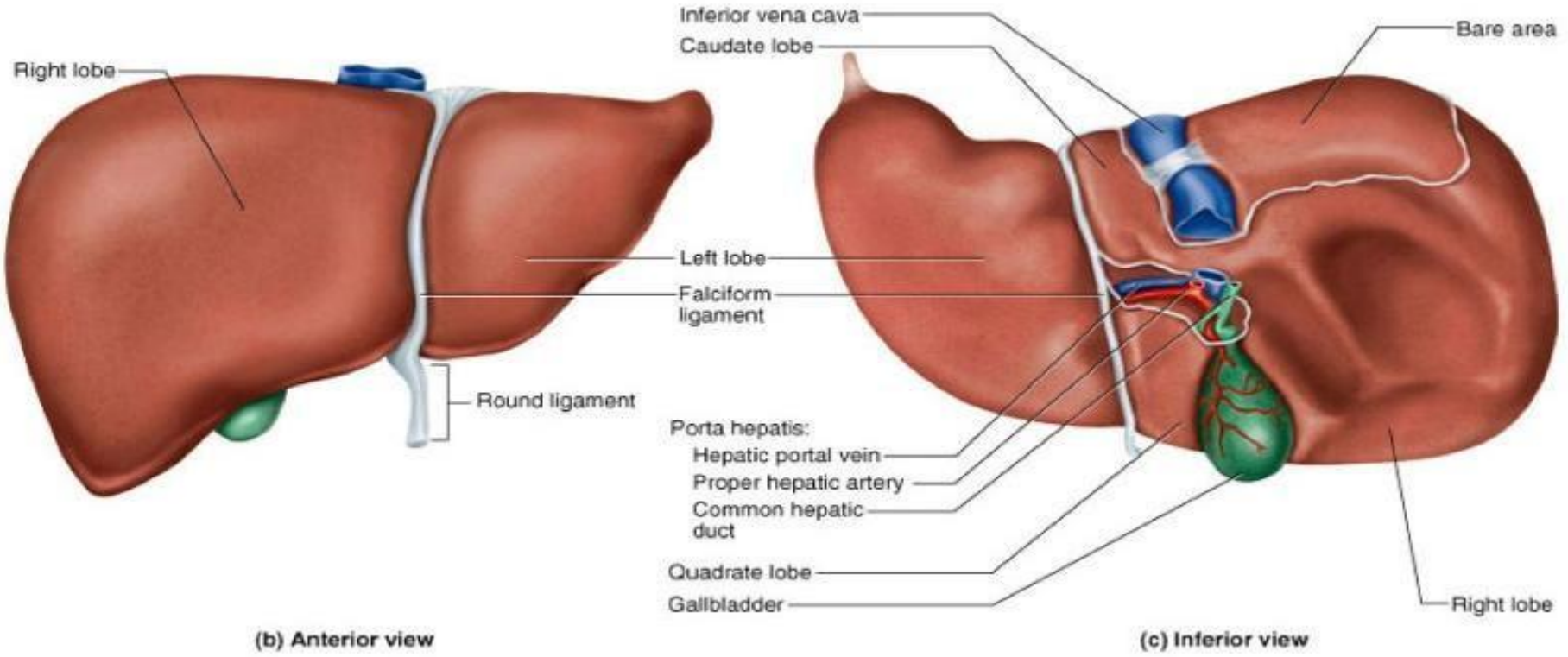
Chronic Liver diseases

(cholestatic liver disease)

Dr Omelkhir Banoni



largest intra-abdominal organ.
5% of body weight at birth,
2% in an adult.

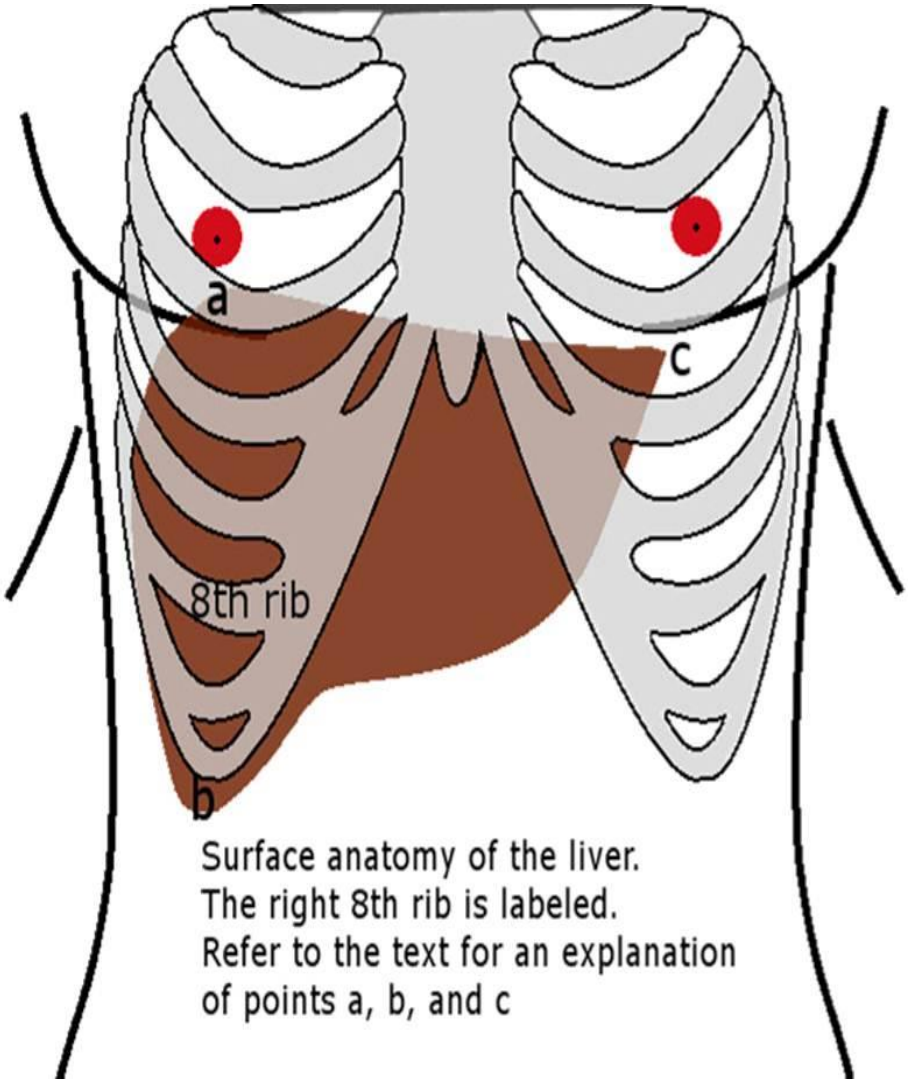
The two major lobes, right and left,
and 2 accessory lobes, quadrate and caudate
The right lobe is six times larger than left lobe

Palpable liver in pediatrics

Extension of liver below the Rt costal margin **Not** more than
3.5cm in neonates
2cm in older children

below the costal margin in the right midclavicular line

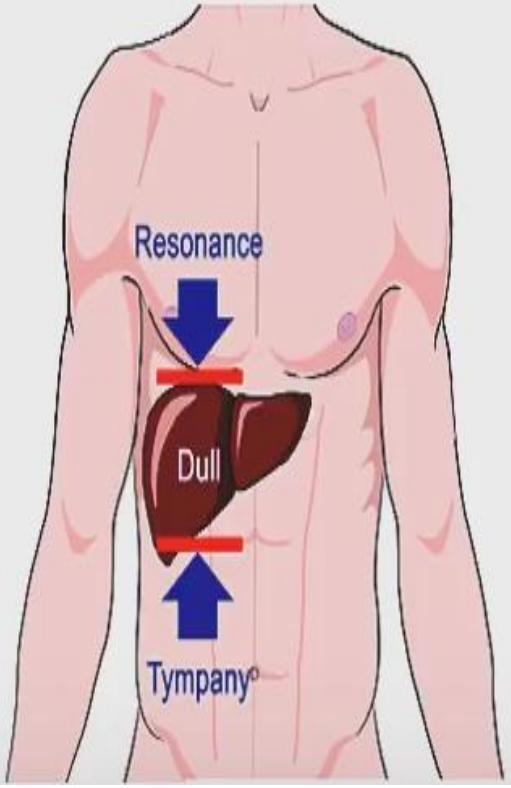
- ✓ Soft
- ✓ Smooth
- ✓ Nontender



Surface anatomy of the liver.
The right 8th rib is labeled.
Refer to the text for an explanation of points a, b, and c

The liver span

	females	males
Neonates- < 1 yr	4.5 -5 cm	4.5 - 5 cm
1-5 yrs	5 - 5.5 cm	5-6 cm
5- 10 yrs	5.5 - 6 cm	6- 7 cm
10-12 yrs	6.5-7 cm	7-8 cm

