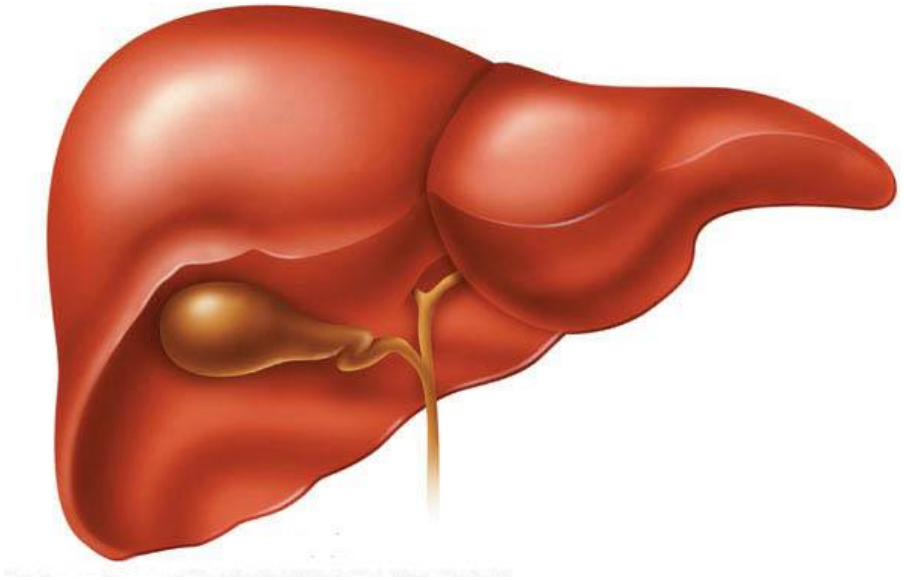
Pathophysiology of GIT II

Exocrine pancreas

Liver

Biliary tract



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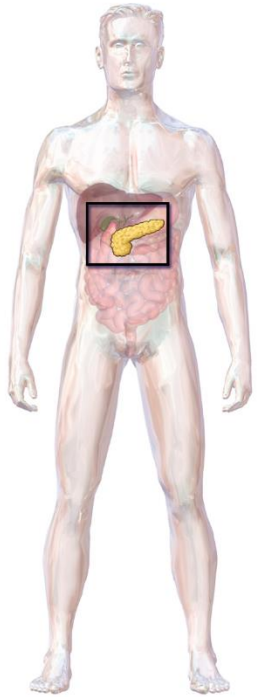
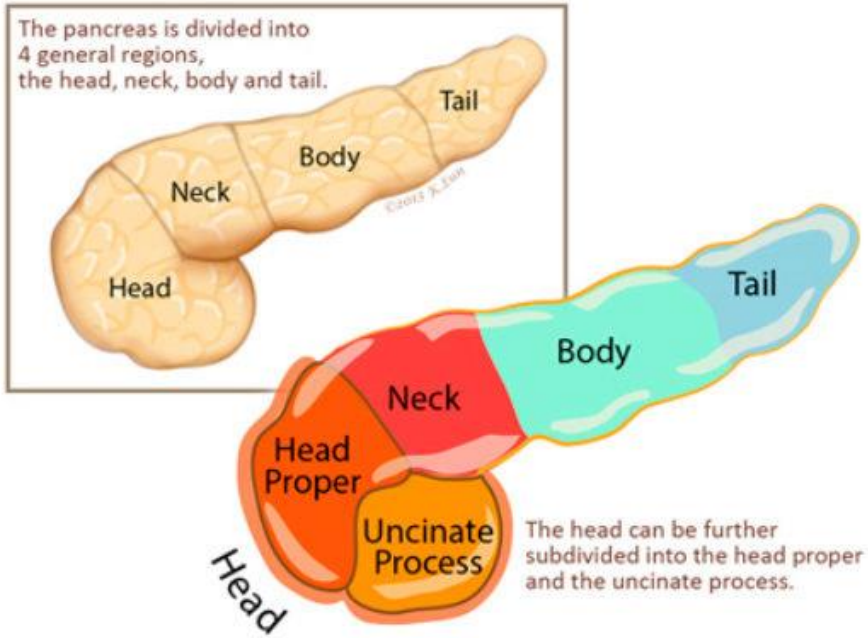
Pancreas - anatomy





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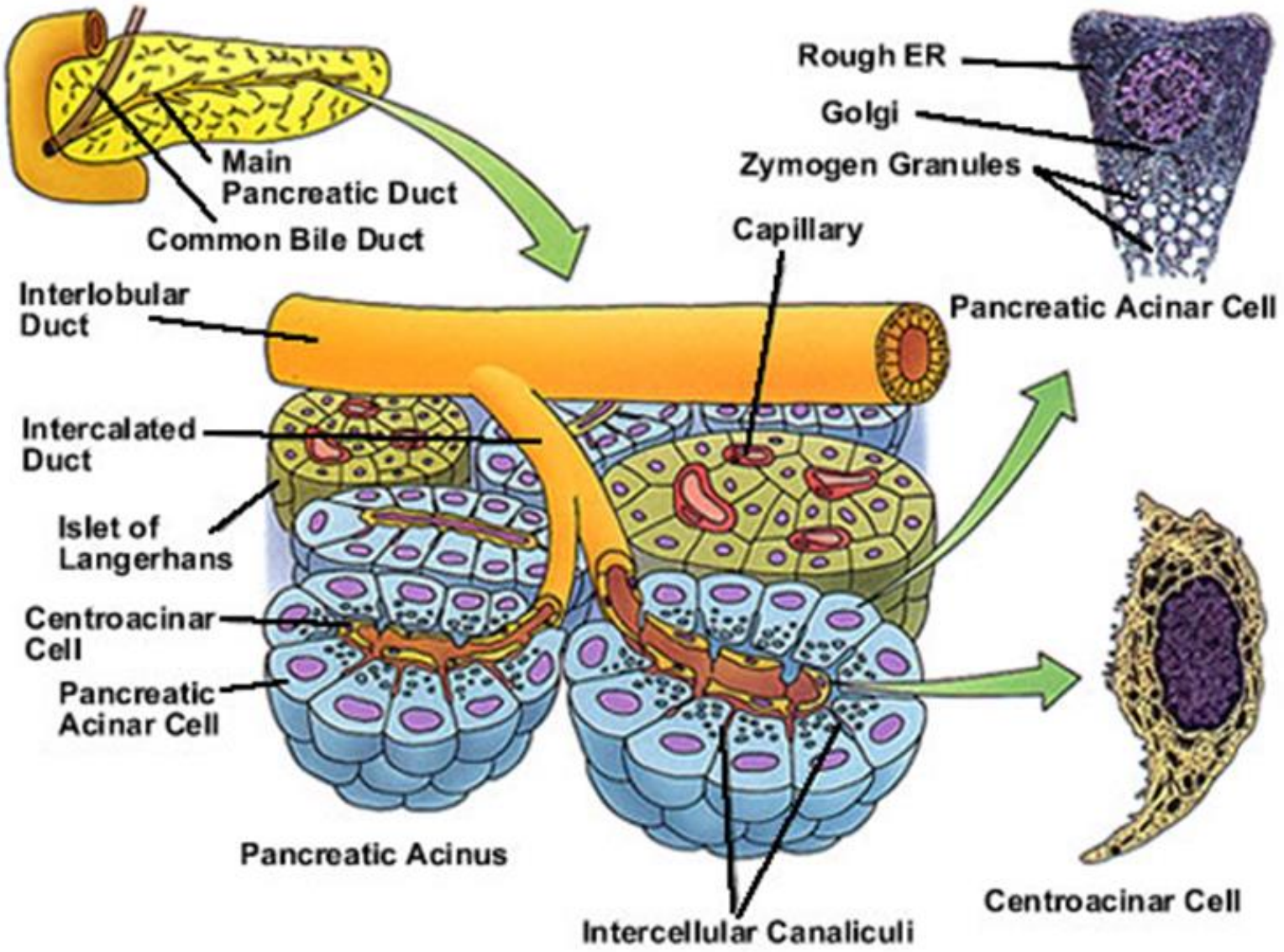
Pancreas – structure & function



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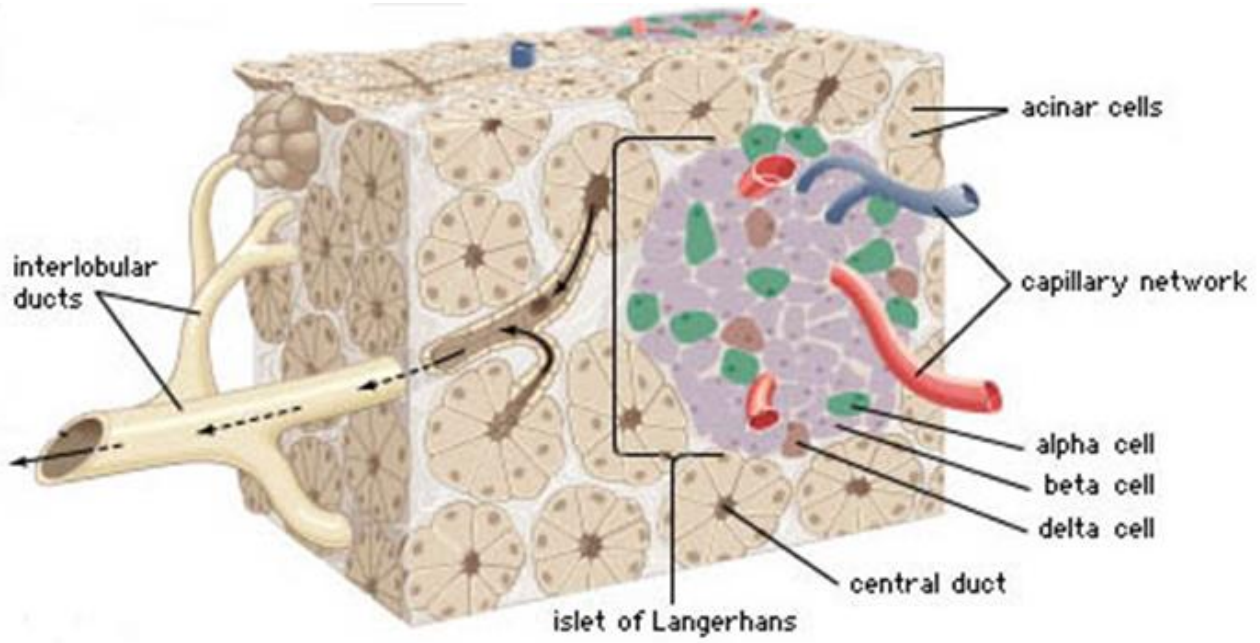
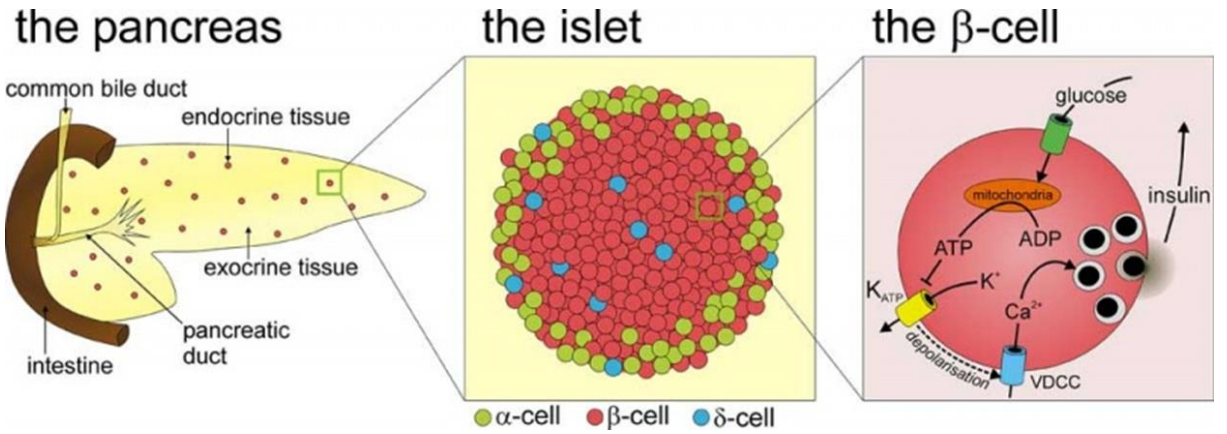
Pancreas – endocrine gland (2%)

- β-cells
  - insulin
- α- cells
  - glucagon
- δ-cels
  - somatostatin
  - pancreatic polypeptide
  - amylin





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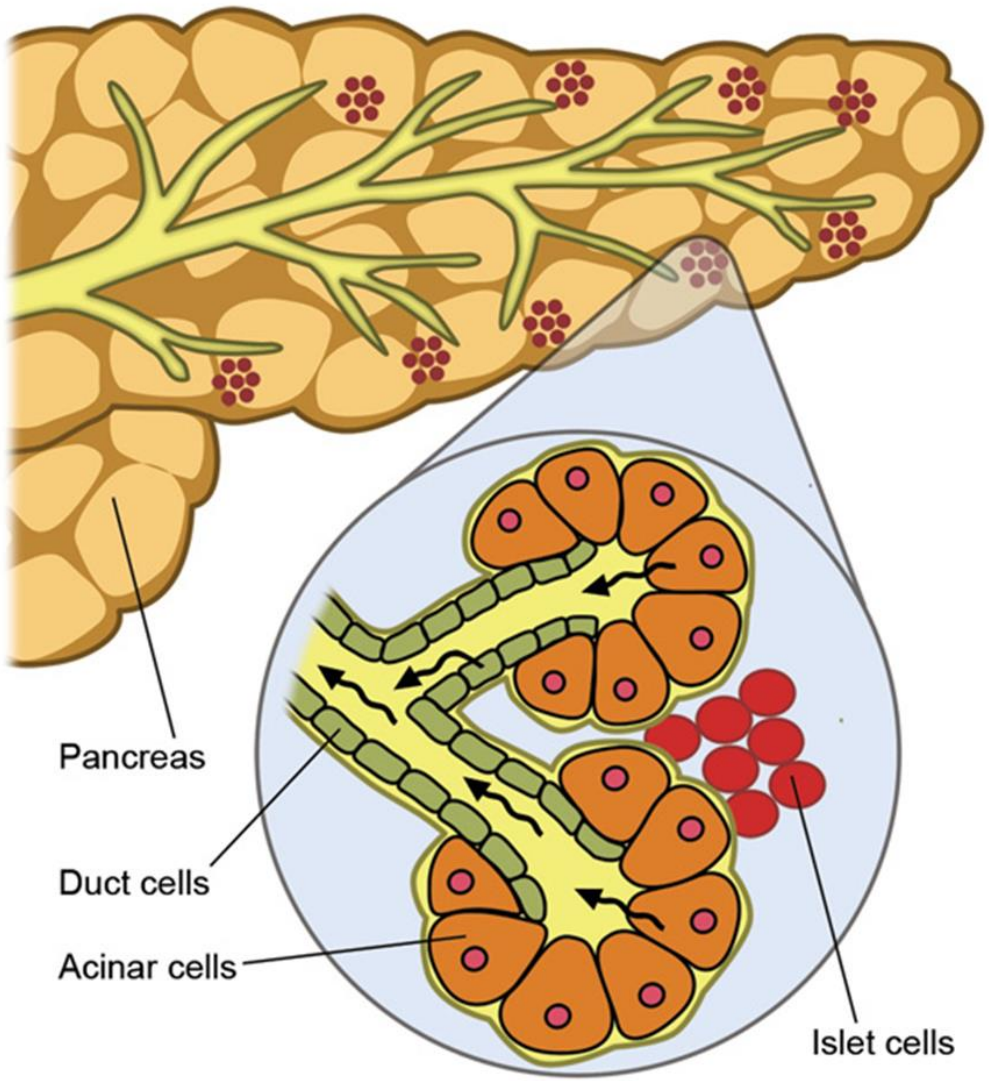
Pancreas – exocrine gland (85%)



- secretion of 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 and somatostatin (ileum)
  - composition
    - ions and water (← **secretin**)
      - Na, Cl, K and HCO3- (up to 150 mmol/l)
      - HCO3- 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 A2
    - inhibitors of trypsin (α1-antitrypsin)
- disorder of secretion – **exocrine pancreatic insufficiency**
  - most often due to chron. pancreatitis
  - carcinoma of pancreas, cystic fibrosis, protein malnutrition

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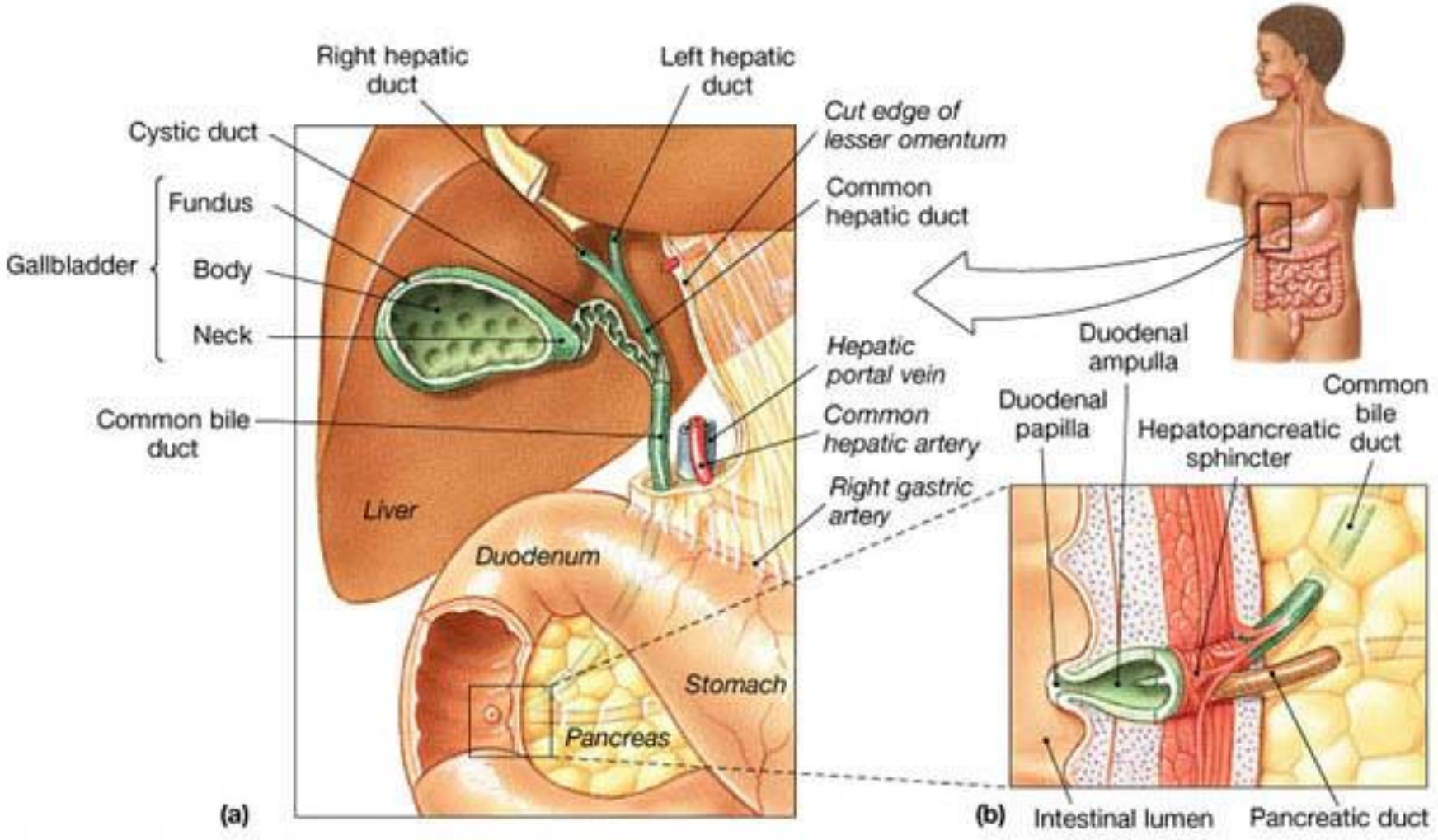
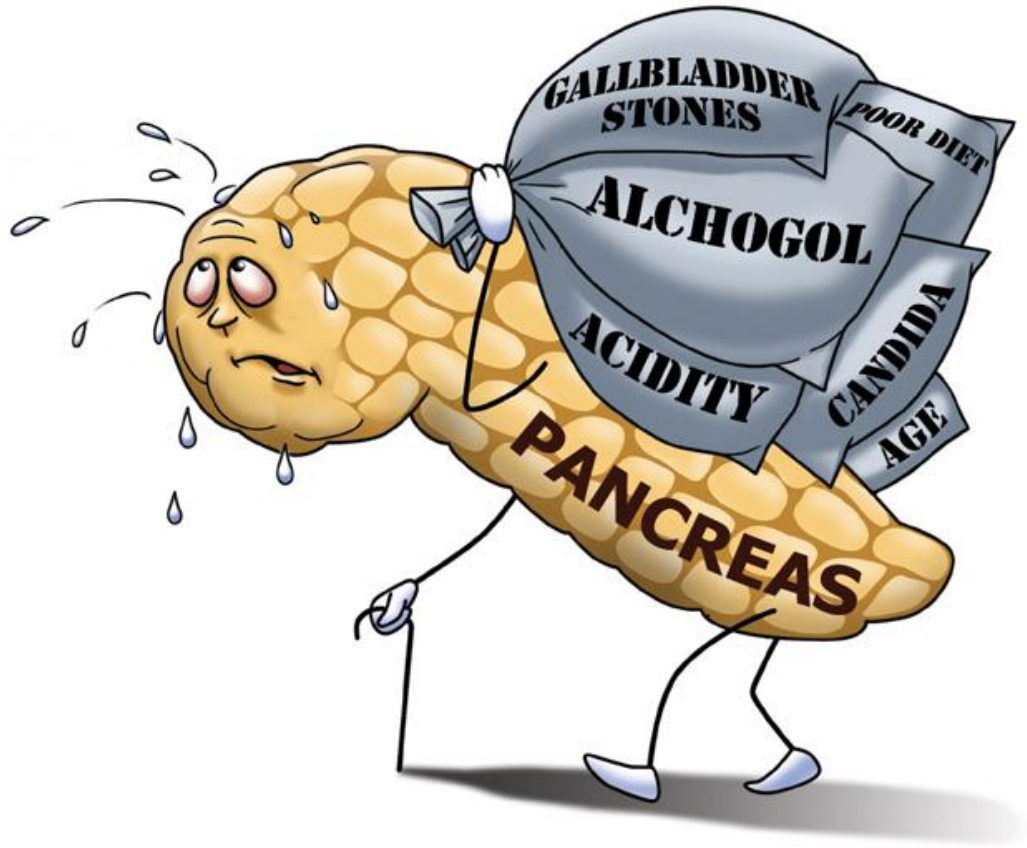
Anatomic aspects important for pancreatic PP





PANCREATIC DISEASES

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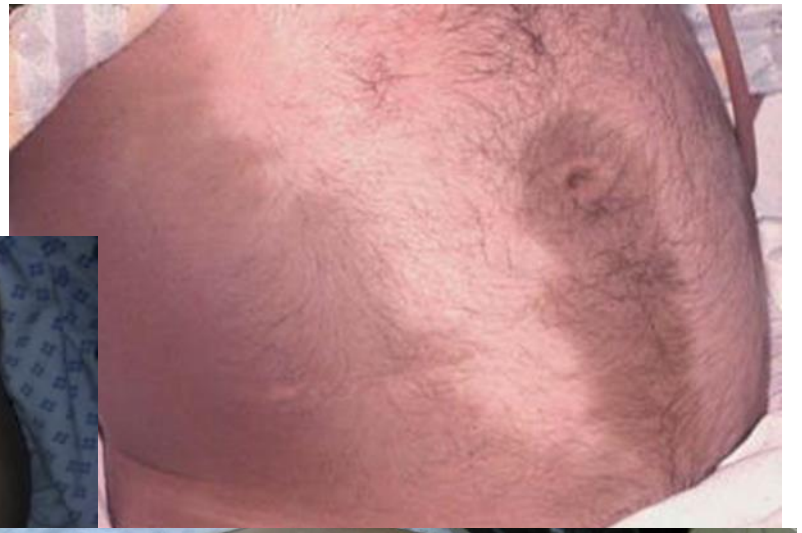
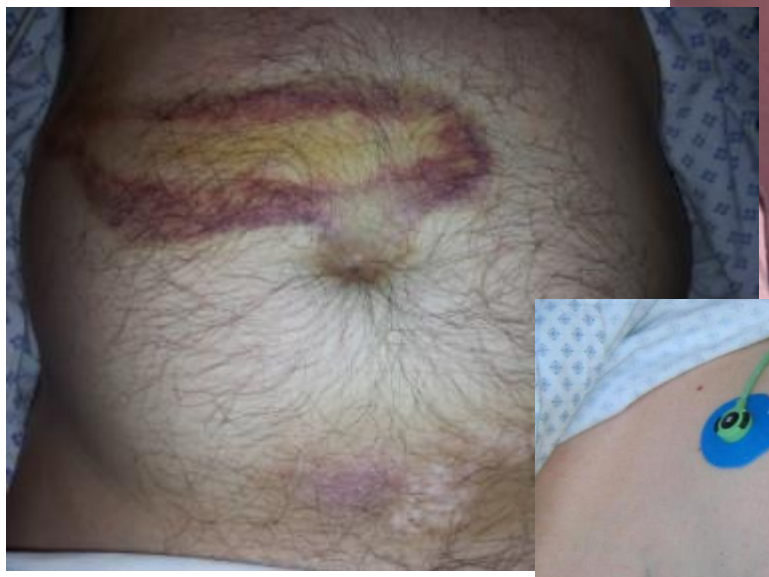
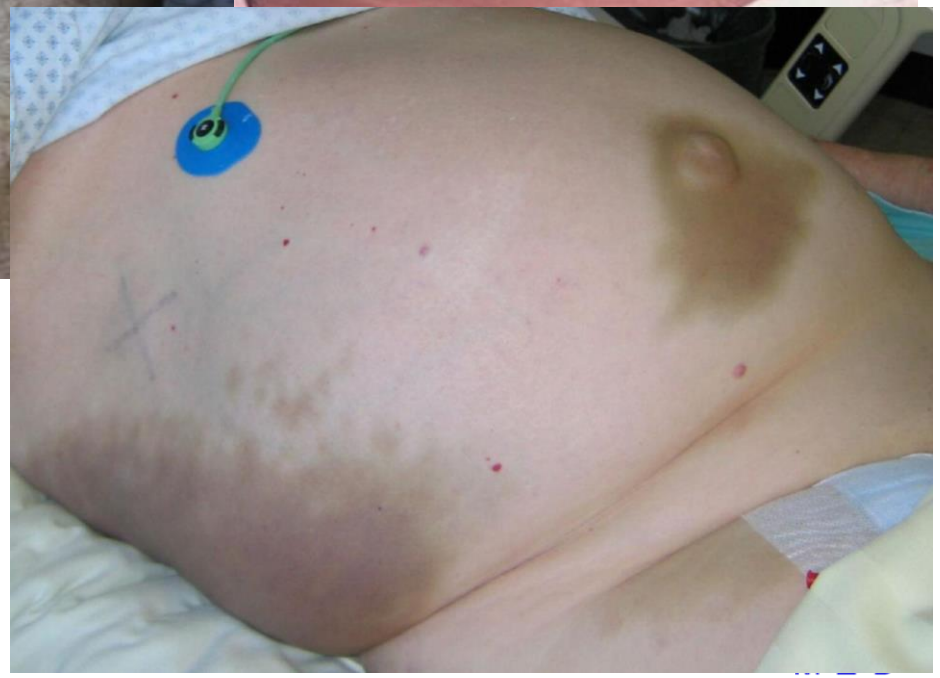
Acute pancreatitis

