LIVER FUNCTION TESTS

Jaundice – Classification

- Normal Serum Bilirubin (SB) is 0.3 to 1.0 mg%
- Jaundice is increased levels of SB > 1.0 mg%
- Over production of Bilirubin (Hemolytic)
  - From hemolysis of RBC
  - Lysis of RBC precursors – Ineffective erythropoesis
- Impaired hepatic function (Hepatitic)
  - Hepatocellular dysfunction in handling bilirubin
    - Uptake, Metabolism and Excretion of bilirubin
- Obstruction to bile flow (Obstructive)
  - Intrahepatic cholestasis
  - Extrahepatic Obstruction (Surgical Jaundice)

Clinical Aspects of Jaundice

- Clinically detectable if SB is >2.0 mg%
- With edema and dark skin – Jaundice is masked
- What is special about the sclera ? – Rich Elastin
- Darkening of the urine – Differential Diagnosis
- Skin discoloration – Yellowish, - Carotinemia – Eyes N
- Mucosa – hard palate (in dark skinned)
- Greenish hue of skin and sclera - due Biliverdin – indicates long standing jaundice
- Generalized Pruritus – Obstructive Jaundice – Why ?

Clinical History – Imp clues

- Duration of jaundice – Acute / Chronic
- Abdominal pain v/s painless jaundice
- Fever – Viral / bacteria /sepsis
- Arthralgia, rash, glands; Pruritus - obstructive
- Appetite – Hepatocellular / Malignancy
- Weight loss – Malignancy – CAH
- Colour of stools –chalky white –obstructive
- Family history – Hemolytic – Inherited dis.
- H/o transfusion, promiscuity, IDU
- Alcohol abuse, Medications – INH, EM, Largactil

Coloured Urine – Differ. Diagnosis

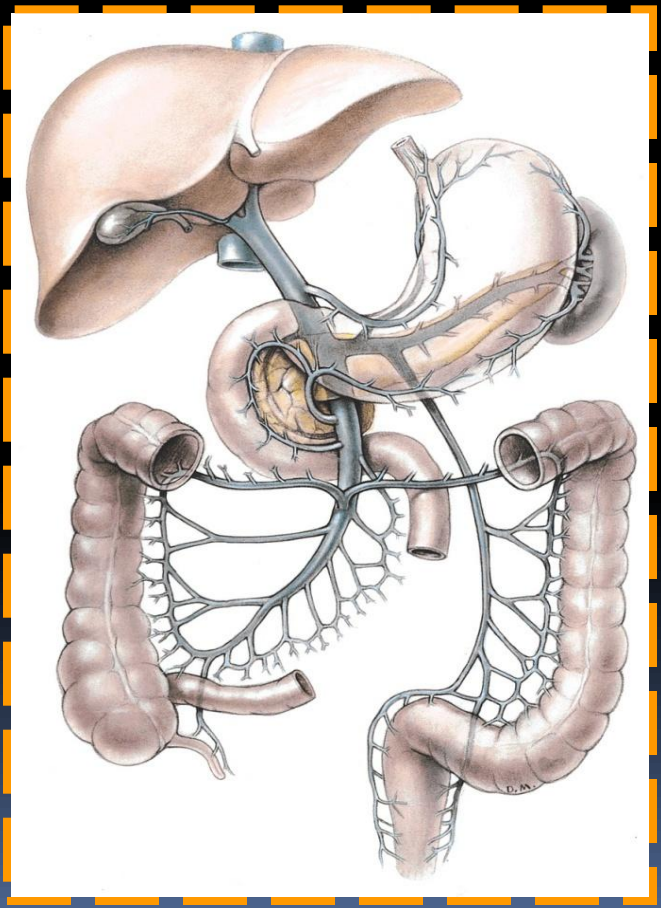
- Bilirubin in urine due to Jaundice (CB)
- Concentrated urine in dehydration
- Fluid deprivation syndromes
- Sulfasalazine use – for Ulcerative colitis
- Rifampicin, Pyridium and Thiamine use
- Red urine – Porphyria,
- Hemoglobin & Myoglobinuria, Hematuria
- Dark black urine in Ochranosis - HGA
- Melanin excretion from Melanoma
- Red sweat in Clofazamine, Rifampicin

Fate of Senescent RBC

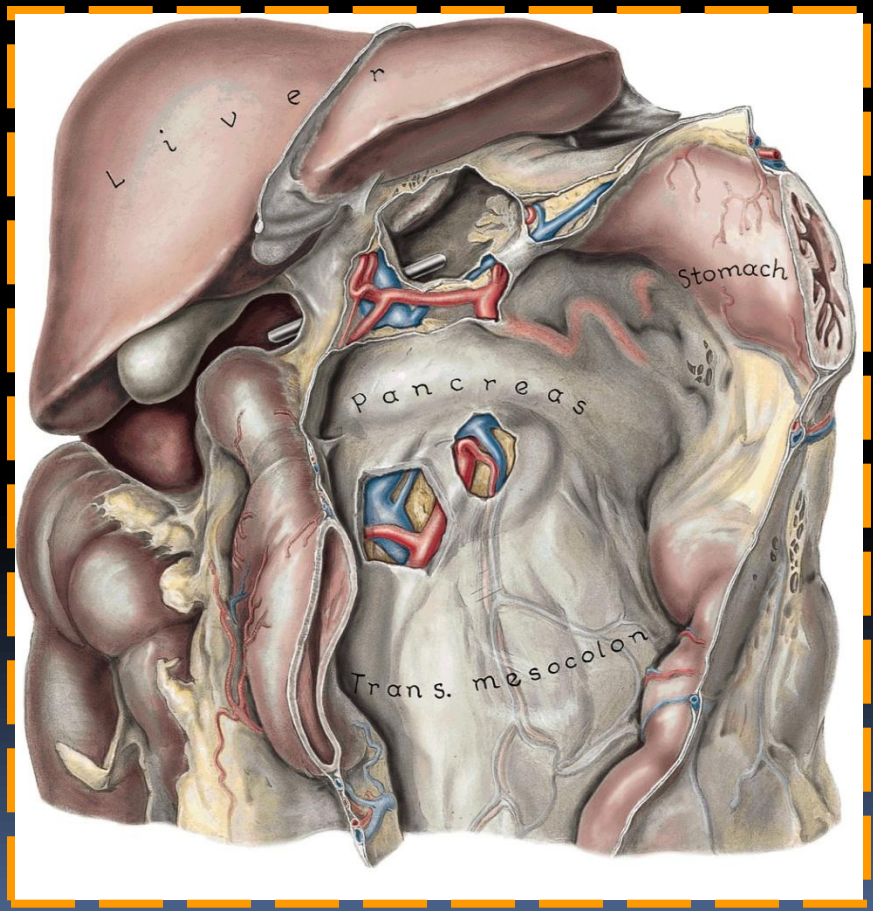
- RBC life span in blood stream is 90-120 days
- Old RBCs are phagocytosed and/or lysed
- Lysis occurs extravascularly in the RE system subsequent to RBC phagocytosis
- Intravascular Hemolysis of young RBC
- This is due to hemolytic diseases of RBC

