Summer Pathophysiology course 2006 -2007

LIVER DISORDERS

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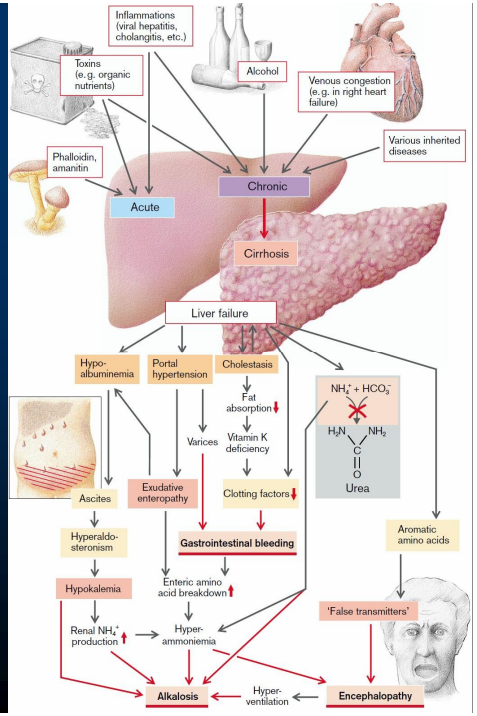
LIVER FAILURE

- **Definition:** inability of the liver to fulfill normal functions
- **Causes:**
  - § *inflammation* – persistent viral hepatitis;
  - § *alcohol abuse*, the most common cause;
  - § *side effects of* - folic acid antagonists,
  - § *impairment of venous return* - right heart failure
  - § *inherited* – glycogenoses, Wilson's disease, galactosemia, hemochromatosis, alpha 1-AT def.
  - § *cholestasis*
- **Consequences:**
  - § Plasma proteins – hypoalbuminemia, complement, coagulation factors
  - § Avitaminoses of fat soluble vit. (vit.K - II, VII, IX, and X)
  - § Detoxication – hyperammonemia, bilirubin-jaudice etc.
  - § Alkalosis, hypokalemia,
  - § Portal hypertension, ascites,, encephalopathy



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Liver failure

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- Esophageal varixes
- Ascites
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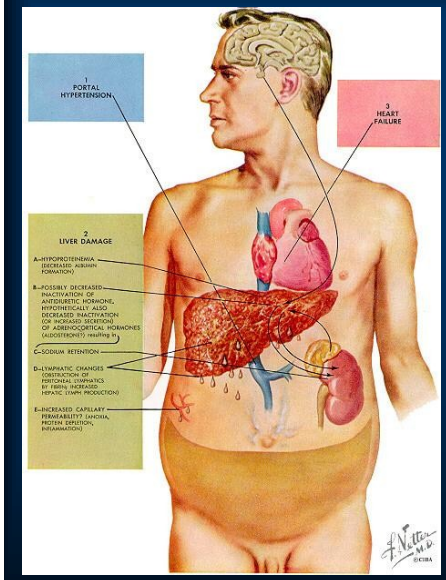
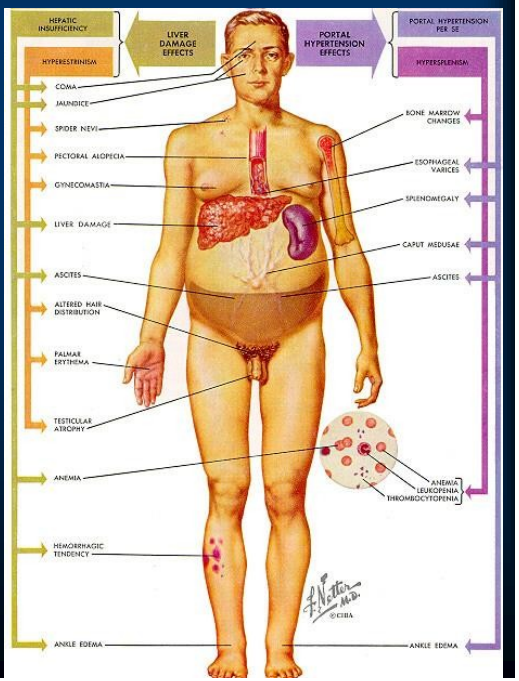
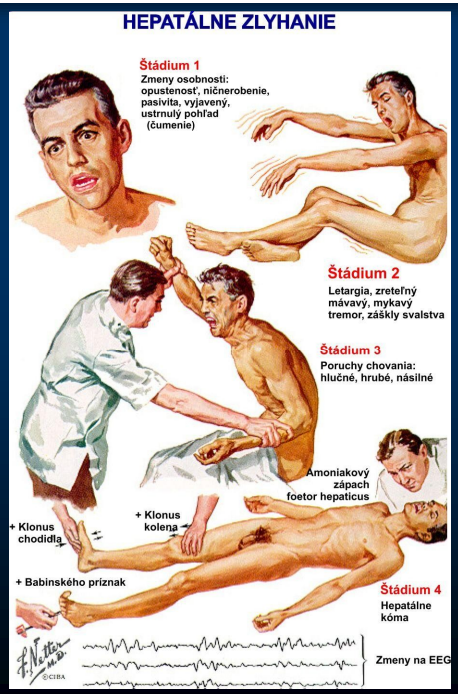
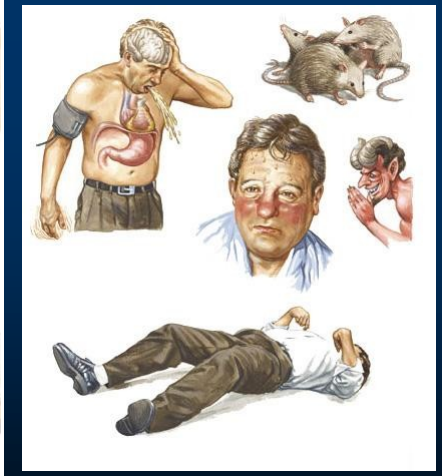
- Liver failure – hepatic encephalopathy



