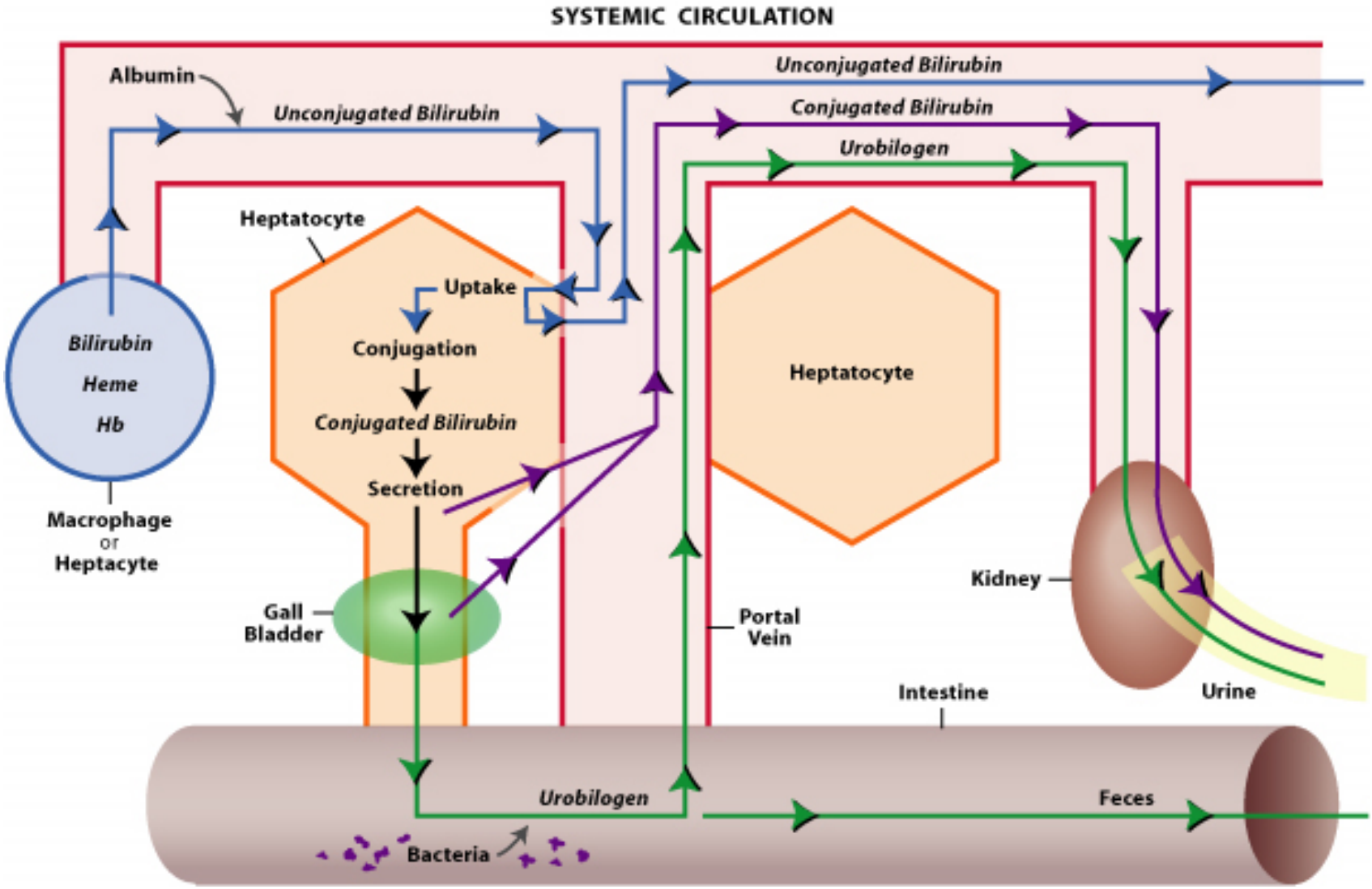

Alcohol intake
Acetaldehyde
Bacterial overgrowth
Tight junctions
Increased permeability
Translocation
Portal vein
LPS
TLR4
Trif
Kupffer cells
p47phox
NFκB
PMN
TNFα,IL1β
IL12, IL18
Hepatocytes
Hepatocyte injury

