بسم الله الرحمن الرحيم

Jaundice

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JAUNDICE

- **Definition:**

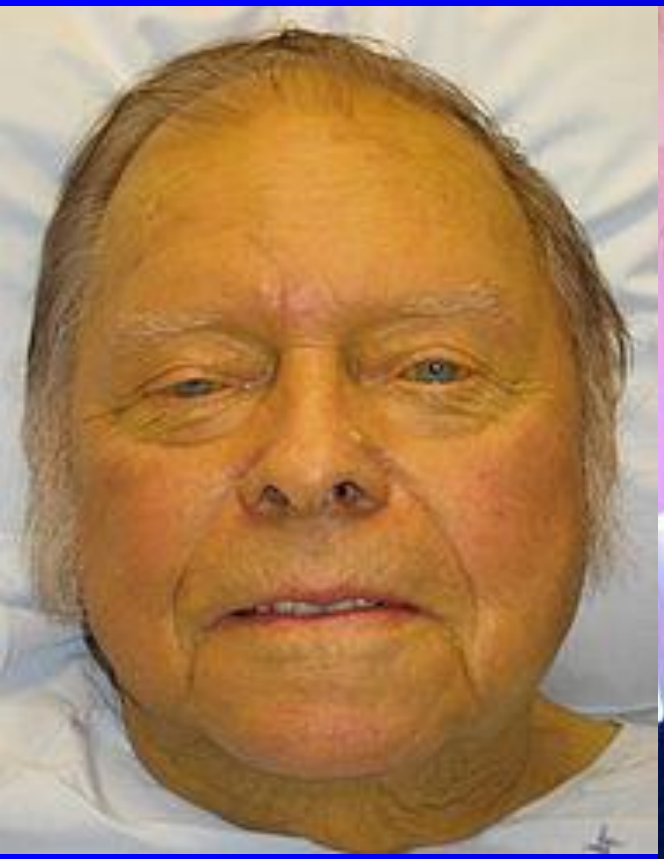
  Yellow discoloration of the skin and mucous membrane due to hyperbilirubinaemia.

Jaundice is best observed in the sclera since elastin in the sclera binds bilirubin.

*Normal bilirubin level<1 mg/dl.

*Jaundice >2.5 mg/dl.

- **Pseudojaundice**: in hypercarrotinemia, the skin may turn yellowish due to the presence of beta-carotene; this is not related to bilirubin or bile



Sources of Bilirubin

- * 85% from the breakdown of old RBCs-the normal RBC survives 120 days, so every day 1/120 of blood is turning over.
- * 15% from other heme-containign enzymes, cytochromes, myoglo-bin, and immature RBCs in the bone marrow.

Bilirubin metabolism

Bilirubin is produced mainly from the breakdown of old RBCs in the reticuloendothelial system.

RBCs → Haemoglobin → Haem + globin

Haem

↓ Heme oxygenase

Biliverdin + Iron

↓ Biliverdin reductase

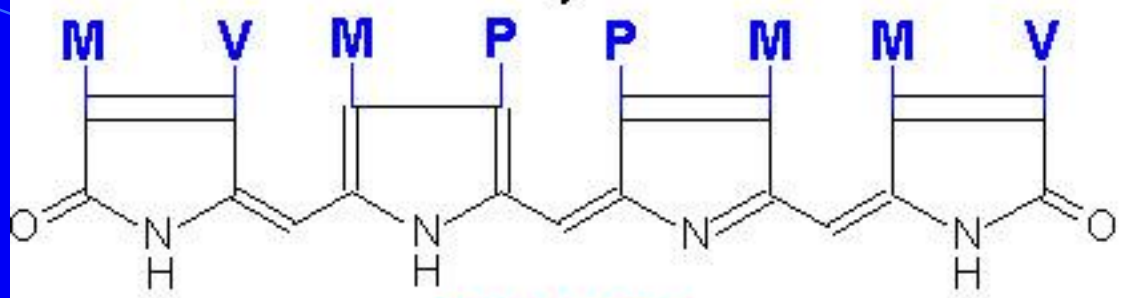
Indirect bilirubin

Heme

heme oxygenase

$NADPH + O_2$

$CO + Fe^{3+} + NADP^+$

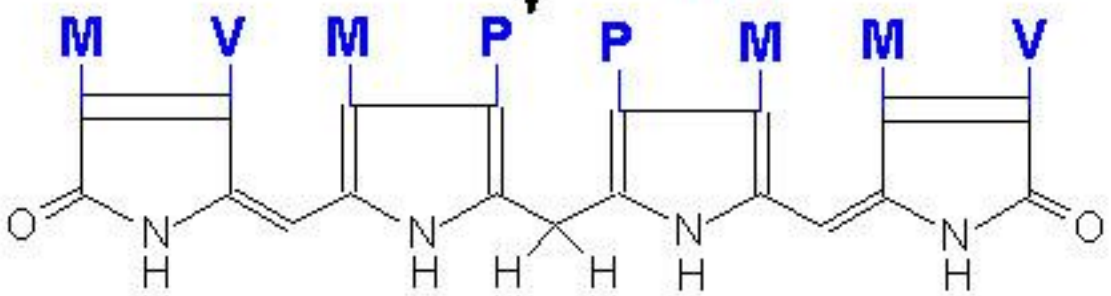


Biliverdin

biliverdin reductase

NADPH

$NADP^+$



Bilirubin

Indirect bilirubin is unconjugated (water insoluble and cann't pass in the urine) is transported to the liver attached to albumin. It is taken by the liver and conjugated with glucuronic acid to form conjugated or direct bilirubin by glucuronyl transferase and then excreted by the liver into bile. The direct bilirubin is water soluble and can pass in the urine

After excretion from the liver it pass in the biliary tract till reaching the intestine where bacteria deconjugate and reduce it to stercobilinogen (urobilinogens) which pass in the stool giving it the normal yellow colour.

Part of stercobilinogen is absorbed from the terminal ileum passes to the liver via the enterohepatic circulation and re-excreted into the bile and part reach the general circulation and is excreted by the kidney as urobilinogen.

Erythrocytes

Macrophages of the Spleen & Bone Marrow

heme

bilirubin

bilirubin(conjugated)

