Jaundice

Prof. G. Zuliani

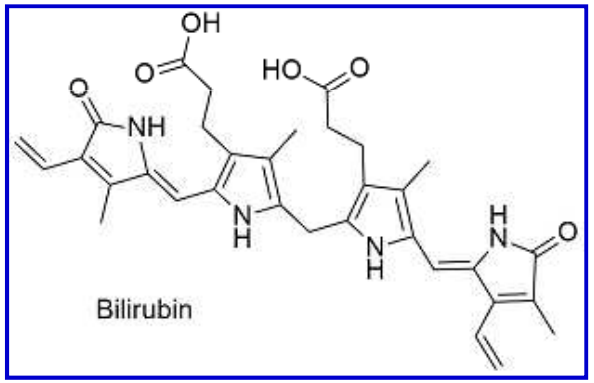
Jaundice

Definition:

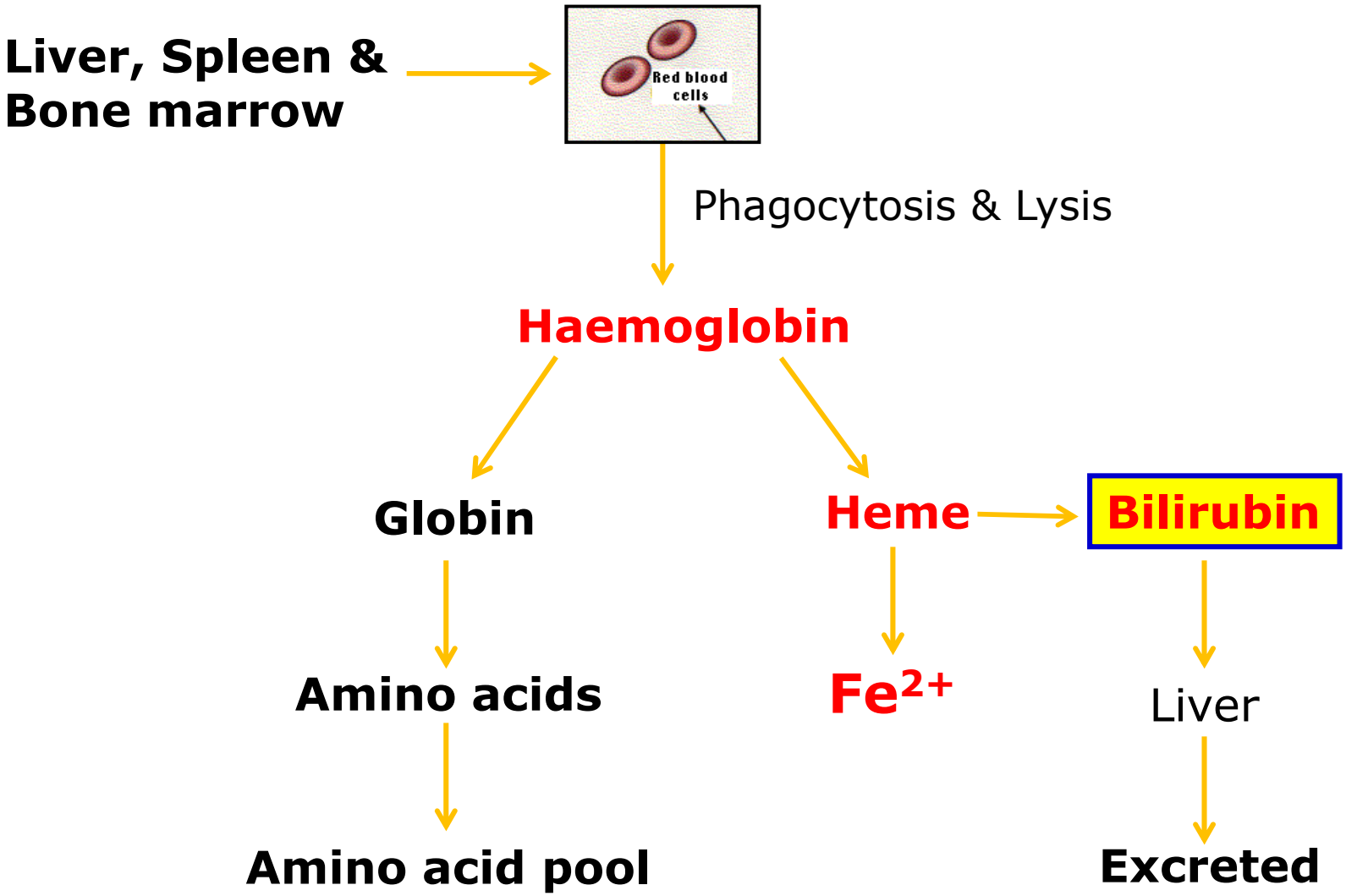
- Accumulation of a yellow pigment (bilirubin) in the skin and other tissues
- Yellow discoloration of sclera, skin, mucous membranes due to deposition of bile pigment bilirubin

Bilirubin Metabolism

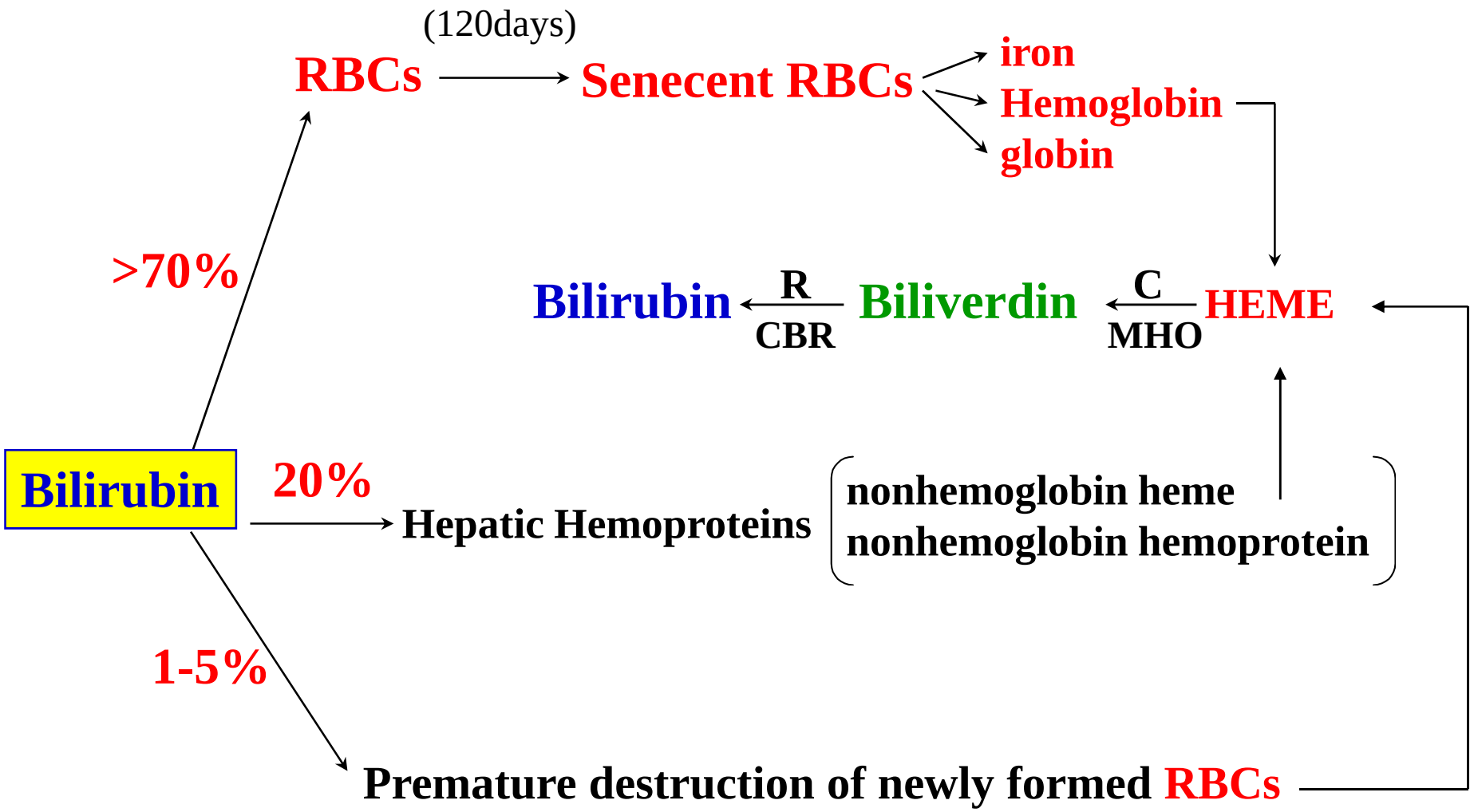
- Formation
- Transport in plasma
- Hepatic transport
  - Hepatic uptake
  - Conjugation
  - Biliary excretion
- Enterohepatic circulation