Consequences of liver cirrhosis

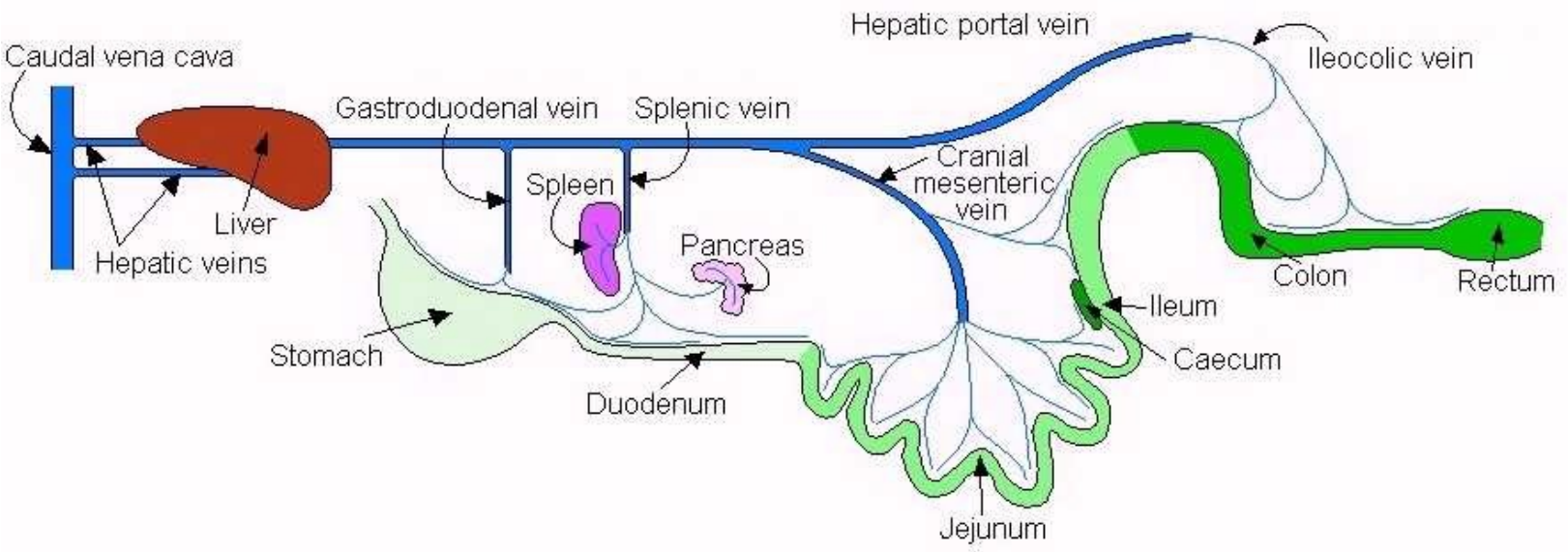
- portal hypertension
- hypoalbumiemia
- disorder of hemostasis
  - vitamin K deficit and thus inadequate formation of clotting factors
- suppression of bone marrow
  - due to bleeding, hypersplenism and low K vitamin resorption
- hyperbilirubinemia or icterus
- decreased degradation of circulating hormones
  - aldosterone
    - loss of K by urine, intracel. acidosis, **metabolic alkalósis**
      - decreased ionization of NH_3!!!!
  - androgens – increased conversion to estrogens in periphery
    - gynecomasty in men
    - pavloučkové névy
- metabolic consequences
  - abnormal metabolism of AA (↑ conc. of aromatic AA – atyp. neurotransmitters in CNS)
  - disorder of glucoregulation
  - impaired urea cycle
- intrahepatic cholestasis



