

Cholestasis



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Liver Function Tests (LFT)

Diagnosis of liver disease.

Monitoring disease *progression*

Liver disease *severity*

Efficacy of *treatments* 📢

Prothrombin time (PT) , serum bilirubin and albumin concentrations, can predict survival

ALKALINE PHOSPHATASE

Catalyze the hydrolysis of phosphate esters at an alkaline pH

Sites:

Liver

Bone

Placenta,

Intestine, Leukocytes and kidneys



Low Alkaline Phosphatase

- Hypomagnesemia
- Zinc deficiency
- Pernicious anemia
- Hypothyroidism 
- Hypophosphatemia
- Progressive familial cholestasis
- Cholestasis of pregnancy

Identification of the source of the elevated Alk.Ph

5'-nucleotidase

Leucine aminopeptidase

Gammaglutamyl transpeptidase (GGT)



These enzyme tests are not elevated in bone disorders,

Leucine aminopeptidase and possibly 5'-nucleotidase are not elevated in pregnancy

GAMMA-GLUTAMYL TRANSPEPTIDASE

- GGT is present in cell membranes in many tissues:
- kidneys, pancreas, 📢, liver, spleen, heart, brain, and seminal vesicles .
- It is thought to play a role in amino acid transport.

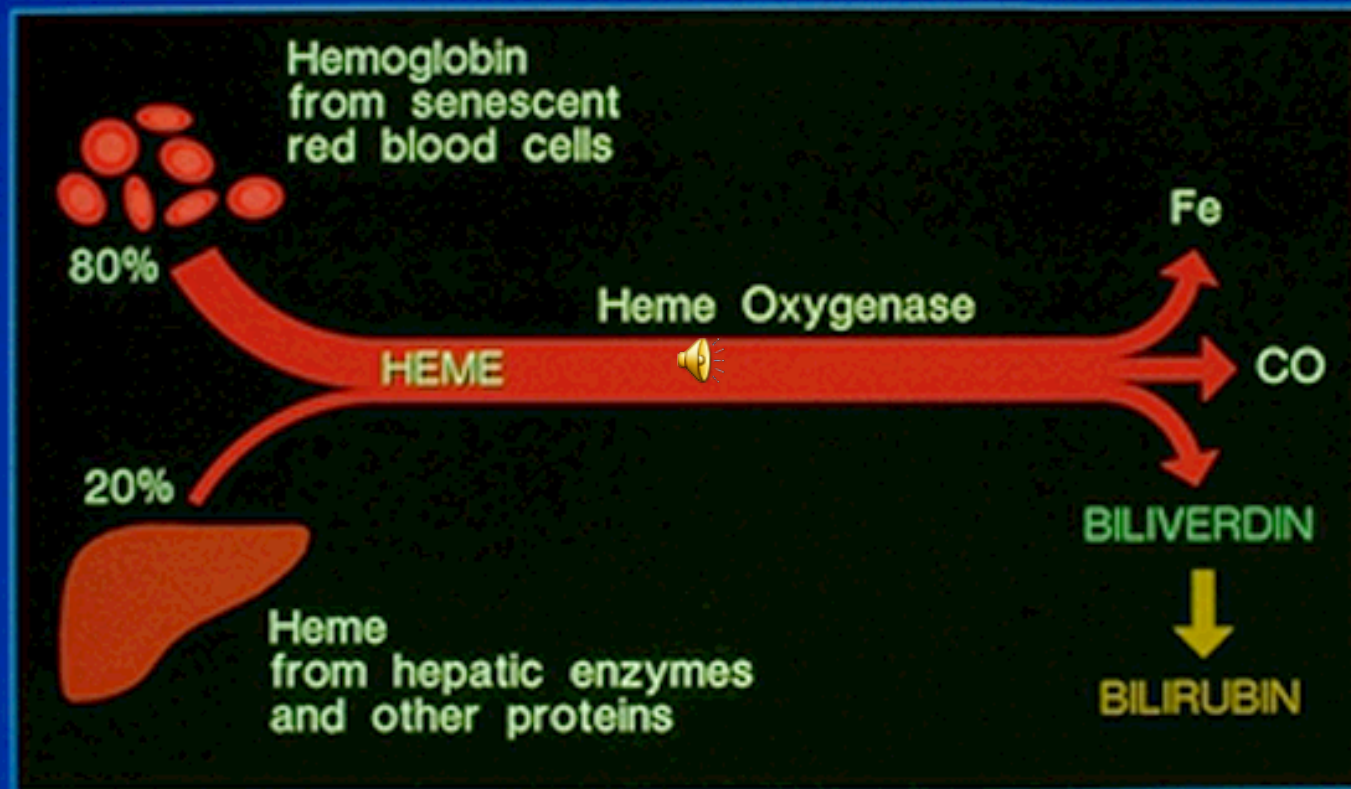
Diffuse Infiltrative Liver Disease

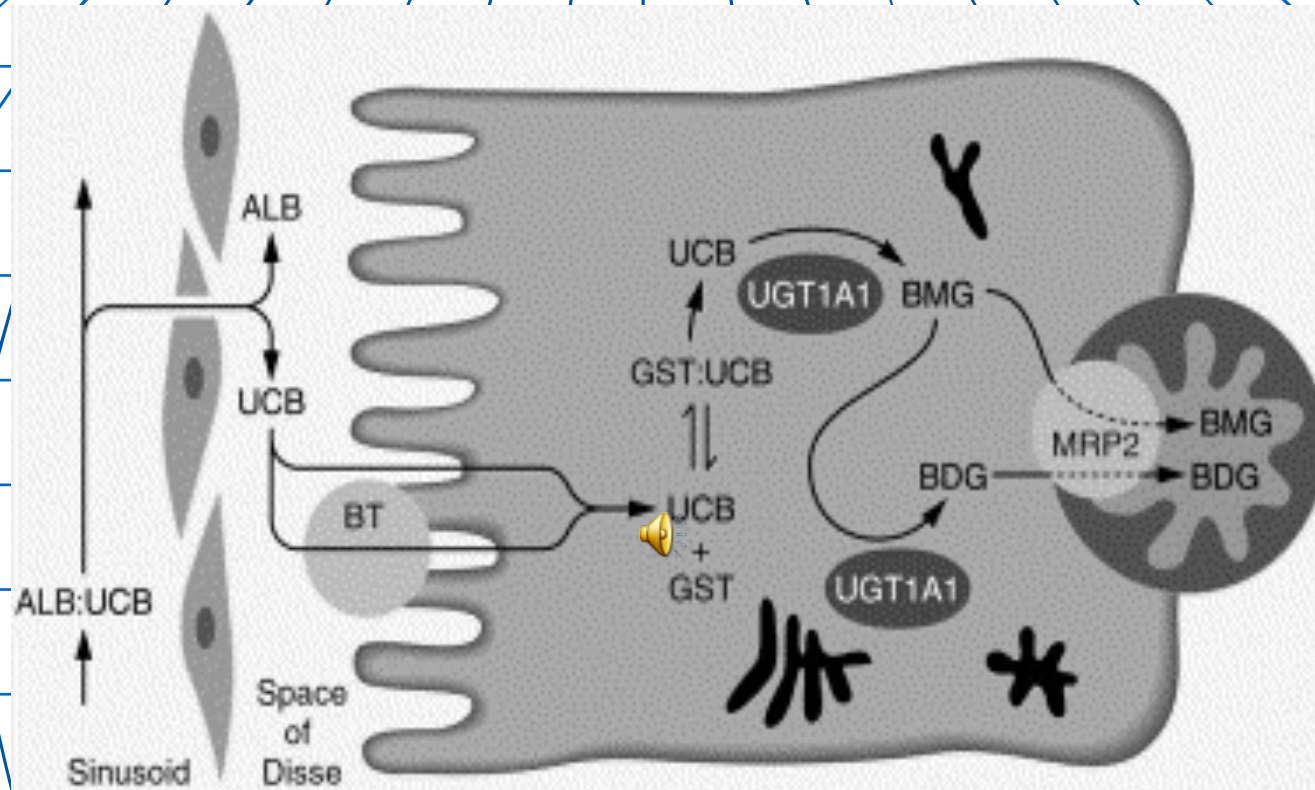
- Sarcoidosis
- Visceral leishmaniasis
- Miliary Tuberculosis
- Amyloidosis 
- Diffuse metastasis
- Lymphoma
- Hepatocellular carcinoma

BILIRUBIN

- Catabolic product of heme metabolism, which is formed by breakdown of heme present in hemoglobin, myoglobin, cytochromes, catalase, peroxidase, and tryptophan pyrrolase.
- Daily bilirubin production (250 to 400 mg) is derived from hemoglobin (80%)
- the remaining 20% being contributed by other heme proteins.

SOURCES OF BILIRUBIN





ALB = Albumin

GST = Glutathione-S-Transferase

UGT1A1 = Bilirubin-UDP-Glucuronosyltransferase

MRP2 = Multidrug Resistance-associated Protein 2

UCB = Unconjugated Bilirubin

BMG = Bilirubin Monoglucuronide

BDG = Bilirubin Diglucuronide

BT = Proposed Bilirubin Transporter

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BILIRUBIN METABOLISM

UPTAKE

TRANSPORT

CONJUGATION

EXCRETION

Sinusoid

Bilirubin
Albumin

Bilirubin
+
Ligandin

Bilirubin
Monoglucuronide

E.R.