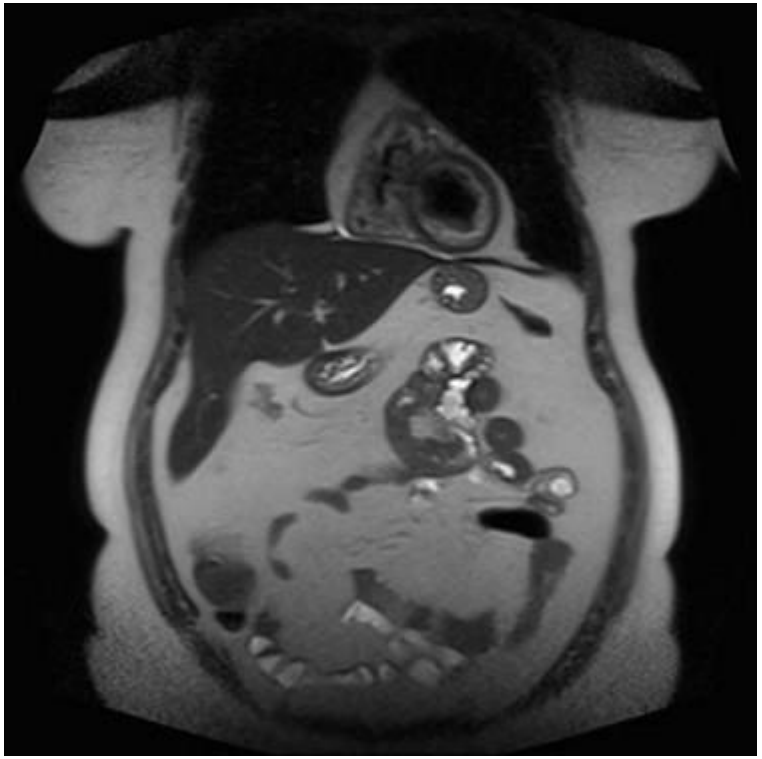



Liver size
Craniocaudal diameter at midclavicular line (c
Percentiles
97
95
90
75
50
25
10
5
3
13
12
11
10
9
8
7
6
5
0
1
2
3
4
5
6
7
Age (years)

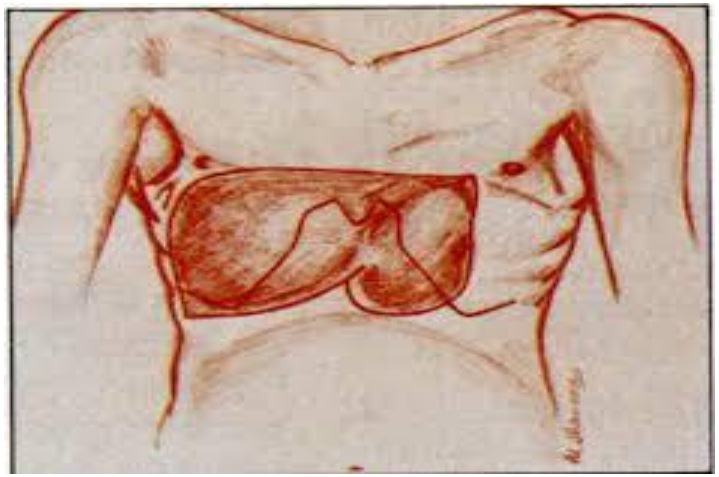
(Riedel lobe)

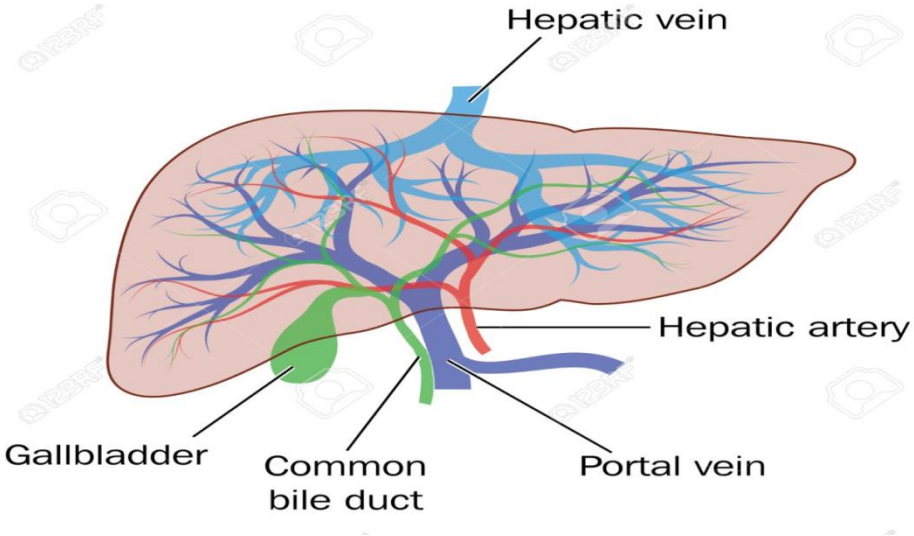
Tongue like projection .

The lower edge of the right lobe of the liver extends downward (Riedel lobe) and can normally be palpated as a broad mass in some people.



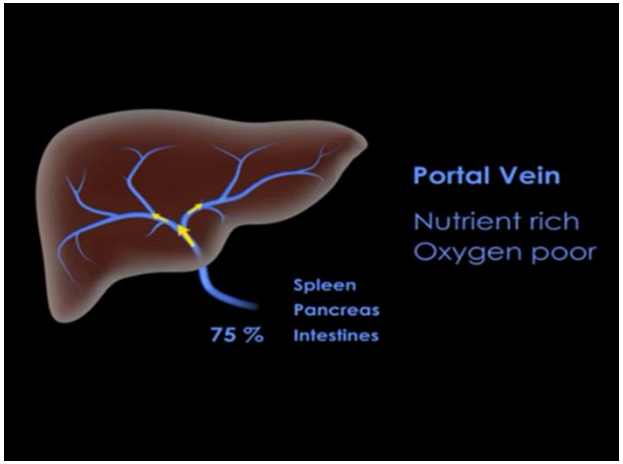
An enlarged left lobe of the liver is palpable in the epigastrium of some patients with cirrhosis

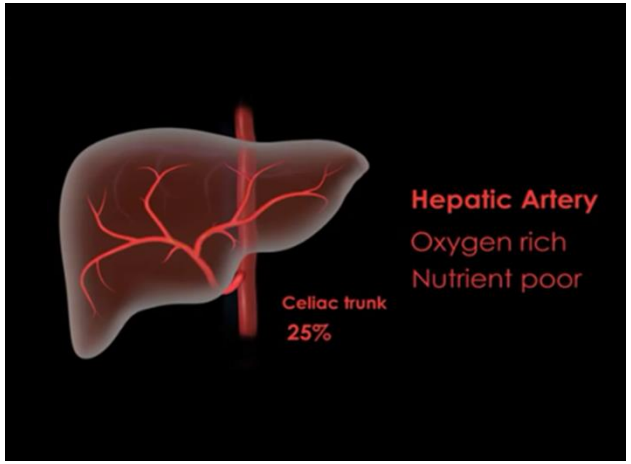


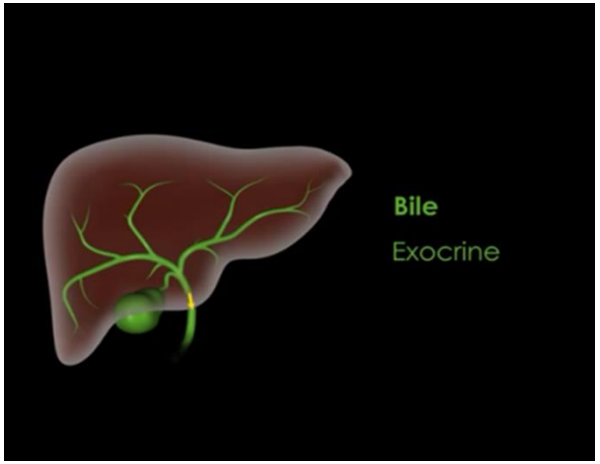


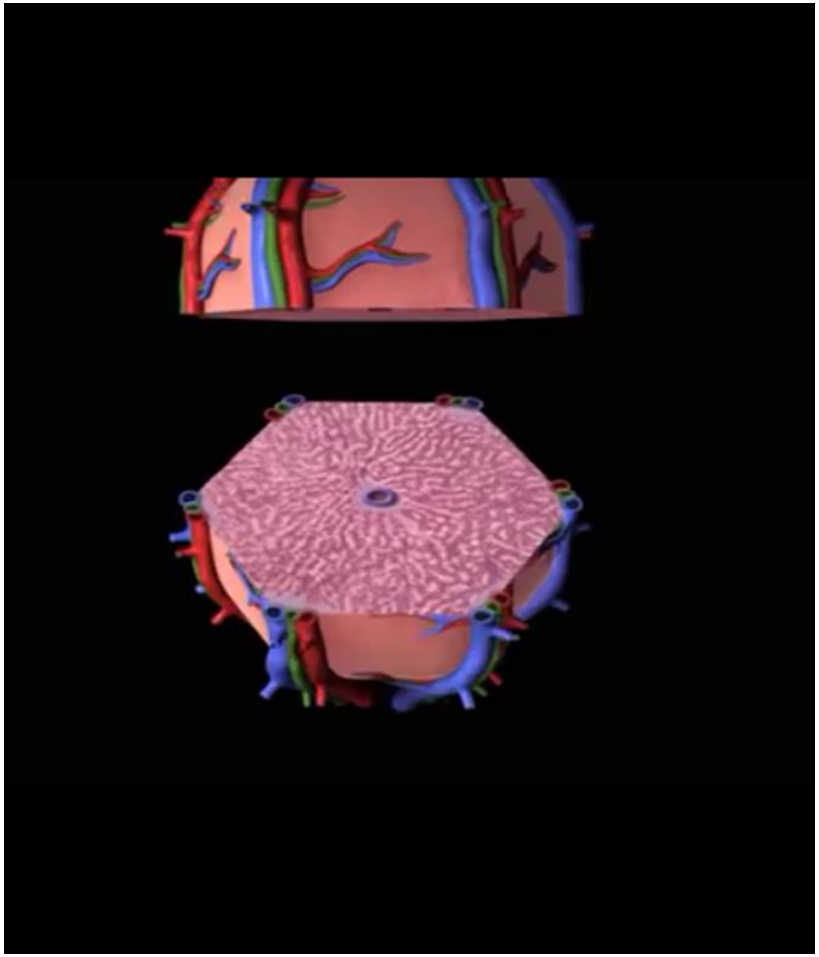
Functionally the liver consists of 3 systems;