Hyperbilirubinemia/icterus

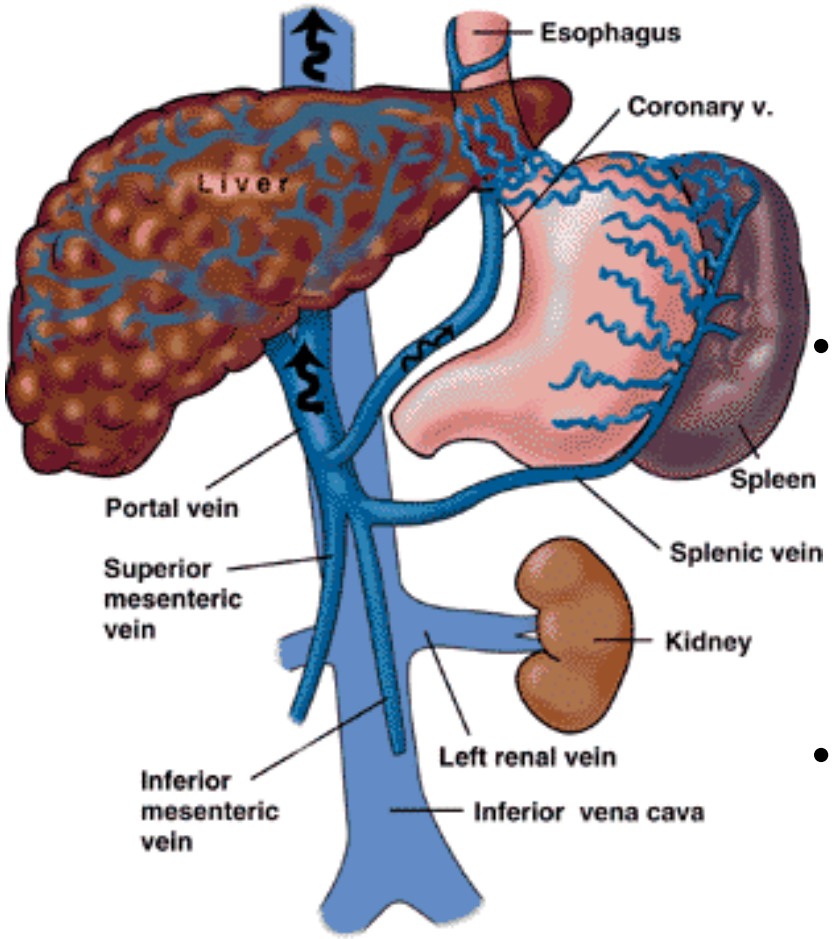


Portal hypertension



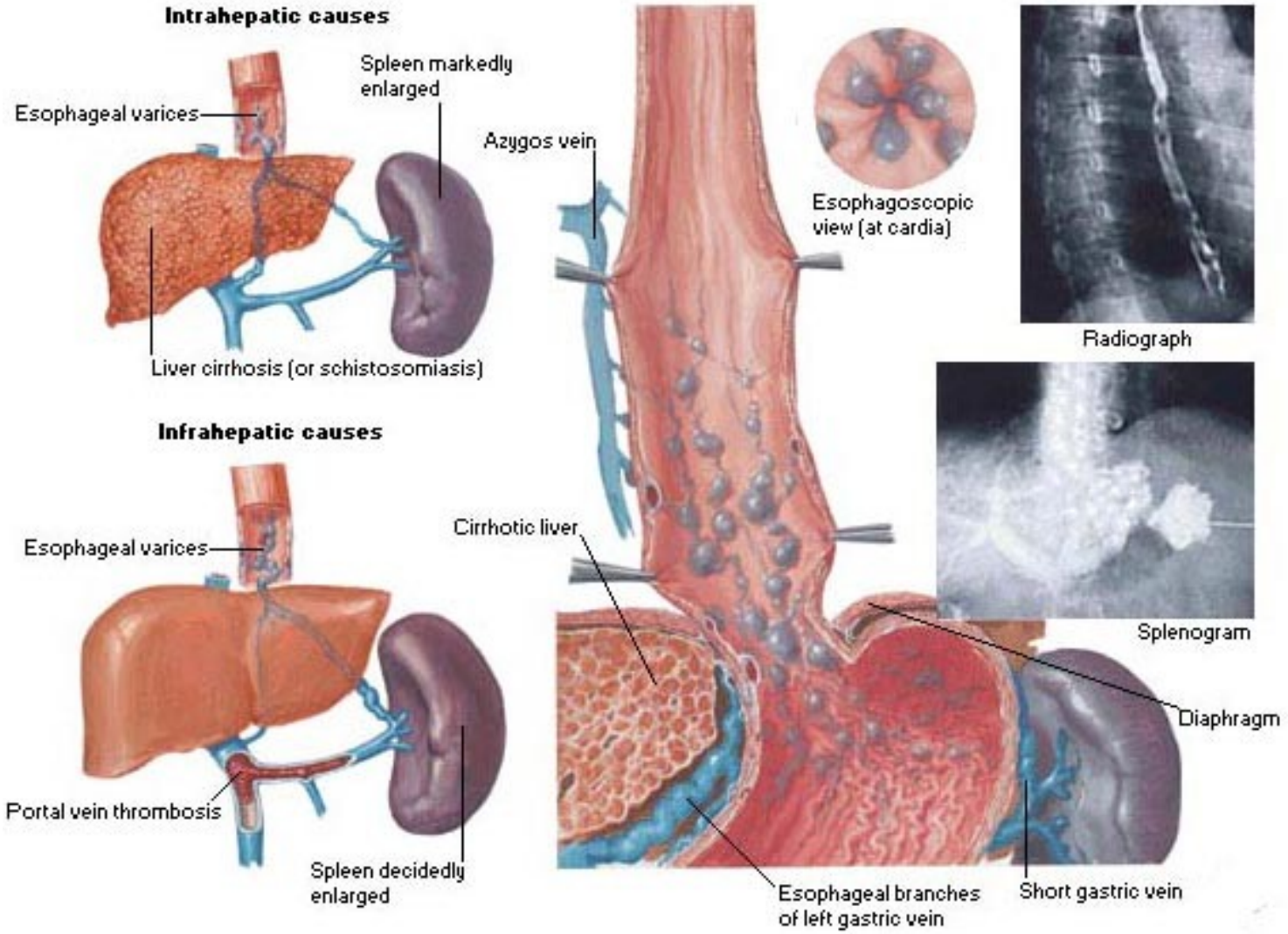
- normal pressure in portal circulation 5 – 15 mmHg
- localization of portal hypertension
  - pre-hepatic
    - thrombosis v. portae, malformation, compression
  - intra-hepatic
    - due to cirrhosis, parasites
  - post-hepatic
    - right heart failure (hepatosplenomegaly), thrombosis of liver veins (Budd-Chiari syndrome), compression by tumour
- increased pressure before liver sinusoids does not create pressure overload for liver, after sinusoids it does, therefore damage is greater