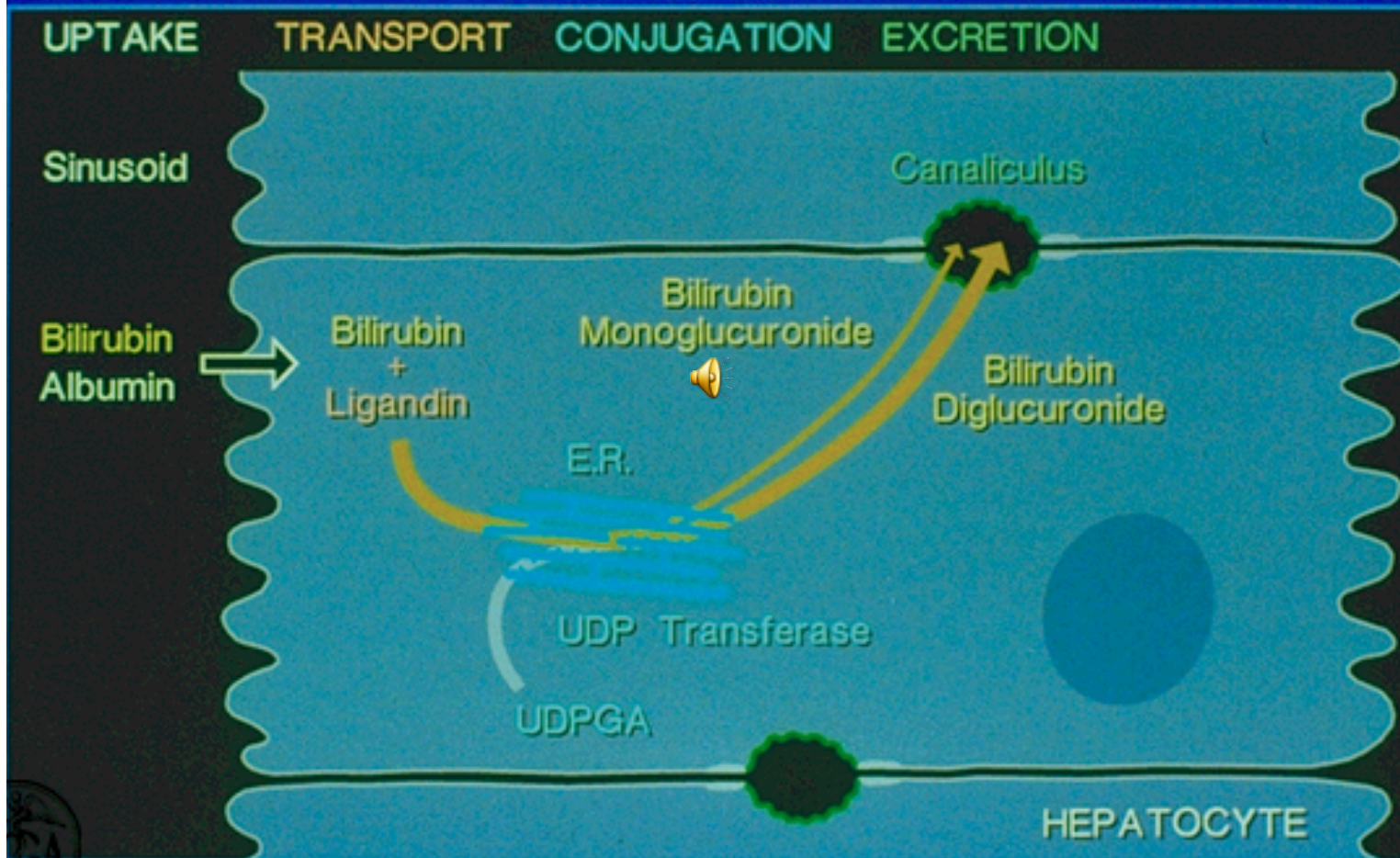
UDP Transferase

UDPGA

Canaliculus

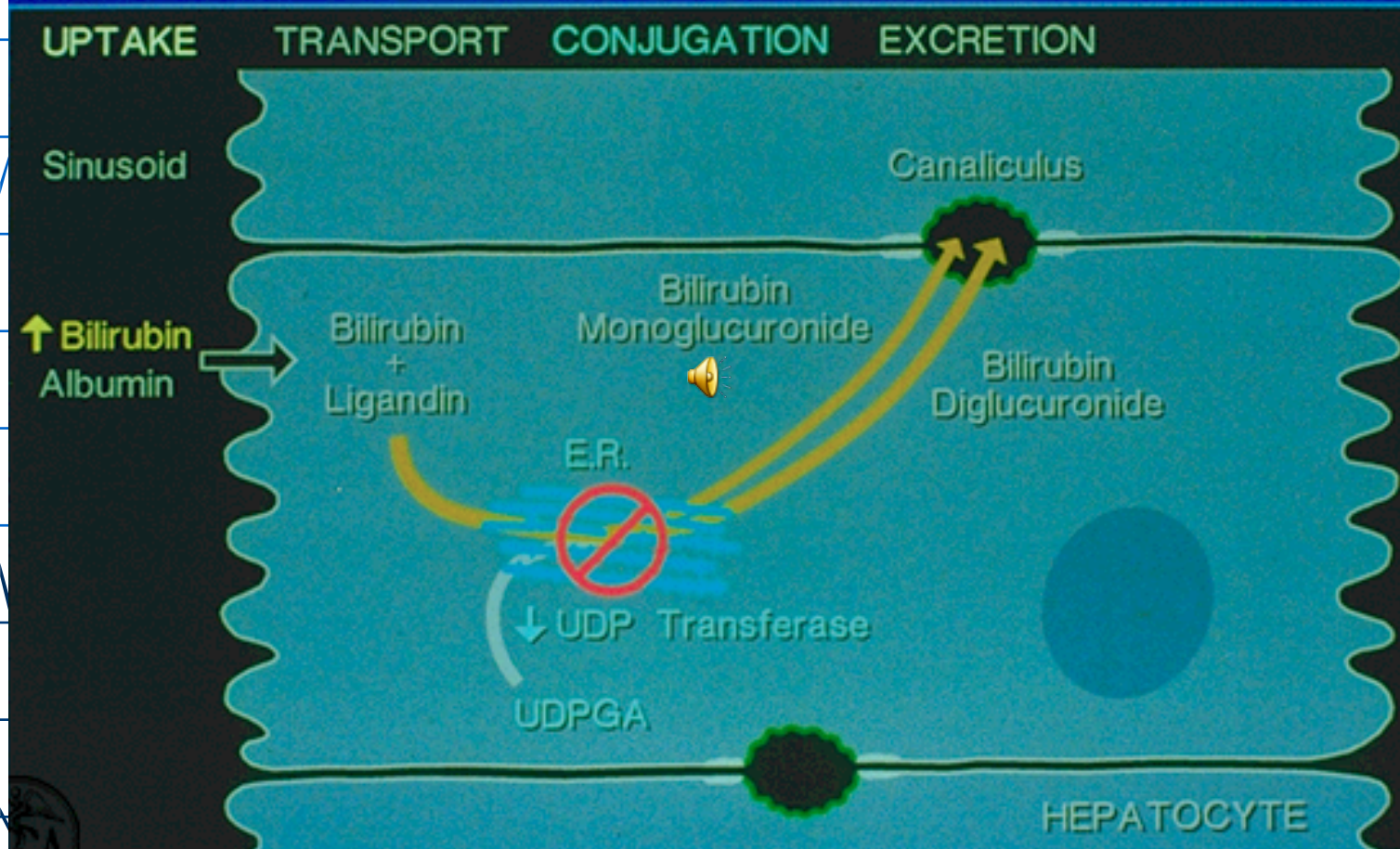
Bilirubin
Diglucuronide

HEPATOCTYTE



Bilirubin Metabolism

GILBERT'S SYNDROME



Bilirubin Metabolism

CRIGLER-NAJJAR SYNDROME

UPTAKE

TRANSPORT

CONJUGATION

EXCRETION

Sinusoid

Canaliculus

Bilirubin
Albumin

Bilirubin
+
Ligandin

Bilirubin
Monoglucuronide

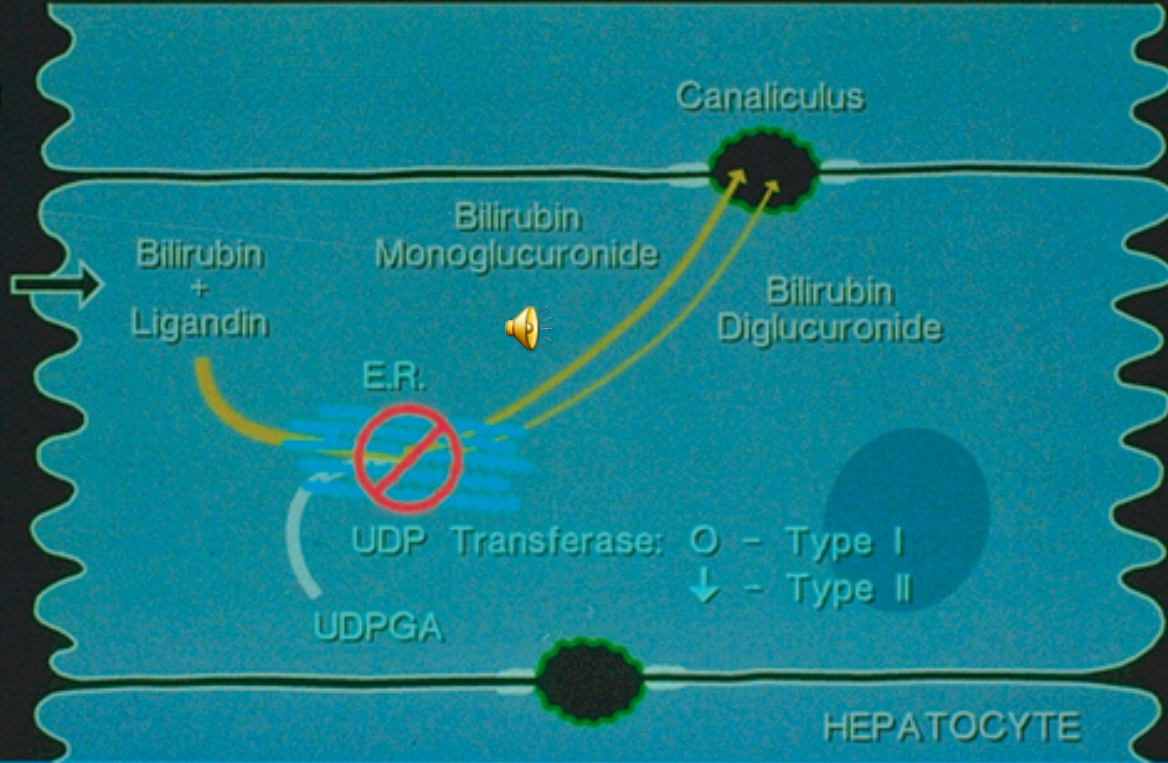
Bilirubin
Diglucuronide

E.R.

UDP Transferase: O - Type I
↓ - Type II

UDPGA

HEPATOCYTE



Bilirubin Metabolism

DUBIN-JOHNSON SYNDROME



UPTAKE

TRANSPORT

CONJUGATION

EXCRETION

Sinusoid

Canaliculus

Bilirubin
Albumin

Bilirubin
+
Ligandin

Bilirubin
Monoglucuronide

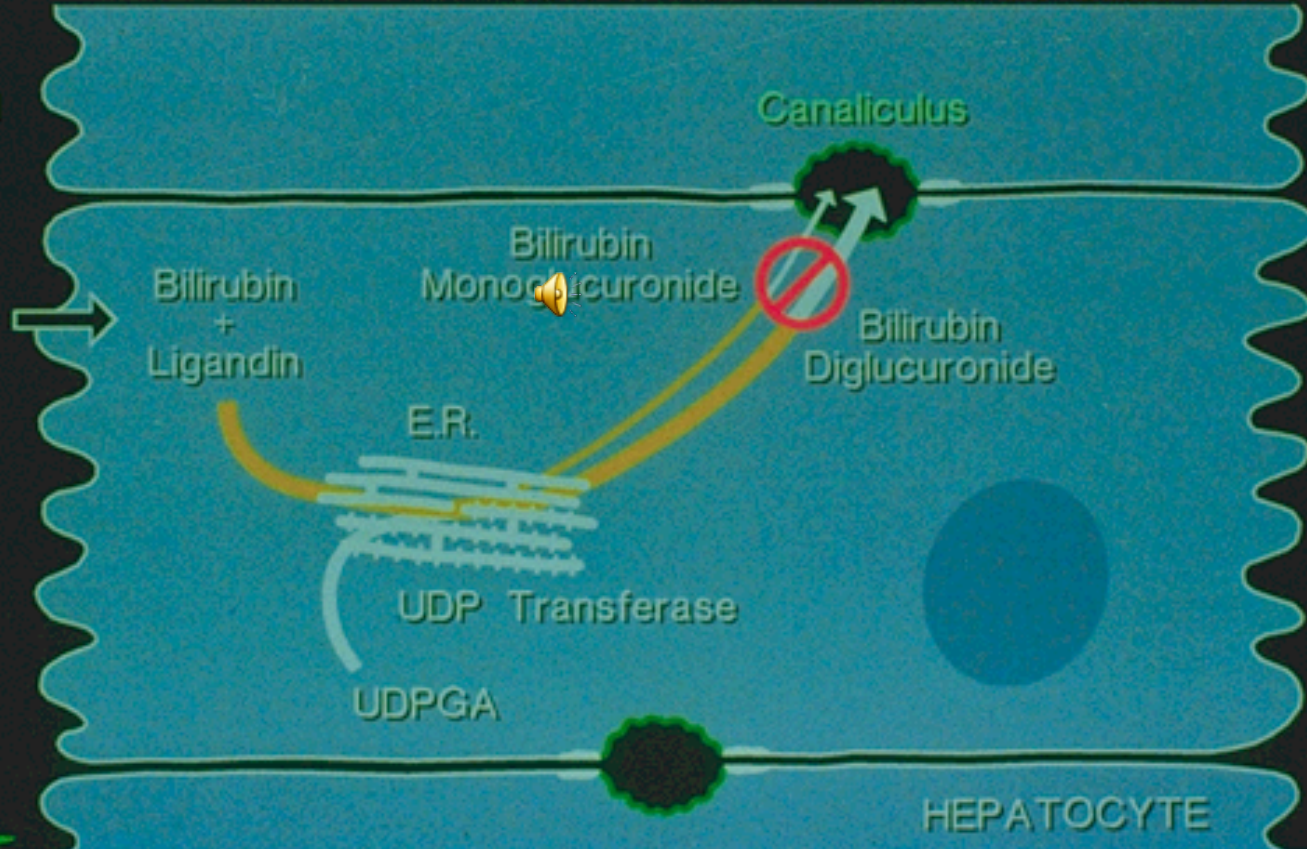
Bilirubin
Diglucuronide

E.R.