The Hepatobiliary & Portal System

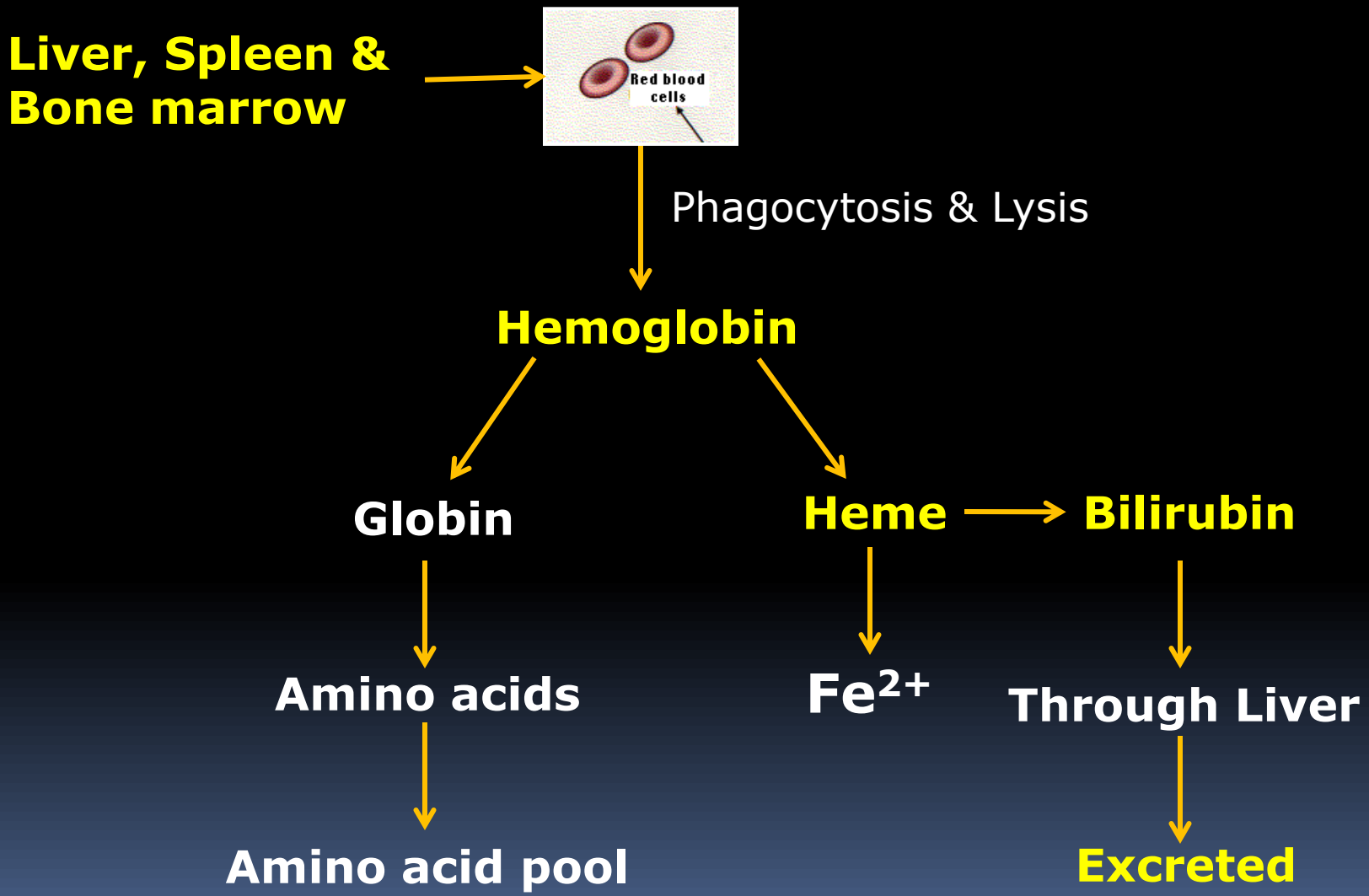
Hepatobiliary Tree



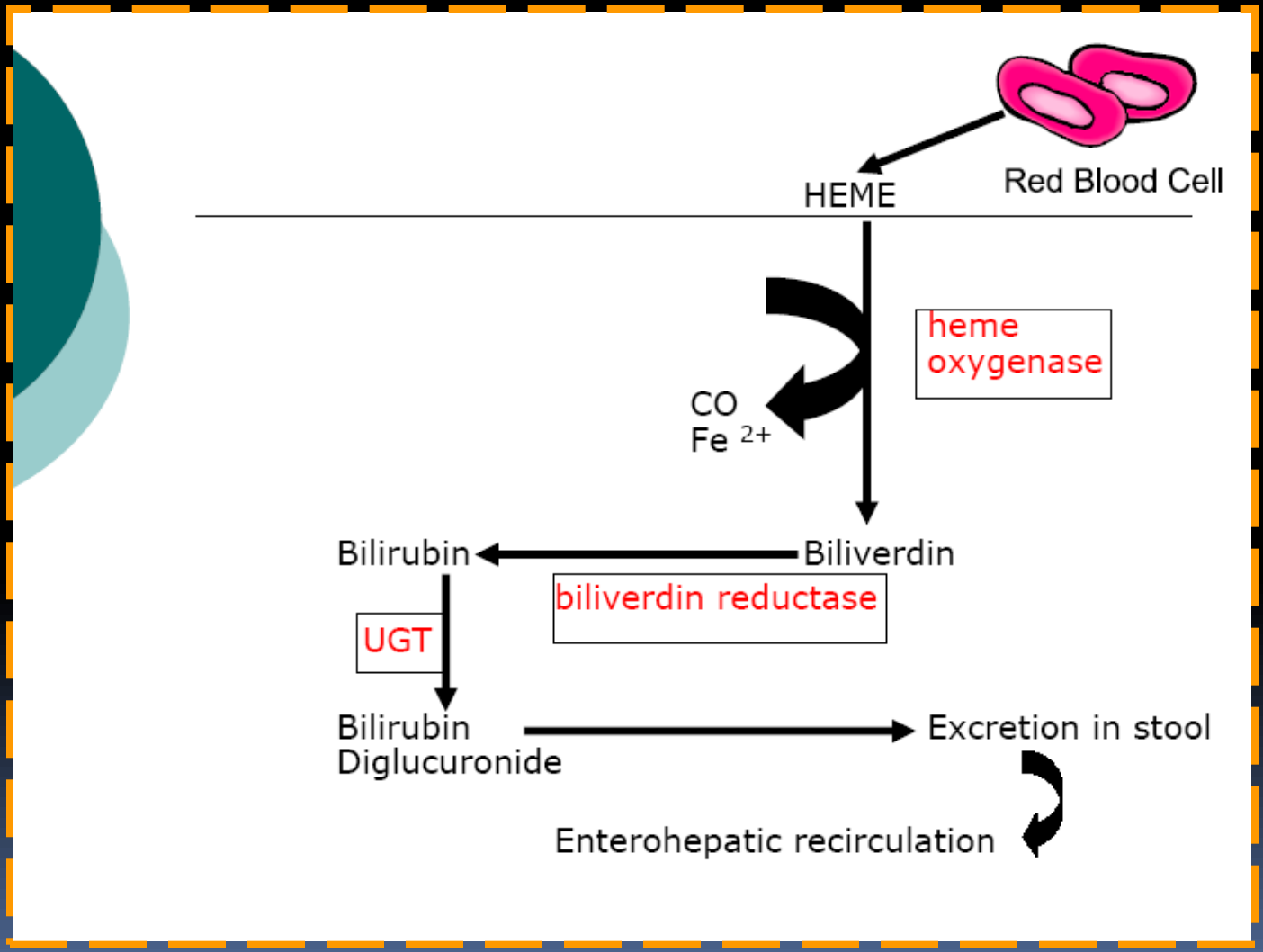
Portal Circulation



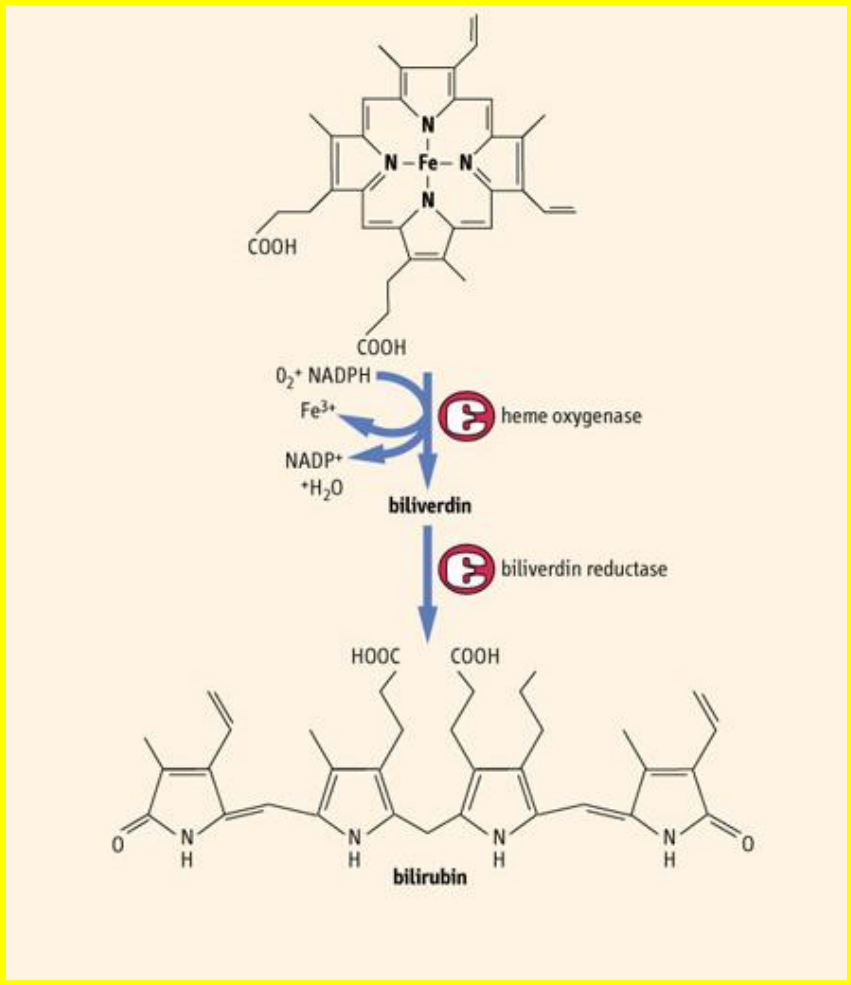
E V Pathway for RBC Scavanging

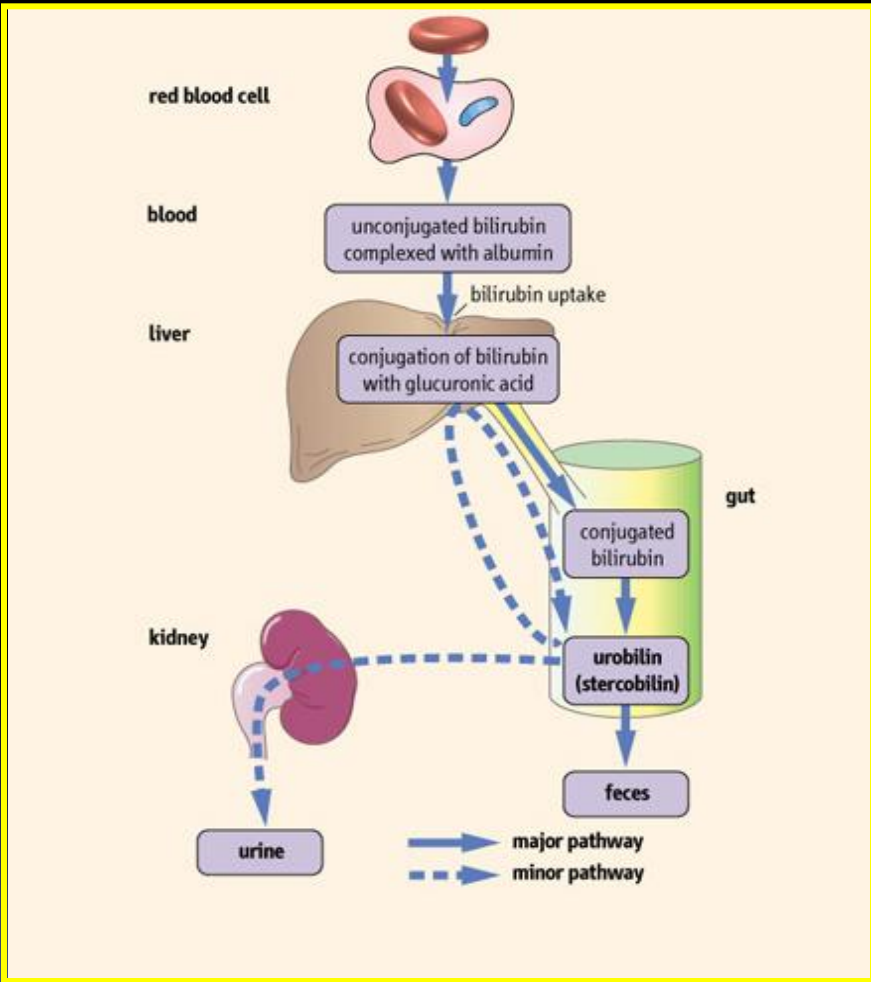


Bilirubin Handling



Bilirubin Metabolism - Summary





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	Nil	+
Vanden Berg Reaction	Indirect	Direct
Temporary Albumin Binding	+++	0
Irreversible Delta Bilirubin	0	++