Portal hypertension



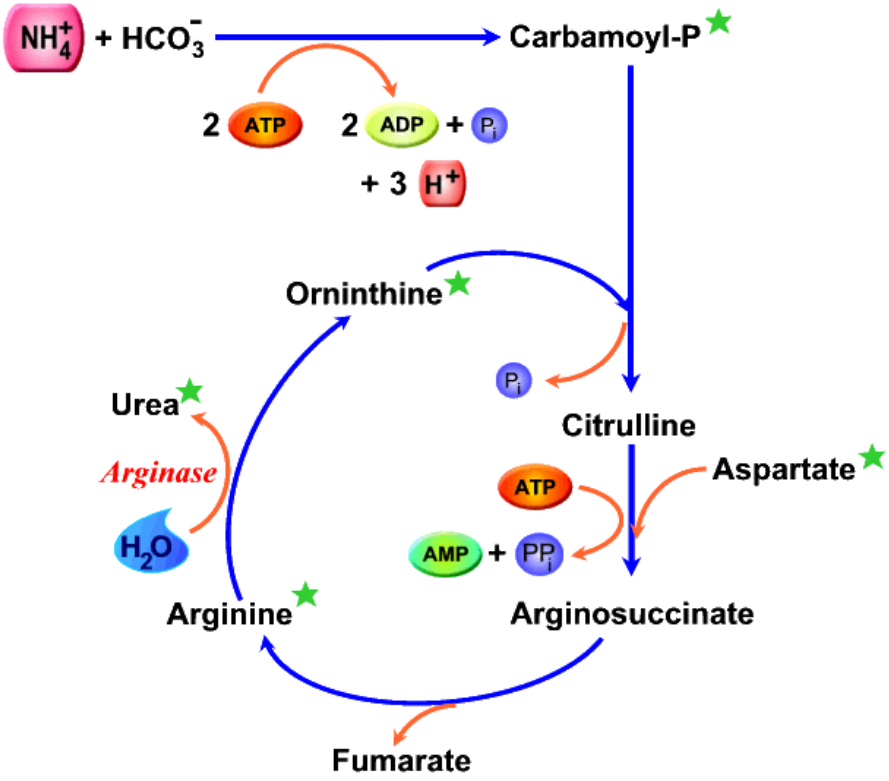
- 1) congestion of blood in the v. portae and stasis of blood in splanchnic organs
  - stomach and intestine
    - malnutrition and maldigestion
    - erosion and ulcers
    - increased permeability for bacteria
  - spleen
    - hypersplenism → destruction of Ery and platelets
- 2) blood flow through portocaval anastomoses directly to systemic circulation
  - normally there are small veins
  - under the high pressure risk of mechanical damage and bleeding
    - vv. oesophageae (esoph. varices)
    - vv. rectales (hemoroids)
    - vv. paraumbilicales (caput Medusae)
- 3) ascites and edemas
  - fluid in peritoneal cavity due to portal hypertension + hypoalbumiemia + retention of Na (aldosterone)
  - increased permeability for bacteria = spontaneous bact. peritonitis
- 5) hepatorenal syndrome