UDP Transferase

UDPGA

HEPATOCTYTE

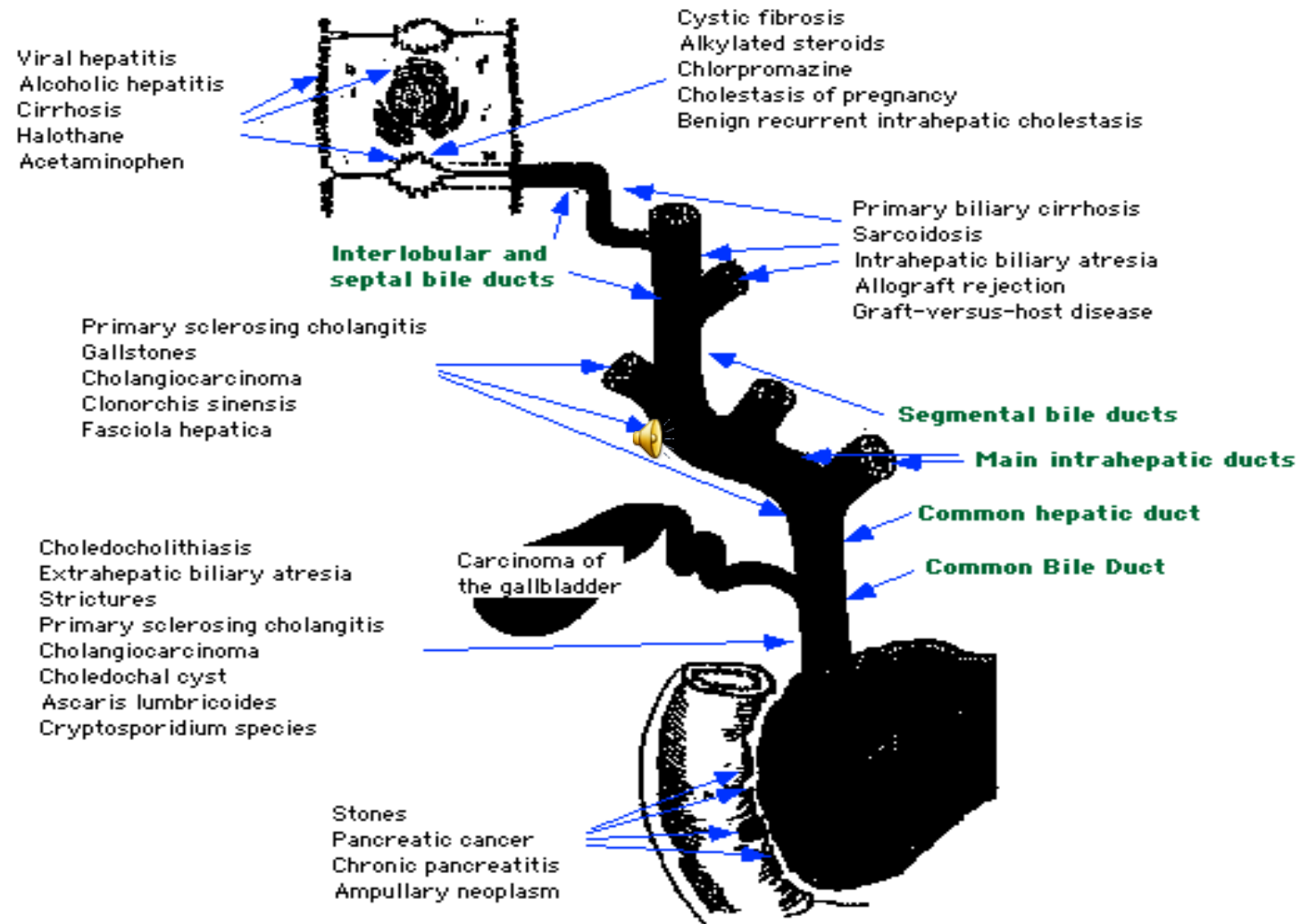


Normal values

- Between 0.2 and 0.9 mg/dL (2 to 15.4 mmol/L) in %95 of the general population,

- < 1 mg/dL (18 mmol/L) in %99
- Direct bilirubin represents up to 30 percent, or 0.3 mg/dL

Diseases and their Histopathologic Sites of Interference with Hepatobiliary Excretion



Jaundice classification

Prehepatic

Overproduction

Impaired uptake
by the liver

Unconjugated
Hyperbilirubinemia

Hepatic

Decrease conjugation

Unconjugated
Hyperbilirubinemia

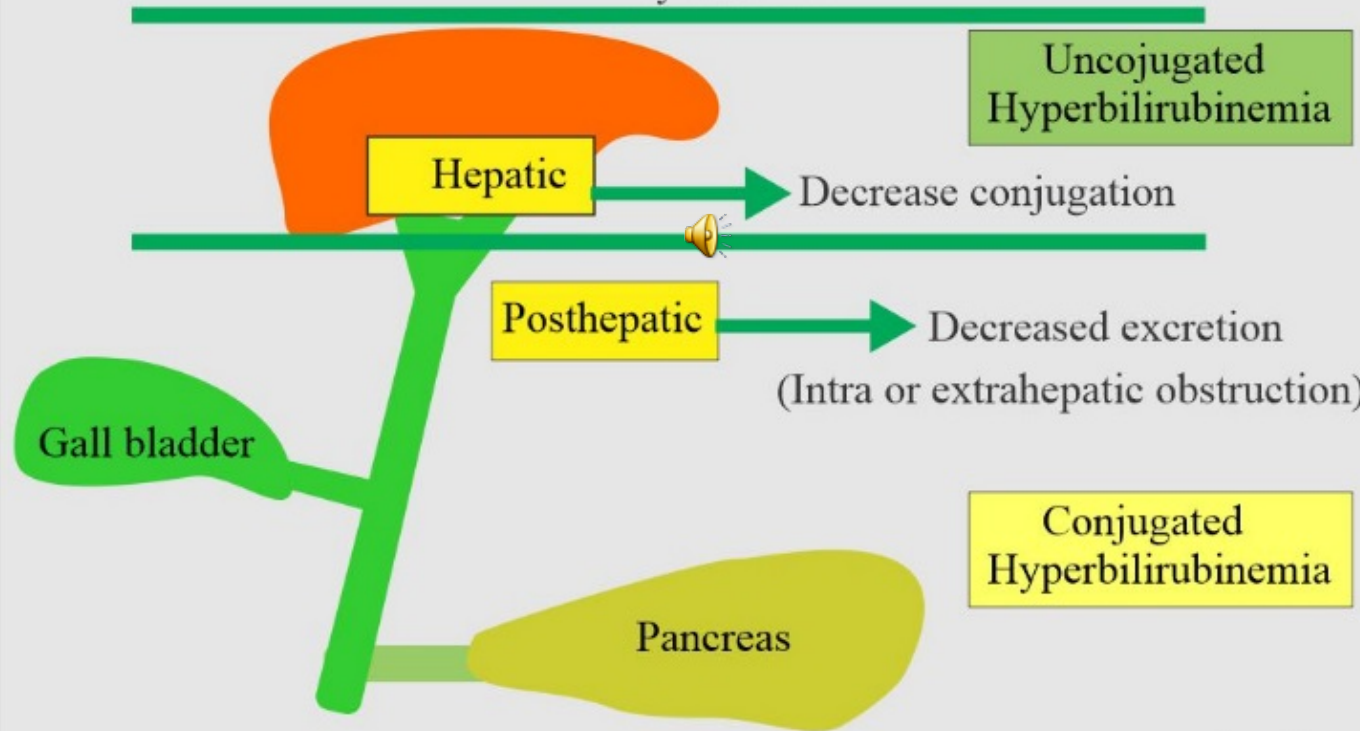
Posthepatic

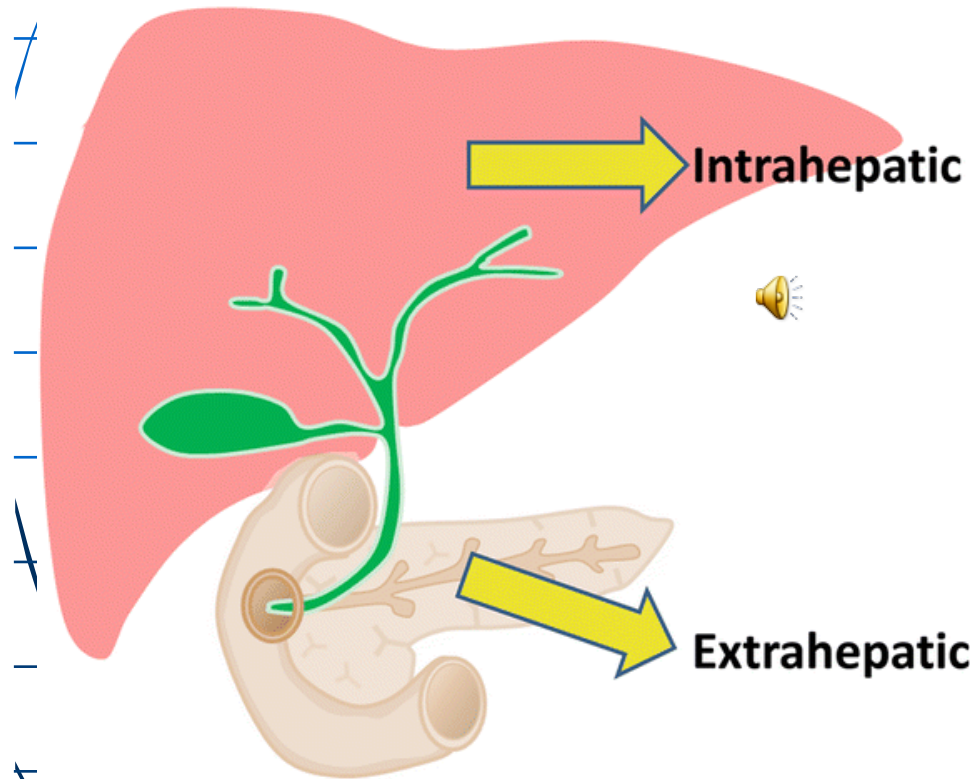
Decreased excretion
(Intra or extrahepatic obstruction)