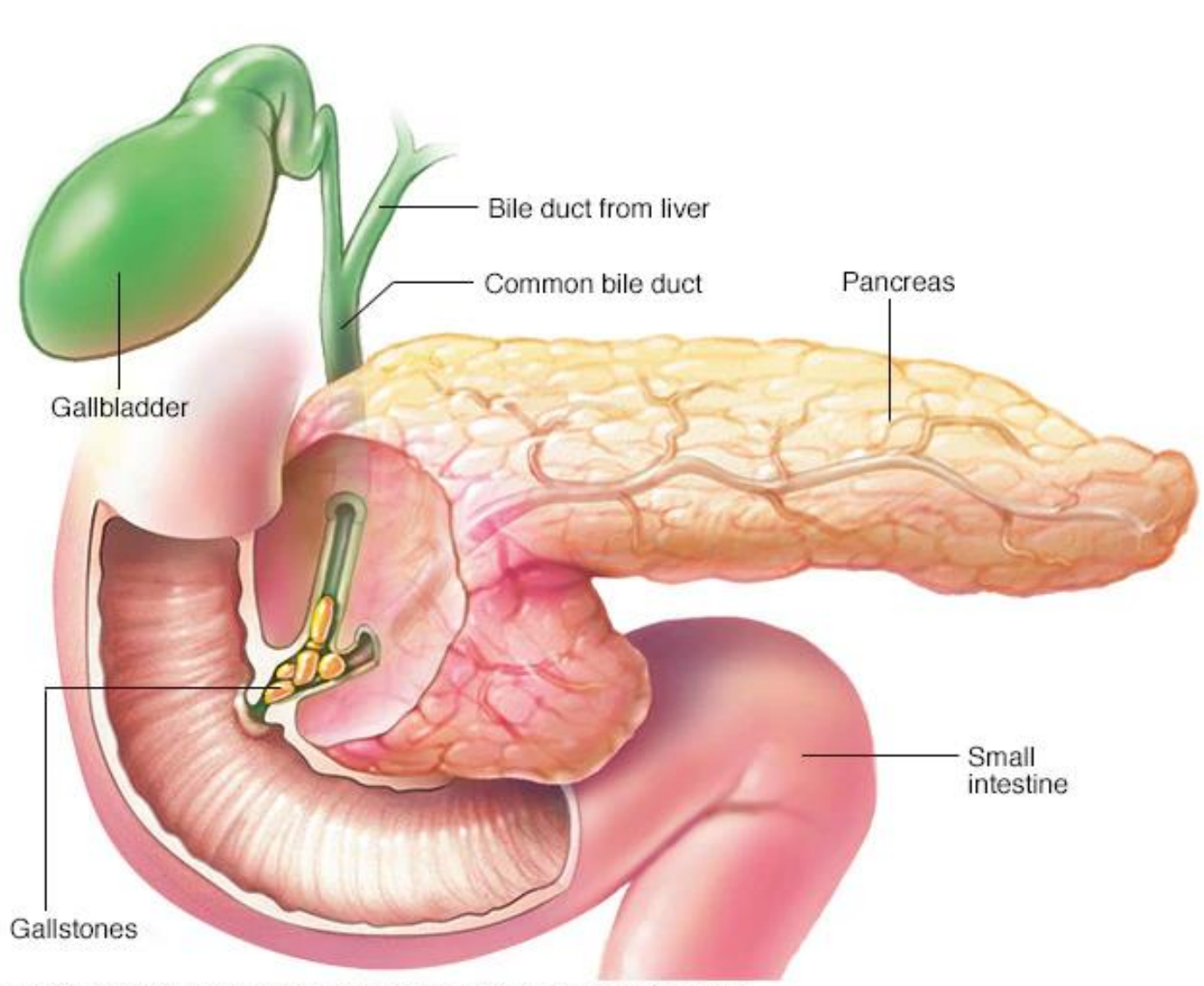
- acute destruction of pancreatic tissue and neighbouring tissue due to **autodigestion by pancreatic enzymes activated directly in the gland**
- forms
  - mild – interstitial oedema of the gland
  - severe (haemorrhagic-necrotic) - very serious condition associated with high mortality
- symptoms
  - intensive pain
  - nausea and vomiting
  - meteorism
  - fever
  - circulatory shock
- diagnostics - laboratory
  - **alpha-amylase** (event. pancreatic isoenzyme)
    - ≥3-times increase in blood, present in urine too
    - diff. dg. biliary inflammation or obstruction, appendicitis, gynaecologic, renal insufficiency, macroamylasemia, salivary gland trauma, parotitis)
  - **lipase** (specific)







Aetiology of acute pancreatitis



- biliary (60-80%)
  - blockade of common bile duct or papilla Vateri by gallstone and subsequent increase of intra-ductal pressure
- alcohol (20-30%)
  - relaxation of sphincter of Oddi
  - reflux of the intestinal juice and bile into the pancreatic duct and activation of enzymes
  - increased viscosity of pancreatic juice and its stagnation if the duct
  - fusion of zymogenic granules with lysosomes and activation of trypsin
- idiopathic (10%)
- other causes
  - abdominal trauma
  - infection
  - hypertriglyceridemia
  - hypercalcaemia
  - drugs

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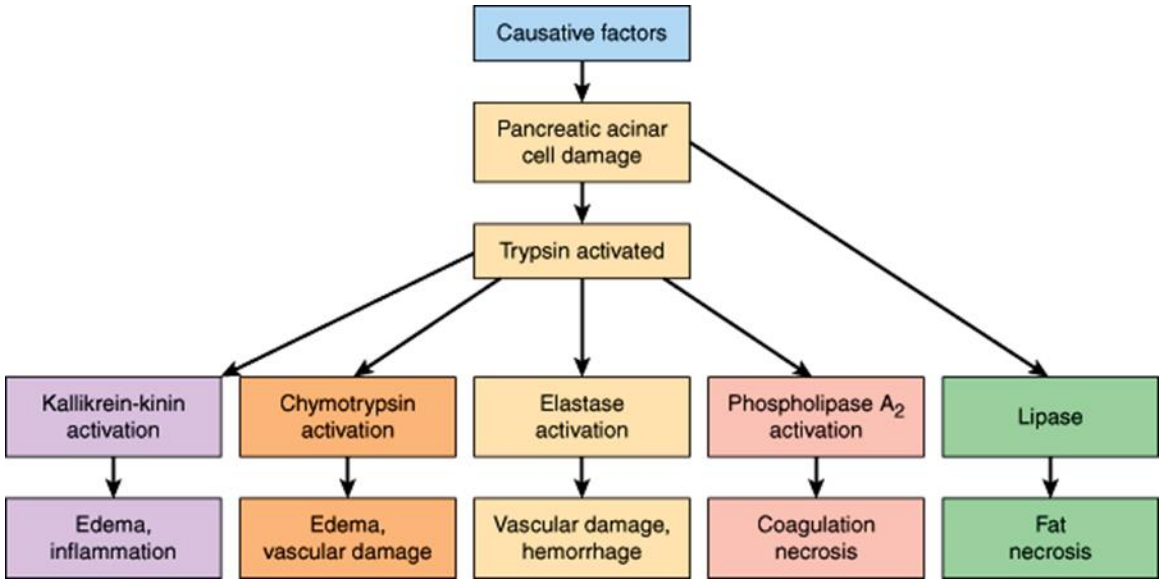
Pathogenesis of acute pancreatitis

- intracellular (in acinar cells) and extracellular (in ducts) activation of trypsinogen to trypsin (by cathepsine B in low pH) and subsequently of other proteolytic enzymes/cascades responsible for autodigestion of gland and systemic effects
  - chymotrypsin, elastase, phospholipase and carboxypeptidases
    - elastase digests elastin in vessel walls → haemorrhage into gland, leak of juice into circulation and damage of systemic circulation
    - lipolysis of pancreas by pancreatic lipase and phospholipase A2
  - complement
  - kallikrein – kinin system
- overrunning of protective mechanisms – anti-proteases (SPINK1, α1 anti-trypsin etc.)
- local effects
  - pancreas oedema, hyperaemia and autodigestion
    - necrosis
    - deposition of calcium – fatty necrosis
  - C5 chemo-attraction and infiltrations by PMNs → inflammation and release of cytokines
- systemic effects
  - SIRS and event. sepsis (peritonitis)
  - ARDS (phospholipase → lecithin → pulmonary surfactant)
  - hypovolemic shock
    - event. AKI
  - DIC



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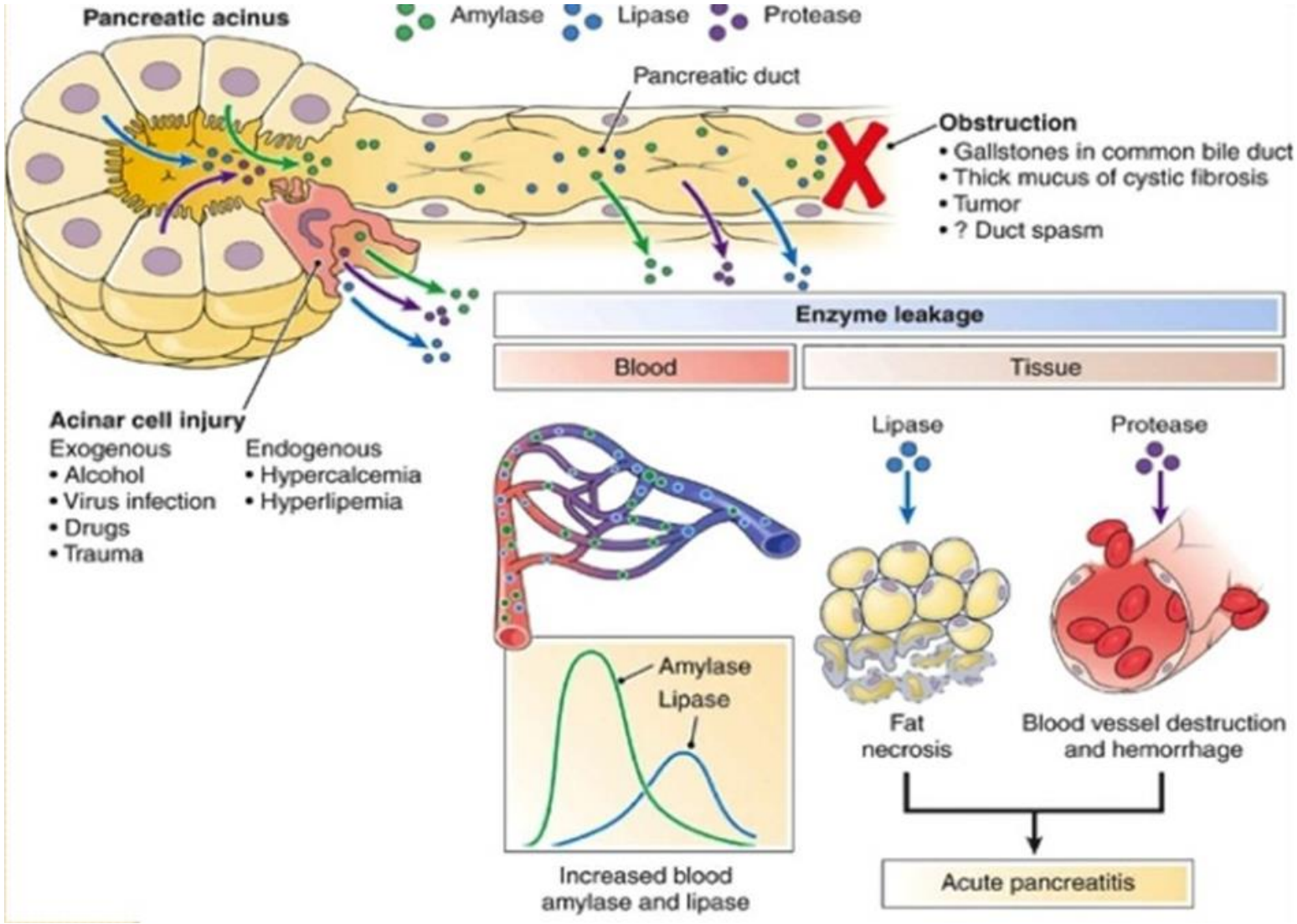
Pathogenesis of acute pancreatitis



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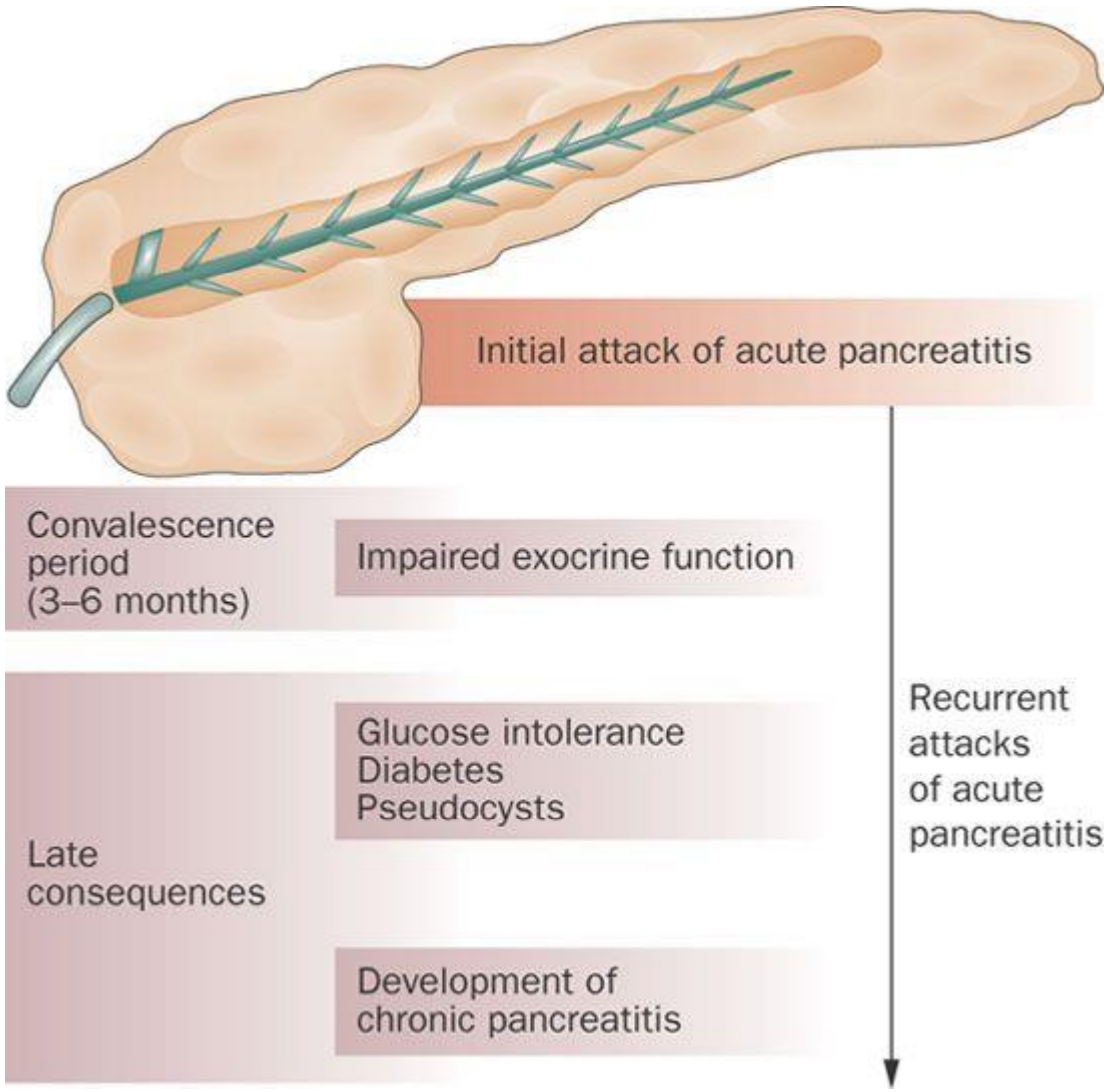
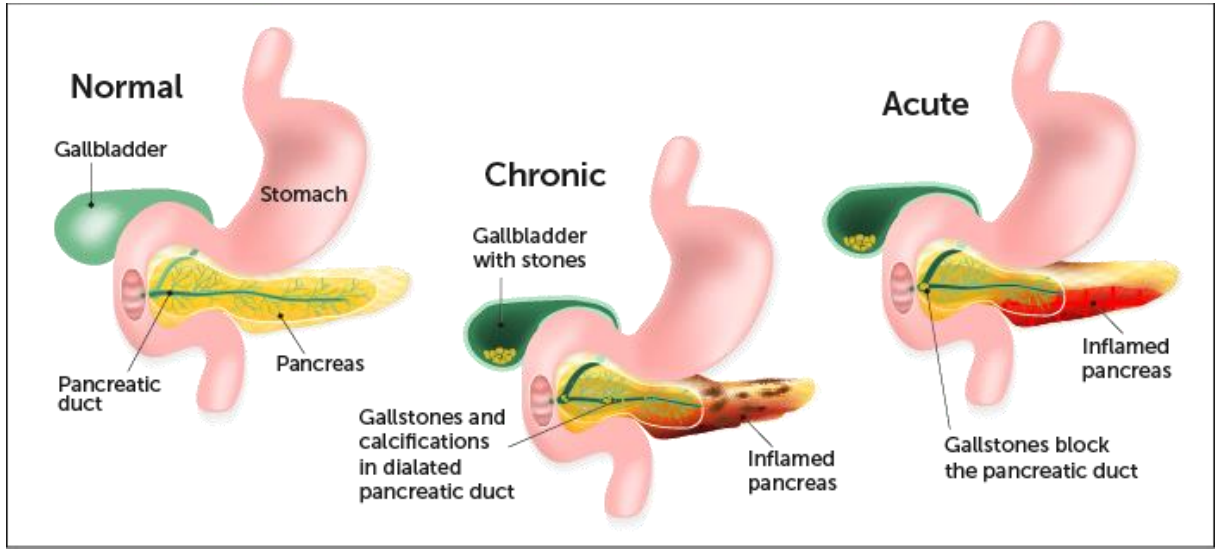
Natural history of pancreatic disease





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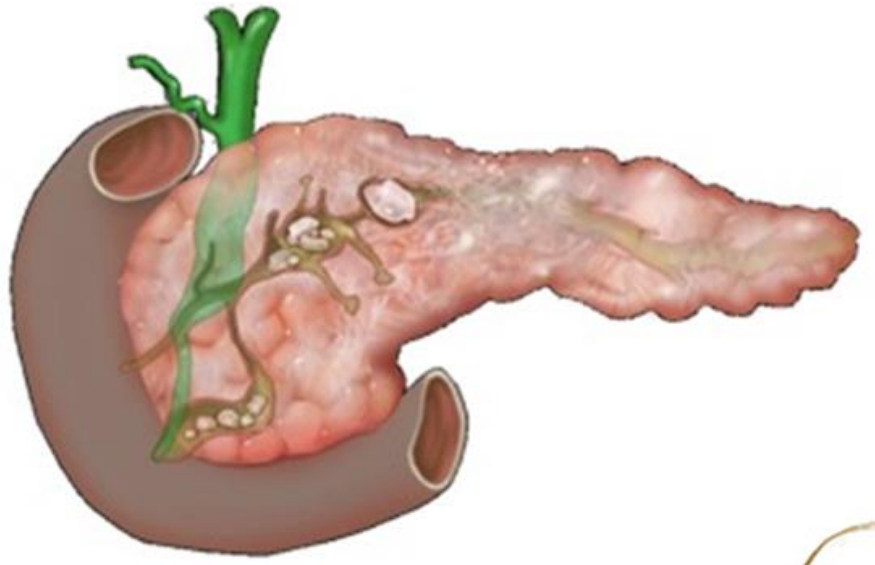
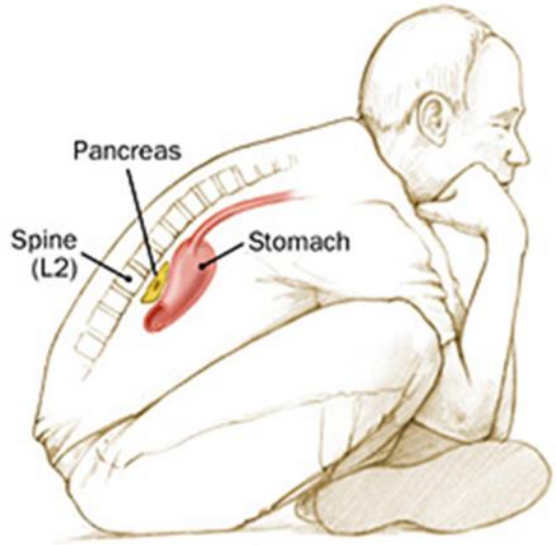
Chronic pancreatitis

- chronic inflammation of pancreas leading to **progressive dysfunction and structural damage** of pancreatic acini with **stenosis and dilation of ducts, fibrosis and atrophy of gland and calcium depositions in ducts**
- aetiology
  - **alcohol abuse (70 – 90%)**
    - >5 yrs. in quantity of 150 g/day and more
    - BUT!! only 5-15 % of heavy drinkers have chron. pancreatitis
    - evidently other factors are important
      - genetic
        - cationic trypsinogen gene (PRSS1) – gain of function mutation
        - serine protease inhibitor Kazal type (SPINK1) – loss of function mutation
        - cystic fibrosis trans-membrane conductance regulator (CFTR)
        - chymotrypsiniogen
        - cathepisn B
        - calcium sensing receptor
      - dietary
      - others
  - **idiopathic (20 – 30%)**
  - hypertriglyceridemia
  - hypocalcaemia
  - chron. malnutrition
  - tropical form
  - hereditarily
  - cystic fibrosis
- clinical forms
  - painful
    - pain is typically localised in epigastrium and propagates to back
    - nausea and vomiting van be present too
  - silent (approx. 5 %)





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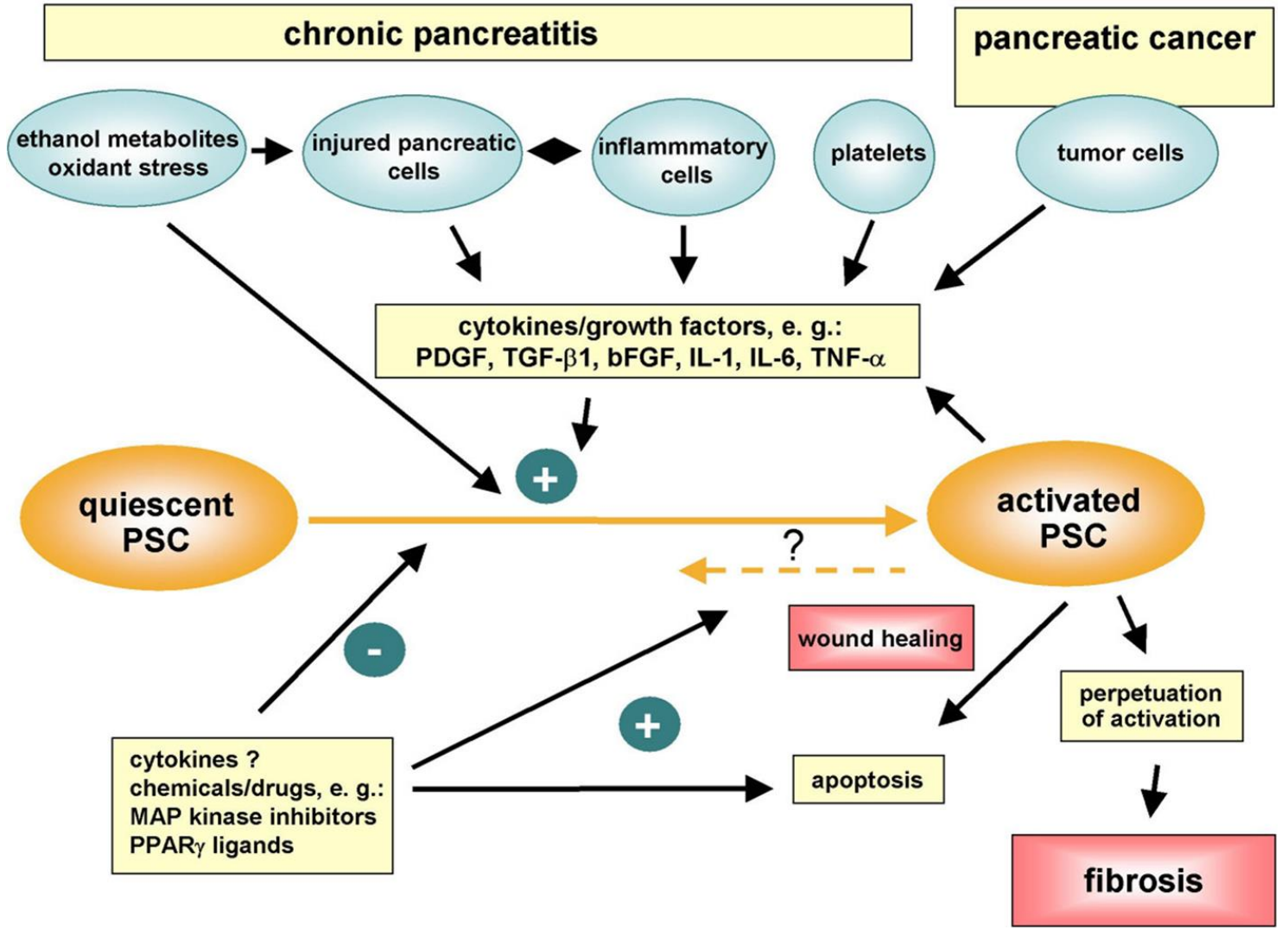
Pathogenesis of chron. pancreatitis