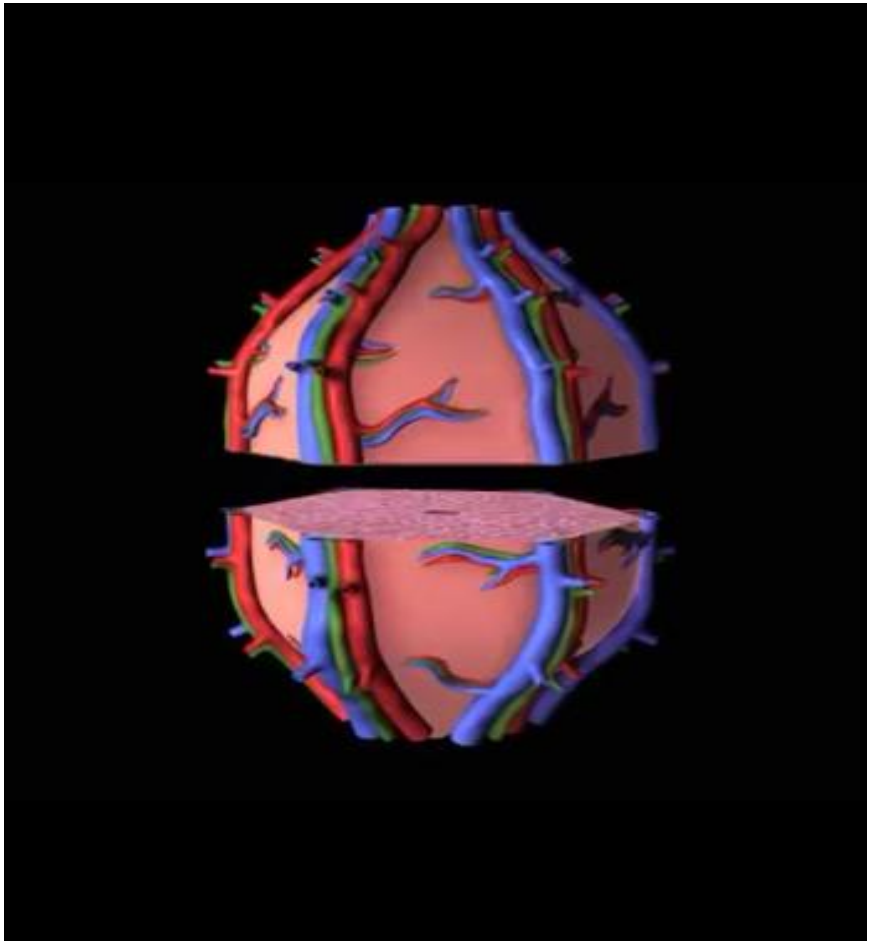
- Liver Cell (Hepatocyte) Systems → arranged in hexagonal and pentagonal units called hepatic lobules.
- Biliary System.
- Blood Circulatory System.