Conjugated
Hyperbilirubinemia

Gall bladder

Pancreas





Intrahepatic

Extrahepatic

Hepatobiliary infections

Inherited/metabolic dis

Ductal anomaly

Endocrine dis

Prematurity

Drugs

Ischemia

Parenteral nutrition

Sepsis

Biliary atresia

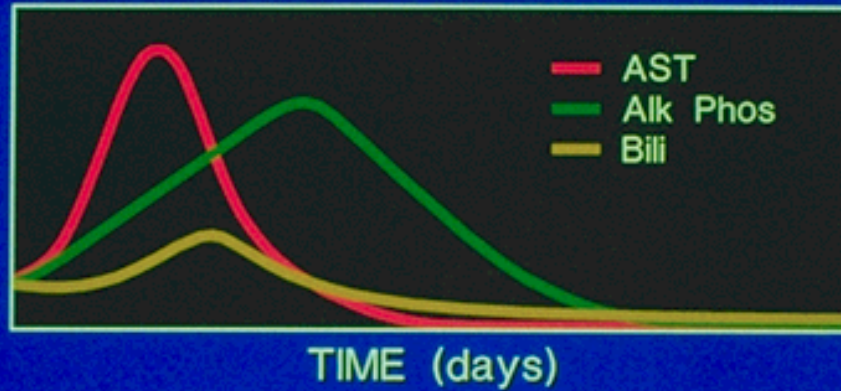
Choledochal cyst

Tumor

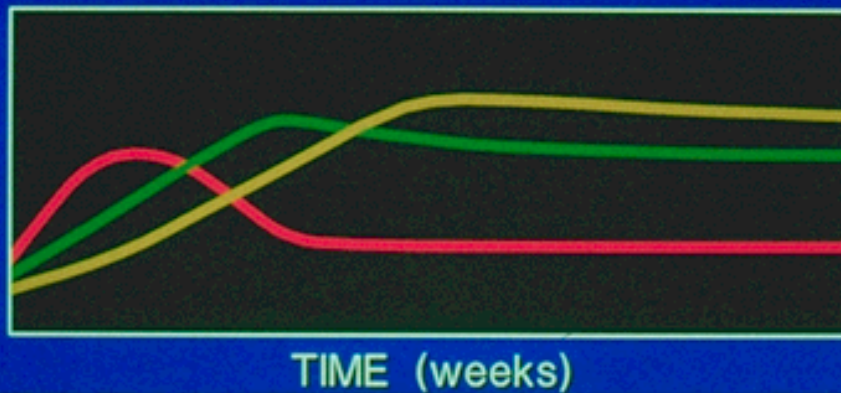
Cholelithiasis

PATTERN OF LIVER CHEMISTRIES IN BILIARY OBSTRUCTION

ACUTE
TRANSIENT

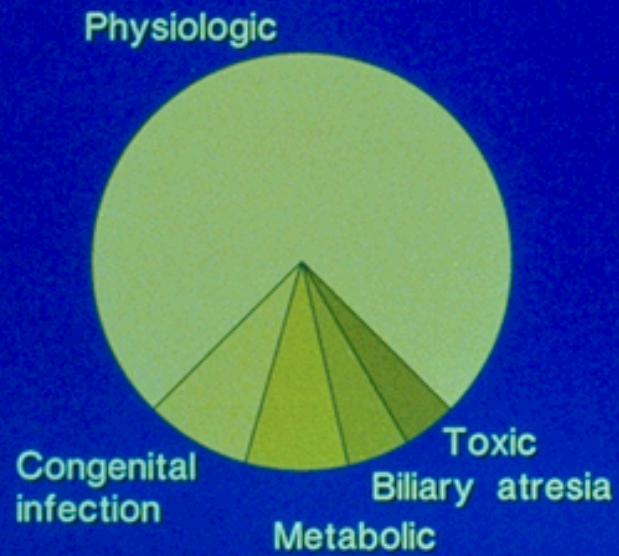


CHRONIC

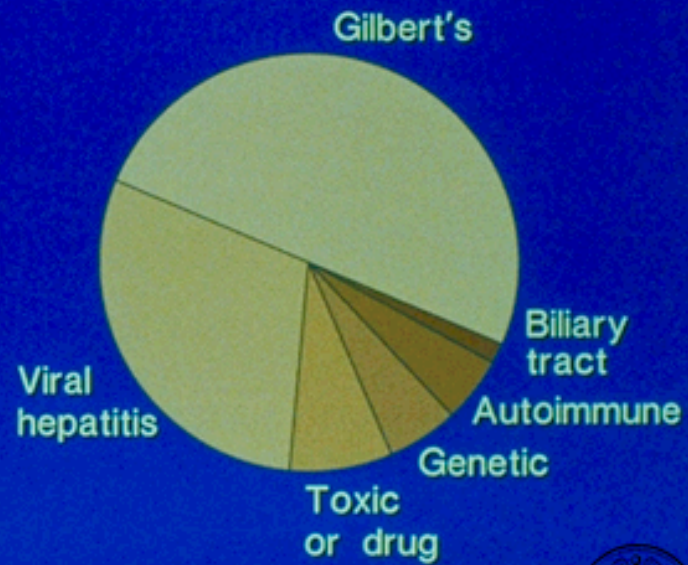


ETIOLOGY OF JAUNDICE

Infants

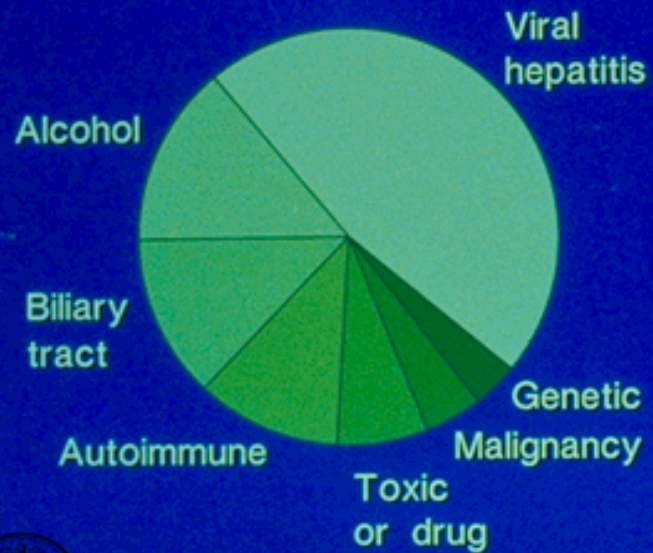


Adolescents

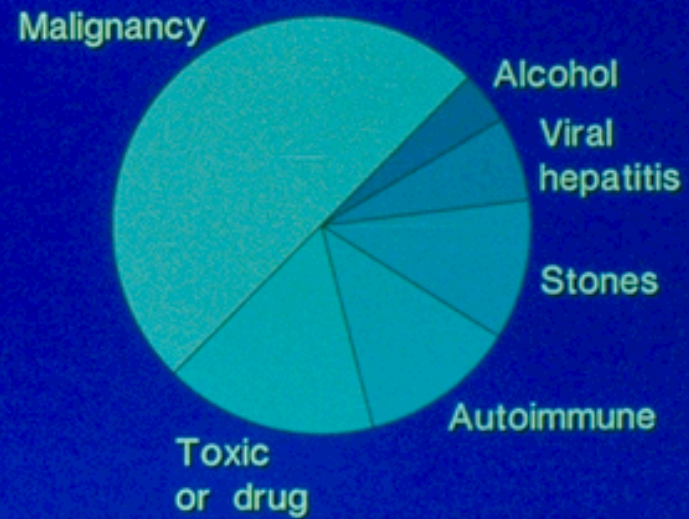


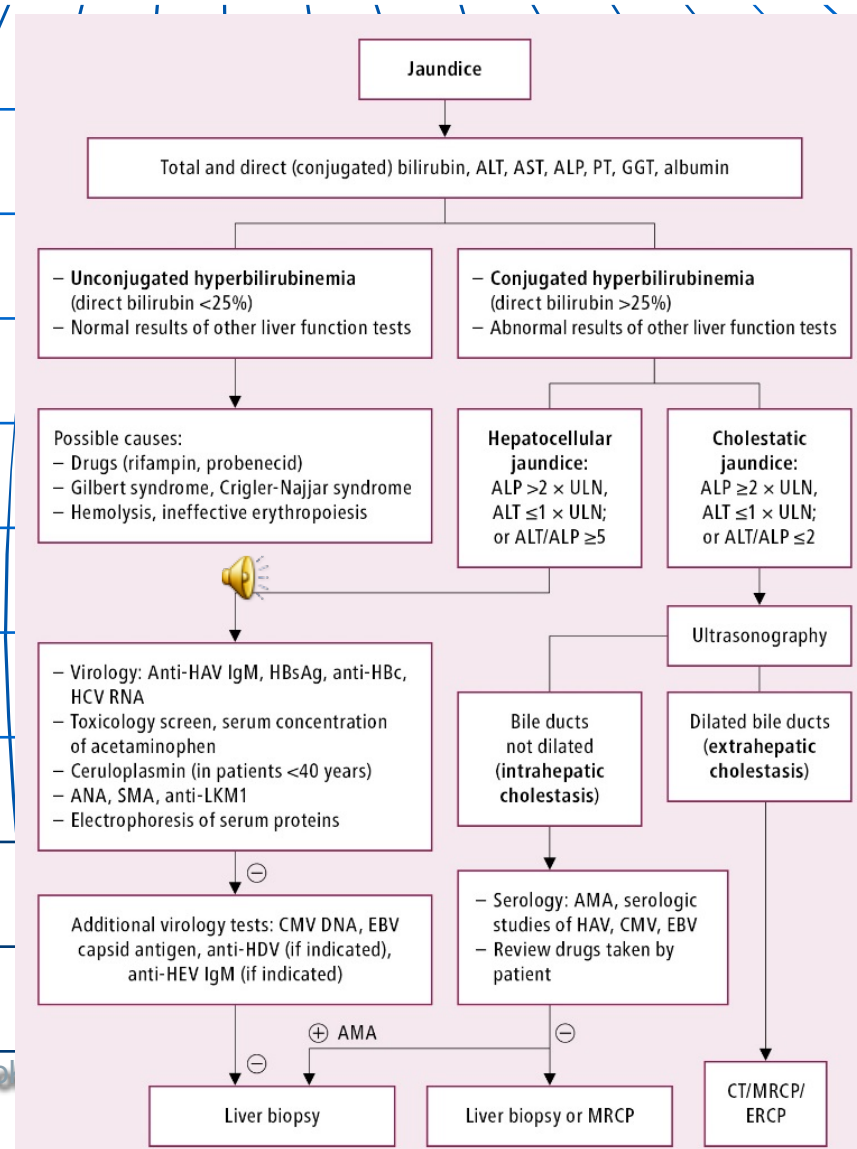
ETIOLOGY OF JAUNDICE

Young Adults



The Elderly





ALGORITHM FOR PATIENT WITH JAUNDICE

History (focus on medication/drug exposure)
Physical examination
Lab tests: Bilirubin with fractionation,
ALT, AST, alkaline phosphatase,
prothrombin time, and albumin

Isolated elevation
of the bilirubin

Direct
hyperbilirubinemia
(direct > 15%)

Inherited disorders
Dubin-Johnson
syndrome
Rotor syndrome

Indirect
hyperbilirubinemia
(direct < 15%)

Drugs
Rifampicin
Probenecid

Inherited disorders
Gilbert syndrome
Crigler-Najjar syndrome

Hemolytic disorders
Ineffective erythropoiesis

Bilirubin and other
liver tests elevated

Hepatocellular pattern:
ALT/AST elevated out
of proportion to
alkaline phosphatase

1. Viral serologies
Hepatitis A IgM
Hepatitis B surface
antigen and core
antibody (IgM)
Hepatitis C RNA
2. Toxicology screen
Acetaminophen level

Results
negative

Additional virologic testing
CMV DNA, EBV capsid
antigen
Hepatitis D antibody
(if indicated)
Hepatitis E IgM
(if indicated)

Results
negative

Liver biopsy

Cholestatic pattern:
Alkaline phosphatase
elevated out of
proportion to ALT/AST

Ultrasound

Dilated ducts:
Extrahepatic
cholestasis

CT/ERCP

Ducts not dilated:
Intrahepatic
cholestasis

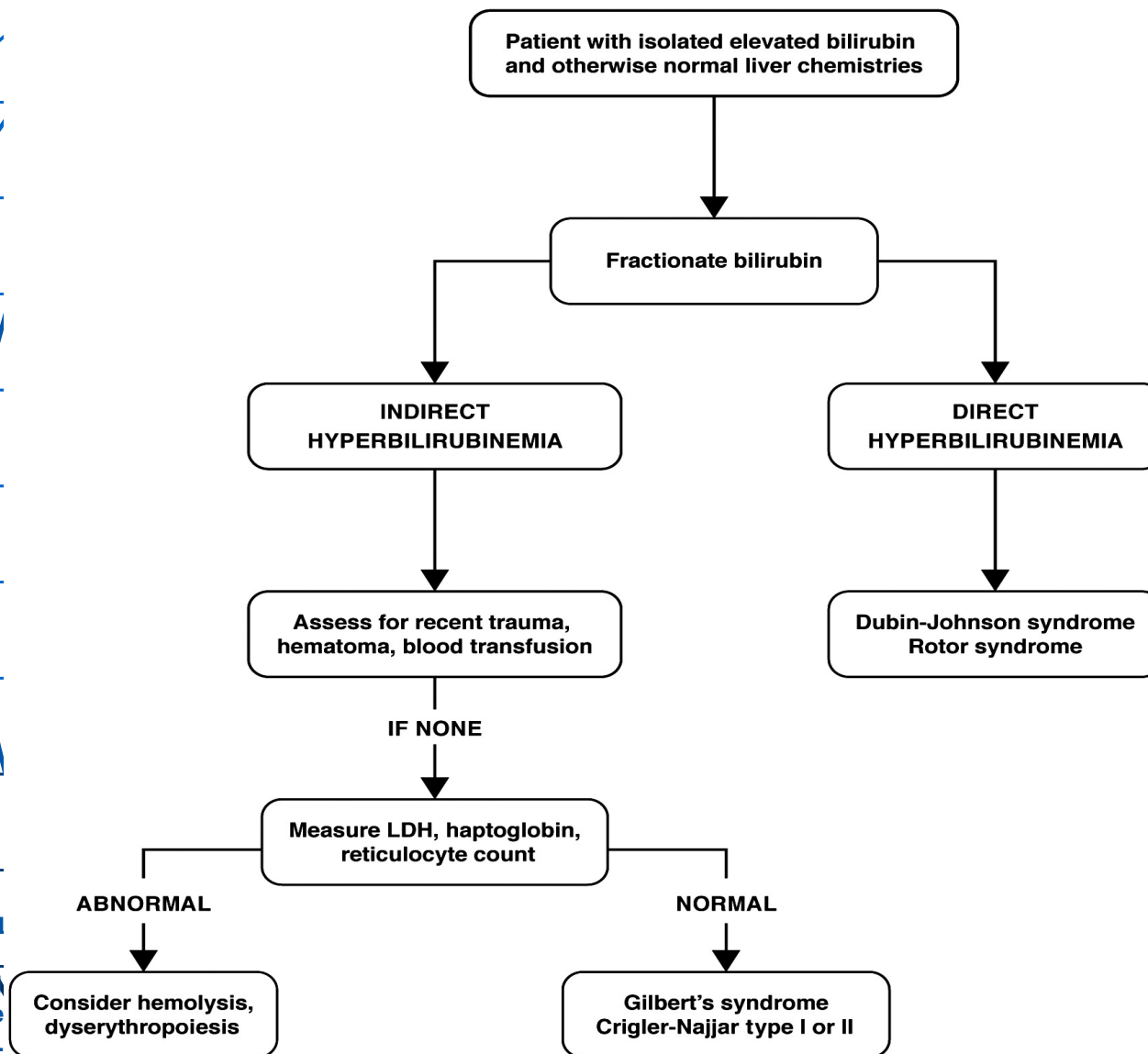
Serologic testing
AMA
Hepatitis serologies
Hepatitis A, CMV, EBV
Review drugs