- alcohol metabolism produces toxins causing lipid peroxidation, inflammation and increase of cytoplasmic Ca
  - liver → acetaldehyde
  - pancreas → fatty acid ethanol esters (FAEEs)
- alcohol increases viscosity of pancreatic juice → precipitation of proteins and obstruction od ducts
- inflammatory signals stimulate pancreatic stellate cells (PSC) to produce connective tissue → fibrosis of the gland



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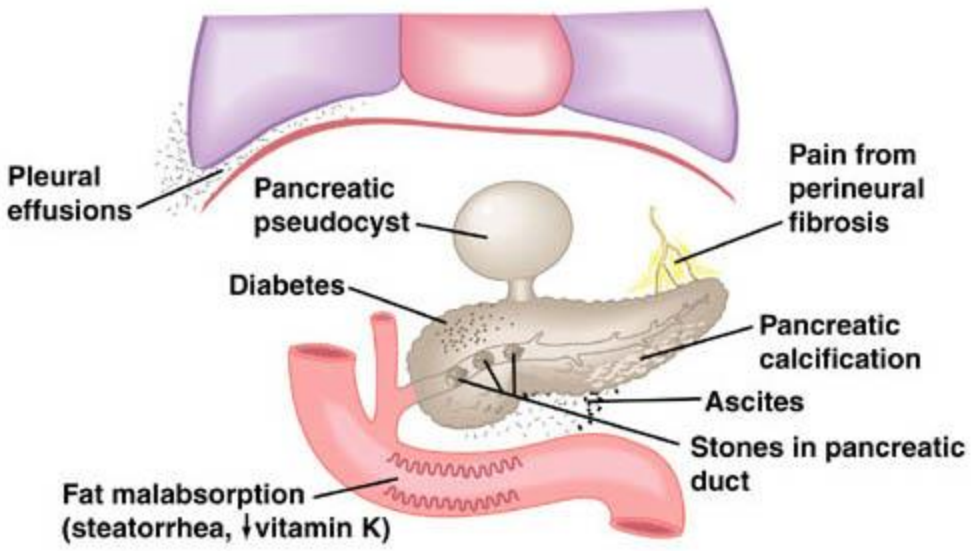
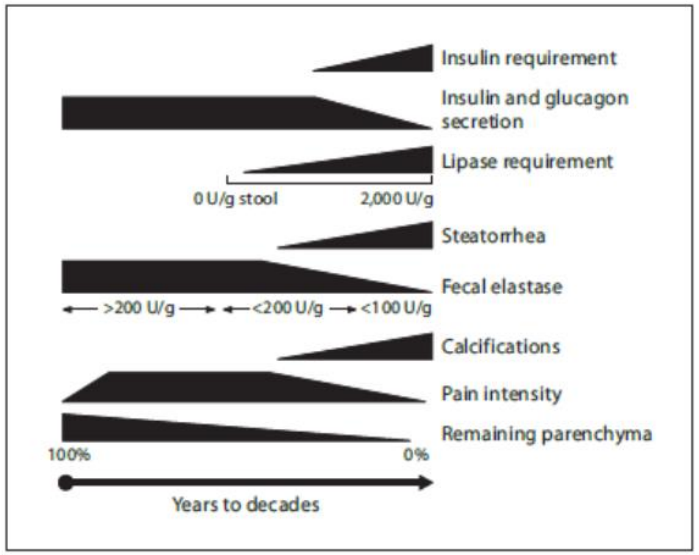
Consequences of chron. pancreatitis





- Malabsorption of macro- and micronutrients
  - absence of lipase
    - maldigestion and malabsorption of fats (→ **steatorrhea, diarrhoea**)
    - **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) → anaemia
  - pain
- **secondary diabetes mellitus** (destruction of islets of Langerhans)
- complications
  - cysts, closure of ducts, leak of juice to peritoneal and pleural cavity

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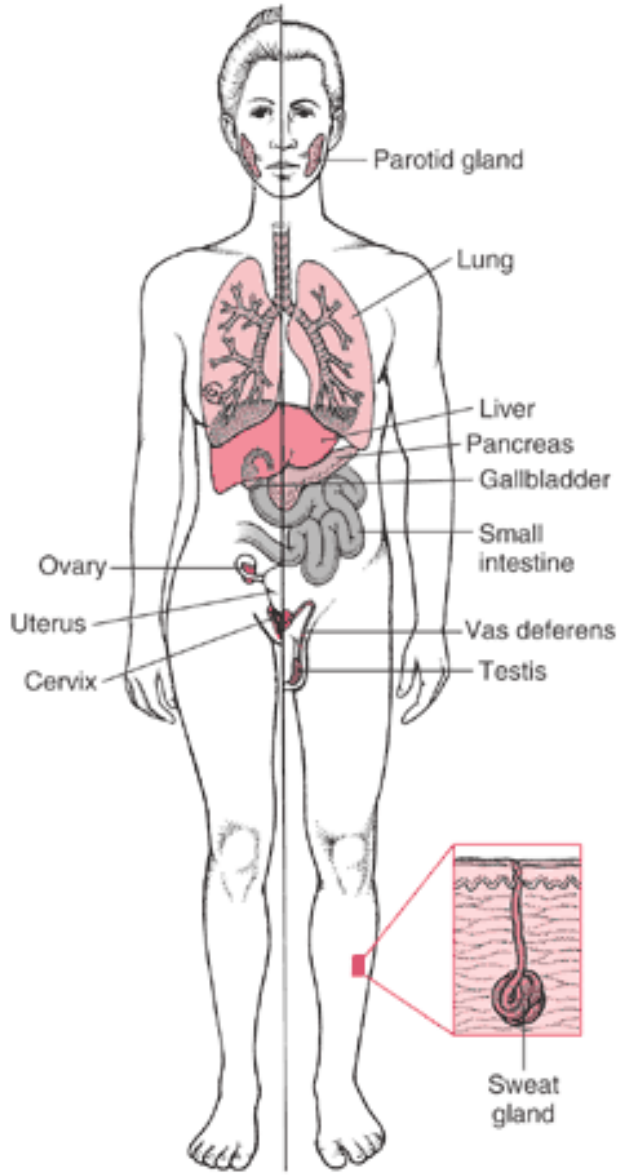
Cystic fibrosis (mucoviscidosis)

- 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



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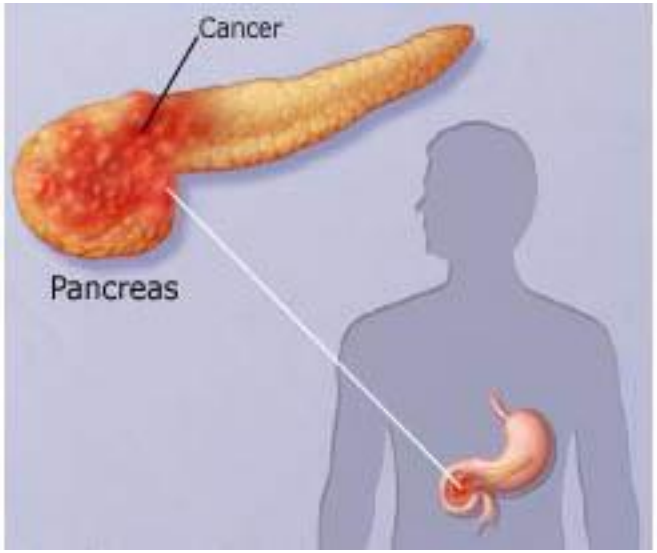
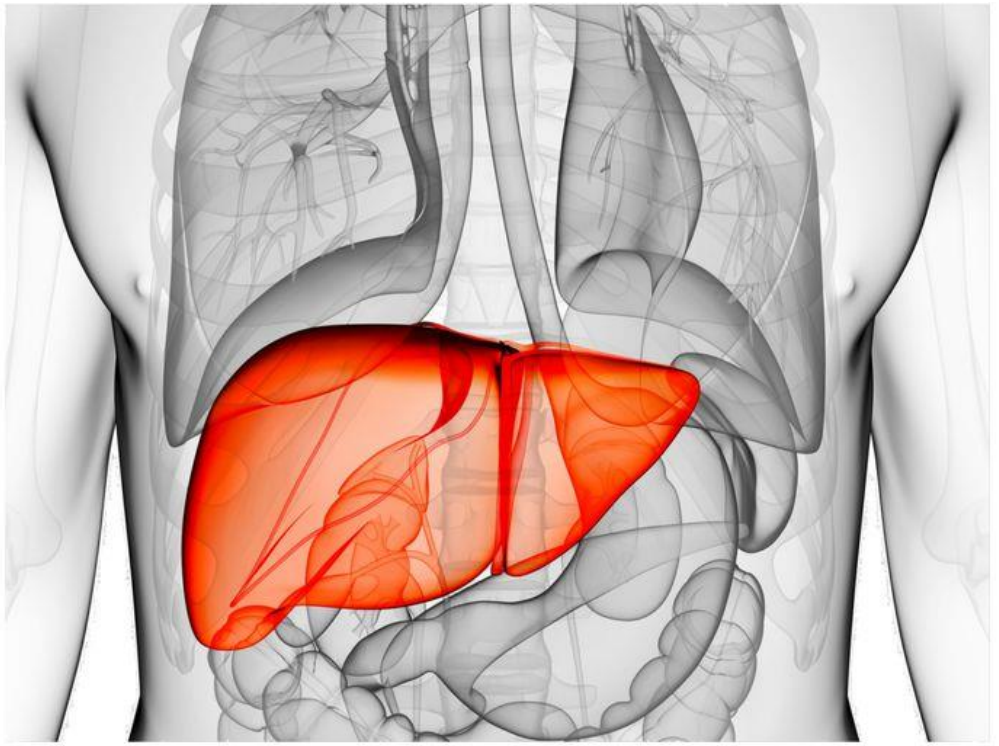
Tumours of pancreas

- 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
- tumours of endocrine pancreas
    - insulinoma (hypoglycemia)
    - gastrinoma (Zollinger-Ellison syndrome)
    - VIPoma (diarrhea, hypokalemia)
    - carcinoid





LIVER DISEASES

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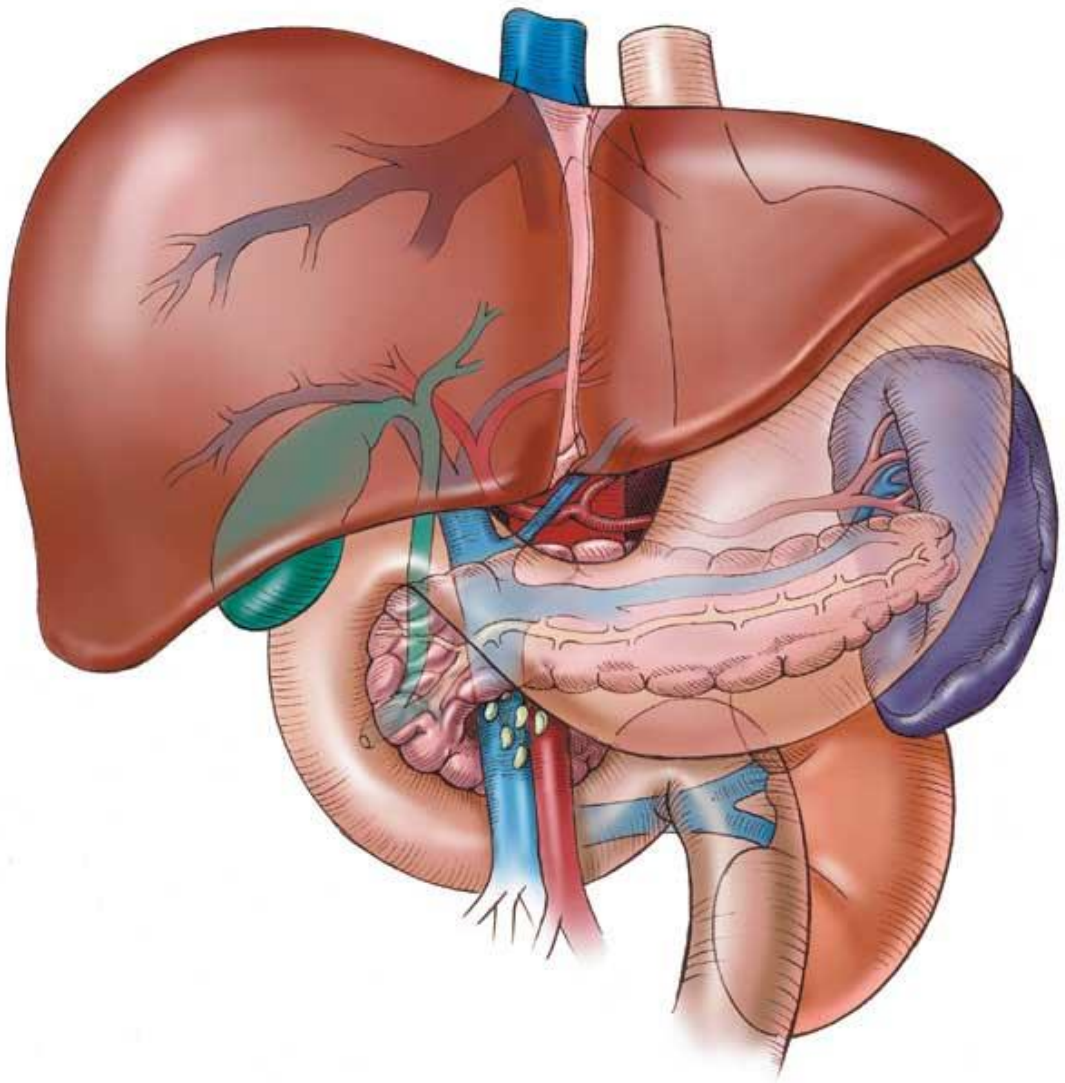
Anatomy and histology of liver



- 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
- functions of the 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

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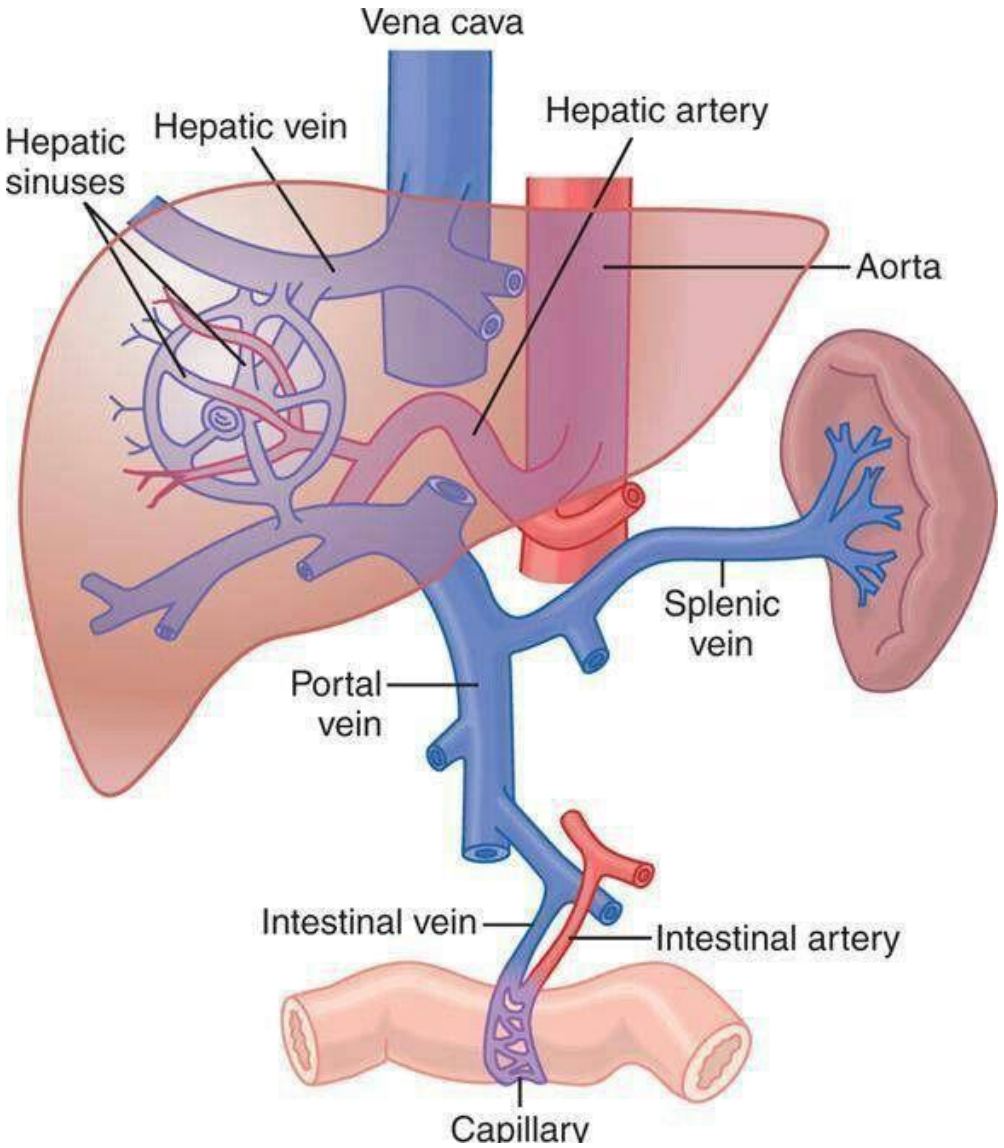
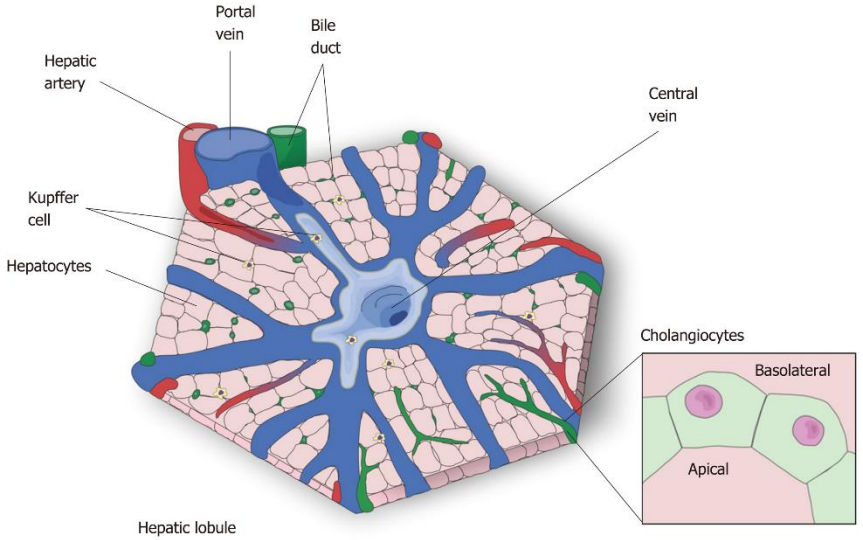
Liver blood supply



- 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



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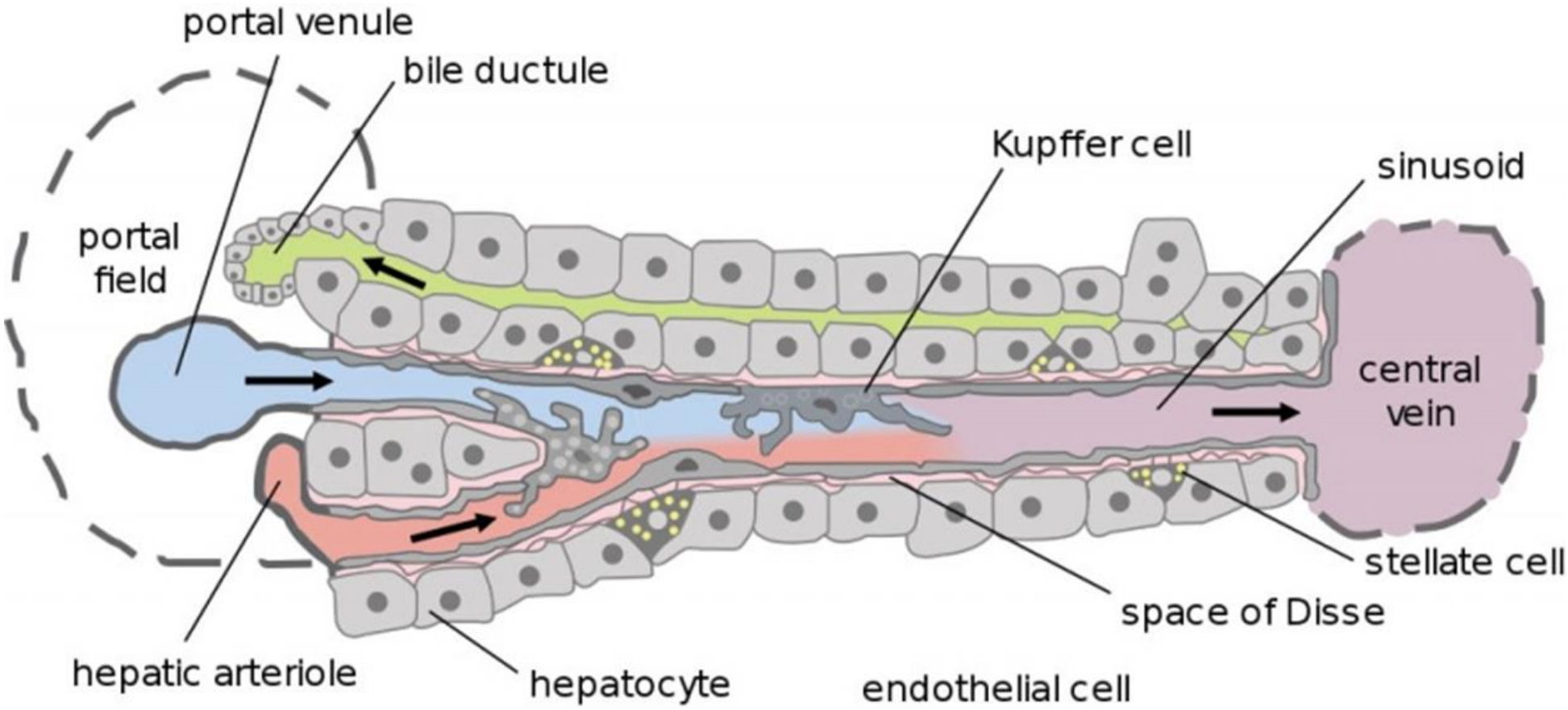
Liver sinusoids – from portal triad to central vein