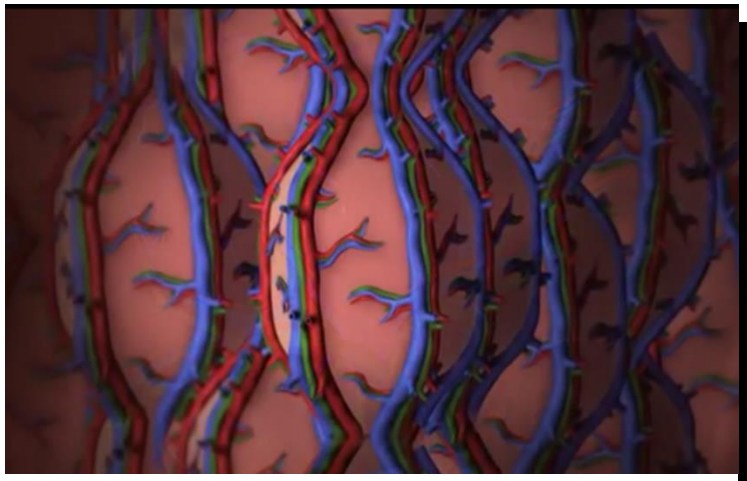


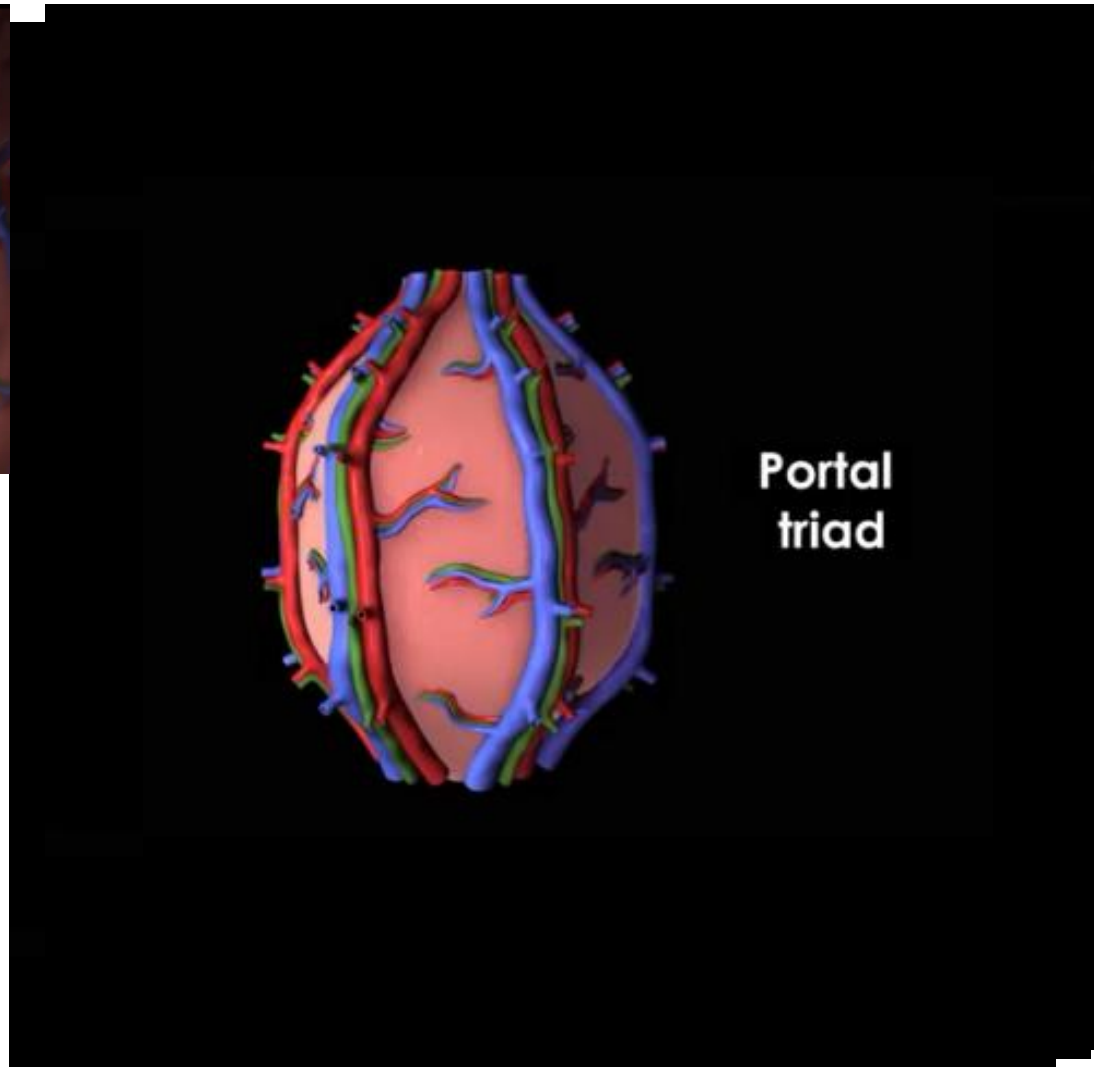




Liver Cell (Hepatocyte) Systems →

arranged in hexagonal and pentagonal units called **hepatic lobules**

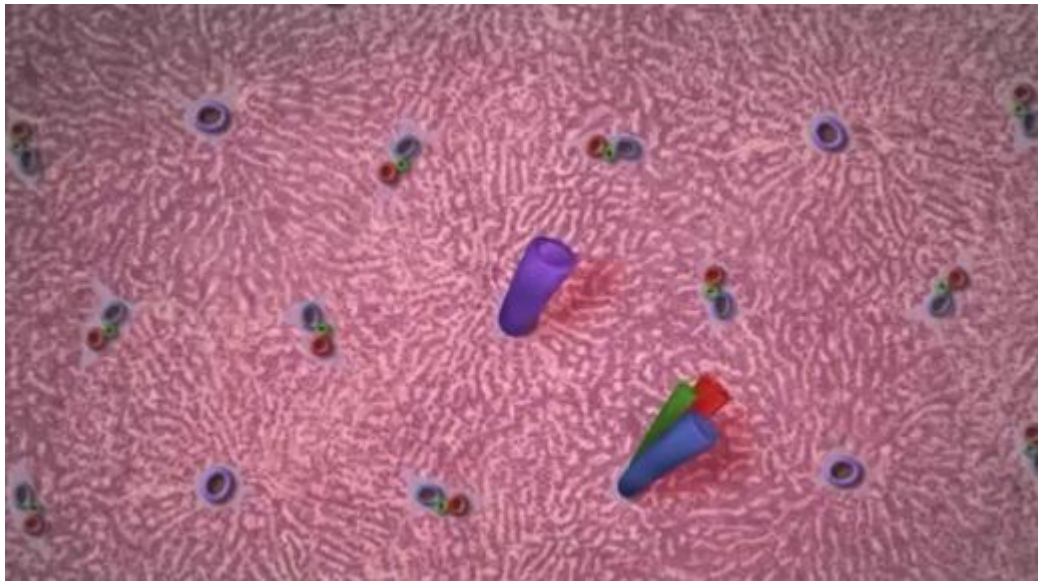


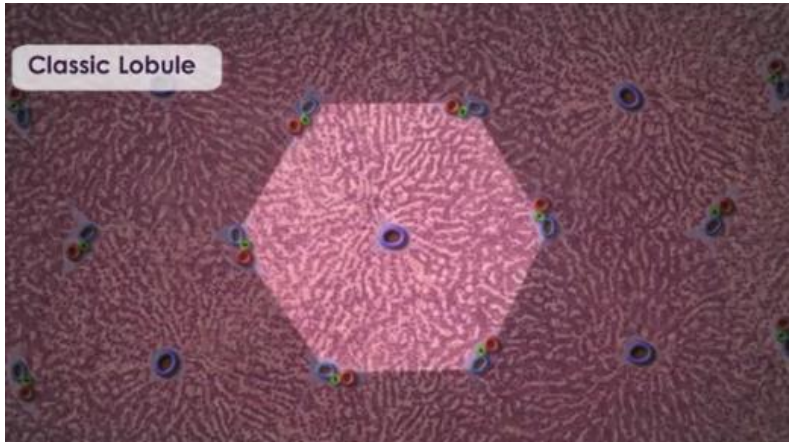


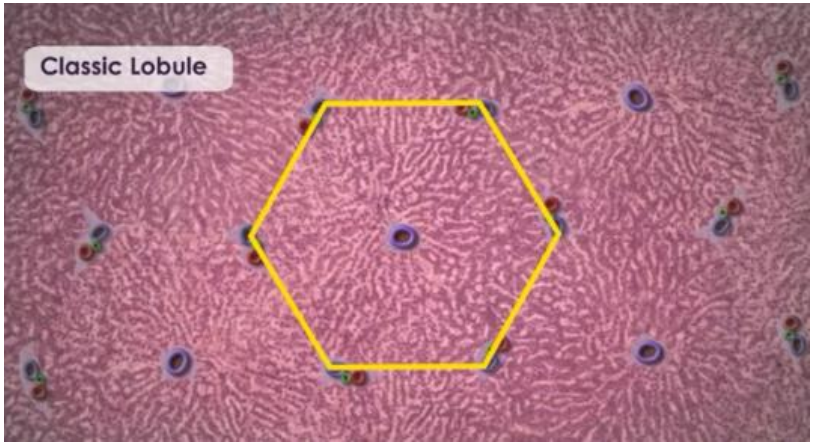
1.Filtration of blood and
2.formation of bile

take place in functional and structural unit of the liver the lobule

(hepatic lobule)




Classic Lobule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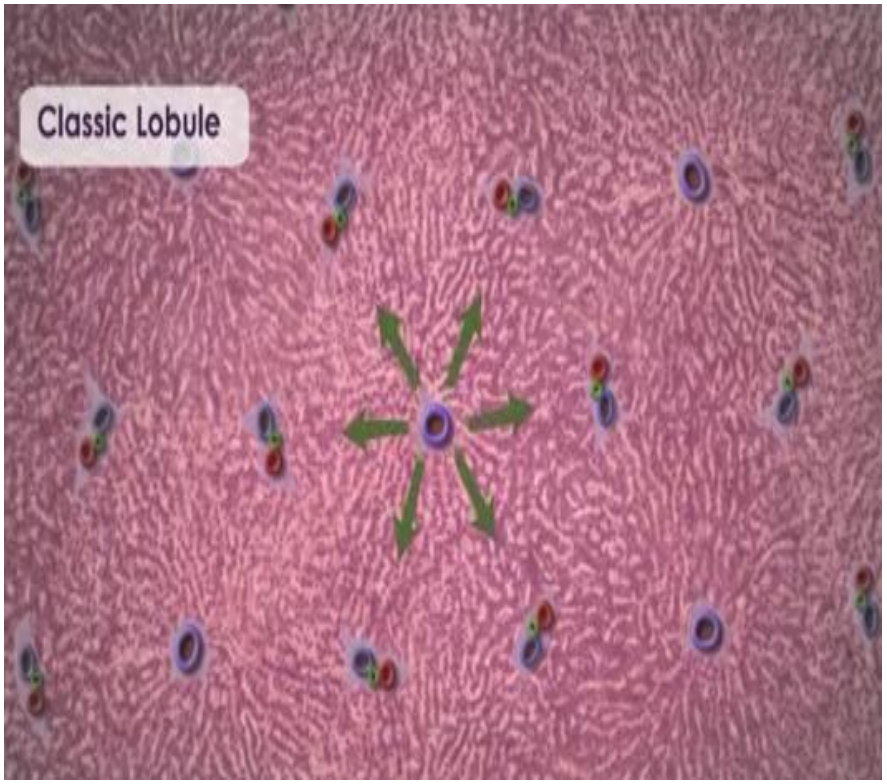
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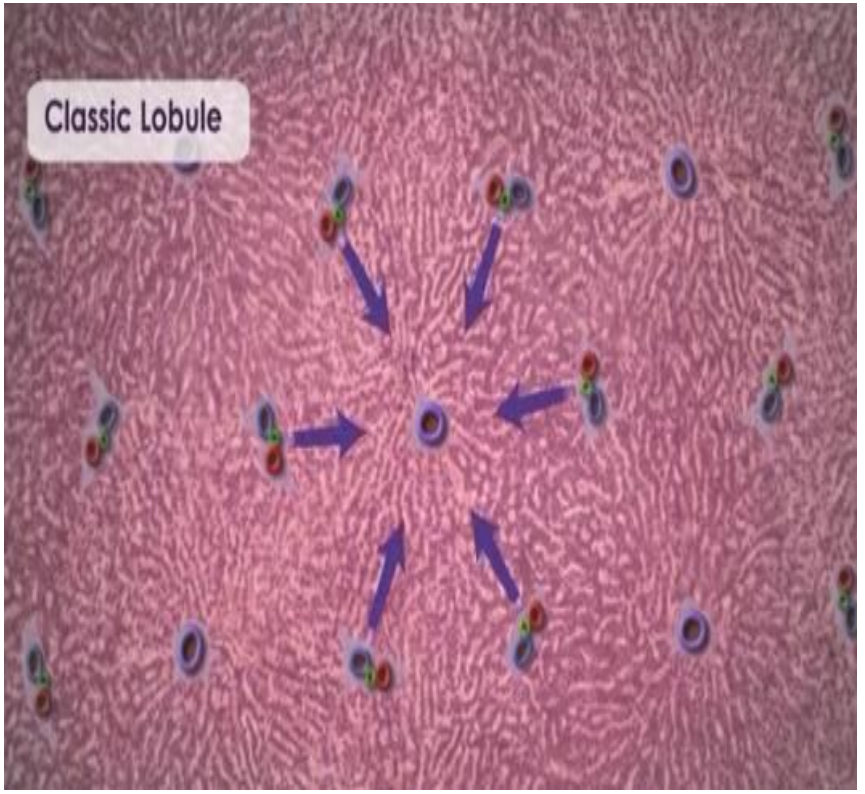
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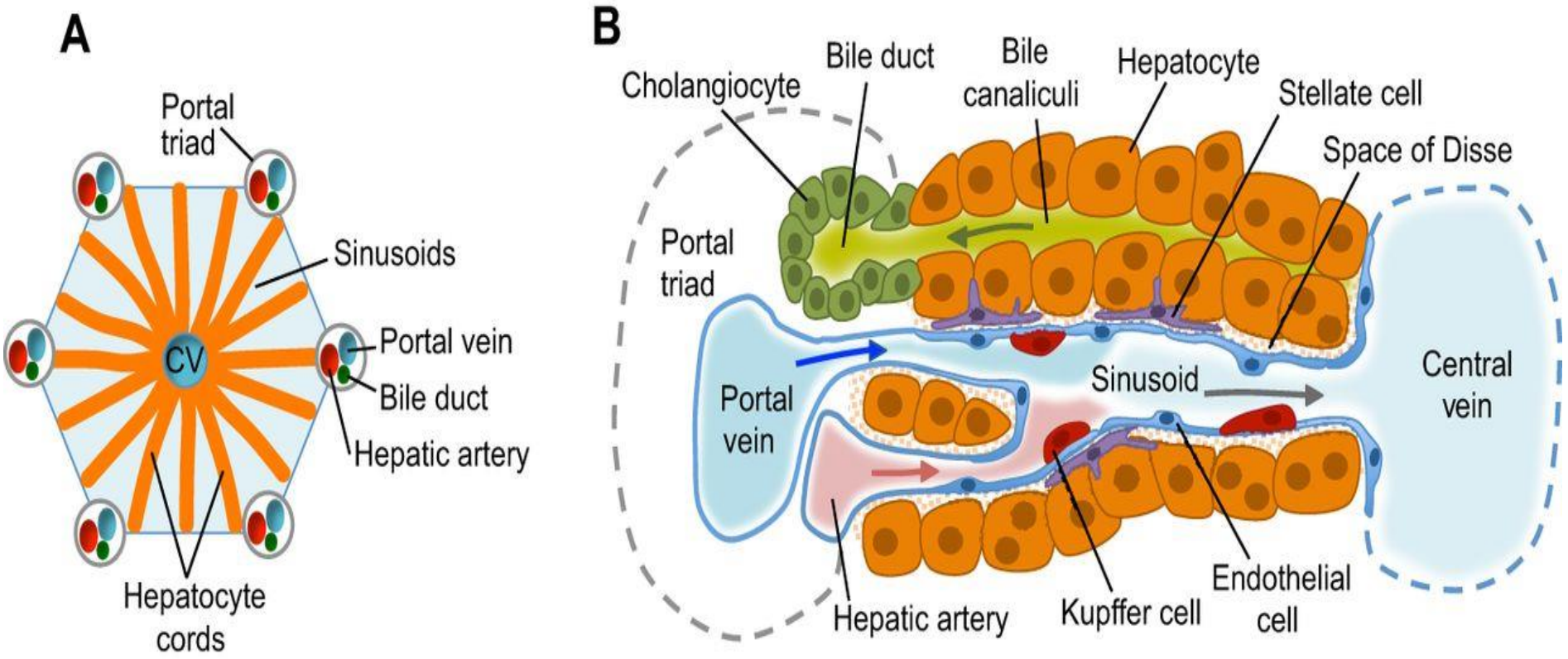
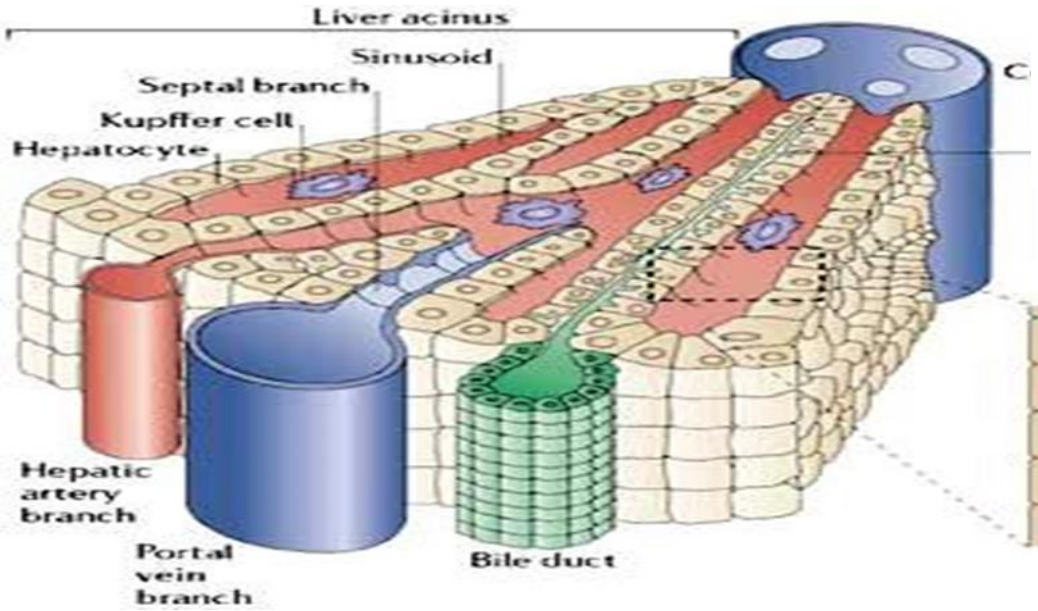
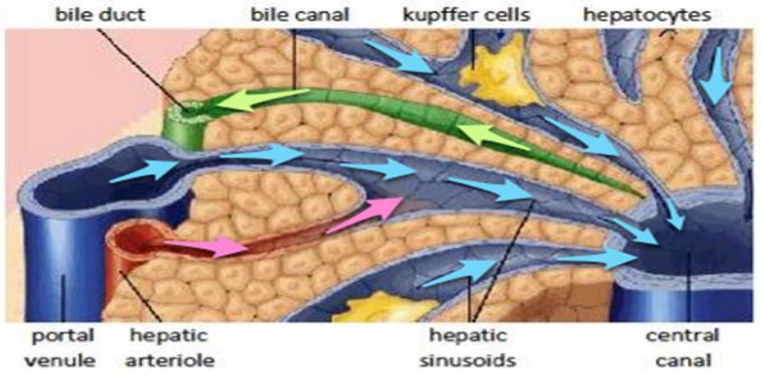
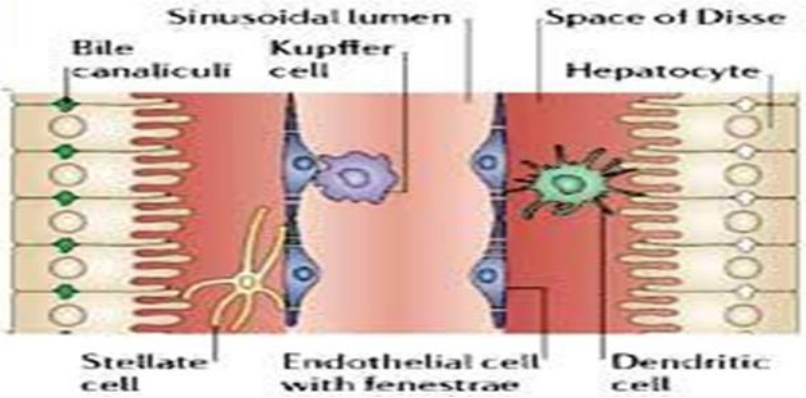