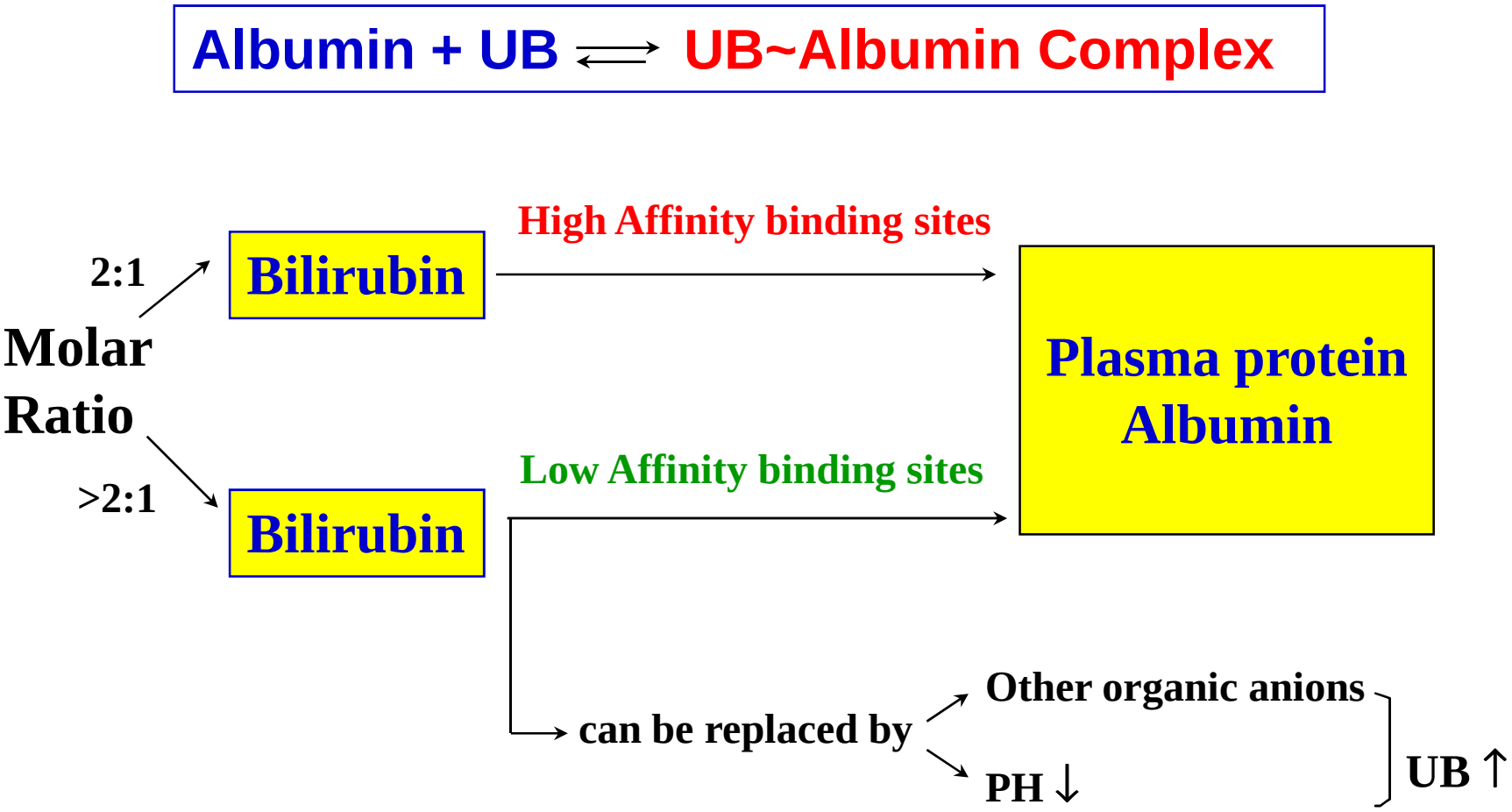
Bilirubin formation



Bilirubin formation



Plasma transport of Bilirubin



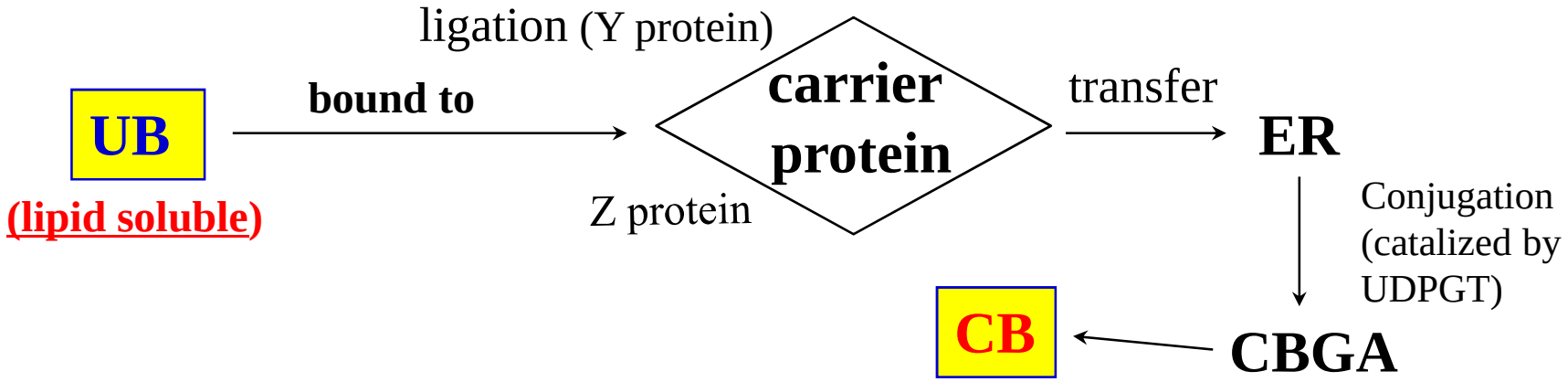
Hepatic Bilirubin Transport

1. Hepatic Uptake of Bilirubin

UB~Albumin Complex are separated

Bilirubin —taken up (receptor ?)→ **Plasma membrane of the liver**

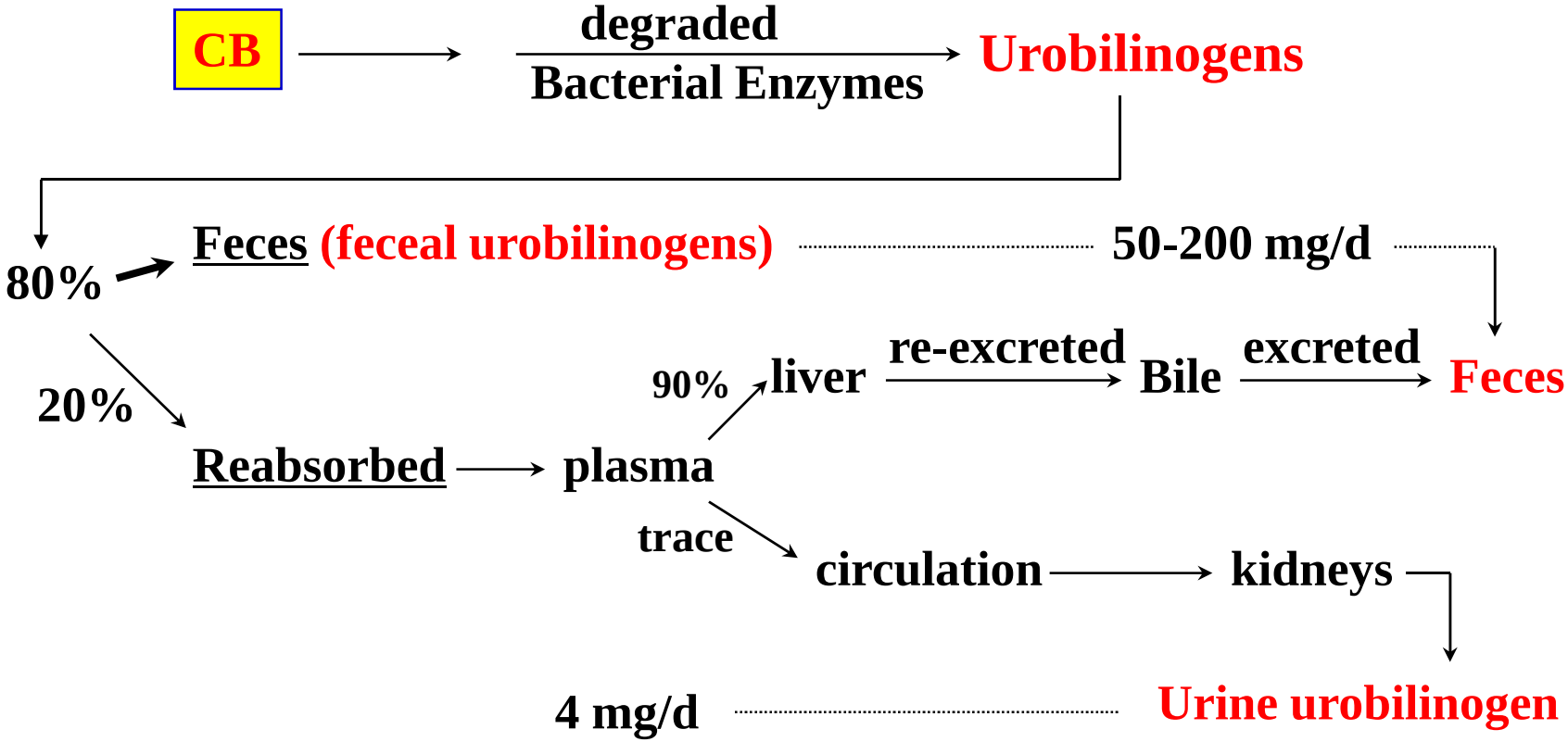
2. Conjugation of Bilirubin



3. Biliary Excretion of Bilirubin (water soluble)

CB —**Transfer across Microvillar membrane**→ **Bile canaliculus**

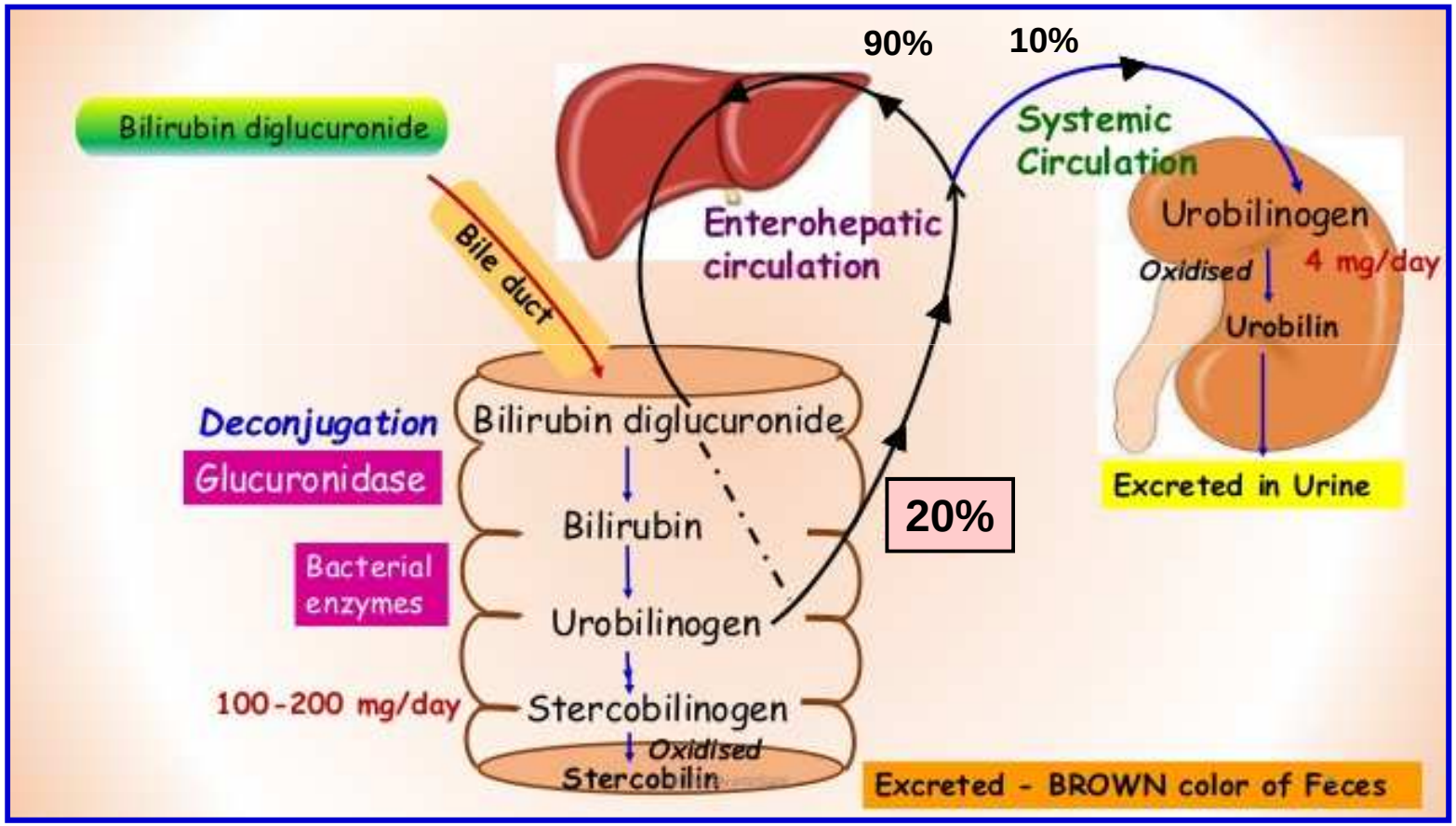
Entero-Hepatic circulation



The serum of normal adults contains ≤1 mg of bilirubin/100 ml

In healthy adults
- The direct fraction is usually <0.2 mg/100 ml
- The indirect fraction is usually <0.8 mg/100 ml