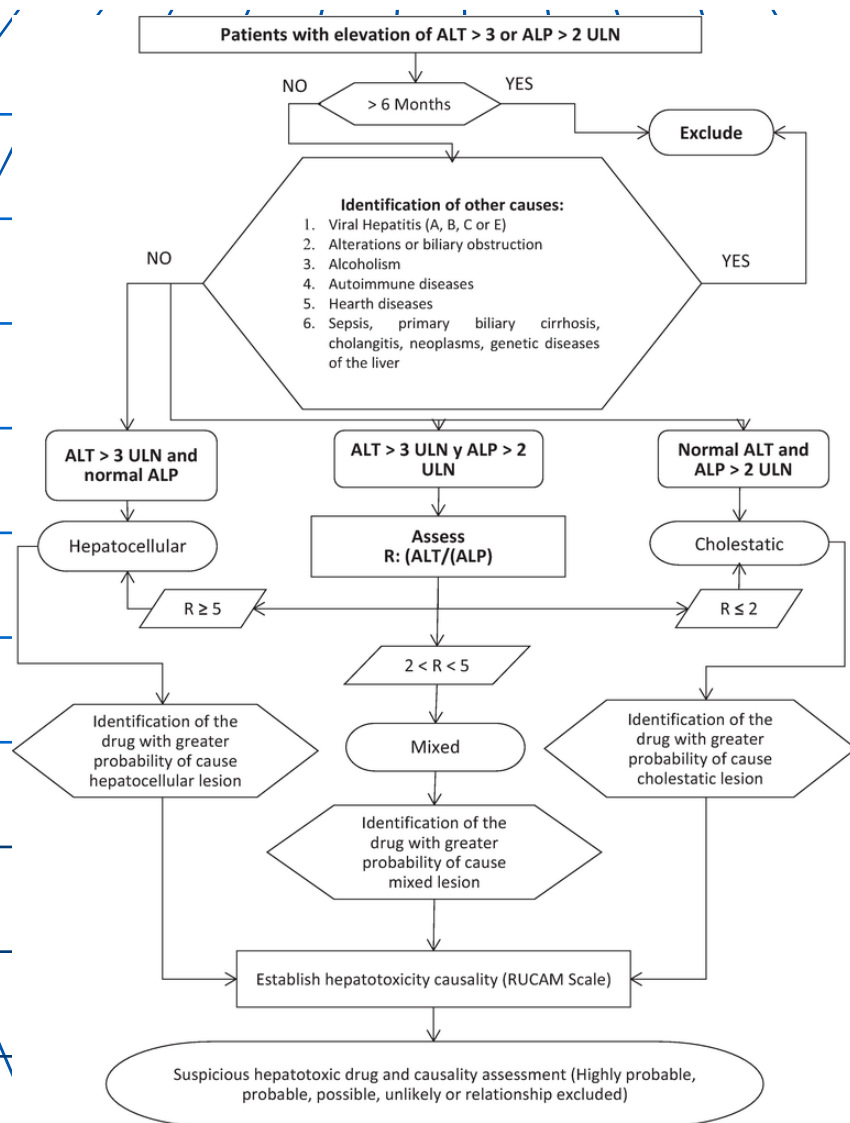
Results
negative

MRCP/Liver biopsy

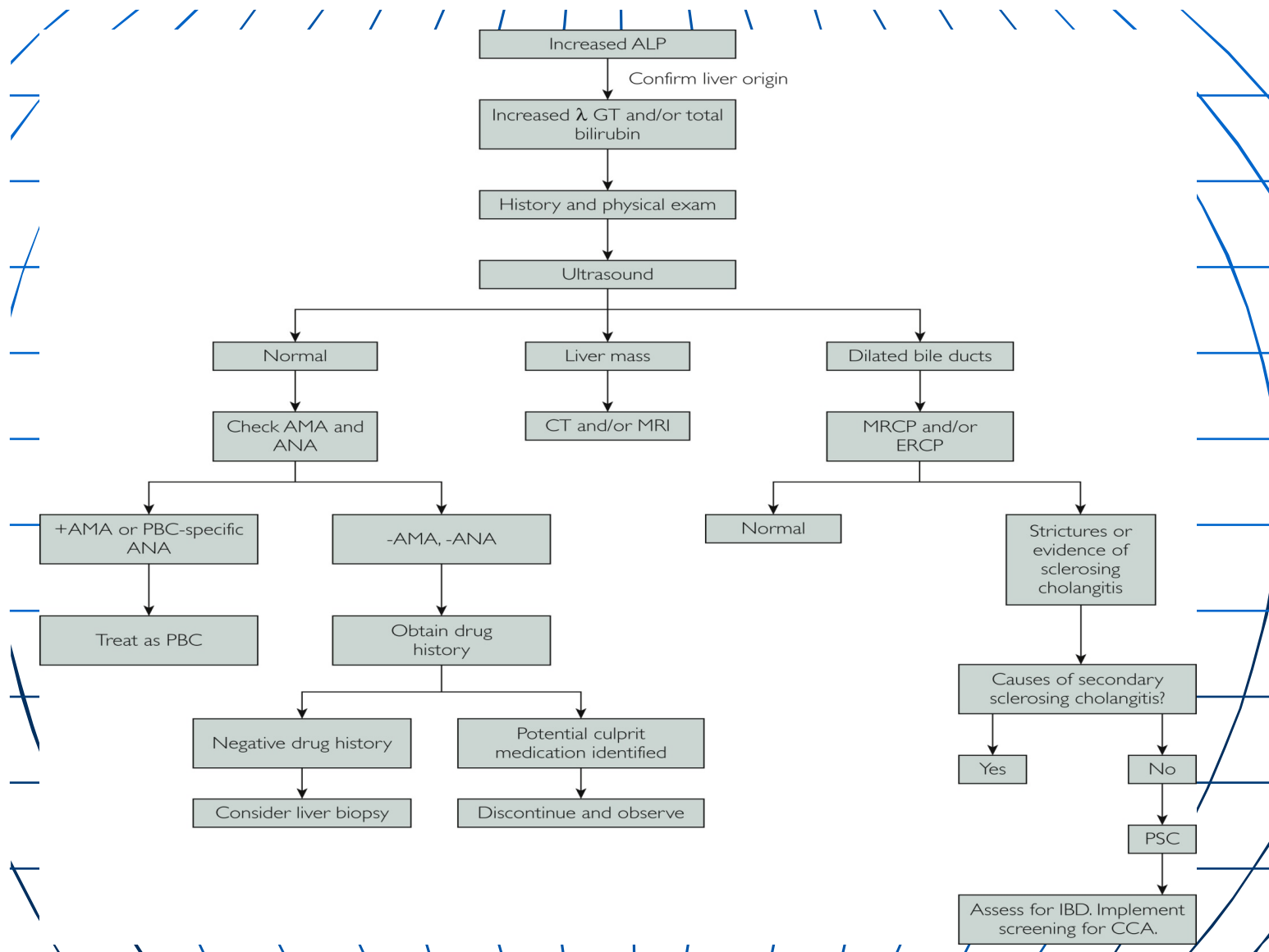
AMA
positive

Liver biopsy

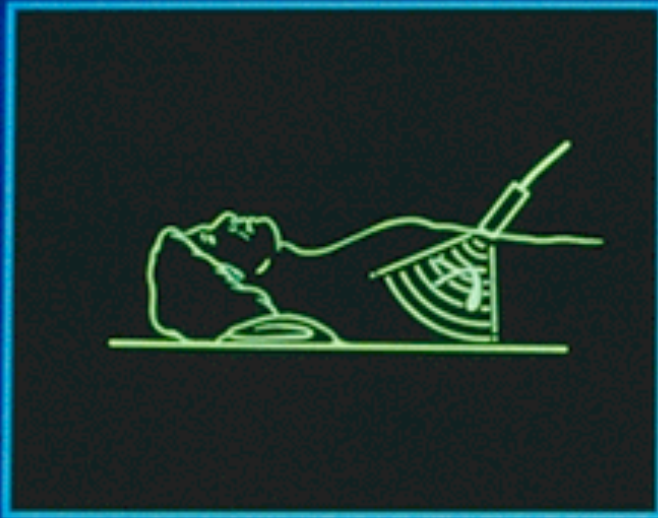




ALT: alanine-aminotransferase; ALP: alkaline phosphatase; ULN: upper limit of normal



ULTRASONOGRAPHY



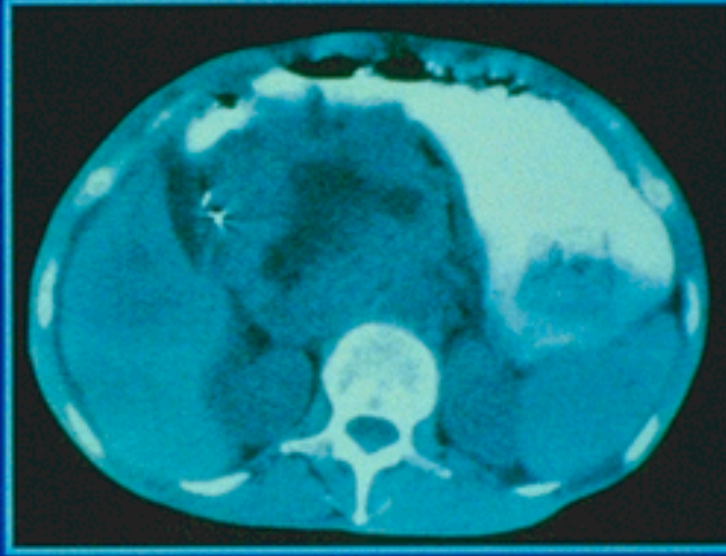
ADVANTAGES

No ionizing radiation
Portable
Multiple planes
Biopsy localization

LIMITATIONS

Operator dependent
Patient dependent
Interpretation subjective
Poor for intraductal stones

COMPUTED TOMOGRAPHY



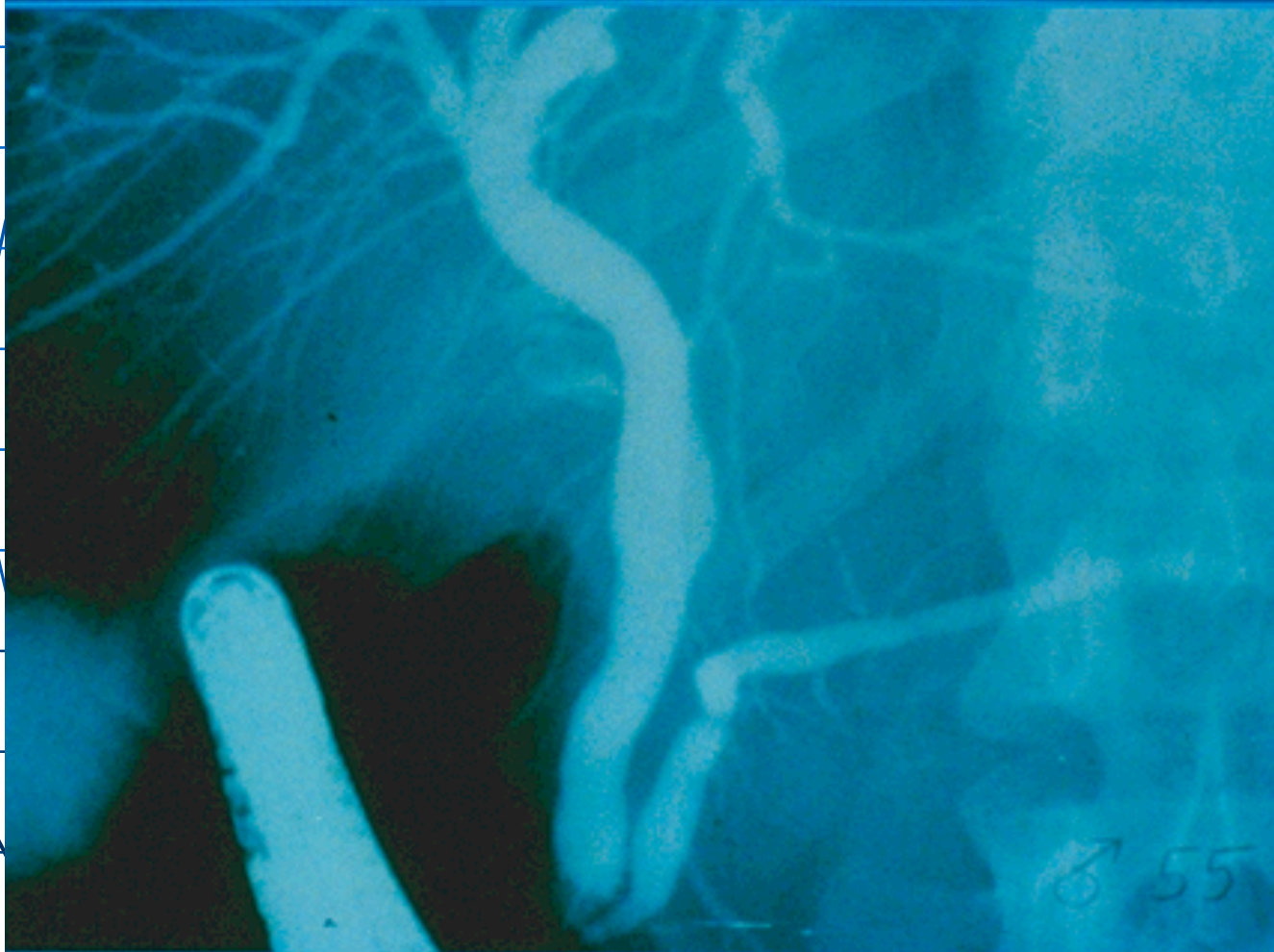
ADVANTAGES

- Complete anatomy
- Tissue characterization
- Reproducible
- Precise biopsy localization