Liver

Small Intestine

bile

Gall bladder

Large Intestine

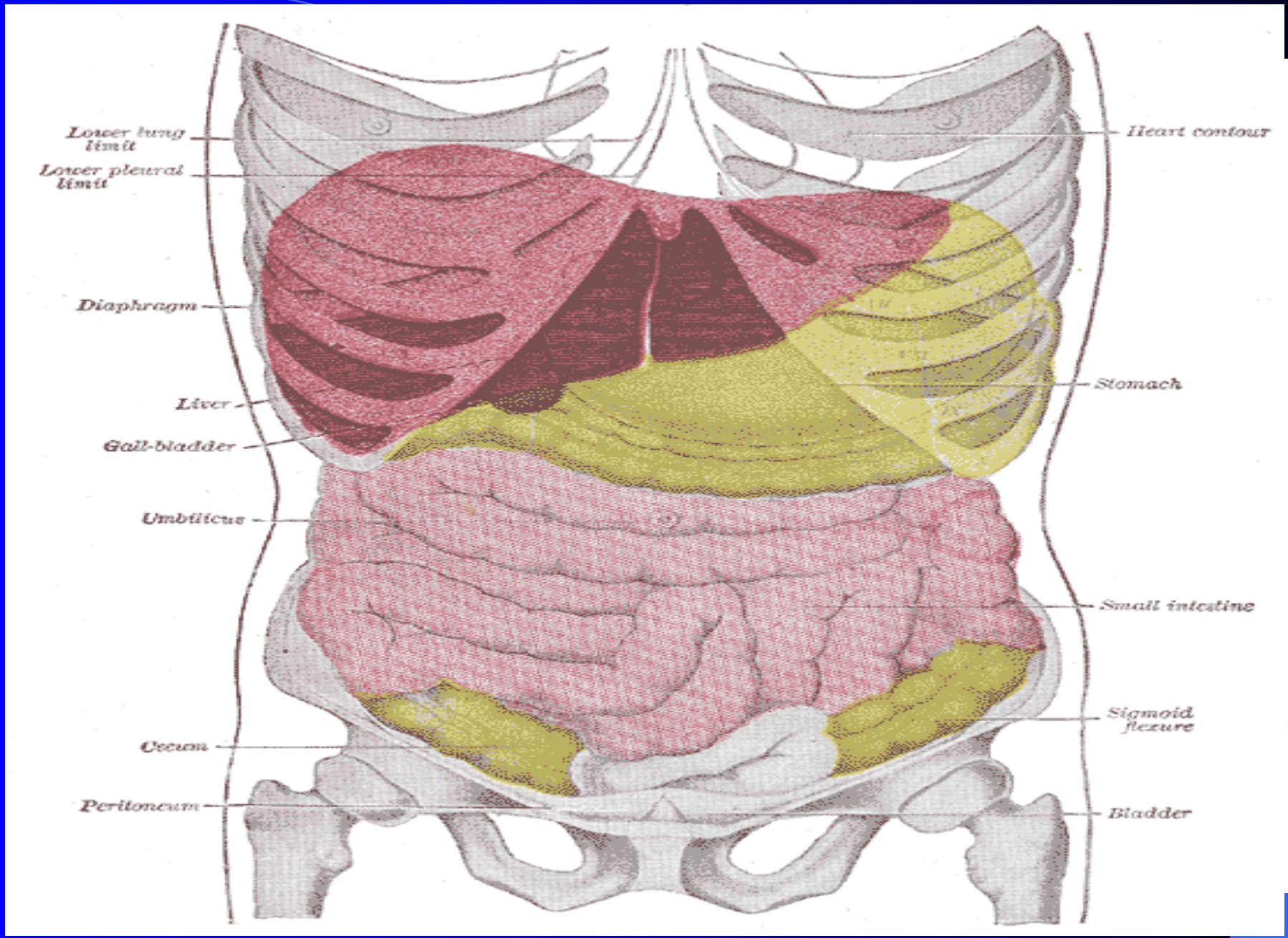
Urobilinogen

Stercobilin

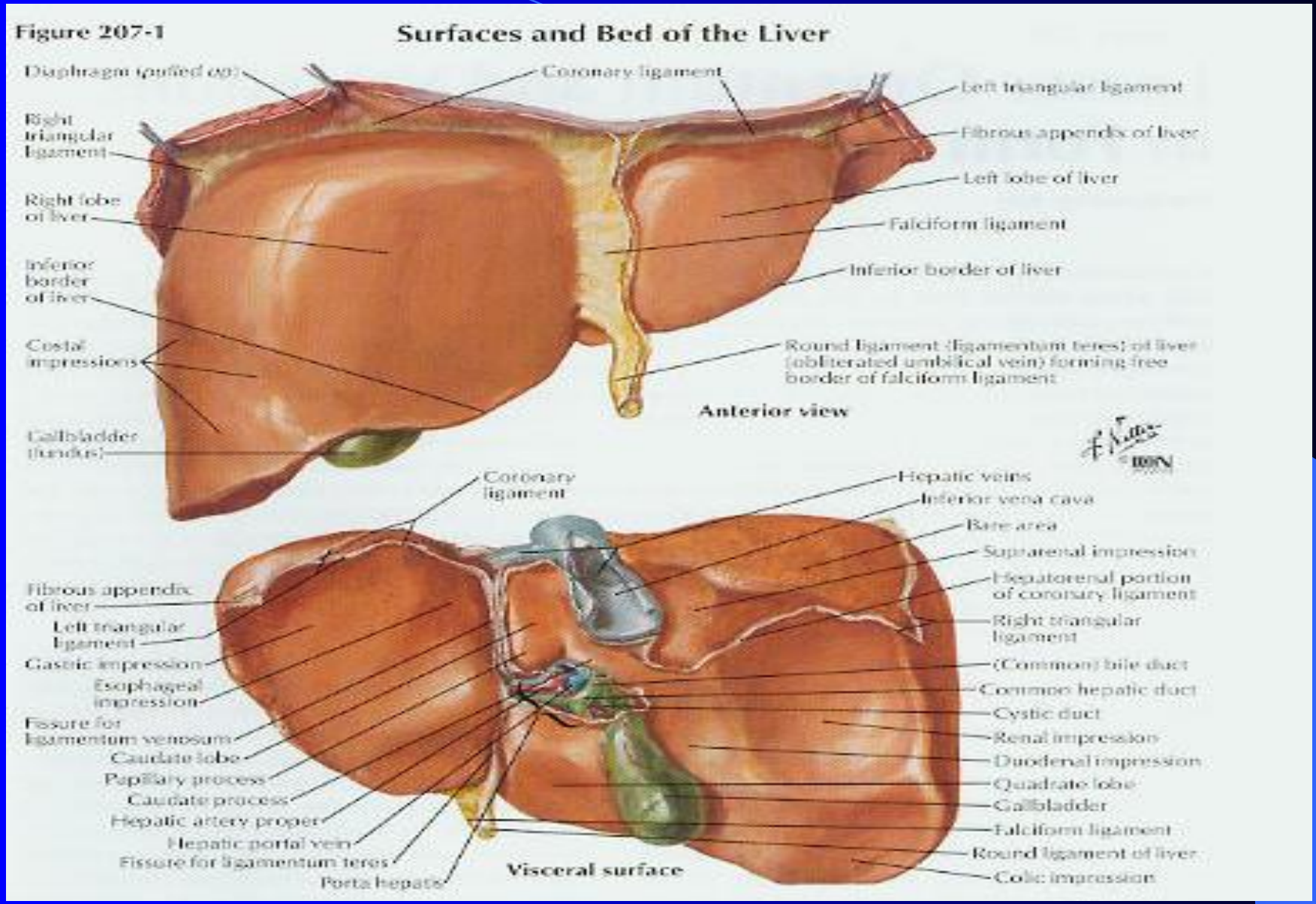
Urobilin

Comparison between conjugated and unconjugated bilirubin

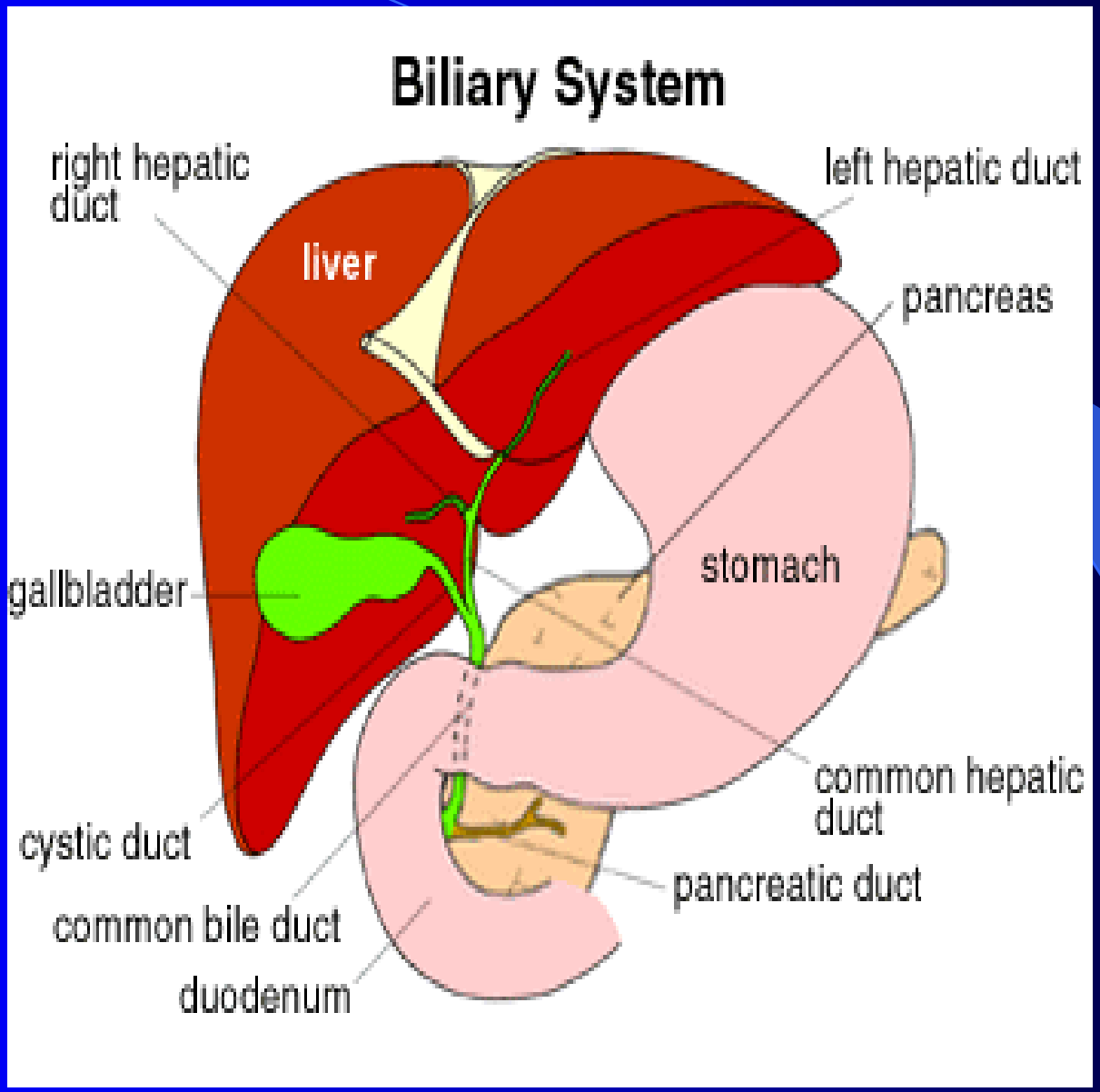
Conjugated bilirubin, choli bilirubin, Direct	Unconjugated bilirubin, Haembilirubin, Indirect
water-soluble	Lipid-soluble
Normally in bile	Normally in plasma
filtered by kidney	Not filtered by kidney

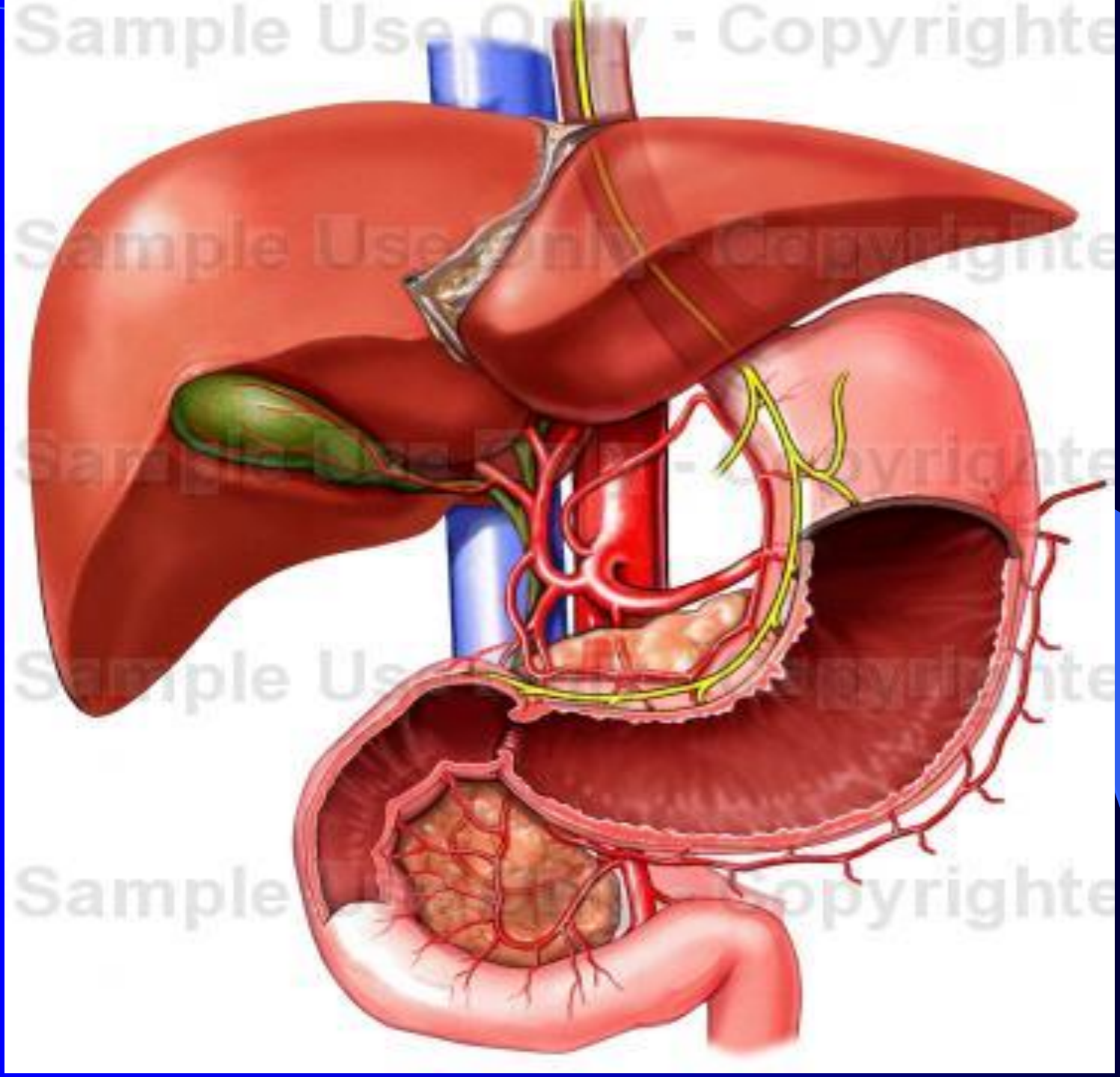

Lower lung limit
Lower pleural limit
Diaphragm
Liver
Gall-bladder
Umbilicus
Cecum
Peritoneum
Heart contour
Stomach
Small intestine
Sigmoid flexure
Bladder