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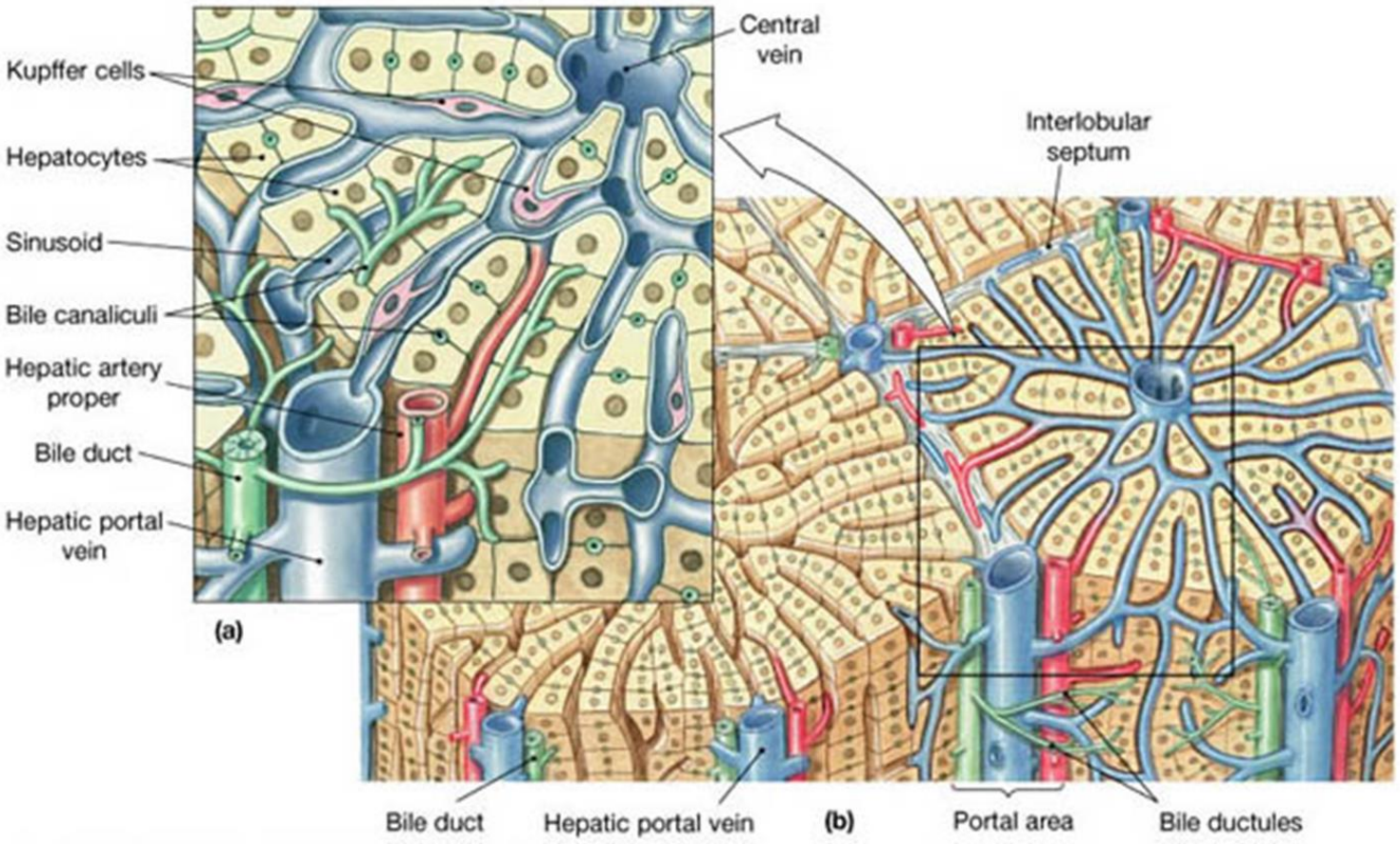
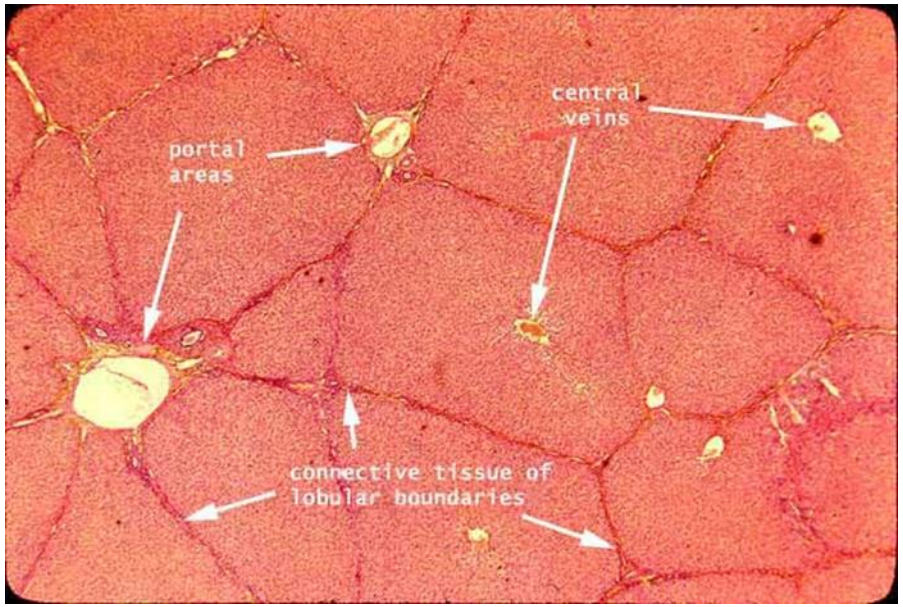
Morphology of liver – hepatic lobule





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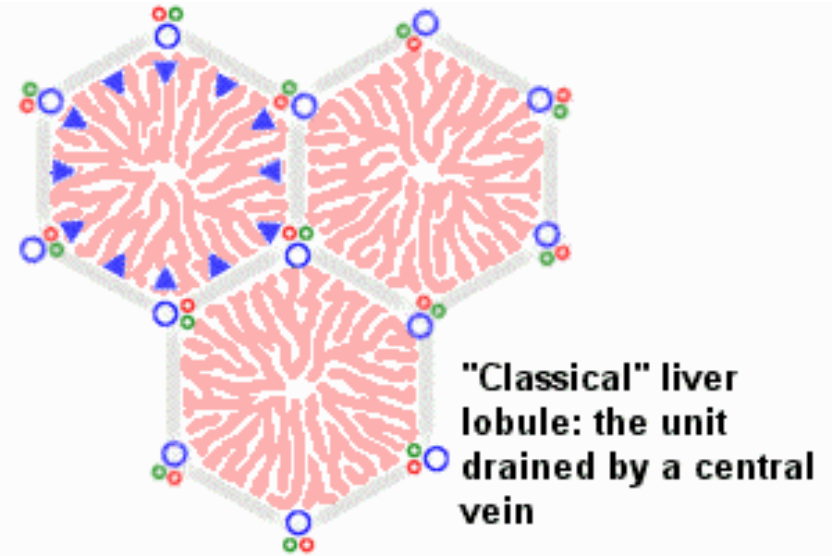
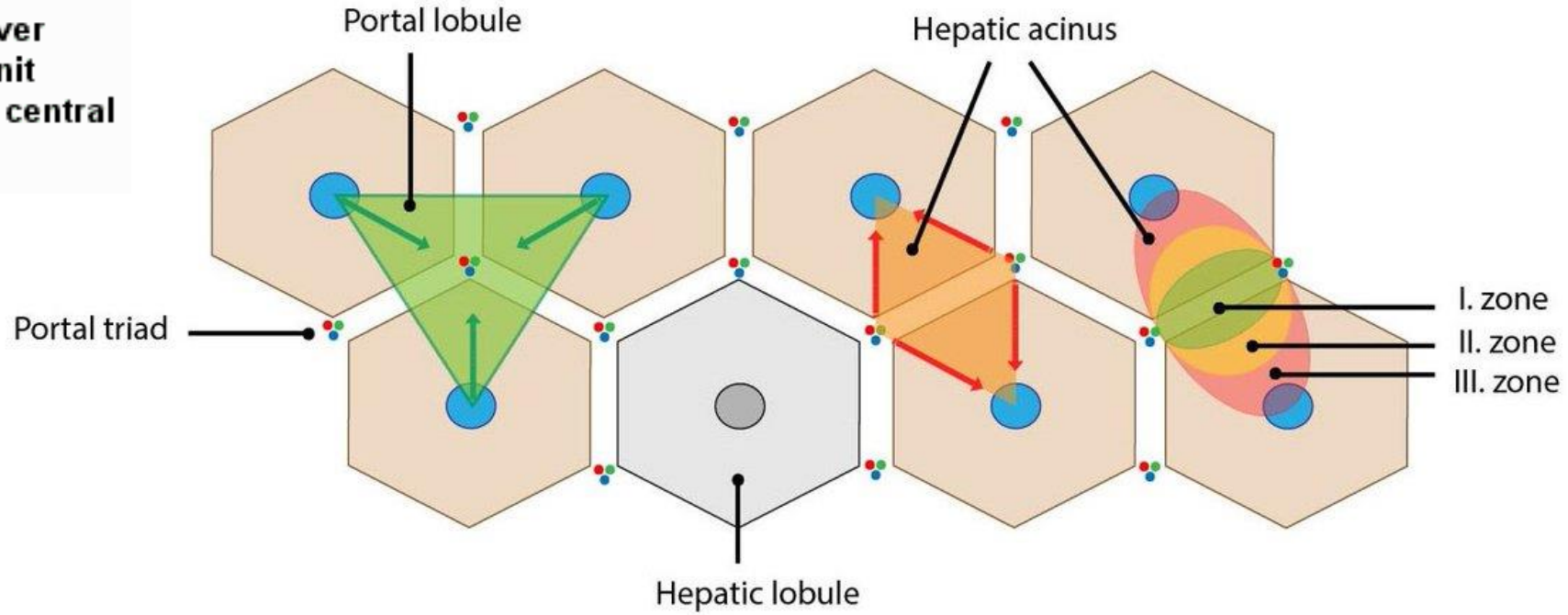
Liver lobule vs. portal lobule vs. acinus



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



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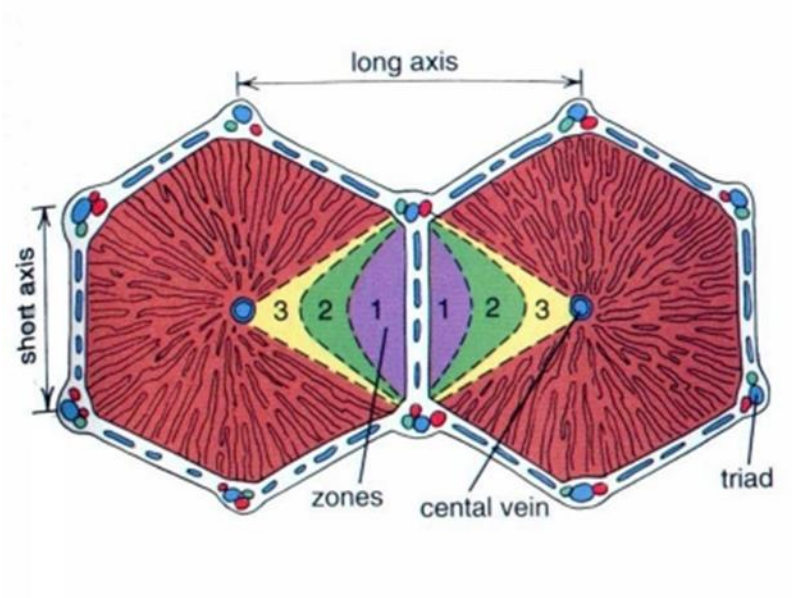
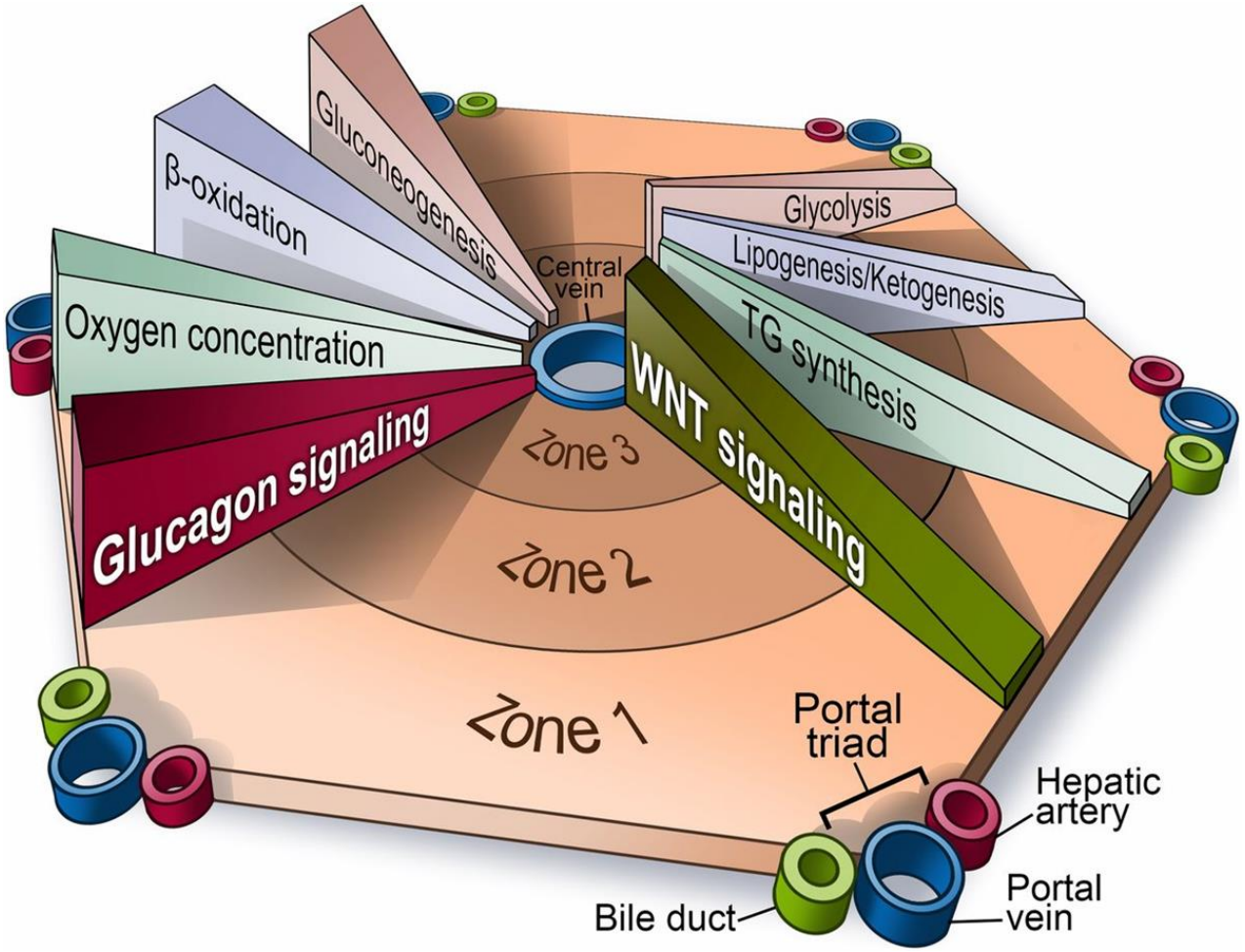
A concept of „liver acinus“ helps to explain „zonality“ of the liver parenchyma/hepatocytes as a function of O_2 availability, nutrients, hormones etc.





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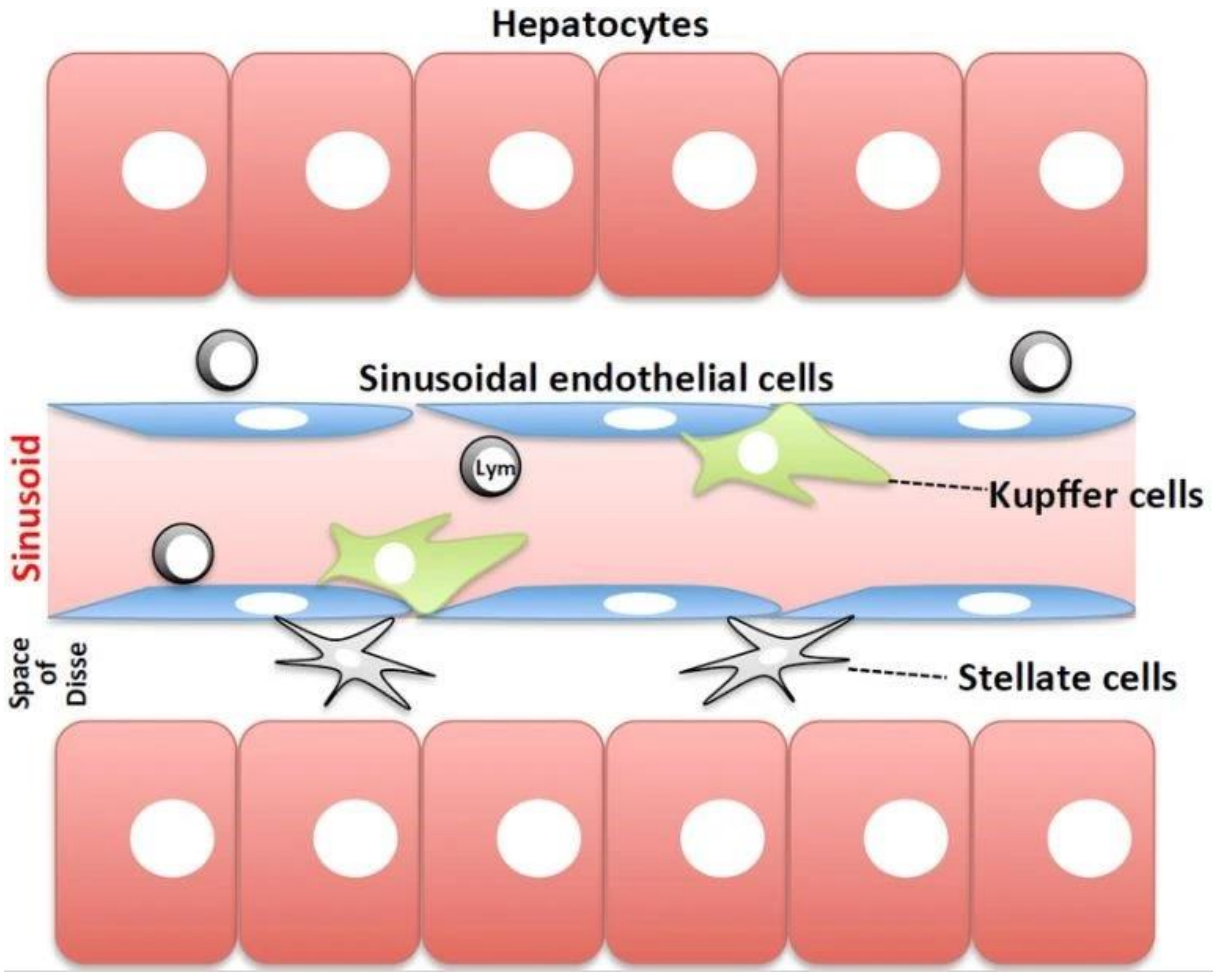
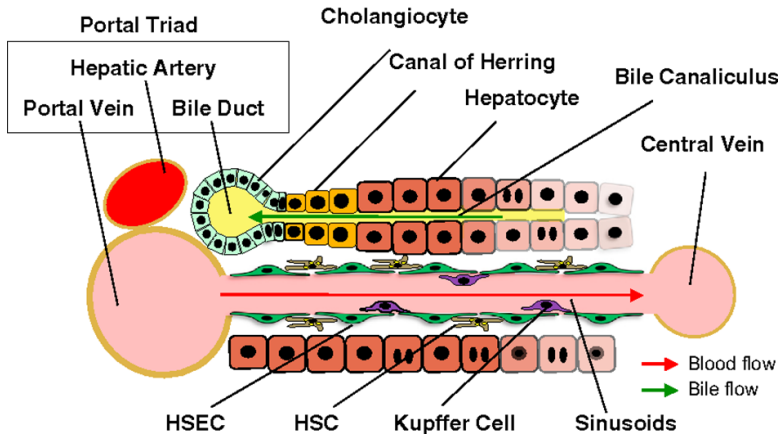
Buňky jater – RES a hepatocytes



- RES
  - endothelia
  - Kuppfer cells (macrophages)
  - hepatic stellate cells (Ito cells)
  - cholangiocytes
- hepatocytes
  - both hepatocytes and cholangiocytes participate in liver regeneration



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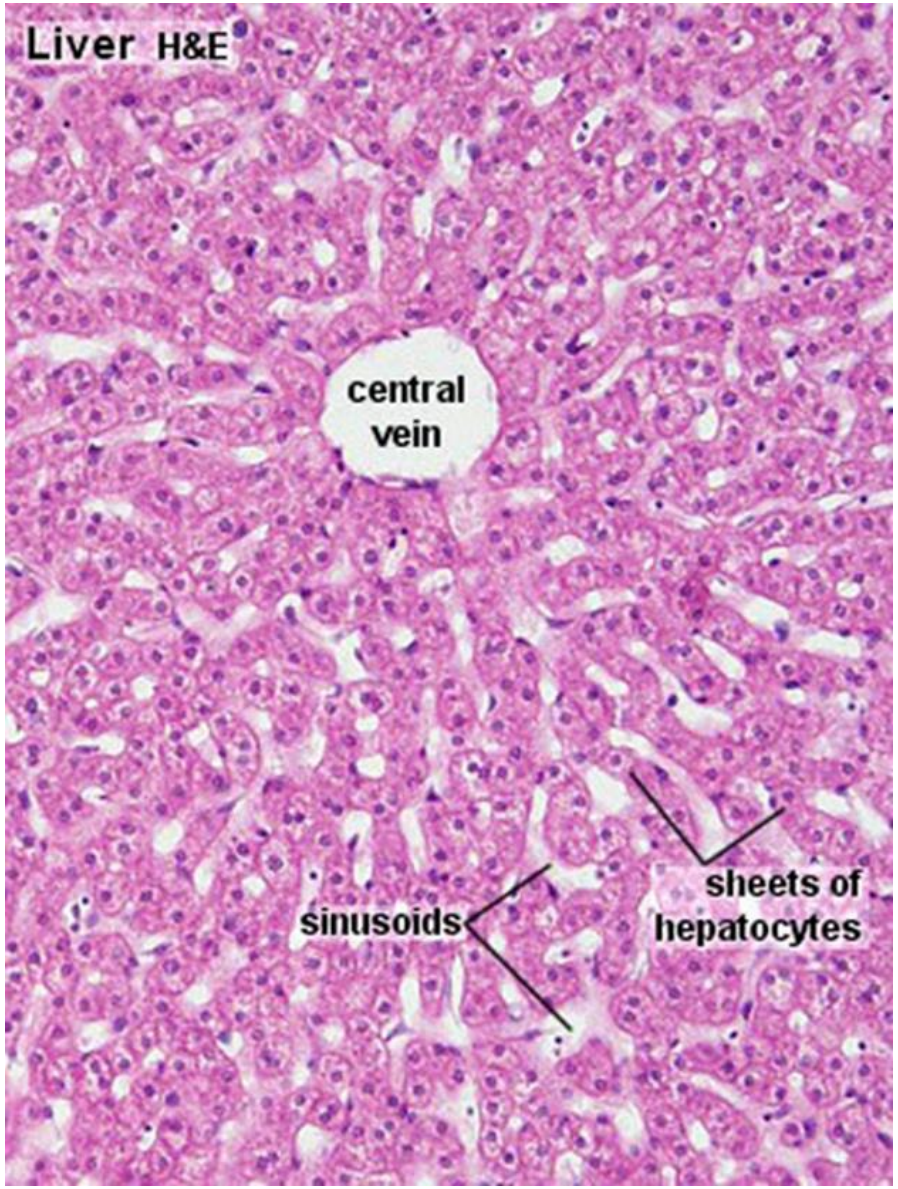
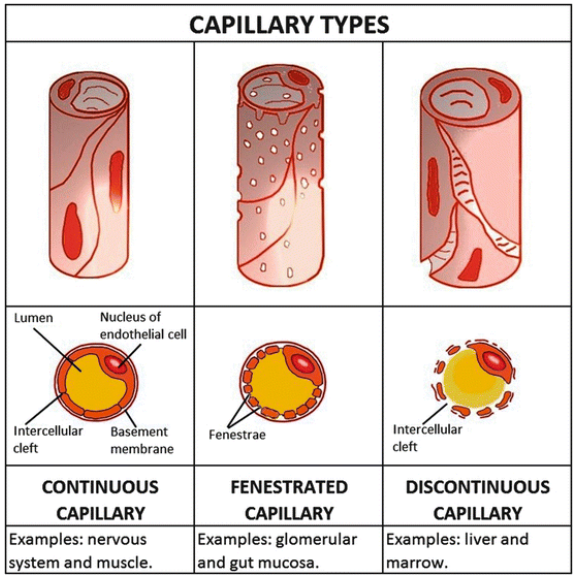
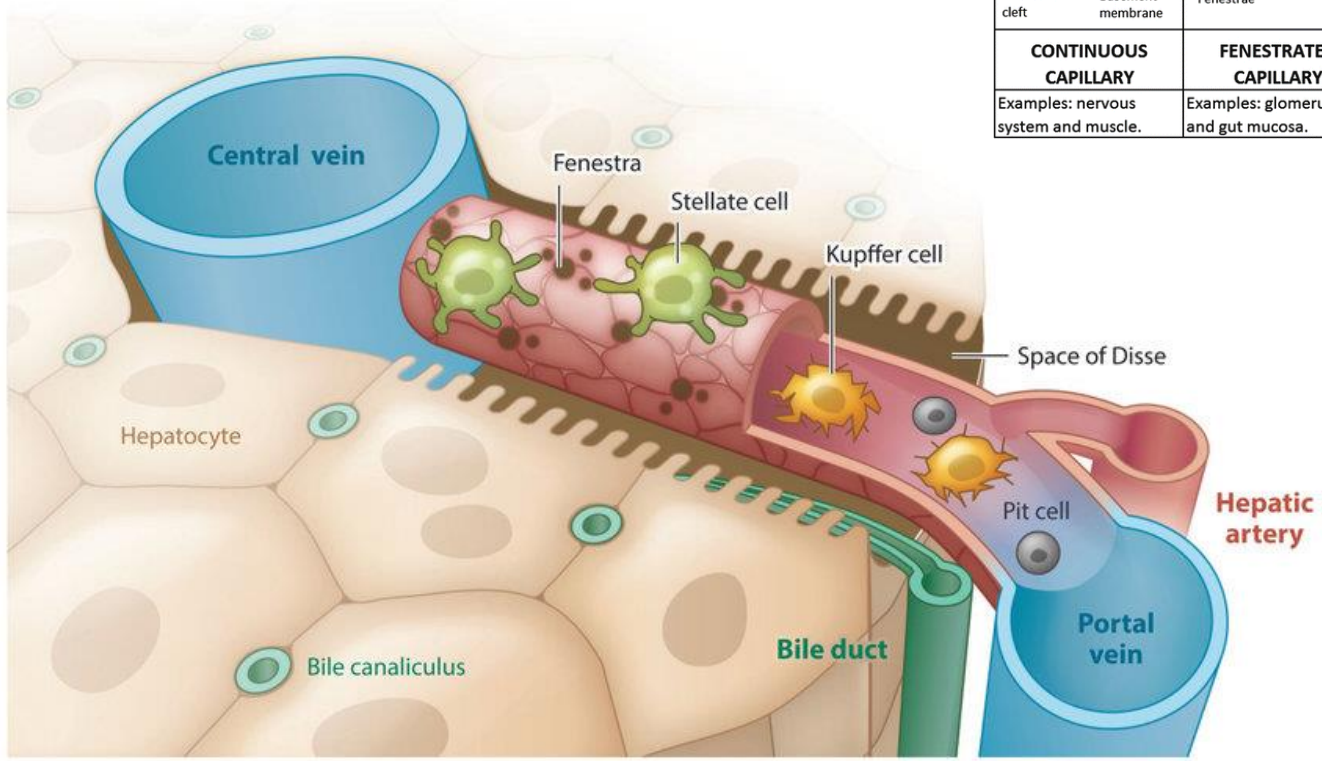
Liver sinusoids







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Markers of liver damage/disease

- tests of excretory function
  - bilirubin (serum and urine)
    - total, conjugated, unconjugated

- tests of synthetic function
  - total protein
  - albumin
    - sensitive marker of chronic disease
  - globulin
    - ratio A/G
  - prothrombin time (PT vs. INR)
    - extremely sensitive marker of both acute and chronic liver disease
    - complex marker of insufficient formation o factors 1, 2, 5, 7, 9, 10 in individuals without K vitamin deficiency, warfarin, thrombophilia etc.