Entero-Hepatic circulation



Bilirubin Metabolism

- UNCONJUGATED BIL (UB): because of its tight albumin binding and lipid solubility, it is not excreted in urine

- CONJUGATED BIL (CB): is less tightly bound to albumin and is water soluble; so it is filtered at the glomerulus and appears in the urine

Bilirubin and its nature

Properties	Unconjugated	Conjugated
Normal serum fraction	90%	10%
Water solubility (polarity)	0 (non polar)	+ (polar)
Affinity to lipids (kernicterus)	+++	±
Renal excretion	no	+
Van den Berg Reaction	Indirect	Direct
Temporary Albumin Binding	+++	0

Jaundice classification by bilirubin type

1. Predominantly unconjugated hyperbilirubinaemia **(UB)**

2. Predominantly conjugated hyperbilirubinaemia **(CB)**

Table 2. Causes Of Indirect Hyperbilirubinemia

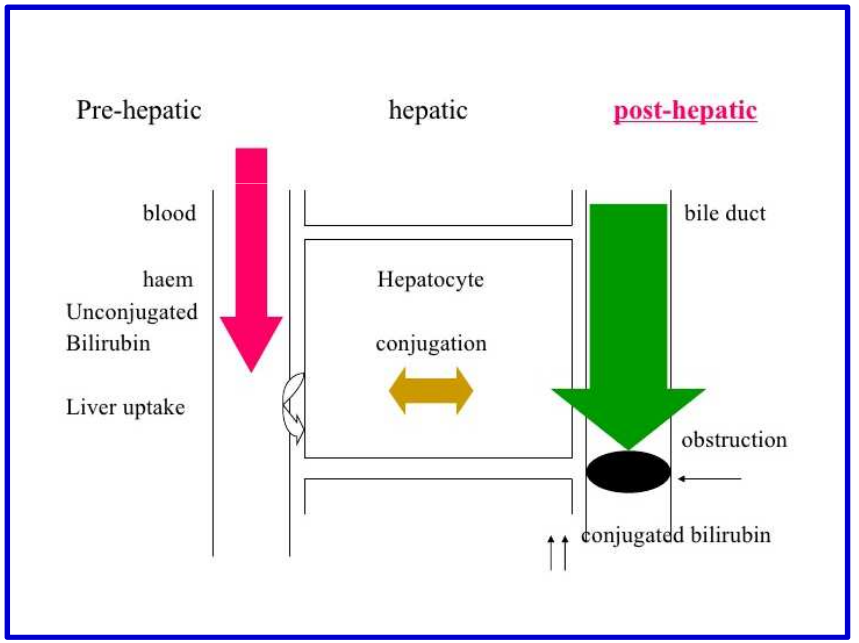
Increased bilirubin production	Hemolysis (intravascular or extravascular) Impaired RBC synthesis (megaloblastic, sideroblastic, iron deficiency anemia, lead poisoning)
Impaired hepatic bilirubin uptake	Congestive heart failure Portosystemic shunts Drugs (rifampin, probenecid)
Impaired bilirubin conjugation	Crigler-Najjar syndrome Gilbert's syndrome Neonates Hyperthyroidism Ethinyl estradiol Liver diseases (chronic persistent hepatitis, advanced cirrhosis, Wilson's disease)

Table 4. Causes Of Direct Hyperbilirubinemia

Extrahepatic cholestasis (biliary obstruction)	Choledocholithiasis Intrinsic and extrinsic tumors Primary sclerosing cholangitis AIDS cholangiopathy Acute or chronic pancreatitis Strictures Parasitic infections
Intrahepatic cholestasis	Viral hepatitis Alcoholic hepatitis Non-alcoholic steatohepatitis Primary biliary cirrhosis Drugs and toxins Sepsis/hypoperfusion Infiltrative diseases Total parenteral nutrition Pregnancy Cirrhosis
Hepatocellular injury	

Jaundice classification by Pathophysiology

1. Hemolytic Jaundice
2. Obstructive Jaundice (cholestasis)
3. Hepatic Jaundice



1. Hemolytic Jaundice

Overproduction

Hemolysis (intra and extra-vascular)

- **Inherited or genetic disorders**
- **Acquired immune hemolytic anemia**
  (autoimmune hemolytic anemia)
- **Non-immune hemolytic anemia**
  (paroxysmal nocturnal hemoglobinuria

Ineffective erythropoiesis (thalassemia)

Overproduction may overload the liver with UB

Table 3. Causes Of Hemolysis

Congenital	Hereditary spherocytosis Glucose-6-phosphate dehydrogenase deficiency (G6PD) Sickle cell disease
Acquired	Autoimmune Cold and warm agglutinins Drug-induced Microangiopathic hemolytic anemia (MAHA), disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS) Paroxysmal nocturnal hemoglobinuria (PNH) Mechanical valve

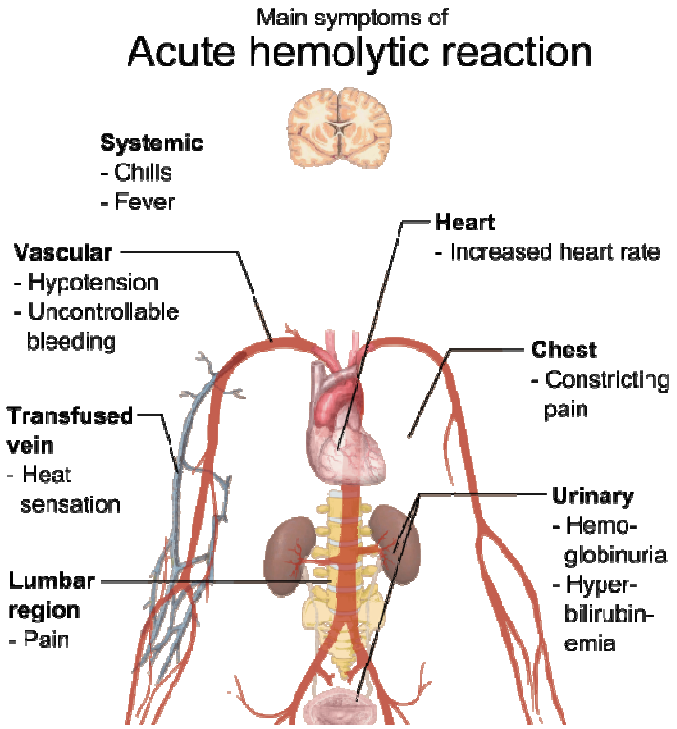
1. Hemolytic Jaundice

Symptoms:

- illness, weakness, fever, dark urine, anemia, splenomegaly

Lab:

- ***↑UB, NO bilirubinuria***
- ***Anemia***
- ***↓haptoglobin***
- ***↑fecal and urine urobilinogen***
- hemoglobinuria (only in massive intravascular hemolysis)
- ↑ reticulocyte counts



2. Obstructive Jaundice

Pathogenesis

- it is due to intra or extra hepatic obstruction of bile ducts

- **Intrahepatic Jaundice:** e.g. primary biliary cirrhosis (PBC)
- **Extra Hepatic Biliary Obstruction:** gallstones, stricture, inflammation, tumors (ampulla of Vater)

Etiology of Obstructive Jaundice

A. Intrahepatic cell damage/blockage of bile canaliculi:

- **Infiltrative tumors**
- **Primary biliary cirrhosis (PBC)**
- **Primary Sclerosing Cholangitis (PSC)**
- Intrahepatic biliary hypoplasia or atresia

Table 6. Causes Of Intrahepatic Cholestasis

Acute hepatocellular injury	Viral hepatitis Alcoholic fatty liver/hepatitis Non-alcoholic steatohepatitis
Chronic hepatocellular injury	Primary sclerosing cholangitis Primary biliary cirrhosis Drugs Hepatitis Cirrhosis
Multifactorial	Total parenteral nutrition Systemic infection Postoperative Sickle cell disease/crisis Organ transplantation (rejection, graft vs. host, venoocclusive disease)
Miscellaneous	Hypotension/hypoxemia/congestive heart failure (CHF) Budd-Chiari syndrome Parasitic infection
Inherited/endocrine	Benign recurrent cholestasis Pregnancy Thyrotoxicosis
Infiltrative/granulomatous	Amyloidosis Lymphoma Sarcoidosis Tuberculosis

Etiology of Obstructive Jaundice

B. Extrahepatic obstructive of bile ducts:

- **Compression obstruction from tumors (e.g. pancreas)**
- **Intraluminal gallstones**
- **Stenosis-postoperative or inflammatory**
- Congenital choledochal cyst
- Extrahepatic biliary atresia

Table 5. Causes Of Extrahepatic Cholestasis

Tumors	Cholangiocarcinoma Pancreatic carcinoma Periampullary carcinoma Metastatic disease
Infection	AIDS cholangiopathy cytomegalovirus (CMV), *Cryptosporidium* spp, HIV Parasitic infection *Ascaris lumbricoides*
Cholangiopathy	Choledocholithiasis Biliary stricture Primary sclerosing cholangitis Sphincter of Oddi dysfunction
Pancreatitis	Acute or chronic