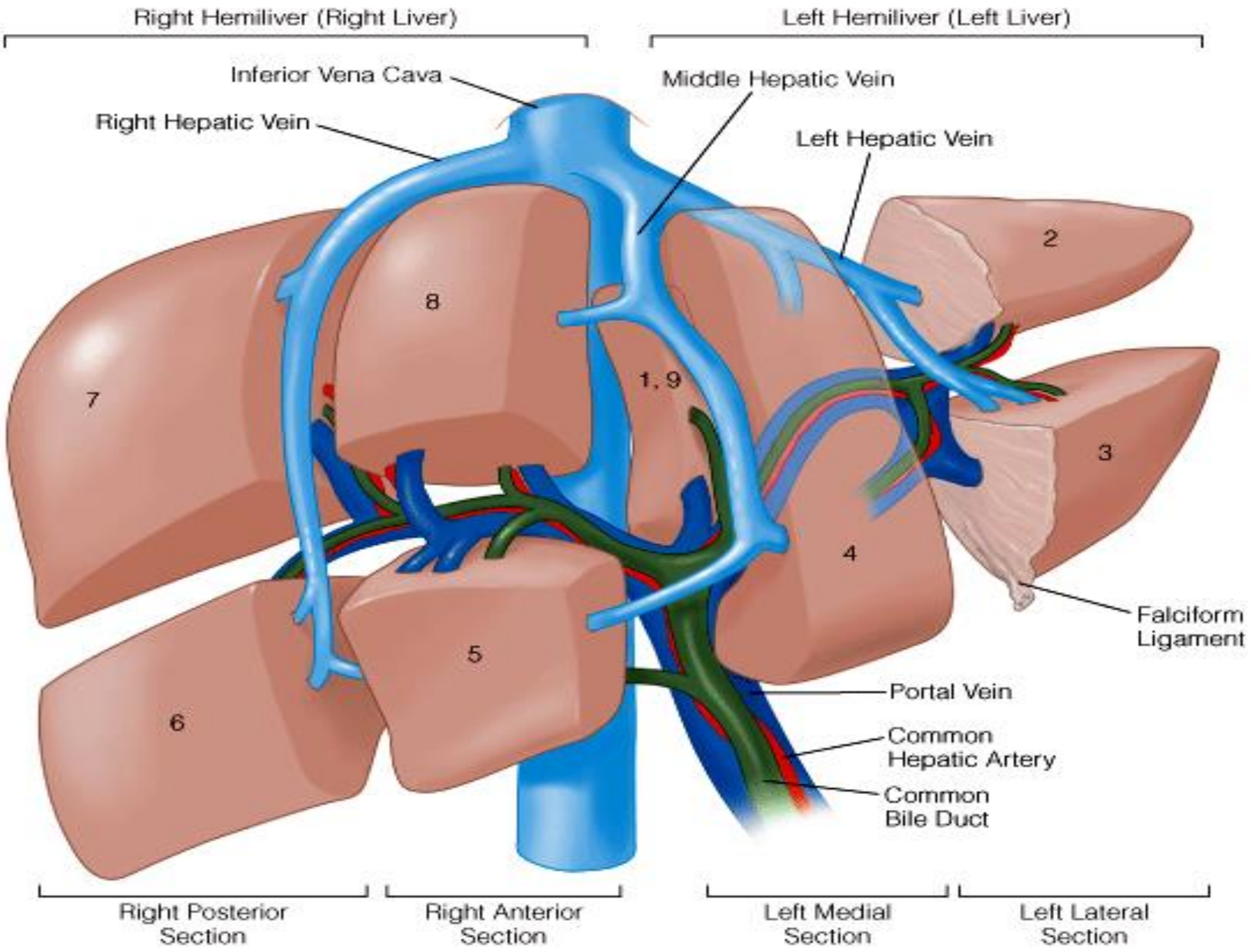
Gross Hepatic Anatomy

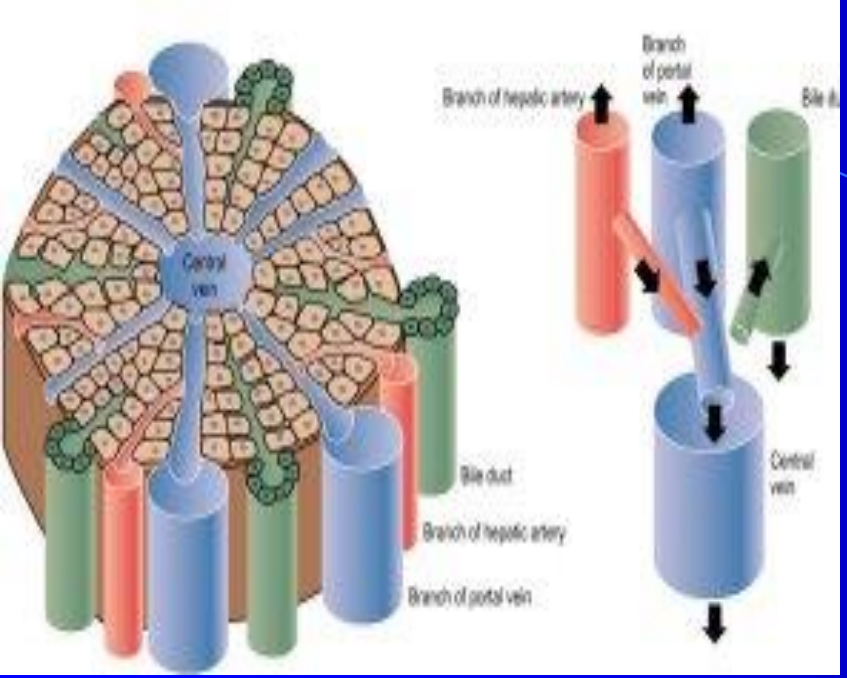


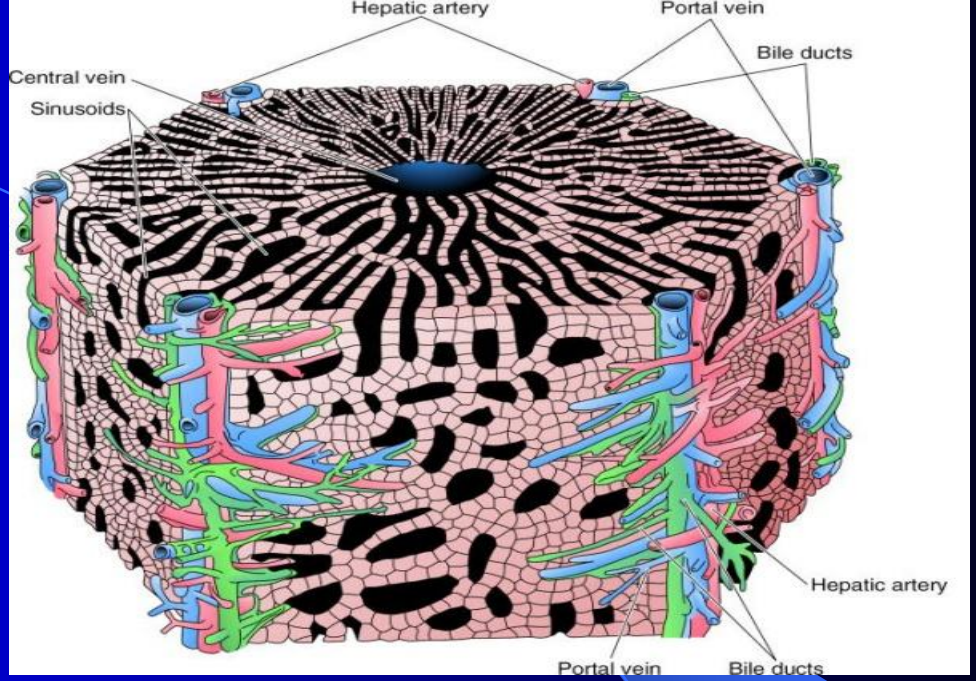
Gross Hepatic Anatomy

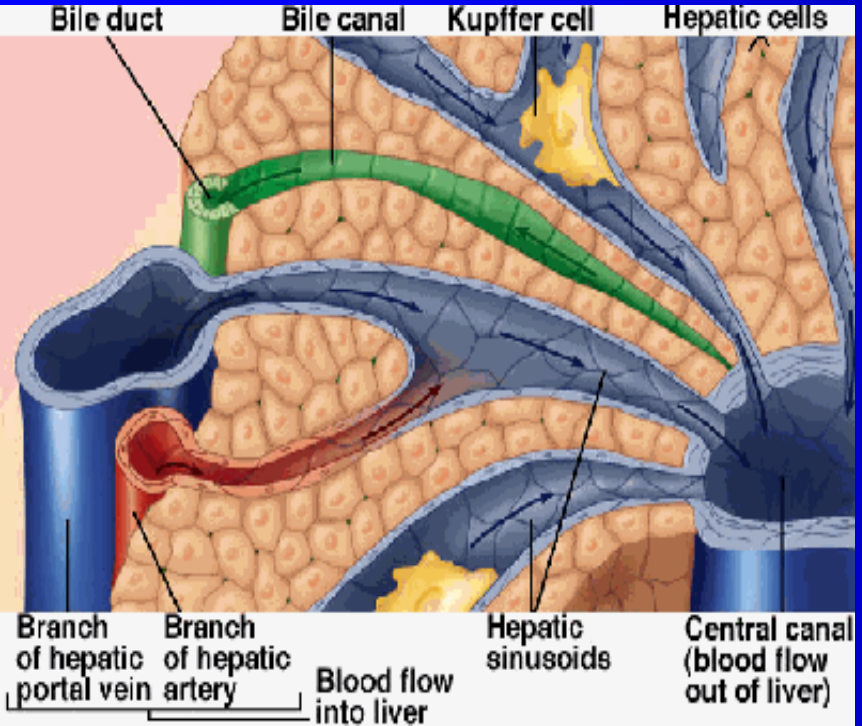


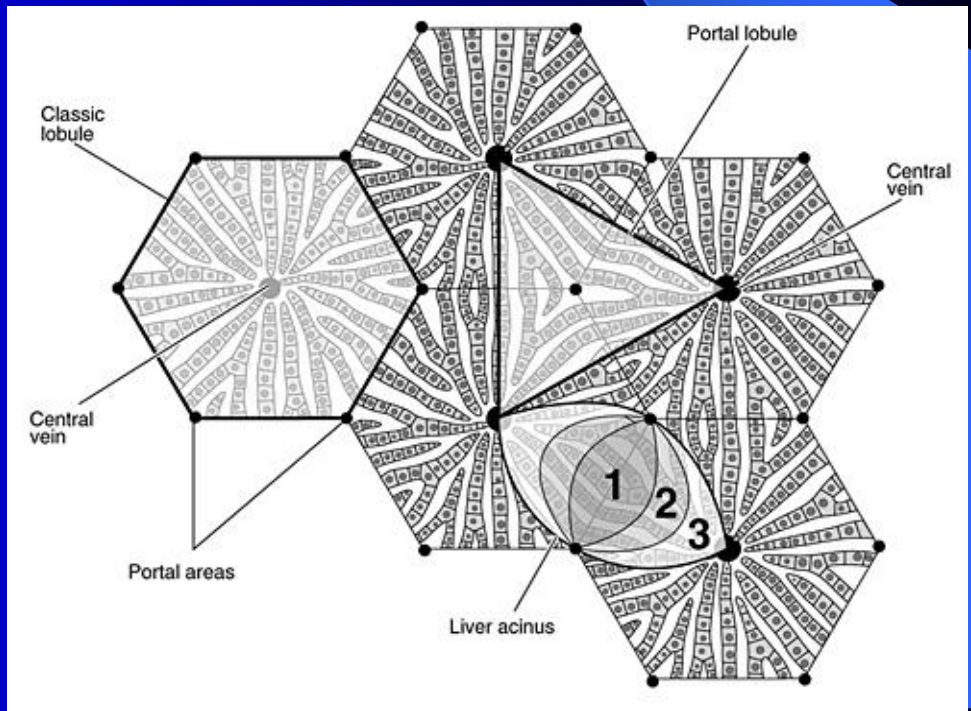


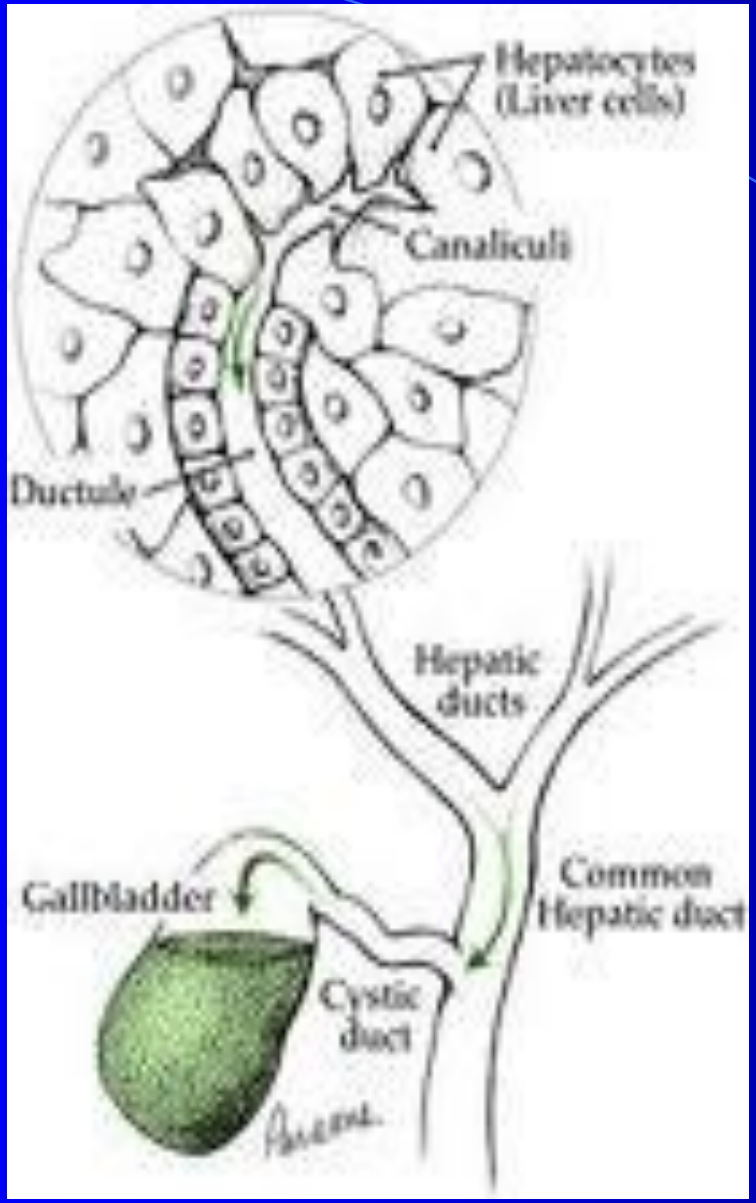


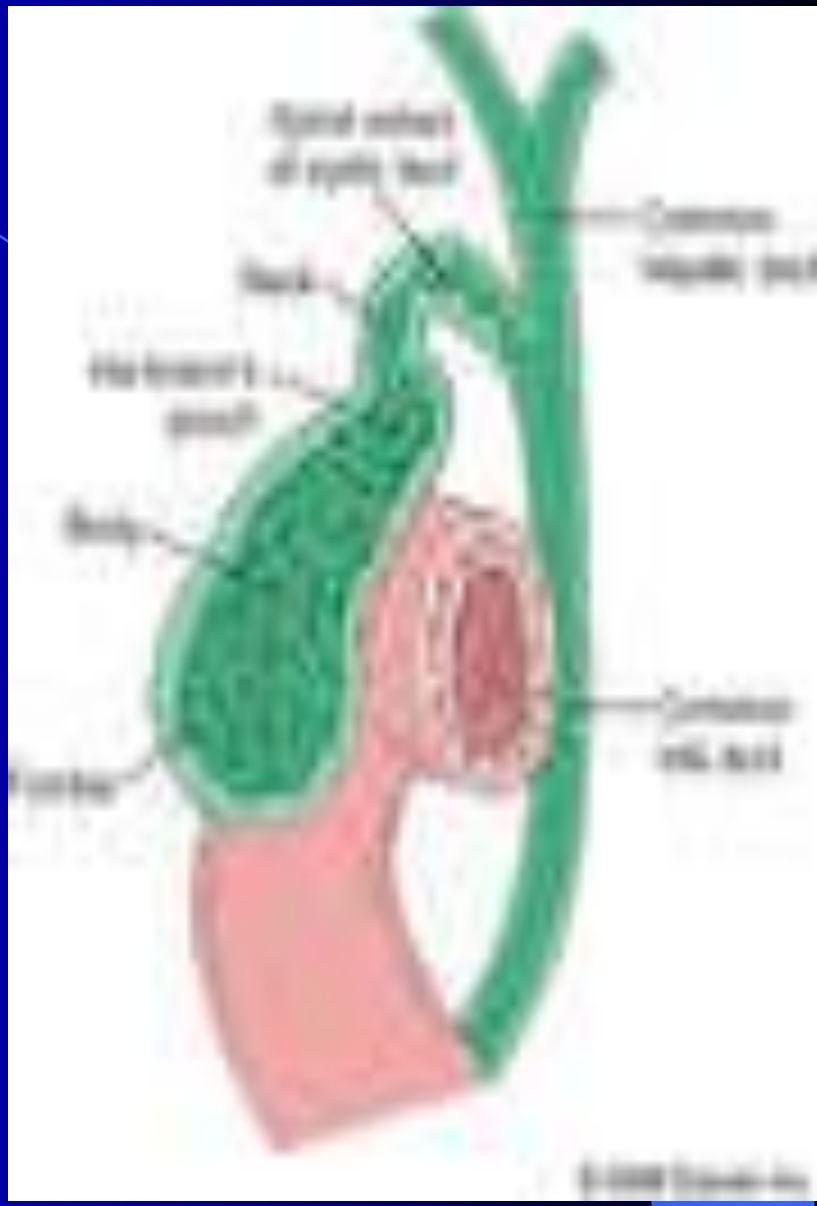

Central vein
Branch of hepatic artery
Branch of portal vein
Bile duct
Branch of hepatic artery
Branch of portal vein
Central vein


Hepatic artery
Portal vein
Bile ducts
Central vein
Sinusoids
Hepatic artery
Portal vein
Bile ducts


Bile duct
Bile canal
Kupffer cell
Hepatic cells
Branch of hepatic portal vein
Branch of hepatic artery
Blood flow into liver
Hepatic sinusoids
Central canal (blood flow out of liver)


Portal lobule
Classic lobule
Central vein
Central vein
Portal areas
1
2
3
Liver acinus


Hepatocytes
(Liver cells)
Canaliculi
Ductule
Hepatic
ducts
Gallbladder
Common
Hepatic duct
Cystic
duct



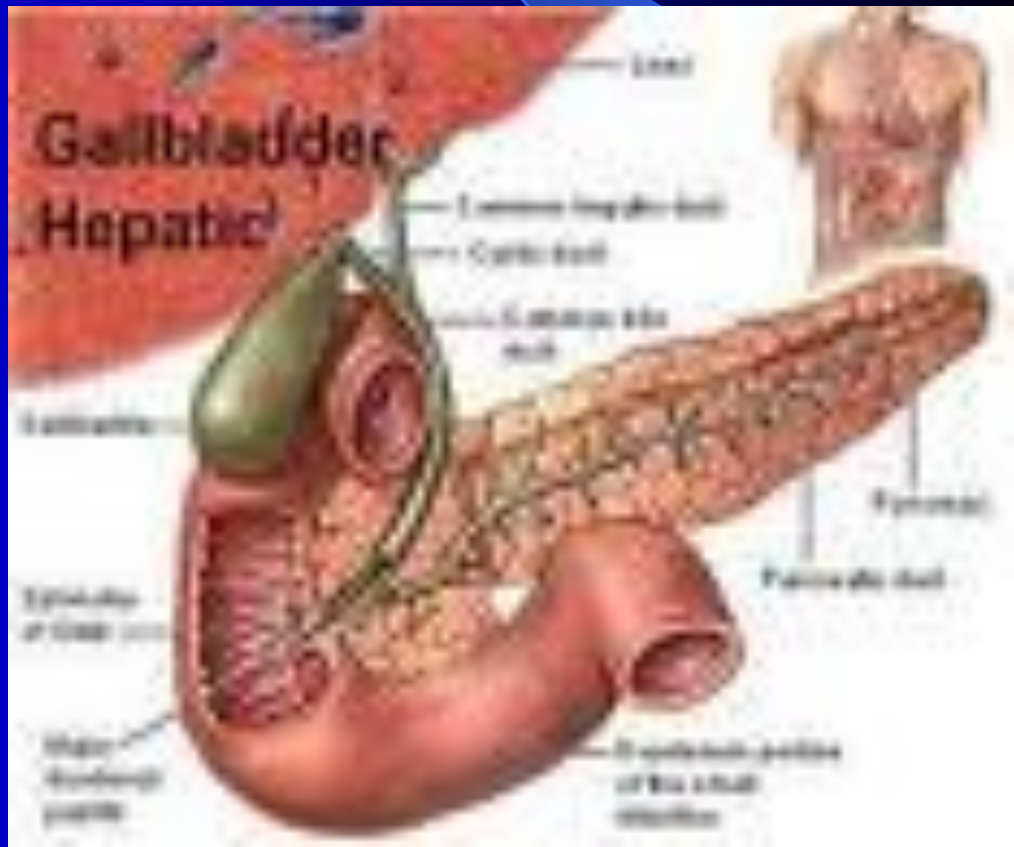
Normal Bile Physiology

- 1500ml bile/day

  2 roles: 1. excretion

  2. emulsification of fat

- Water (98%)
- Bile Salts
- Bile pigments (Bilirubin)
- Fatty Acids
- Lecithin
- Cholesterol



Major Causes of Jaundice

Pre-hepatic

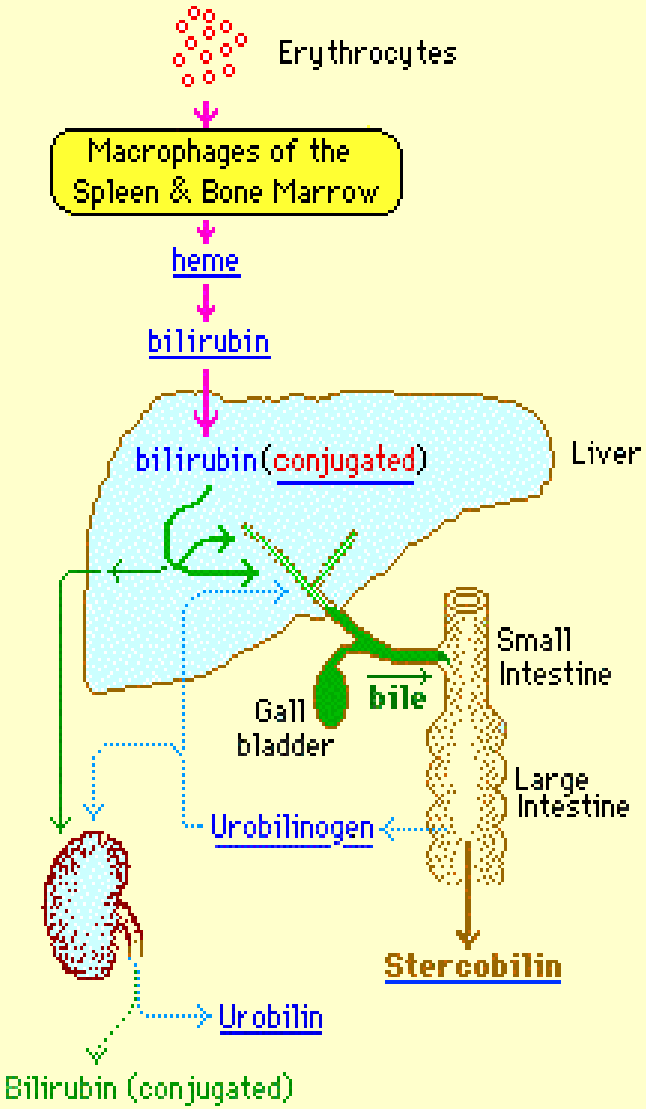
- Haemolysis
- Ineffective erythropoiesis