- tests of liver „cytotoxicity" (enzymes)
  - AST/ALT
    - markers of typically active inflammation/ damage
    - uninformative for estimation of residual functional capacity of liver
  - GMT/ALP
    - obstruction of biliary tract
    - GMT specifically increased in alcohol abuse

- tests of storage function
  - iron metabolism parameters
  - B12

- tests of detoxifying function
  - ammonia
  - urea

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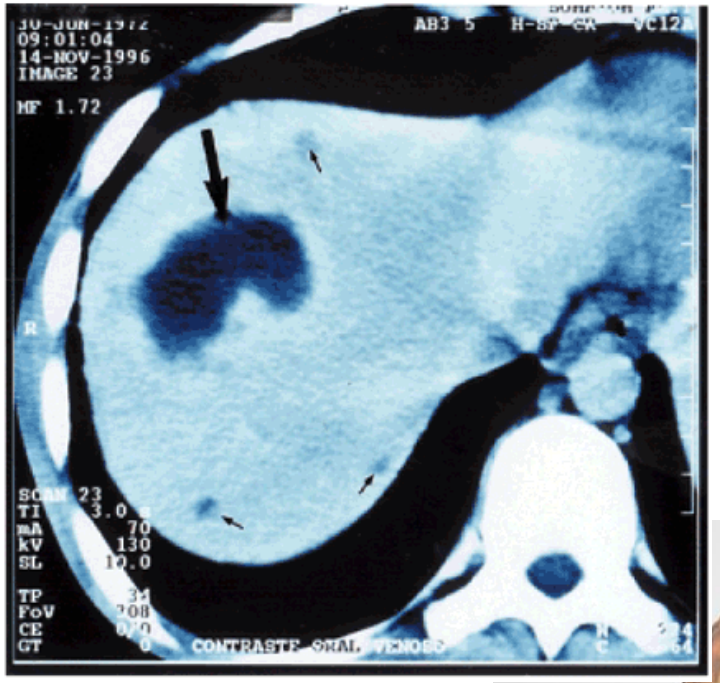
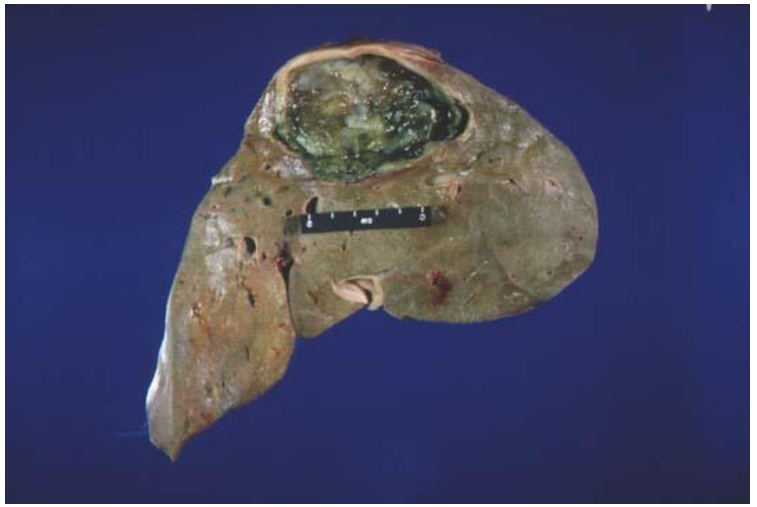
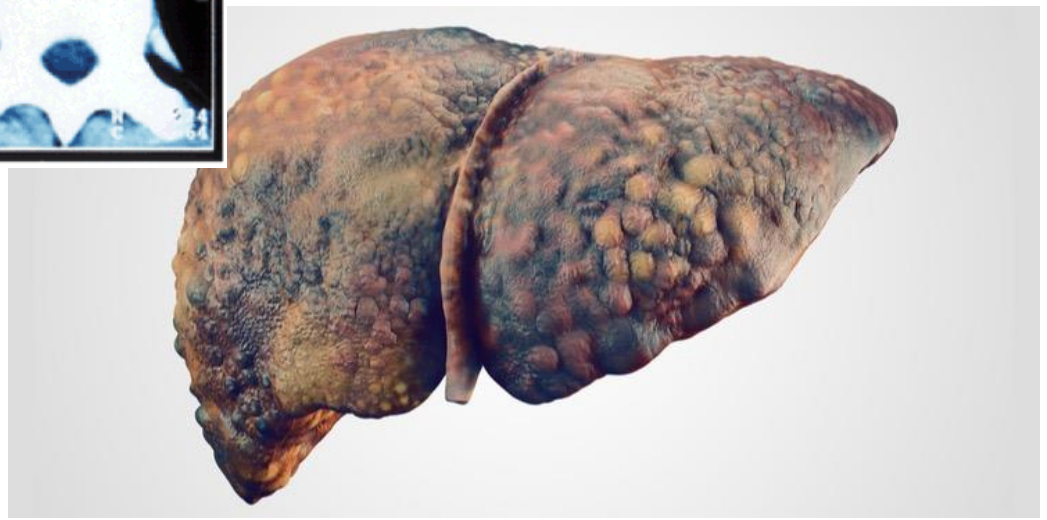
Aetiology of liver damage

- **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
- **metabolic disorders**
  - **common - NAFLD**
  - rare
    - heredit. hemochromatosis
    - Wilson disease
    - porphyria
    - glycogenosis
- autoimmune
  - autoimmune hepatitis
  - prim. biliary cirrhosis
  - primary sclerosing cholangitis
- tumours
  - primary (hepatocellular carcinoma, HCC)
  - metastases







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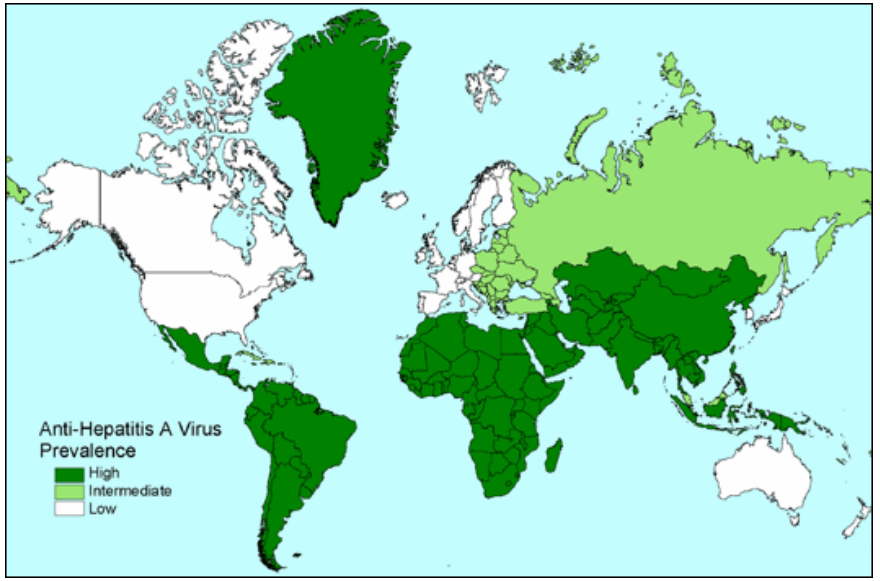
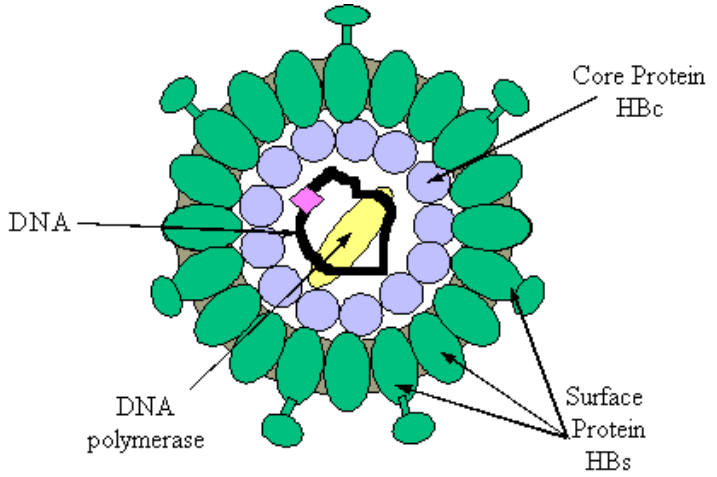
Liver infection – viral hepatitis

- time course
  - acute
    - usually 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
    - faecal-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





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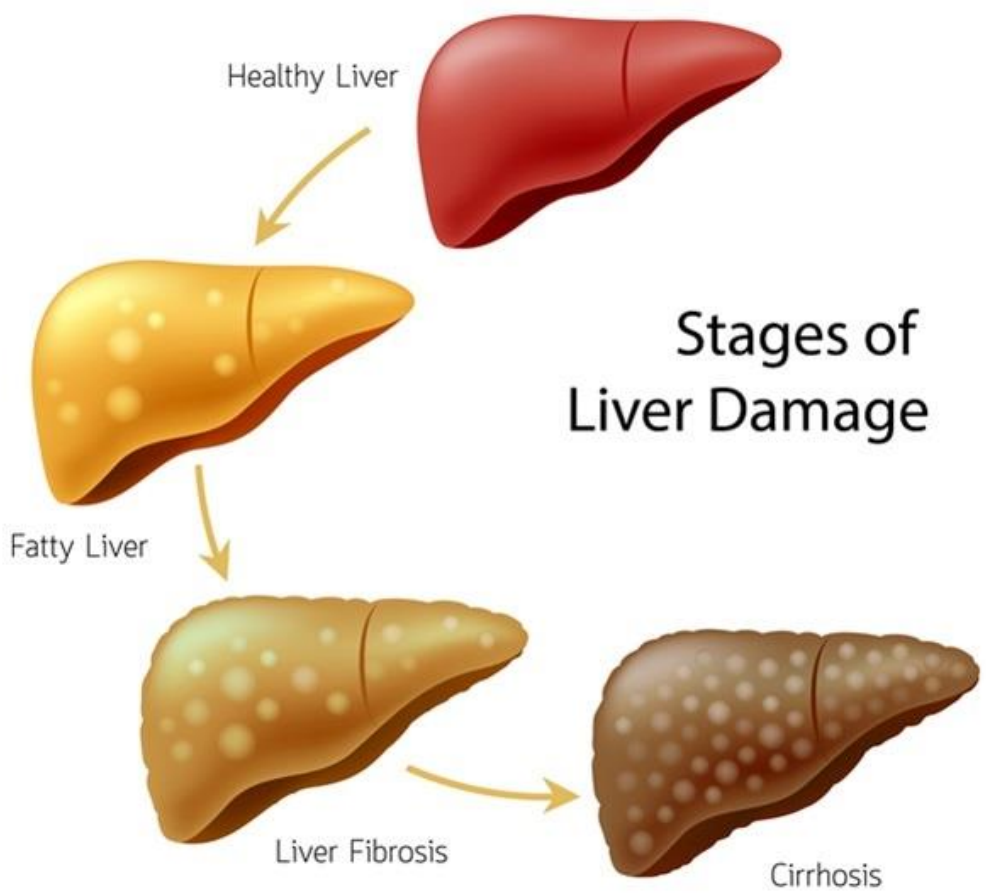
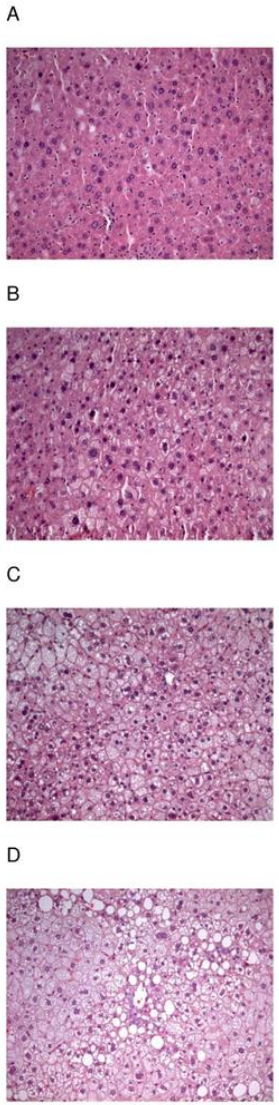
	Hepatitis A virus (HAV)	Hepatitis B virus (HBV)	Hepatitis C virus (HCV)	Hepatitis D virus (HDV)	Hepatitis E virus (HEV)
Viral genome	RNA	DNA	RNA	RNA	RNA
Transmission	Faecal-oral route	Blood and other body fluids	Blood	Blood and other body fluids	Faecal-oral route
Incubation period	14–28 days	30–180 days	14 days –6 months	HDV requires HBV for replication	14–70 days
Diagnosis	• Anti-HAV-specific AB • HAV RNA	• HBV surface protein • Anti-HBV-specific AB	• Anti-HCV-specific AB • HCV RNA	• Anti-HDV-specific AB • HDV RNA	• Anti-HEV-specific AB • HEV RNA
Possible chronic infection	No	Yes	Yes	Yes	Yes
Vaccine	Yes	Yes	No	No	Yes (in China only)

Despite variable aetiology, liver reaction t damage always proceeds through the same stages



- liver reacts the same way to various aetiologies 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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Reaction of liver to damage

(Painting: Christian Griepenkerl's Prometheus Tortured by the Eagle, 1800's)

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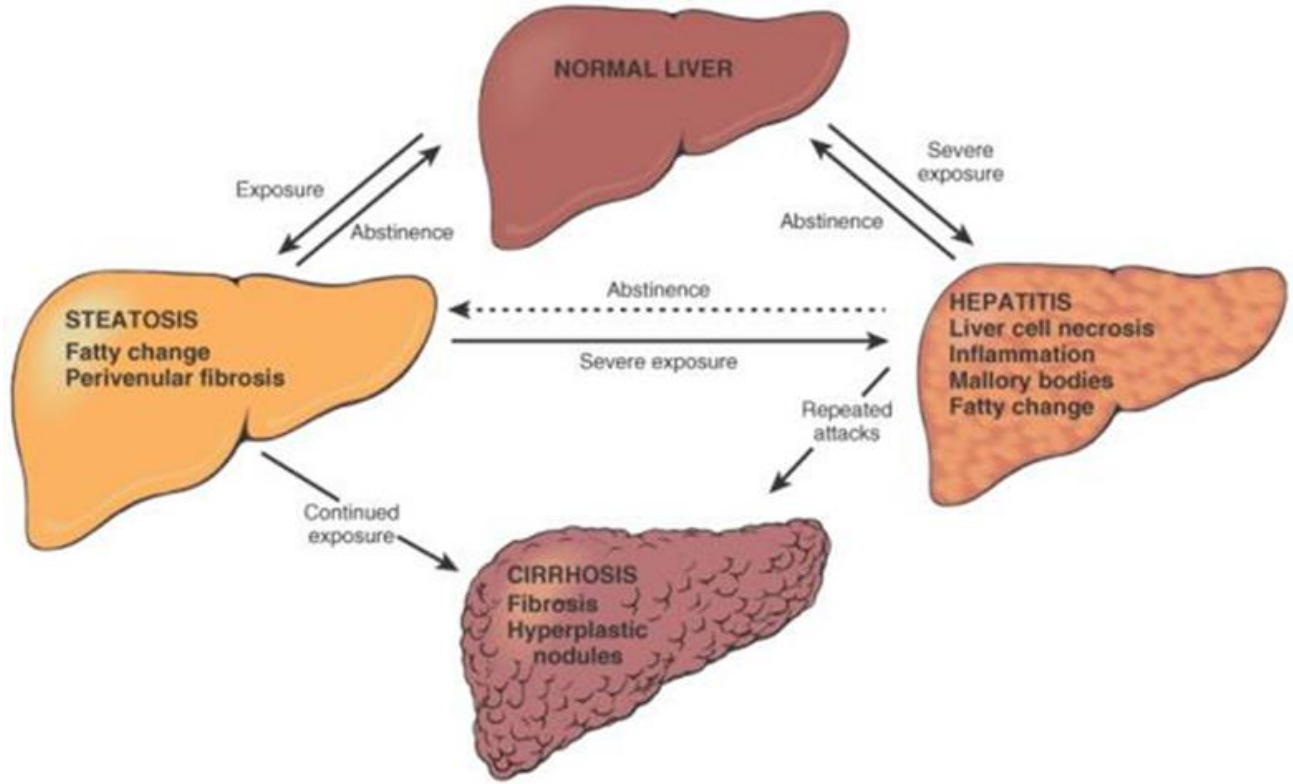
Issue of reversibility - liver regeneration

- sources of cells
  - (1) intrinsic liver cells
    - hepatocytes
    - cholangiocytes
    - progenitor/stem cells
    - regenerative potential depends on
      - location (zones 1 - 3)
      - extent of damage or hepatectomy
        - hypertrophy
        - hyperperplasia
        - dedifferentiation in progenitor cells
        - trans-differentiation of cholangiocytes into hepatocytes
  - (2) mesenchymal stem cells?



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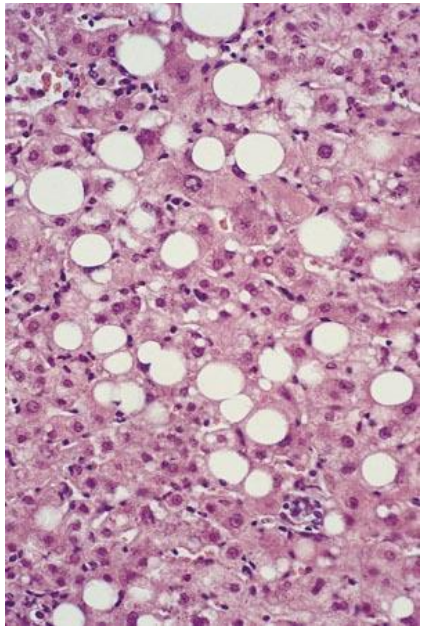
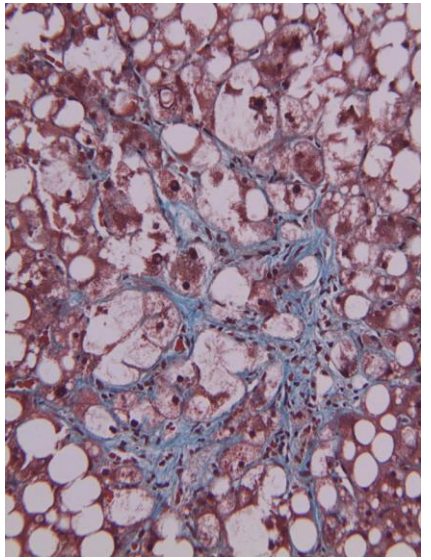
(1 -2) Initial (reversible) liver damage

- **(1) 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**
- **(2) 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.
- aetiology 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





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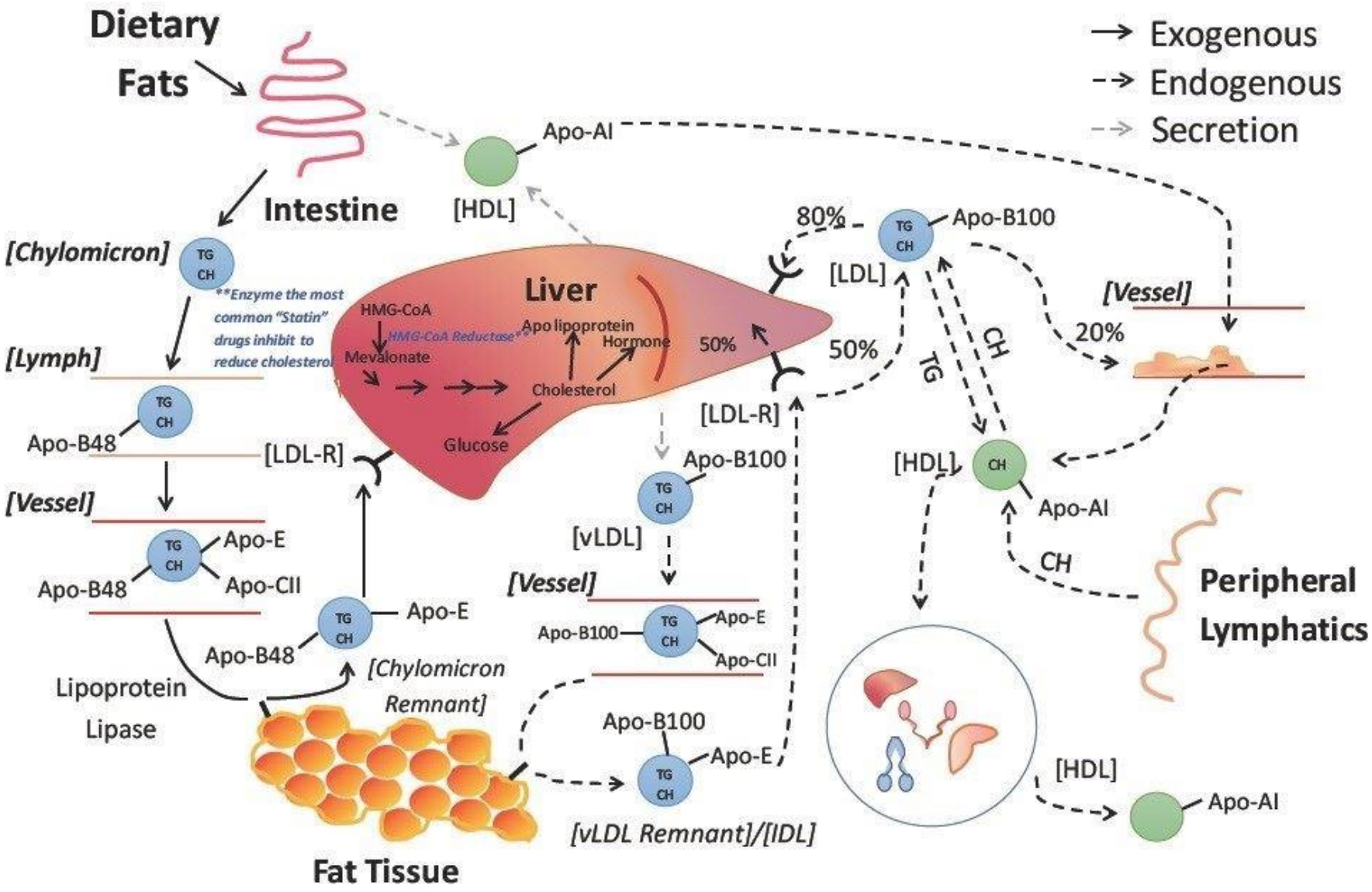
Central role of liver in lipid metabolism



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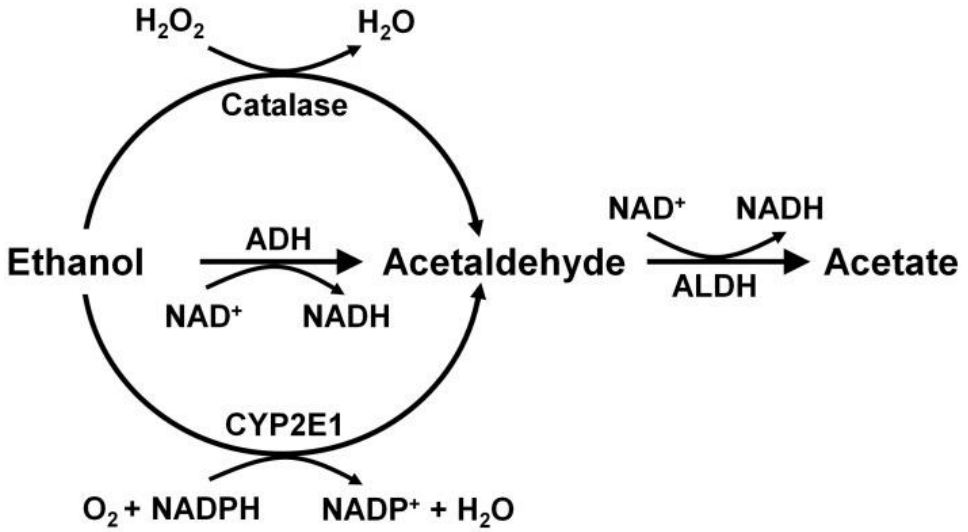
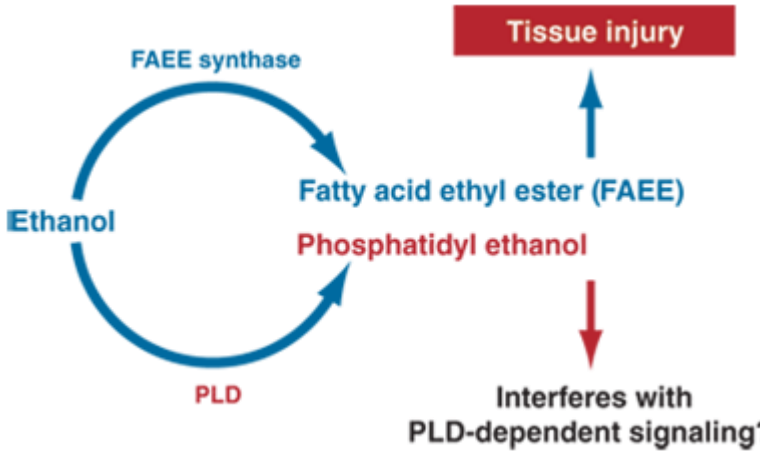
Alcoholic steatosis - ethanol metabolism