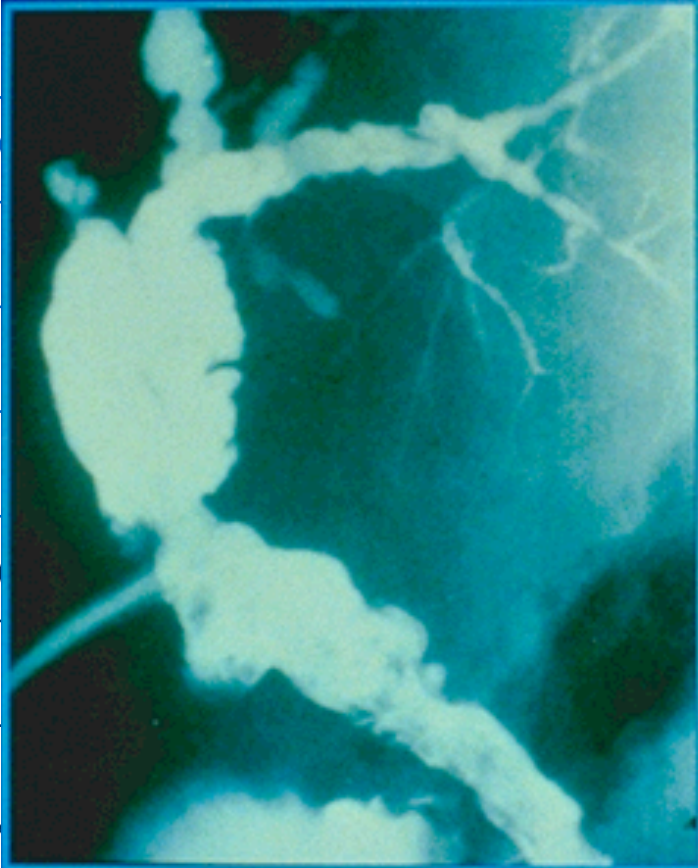
LIMITATIONS

- Axial sections only
- Ionizing radiation
- Contrast side effects
- May miss gallstones

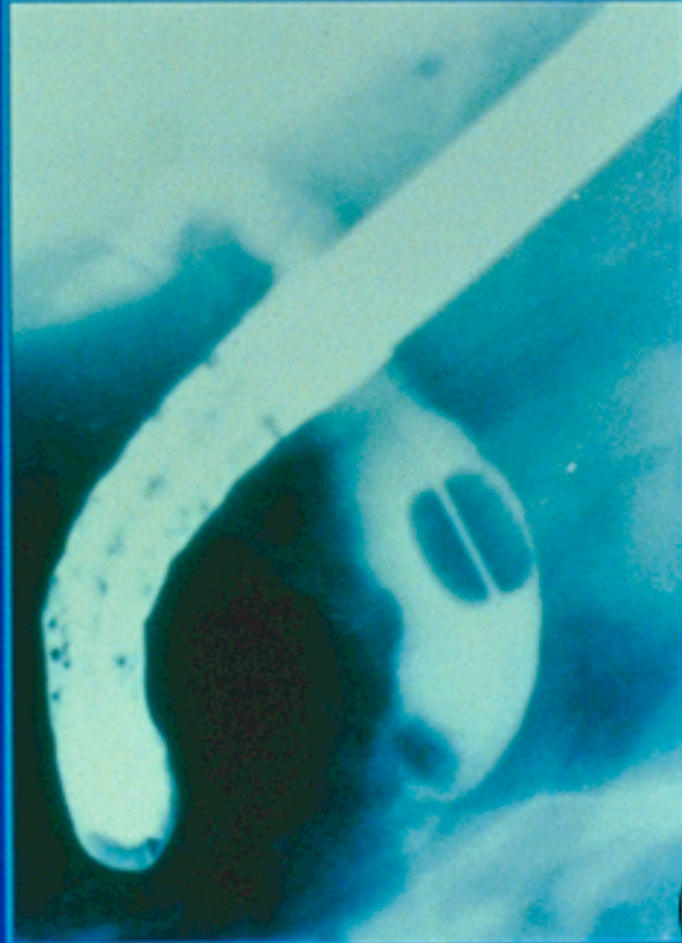
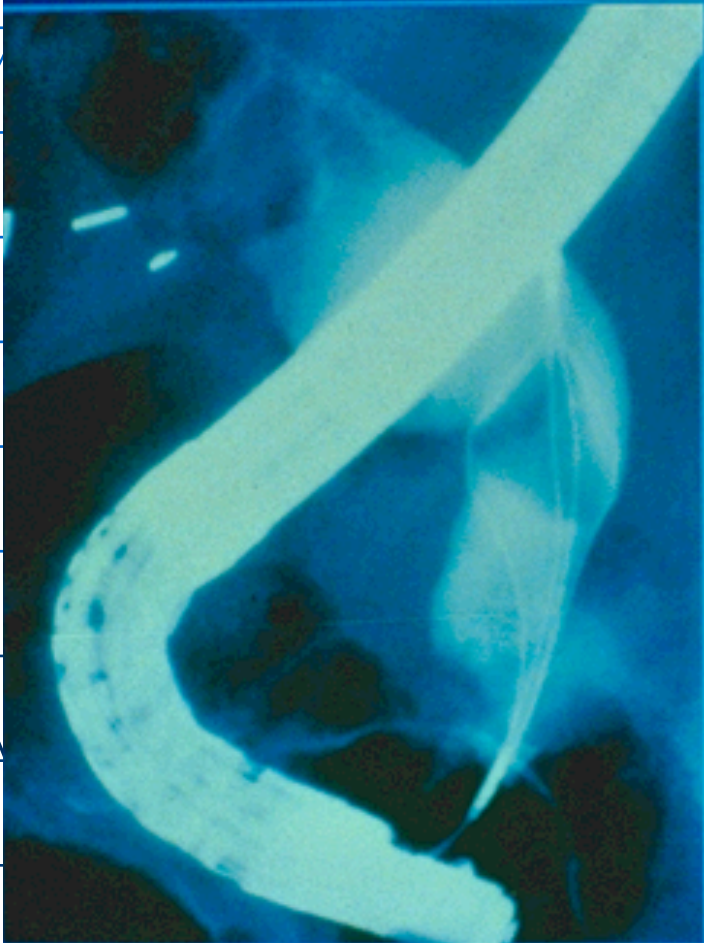
NORMAL ERCP



SCLEROSING CHOLANGITIS



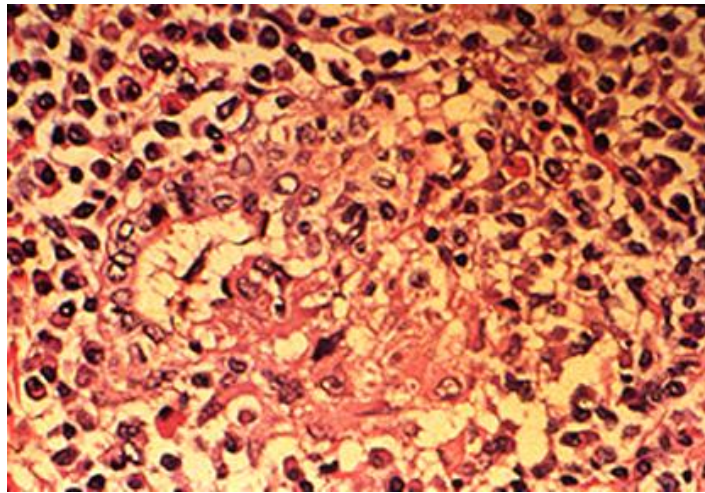
STONE EXTRACTION



Case 1

- Middle age woman
- Fatigue, pruritus
- Hepatosplenomegaly
- T: 37.4
- AST: 45 U/L
- ALT: 55 U/L
- ALP: 545 U/L
- GGT: 143 U/L
- Liver ultrasonography:
- Normal diameter of intra and extra hepatic biliary ducts
- GB wall thickness was normal and contained neither stone nor sludge

- AMA: neg
- HAV Ab IgM: Neg



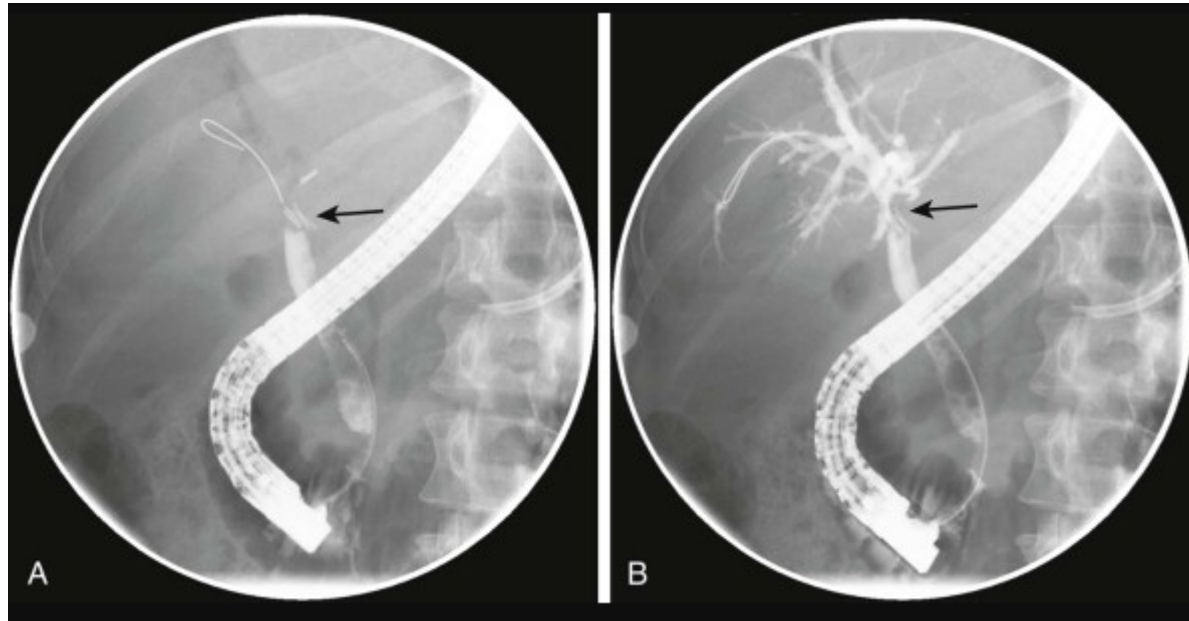
Case 2

- Middle age man
- UC on Azathioprine and mesalazine
- RUQ pain, fever, icterus
- Hepatosplenomegaly
- T: 38.4
- AST: 445 U/L
- ALT: 455 U/L
- ALP: 545 U/L
- GGT: 142 U/L
- Liver ultrasonography:
- Normal diameter of intra and extra hepatic biliary ducts
- GB wall thickness was normal and contained neither stone nor sludge