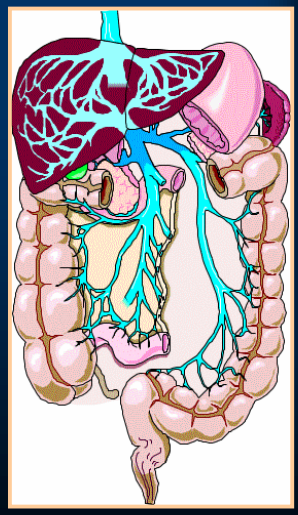






Introduction

- History: 17th century - structural changes in the portal circulation cause gastrointestinal bleeding, 1902 - Gilbert and Carnot introduced the term "portal hypertension„
- Definition: pressure in the portal venous system that is at least 5 mm Hg higher than the pressure in the inferior vena cava; most serious sequelae of chronic liver disease
  - § Normal: 4–8 mmHg (1–4 mmHg higher than the hepatic vein free pressure, and not more than 6 mm Hg higher than right atrial pressure)
  - § Hypertension: > 10 mmHg
- Cause: obstruction to blood flow from any point in the portal system's origin (in the splanchnic bed) through the hepatic veins (exit into the systemic circulation) or increase in blood flow in the system



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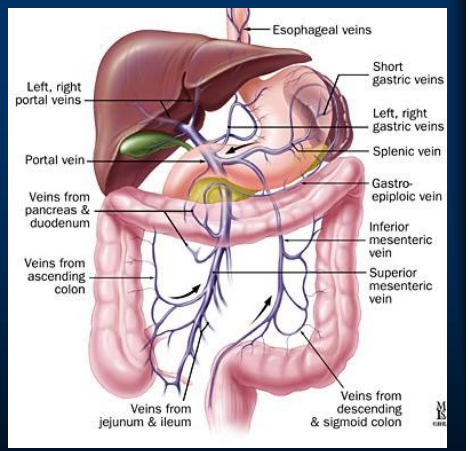
Portal hypertension

Portal system

- Liver receives 1.5 l/min of blood
- hepatic vascular system is less influenced by vasodilation and vasoconstriction
- hepatic artery blood flow is inversely related to portal vein flow (hormonally mediated)
- Portal vein system:
- supplies 70% of the blood flow to the liver, but only 40% of the liver oxygen supply (remainder hepatic artery), blood mixes in the sinusoids
- Spleen, Pancreas, Stomach, Bowels, Rectum
- Liver: sinusoids, central vein, hepatic veins



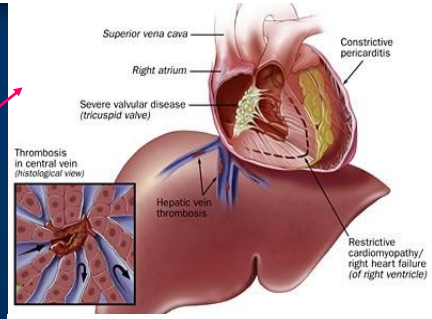
CAUSES 1

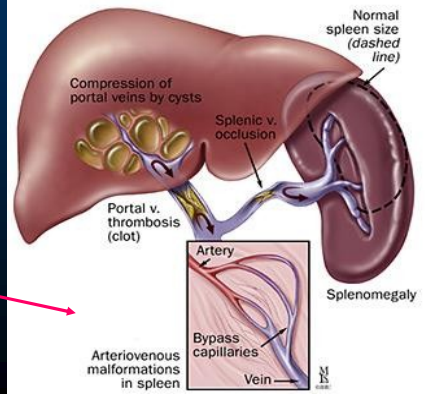
Suprahepatic causes

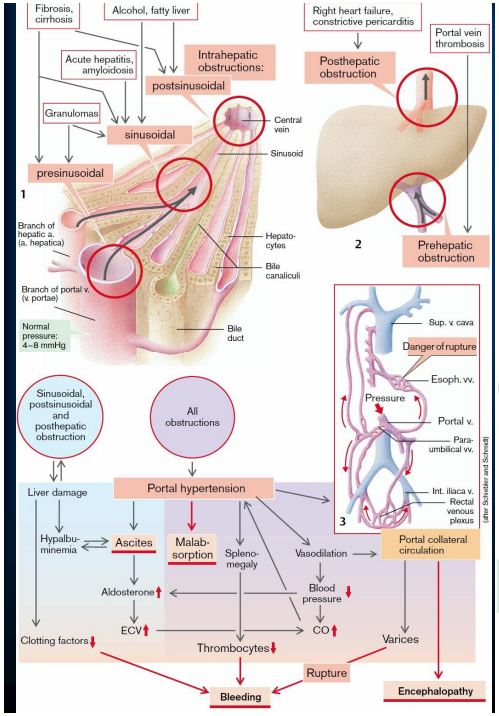
- cardiac disease, inferior vena cava thrombosis or webs.
- Hepatic vein thrombosis, or Budd-Chiari syndrome, has multiple etiologies - hypercoagulable state
- Liver fibrosis can result from suprahepatic disease