- oxidative
  - by enzyme alcohol dehydrogenase (ADH, 85%) to acetaldehyde
    - toxic intermediate acetaldehyde undergoes conversion to acetate (to Krebs cycle)
    - this conversion requires NAD^+ (to NADH) and changes redox state in liver
    - **mismatch of NADH/NAD^+ is essential because it blocks gluconeogenesis and beta-oxidation of FFA with subsequent increase lipogenesis (FFA formation) and their esterification to TAG and thus steatosis**
  - by catalase
  - by MEOS
- non-oxidative
  - formation of molecules called fatty acid ethyl esters (FAEEs) from the reaction of alcohol with fatty acids–weak organic acids that play functional roles in human cells
  - enzyme phospholipase D (PLD), which breaks down phospholipids (primarily phosphatidylcholine) to generate phosphatidic acid (PA)





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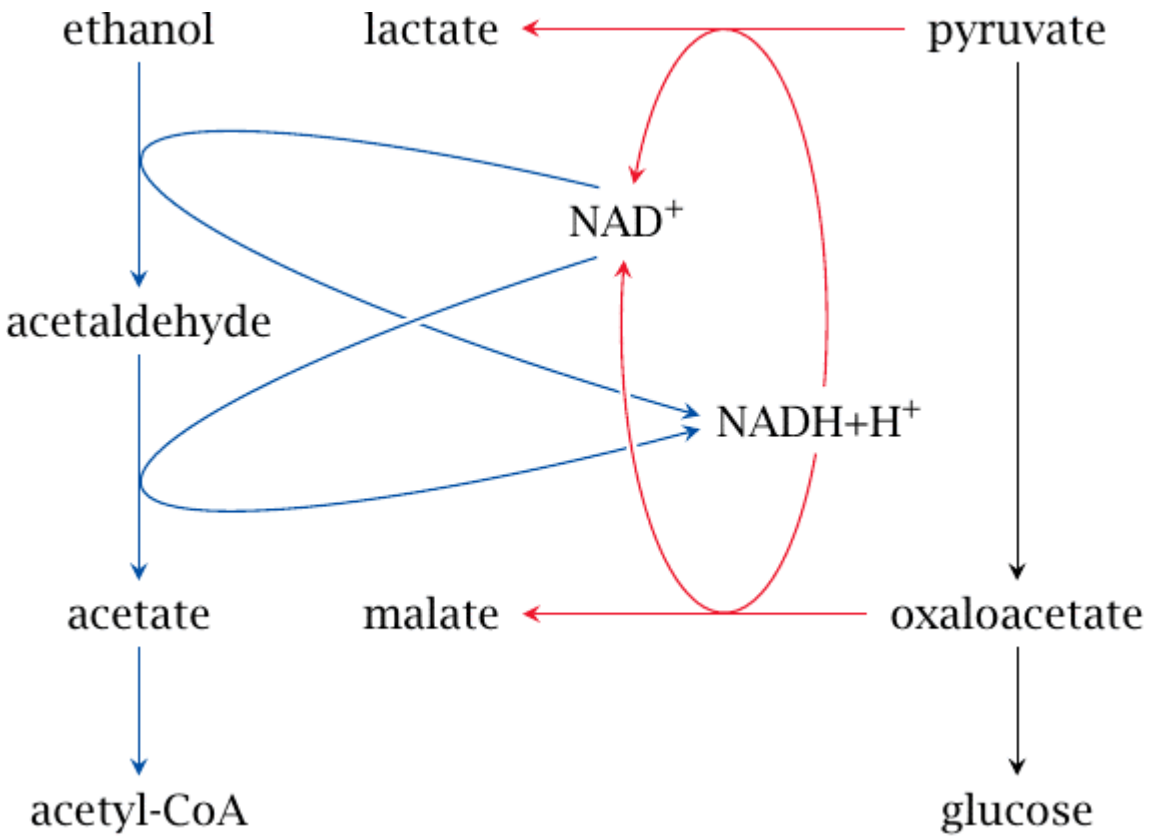
Metabolic consequences of ethanol detoxification by ADH



- ethanol degradation inhibits gluconeogenesis
  - in alcoholic patients, this problem is often compounded by a low intake of carbohydrates
  - clinically manifest hypoglycaemia with unconsciousness is a well-known and potentially dangerous complication in alcohol addiction
    - hence alcoholic ketoacidosis
- consequently, fatty acid synthesis is activated in hepatocytes as a metabolic compensation to ensure energy substrates
- at the same time, FA oxidation is inhibited by the lack of NAD^+

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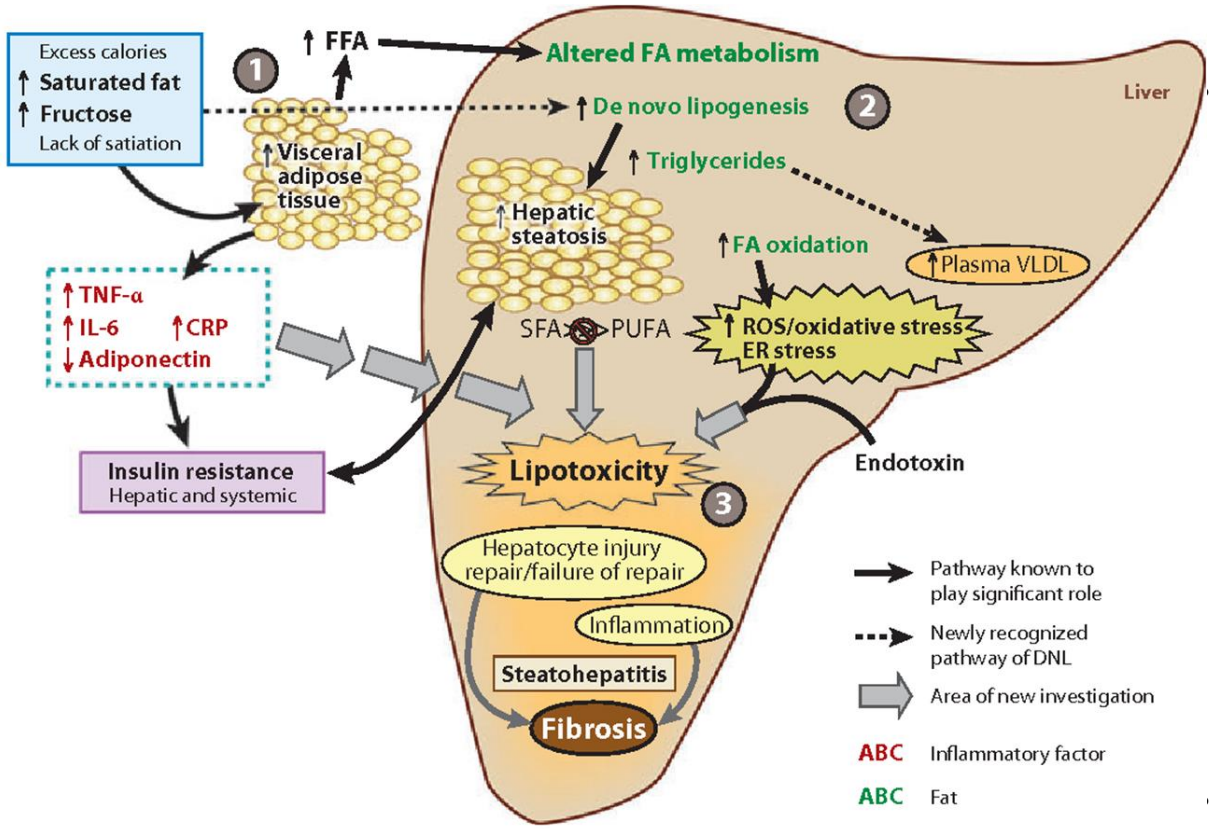
NAFLD and NASH



- prevalence ~20 - 30% in industrialised countries (associated with **OBESITY**!!!)
- can be difficult to dissect from alcoholic damage in countries where alcohol consumption is socially accepted and common
  - definition of non-alcoholic aetiology: 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

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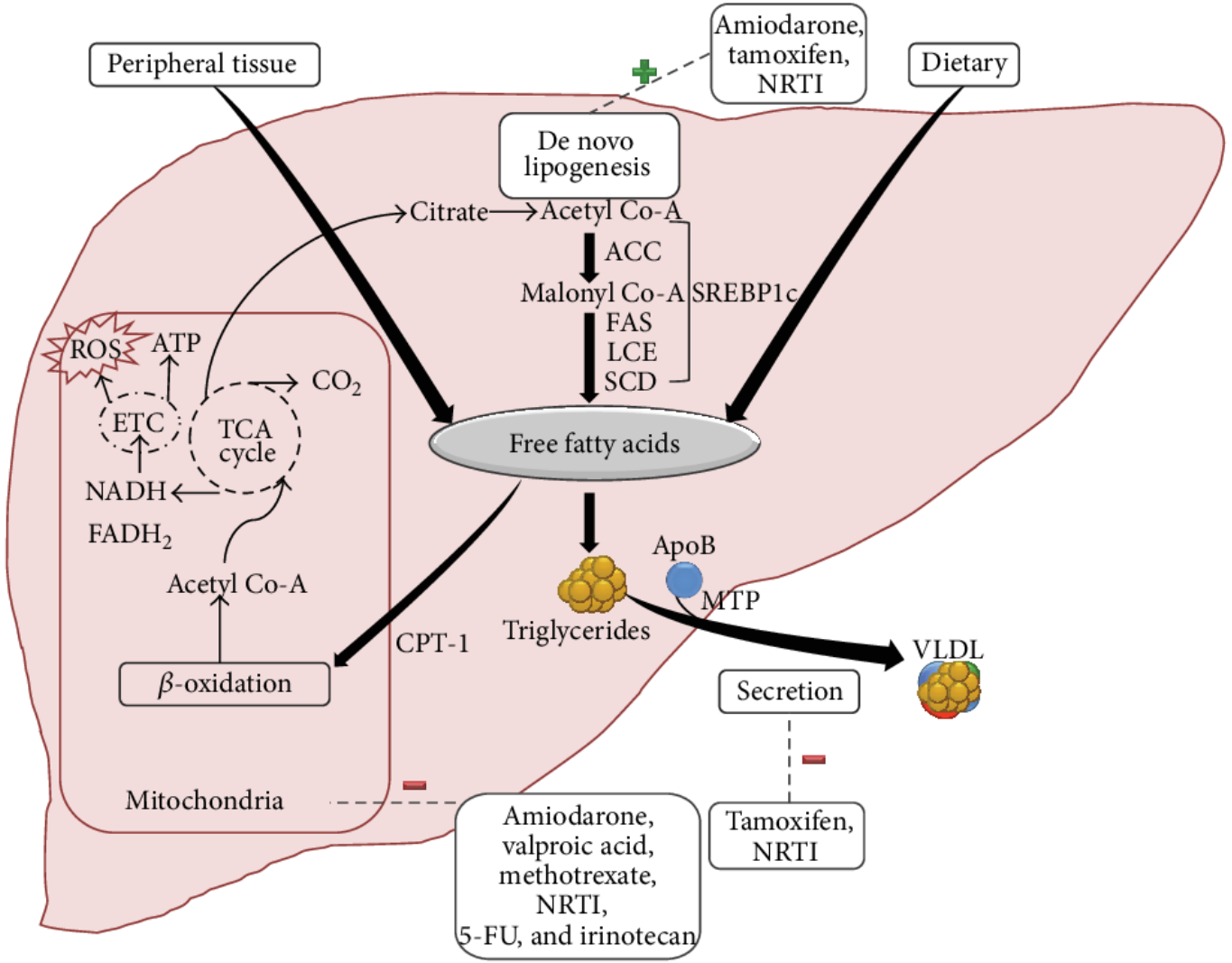
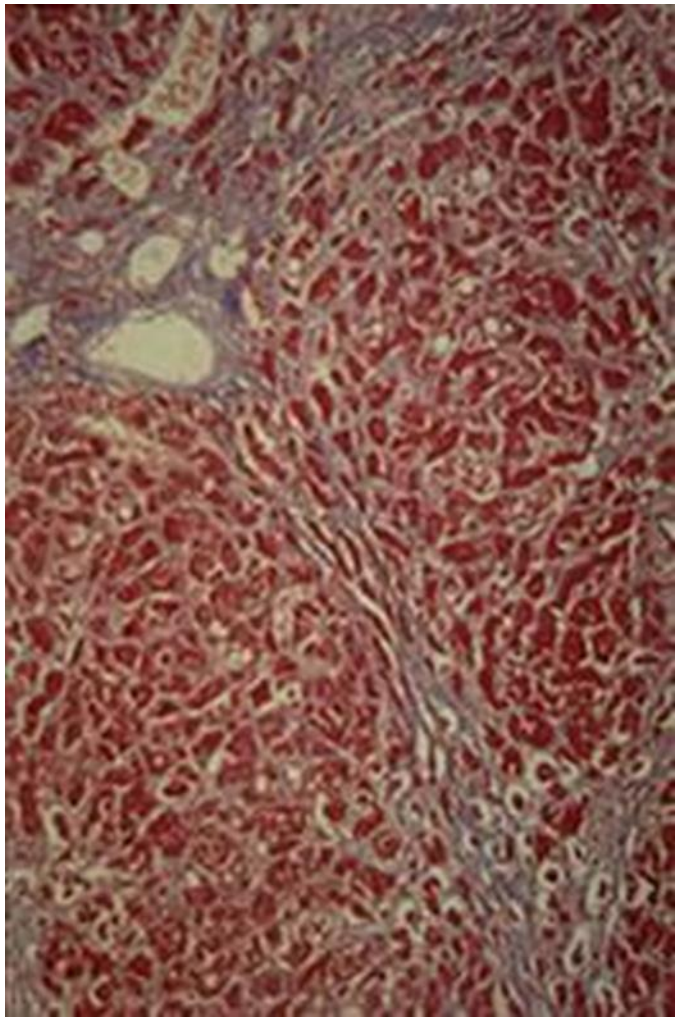
Many ways to fatty liver (viral, dietary, alcohol, T2DM, drugs, …)



(3) More advanced (reversible?) liver damage

- result of chronic damage of hepatocytes
  - infection, alcohol, toxic substances, accumulation of metals (Cu, Fe), drugs, …
- collagen in normal liver
  - I and III in periportal areas
  - IV in Disse space
- **(3) 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



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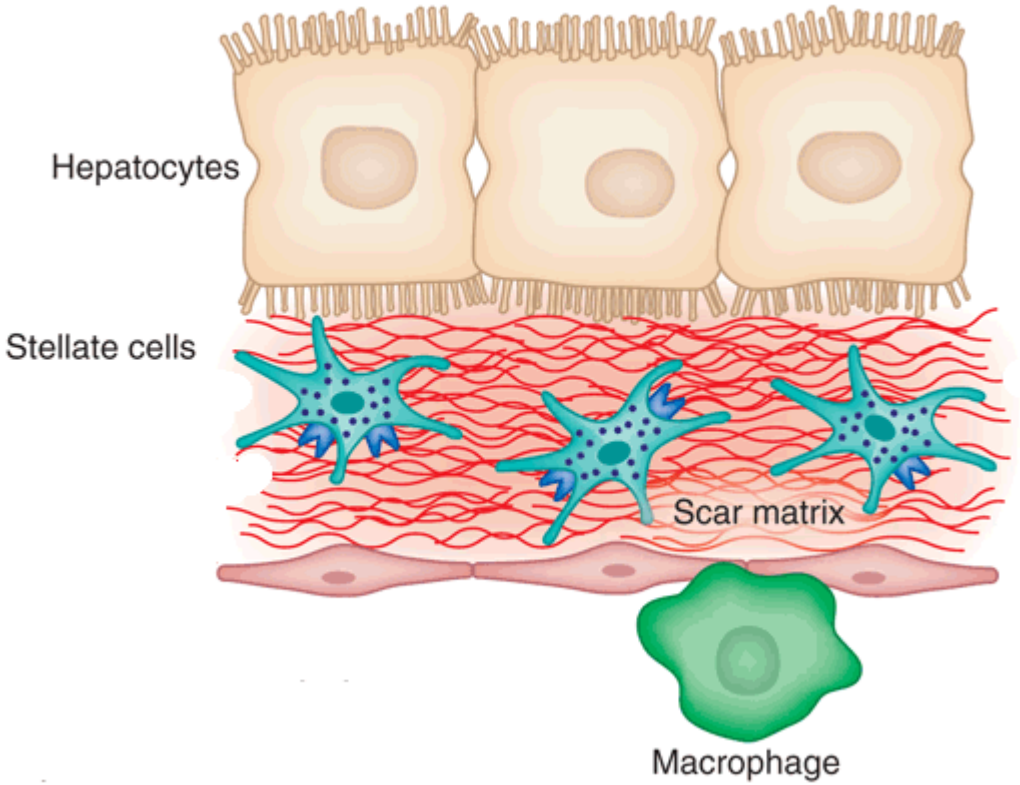
Activation of HSC in fibrosis



- 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)

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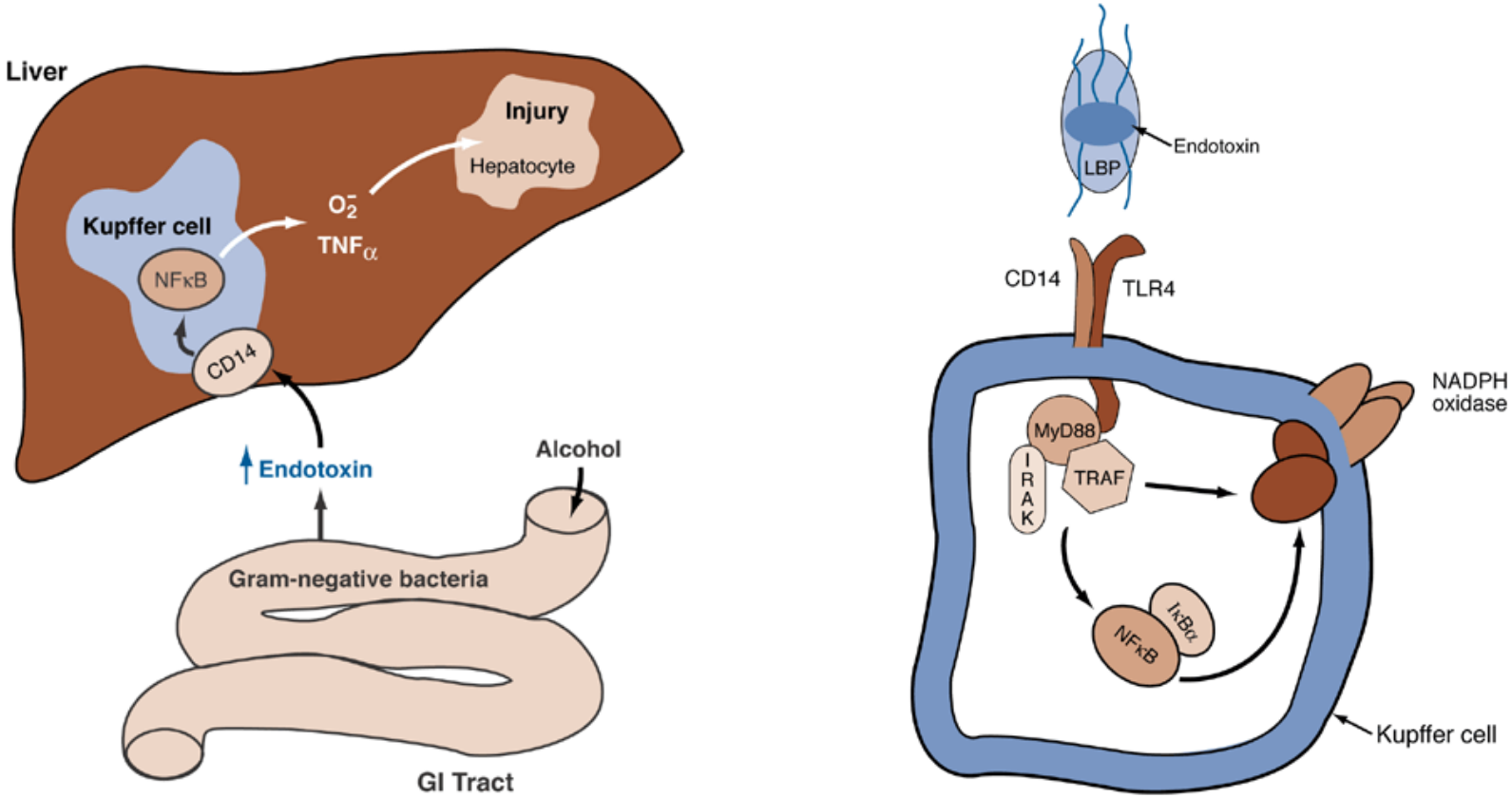
Alcohol and liver - endotoxin



- 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)

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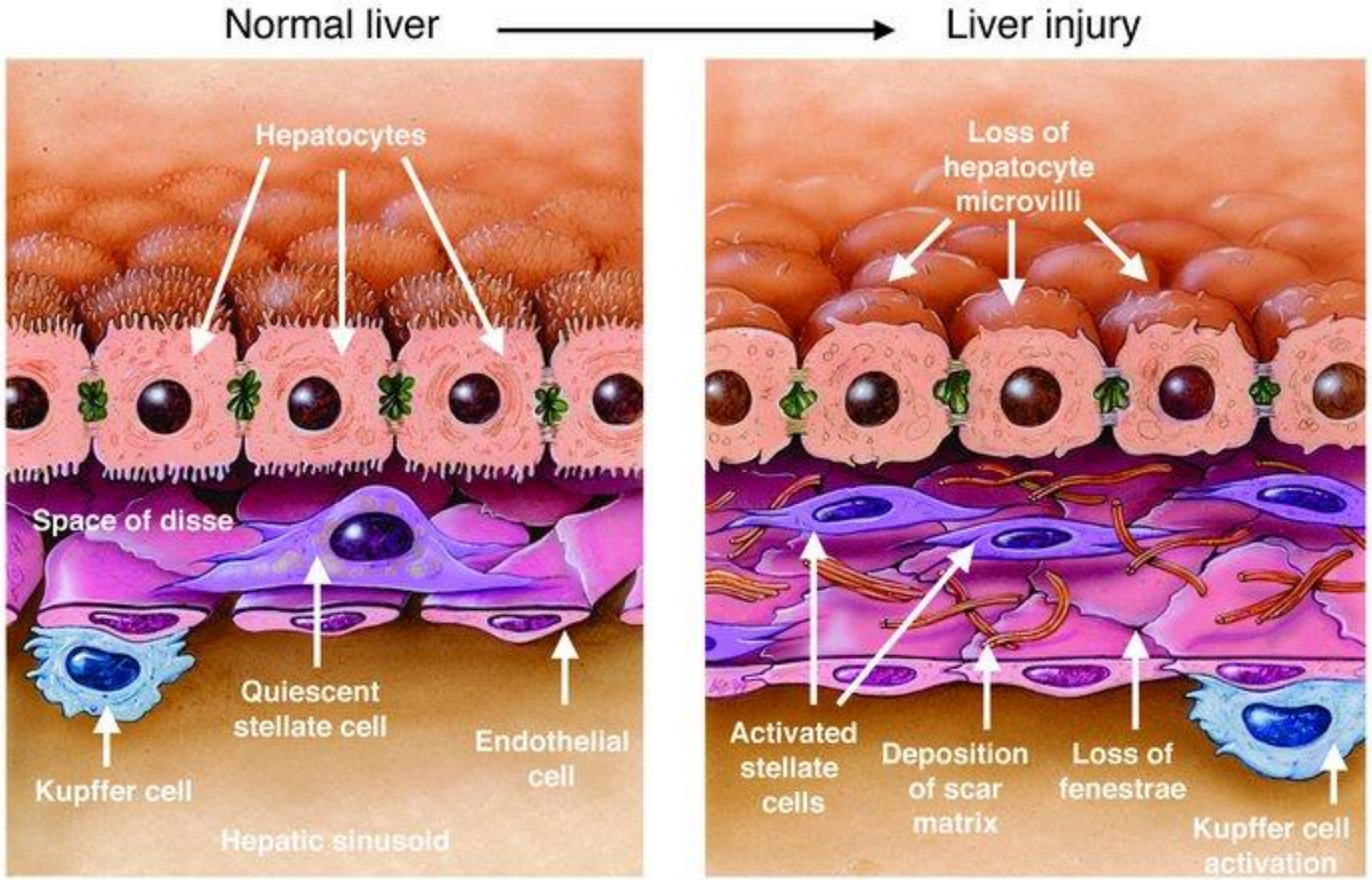
Role of HSC in l. fibrosis on hepatic sinusoidal cells