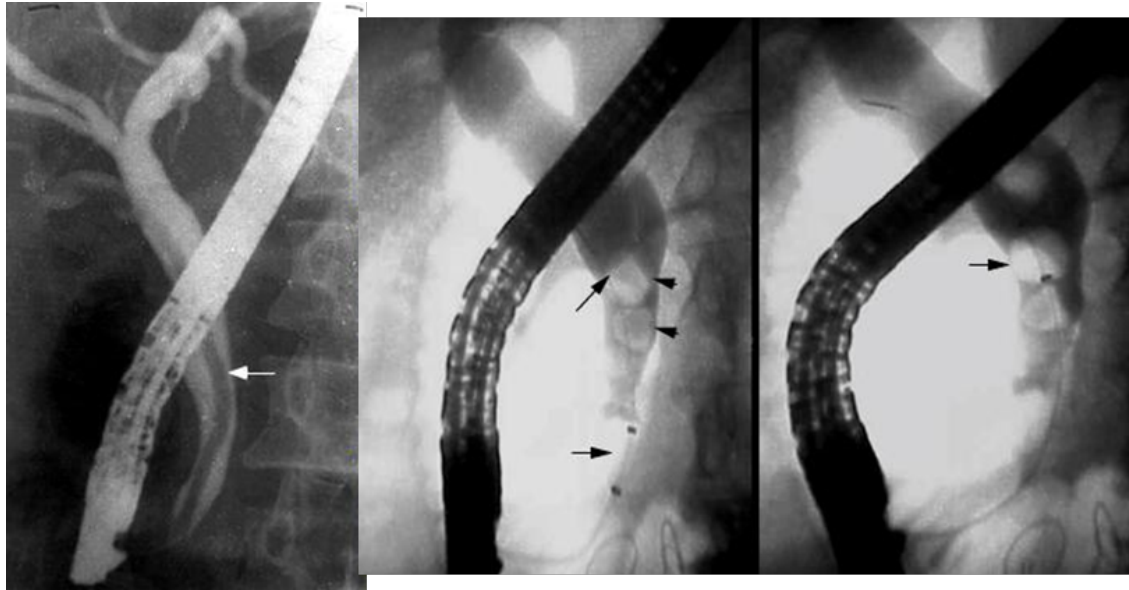
Case 3

- RUQ pain, icterus post cholecystectomy state
- T: 38
- AST: 345 U/L
- ALT: 355 U/L
- ALP: 545 U/L
- GGT: 103 U/L
- Liver ultrasonography:
- The extra hepatic biliary ducts are dilated
- GB was not seen.



Case 4

- RUQ pain, icterus
- T: 38
- AST: 345 U/L
- ALT: 355 U/L
- ALP: 545 U/L
- GGT: 103 U/L
- Liver ultrasonography:
- The extra hepatic biliary ducts are dilated
- GB wall thickness was normal and contained neither stone nor sludge



Case 5

- Pruritus, icterus
- Co-amoxiclav for pharyngitis
- T: 37
- AST: 345 U/L
- ALT: 355 U/L
- ALP: 545 U/L
- GGT: 103 U/L
- Liver ultrasonography:
- The intra and extra hepatic biliary ducts are normal
- GB wall thickness was normal and contained neither stone nor sludge

Case 6

- RUQ pain, Pruritus, icterus
- T: 37.8
- AST: 345 U/L
- ALT: 355 U/L
- ALP: 545 U/L
- GGT: 103 U/L
- Liver ultrasonography:
- The intra biliary ducts are dilated
- Multiple cysts in both lobes
- GB wall thickness was normal and contained neither stone nor sludge

Case 7

- RUQ pain, Pruritus, icterus
- T: 37.8
- AST: 345 U/L
- ALT: 355 U/L
- ALP: 545 U/L
- GGT: 103 U/L
- Liver ultrasonography:
- The intra biliary ducts are dilated
- Multiple cysts in both lobes
- GB wall thickness was normal and contained neither stone nor sludge



Case 8

- RUQ pain, Pruritus, icterus
- T: 37.4
- AST: 35 U/L
- ALT: 45 U/L
- ALP: 645 U/L
- GGT: 233 U/L
- Liver ultrasonography:
- The intra biliary ducts are dilated
- GB wall thickness was normal and contained neither stone nor sludge



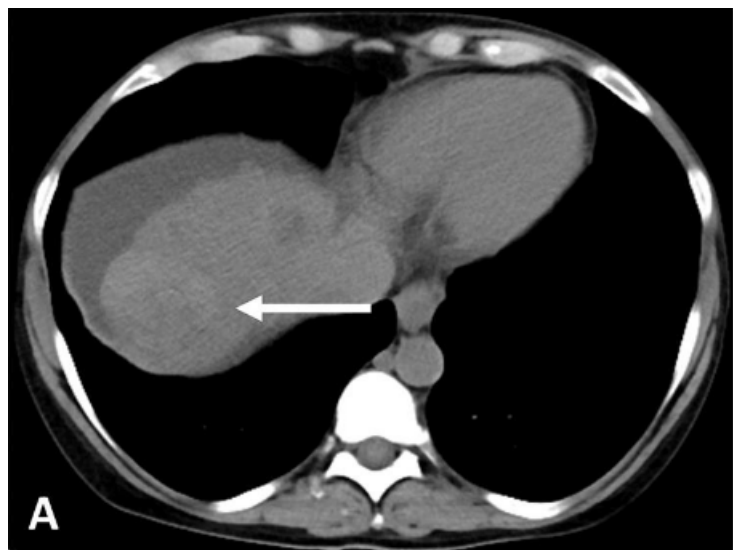
Case 9

- RUQ pain, Pruritus, icterus
- T: 37.4
- AST: 35 U/L
- ALT: 45 U/L
- ALP: 645 U/L
- GGT: 233 U/L
- Liver ultrasonography:
- The intra and extra biliary ducts are dilated
- GB is dilated. The wall thickness is normal and contains multiple stones.



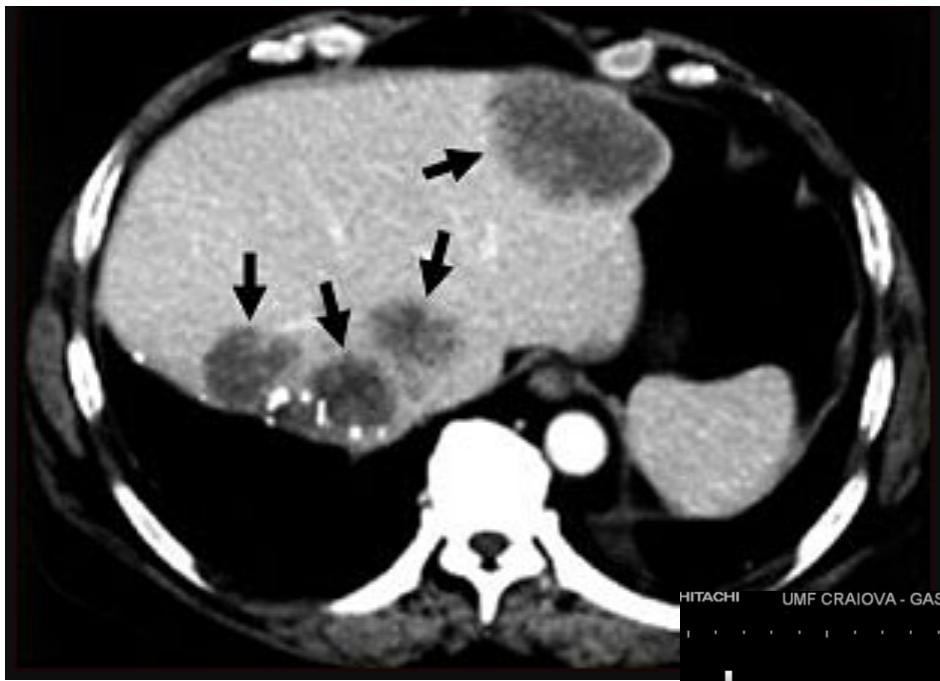
Case 10

- RUQ pain, Pruritus, icterus
- HBs Ag+
- T: 37.4
- AST: 35 U/L
- ALT: 45 U/L
- ALP: 645 U/L
- GGT: 233 U/L
- Liver ultrasonography:
- Hypodense mass lesions in liver.
- Small size liver with coarse echotexture.
- Mild ascites.
- GB wall thickness is normal. It contains multiple stones.



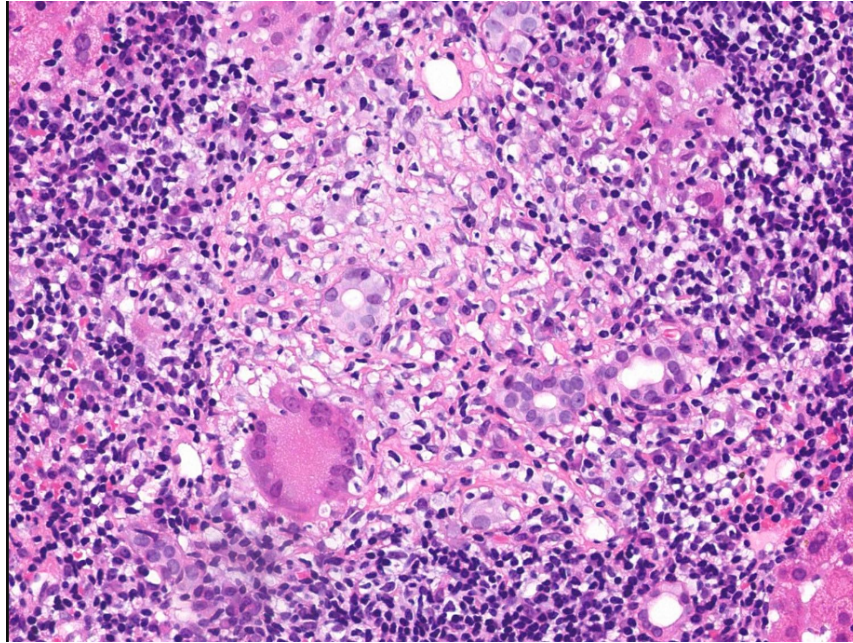
Case 11

- RUQ pain, Pruritus, icterus, anemia, constipation
- T: 37.4
- AST: 35 U/L
- ALT: 45 U/L
- ALP: 645 U/L
- GGT: 233 U/L
- Liver ultrasonography:
- Target shape hypoecho lesions in both liver lobes.
- GB wall thickness is normal. It contains multiple stones.



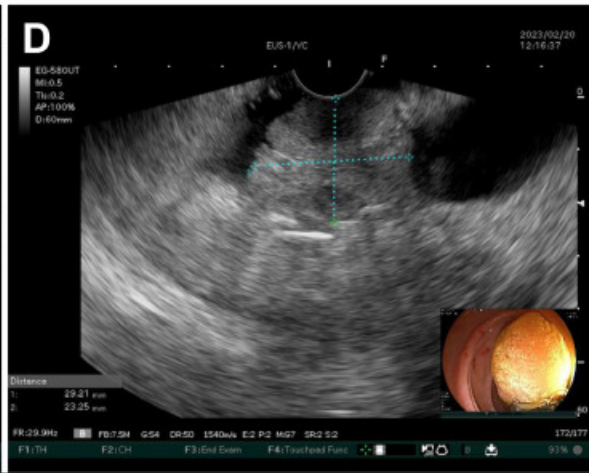
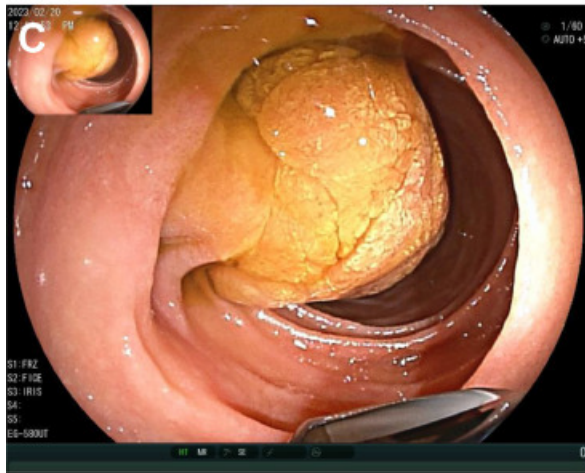
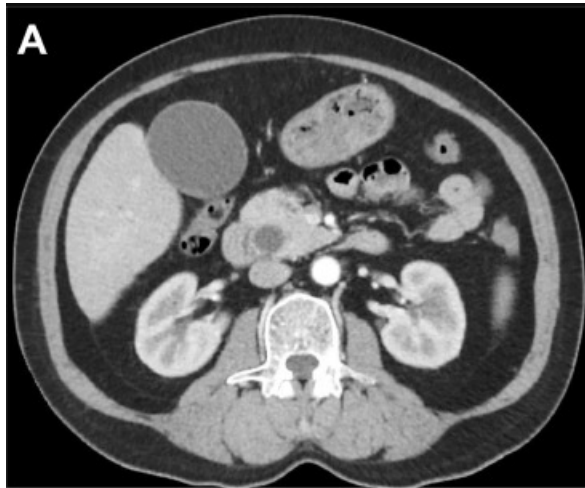
Case 12

- Dyspnea, Pruritus, anemia, macular skin rash
- T: 37.4
- AST: 35 U/L
- ALT: 45 U/L
- ALP: 645 U/L
- GGT: 233 U/L
- Liver ultrasonography:
- The intra and extra biliary ducts are normal.
- GB wall thickness is normal. It contains multiple stones.