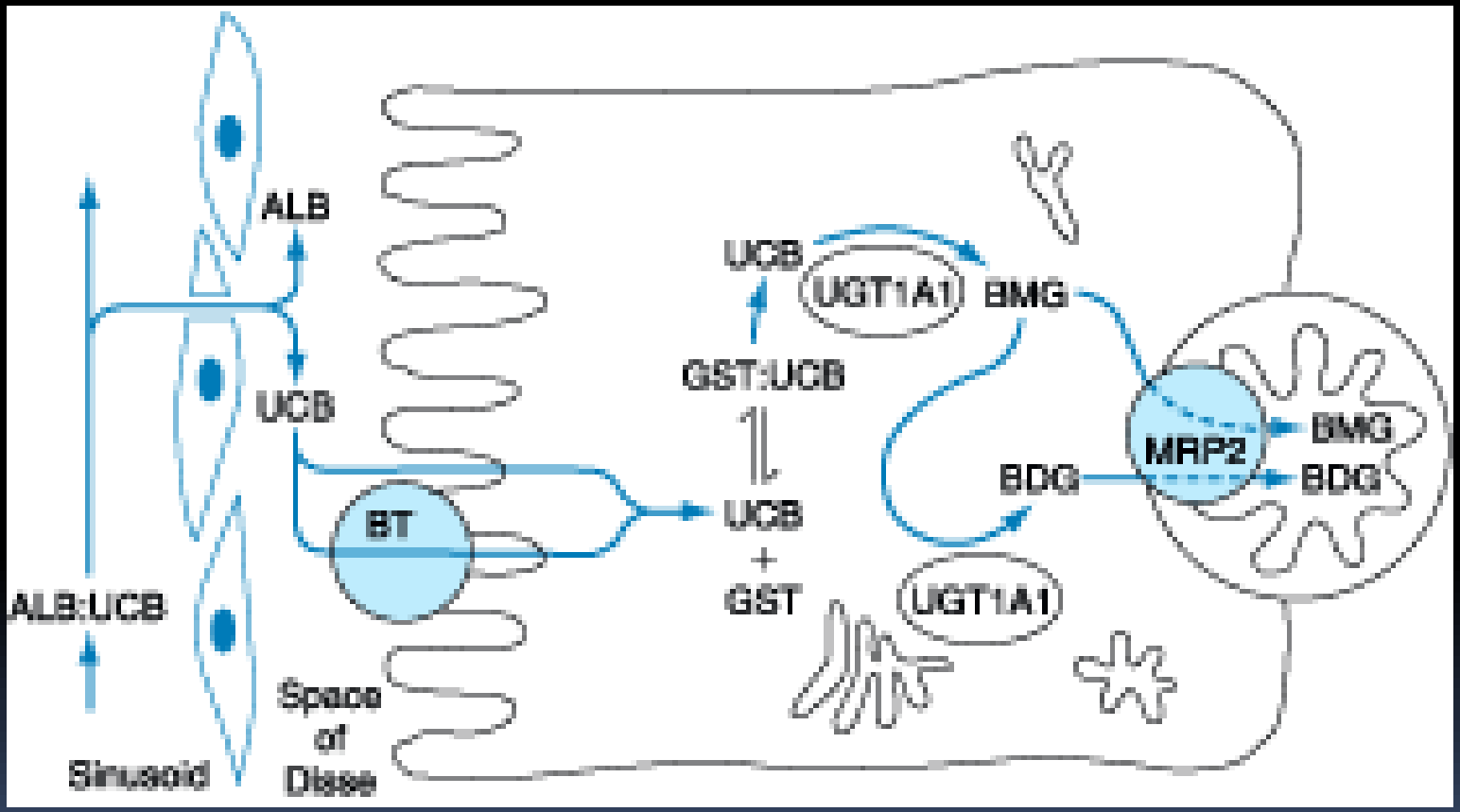
Bilirubin in the Liver Cell

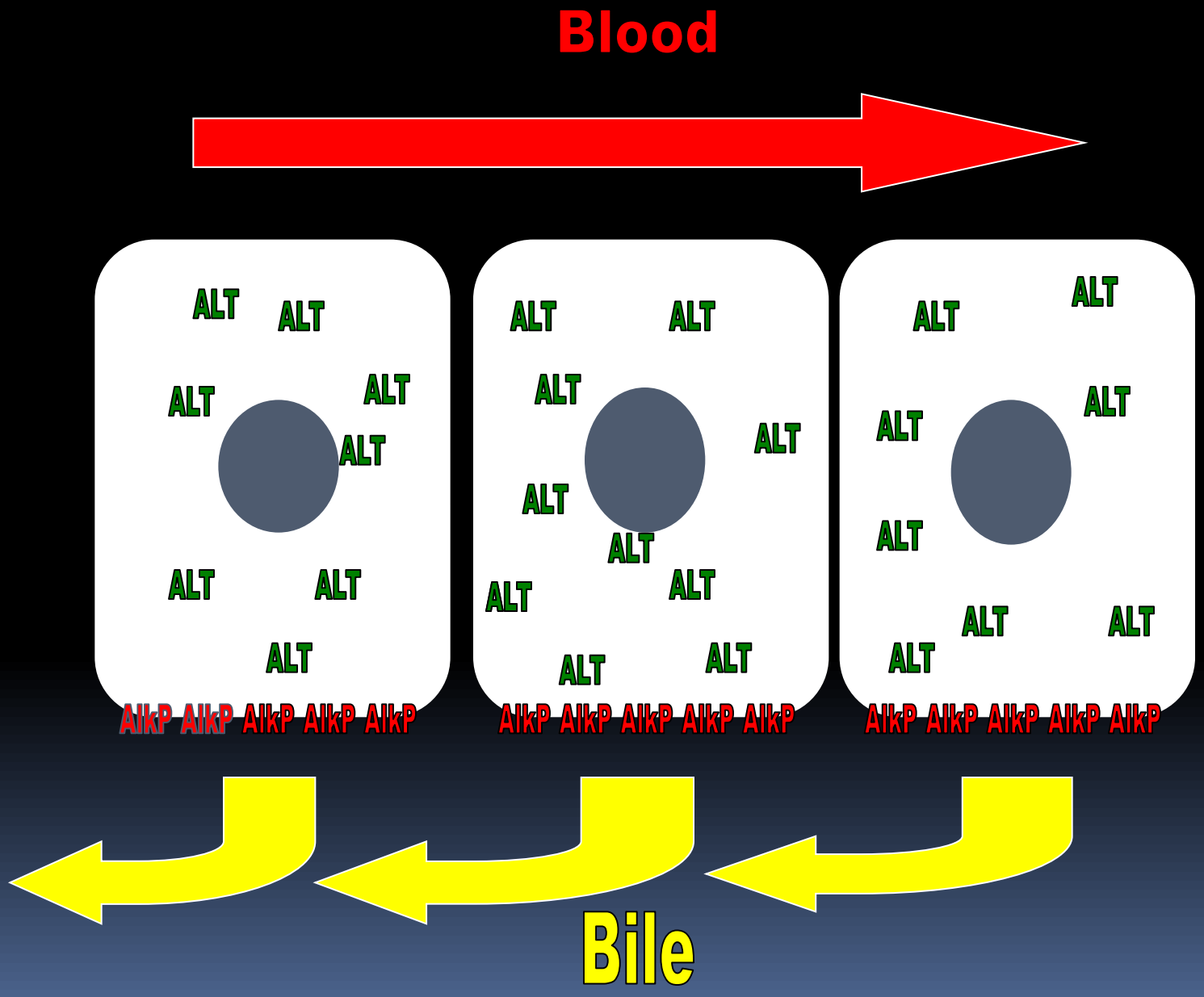
1
- Hepatocyte (HC) uptake of UCB
- Alb+UCB dissociates and UCB enters HC
- By passive diffusion into HC – Ligandin bound
- Insoluble UCB is to be made soluble in HC

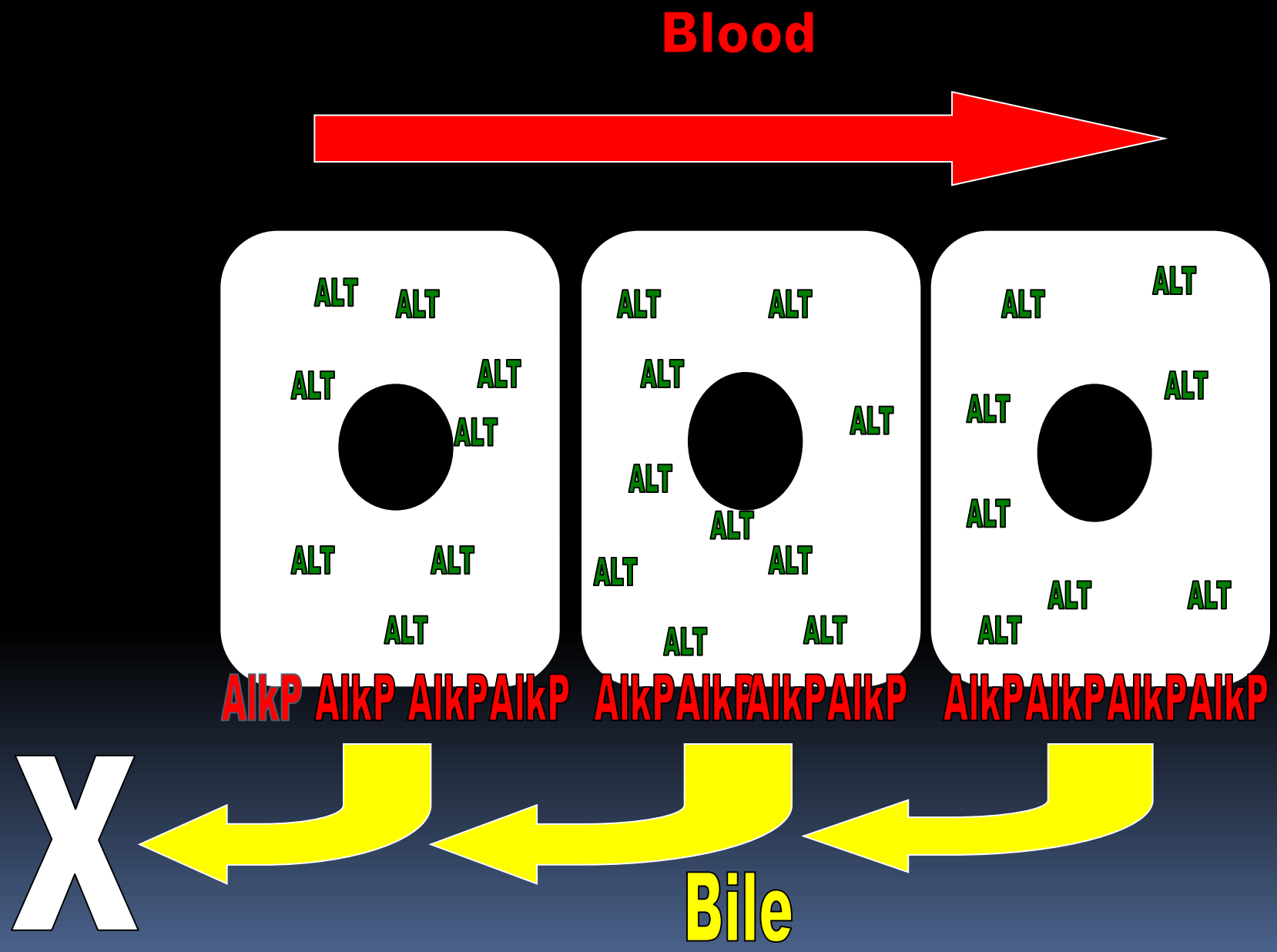
2
- Conjugation in ER of Hepatocyte (HC)
- Formation of mono and di glucuronides BMG, BDG
- UDP Glucuronosyl transferase is energy depend.
- Insoluble UCB made water soluble for excretion