Esophageal varices

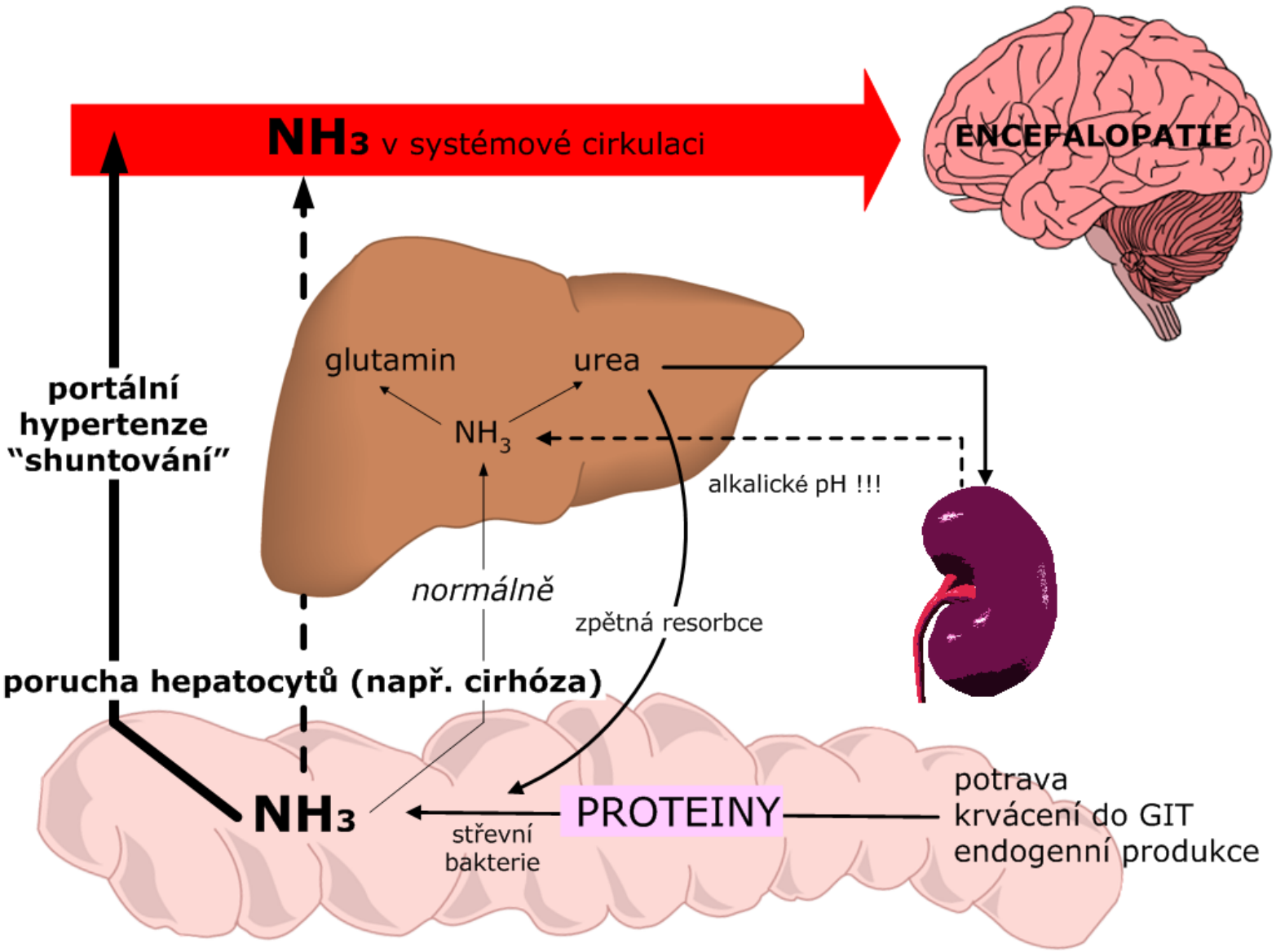


Liver encephalopathy

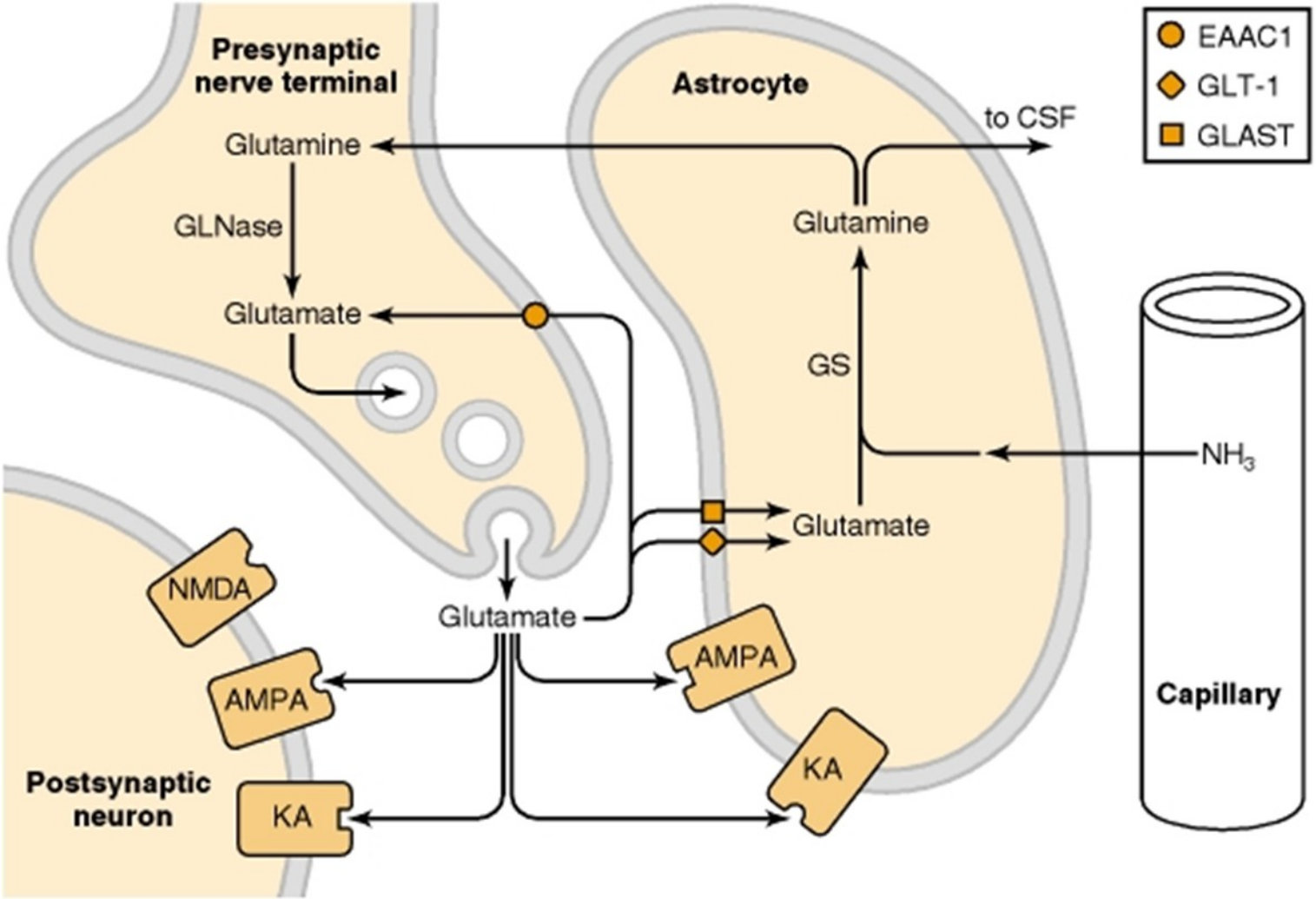
- abnormalities of conscience (quantitative and qualitative), behavior and neuromuscular functions
  - reversible only in initial stages
- impaired detoxification of ammonia in urea cycle
  - sources of ammoniac
    - oxidative de-amination by glutamatdehydrogen from Glu
    - glutaminase from Gln to Glu
    - degradation of purines and pyrimidines
    - de-amination by monoaminooxidase
    - synthesis of hem
    - bacteria in large intestine
  - ammoniac >50μmol/l toxic for CNS
  - in blood as NH^3/NH^{4+}
    - balance depends on pH (normally 99% ionised)
    - alcalosis increases free ammoniac and thus toxi
  - urea (= ornithin) cycle in liver dally produces 40 g urea
    - $CO^2 + NH^{4+} \rightarrow CO(NH_2)_2 + H_2O + 2H^+$
    - 5 enzymes – mitochondria and cytosol
  - urea excreted by kidney
- blood from splanchnic contains not only nutrients by also toxins (ammoniac, mercaptans, phenols etc. produced by bacteria)
- if not properly detoxified in liver
  - formation of "false" neurotransmitters in brain
    - change of behavior and conscience, "flapping" tremor, apraxia