Hepatocytes

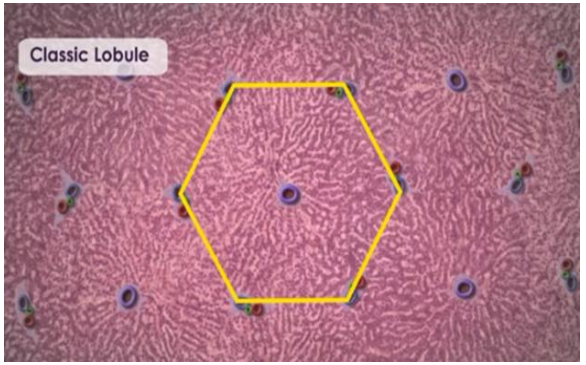
bile duct cells (cholangiocytes)



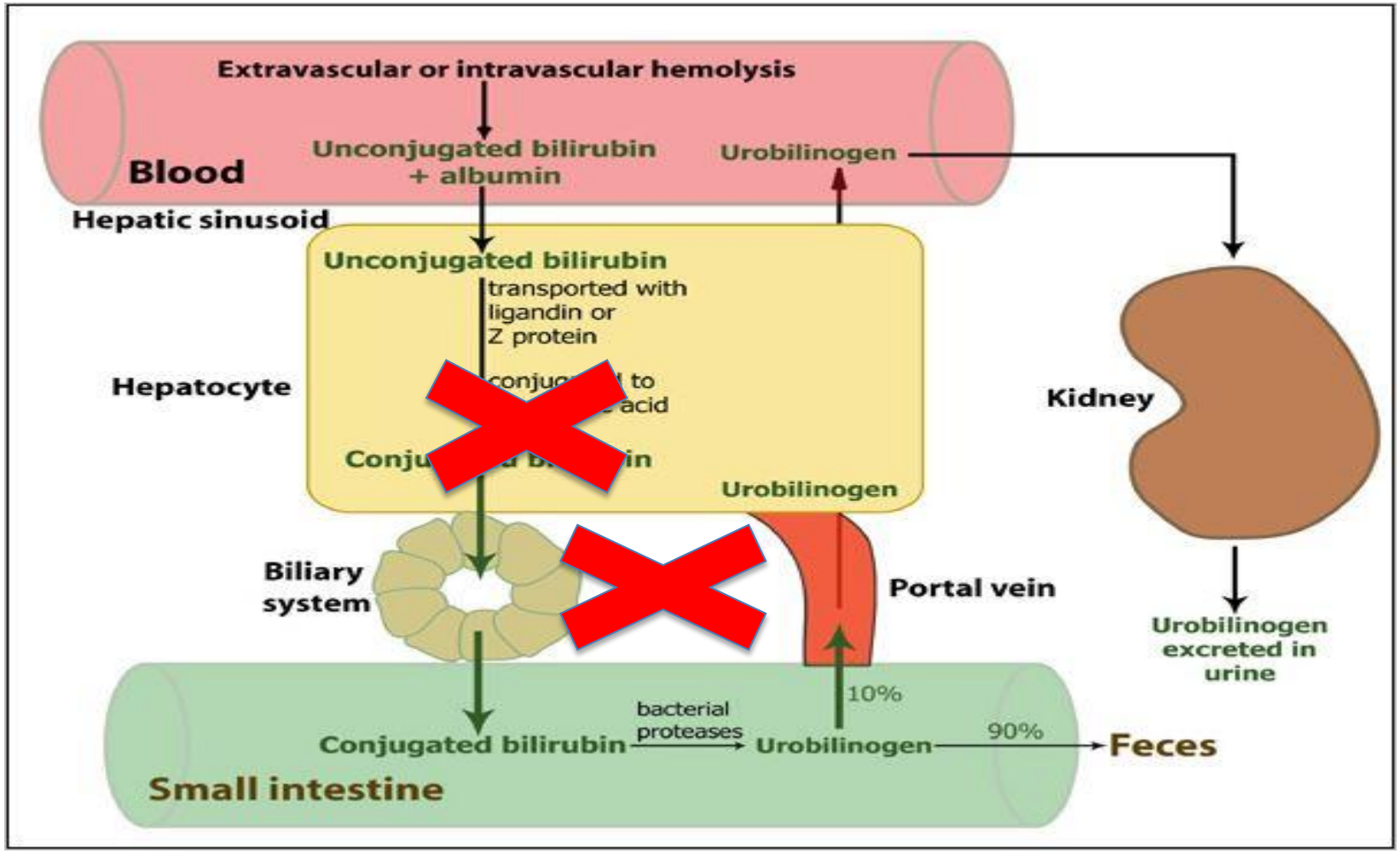




The hepatic lobule is the structural unit of the liver.