3
- Excretion in into biliary canaliculi
- Rate limiting step in metabolism
- CB 50% is not protein bound – no loss of albumin
- Remaining 50% δ bilirubin – Irreversibly bound

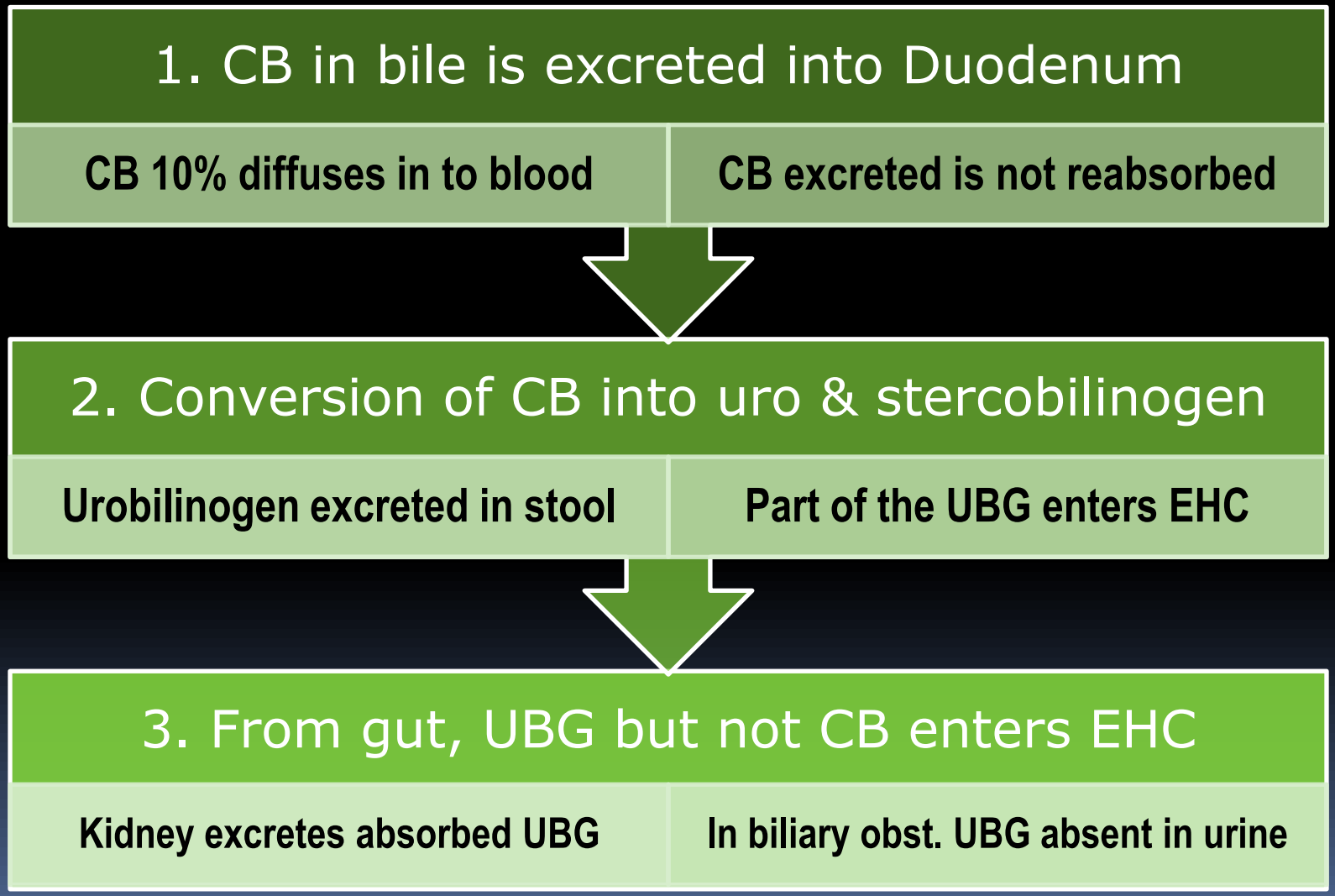
Bilirubin in Liver Cell - Schematic



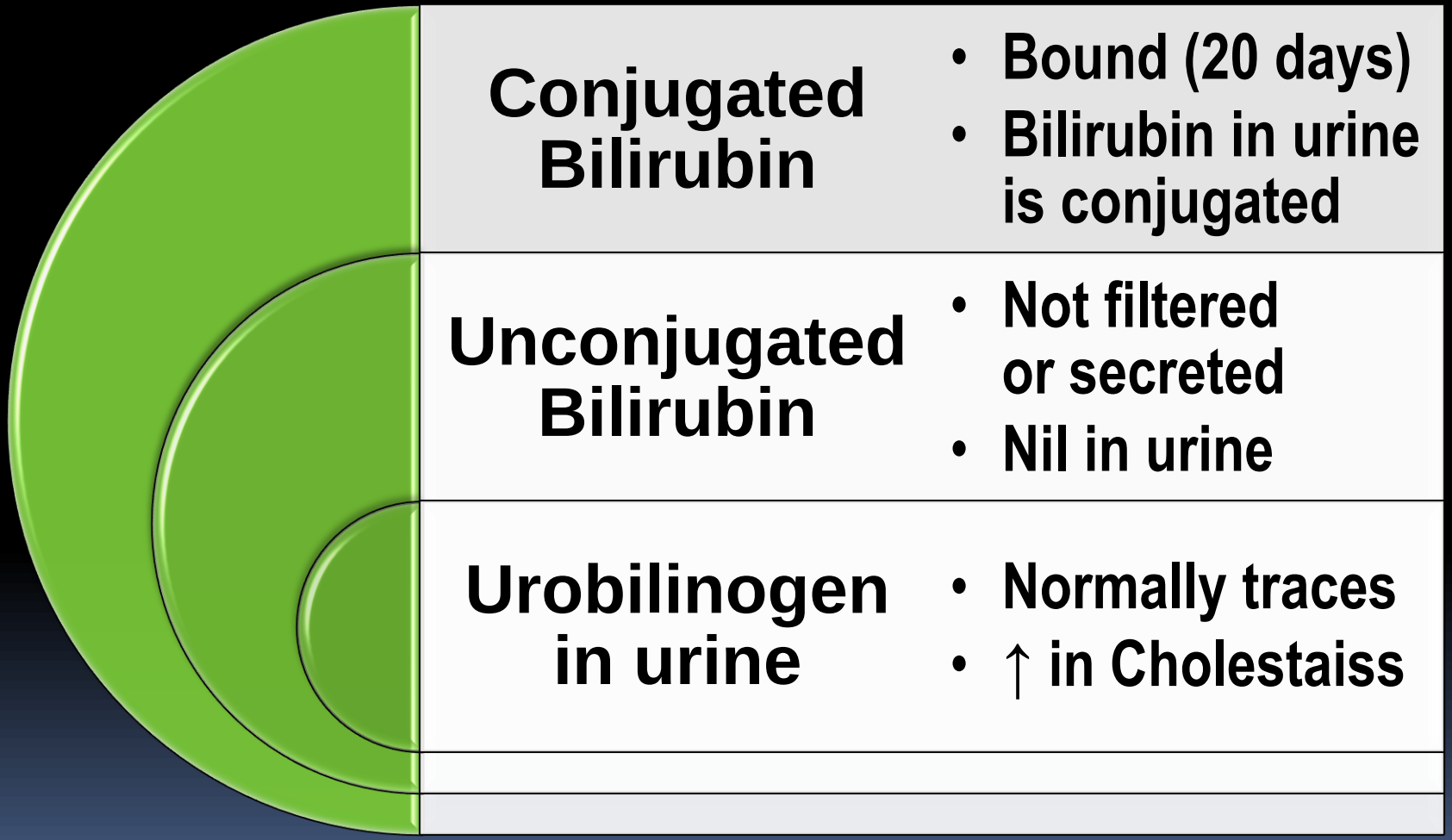

Blood
ALT
AlkP
Bile


Blood
ALT
AlkP
X
Bile

Bilirubin in the Intestine



Bilirubin handling in Kidney



An Approach to Jaundice

- Is it isolated elevation of serum bilirubin ?
- If so, is the↑unconjugated or conjugated fraction?
- Is it accompanied by other liver test abnormalities ?
- Is the disorder hepatocellular or cholestatic?
- If cholestatic, is it intra- or extrahepatic?
- These can be answered with a thoughtful
- History and physical examination
- Interpretation of laboratory tests and
- Radiological tests and procedures.

Bilirubin testing

- Van den Berg Reaction
- SB + SAA $\Rightarrow$ Diazo compound formed
- Diazo is chromogenic – Colourimerty
- Reaction in H_2O medium – Direct – CB
- Reaction in ethnol medium – Indirect
- Indirect includes CB and UCB = Total B
- Time is the essence of the direct test
- Foam test, Ictotest for urine – CB only

Normal values for LFT

Features	Healthy Normal
Total Bilirubin	Less than 1.00 mg
Conjugated Bilirubin	Less than 0.15 mg
AST (SGOT)	Less than 31 i.u/L
ALT (SGPT)	Less than 35 i.u/L
Alkaline phosphatase	Less than 112 i.u /L
GGT and 5' Nucleosidase, CDT	Significantly ↑ in ALD
Urine Bilirubin	Absent
Urine Urobilinogen	In trace quantity
Urine Bile Salts	Absent

Lab Diagnosis of Jaundice – D.D

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

Liver Function Tests (LFT)

Liver function test	Normal Range	Value
Bilirubin Total Conjugated	0.1 to 1.0 mg < 0.2 mg	Dx. Of Jaundice, Severity
Alkaline phosphatase	25-112 iu/L	Dx of Obstructive Jaundice
Aspartate transaminase (AST/SGOT)	5-31 iu/L	Early Dx and follow up
Alanine transaminase (ALT/SGPT)	5-35 iu/L	AST/ALT > 1 in ALD
Albumin	3.5-5.0 g/dL	Assess severity of disease
Prothrombin time (PT)	12-16 s	Assess severity of disease

Utility of Liver Function Tests

LFT	Utility of the test
ALT/SGPT	ALT ↓than AST in alcoholism
Albumin	Assess severity / chronicity
Alk. phosphatase	Cholestasis, hepatic infiltrations
AST/SGOT	Early Dx. of Liver disease, F/up
Bilirubin (Total) /Conjug.	Diagnose jaundice
Gamma-globulin	Dx. F/up Chronic hepatitis & cirrhosis
GGT	Dx alcohol abuse, Dilantin toxicity

Non Hepatic causes of abnormal LFT

Abnormal LFT	Non hepatic causes
Albumin	PLE, Nephrotic syndrome Malnutrition, CHF
AKP	Bone disease, Pregnancy, Malignancy , Adv age
AST	MI, Myositis, I.M.injections
Bilirubin	Hemolysis, Sepsis, Ineffective erythropoiesis
PTT	Antibiotics, Anticoagulant, Steatorrhea, Dietary

Algorithmic approach for Jaundice

How to clinically evaluate the patient ?