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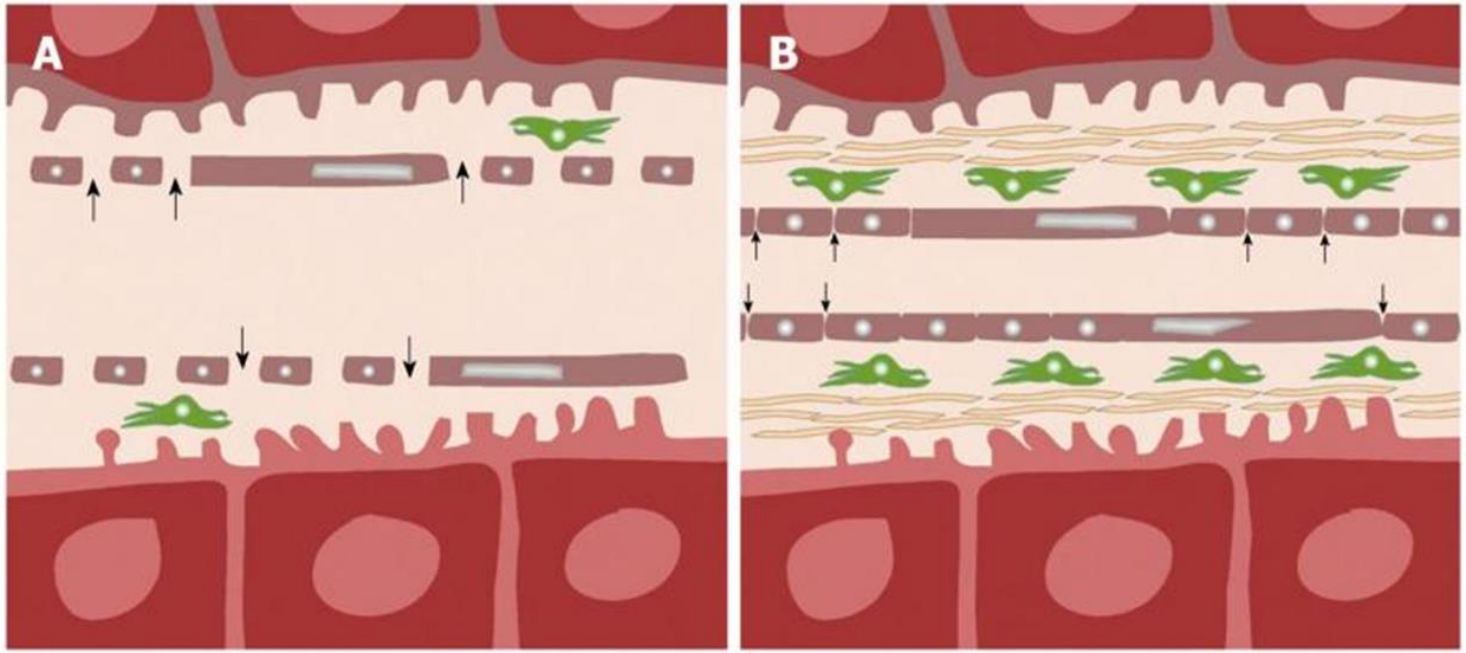
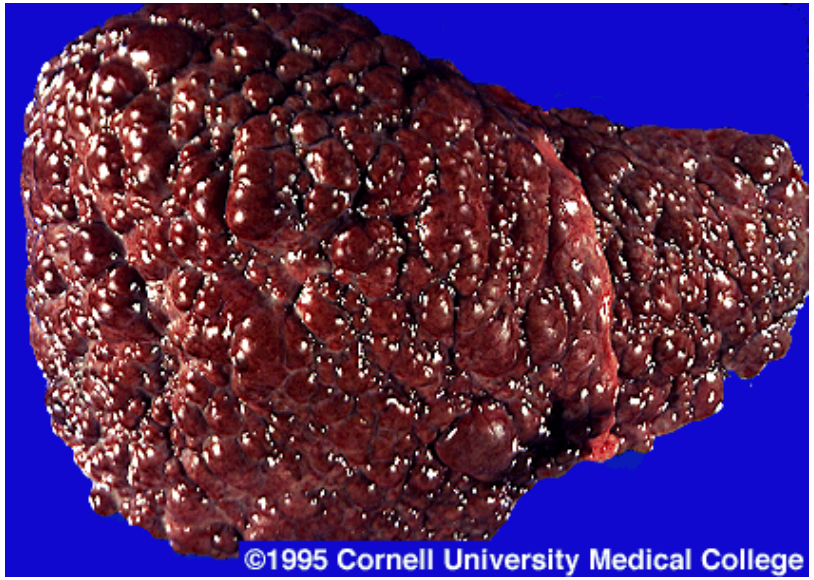
Pathophysiological differences between normal (A) and fibrotic/cirrhotic (B) liver

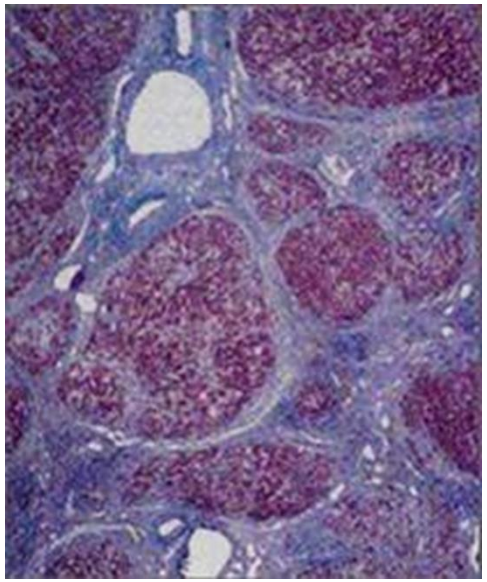


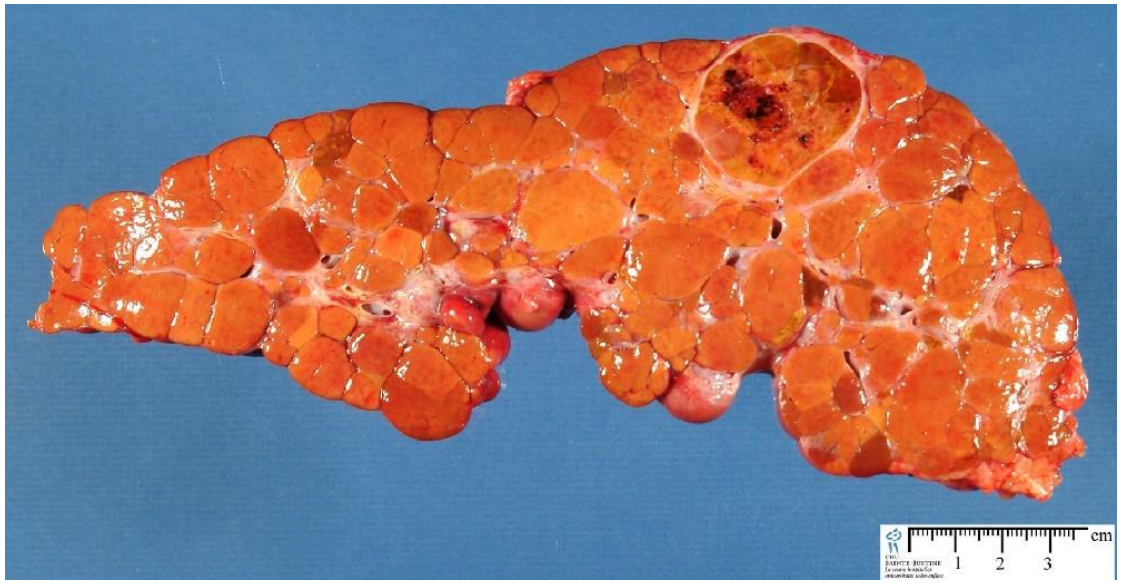
- In normal liver (A), normal fenestrae along the hepatic sinusoids allow free passage of blood (arrows) into the Space of Disse, in which, stellate cells (green) are found. In liver cirrhosis (B), there is an increase in the number of stellate cells, associated with deposition of collagenous fibers in the Space of Disse, and loss of fenestrae as the sinusoids become more capillary-like. As a result, transfer of low-molecular-weight compounds (e.g. contrast medium) from the sinusoids into the Space of Disse becomes more impeded (small arrows).

(4) Advanced (ireversible) liver

- **cirrhosis (C)**
  - irreversible (?) change of architecture (lobules, vessels, collagen)
  - parallel processes: steatosis + inflammation + fibrosis + necrosis + nodular regeneration
    - not so much pure loss of functional parenchyma but disconnection of functional hepatocytes from liver circulation
  - increased pressure in portal circulation = portal hypertension
    - need for shunting between portal and systemic circulation by-passing the liver
  - ↑ risk of carcinoma
- histologically (diagnosed form liver biopsy)
  - micronodular
    - typical for alcohol, primary biliary cirhosis, hemochromatosis
  - macronodular
    - typical for viral, autoimmune hepatitis, drugs, toxins, Wilson disease, ...
- clinical correlate:
  - none – compensated cirrhosis
  - liver failure – decompensated cirrhosis







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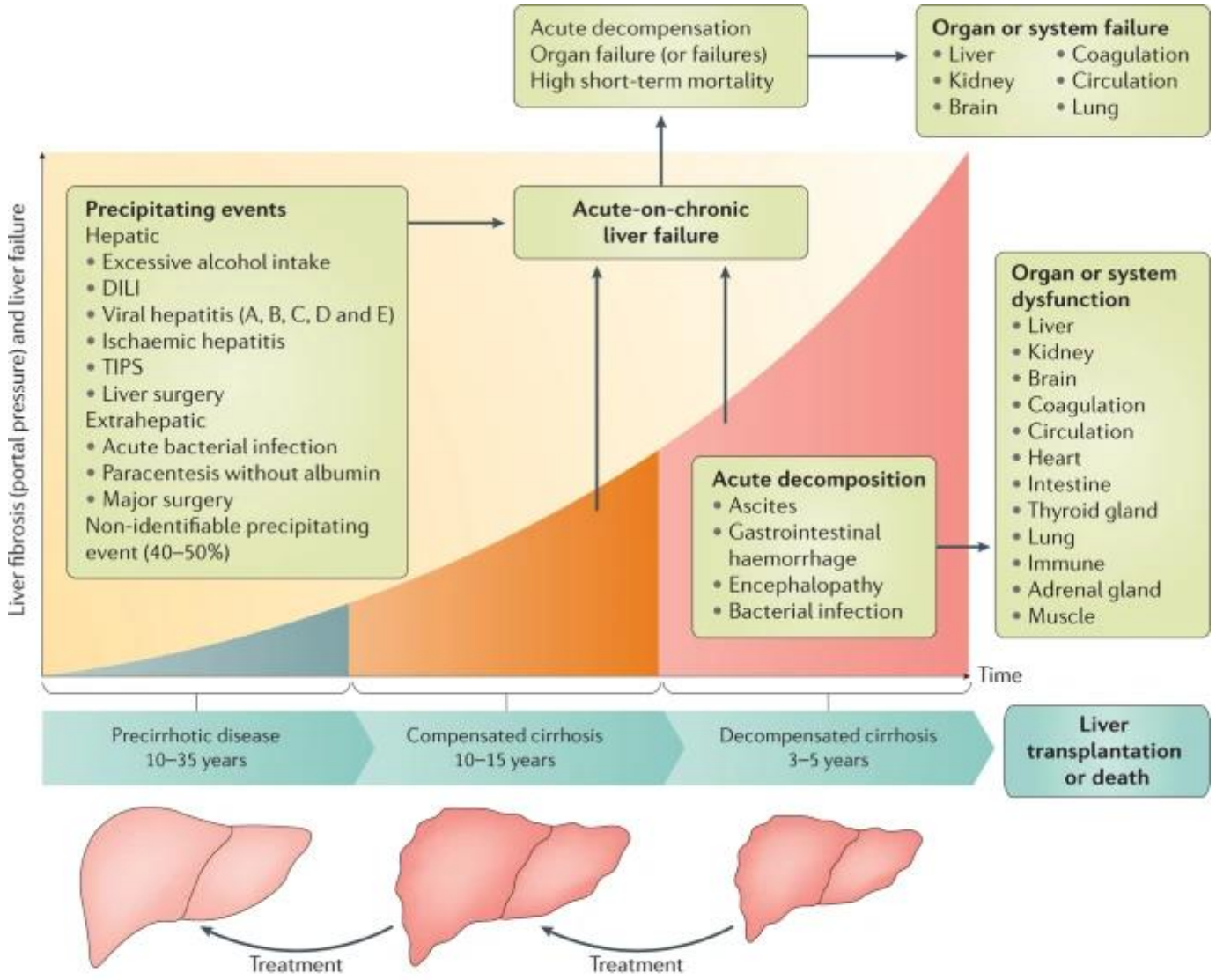
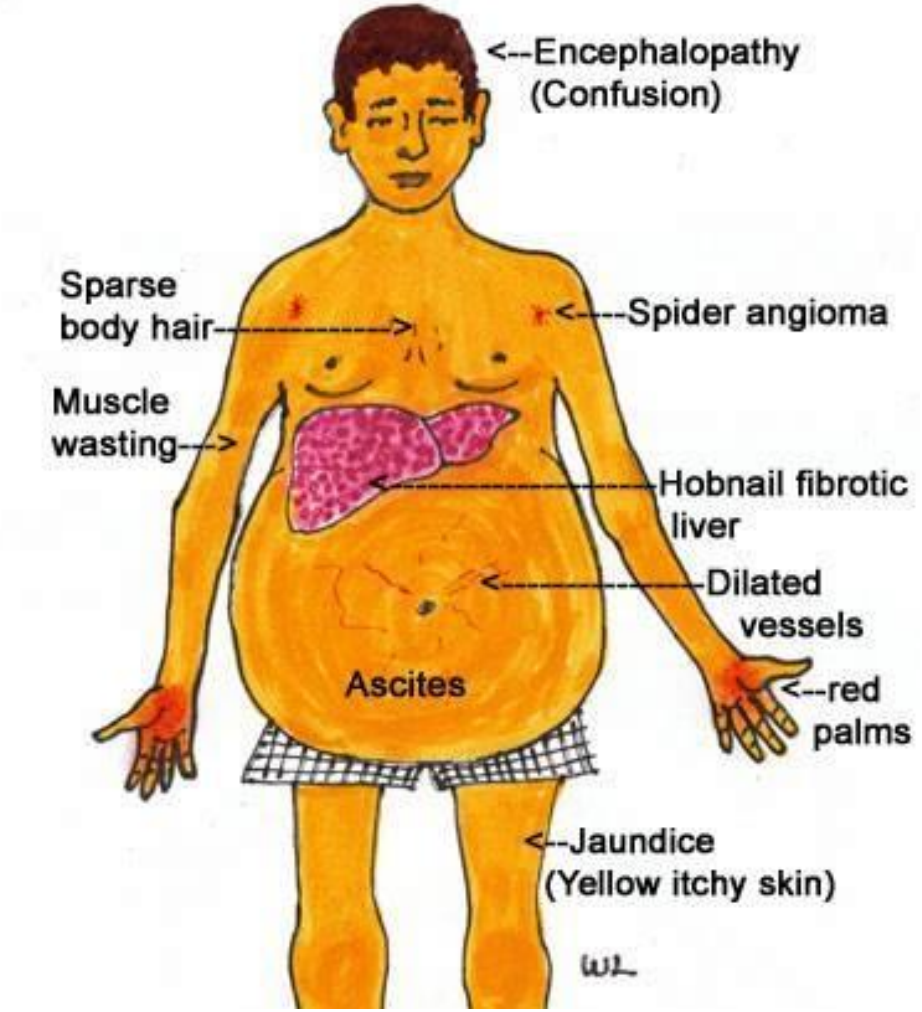
Clinical course of liver cirrhosis



Liver failure

- cause
  - progression of chronic liver disease = cirrhotic
  - acute fulminant hepatitis, intoxication etc. = non-cirrhotic
- signs and symptoms
  - weakness, weight loss
  - hyperbilirubinemia or icterus (jaundice) due to intrahepatic cholestasis and destruction of hepatocytes
  - portal hypertension
    - ascites, splanchnic congestion,
  - bleeding
    - due to deficit of clotting factors and low K vitamin resorption
    - due to thrombocytopenia caused by bleeding, hypersplenism
  - oedema, ascites due to hypoalbumiemia
  - prolonged action of hormones due to decreased degradation of circulating hormones
    - aldosterone
      - loss of K by urine, intracel. acidosis, metabolic alkalosis
        - decreased ionization of NH3!!!!
    - androgens – increased conversion to oestrogens in periphery
      - gynecomastia in men
      - spider nevi
  - liver encephalopathy due to hyperamonemonia and abnormal AA metabolism
    - impaired urea cycle
    - ↑ conc. of aromatic AA – atyp. neurotransmitters in CNS
  - anaemia due to suppression of bone marrow
  - metabolic consequences
    - disorder of glucoregulation
  - hepato-renal syndrome
    - due to low effective circulating volume (congestion, ascites, oedemas) and subsequent activation of RAAS
  - hepato-pulmonary syndrome
    - pulmonary congestion and subsequent ventilation/perfusion mismatch



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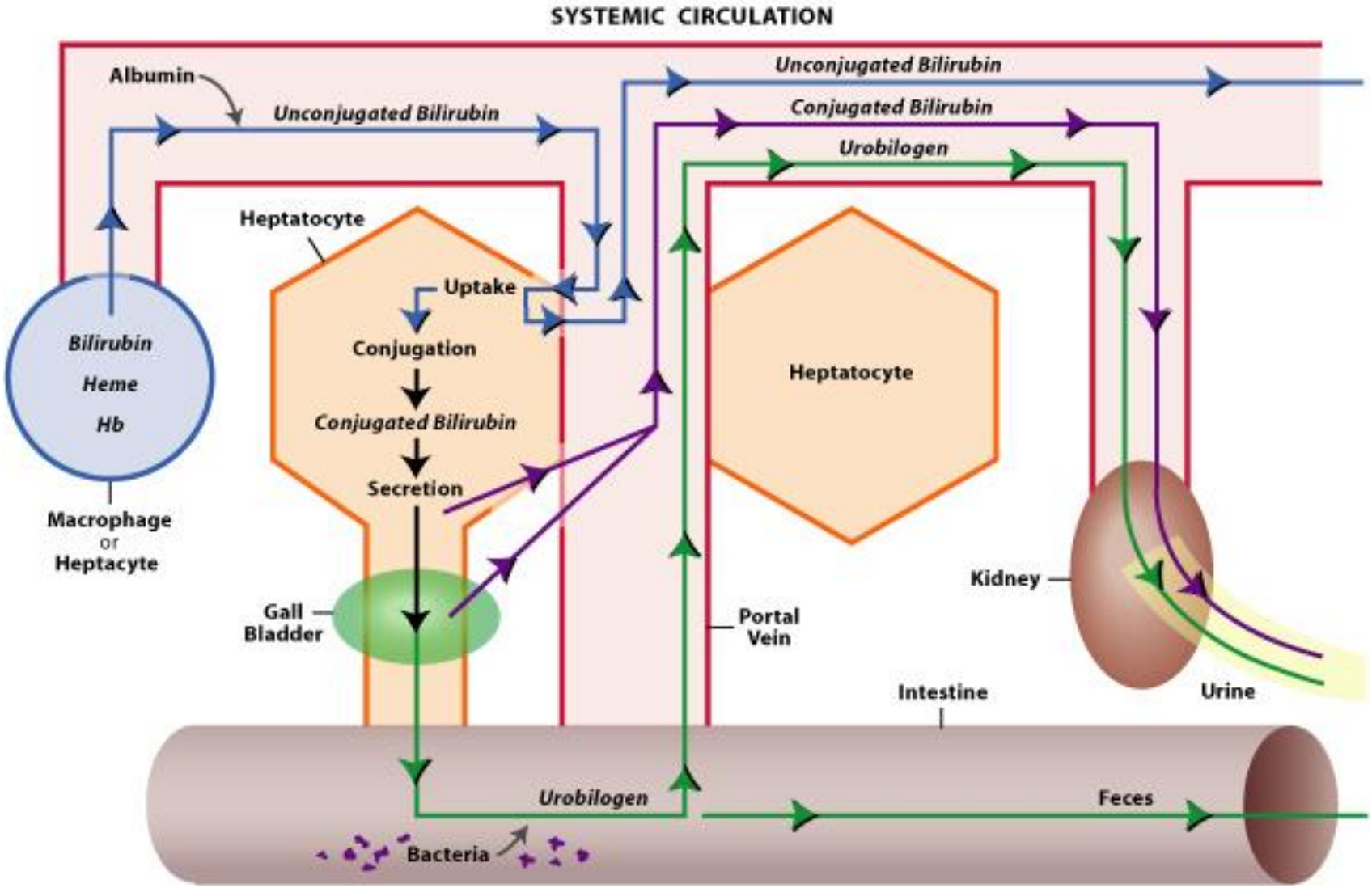
Hyperbilirubinemia/icterus



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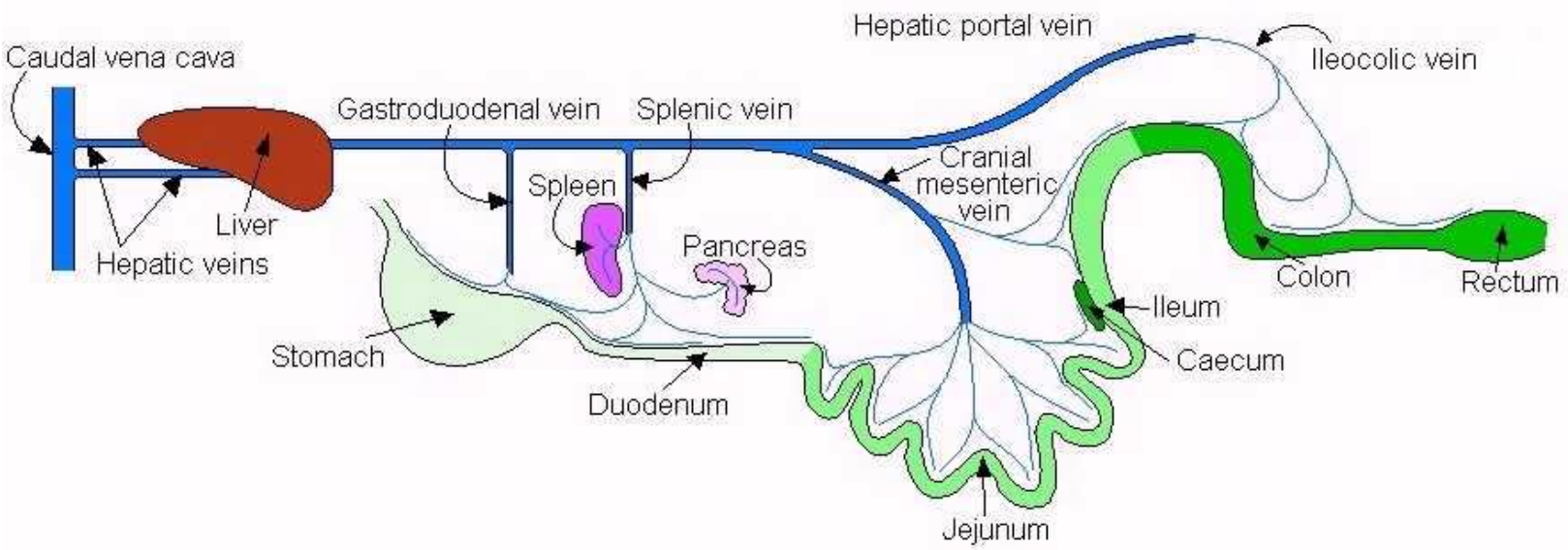
Portal hypertension



- normal pressure in portal circulation 5 – 15 mmHg
  - pressure gradient to v. cava is extremely low, therefore, any change of liver sinusoid diameter has a massive impact on resistance
- 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

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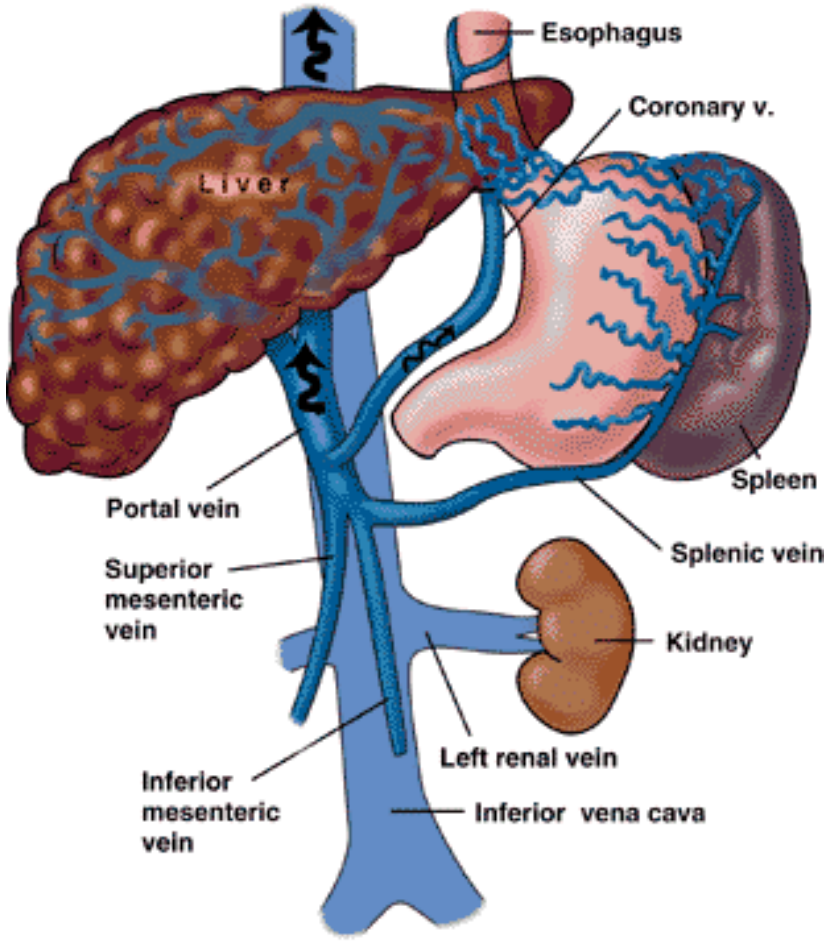
Portal hypertension



- 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 - splenomegaly
    - **hypersplenism** → destruction of Ery and platelets
- 2) blood flow through **portosystemic shunts / 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**