Case 13

- RUQ pain, intermittent icterus, anemia, melena
- T: 37.4
- AST: 35 U/L
- ALT: 45 U/L
- ALP: 645 U/L
- GGT: 233 U/L
- Liver ultrasonography:
- The intra hepatic biliary ducts are not dilated
- CBD is mildly increased in size
- GB wall thickness is normal. It contains multiple stones.



Case 14

- A pregnant woman (P1G1) with gestational age of 36 weeks presented with **pruritus**, **dark urine**, **epigastric pain**, **fatigue**, and **anorexia**. The Gynecologist referred her for further evaluation.
- PMH and Medication Hx: Neg
- Physical examination:
 - Vital signs are stable
 - Ichterus
 - Scar of itching

Case 14

- **Plt: 235000 (Per microliter)**
- **Hb: 12.5 (g/dl)**
- **WBC: 5600 (Per microliter) / (PMN: 56%)**
- **Cr: 1.1 (mg/dl) / BUN: 40 (mg/dl) / Uric acid: 6.6 (mg/dl)**
- **K: 4.5 (mEq/L) /Na: 135 (mEq/L)**
- **P Co2: 24 / HCo3: 22 (mEq/L) / Ph: 7.42**
- **Lipase: 40 (mg/dl)**
- **AMA: Negative**
- **AST: 50 U/L**
- **ALT: 44 U/L**
- **Alp: 970 U/L**
- **GGT: 120 U/L**
- **Bili T: 3 mg/dl**
- **Bili D: 1.8 mg/dl**
- **INR: 1.1**
- **Ammonia: 5**
- **BS: 98 mg/dl**

Case 14

- **Abdominal ultrasonography:**
 - **Normal parenchyma echotexture without any space occupying lesion**
 - **Normal appearing intra and extra bile ducts regarding size and shape**
 - **Portal vein diameter in normal range**
 - **Round liver borders**
 - **Gall Bladder is well distended and has normal wall thickness.**
 - **Spleen size in normal range**
 - **No free fluid in abdominal / pelvic cavity**

Case 14

- **UDCA 300 mg/ TDS started**
- **Symptomatic improvement**
 - Pruritus
 - Fatigue
- **Biochemical improvement**
 - Bili
 - GGT
- **AST: 50 U/L**
- **ALT: 44 U/L**
- **Alp: 970 U/L**
- **GGT: 67 U/L**
- **Bili T: 1.8 mg/dl**
- **Bili D: 0.8 mg/dl**
- **INR: 1.1**
- **Ammonia: 5**
- **BS: 98 mg/dl**

Intrahepatic cholestasis of pregnancy

- Is the most common pregnancy-related liver disease.
- Typically presenting in the second or third trimester
- The prevalence of ICP is 0.1% to 2%.
- ICP is thought to be due to a genetic mutation in bile salt transport across the transport membrane.
- Risk factors for it include:
 - Advanced maternal age
 - Multiparity
 - A previous history of cholestasis with oral contraceptive use
 - A personal or family history of IHCP

Intrahepatic cholestasis of pregnancy

- The **classic symptom** of ICP is:
- **Pruritus**
- **Epigastric pain**
- **Fatigue**
- **Anorexia**
- **Jaundice**

Intrahepatic cholestasis of pregnancy

- The typical laboratory finding in ICP is:
- **An elevation in bile acid** are typically $>10 \mu\text{mol/l}$ with **increased cholic acid** levels and **decreased chenodeoxycholic acid** levels.
- **AST and ALT levels range from normal levels to 10 times to 20 times normal.**

Intrahepatic cholestasis of pregnancy

- **Adverse outcomes** are associated with ICP, including:
 - **Preterm birth**
 - **Meconium-stained amniotic fluid**
 - **Fetal distress**
 - **Stillbirth**
- **Fetal prognosis** is most strongly linked to **gestational age** at delivery and **birth weight**.

Intrahepatic cholestasis of pregnancy

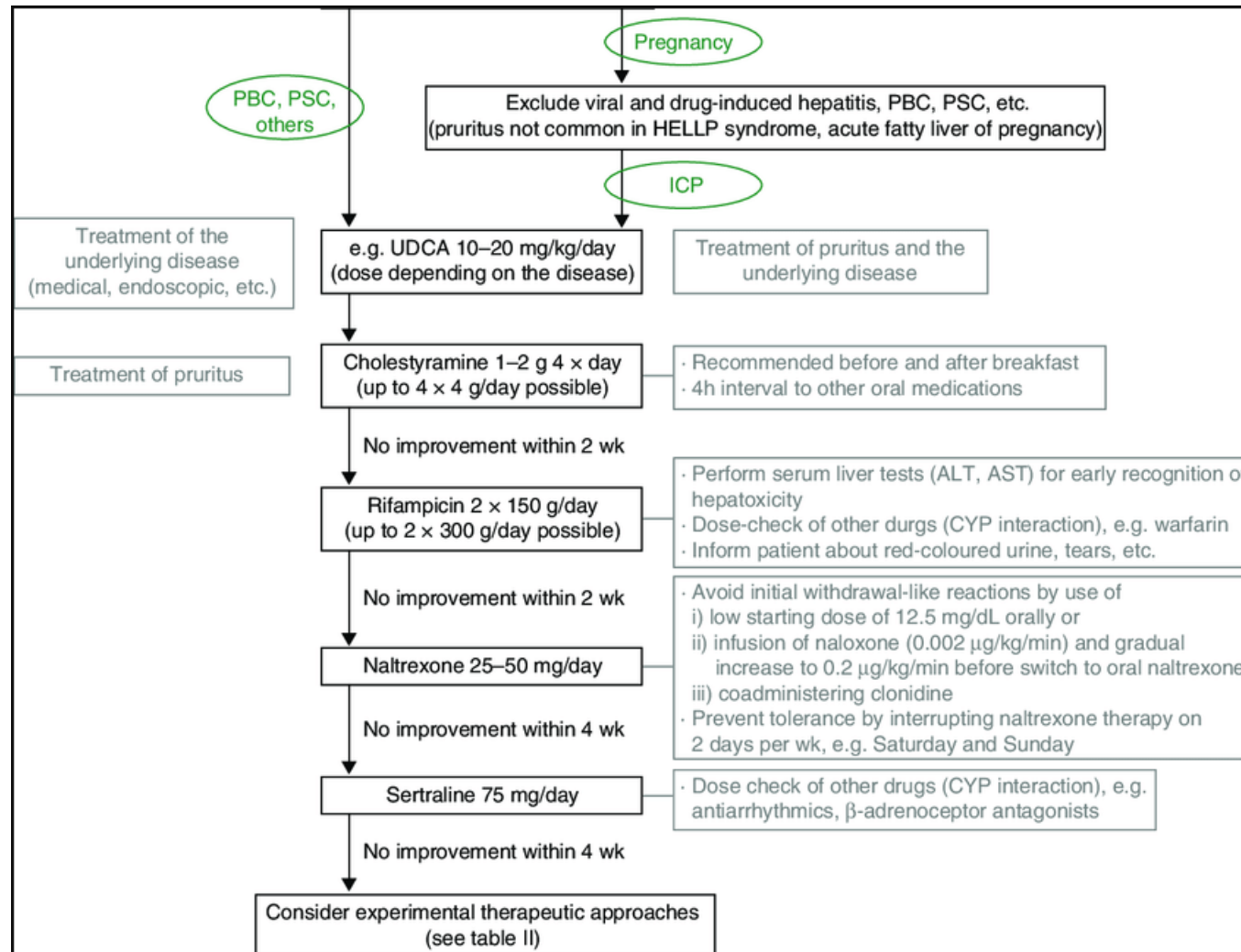
- **Ursodeoxycholic acid** (UDCA) at a dose of 10-15 mg/kg/day.
- **Early delivery** at 37 weeks is recommended.
- Management of ICP should be performed by a dedicated team; **monitoring of serum bile acids is recommended**,
- although there is no general consensus on a correlation between severe complications and high serum bile acid levels.
- Evaluation for alternative etiologies should be pursued if cholestasis fails to resolve after delivery.

Treatment

- Wearing cotton and loose-fitting clothes
- Cold water baths
- Using detergents and mild soaps
- Avoiding hot water baths
- Applying creams with chamomile and calendula
- Opt for mild bath shower gels
- Proper resting whenever you are tired
- Avoid humid and hot weather conditions

Treatment

- **Vitamin K Supplements**
- **Steroids**
- Aid with early maturity of baby's lungs.
- **Ursodeoxycholic acid**



Treatment

- A mix of organic vegetables and fruits
 - pumpkin, carrots, red cabbage, cauliflower,
- Food is rich in omega-3 / 6 fatty acids
- High protein food options
 - beans, nuts, eggs, and fish.
- Low-fat diet
 - Rice, wheat, oats, corn, and others.
- Lemon juice normalizes the bile acids.
- Increased water amount to flush the toxins.

Case 1

- 49 y/o obese diabetic male referred for blood donation
- Found to be HBsAg +ve
- AST: 78 IU/L
- ALT: 138 IU/L
- ALP: 230 IU/L
- HBeAg: -ve
- HBeAb: +ve

What will you do?

- Sonography?
 - Mild enlargement of liver
 - Increase echogenicity of liver
 - Spleen 109mm
- Viral count?
 - 1800 IU/ml
- FibroScan?
 - 4.3 KP
- Liver biopsy?

Liver Biopsy

- Fat droplets in 50% of hepatocytes
- No fibrosis
- Inflammation in pericentral area (zone 3)
- PMN infiltrates

How will you treat him?

- Lamivudine
- Tenofovir
- Weight loss
- Exercise

Case 2

- 49 y/o obese diabetic male referred for blood donation
- Found to be HBsAg +ve
- AST: 138 IU/L
- ALT: 78 IU/L
- ALP: 230 IU/L
- HBeAg: -ve
- HBeAb: +ve

Other Lab Data

- **CBC:**
 - Hgb: 12.4 g/dL, WBC: 3,300 /mm³, Platelet: 89,000 /mm³
- **PT: 13.5 sec, control: 13 sec**
- **Albumin: 3.9 gr/dl**
- **Sonography:**
 - Liver normal size with coarse echo
 - Spleen 130mm
- **Viral count**
 - 2,340,000 IU/ml

Case 3

- 29 y/o male referring with jaundice and RUQ pain for 10 days
- AST: 1300 IU/L
- ALT: 1900 IU/L
- Bilirubin: 9.3 mg/dL
- HBsAg +ve
- PT: 12.5 sec
- Albumin: 4.3 g/dL

- **Sonography**
 - Increased liver size
 - Hypoechoic liver
- **Viral count**
 - 120,000,000 IU/ml

- One week later:
- AST: 400 IU/L
- ALT: 170 IU/L
- What has happened?
- Bilirubin: 19 mg/dL
- PT: 19 sec
- Albumin: 4.2 g/dL
- Patient is confused

Case 4

- A 44 y/o obese lady complains of occasional very severe RUQ and epigastric pain which radiates to back
- The attacks occur every 4-5 months and forces her to ER
- In ER she usually receives IV ranitidine and PO lidocaine. The pain continues for 3-4 hours then gradually wanes off.

- Endoscopy has been performed a few times and has been normal
- Sonography performed in ER was normal
- LFT in ER:
 - AST: 160 IU/L
 - ALT: 75 IU/L IU/L
 - ALP: 290 IU/L

- Another sonography performed on the next day showed some sludge in gall-bladder and diffuse increased liver echogenicity
- LFT next day:
 - AST: 26 IU/L
 - ALT: 48 IU/L
 - ALP: 320 IU/L

- HBsAg: -ve
- HCV Ab :-ve
- Normal CBC
- Normal lipase and amylase
- What do you think?
- How can you prove it?