What tests will help us in D.D ?

What imaging modalities will be useful ?

How to monitor the progress ?

First Step

Estimate Serum Bilirubin

Is it less than 1 mg % - Normal

Is it more than 1 mg % - Elevated

Second Step : If SB > 1.0 mg

Is it unconjugated bilirubin ?

Haemolytic Jaundice

Is it Conjugated Bilirubin ? (> 20%)

Hepatocellular jaundice

Obstructive jaundice

↑ in Unconjugated Bilirubin

- **Hemolytic Jaundice - Uncommon**
- **1. Hemolytic Disorders + Anemia**
  - **Inherited – Sphero, SS, G6PD, PK**
  - **Acquired – MAHA, PNH**
- **2. Ineffective Erythropoesis –B_{12}, Fe, F**
- **3. Drugs – Rifampicin, Probenecid**
- **4. Inherited –Crigler Najjar, Gilberts**

Third Step : If CSB is increased

- Do - AST and ALT (SGOT and SGPT)
- Elevated AST and ALT
- Hepatocellular jaundice
- AKP, 5N, GGT will be normal
- Do - Alkaline Phosphatase and GGT
- AKP, GGT ↑↑ in Obstructive Jaundice
- AST and ALT will be normal

Fourth Step : Hepatocellular

Hepatocellular – Features and D.D

Conjugated SB is increased

AST and ALT are increased

AKP, 5NS, GGT are normal

Hepititis – A,B,C,D,E, CMV,EBV

Toxic Hepatitis – Drugs, Alcohol

Malignancy – Primary Ca

Cirrhosis – ALD, NAFLD

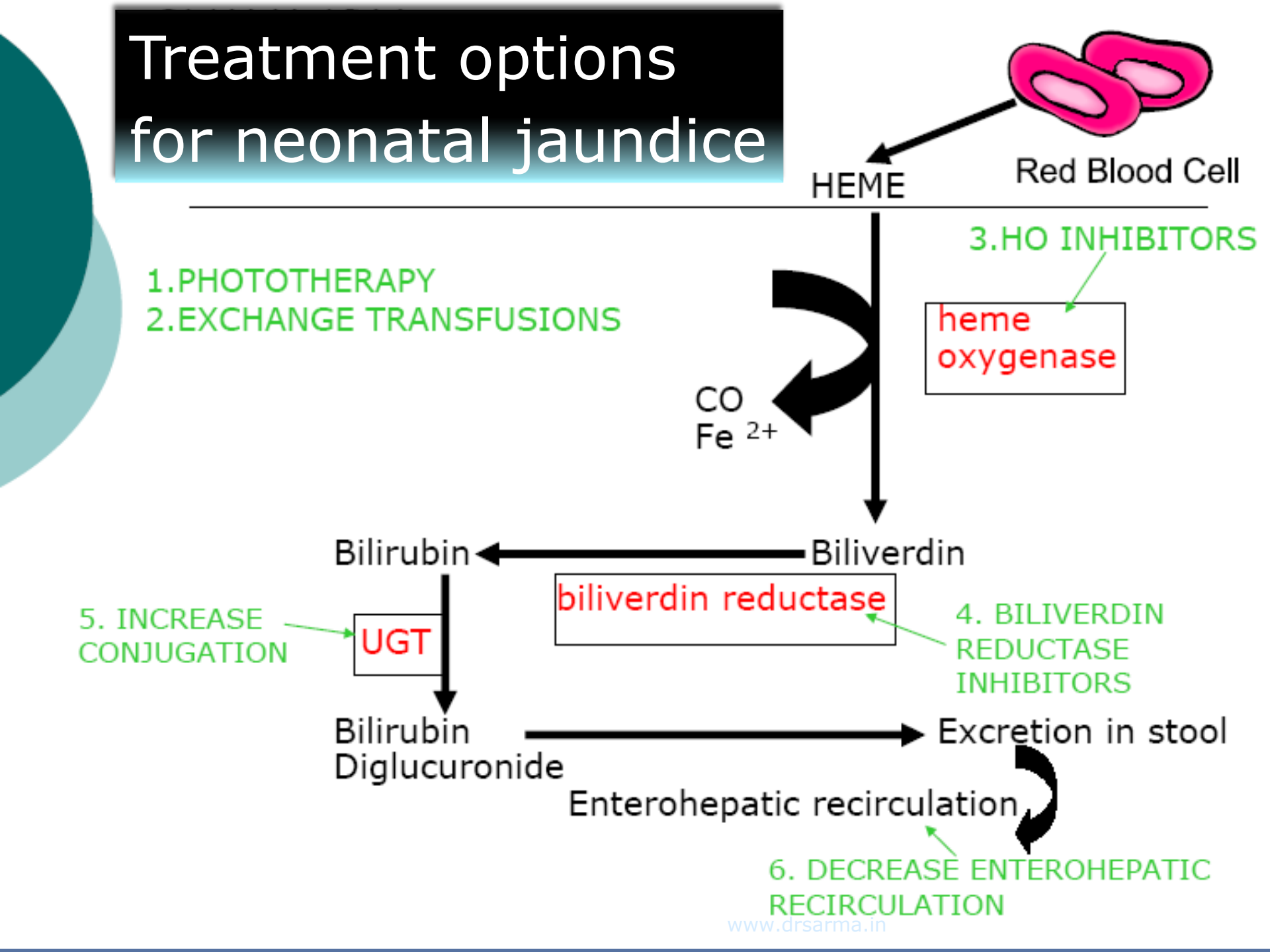
What imaging we need

- Ultrasonography – 98% Sp, 90% Sen.
- For GB stones USG better than CT
- For duct stones –only 40% seen in USG
- PTC – Extrahepatic obstr. – drainage
- ERCP – Distal biliary obstruction Dx.Rx.
- MRCP – Most useful for duct stones

Neonatal Jaundice

- Neonatal jaundice is common
- 50% healthy term infants
- Re-emergence of kernicterus
- In utero bilirubin is handled by placenta and mother's liver
- After birth, neonate to has cope with increase in bilirubin production and the immature liver cannot handle for a few days

Treatment options for neonatal jaundice

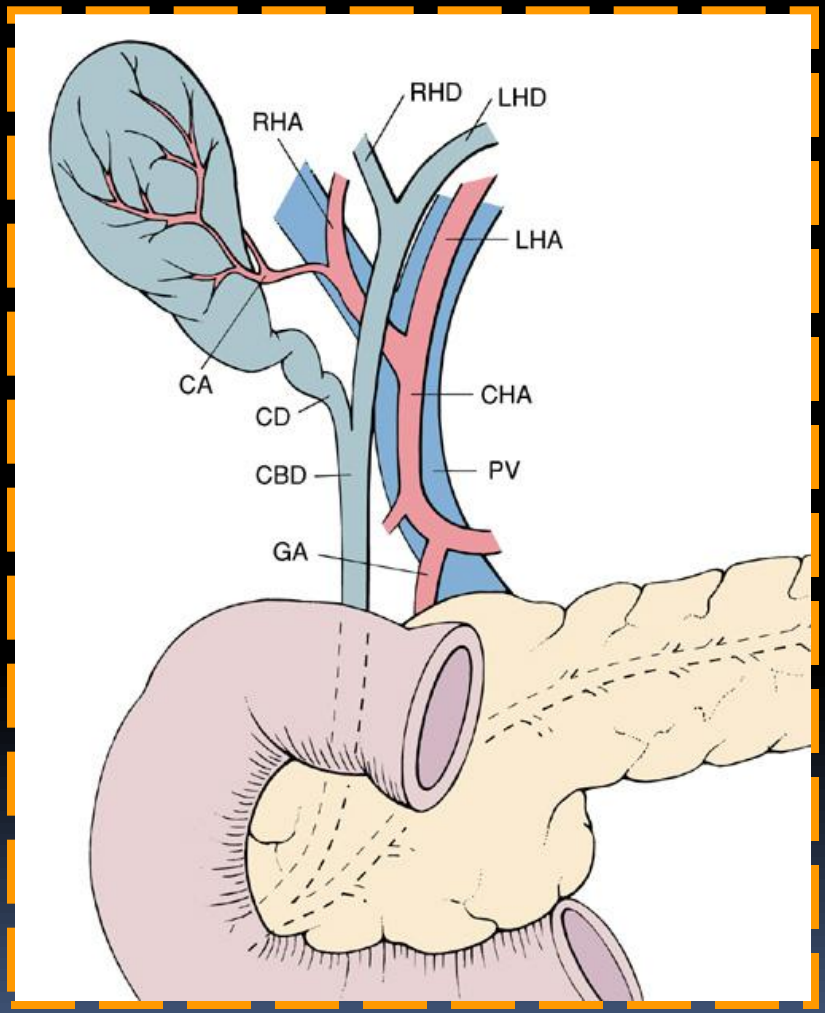


Basis of photo therapy ?

- UCB is not water soluble in its form
- Blue light confrontational change in UBG
- Its Photo Isomers are water soluble
- Blue light converts the UCG into its photo isomers
- The soluble photo isomers pass through the Glomerular filter and get excreted
- Thus conjugation in liver is by passed.