Hepatic

- Prematurity
- Gilberts
- Drugs
- Hepatitis: viral, NASH
- Alcohol / cirrhosis
- Tumours
- Extrahepatic sepsis

Post-hepatic 'Obstructive'

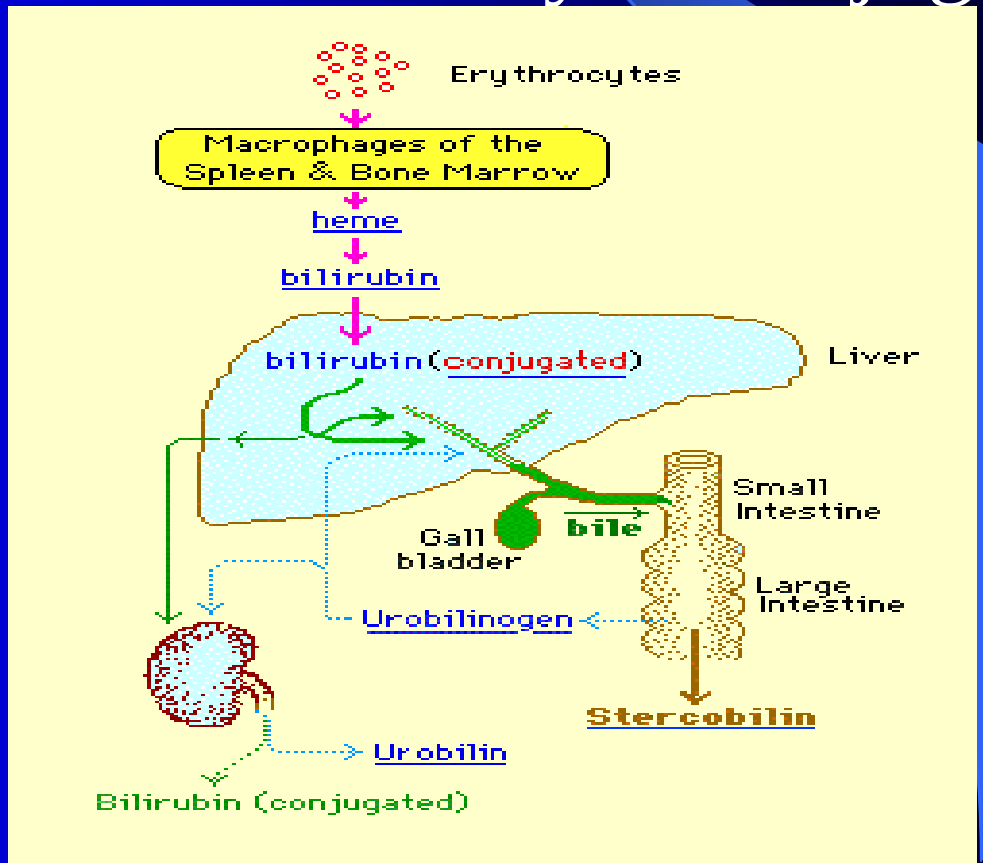
- Gallstones (in the lumen)
- Bile duct stricture (in the wall)
- Ca pancreas (extrinsic)



Unconjugated hyperbilirubinemia caused by:

*An overproduction of bilirubin, overcoming the uptake and conjugating abilities of the liver.

*A failure of the liver cells to take up the pigment from the blood or inability to conjugate the bilirubin.



Clinical Conditions Related to Increased Unconjugated Hyperbilirubinemia

Haemolytic jaundice
Gelbert's Syndrome
Crigler-Najjar Syndrome (Type I)
Crigler-Najjar Syndrome (Type II)
Neonatal Jaundice

Causes of unconjugated hyperbilirubinemia:

Excessive hemysis.

Gilbert's syndrome:

Most common cause of unconjugated hyperbilirubinemia; an inborn error of metabolism affecting bilirubin uptake as well as conjugation in the liver; totally asymptomatic: mild hyperbilirubinemia.

*Crigler-Najjar Syndrome (Types I and II): Usually lethal, pediatric illness; congenital total or relative deficiency of glucuronyl transferase.

*Neonatal jaundice:

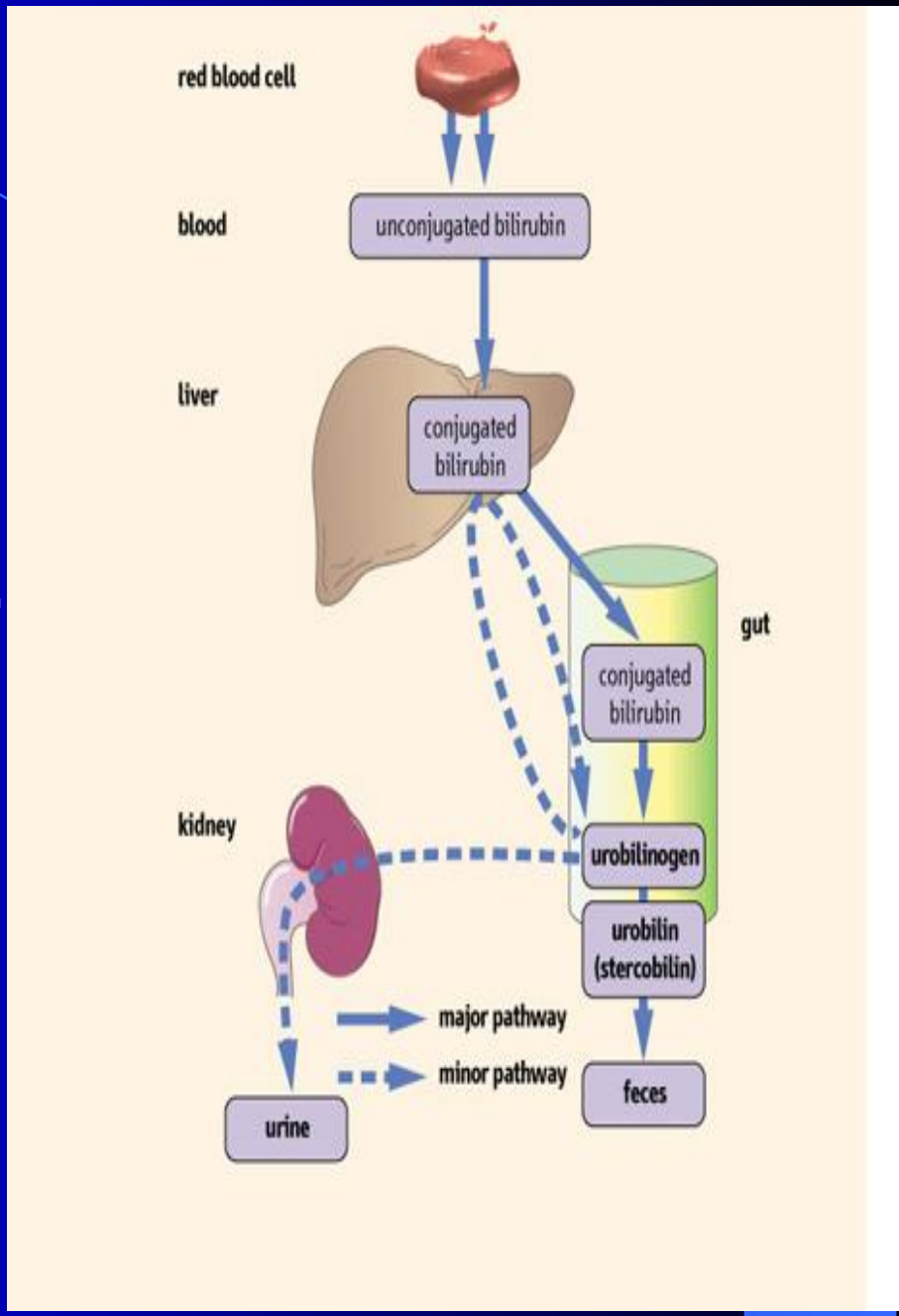
In infants, the liver may be unable to function at full capacity, therefore there is decreased conjugation.

The high levels of bilirubin may cause seizures (kernicterus).

Treatment is phototherapy, which makes bilirubin more water soluble to be excreted into the bile.

I) Excessive hemysis (Haemolytic jaundice):

Excessive haemolysis of RBCs leads to formation of unconjugated (indirect) bilirubin in excess which is beyond the capacity of the liver cells to conjugate it completely, so part of it is retained in the blood, also the conjugated bilirubin excreted in the bile is increased → increased faecal stercobiliogen which results in dark coloured stools.



- **Characters of haemolytic jaundice:**
- Usually mild jaundice (lemon yellow) associated with pallor due to anaemia, dark colour of the stool, normal colour of the urine on voiding but darken on standing, absence of signs of liver cell failure, during investigation show: increase serum indirect bilirubin with normal liver enzymes (ALT, AST), increase urine urobilinogen and faecal stercobilinogen, anaemia with reticulocytosis.

Causes of haemolytic jaundice

***Inherited**

- Red cell membrane defect: Hereditary spherocytosis, Hereditary elliptocytosis
- Haemoglobin abnormalities: Thalassaemia, Sickle cell disease
- Metabolic G6PD deficiency, Pyruvate kinase deficiency

***Acquired**

Immune

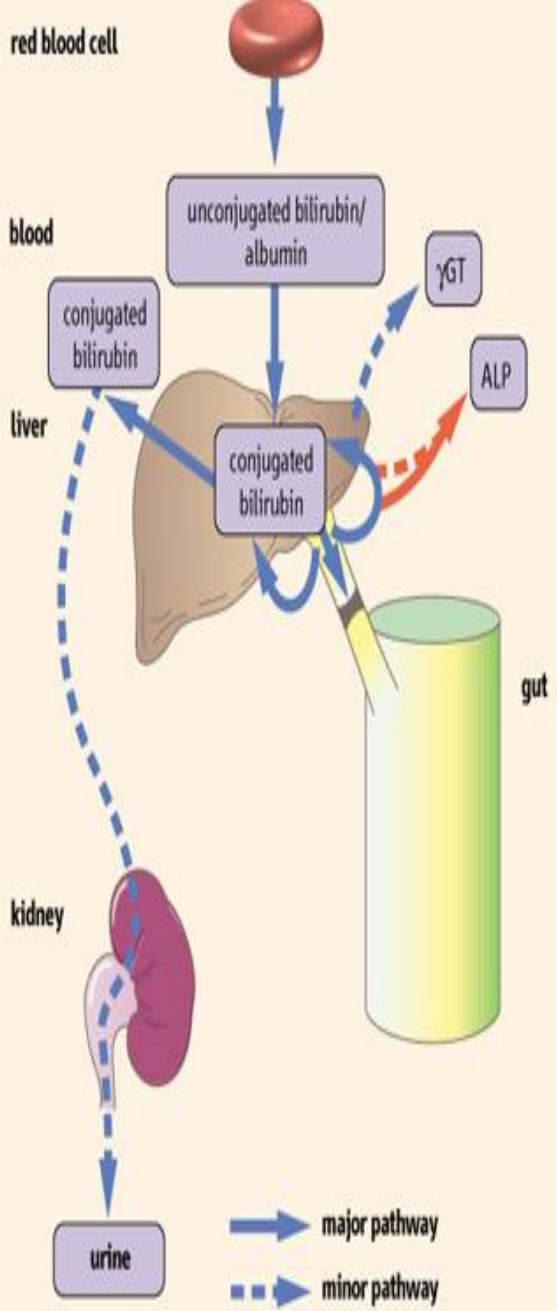
- Autoimmune: Warm, Cold
- Alloimmune:Haemolytic transfusion reactions, Drug induced

Non immune

- Acquired membrane defects: Paroxysmal nocturnal haemoglobinuria
- Mechanical: Valve prosthesis March haemoglobinuria
- Miscellaneous: Infections. e.g. malaria, Hypersplenism Burns

2) Decreased bilirubin excretion and/or obstruction of the biliary tract (obstructive jaundice):

Haemoglobin catabolism is normal, indirect bilirubin is conjugated in the liver into direct bilirubin at a normal rate, but the later is prevented from reaching the intestine and so regurgitate into the blood stream. The serum direct bilirubin level is increased and appears in the urine leading to dark urine, intestinal stercobilinogen markedly decreased pale coloured stool, urobilinogen not present in the urine.



- **Characters of the obstructive jaundice:**
- Usually severe jaundice (olive green), markedly pale stool with markedly dark coloured urine, severe pruritis, absence of signs of liver cell failure, investigations shows: normal serum indirect bilirubin with severe rise of serum direct bilirubin, mildly elevated liver enzymes with severe rise in serum alkaline phosphatase, markedly decrease of urinary urobilinogen and faecal stercobilinogen.

Causes of obstructive jaundice

*Intrahepatic biliary obstruction caused by primary biliary cirrhosis, drugs as chlorpromazine.

*Extrahepatic biliary obstruction: caused by:

- Inside the lumen of the common bile duct as stone and rarely parasites e.g. ascaris.
- In the wall of the common bile duct as stricture and carcinoma of the bile duct.
- Compression of the common bile duct from outside caused by cancer head of the pancrease and enlarged lymph node at the porta-hepatis.

Conjugated Hyperbilirubinemia: cuased by:

*Intrahepatic cholestasis: "medical jaundice".

*Extrarahepatic cholestasis: (obstruction)="surgical jaundice".

Note: The proportion of conjugated to unconjugated bilirubin does not distinguish hepatocellular forms from cholestatic forms, but the serum alkaline phosphatase can usually distinguish between the two.