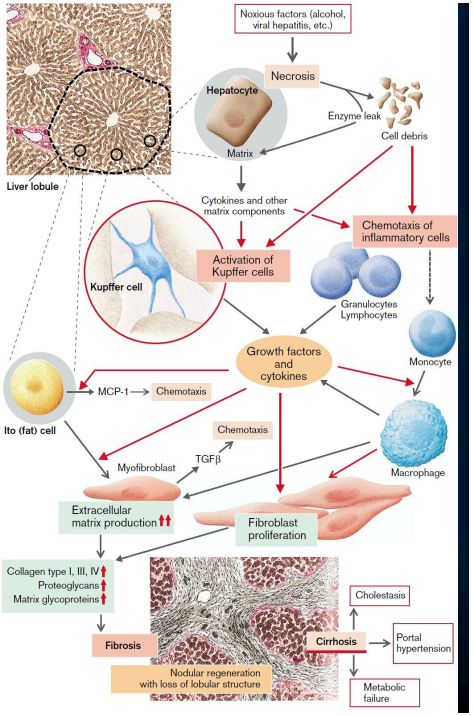
Infrahepatic causes

- Arteriovenous malformation of the splenic vasculature,
- splenomegaly
- portal vein thrombosis





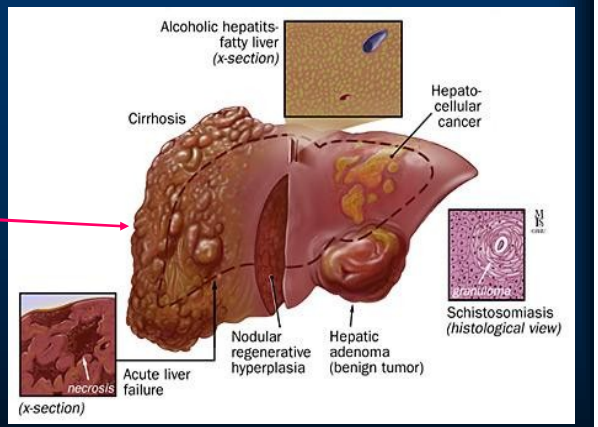




PORTAL HYPERTENSION- CAUSES 2

Hepatic causes

- Cirrhosis - most common cause of p. hypertension
  - § chronic viral hepatitis C - the most common cause of cirrhosis
  - § alcohol-induced
  - § cholestatic
  - § hemochromatosis,
  - § alpha 1-antitrypsin deficiency
  - § drug-induced liver disease
  - § hepatitis B
- Schistosomiasis, cancer



cytokines as TNF-alpha - stimulate endothelial vasodilators (NO, PGI) + non-endothelial vasodilators (glucagon) -> pressure and flow in the splanchnic vasculature

PORTAL HYPERTENSION- TYPES

Type	Pressure		Location	Cases
	spleen	sinus		
Presinusoidal	ñ	N	Prehepatic	blockade of portal, mesenterial or spleen veins (tumors, neonatal umbilical sepsa, trombophlebitis, polycytemia - viscosity)
	ñ	N or ñ	Hepatic	congenital fibrosis, schisostomiasis, viral hepatitis, alcoholic & biliary fibrosis, thrombosis, non/alcoholic cirrhosis
Postsinusoidal	ñ	ñ or N	Hepatic	alcoholic cirrhosis, Budd? Chiari sy.
	ñ	ñ	Posthepatic	block of hepatic veins } thrombosis|, right heart failure, constrictive pericarditis, etc.|

PORTAL HYPERTENSION - CONSEQUENCES

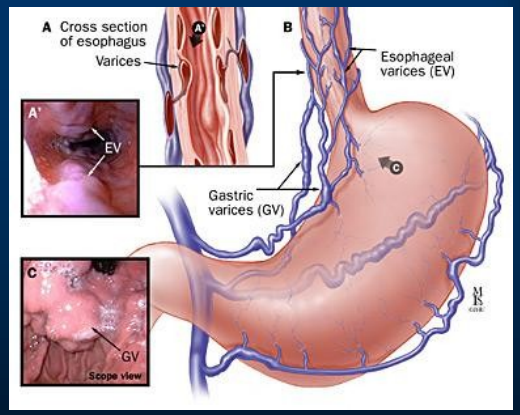
- Venostasis - impaired secretion, absorption in GUT
- Splenomegaly - enlargement of spleen - hemolysis
- Collateral circulation - opening and dilation of shunts
  - § varices (esophageal veins)
  - § haemorrhoides (rectal veins)
  - § superfitial veins (umbilical, paraumbilical - Caput medusae)
- Ascites - lymphatic fluid that leaks across hepatic sinusoidal endothelium due to high hepatic sinusoidal pressure
  - **ñ ò** hydorstatis pressure + **ò** degradation of aldosteron, AHD
- Hepatic encephalopathy (ammonium + toxins bypassing liver]