Post hepatic Obstructive Jaundice

- Painful v/s painless
- Obstruction can be
  - Luminal (stone)
  - Stricture (benign v/s cholangiocarcinoma)
  - Extra luminal pancreatic cancer, Sec. lymph nodes
- Investigate & treat with
  - Radiology (US, CT, MRCP)
  - ERCP / PTC



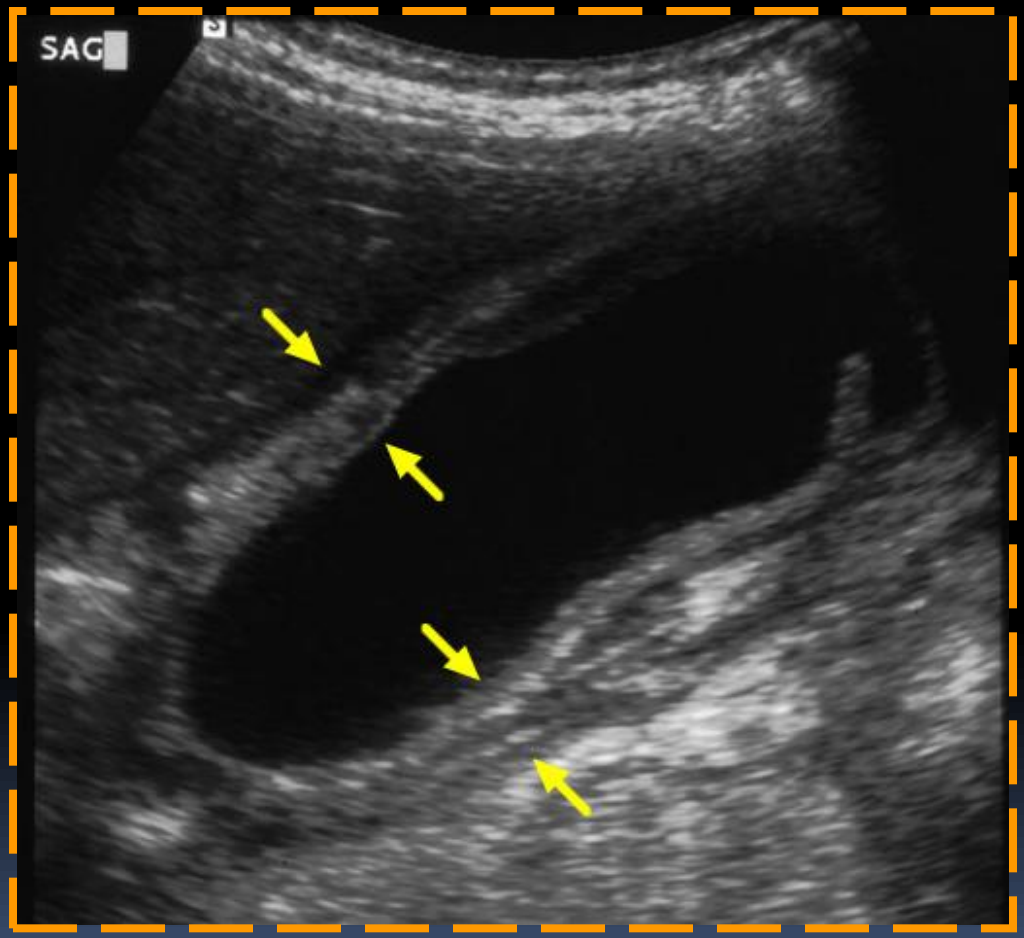
Chronic Liver Disease (CLD)

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

Hepato toxic drugs

Conventional Drugs	Natural Substances
Acetaminophen, Alpha-methyldopa	Vitamins, Hypervitaminosis A
Amiodarone, Dantrolene, Diclofenac	Niacin, Cocaine, Mushrooms
Disulfiram, Fluconazole, Glipizide	Aflatoxins, Herbal remedies
Glyburide, Isoniazid, Ketaconazole	Senecio, crotaliaria,
Labetalol, Lovastatin, Nitrofurantoin	Pennyroyal oil, Chapparral,
Thiouracil, Troglitazone, Trazadone	Germander, Senna, Herbal mix.

Acute Cholecystitis



GB wall is thickened and striated.
Courtesy of Udo Schmiedl, M.D.

Causes of Cholestatic Jaundice

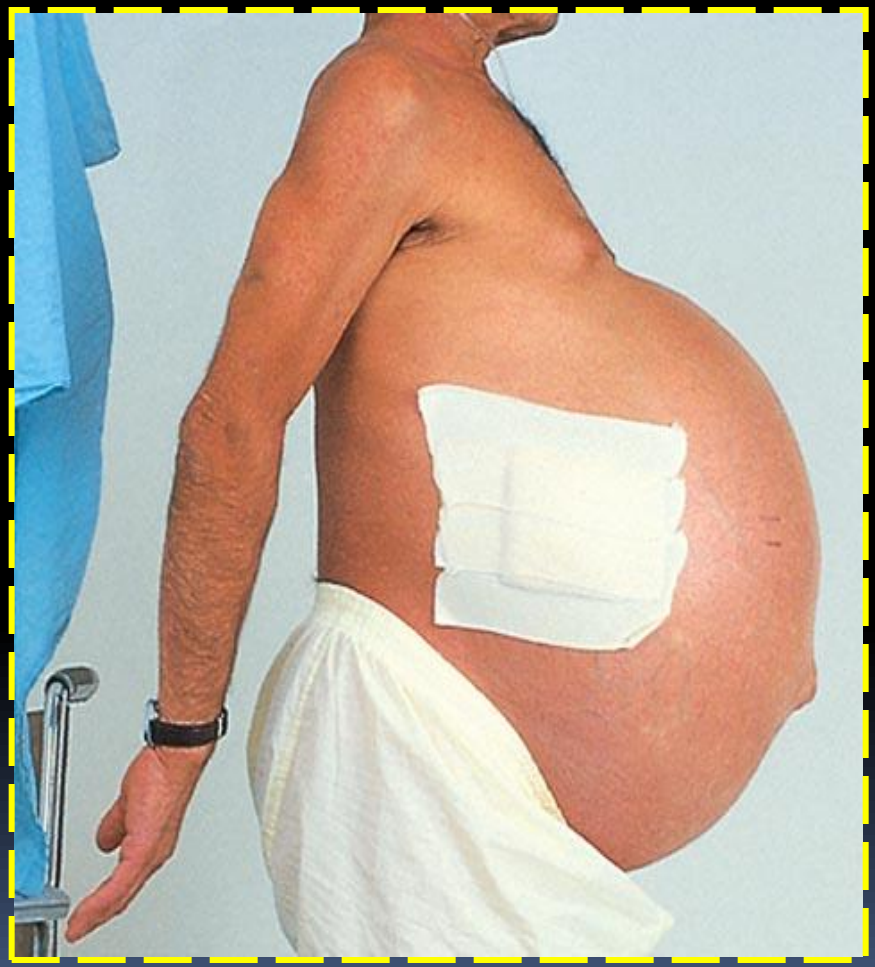
Intrahepatic	Extrahepatic
Acute liver injury, Viral hepatitis	Choledocholithiasis
Alcohol hepatitis, Drugs	Stone obstructing CBD, CD
Chronic liver injury, PBC, PSC	Biliary strictures
Autoimmune cholangiopathy	Cholangiocarcinoma
Drugs, Total parenteral nutrition	Pancreatic carcinoma
Systemic infection, Postoperative	Pancreatitis, Periampullary Ca
Benign causes, Amyloid, lymphoma	PSC, Biliary atresia, duct cysts

Drugs causing Cholestasis

- Anabolic steroids (testosterone, norethandrolone)
- Antithyroid agents (methimazole)
- Azathioprine (Immunosuppressive drug)
- Chlorpromazine HCl (Largactil)
- Clofibrate, Erythromycin estolate
- Oral contraceptives (containing estrogens)
- Oral hypoglycemics (especially chlorpropamide)

Complications of CLD

- Portal hypertension
  - Varices
  - Ascites
  - Hypersplenism
- Synthetic dysfunction
  - Coagulopathy
  - Encephalopathy
- Immunodeficiency
- Malnutrition
- Hepato-cellular carcinoma



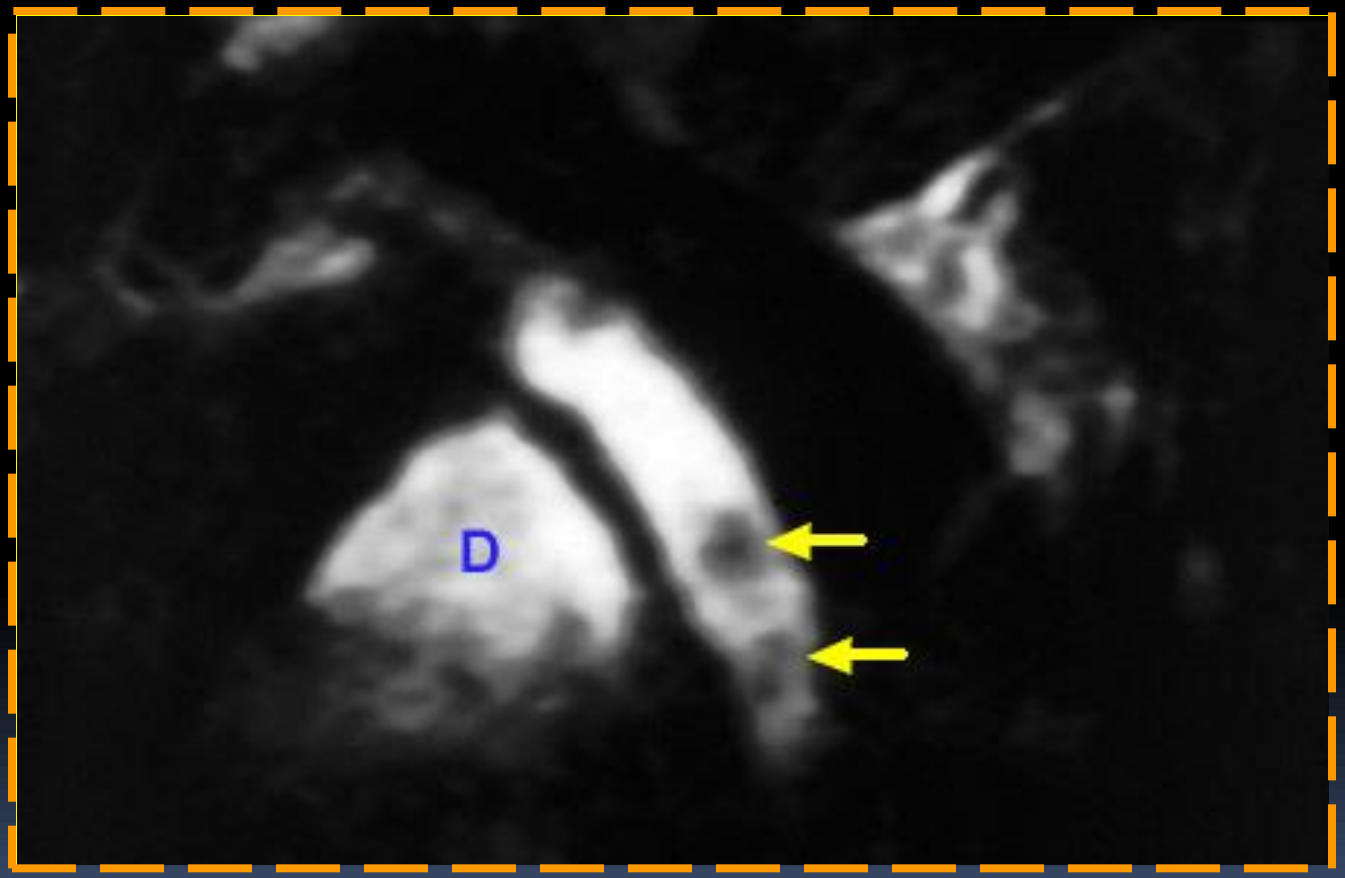
Manifestations of Wilson's Disease

Hepatic	Psychiatric
CAH, Cirrhosis, Fulminant hepatitis	Behavioral, organic dementia,
Early Neurological	Psychoneurosis, manic-depressive
Incoordination, dysarthria,	Schizophrenic psychosis
Resting and intention tremors	Ophthalmic
Excessive salivation, dysphagia	KF ring, sunflower cataract
Mask-like facies, ataxia	Hematologic and others
Late Neurological	IV hemolysis, Hypersplenism
Dystonia, spasticity, Rigidity, TCS	Distal RTA, Osteomalacia, OS

KF Ring of Periphery of Iris

Courtesy of Robert L. Carithers, Jr., M.D.