Bilirubin metabolism

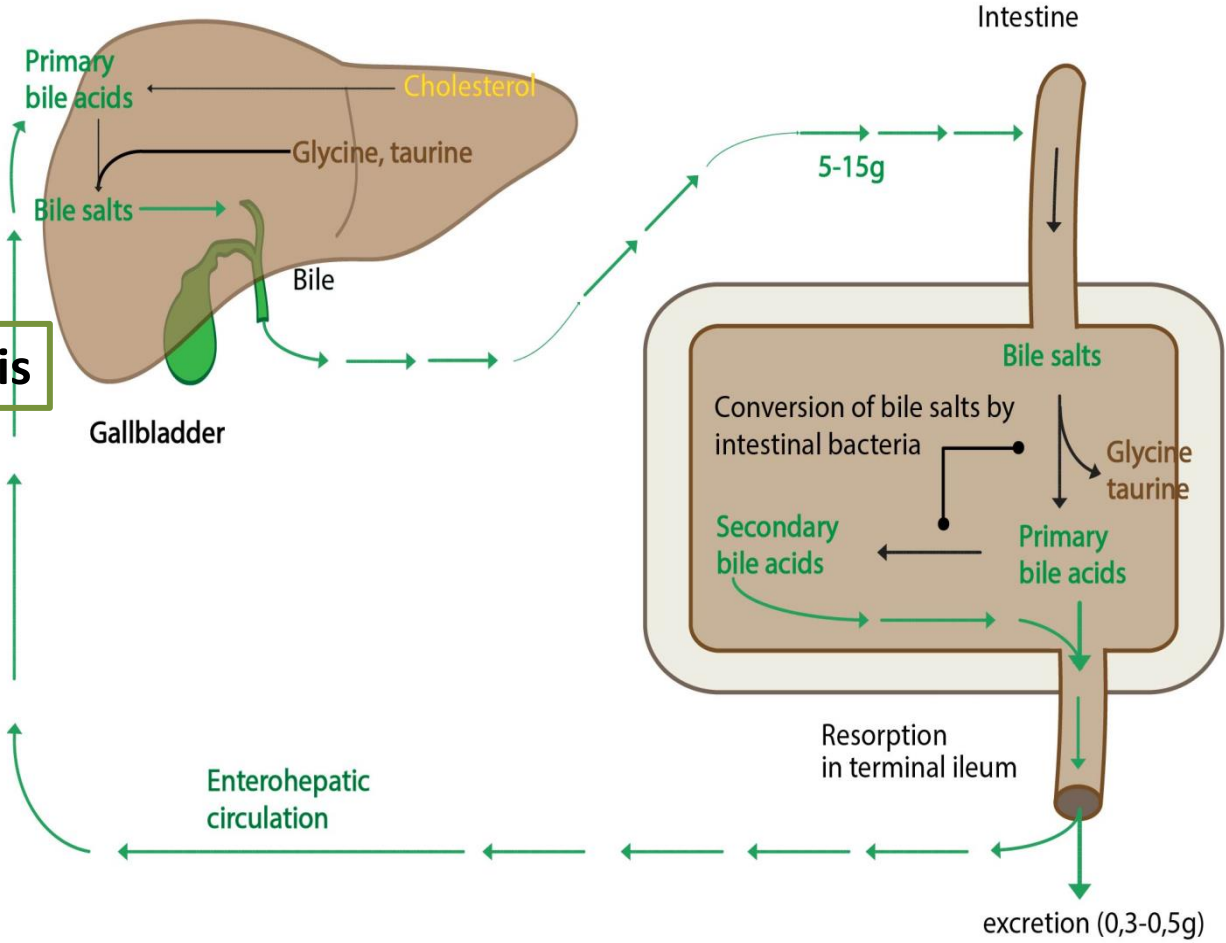


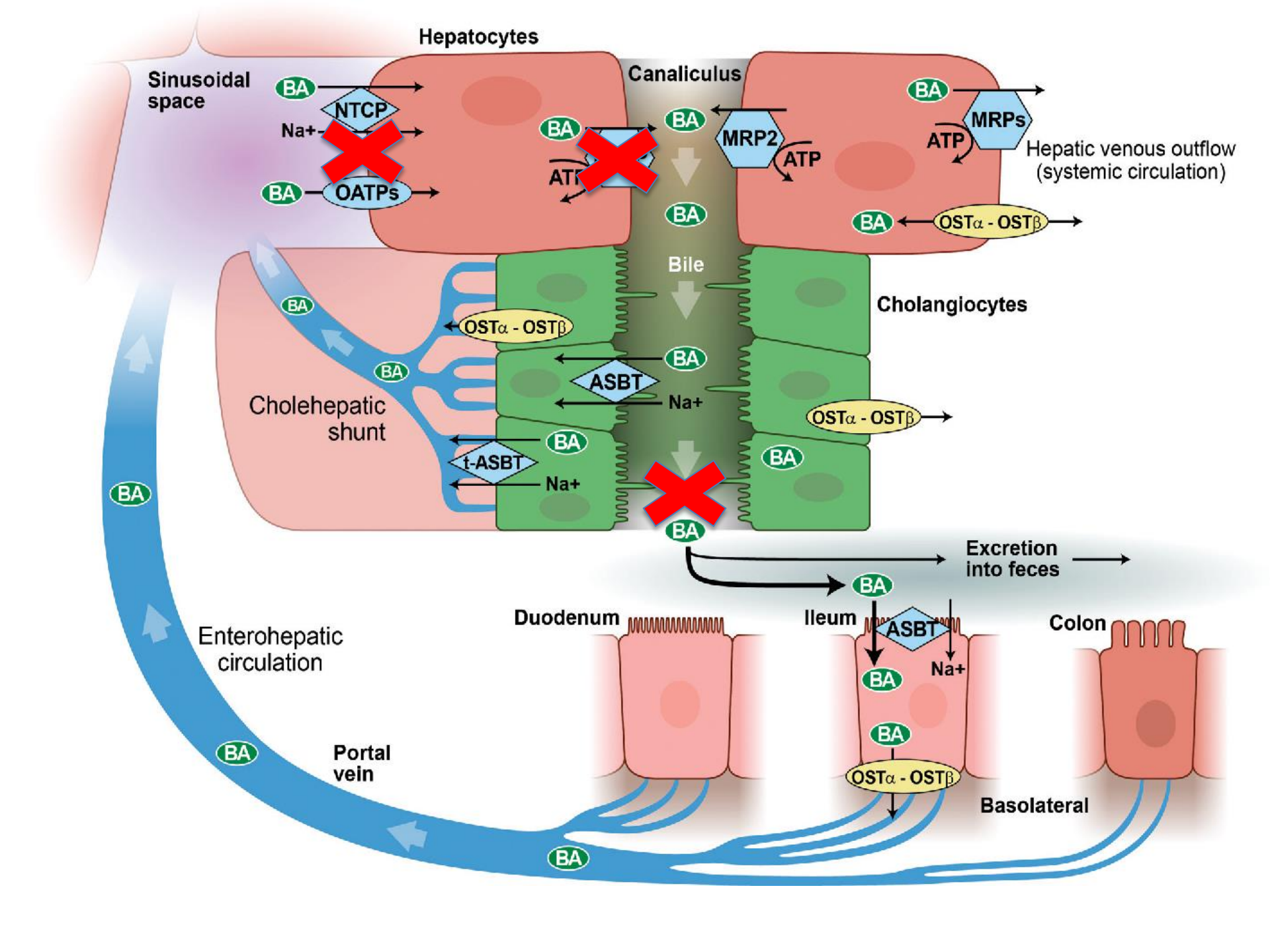
Bile salts metabolism

The two major bile acids,
- ✓ cholic acid
- ✓ chenodeoxycholic acid

secreted into bile
When conjugated with taurine and glycine as
Bile salts

Defective bile acid biosynthesis




Hepatocytes
Sinusoidal space
Canaliculus
BA
NTCP
Na+
OATPs
MRP2
ATP
MRPs
Hepatic venous outflow (systemic circulation)
OSTα - OSTβ
Bile
Cholangiocytes
Cholehepatic shunt
ASBT
t-ASBT
Excretion into feces
Enterohepatic circulation
Portal vein
Duodenum
Ileum
Colon
Basolateral

Liver enzymes commonly measured in the serum include:

- ✓ Alanine aminotransferase (ALT, formerly called SGPT)
- ✓ Aspartate aminotransferase (AST, formerly called SGOT)
- ✓ Alkaline phosphatase
- ✓ Gamma-glutamyl transpeptidase (GGT)
- ✓ 5'-nucleotidase