Complications:
- haematemesis (vomiting of blood) rupture of esophageal varices
- melena (black tarry stool - upper tract bleeding)

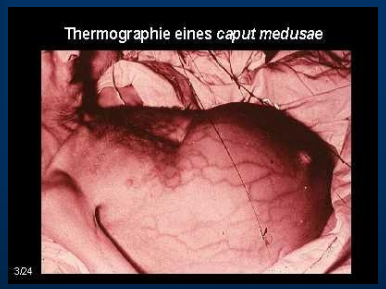
Esophageal varices

- varicose veins in the esophagus or stomach
- rupture – complication in 40%, danger is low if hepatic ven. pressure < 12 mm Hg

Therapy:
- Medicaments:
- beta-blockers (decrease resting heart rate by 25%. vasopressin - decreasing splanchnic blood flow (central venous access)
- Somatostatin – vasoconstrictor in splanchnic bed

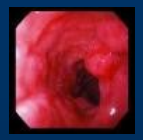


PORTAL HYPERTENSION



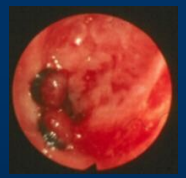
Caput medusae

Varices



Duodenum

Stomach

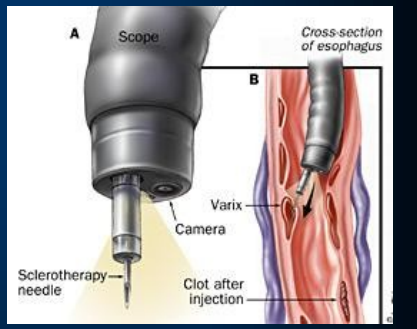


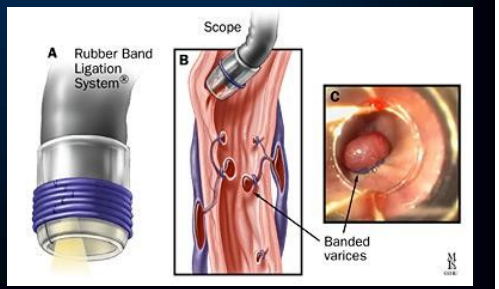
Esophgeal varices

Common tests that are used to evaluate liver function include: albumin ALP ALT AST bilirubin bilirubin; urine GGT LDH PT total cholesterol , total protein

Therapy

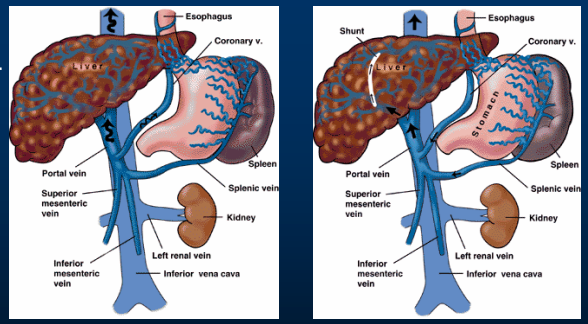
- Sclerotherapy - 1–10 mL of sclerosing agent (sodium morrhuate, sodium tetradecyl sulfate, ethanolamine oleate, or absolute alcohol) into and around the varices, Common side effects include tachycardia, chest pain, fever, and ulceration at the injection site.
- Banding small elastic rings over a suctioned varix. Banding has fewer side effects than sclerotherapy
- Balloon tamponade is useful to control variceal bleeding through compression high risk of complications, especially aspiration.





The Transjugular Intrahepatic Portosystemic Shunt (TIPS)

stent (a tubular device) is placed in the middle of the liver to reroute the blood flow



Introduction

- Definition: presence of excess fluid in the peritoneal cavity; frequently develops in chronic liver disease, but may be due to a wide range of causes.
- Types:
  - § Transudative ascites (low protein) hepatic congestion – from hepatic sinusoids into interstitium, liver capsule, peritoneum
  - § Exudative ascites (higher protein) from the peritoneum
- Mechanisms:

(1) ñ Blood hydrostatic pressure (Portal hypertension)

Reasons: liver disease, abdominal tumors, heart failure, constrictive pericarditis

(2) ò Osmolarity of plasma

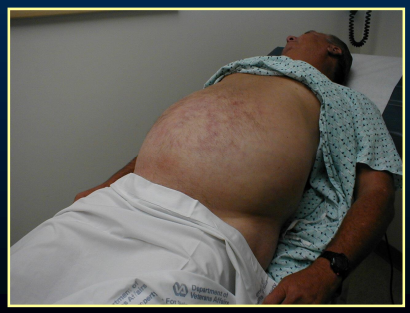
Reasons: liver diseases, malnutrition, renal failure, nephrotic sy.