Clinical Conditions Related to Increased Conjugated Hyperbilirubinemia

	Duben-Johnson Syndrome	Rotor Syndrome
Defect (hepatocytes)	Secretory	Transport
Presence of Pigmentation	Yes	No
Metabolism	Abnormal Porphyrin Metabolism	None

Acholuric Vs. Choluric

ACHOLURIC – absence of bile in urine

- Hemolytic type

CHOLURIC – presence of bile derivatives in the urine

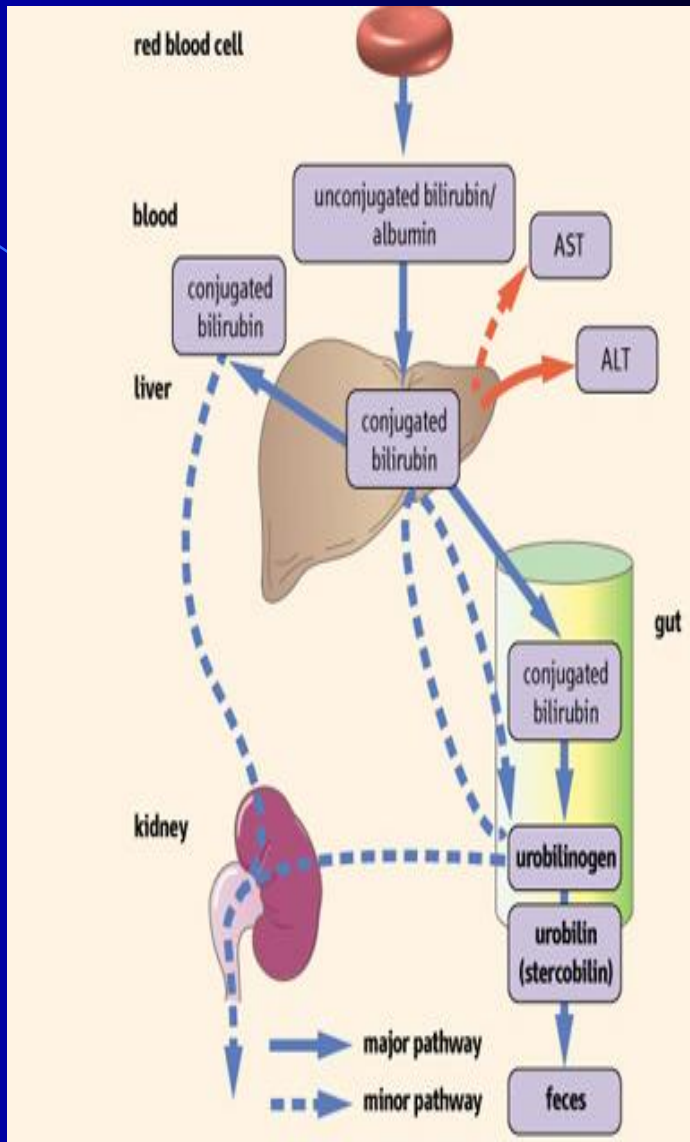
- Obstructive type

3) Reduced hepatic conjugation or execretion of bilirubin (Hepatocellular jaundice).

Haemoglobin catabolism is at normal rate,but the liver cells are functionally incapable of conjugating and excreting all bilirubin, accordingly part of indirect bilirubin is retained in the blood and part of direct bilirubin is unable to reach the intestine and

regurgitate in the blood with some bile salts. The stercobilinogen is mildly affected but the amount absorbed from the intestine can't be fully re-excreted by the liver and

excreted in the urine as urobilinogen in increased amounts.



- **Characters of hepatocellular jaundice:**
- Usually moderate jaundice (orange yellow), mildly pale stool with dark coloured urine, may be pruritis, presence of signs of liver cell failure, investigations show increase serum indirect and direct bilirubin, elevated liver enzymes with prolonged prothrombin time and low serum albumin, increase urinary urobilinogen with low faecal stercobilinogen

Causes of hepatocellular jaundice:

- Viral hepatitis
- Liver cirrhosis.
- Toxic hepatitis due to chemicals.
- Chronic hepatitis.

Diagnosis of a case of jaundice

History

Examination

Investigations

- Liver function tests: as serum direct and indirect bilirubin, liver enzymes (as ALT & AST and alkaline' phosphatase), prothrombin time and serum albumin.
- CBC and reticulocytic count.
- Plain X-ray may show gall stones in 10% of cases.
- Abdominal ultrasonography show size of the liver, cirrhosis, extrahepatic and intrahepatic biliary dilatation.
- Endoscopic retrograde cholangiography and pancreaticography (ERCP).
- Magnetic resonance cholangiography and pancreaticography (MRCP).
- Liver biopsy.
- Liver scanning.
- Surgical exploration.

History

1. Jaundice

2. Pale stools, dark urine?

YES = POST HEPATIC

PAIN?

YES

Colicky
Fatty food intolerant

GALLSTONES

NO

Wt loss
Back Pain
Non-specific symptoms

MALIGNANCY

ASSOCIATED FEVERS / RIGORS?

Gram –ve Septicaemia

NO = PRE HEPATIC

Pre-hepatic:

Hepatic

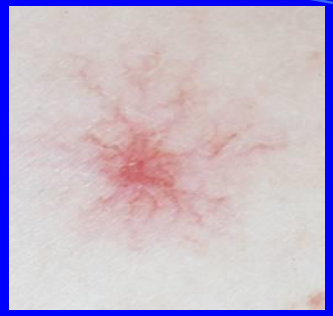
IV Drug abuse
blood transfusions
Travel
flu-like illness

} Hepatitis

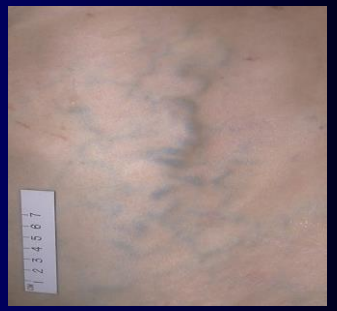
Excess alcohol intake
Obesity

} Cirrhosis/ NASH

Drug History



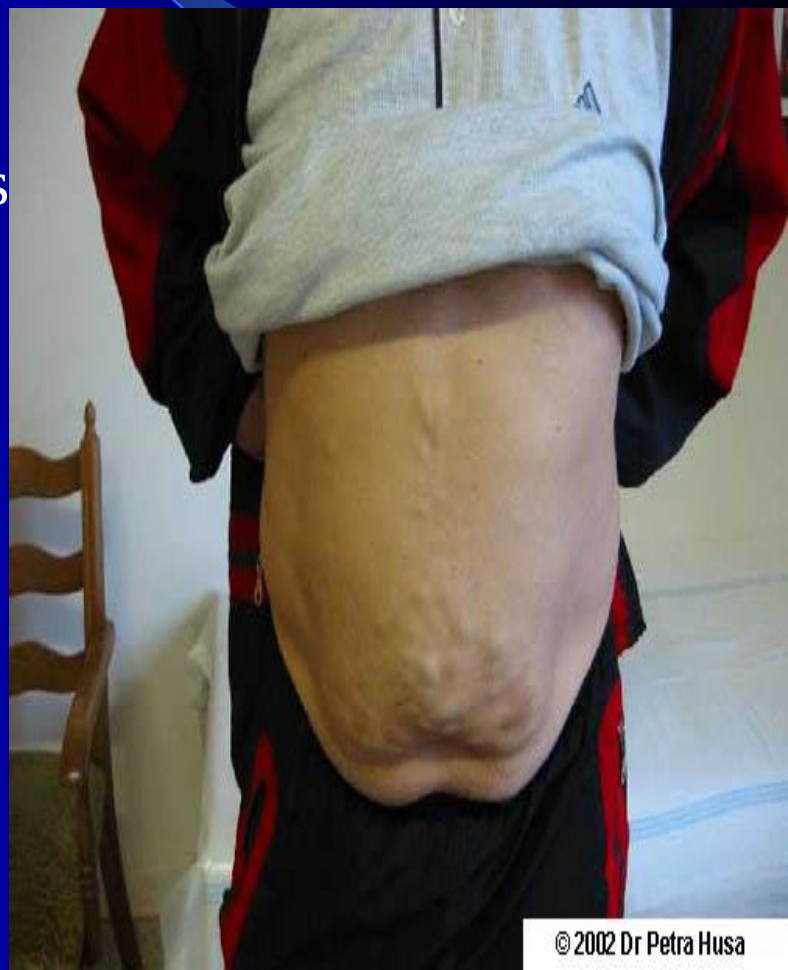
Examination



- Stigmata Chronic Liver disease

- Hepatomegaly – texture,edge, nodules
- Hepatosplenomegaly
- Ascites –shifting dullness
- Portal hypertesion

- Obvious iv drug use

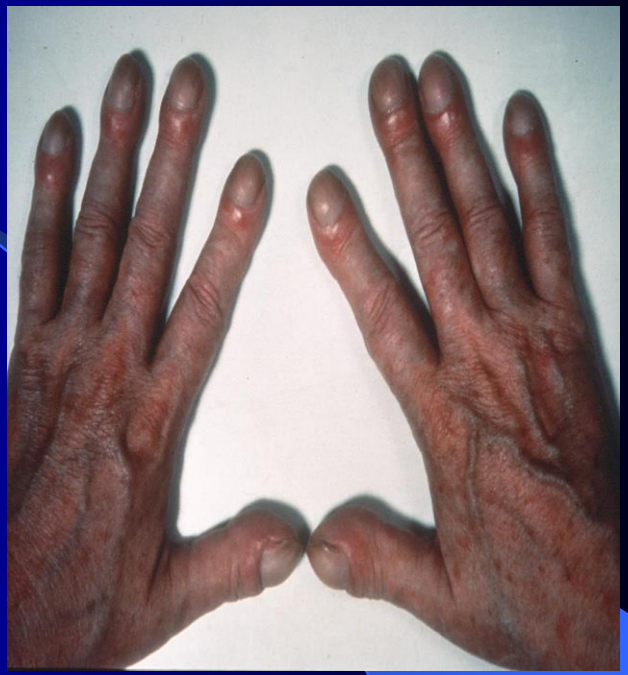


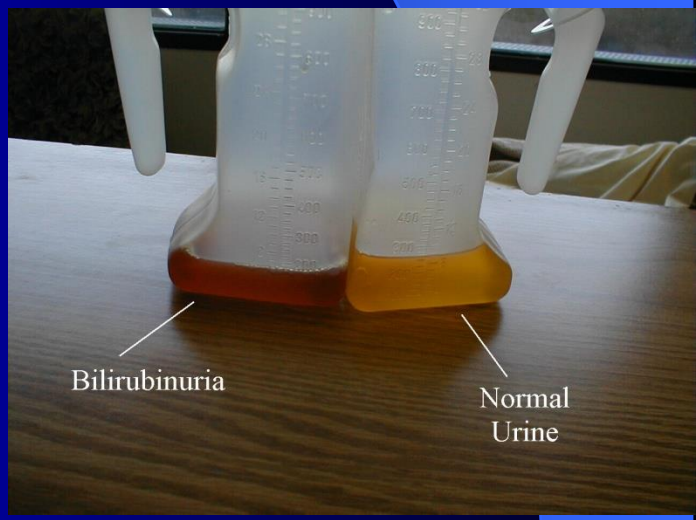
Examination – obstructive jaundice

- Temp
- Tachycardic +/- hypotensive

} cholangitis

- Cachexia, Virchow's node,clubbing
- Murphy's sign
- Courvoisier's law 'If in the presence of jaundice the gallbladder is palpable then the cause of the jaundice is unlikely to be gallstones'
- Urine



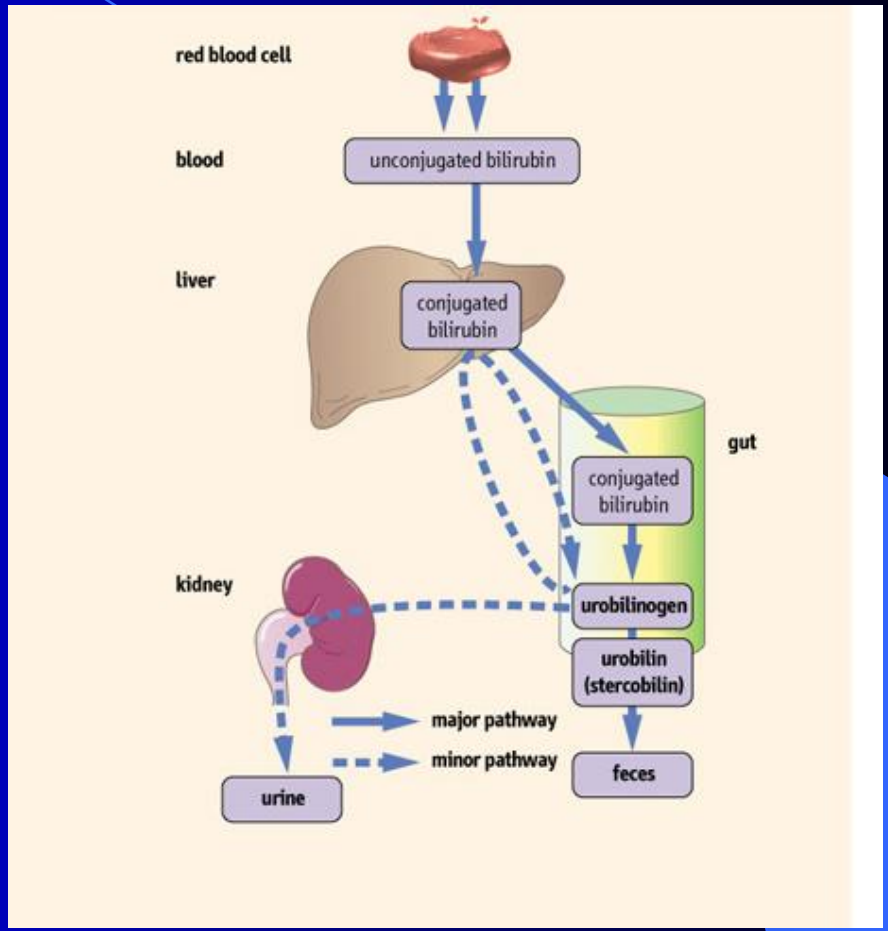


Prehepatic

- Unconguated Bil ↑
- LFT's N

- haptoglobins ↓
- Reticulocytes ↑
- Coombs test +ve
- Clotting screen

- Urine urobilinogen



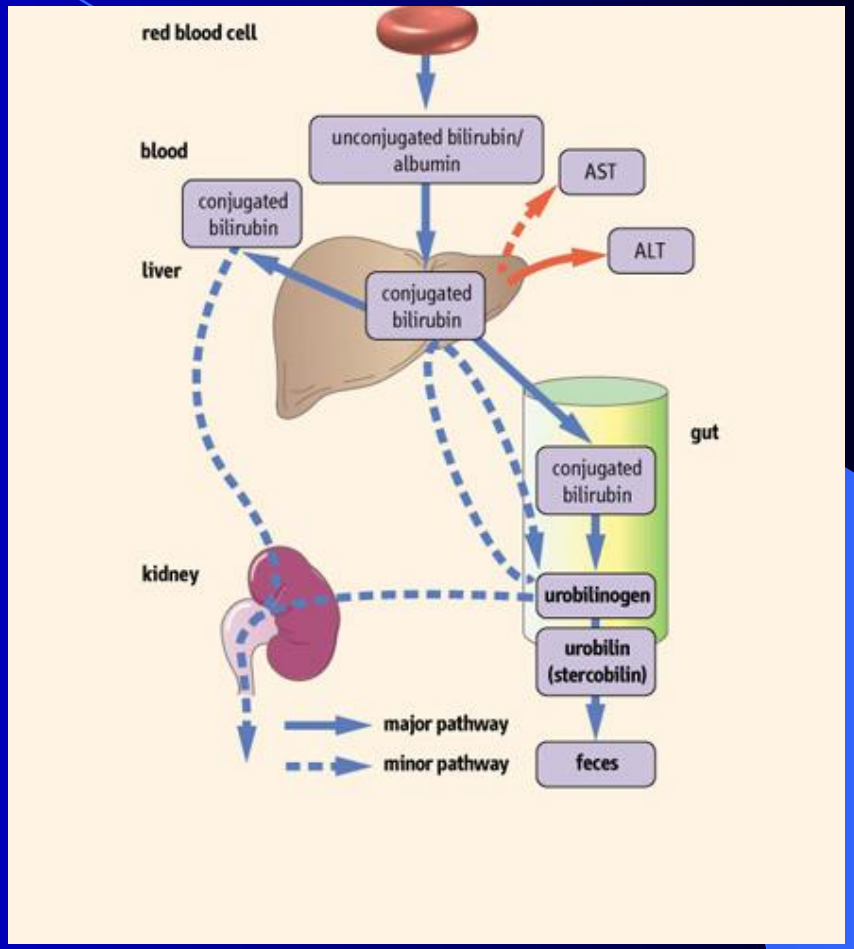
Hepatic

- ALT ↑ ↑ ↑
- ALP N or ↑
- Bil ↑

- Albumin ↓
- INR ↑

- Hepatitis serology
- Autoantibodies
  - Anti-mitochondrial PBC
  - Anti-nuclear & antimicrosomal, Autoimmune hepatitis