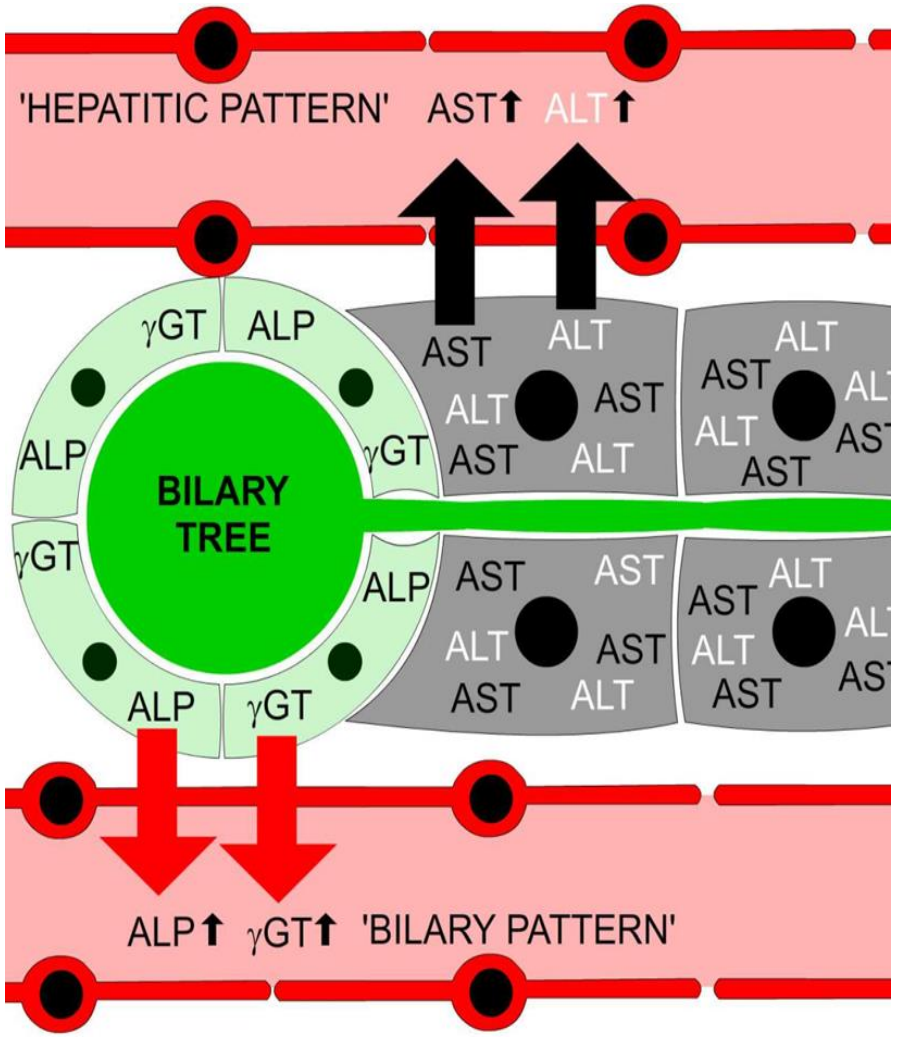
In Hepatocellular injury membranes of hepatocytes become permeable when damaged (ALT) and (AST) escape into bloodstream

Hepatocyte injury can be caused by
viral infection,
Drugs,
toxins,
immunologic, or
IEM.

The liver can be secondarily involved in
neoplastic (metastatic)
non neoplastic (storage diseases, fat infiltration)

systemic conditions (IBD, Celiac)
infectious processes (Ecoli, kleb,pseudo)
Cardiac congestive heart failure, cyanotic HD)
or acute hypoxia and shock
Hematology disease

In Cholestasis obstructed/damaged intra- and extra- hepatic bile ducts ALP & GGT



biochemical markers of liver injury.

- ✓ Alanine aminotransferase (ALT)
- ✓ aspartate aminotransferase (AST)
- ✓ alkaline phosphatase, GGT

bilirubin /Blood suger

markers of hepatocellular synthetic function.

- ✓ Albumin,
- ✓ Prothrombin time & INR

PATTEREN OF LIVER DISEASES

	hepatocellular	Cholestatic
ALT	↑↑↑	↑
AST	↑↑↑	↑
ALP	↑	↑↑↑
GGT	↑	↑↑↑
TOTAL BILI	↑↑	↑↑
INDIRECT BILI	↑	↑
BIRCT BILI	↑	↑↑↑

Cholestasis in neonates and children

Cholestasis

Greek ward means **stoppage of bile**

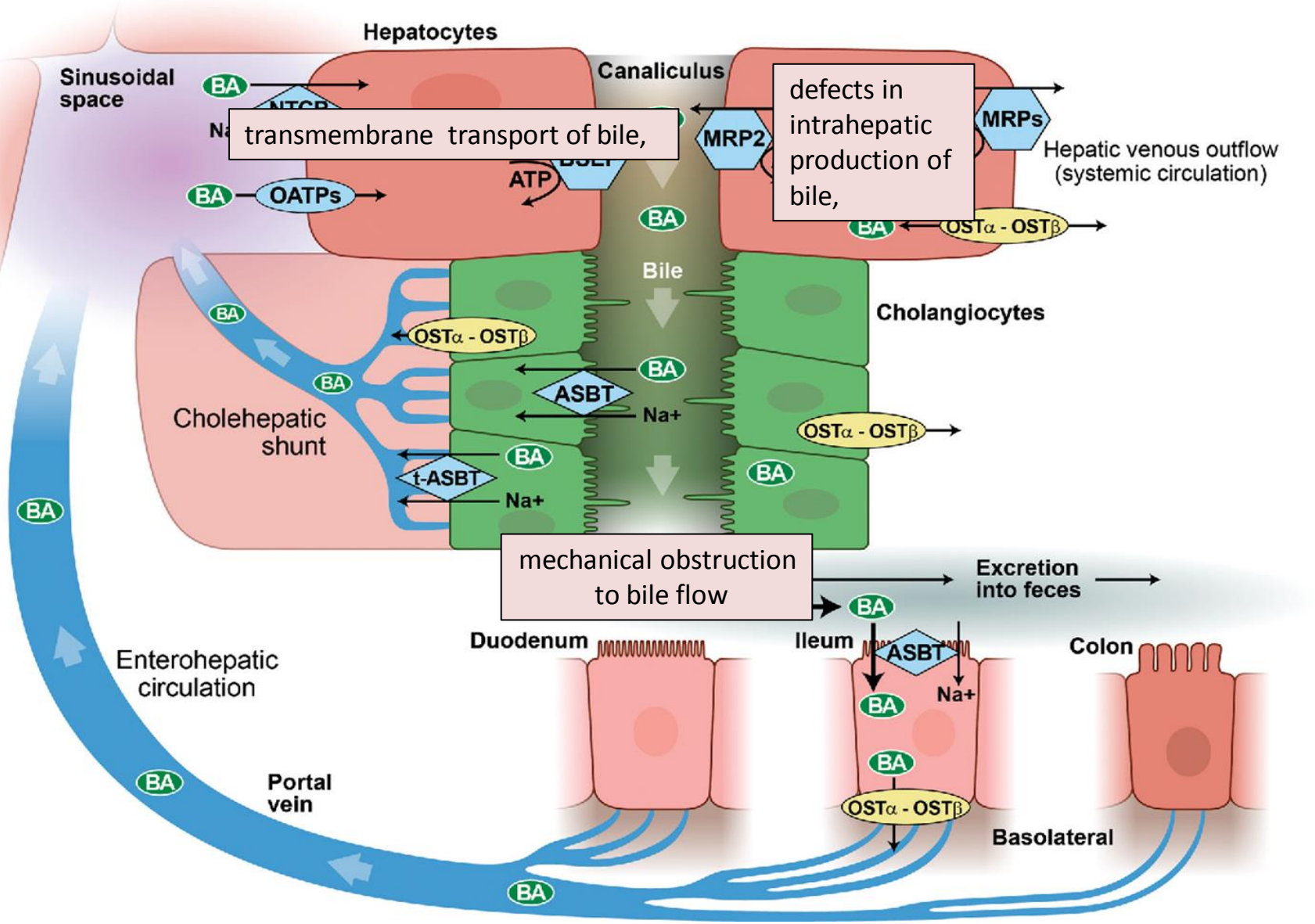
Reduced bile flow

impairment in the excretion of bile can be caused by

- ✓ defects in intrahepatic production of bile,
- ✓ transmembrane transport of bile,
- ✓ or mechanical obstruction to bile flow.

conjugated bilirubin,
cholesterol,
bile acids, and
All accumulate in serum.

diagestion and absorption of fat and fat soluble vitamins


Hepatocytes
Sinusoidal space
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transmembrane transport of bile,
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mechanical obstruction to bile flow
Excretion into feces
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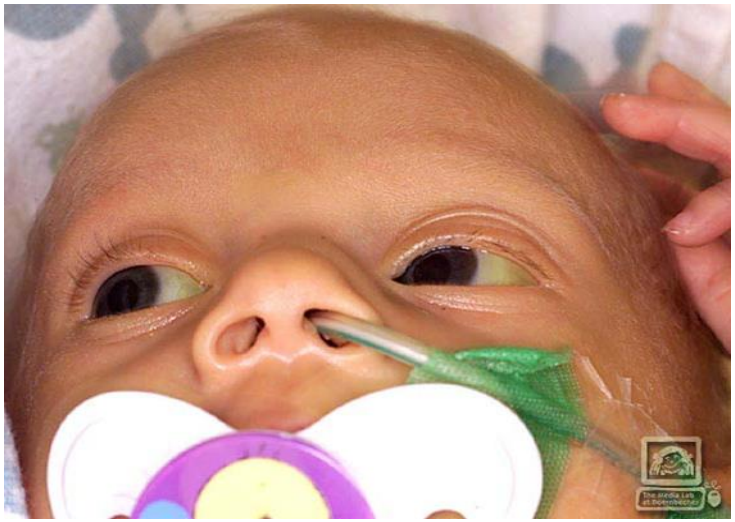
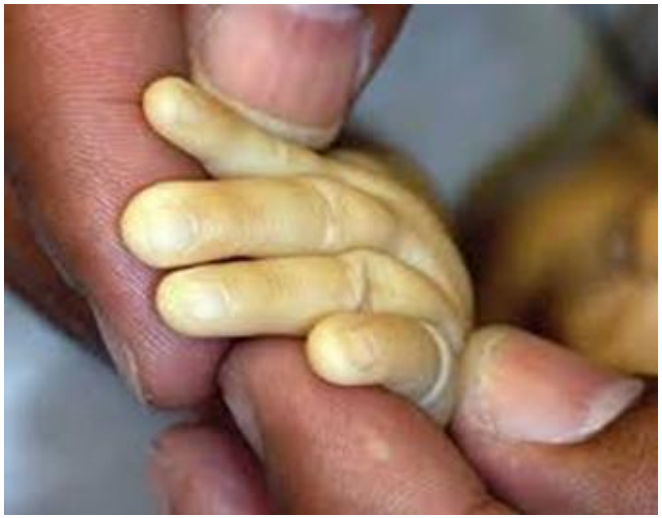
The term "neonatal cholestasis" is often used to refer to cholestatic liver disease that is present at birth and/or develops within the first few months of life, rather than referring strictly to the neonatal period (the first 28 days of life)

"neonatal cholestasis" Clinically jaundice & biochemically conjugated hyperbilirubinemia

Jaundice (Icterus)

Yellow discoloration of the sclera, skin, and mucous membranes





Bilirubin occurs in plasma in 4 forms:

- unconjugated bilirubin tightly bound to albumin
- free or unbound bilirubin (responsible for kernicterus, because it can cross cell membranes);

- conjugated bilirubin (the only fraction to appear in urine/ water soluble);
- δ fraction (bilirubin covalently bound to albumin)

Liver disease must be suspected in the infant who appears only mildly jaundiced but has **dark urine or acholic (light-colored) stool**

Jaundice may be the earliest and only sign of hepatic dysfunction.