(3) ñ Lymphathetic pressure

Reasons: abdominal tumors, cirrhosis

(4) Retention of water

Reasons: cirrhosis (ò breakdown of ALDO -> Na^+ ð ADH ðH_2O)



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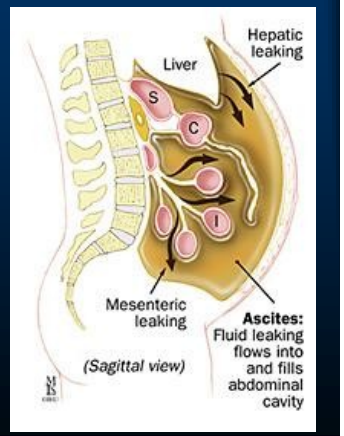
Ascites

Ascites

- **Symptoms**:
  - § **asymptomatic**
  - § **symptomatic**
    - early satiety, abdominal girth, or respiratory distress),
    - acute oliguria, abdominal distention, tympany of the top, bulging flanks, puddle sign, fluid wave, or shifting dullness on physical examination.
  - § side effects - hyponatremia, hyperkalemia, hypokalemia, dehydration, hypotension, and azotemia.

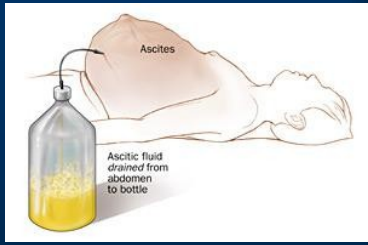
oncotic pressure – decrease
splanchnic lymph - increase Intra-abdominal fluid is normally absorbed by the peritoneum,
high intraperitoneal pressure results in net increase in absorption.

Ascites	
Portal Hypertension	**Non-portal hypertension**
Cirrhosis	Tuberculosis
Cardiac disease	Pancreatic ascites
Liver tumors	Carcinomatosis
Hepatic failure	Nephrotic syndrome
Hepatic vein thrombosis	Lymphatic obstruction
Portal vein thrombosis	



Ascites

- Treatment:
  - § Diuretic therapy, to reduce sodium retention by kidneys, (blocking aldosterone effects. Restrict Na to less than 2 g per day, water restriction (1.5 liters per day) adequate but not necessary unless patients develop hyponatremia.
  - § Abdominal paracentesis – sterile aspiration of ascites; large-volume paracentesis -> intraperitoneal pressures drop -> rapid reaccumulation of ascites.



- Laboratory analysis:
  - § protein content, cytological analysis, cultures (infections), Albumin gradient greater than 1.1 g/dL between serum and ascitic fluid → portal hypertensive origin of ascites
- Complication:
  - § Spontaneous bacterial peritonitis (SBP) is very high (low oncotic pressure), difficult to diagnose, pain is often absent, 70% Gram-negative bacilli (Streptococcus, Staphylococcus) PMN counts that exceed 250/ml

(3) ICTERUS - MANIFESTATIONS

Definitions:

Icterus - symptom - visible yellow coloring of tissues (eyes, skin, mucosa, organs) due to accumulation of lipophic pigment - bilirubin in membranes of cells in tissues

Hyperbilirubinaemia - always present in icterus; however icterus not always accompany it

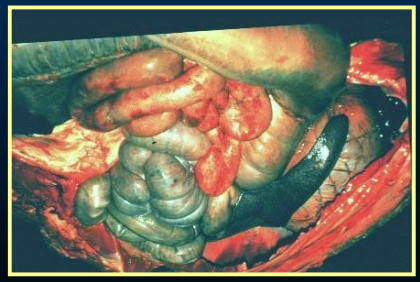
Normal bilirubin: < 20 µmol/l

Hyperbilirubinaemia: > 20 µmol/l

Icterus: ussually > 30-35 µmol/l
in many cases > 300 µmol/l

Subicterus: transient reaction
(e.g. reabsorption of haematomas)

Yellow tinge of sclera & organs



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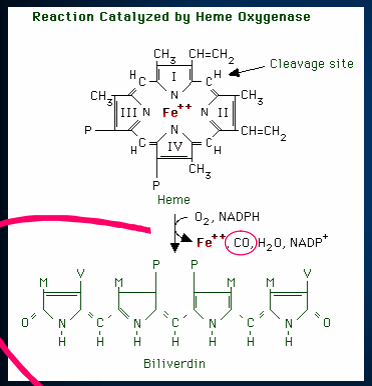
Icterus

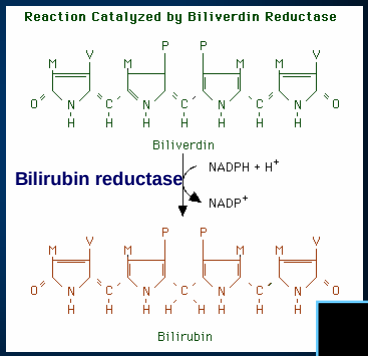
BILIRUBIN METABOLISM

(1) Cleavage of the heme ring by a microsomal heme oxygenase

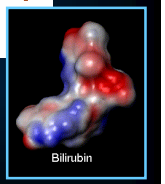


only endogenous source of CO

(2) Reduction of biliverdin to bilirubin

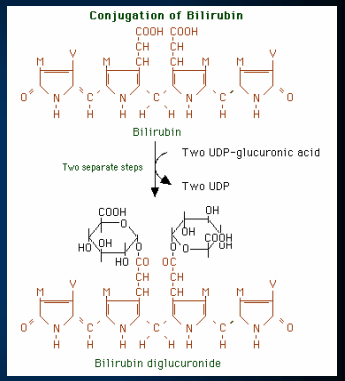


1g Hb 620 mmol Bi; 250-350 mg daily
15-20% immature red cells
80-85% senescent red cells