- Caeruloplasmin ↑
  - Wilson's
- γ-Globulins ↑
  - Cirrhosis esp autoimmune
- Transferrin ↑ ↑
  - Haemochromatosis ↑
- α-foetoprotein, αFP ↑
  - HCC in cirrhosis

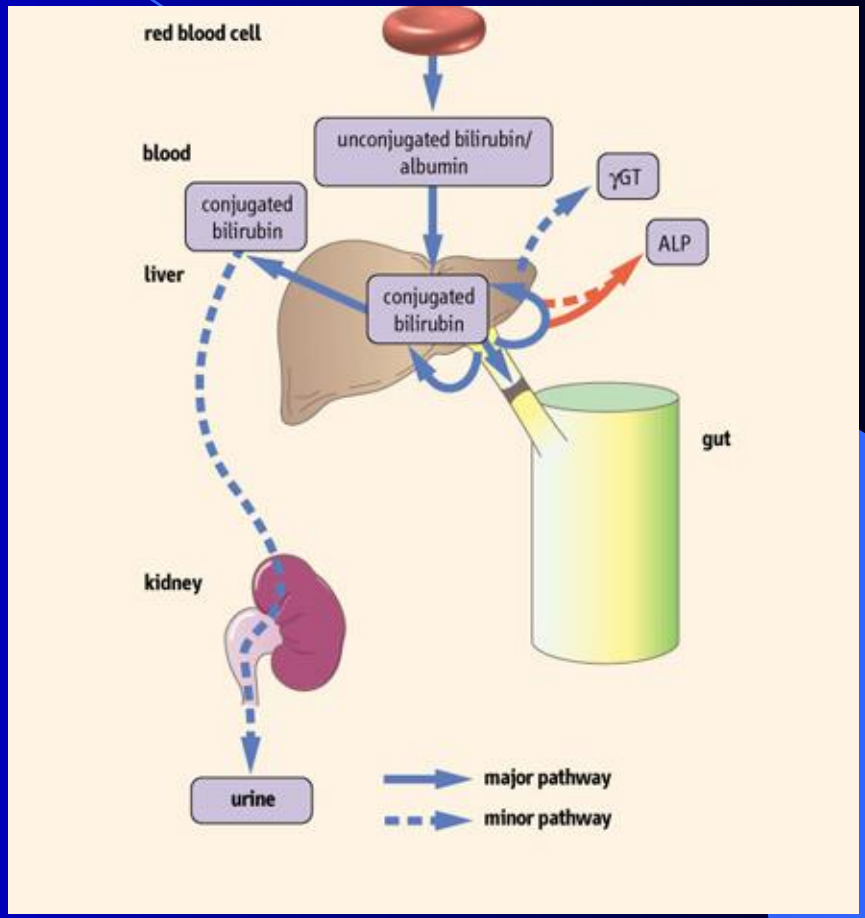


Post - hepatic

- ALT N or ↑
- ALP ↑ ↑ ↑
- Bil ↑

- INR ↑

- CEA, Ca19.9 ↑
  - Panc & cholangio Ca

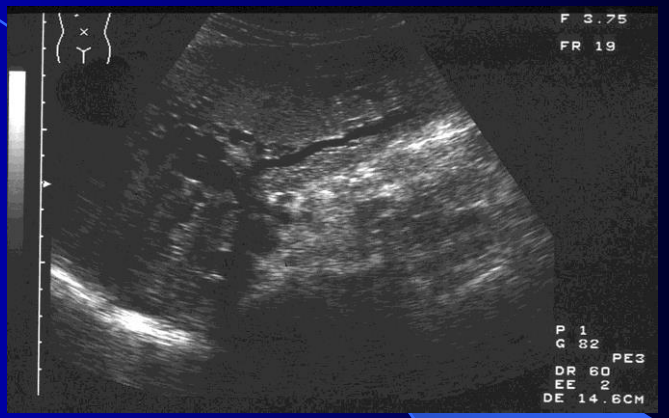


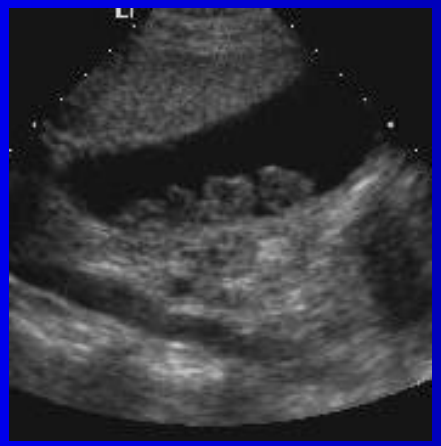
LFTs and urine summary

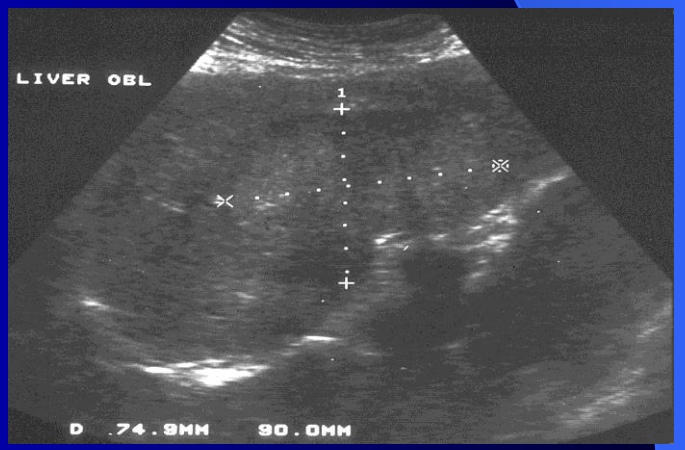
	Blood			Urine	
	ALT	**ALP**	**Bil**	**Urobilinogen**	**Bilirubin**
Pre-hepatic	N	N	↑↑	Present	absent
Hepatic	↑↑↑	N or ↑	↑↑	N	Present
Post-hepatic	N or ↑	↑↑↑	↑↑	absent	Present

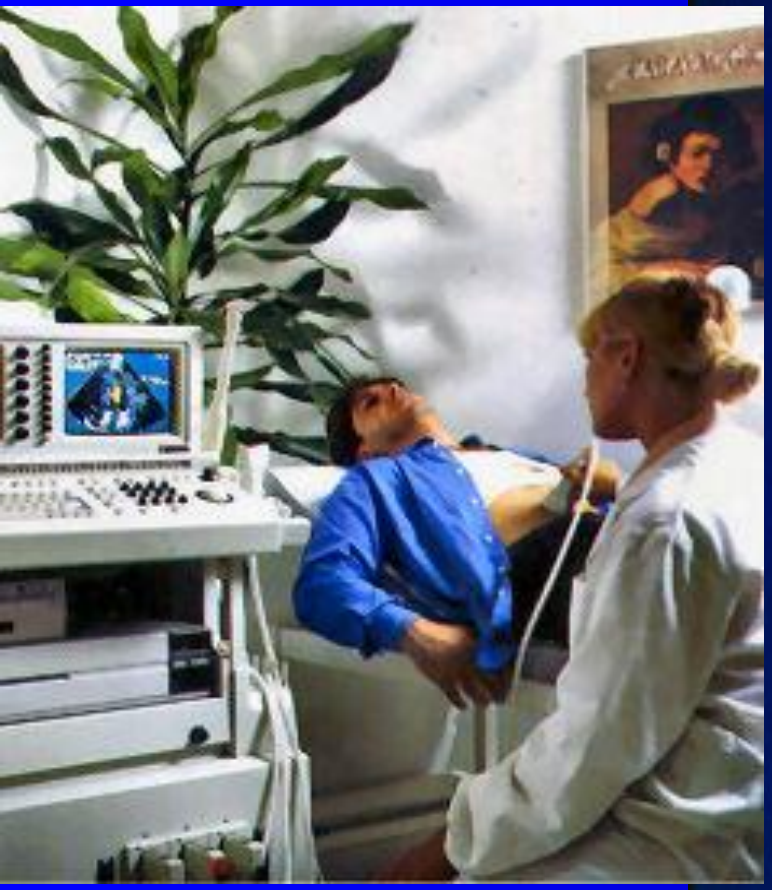
Imaging - Ultrasound

- Key investigation
- Distinguish obstruction from hepatic cause
- Identify gallstones

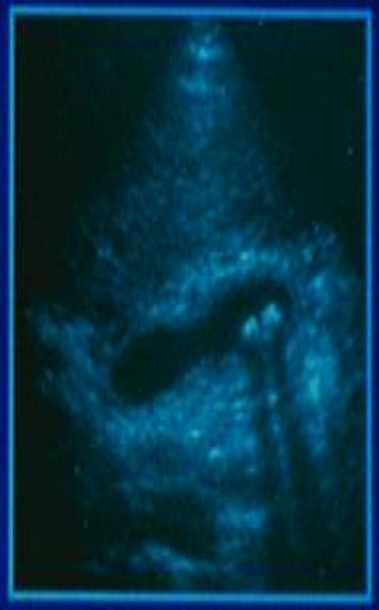








ULTRASONOGRAPHY



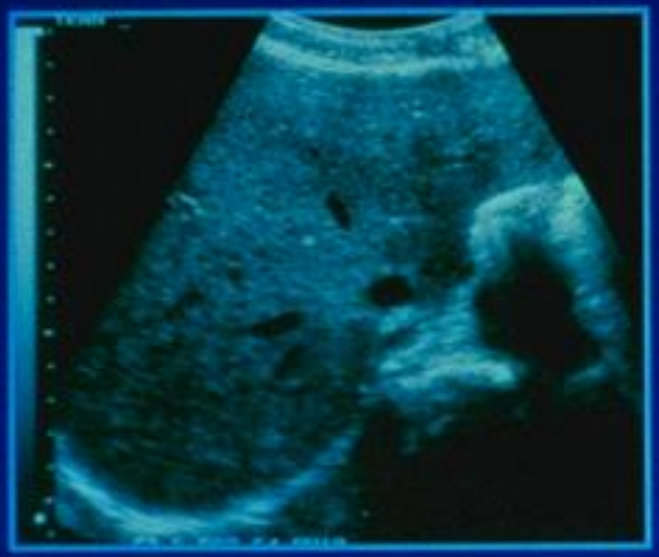
ADVANTAGES	LIMITATIONS
No ionizing radiation	Operator dependent
Portable	Patient dependent
Multiple planes	Interpretation subjective
Biopsy localization	Poor for intraductal stones

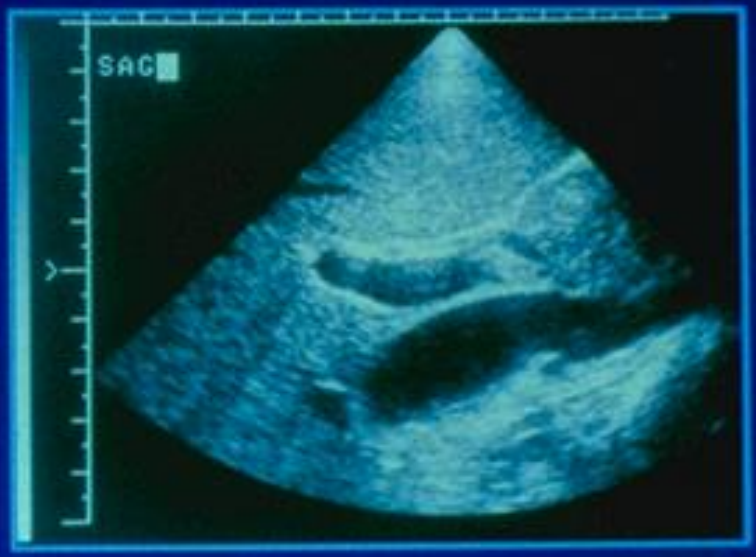
Imaging - Ultrasound

- Key information from report
- *Duct size*
- CBD normally < 7mm
- Are both intrahepatic and extrahepatic ducts dilated?