Intestine and liver - ammonia

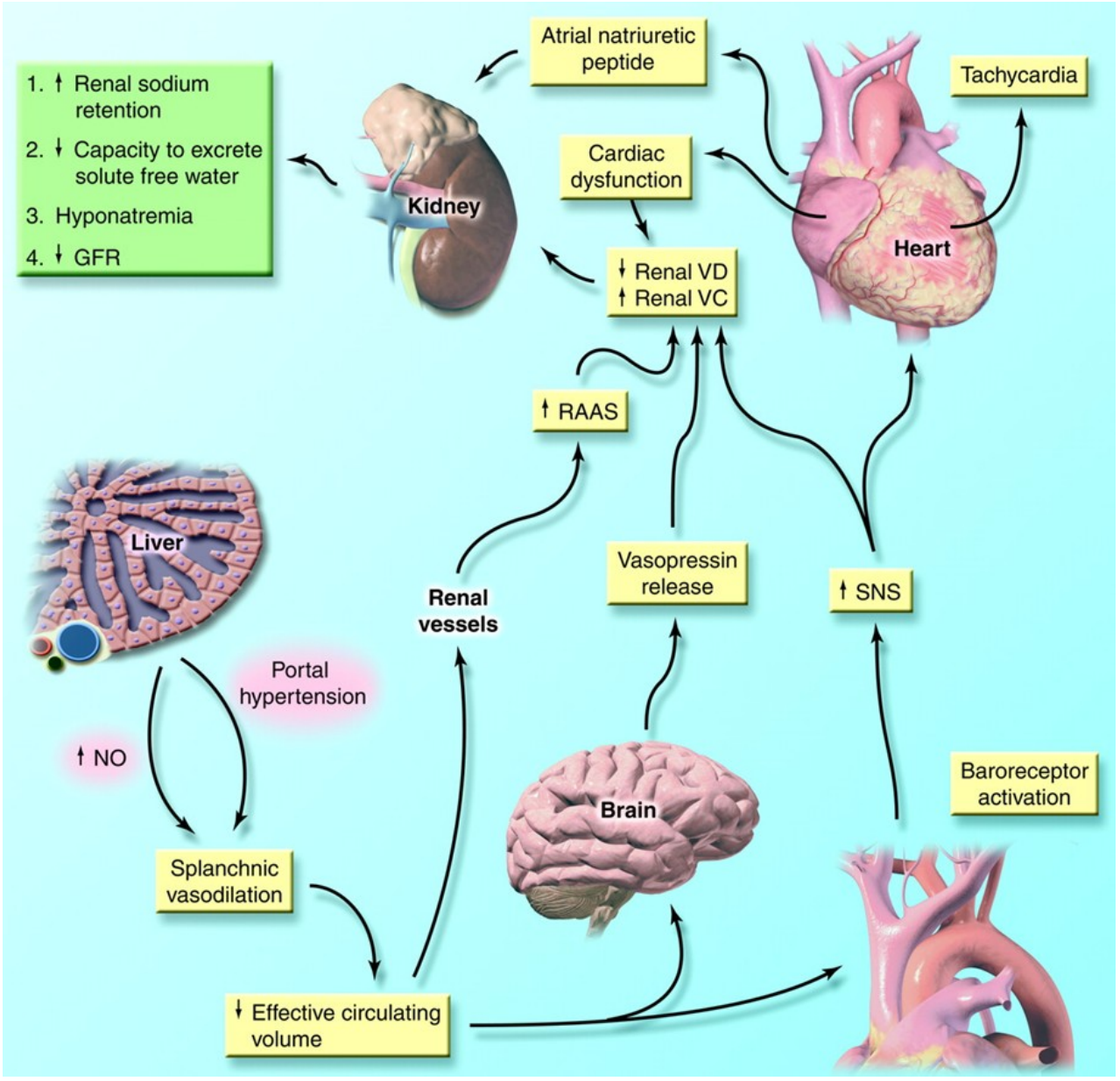


Impaired balance of excitatory and inhibitory AA in the brain



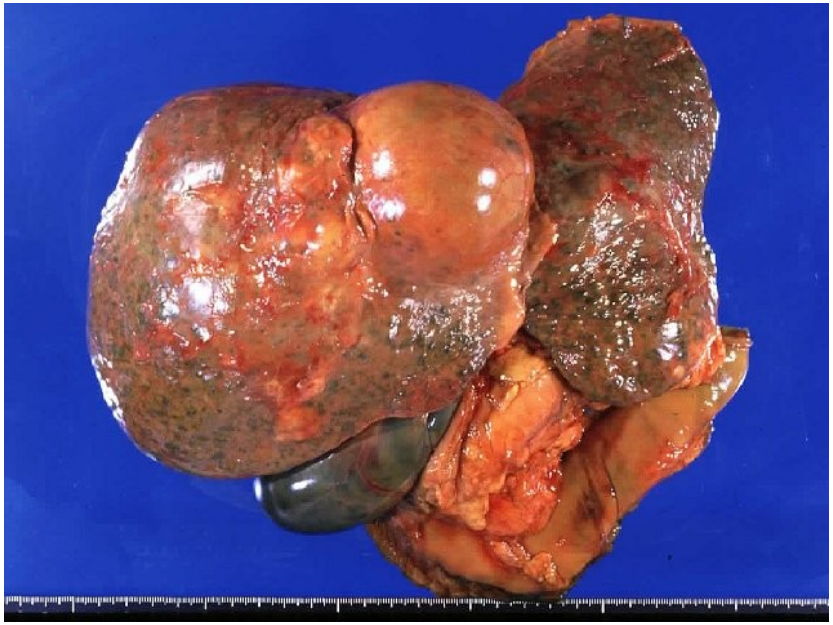
Hepatorenal syndrome

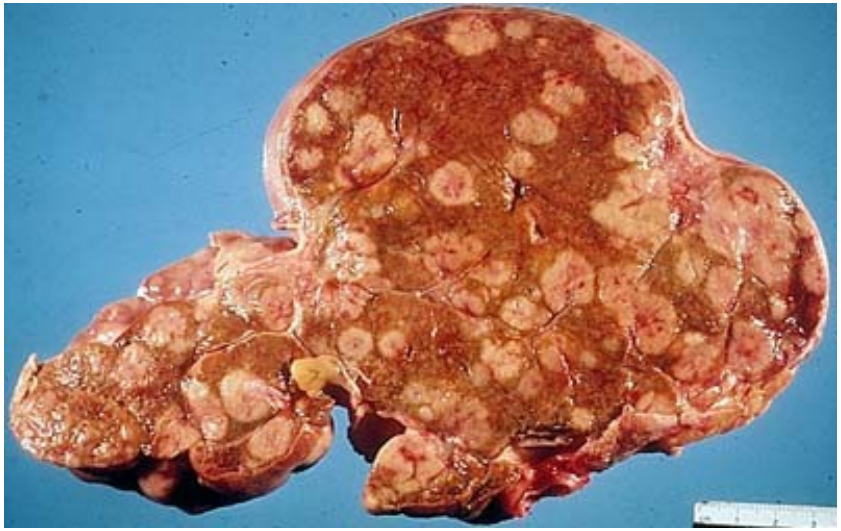
- kidney failure accompanying liver disease without pre-existing kidney pathology
- etiology
  - Na and water retention
    - hyper-aldosteronemia
  - however, effective circulating volume is decreased due to escape to the third space (ascites)
    - hypoalbuminemia
  - decrease of renal perfusion and GFR
    - systemic vasodilation but intrarenal vasoconstriction
      - contraction of afferent arterioles (RAS)



Liver tumors

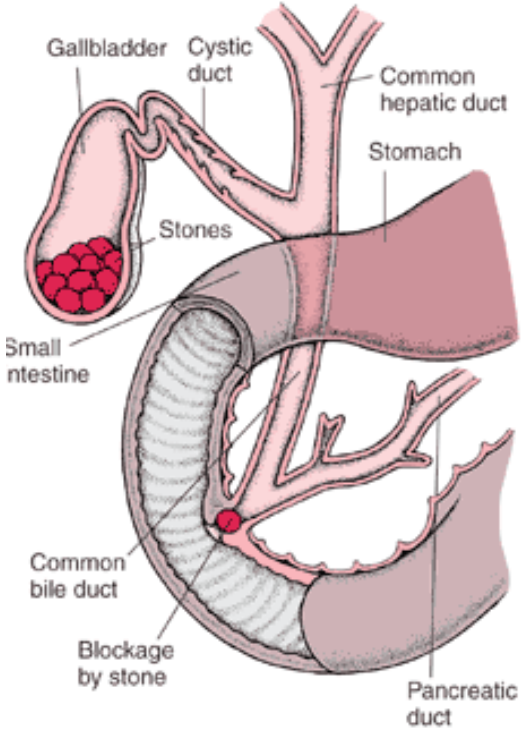
- benign
  - hemangioma
  - hematoma
- malign
  - hepatocellular carcinoma
    - in 70% consequence of cirrhosis
    - prevalence increases
    - poor prognosis
- metastases
  - colorectal carcinoma, …





Pathophysiology of biliary tract

- cholecystolithiasis (gallstones)
  - typically 55-65 yrs ~10% men and ~20% women
  - causes – alteration of the ration between bile components
  - type of stones
    - cholesterol (70-90%)
    - pigmented (calcium + bilirubin)
    - mixed
  - increased concentration of cholesterol
    - diet, obesity
  - decrease of bile acids and phospholipids
    - malnutrition, Crohn disease, resection of ileum
  - cholecystitis
  - stagnation of bile
    - diet, starvation
- complications of cholecystholithiasis
  - biliary colic (blockade of d. cysticus)
  - extrahetal cholestasis (blockade of d. choledochus)
  - inflammation (cholecystitis, cholangoitis)
  - acute pancreatitis



Cirrhosis of the river.