BILIRUBIN METABOLISM

High lipid solublity of bilirubin
- soluble in the lipid bilayers of cell membranes - toxic effect
- transported in the blood by serum proteins



Conjugation to a water-soluble substance
- decreases its lipid solubility
- eases its excretion

Executed in liver micorsomes by attachment of 2 molecules of glucuronic acid in 2 steps: substrate is bilirubin (or bilirubin monoglucuronide)

Van Der Bergh reaction

coupling of bilirubin with a diazonium salt to form a colored complex. *Water soluble forms* **react directly,** to measure *water insoluble form* bound to albumin, alcohol is added to release it into solution, i.e. **react indirectly**

Unconjugated bilirubin ì ì Indirect (Bi- Albumin, Bi- prealbumin)
Conjugated bilirubin ì ì Direct (Bi- monoglucuronid, Bi- diglucuronid

ICTERUS AND HYPERBILIRUBINAEMIA

- Prehepatic (haemolytic) ⇐ increased bilirubin production
- Hepatic (hepatocellular)
  - §pre-microsomal ⇐ decreased uptake into the liver cells
  - §post-microsomal ⇐ impaired conjugation
- Posthepatic (obstructive) ⇐ impaired secretion of conjugated bilirubin

BILIRUBIN & BILE ACIDS

Urine bile pigments

Urobilinogen

1-4 mg (2-7 µmol) water soluble - source: enterohepatic circulation

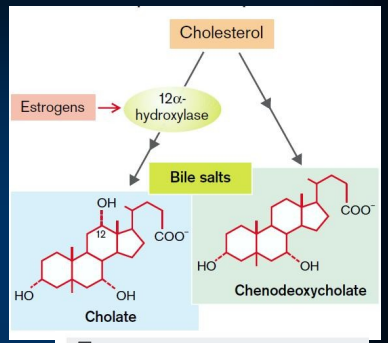
ñHemolytic anaemia, hepatocellular disease

òHeopatobiliry obstruction

Conjugated bilirubin

normally only traces

ñ Hepatocellular disease, Bile obstruction



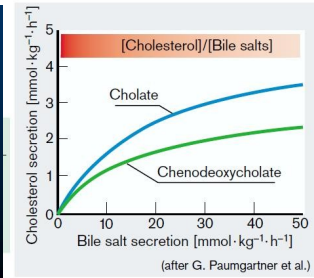
HPQL Bi fractions in plasma (at 450 nm)

alpha fraction : > 90% indirect (u Bi) (water soluble, albumin -bound),
< 10% direct

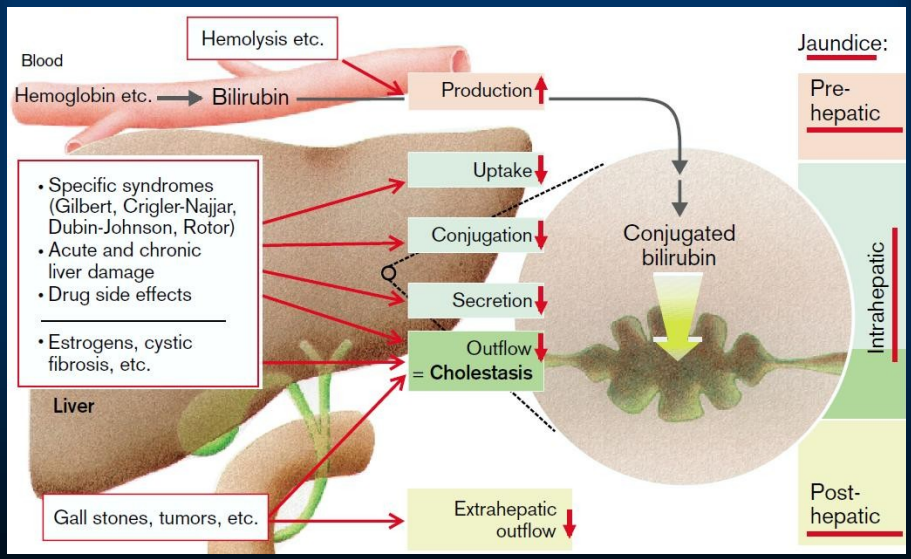
beta fraction: Bi- monoglucurionide

gama fraction: BI- diglucuronide

delta fraction: direct Bi + indirect Bi



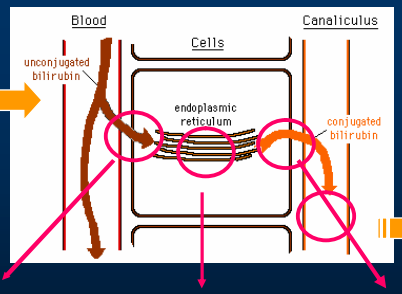
Bile salts - cholate, taurocholate



CAUSES OF ICTERUS

Prehepatic (haemolytic)