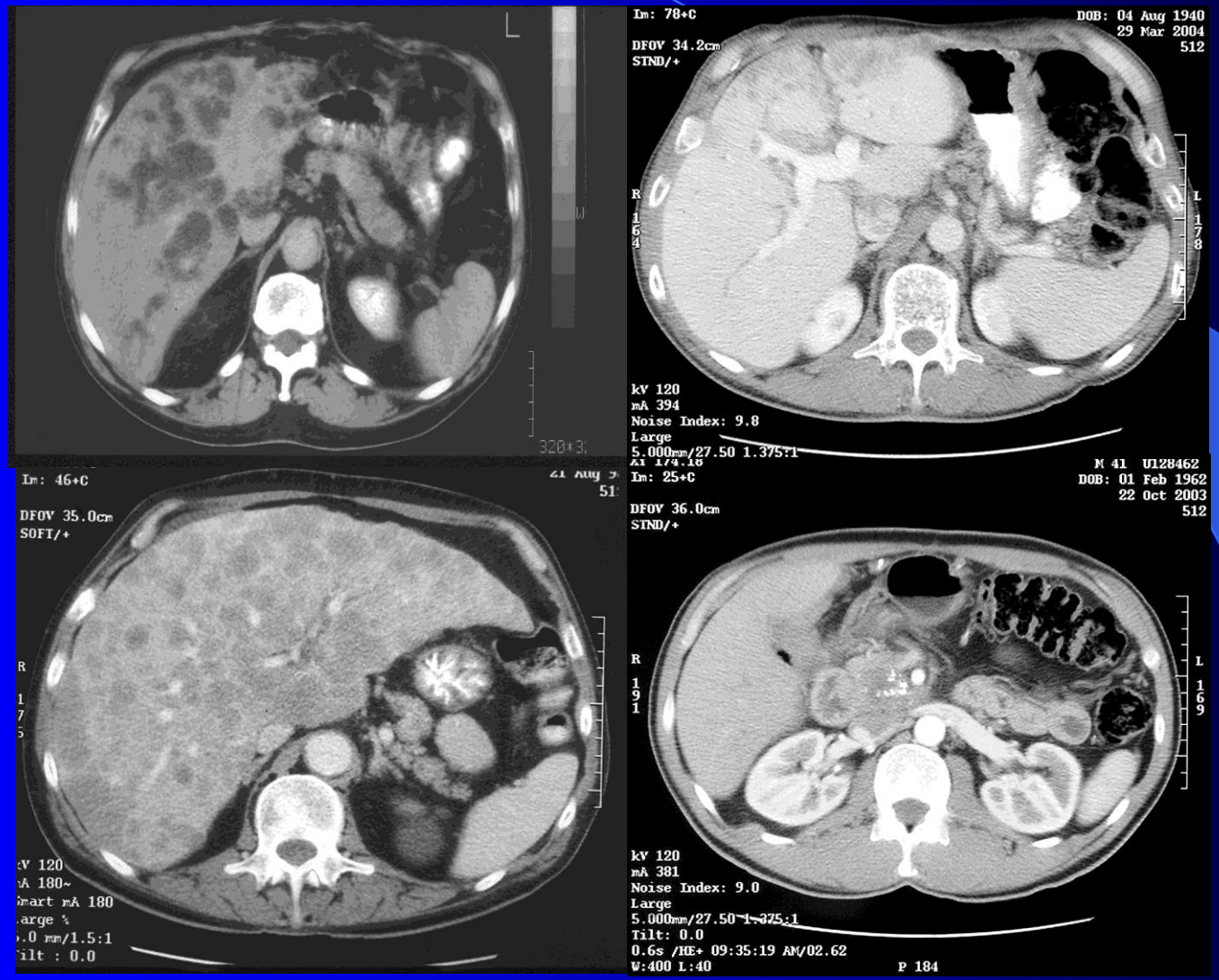
- *If duct increased are calculi present?*
- Gallstones present none seen in CBD but Gallbaldder abnomalities ie GB stones, SLUDGE, increased GB wall thickness
- No gallstones, but CBD ↑ **? Pancreatic malignancy**
- Texture of liver eg normal, fatty, micronodular
- Dioscrete Lesions present

NORMAL HEPATOBILIARY ULTRASONOGRAPHY

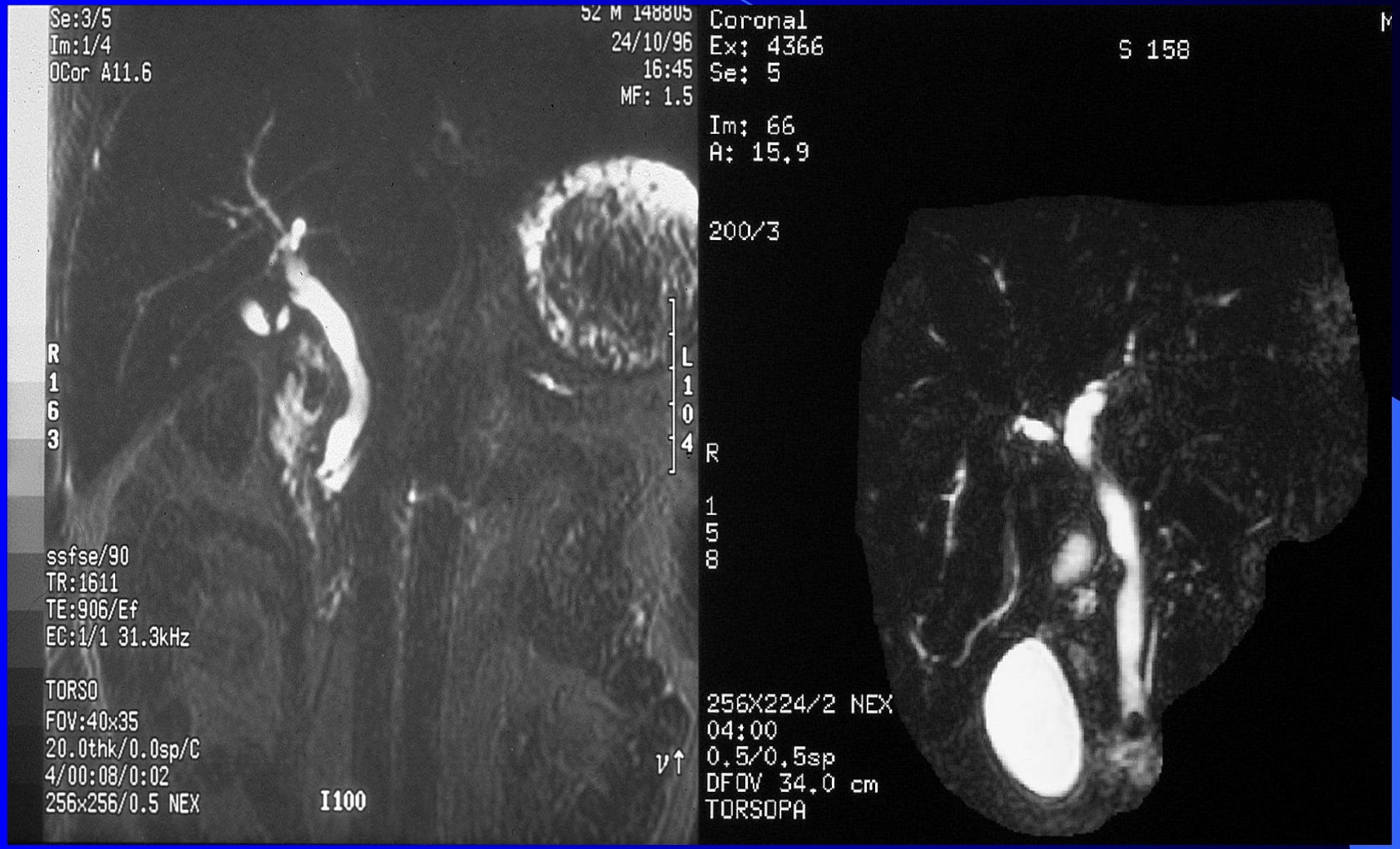




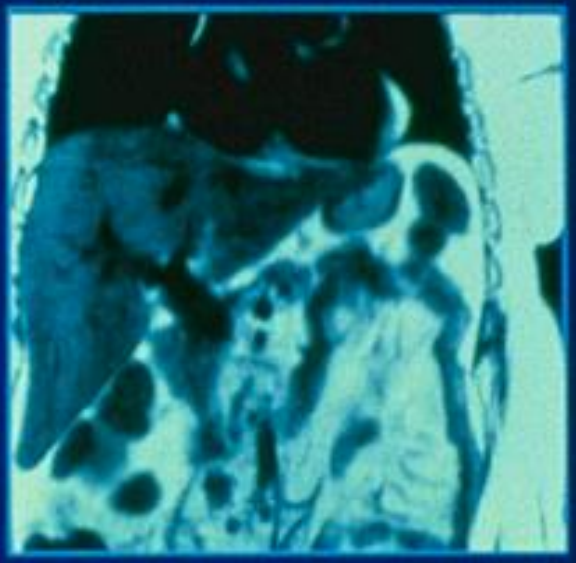
Imaging - CT Scan



Imaging MRCP + MRI

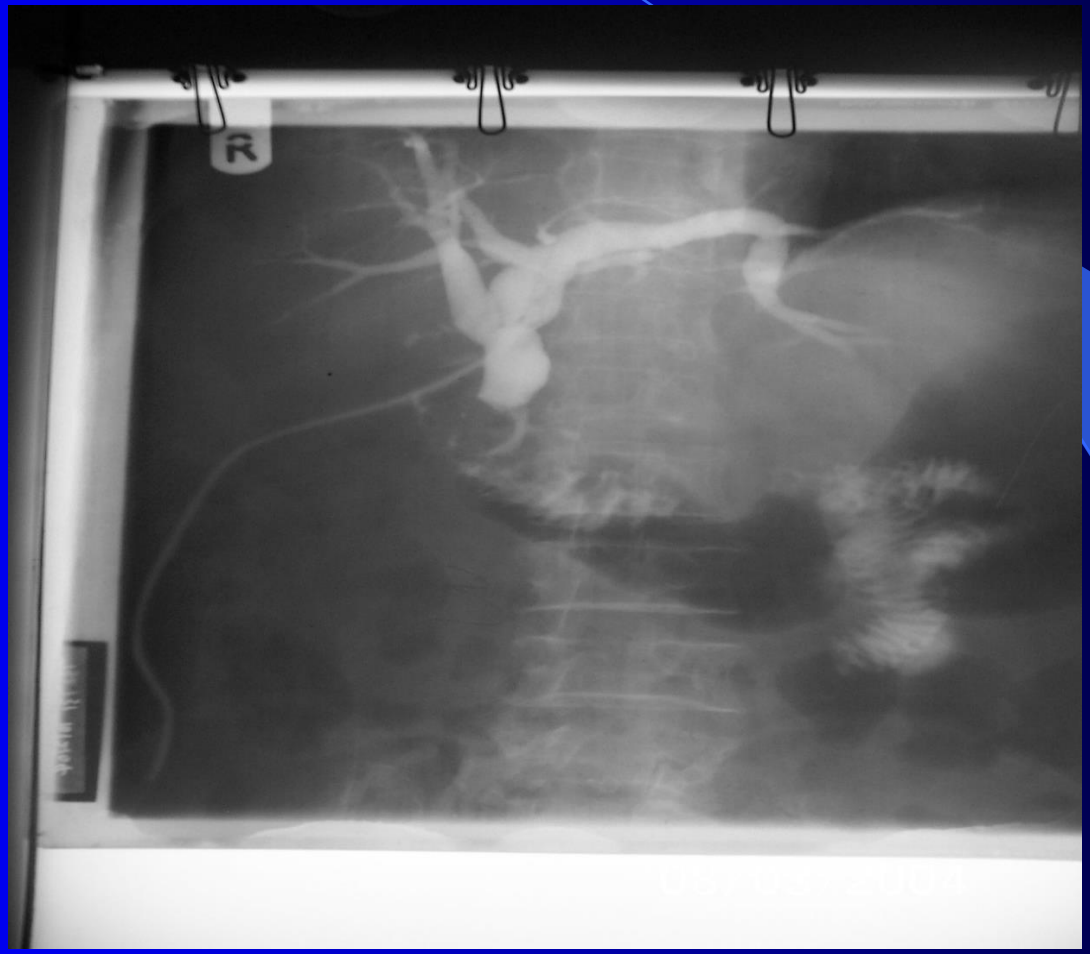


MAGNETIC RESONANCE IMAGING

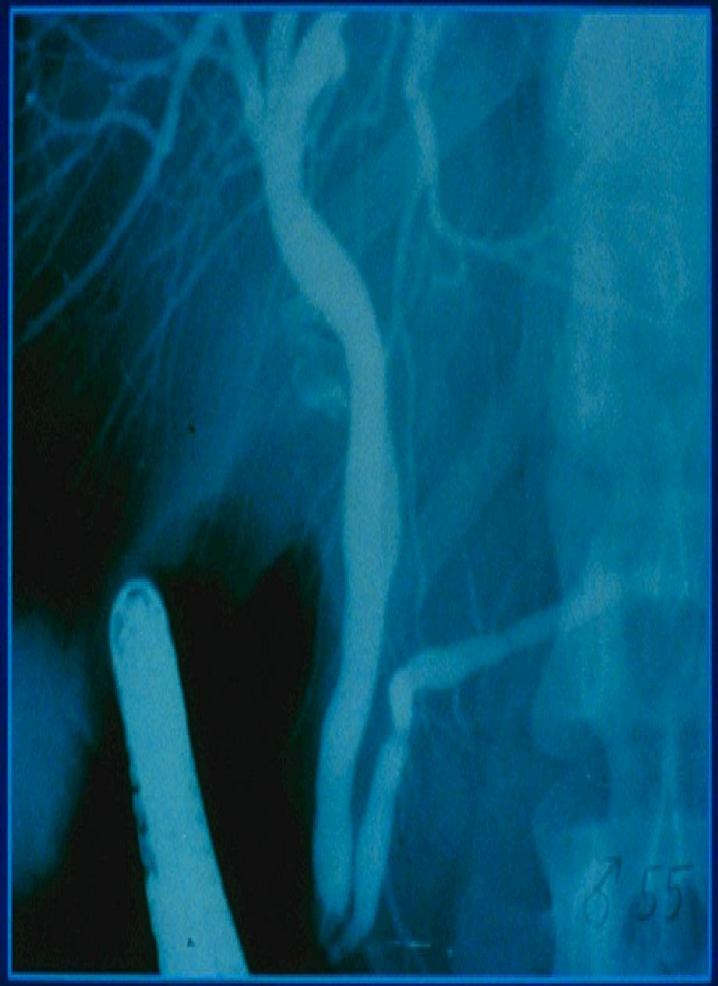


ADVANTAGES	LIMITATIONS
No ionizing radiation	Magnetic hazards
Multiple planes	Limited interventional access
Tissue characterization	Cost
Anatomy and function	Claustrophobia
Spectroscopic analysis	