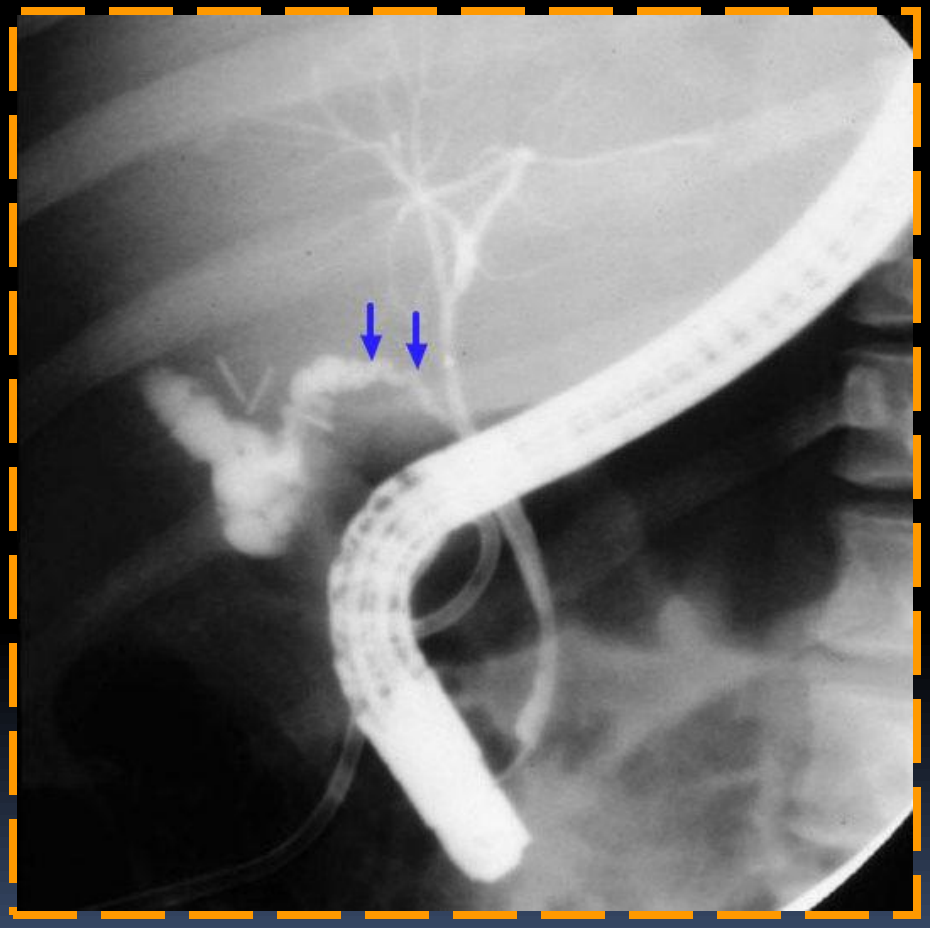
Magnetic Resonance Cholangio-Pancreatography (MRCP)



Two stones in the common bile duct

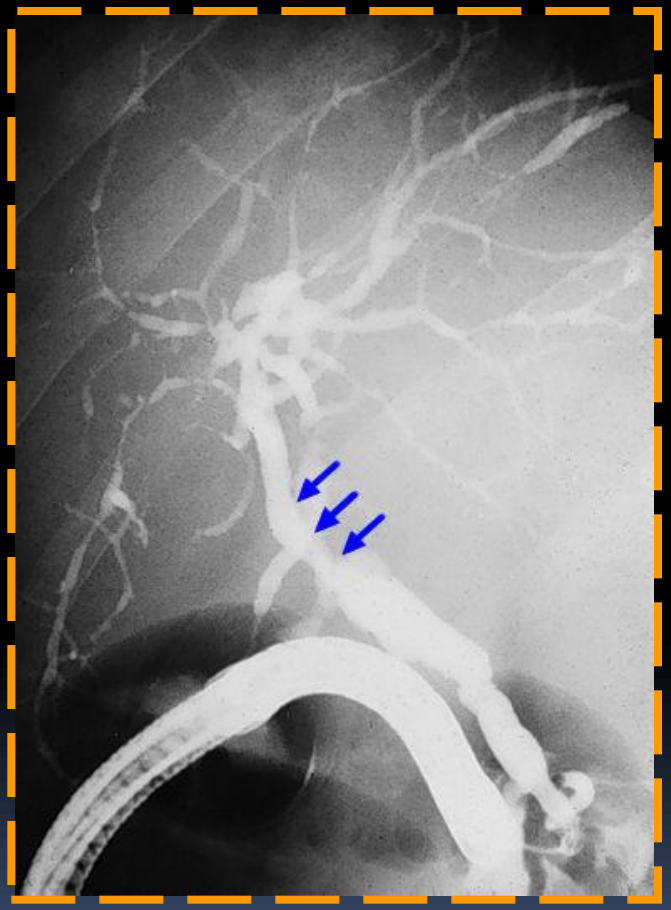
Courtesy of Udo Schmiedl, M.D.

Retrograde Cholangiogram - ERCP



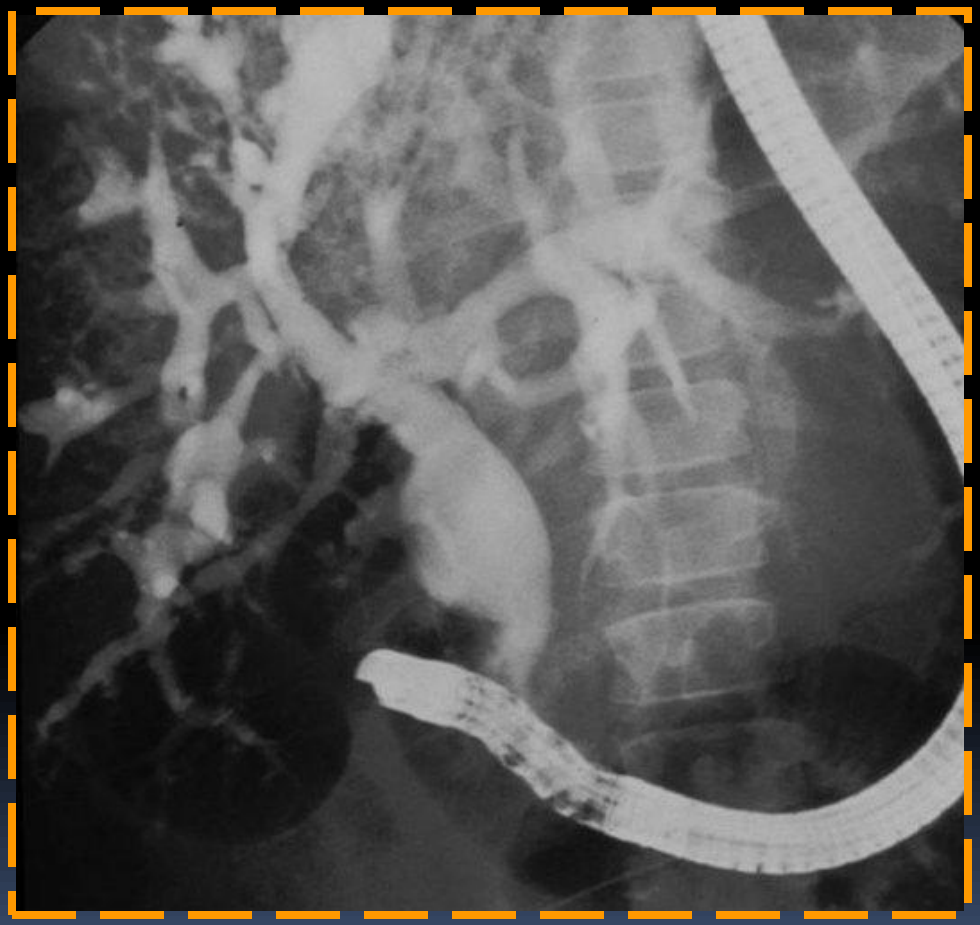
Bile leak from the cystic duct after cholecystectomy
Courtesy of Michael Kimmey, M.D.

Retrograde Cholangiogram - ERCP



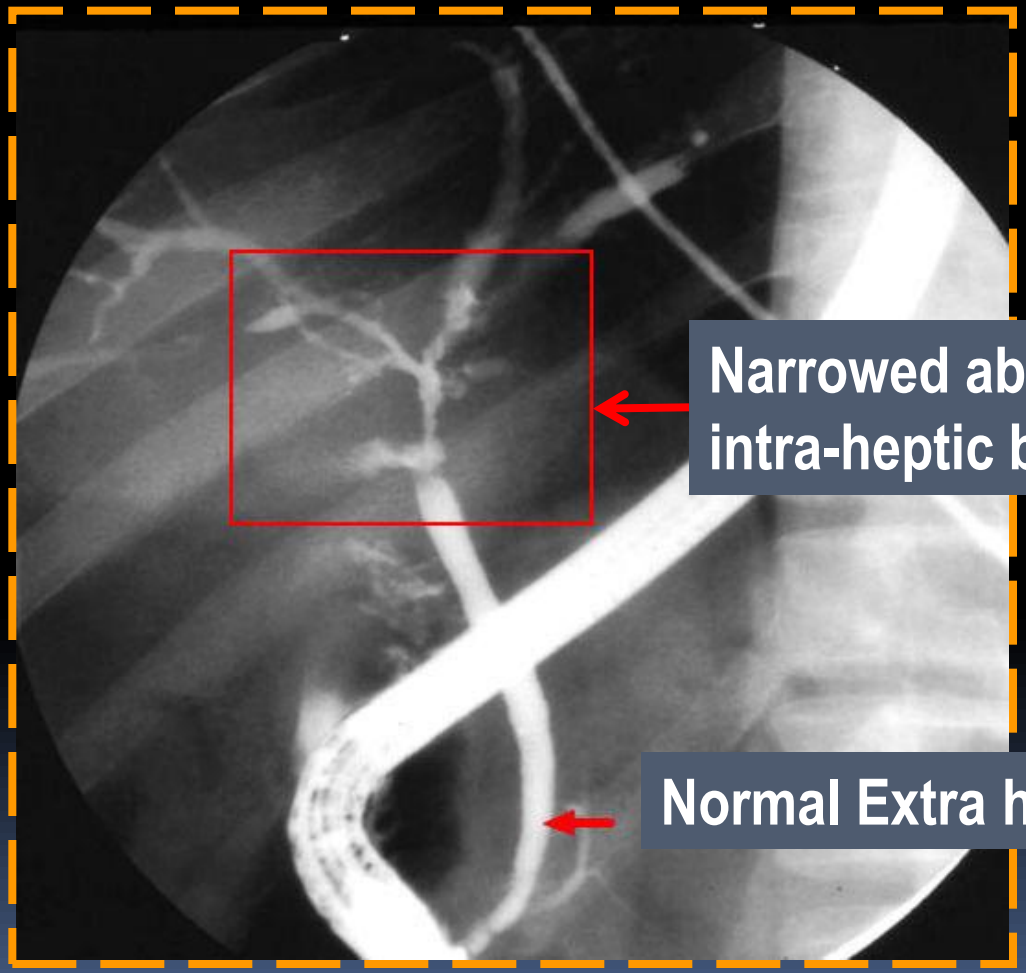
Primary sclerosing cholangitis (PSC) with stricture due to cholangiocarcinoma. Courtesy of Robert L. Carithers, Jr., M.D.