ñ Unconjugated bilirubin



Prehepatic (haemolytic)

ñ Conjugated bilirubin

Premicrosomal

ñ Unconjugated bilirubin

Microsomal

ñ Unconjugated bilirubin

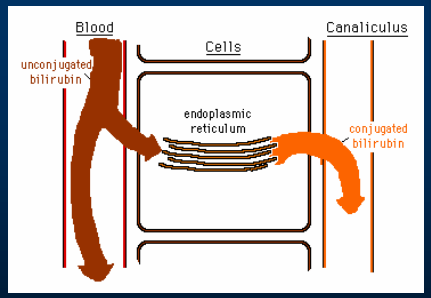
Postmicrosomal

ñ Conjugated bilirubin

Hepatic (hepatocellular)

PREHEPATIC ICTERUS- PRINCIPLES

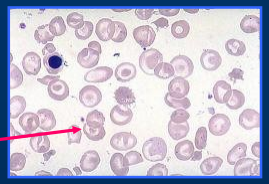
- Bi production exceedes liver's capacity to conjugate
- ñ ñ Unconjugated Bi
- ñ Conjugated Bi
- AST, ALT normal
- γGT normal or ñ
- Stool: dark
- Urine: ñ urobilines, dark orange
- Anaemia: Ery, Hb, Ret

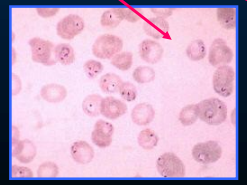


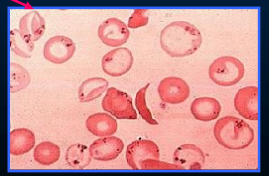
1 - PREHEPATIC ICTERUS

PREHEPATIC ICTERUS - CAUSES

- Reabsorption of hematoma, hyperthermia, burns
- Immature erythrocytes
- Haemathological disorders (haemolytic anaemia), e.g.
  - β- thalasemia
  - spherocytosis
  - sicle cell anaemia
  - malaria (plasmodium)
- Erythroblastosis fetalis (neonatal icterus)







2 - HEPATOCELLULAR ICTERUS

HEPATOCELLULAR ICTERUS

Hepatocelullar diseases

Viral infections: Hepatitis A,B,C, Ebstein-Barr infection, cytomegalovirus, Coxakie

Drugs: amocycilin, tetracyclines, cytotoxins, isoniazid, pracetamolum, phenylbutasone, anaesthetic- halothan

Toxins: alcohol, phosphorus, carbon tetrachloride, trichlorethylene, mycotoxins, aflatoxins, toadstool poisoning

Hypoxia: hypotension, shock, hepatic artery thrombosis

Hyperbilirubinaemia + subicterus

ñ ñ Conjugated Bi

Drugs: steroides, phenotiazines, sulphonamides, rifampicin anticonceptives, probenecid

ñ ñ Unconjugated Bi

Starvation (24-48 h), congestive heart failure, pulmonary embolism,

HEPATOCELLULAR ICTERUS

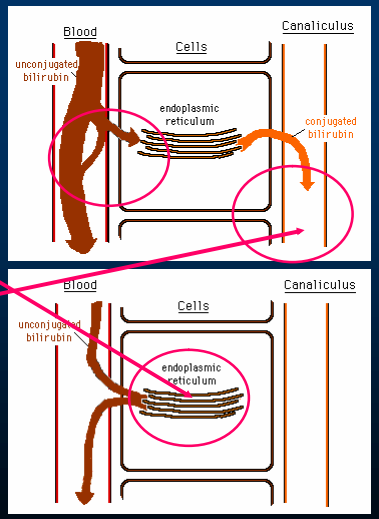
(a) Bi conjugation is insufficient (b) outflow of bile is blocked within liver

Not uniform laboraty data!

- **ñ ñ** Unconjugated Bi
- **ñ** or normal Conjugated Bi
- **ñ ñ** AST: ALT (> 400 U/l)

(150-400 U/l) intrahep. stasis

- **ñ** γGT
- ALP < 300 U/l
- Stool: light (obstruction)
- Urine: **ñ** urobilines, **ñ** c -Bi
  - **§** dark yellow



HEPATIC ICTERUS

- Premicrosomal

  Meulengracht-Gilberts' disease inability of the hepatocytes to take up bilirubin from the blood.