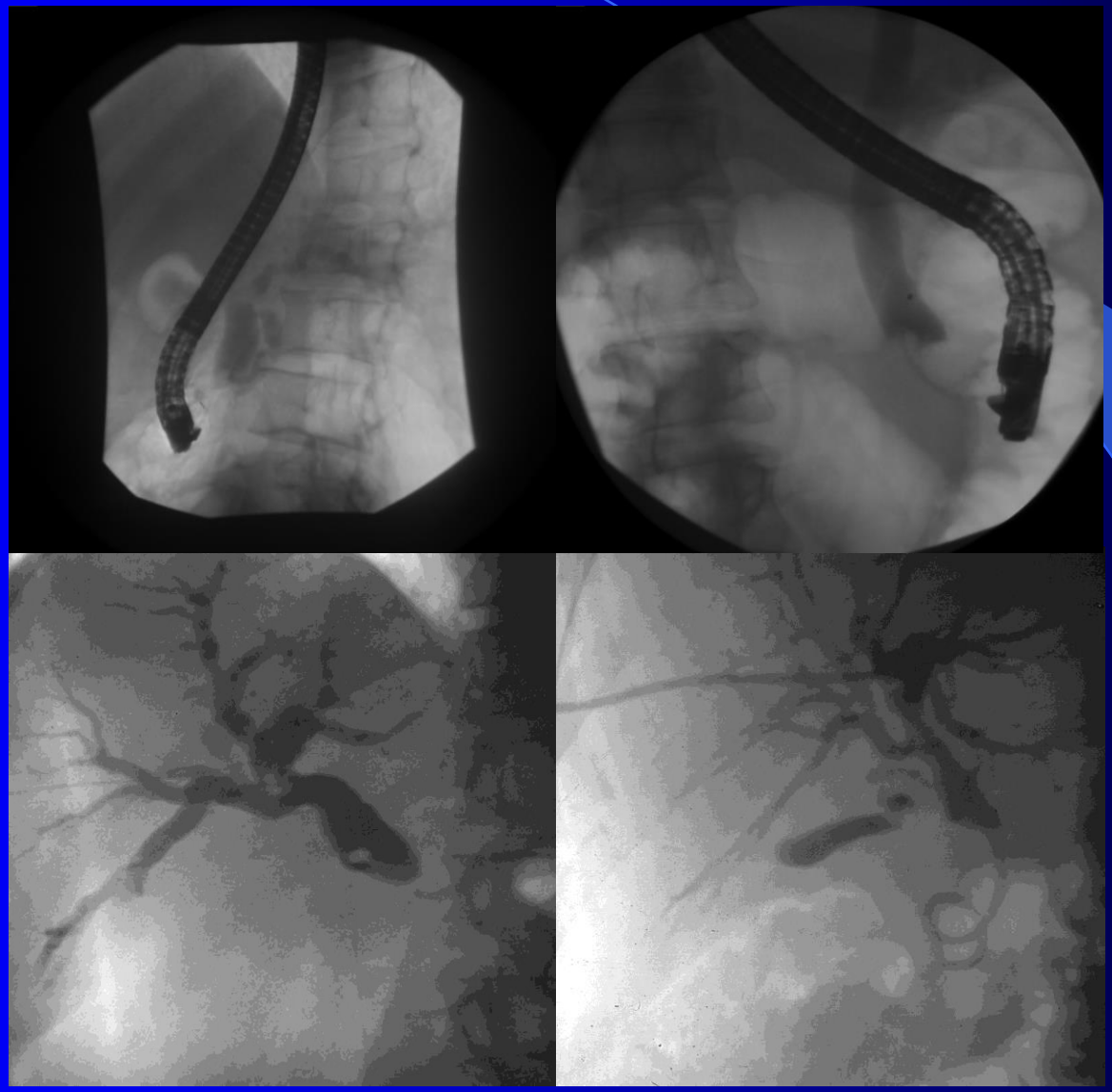
T-TUBE CHOLANGIOGRAM



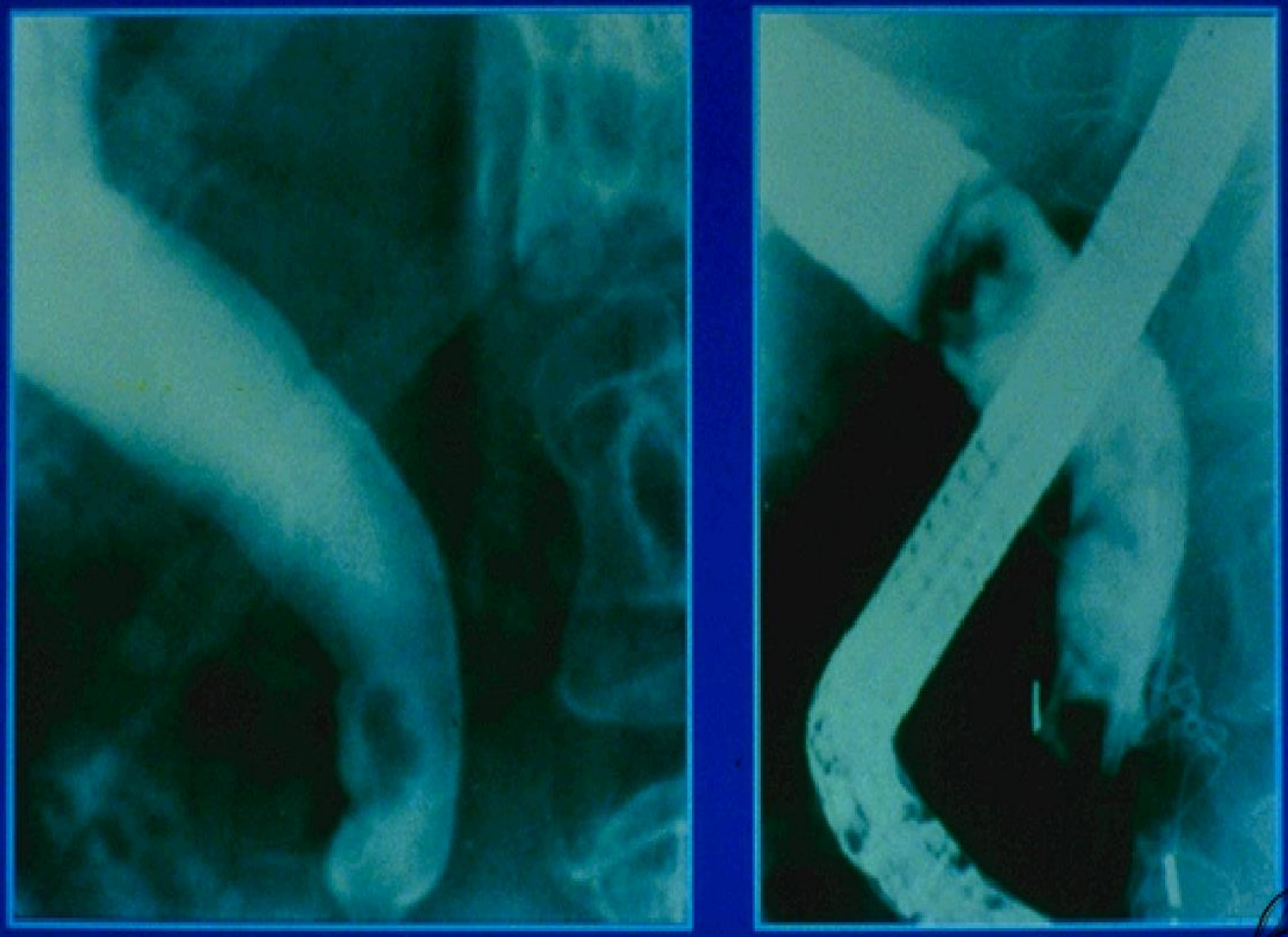
NORMAL ERCP



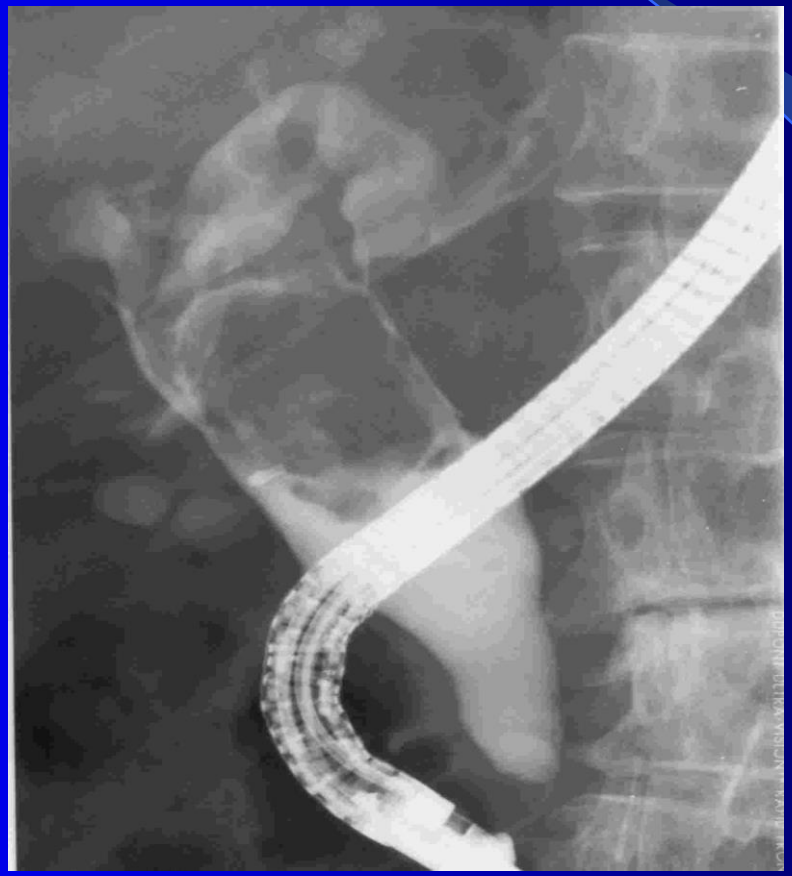
Imaging ERCP



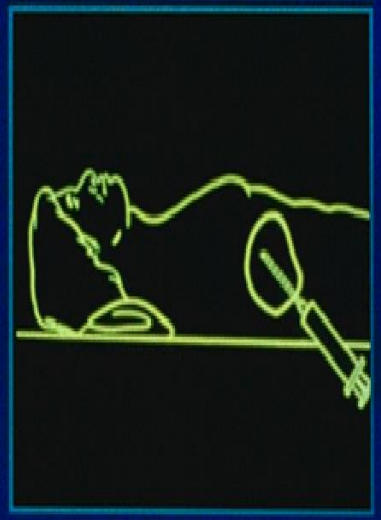
COMMON DUCT STONE

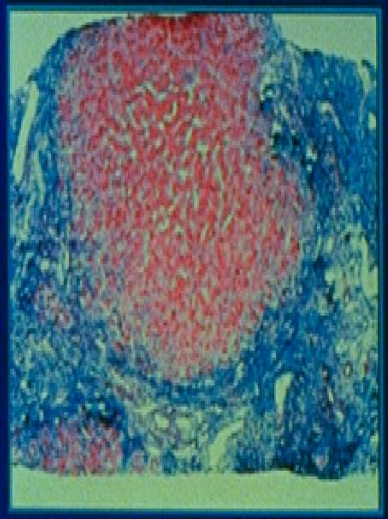


Large CBD Stones

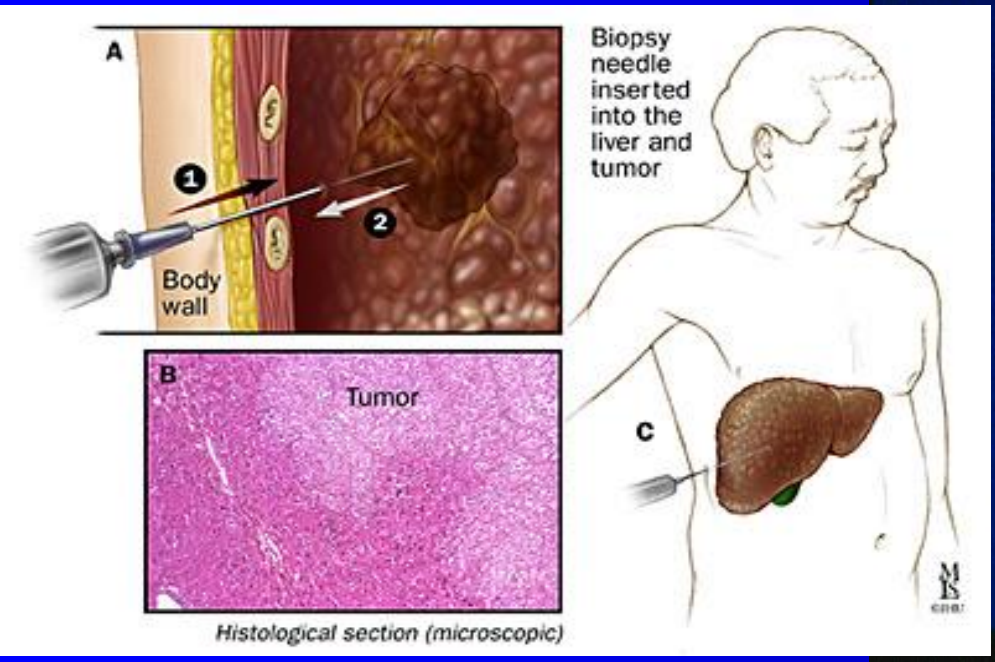


LIVER BIOPSY

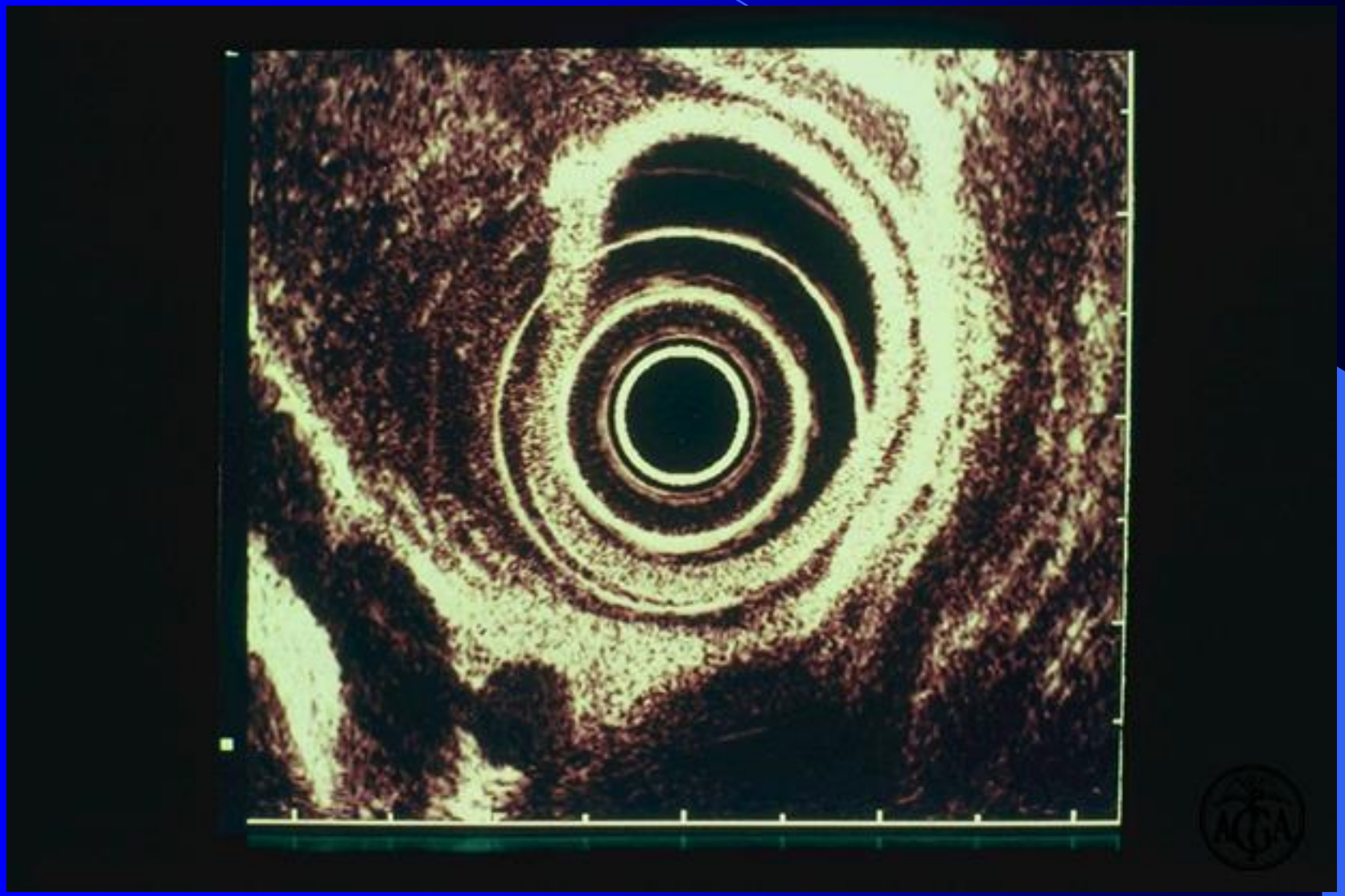




ADVANTAGES	LIMITATIONS
Histologic diagnosis	Invasive
Biochemical assays	Contraindications
	Complications:
	bleeding pneumothorax
	bile leak sepsis
	Pathologist dependent



Endoscopic Ultrasound



Management

- Good history, drives rest of management


Thank You
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