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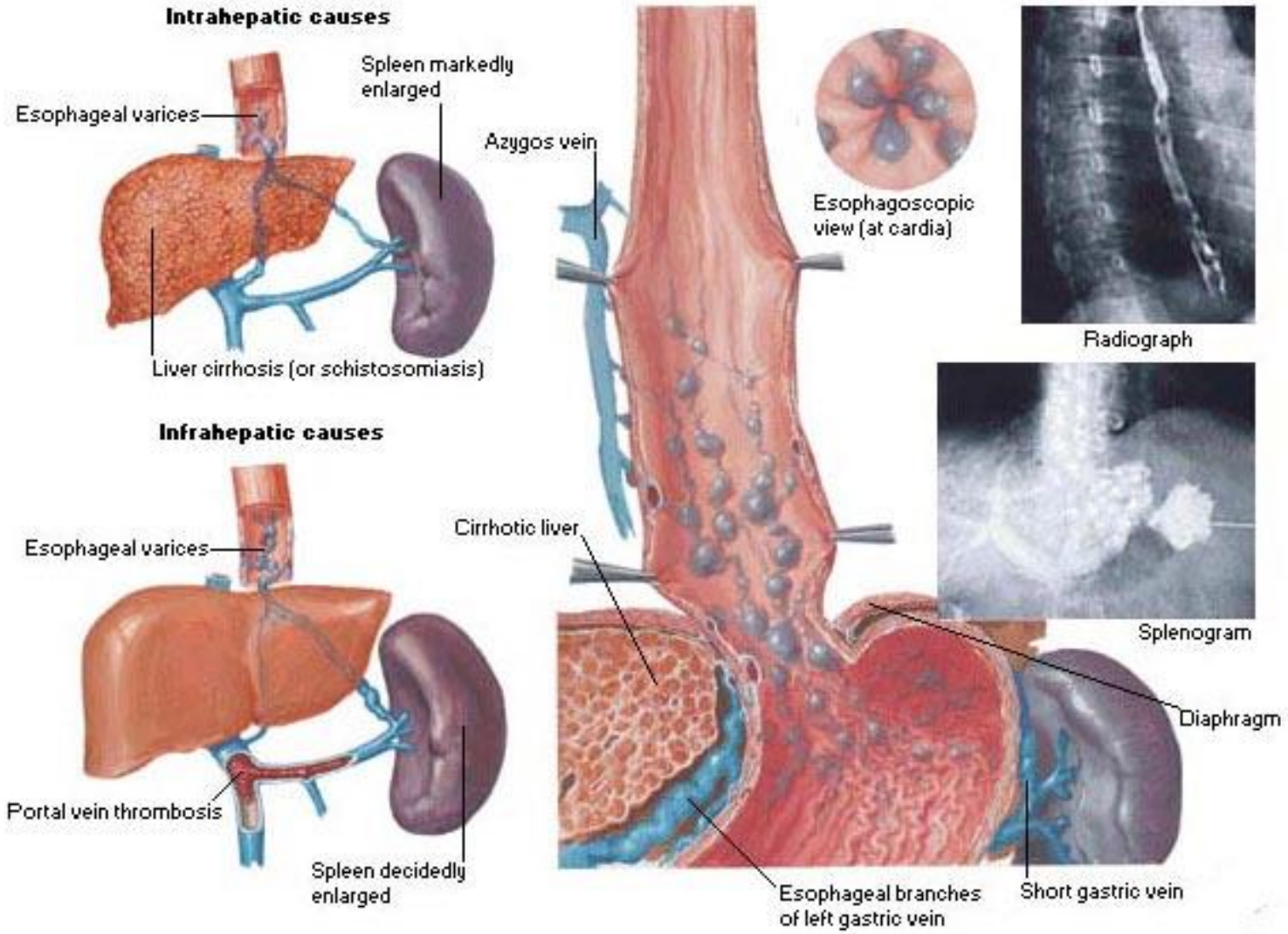
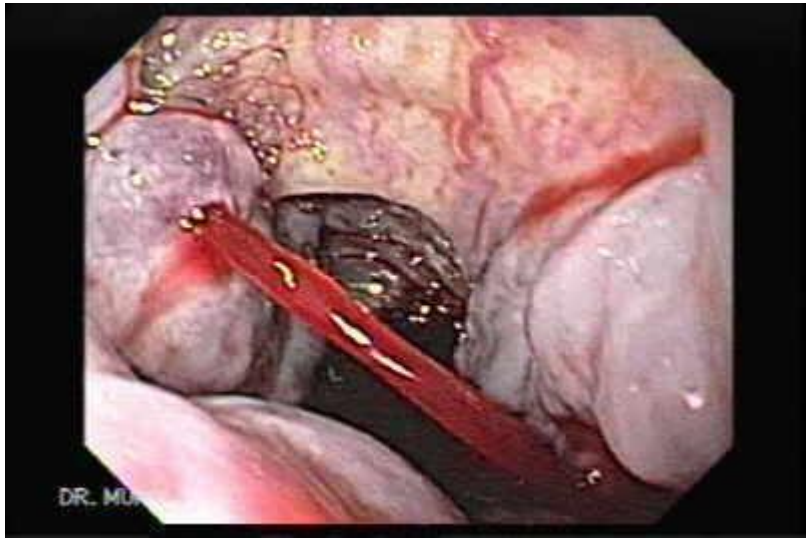
Oesophageal varices





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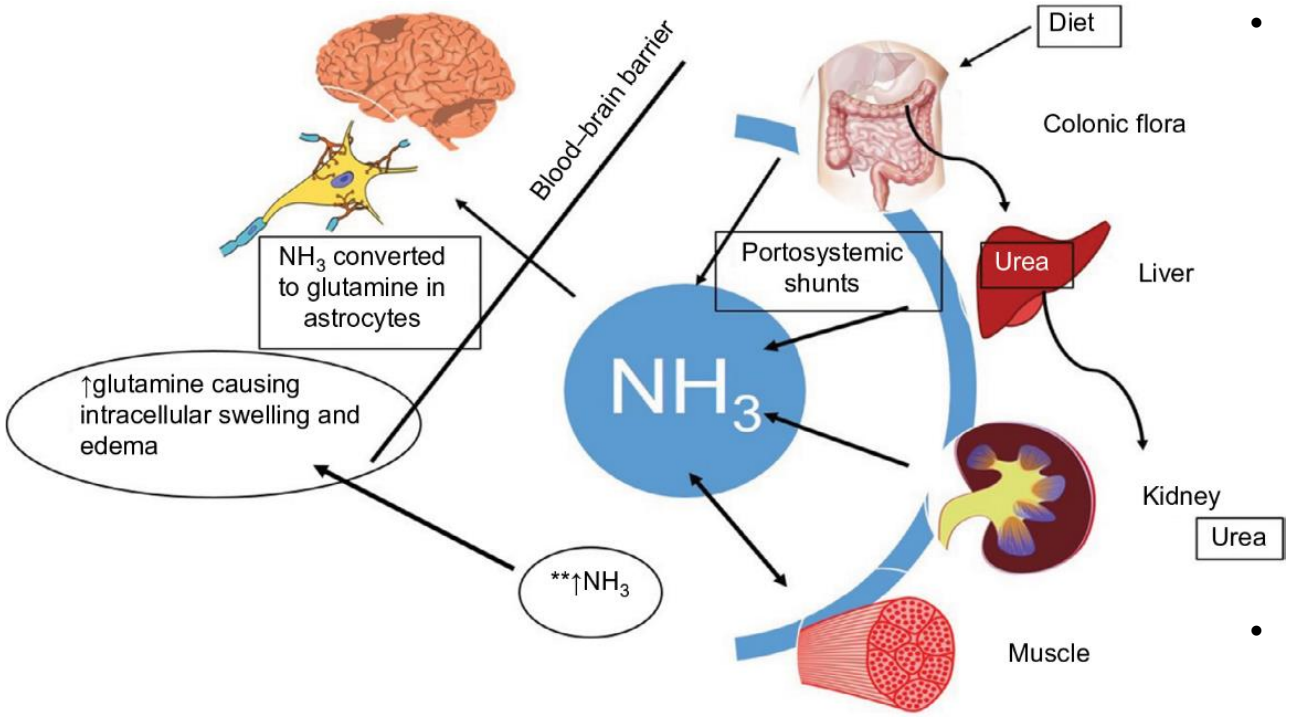
Liver encephalopathy



- abnormalities of conscience (quantitative and qualitative), behaviour and neuromuscular functions
  - reversible only in initial stages
- mechanisms
  - (1) impaired detoxification of ammonia in urea cycle
    - sources of ammoniac
      - oxidative de-amination by glutamatdehydrogenase 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)
      - alkalosis increases free ammoniac and thus toxicity
    - urea (= ornithin) cycle in liver dally produces 20 – 40 g urea
      - $CO^2 + NH^{4+} \rightarrow CO(NH_2)_2 + H_2O + 2H^+$
      - 5 enzymes – mitochondria and cytosol
    - urea excreted by kidney
  - (2) blood from splanchnic contains not only nutrients but also toxins (ammoniac, mercaptans, phenols etc. produced by bacteria)
  - if not properly detoxified in liver
    - formation of "false" neurotransmitters in brain
      - change of behaviour and conscience, "flapping" tremor, apraxia

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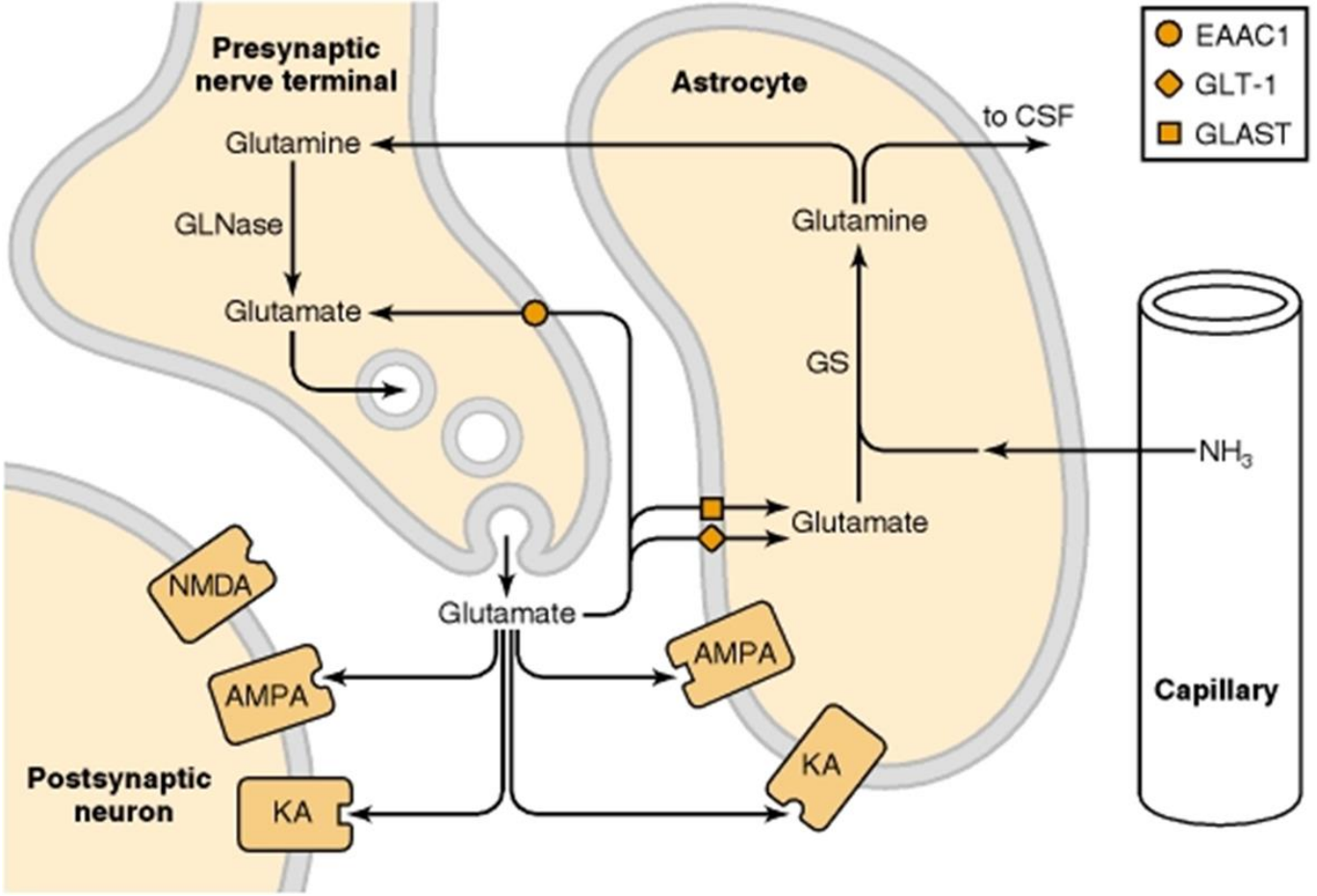
Impaired balance of excitatory and inhibitory AA in the brain



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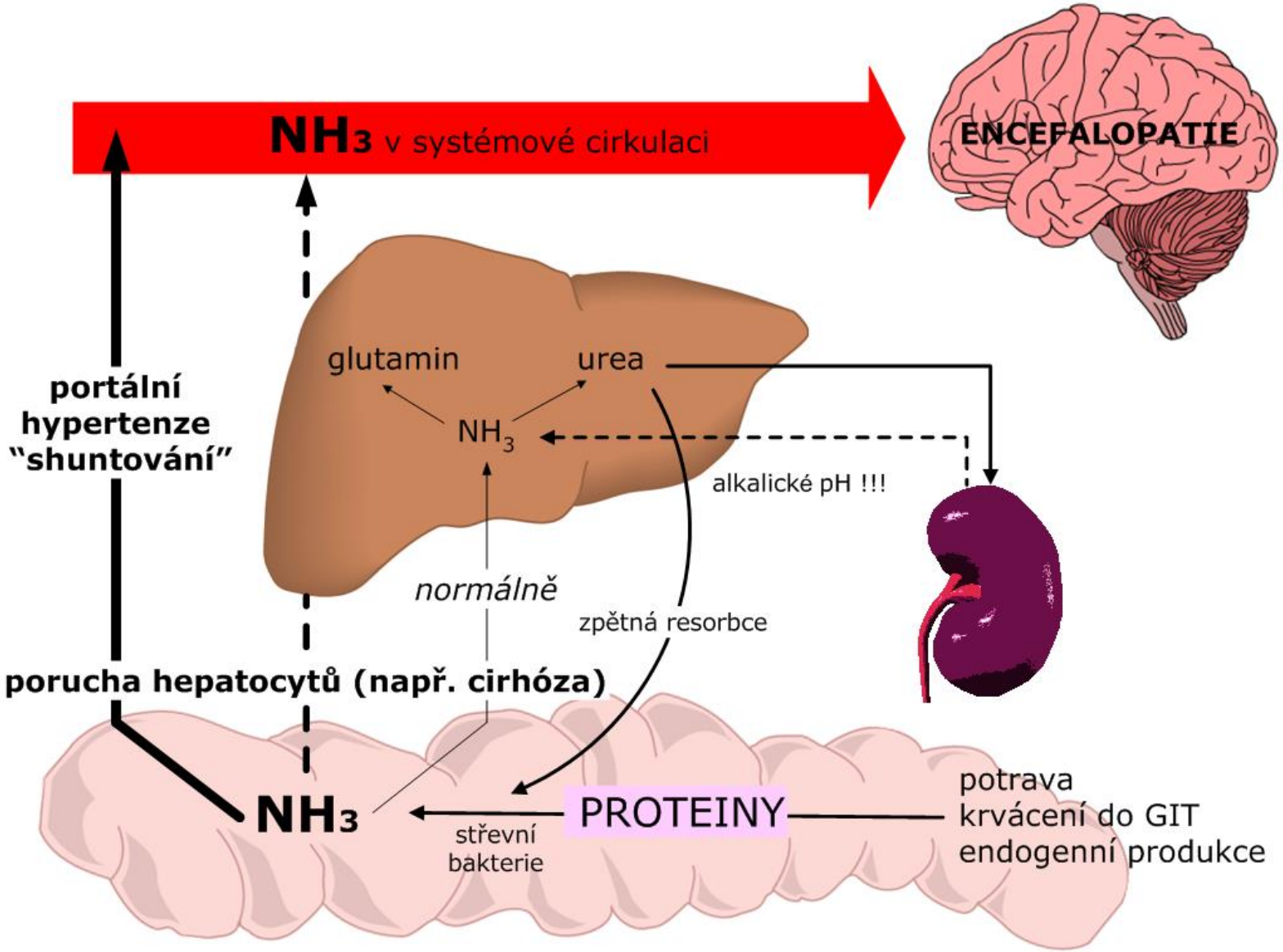
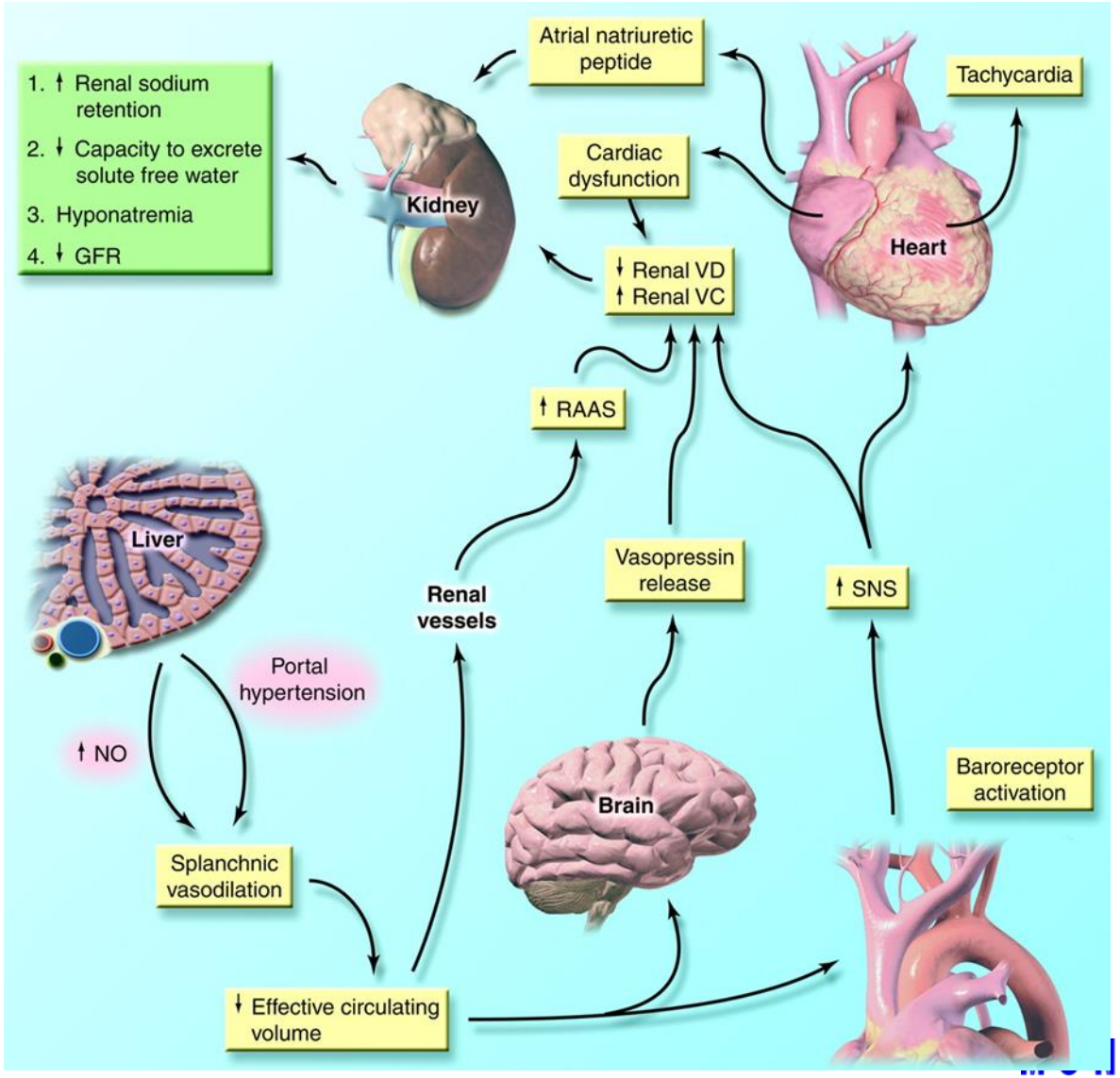
Cross-talk of intestine and liver - ammonia



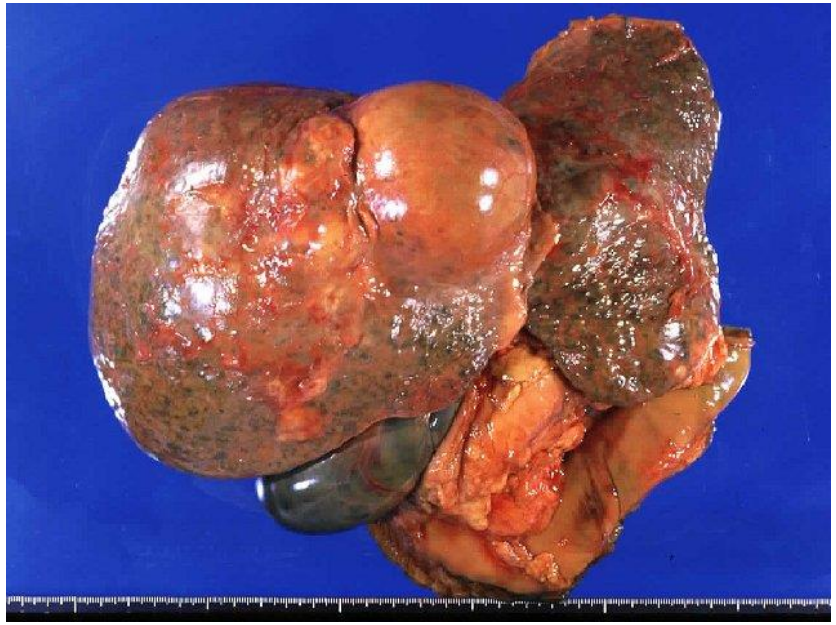
Hepatorenal syndrome

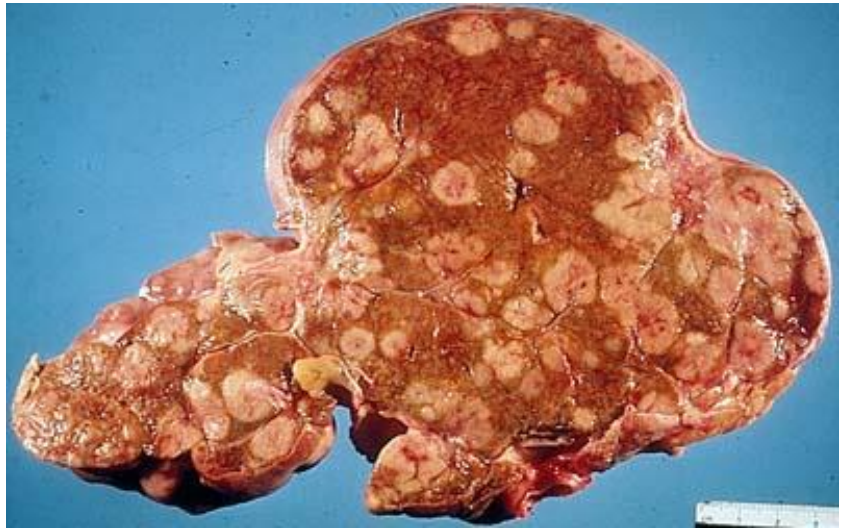
- kidney failure accompanying liver disease without pre-existing kidney pathology
- aetiology
  - Na and water retention
    - hyper-aldosteronemia
  - however, effective circulating volume is decreased due to escape to the third space (ascites)
    - hypoalbuminemia
  - decrease of renal perfusion and 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, …





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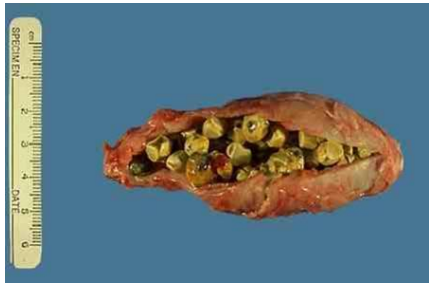
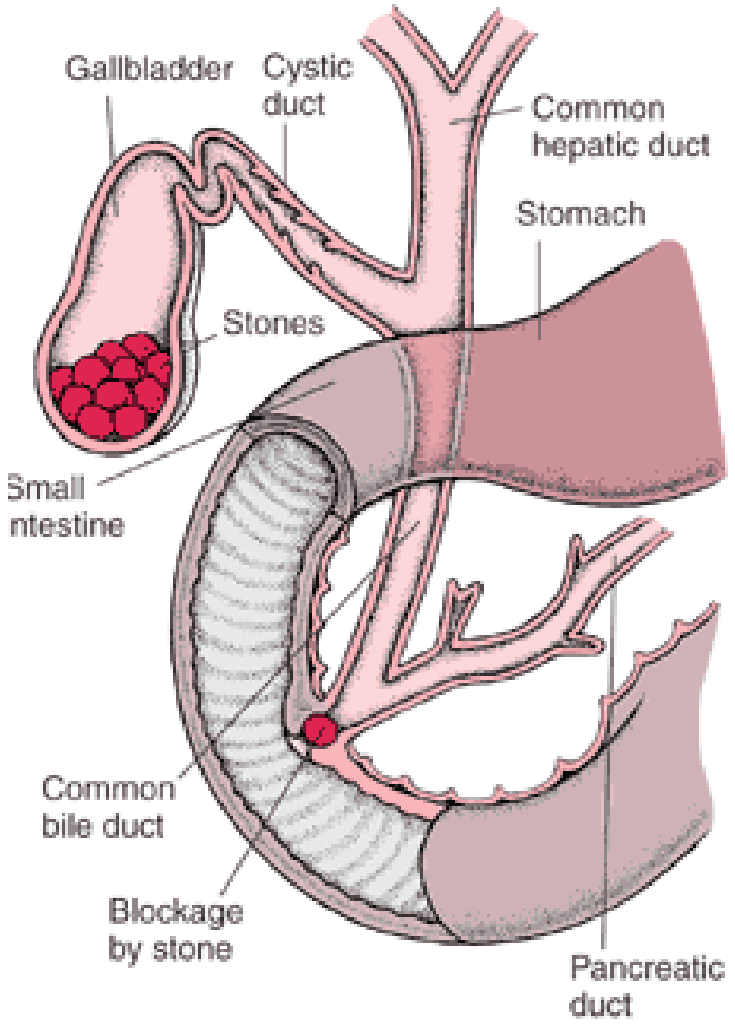
Pathophysiology of biliary tract

- 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





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Cirrhosis of the river.