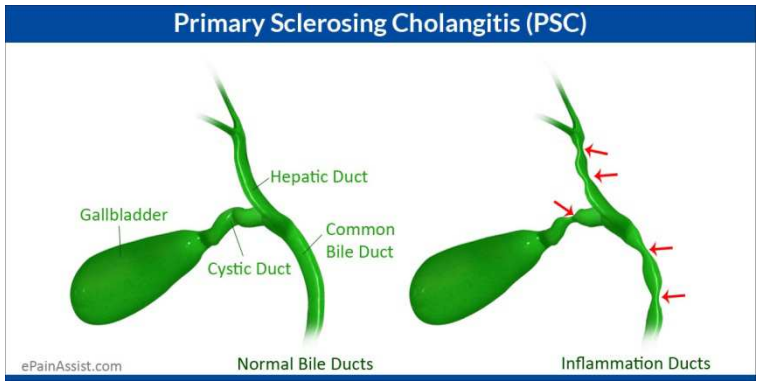
Primary Biliary Cholangitis (PBC)

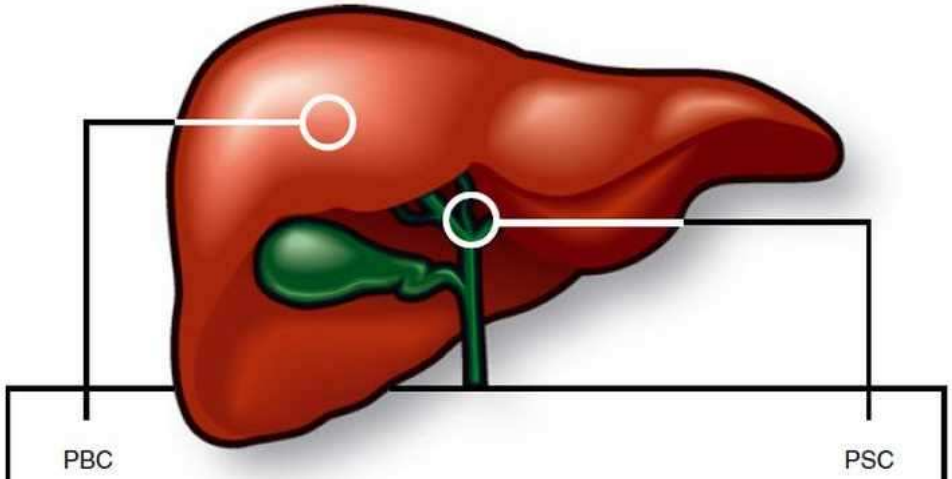
… former "Primary Biliary Cirrhosis"

- Cholestatic liver disease
  - Most common symptoms: **pruritus** and **fatigue**
  - Many patients are asymptomatic and the diagnosis is made by abnormal liver function tests
- Female: male ratio **9:1**
- Diagnosis:
  - Compatible clinical presentation
  - **AMA** titer 1:80 or greater (95% sens/spec)
  - IgM > 1.5 upper limits of normal
  - Liver biopsy: bile duct destruction
- Treatment: Ursodeoxycholic acid 15 mg/kg - cholestiramine

Primary Sclerosing Cholangitis (PSC)

- Cholestatic liver disease
- Inflammation of large bile ducts
- 90% associated with IBD, but only 5% of IBD patients get PSC
- Diagnosis: by ERCP or MRCP
  - No specific autoantibodies, no elevated globulins
  - Biopsy: concentric fibrosis around bile ducts
- Cholangiocarcinoma: 10-15% lifetime risk
- Treatment: Liver Transplantation

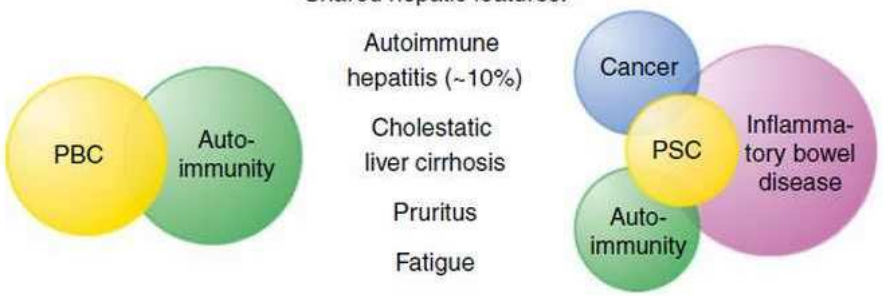




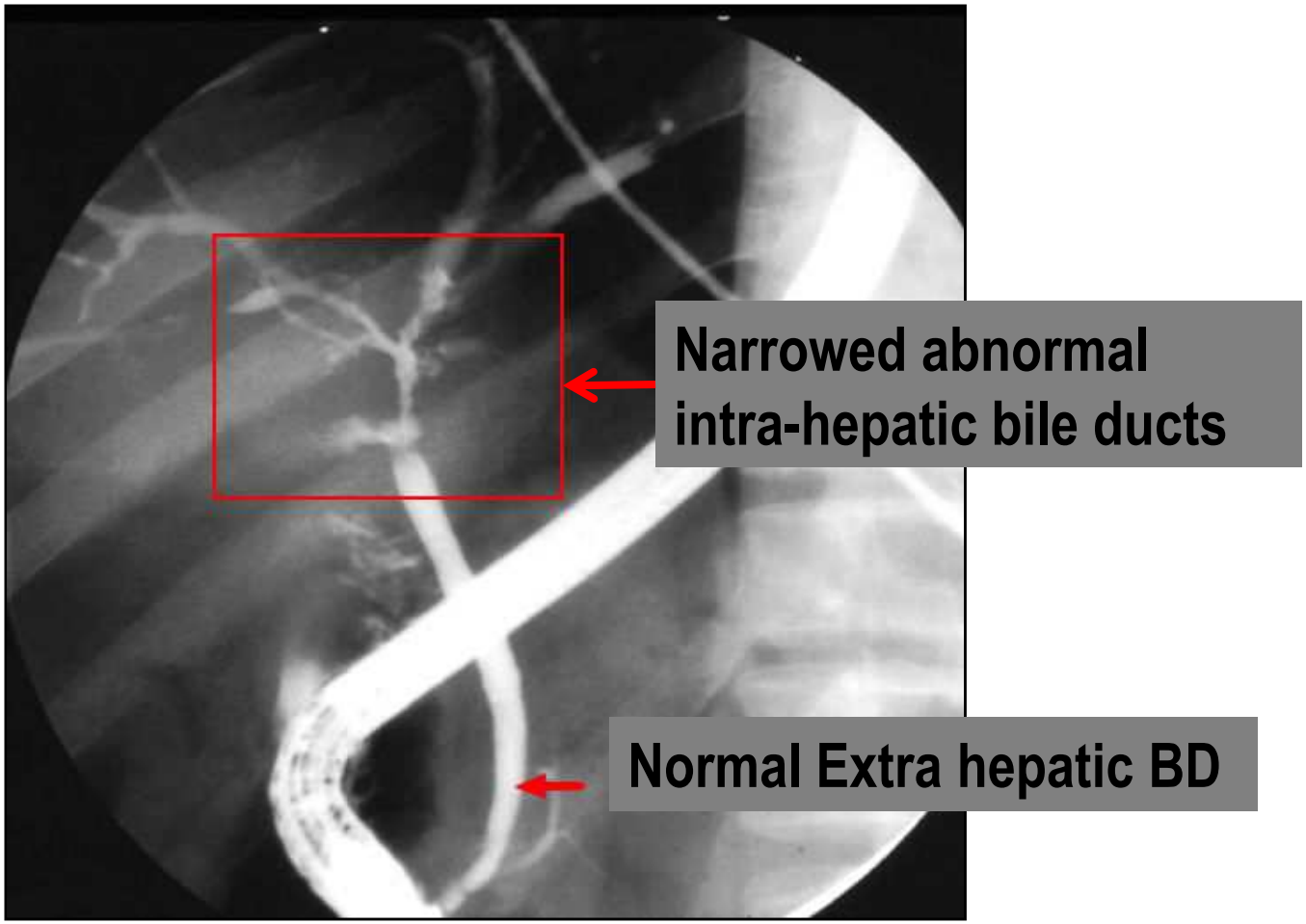
PBC PSC

Interlobular bile duct destruction	Intra-/extrahepatic bile ducts
Prevalence: 0.6–40 per 100.000	Prevalence: 0.2–14 per 100.000
Gender: F>M, 10:1	Gender F<M, 1:2
Age at onset: 50–60 years	Age at onset: 30–40 years
Smoking increases risk	Smoking decreases risk
>28 known risk genes	>16 known risk genes
Autoantibodies (AMA)	Autoantibodies (ANCA?)
Known T cell targets	Unknown T cell targets

Shared hepatic features:

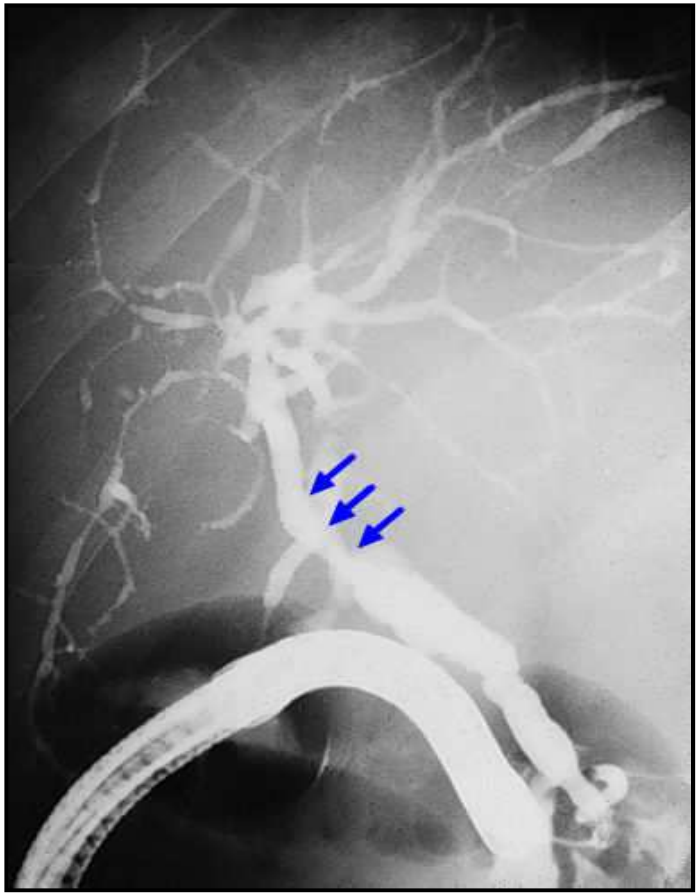


Retrograde Cholangiogram - ERCP



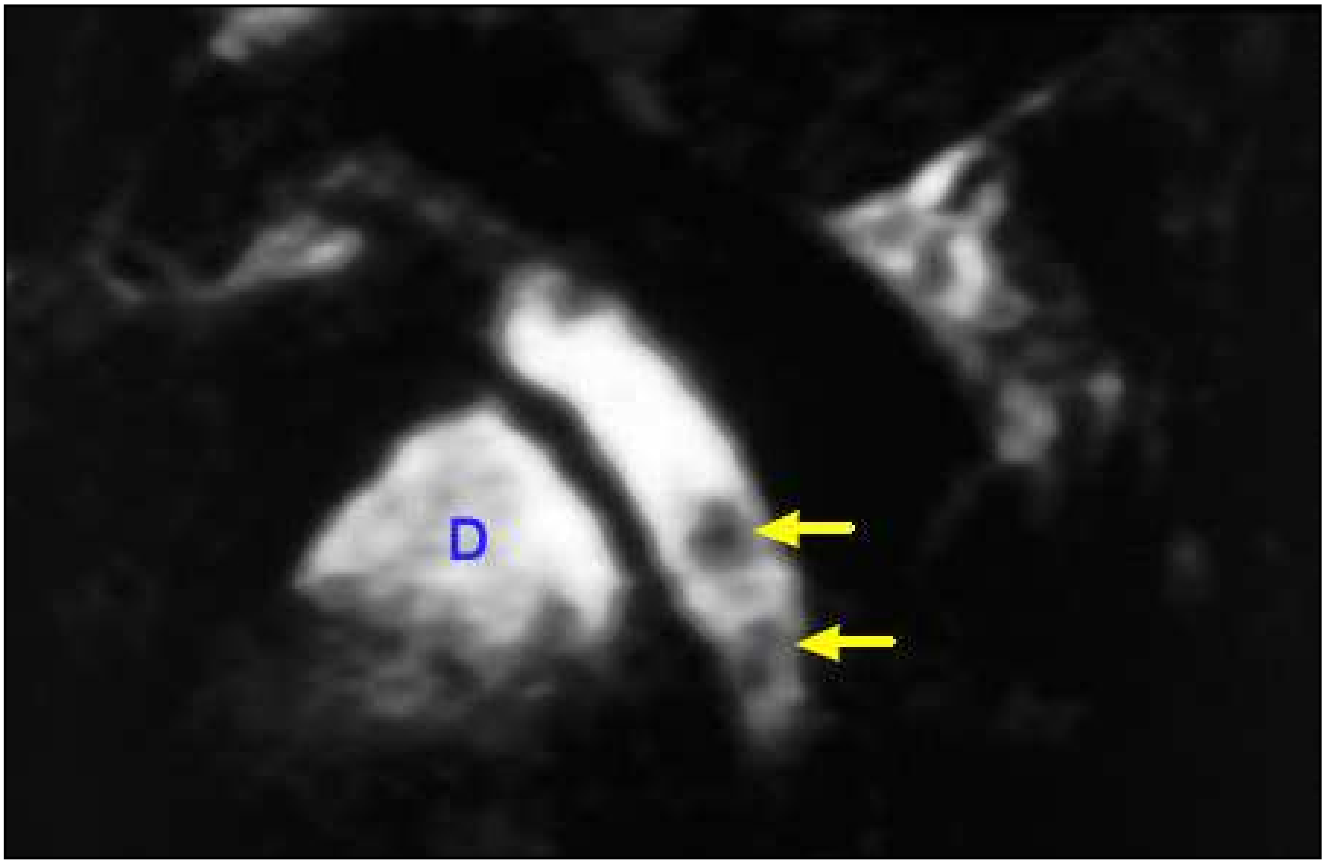
Primary sclerosing cholangitis (PSC)

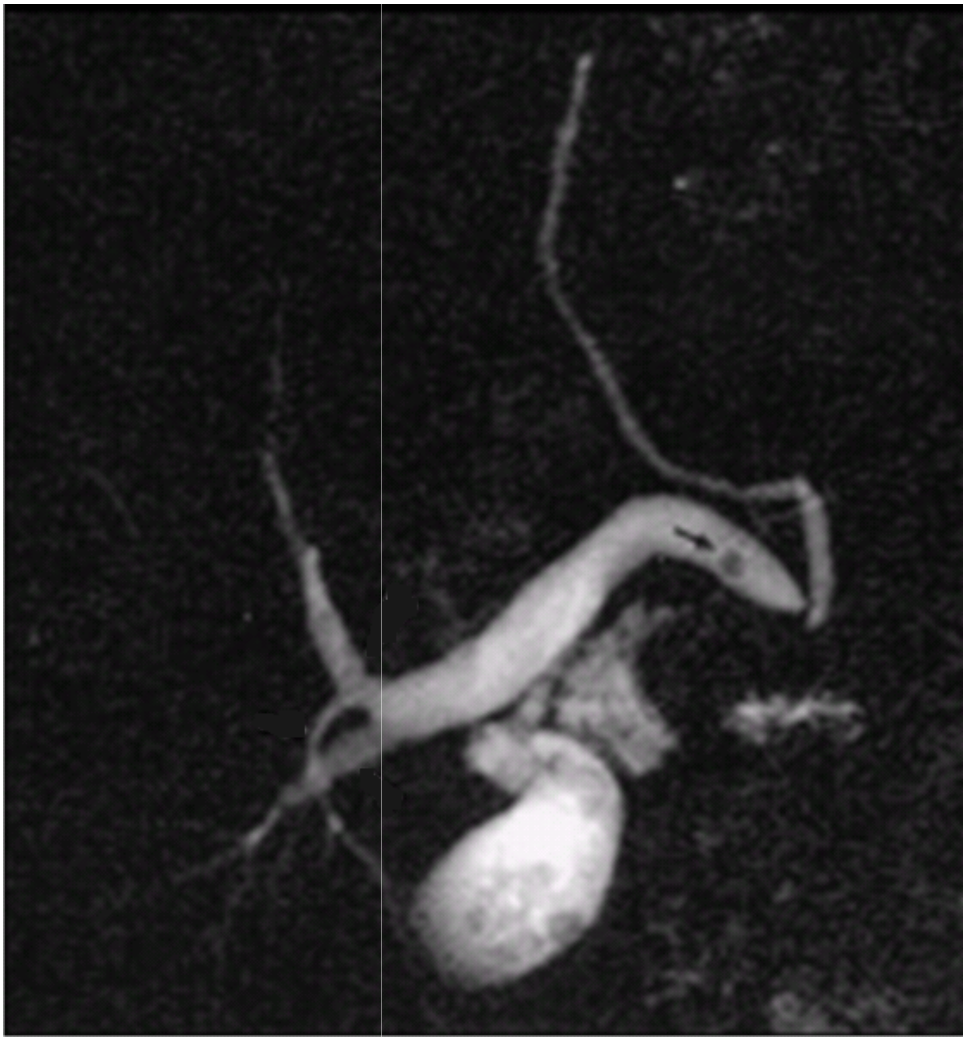
Retrograde Cholangiogram - ERCP



Primary sclerosing cholangitis (PSC) with stricture due to cholangiocarcinoma

Magnetic Resonance Cholangio-Pancreatography (MRCP)

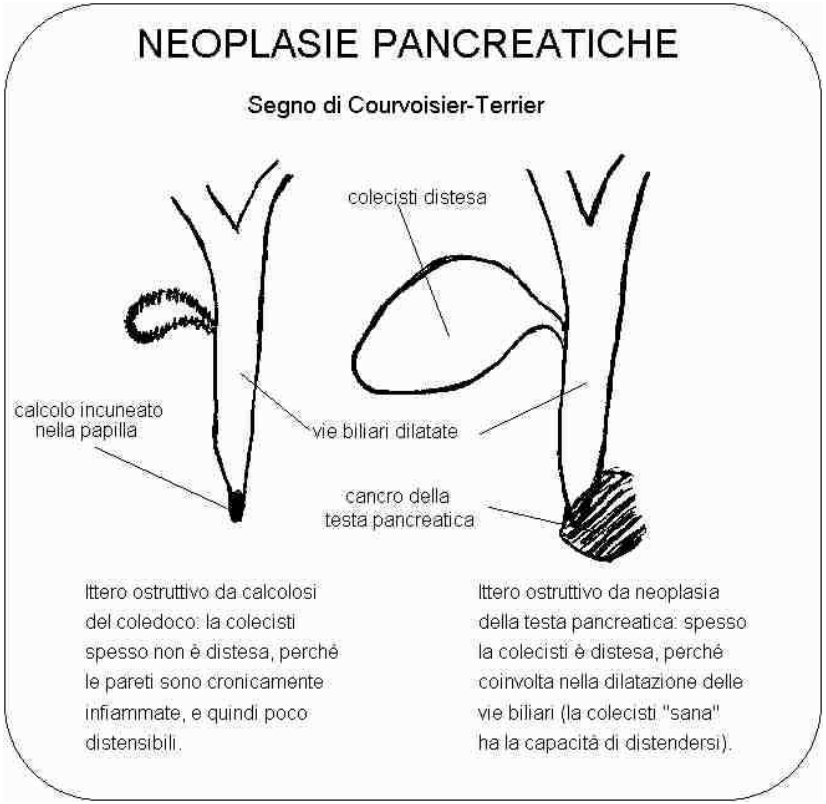




JAUNDICE

Ludwig Courvoisier (1843-1918)

– Courvoisier-Terriers's sign: ***if in the presence of jaundice the gallbladder is palpable, then the jaundice is unlikely to be due to a stone.*** (The pathology and Surgery of the Gallbladder – published 1809)



Cholestasis clinical features

- **Pain:** due to gallbladder disease, malignancy, or stretching of the liver capsule