Retrograde Cholangiogram - ERCP

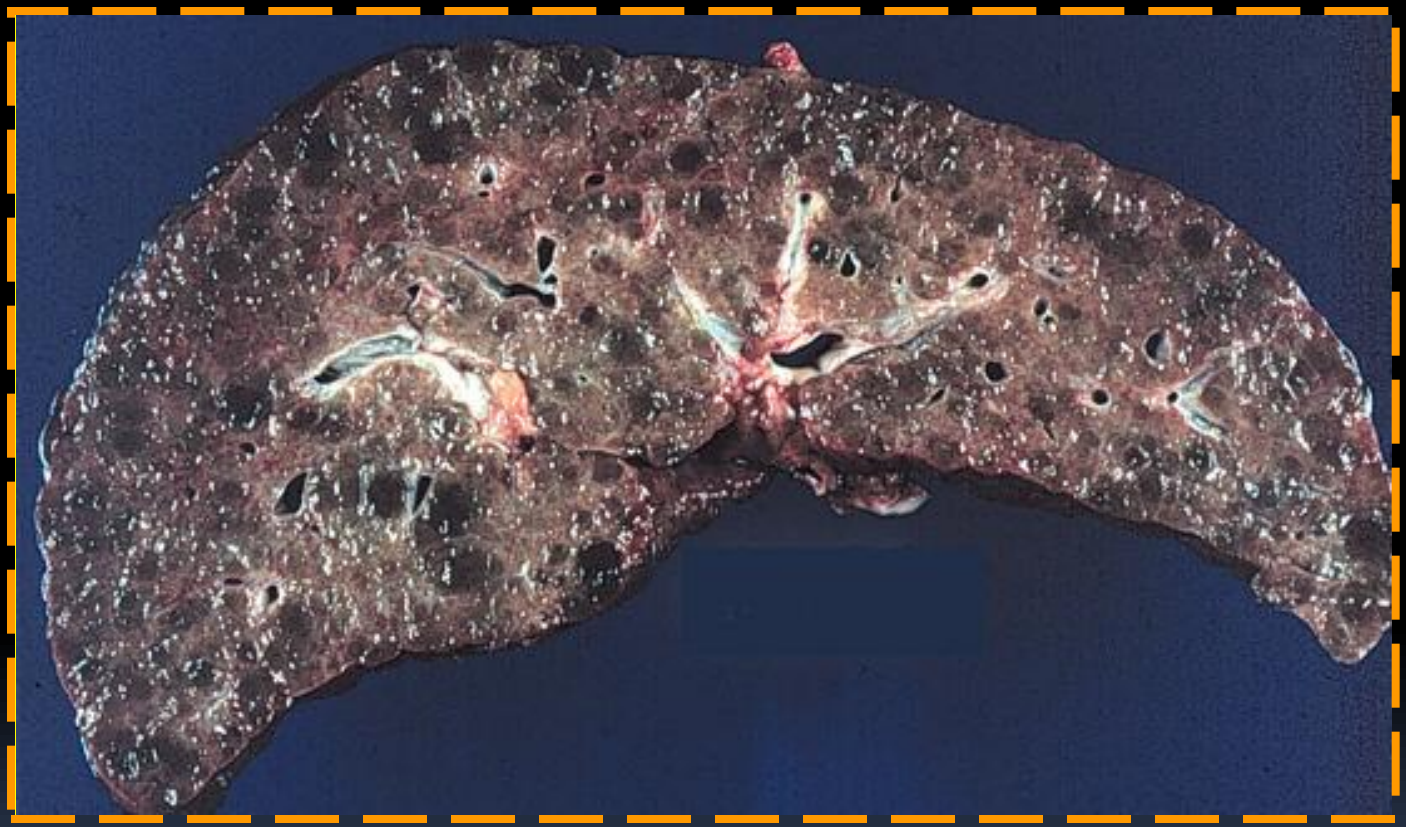


Irregular dilation of intrahepatic and extrahepatic ducts.
Courtesy of Charles Rohrmann, M.D.

Primary Sclerosing Cholangitis

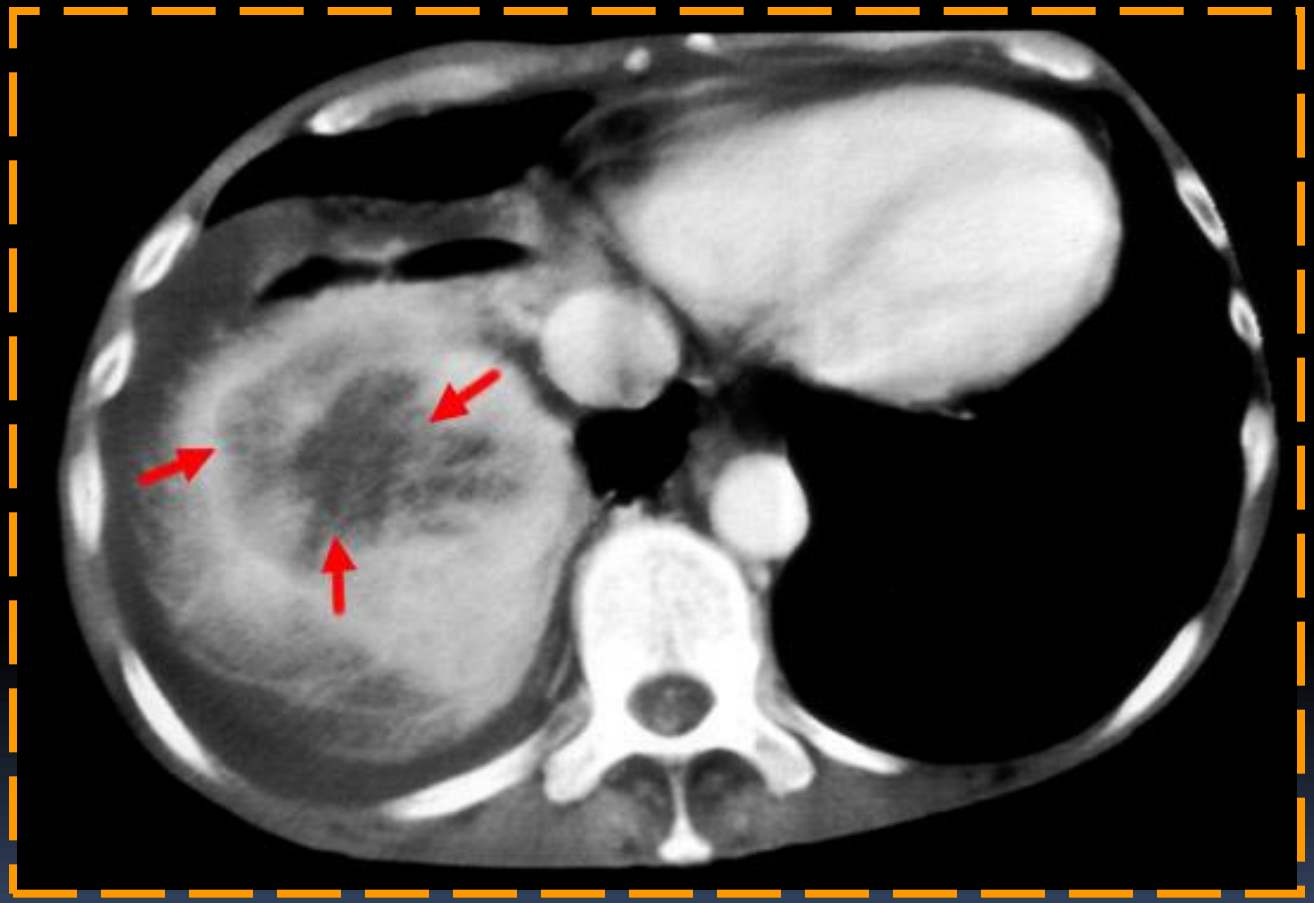


Alcoholic Cirrhosis of Liver



The cut surface of a autopsy liver of a patient with alcoholic cirrhosis - multiple small nodules and diffuse scarring.
Courtesy of Robert L. Carithers, Jr., M.D.

CT Abdomen



A large mass with a hepatoma.
Courtesy of Udo Schmiedl, M.D.

Causes of Jaundice - Frequency

Type	Cause	Clinical example	Frequency
Prehepatic	hemolysis	autoimmune abnormal hemoglobin	uncommon depends on region
intrahepatic	infection	hepatitis A, B, C	common/very common
	chemical/drug	acetaminophen alcohol	common common
	genetic errors: bilirubin metabolism	Gilbert's syndrome Crigler–Najjar syndrome Dubin–Johnson syndrome Rotor's syndrome	1 in 20 very rare very rare very rare
	genetic errors: specific proteins	Wilson's disease α_1 antitrypsin	1 in 200 000 1 in 1000 with genotype
	autoimmune	chronic active hepatitis	uncommon/ rare
	neonatal	physiologic	very common
Posthepatic	intrahepatic bile ducts	drugs primary bilary cirrhosis cholangitis	common uncommon common
	extrahepatic bile ducts	gall stones pancreatic tumor cholangiocarcinoma	very common uncommon rare

When to refer to GE Specialist

- Unexplained jaundice
- Suspected biliary obstruction
- Acute hepatitis - severe or fulminant
- Unexplained abnormal LFTs persisting (for 6 months or greater)
- Unexplained cholestatic liver disease
- Cirrhosis (in non-alcoholic) for consideration of liver transplant
- Suspected hereditary hemochromatosis
- Suspected Wilson's disease
- Suspected autoimmune hepatitis
- Chronic hepatitis C for consideration of antiviral therapy

Conclusions

- Jaundice and liver injury are very common
- Careful history and physical examination are a must
- Acute hepatocellular diseases with jaundice
- Chronic hepatocellular jaundice (CLD)
- Cholestasis and obstructive jaundice
- LFT – SB, CB, – AST. ALT, AKP, 5'NS, GGT, Alb, PT
- Ultasonography, MRCP, ERCP, PTC
- Laparoscopy and liver biopsy
- Treatment as per the cause