  ñ Unconjugated Bi

  Nò Conjugated Bi

  Lucey-Driscoll sy. (steroid icterus)

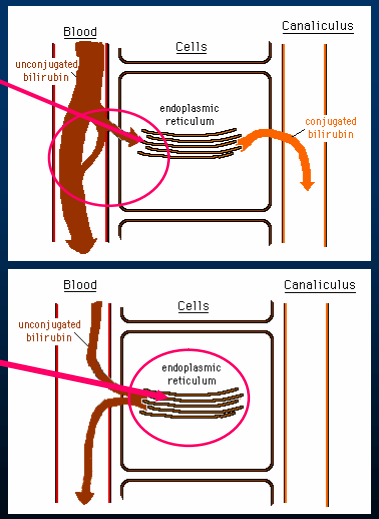
  Prolonged neonatal icterus

- Microsomal

  Crigler-Najjar syndrome type I, II conjugation is impaired

  ñ Unconjugated Bi

  ò ò Conjugated Bi



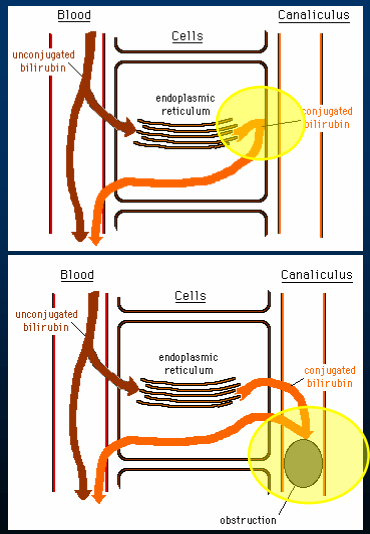
HEPATIC ICTERUS

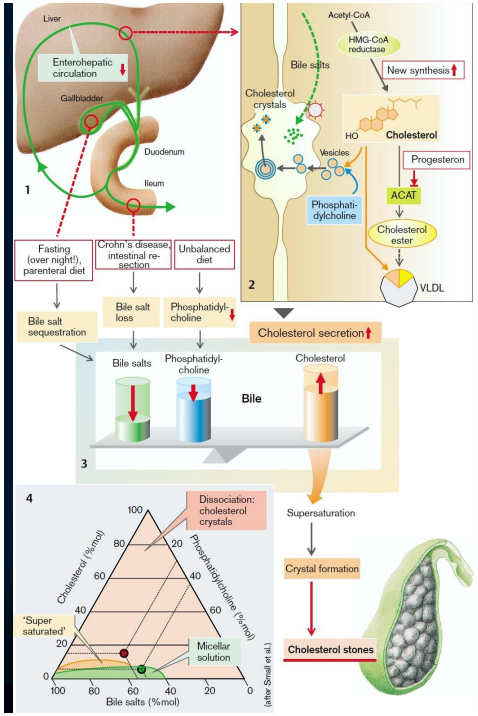
- Postmicrosomal

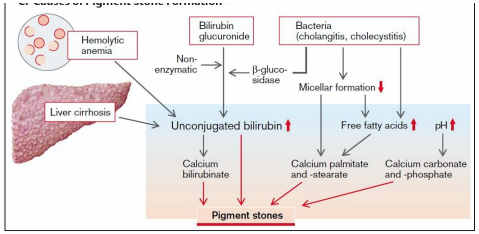
  Dubin-Johnson-Rotor syndrome
  inability of the hepatocytes to export bilirubin to bile ducts
  ñ Conjugated Bi
  N Unconjugated Bi

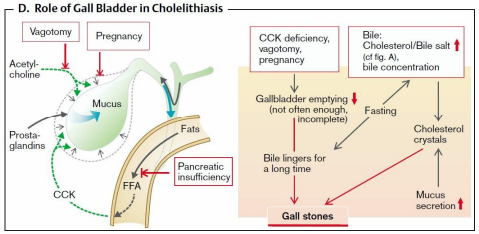
- Intrahepatic cholestasis

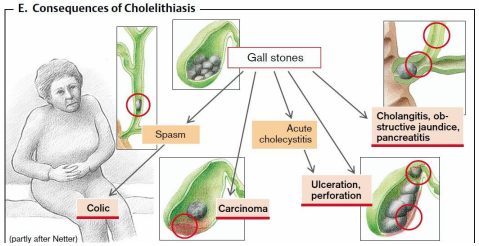
  conjugation is impaired
  ñ Unconjugated Bi
  ñ Conjugated Bi











3 - OBSTRUCTIVE ICTERUS (Hepatobiliary)

OBSTRUCTIVE ICTERUS

- bile outflow into GUT is obstructed
- ñ Unconjugated Bi (sec.)
- ñ ñ Conjugated Bi
- AST, ALT ñ < 400 U/l
- γGT ñ
- ALP ñ ñ (> 300 U/l early indicator of cholestasis)
- Stool: very light (acholic), steatorhrhea
- Urine: ò urobilines, ñ cBi
- Icterus intensive: ñ Bi > 300 µmol/l
- Pruritus

Causes:

Intrahepatic - predominantly obstructive
(acute) Hepatitis A,C, Ascening cholangitis
(chronic) Primary biliary cirrhosis, Sclerosing cholangitis, chronic hepatitis, Weil dis., cholangiocarcinoma

Intrahepatic obstructive with little damage
Recidiving cholestasis in pregnancy, Benign idiopathic cholestasis
Post-operative reflex cholestasis, Steroid, Infections - brucelosis, thyphus
Budd- Chiari sy., Parasites (amebiosis, bilhariosis), Tumors,

Extrahepatic
bile stones, strictures,carcinomas, pancreatitis, biliary atresia

Consequences of cholestasis