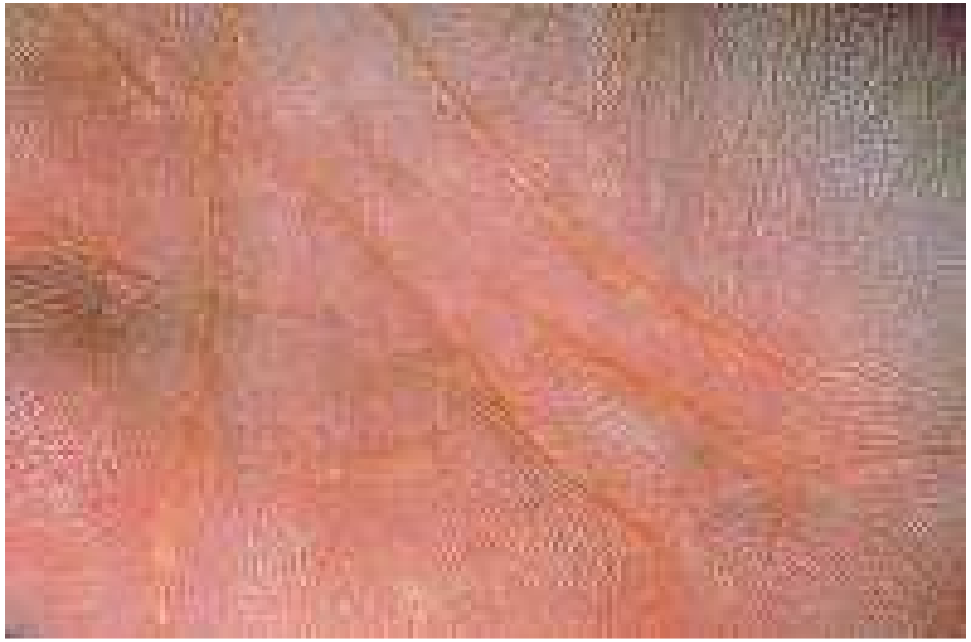
- **Fever:** due to ascending cholangitis
- palpable and/or tender **gallbladder**

- **Enlarged liver**: usually smooth

General signs of cholestasis

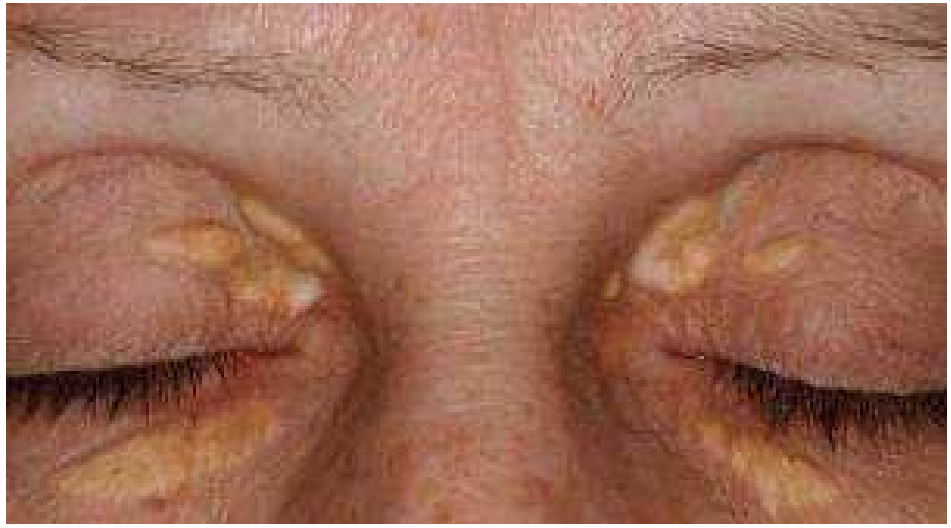
- **Xanthomas:** palmar creases, below the breast, on the neck. They indicate raised serum cholesterol of several months. Xanthomas on the tendon sheaths are uncommonly associated with cholestasis.
- **Xanthelasma** on the eyelids

- **Scratch marks:** excoriation
- **Loose** (tenere), **pale** (chiare), **bulky stools**
- **Dark orange urine**



palmar xanthomas

xanthelasmas



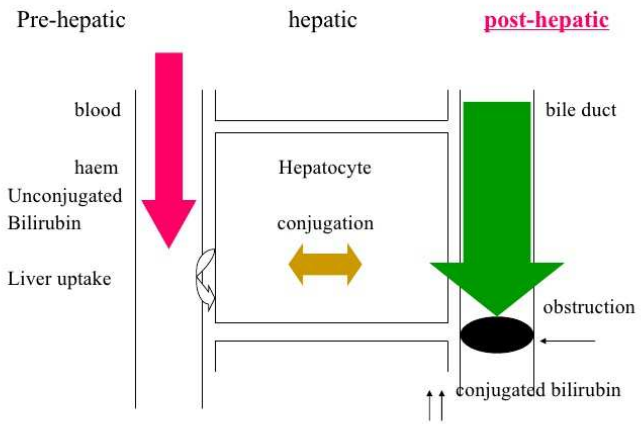
2. Obstructive Jaundice

Lab Findings:

- ***↑Serum Bilirubin: CB***
- ***↓Fecal urobilinogen (incomplete obstruction) or absent (complete obstruction)***
- ***bilirubinuria↑(CB)***
- ALP ↑
- Plasma cholesterol ↑ (lipoprotein x)

3. Hepatic Jaundice

Is due to a disease affecting hepatic tissue, either congenital or acquired, with diffuse hepatocellular injury



3. Hepatic Jaundice

Pathogenesis

- Impaired or absent hepatic conjugation of bilirubin
  - ***Gilbert's syndrome***
  - Grigler-Najjar Syndrome
- Familiar or hereditary disorders
  - Dubin-Johnson Syndrome
  - Rotor syndrome
- **Acquired disorders**
  - **hepatocellular necrosis**
  - **intrahepatic cholestasis**

3. Hepatic Jaundice

Intrahepatic cholestasis/impaired excretion:

- **Hepatitis:** viral, alcoholic, and non-alcoholic
  - Any cause of hepatocellular injury
- **Cirrhosis** or end-stage liver disease
- **Sepsis** and hypoperfusion states
- **Pregnancy**
- **Infiltrative dis.:** TB, amyloidosis, sarcoidosis, lymphomas
- Drugs/toxins: chlorpromazine, arsenic
- **Post-op patient** or post-organ transplantation

Table 7. Differential Diagnosis Of Hepatocellular Jaundice

Neoplasms	Hepatocellular carcinoma Cholangiocarcinoma Metastatic disease (gastrointestinal, genitourinary, bronchogenic)
Hereditary	Wilson's disease Alpha -1- antitrypsin deficiency Hemochromatosis
Miscellaneous	Secondary biliary cirrhosis Cryptogenic cirrhosis
Infections - viral	Hepatitis viruses (A-E) Herpes viruses (CMV, HSV) Hemorrhagic viruses (Ebola, Marburg, Lassa, yellow fever) Adenovirus, enterovirus
Infections – bacterial	Tuberculosis (TB) Leptospirosis Syphilis Abscesses Brucellosis Rickettsia Whipple's disease
Infections – fungal	Candida Blastomyces Cocciodies Histoplasmosis Cryptococcus
Infections – parasitic	Helminths – ascaris, clonorchis, schistosomiasis, echinococcus Protozoa – amebiasis, plasmodia, babesiosis, toxoplasmosis, leishmaniasis
Toxic	Medications Alcohol Chlorinated hydrocarbons Amanita phalloides toxin Aflatoxin Vitamin A1 Arsenic Pyrrolizidine alkaloids
Immunologic	Autoimmune hepatitis Primary biliary cirrhosis Primary sclerosing cholangitis Nonalcoholic steatohepatitis

3. Hepatic Jaundice

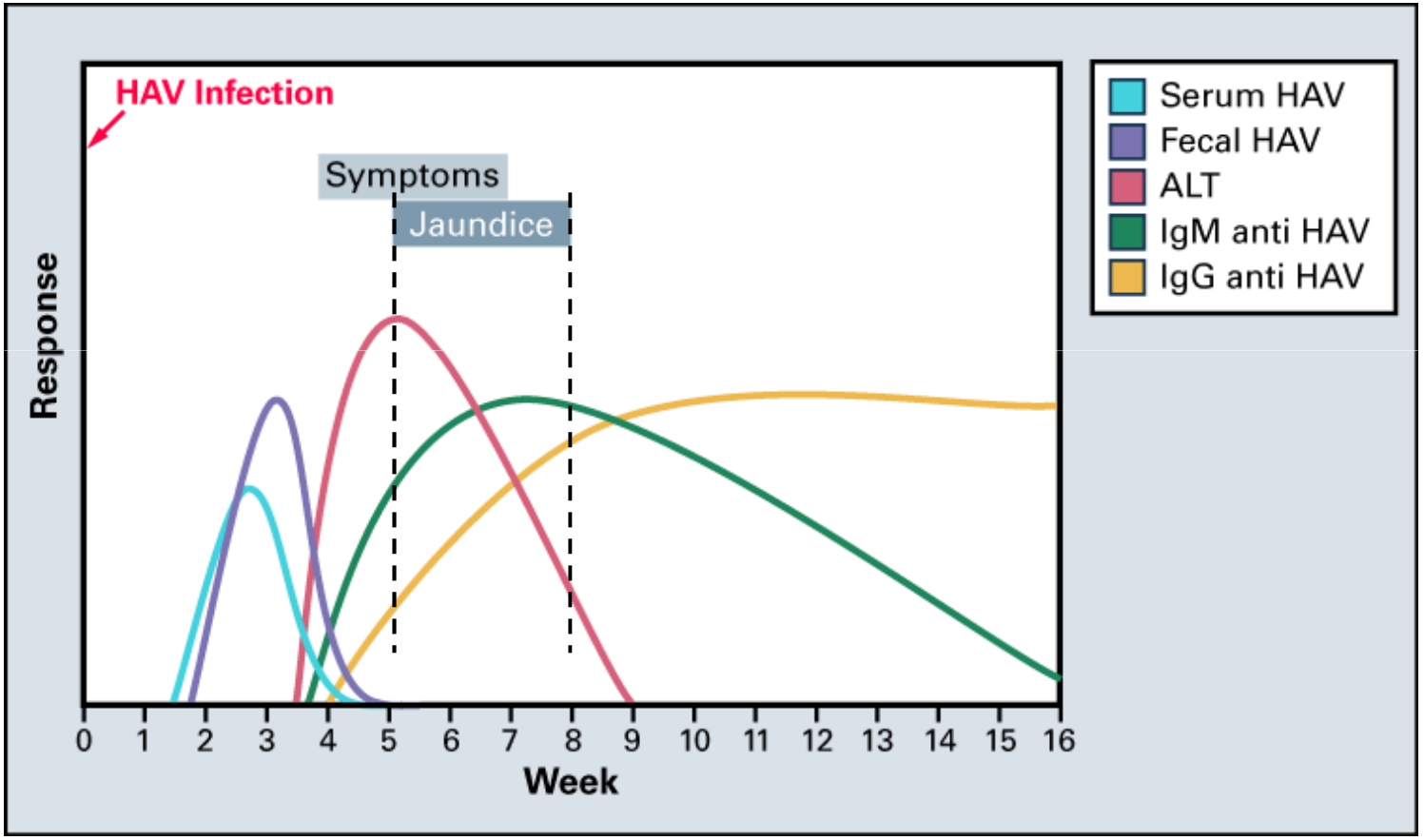
Symptoms:

- weakness, loss appetite, loss weight, hepatomegaly, palmar erythema, spiders

Lab Findings:

- ***liver function tests are often abnormal***
- ***↑both CB and UB, usually***
- ***↑Bilirubinuria***

Hepatic Jaundice in Hepatitis



Hepatic Jaundice in Chronic Liver Disease

- **Alcoholic Liver**
- **Chronic viral hepatitis**
  - **Hepatitis B**
  - **Hepatitis C**
- **Autoimmune liver disease:**
  - **Autoimmune hepatitis**
  - **Primary Biliary Cirrhosis**
- **Inherited conditions**
  - **Haemochromatosis**
  - **Wilson's Disease**
  - **Alpha1-Antitrypsin Deficiency**
- **Non-alcoholic steato-hepatitis (NASH)**
- **Budd-Chiari syndrome**

Potentially hepato-toxic drugs

Conventional Drugs	Natural Substances
Paracetamol, Alpha-methyldopa	**Hypervitaminosis A**
Amiodarone, Dantrolene, Diclofenac	**Niacin, Cocaine, Mushrooms**
Fluconazole, Glipizide	Aflatoxins, Herbal remedies
Glyburide, Isoniazid, **Ketaconazole**	Senecio, crotaliaria
Labetalol, **Statins, Nitrofurantoin**	Pennyroyal oil, Chapparral
Thiouracil, Troglitazone, **Trazodone**	Germander, **Senna**

Paracetamol Toxicity

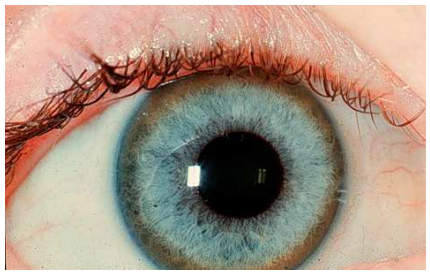
- Danger dosages for a 70 kg patient
  - Toxicity possible >10 g
  - Severe toxicity certain >20 g
  - Lower doses potentially hepatotoxic in:
    - Chronic alcoholics
    - Malnutrition or fasting
    - Tegretol, Phenobarbital, Isoniazide, Rifampicine
    - NOT in acute Ethanol ingestion
    - NOT in non-alcoholic chronic liver disease

“Unusual” Causes of Jaundice

- Ischemic Hepatitis
- Congestive Hepatopathy (CHF)
- Wilson’s disease
- Amanita Phalloides
- AIDS cholangiopathy
- Infiltrative diseases of the liver:
  - Amyloidosis
  - Sarcoidosis
  - Malignancy: lymphoma, metastasis
- Paraneoplastic syndrome (↑ CB)

Wilson's Disease

- Autosomal recessive disease of copper metabolism
- ATP7B gene mutation
- Chronic hepatitis or fulminant hepatitis
- Associated clinical features:
  - Neuropsychiatric disease
  - Hemolytic anemia



- Physical exam: Kayser-Fleischer rings
- Diagnosis: ↓ ceruloplasmin, urinary Cu ↑
- Treatment: D-penicillamine

Intrahepatic Paraneoplastic Colestasis
"Stauffer syndrome"

Disfunzione epatica in corso di neoplasia <u>in assenza di metastasi o infiltrazione epatica</u>

- ***Caratteristica del K renale, può essere associata anche ad altre neoplasie:***
- ***Malattie linfoproliferative***
- ***Sarcomi***
- ***K prostatico***
- ***Neoplasie ginecologiche***
- ***K broncogeno***
- ***Neoplasie del tratto GI***
- ***K midollare tiroideo***
- **QUADRO CLINICO: ittero, febbre, astenia, dolore addominale, epatosplenomegalia e perdita di peso**
- **QUADRO EMATOCHIMICO: ↑ Bil. Dir., ALP, G-GT, AST, ALT, PT**
- **PATOGENESI controversa: produzione da parte delle cellule neoplastiche di GM-CSF, IL-6 e altre sostanze epatotossiche?**

Grave colestasi di origine paraneoplastica in donna ultraottantenne con linfoma B-cellulare anaplastico misconosciuto

Severe paraneoplastic cholestasis in octogenarian woman with unrecognized anaplastic B-cell lymphoma

CECILIA SOAVI, MD, FOTINI SIOULIS, MD, MASSIMO PEDRIALI, MD [*], GIAN MATTEO RIGOLIN MD [**], GIOVANNI ZULIANI, MD PHD

Dipartimento di Scienze Mediche; Sezione di Medicina CardioPolmonare, Università di Ferrara; [*] Dipartimento di Diagnostica per Immagini e Medicina di Laboratorio; Sezione di Anatomia Patologica ed Istologia, Università di Ferrara; [**] Dipartimento di Scienze Biomediche, Sezione di Ematologia, Azienda Ospedaliero-Universitaria Arcispedale S. Anna, Ferrara

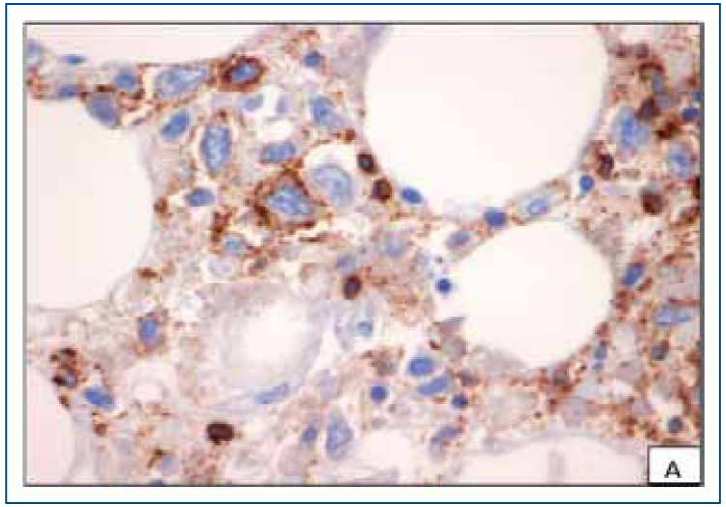


Fig. 1A. Linfoma a grandi cellule B (zoom 40x). L'indagine immunoistochimica ha dimostrato l'origine B-cellulare (CD20+) della neoplasia mesenterica. L'immagine mostra caratteristiche grandi cellule B pleomorfe con nuclei irregolari, eccentrici, talvolta reniformi.

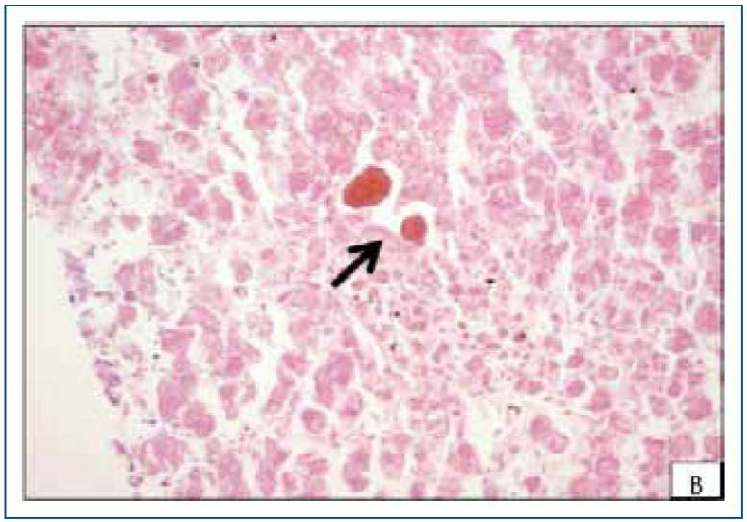


Fig. 1B. Tessuto epatico (zoom 20x). Si può osservare la congestione dei sinusoidi e la colestasi centro-lobulare con presenza di tappi canalicolari (freccia).

Jaundice differential diagnosis

↑ Production	↓ Transport or ↓ Conjugation	Impaired Excretion	Biliary Obstruction
↑ *Unconjugate*	↑ *Unconjugate*	↑ *Conjugated*	↑ *Conjugated*
Hemolysis	Gilbert's	Cancer	Stones
Transfusions	Cirrhosis	Cirrhosis	Strictures
Sepsis	Hepatitis	Hepatitis	Cancer
Burns	Crigler-Najarr	Rotor	Chronic pancreatitis
Hb-pathies	Neonatal	Dubin-Johnson	PBC
	Drug inhibition	Amyloidosis	PSC
		Paraneo	

Jaundice differential diagnosis

Features	Prehepatic (Heamolytic)	Intrahepatic (Hepatocellular)	Posthepatic (Obstructive)
Unconjugated	↑	Normal	Normal
Conjugated	Normal	↑	↑
AST or ALT	Normal	↑ ↑	Normal
Alkaline phos. and GGT	Normal	Normal	↑ ↑
Urine bilirubin	Absent	Present	Increased
Urobilinogen	Increased	Present	Absent

Jaundice differential diagnosis

	Pre-hepatic	Hepatic	Post-hepatic
Urine	No Bilirubin ↑Urobilinogen	? Bilirubin ↑ Urobilinogen	↑Bilirubin ↓Urobilinogen
Faeces	Dark	Pale	Pale
Blood	FBC - Reticulocyte count Coombs' test ↑Bilirubin (<15% – conjugated) ALP Normal PT Normal	↑Bilirubin – mixed conjugated & unconjugated ↑ ALP, γGT ↑AST, ALT ↑ PT – not correctable with Vit K	↑Bilirubin (>15% conjugated) ↑↑ ALP, γGT ↑ PT – correctable with Vit K

Alcoholic Liver Disease

- The history is the key: > 60 grams/day
- **Lab clues: AST/ALT ratio > 2; MCV ↑**
  AST < 300
- **Alcoholic hepatitis:**
  - Anorexia, fever, jaundice, hepatomegaly
  - Treatment:
    - Abstinence
    - Nutrition
    - Consider prednisolone or pentoxifylline

Critical Questions in the Evaluation of the Jaundiced Patient

1. **Acute vs Chronic Liver Disease**
2. **Hepatocellular vs Cholestatis**
3. **Fever**
   - Could the patient have cholangitis?
4. **Encephalopathy**
   - Could the patient have fulminant hepatic failure?

Evaluation of the Jaundiced Patient
HISTORY

- Pain
- Fever
- Confusion
- Weight loss
- Drugs
- Alcohol
- Medications

- pruritus
- malaise, myalgias
- dark urine
- ↑ abdominal girth
- edema
- other autoimmune dz
- prior biliary surgery
- family history liver dz

Evaluation of the Jaundiced Patient
PHYSICAL EXAM

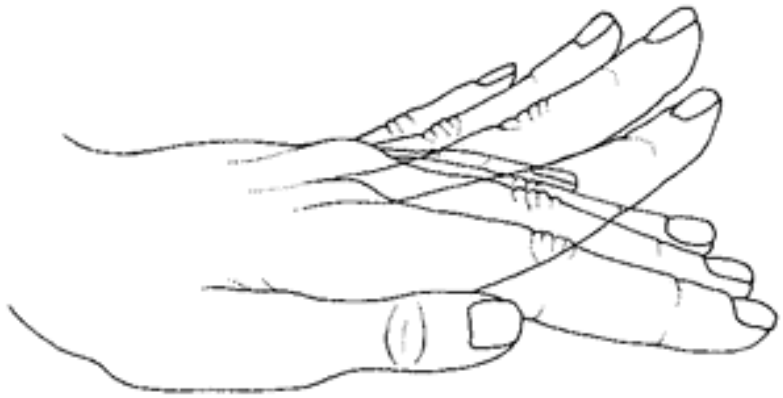
- BP/HR/Temp
- Mental status
- Asterixis
- Abd tenderness
- Liver size
- Splenomegaly
- Ascites
- Edema

- Spider angiomata
- Hyperpigmentation
- Kayser-Fleischer rings
- Xanthomas
- Gynecomastia

Flapping Tremor

An involuntary jerking tremor of wide amplitude elicited upon dorsiflexion of the pronated wrist and spreading of extended fingers; in full-blown flapping tremors, **there is abrupt flexion of the fingers at the metacarpophalangeal joint and flexion of the wrist, occurring asynchronously with each other every few seconds, due to exaggerated reflexes.**

Bilateral flapping tremor is quasi-pathognomonic for metabolic, often alcohol-related, hepatic encephalopathy seen in end-stage cirrhosis due to increased blood ammonia.



Hepatic Encephalopaty

Table 11. Stages Of Hepatic Encephalopathy

Stage	Mental Status	Neuromuscular Function
1	Impaired attention, irritability, depression	Tremor, incoordination, apraxia
2	Drowsiness, behavioral changes, memory impairment, sleep disturbances	Asterixis, slowed or slurred speech, ataxia
3	Confusion, disorientation, somnolence, amnesia	Hypoactive reflexes, nystagmus, clonus, muscular rigidity
4	Stupor and coma	Dilated pupils and decerebrate posturing, oculocephalic reflex

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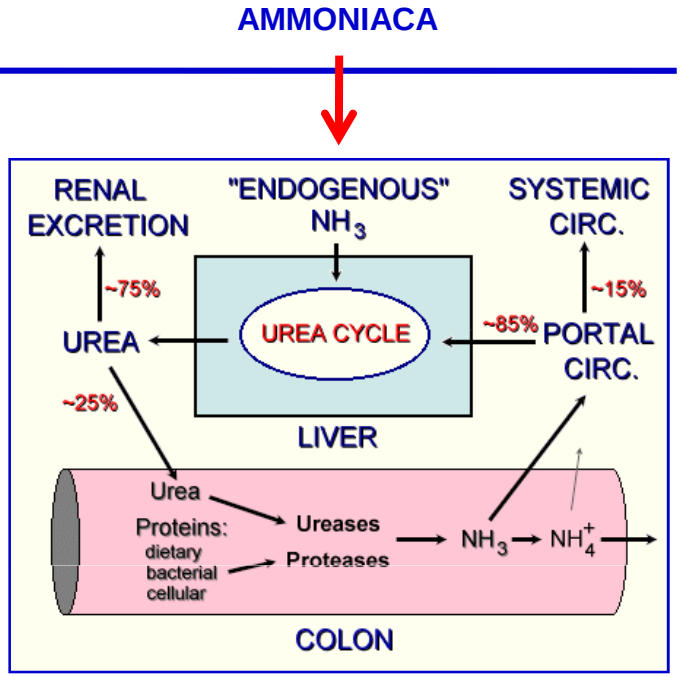
Evaluation of the Jaundiced Patient
LAB EVALUATION

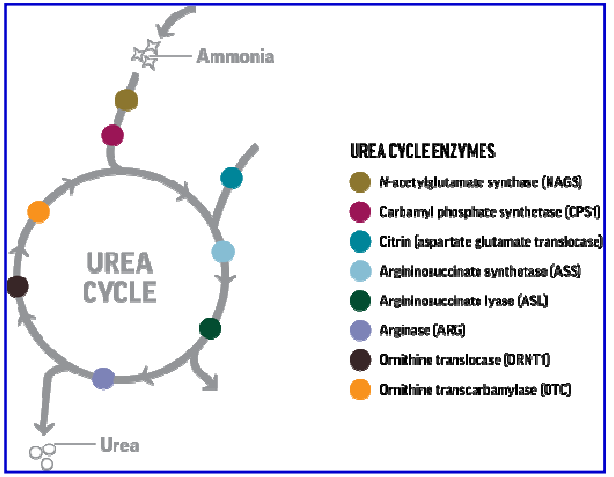
- AST-ALT-ALP
- Bilirubin: total/indirect
- Albumin
- PT-INR
- Glucose
- CBC/plt
- *Ammonia*

- Viral serologies
- ANA-ASMA-AMA
- Quantitative Ig
- Ceruloplasmin
- Iron profile
- Blood cultures

Ammonia

- Ammonia derived from amino acid and nucleic acid metabolism.
- Metabolised only in the liver:
- Urea cycle or Krebs Henseleit cycle
- Ammonia ⟹ Urea .
- Liver damage >80%- ↑ NH_3 & arginine conc. ⟹ Hepatic encephalopathy
- Degree of hepatic encephalopathy is proportional to NH_3 conc. in arterial blood .





Evaluation of the Jaundiced Patient

- Ultrasound:
  - More sensitive than CT for gallbladder stones
  - Equally sensitive for dilated ducts
  - Portable, cheap, no radiation, no IV contrast
- CT:
  - Better imaging of the pancreas and abdomen
- MRCP:
  - Imaging of biliary tree comparable to ERCP
- ERCP:
  - *Therapeutic intervention for stones*
  - *Brushing and biopsy for malignancy*

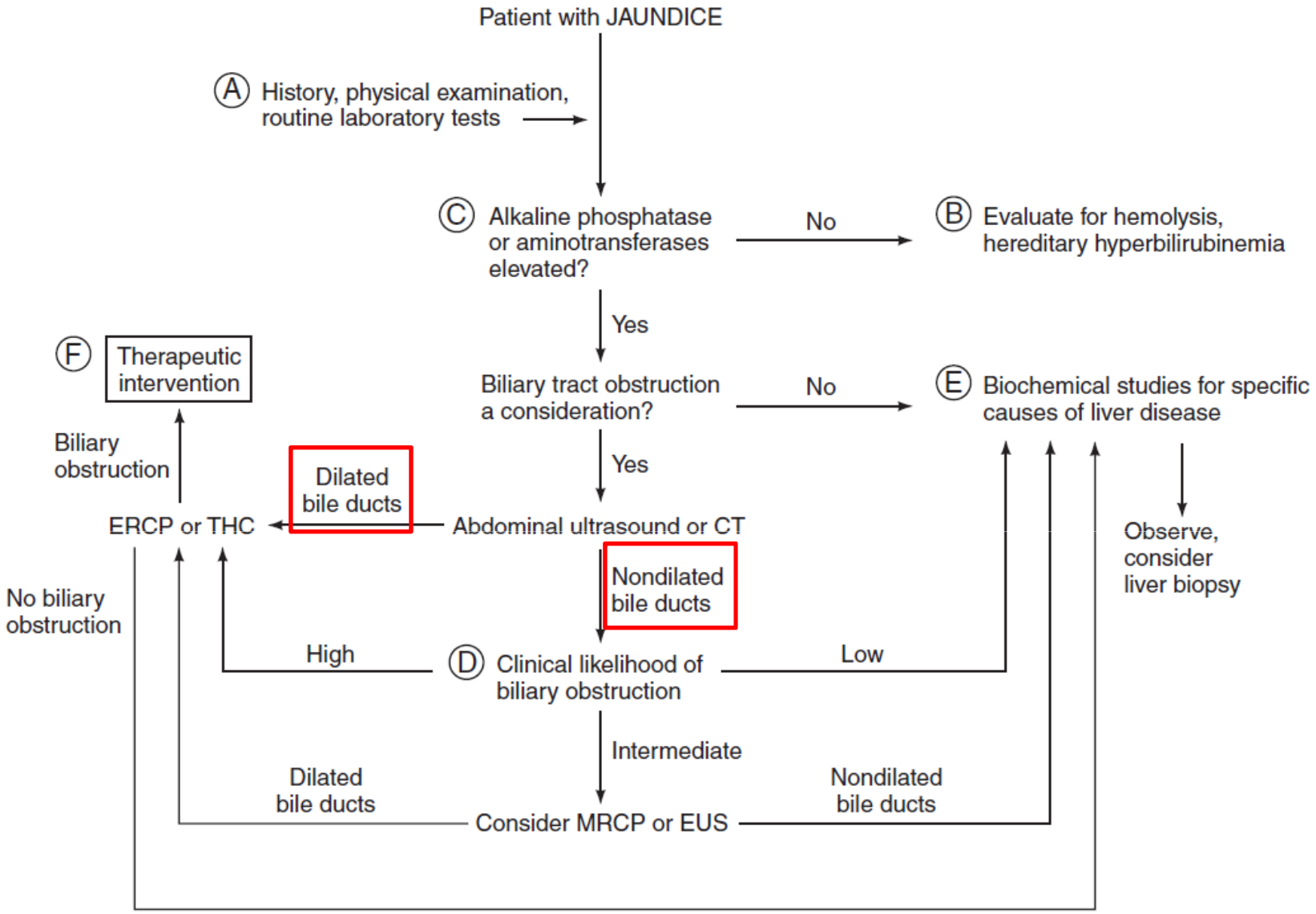
Jaundice differential diagnosis

Differential Diagnosis

- UB or CB
- Exclude UB (e.g. hemolysis or Gilbert Syndrome)
- Distinguish hepatocellular from obstructive
- Distinguish intrahepatic from extrahepatic cholestasis

Table 8. Life-Threatening Conditions Presenting With Jaundice

Fulminant hepatic failure
Acute cholangitis
Massive hemolysis
Neonatal hyperbilirubinemia - kernicterus
Acute fatty liver of pregnancy



EUS, endoscopic ultrasound; THC, percutaneous transhepatic cholaniography. Modified from Lidofsky SD. Jaundice. In Feldman M, Friedman LS, Brandt LJ (eds). Sleisinger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management. Philadelphia: Saunders, 2006:309.