Neonatal cholestasis is defined biochemically as prolonged elevation of the serum levels of conjugated bilirubin beyond the 1st 14 days of life.

it is considered elevated if it is
DB greater than 1.0 mg/dL if the total serum bilirubin is <5.0 mg/dL or
DB greater than 20 % of the total serum bilirubin if the total serum bilirubin is >5.0 mg/dL

Any infant noted to be jaundiced at the two-week well child visit should be evaluated for cholestasis

Jaundice that appears after **2wks** of age, continues to progress, or does not resolve at this

should be evaluated and a conjugated bilirubin level determined

cholestasis (conjugated bilirubin) elevation of any degree in the neonate is always

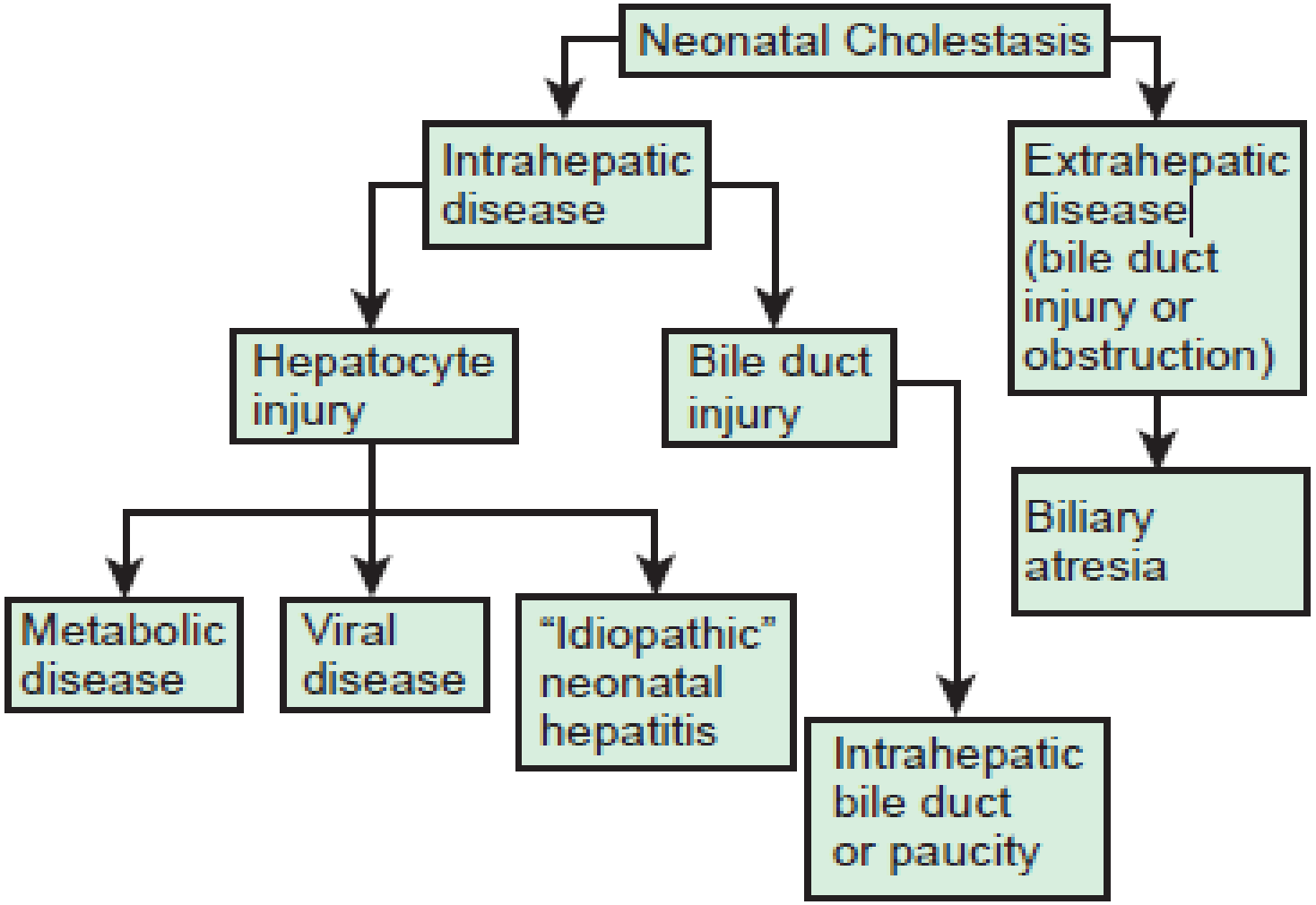
pathologic

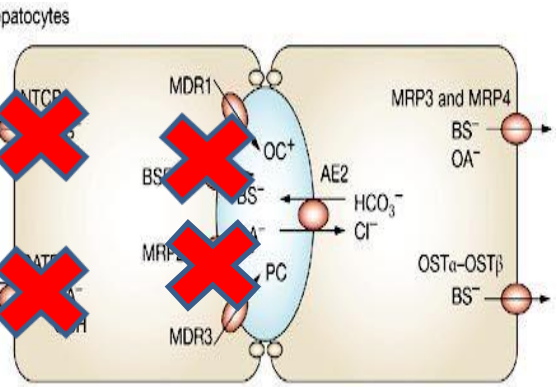
Important to

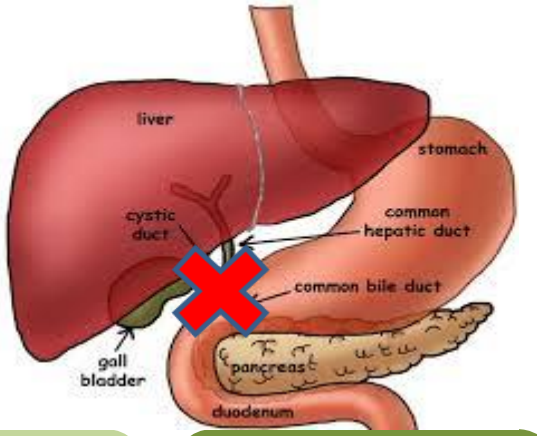
recognize conditions that cause cholestasis for which specific therapy is available to prevent further damage and avoid long term complications such as

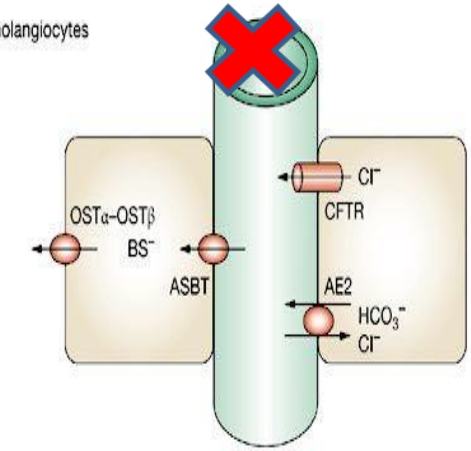
- ✓ Sepsis,
- ✓ Endocrinopathy (hypothyroidism,panhypopituitarism),
- ✓ Galactosemia,
- ✓ Tyrosinemia

- ✓ Extrahepatic Biliary atresia
- ✓ Choledocal cyst
- ✓ Inspissated bile syndrome


Neonatal Cholestasis
Intrahepatic disease
Extrahepatic disease (bile duct injury or obstruction)
Hepatocyte injury
Bile duct injury
Biliary atresia
Metabolic disease
Viral disease
"Idiopathic" neonatal hepatitis
Intrahepatic bile duct or paucity







Hepatocyte & hepatocyte canalicular membrane

- HEPATITS
  - Idiopathic
- PFIC
  - ROTOR
  - DUBIN JOH
- STORAGE DISEASE

Interlobular bile duct

- PAUCITY
- SYDROME
  - Alagille
- NON SYNDROME

Extrahepatic

- EHBA
- Choledocal cyst

Intrahepatic

Extrahepatic

Extrahepatic causes

- Extrahepatic biliary atresia (EHBA)
- Choledocal cyst
- Inspissated bile syndrome
- Tumors and mass

Intrahepatic
Medical

Inflammation
UTI
Sepsis
Viral hepatitis
1. TORCH
2. HBV, HIV,
3. Coxsakie, Echo, parvo

✓ Idiopathic neonatal hepatits

Metabolic
Galactosemia
Tyrosenimia
Alpha one antitrypsin def.
GSD IV
Nieman pick
Gaucher
Cystic fibrosis
Familial cholestasis
PFIC
Dubin johnson
Rotor
Caroli/CHF

Paucity of intrahepatic duct
Syndromic
Nonsyndromic
Endocrine
Hypothyrodism
Hypopitutrism
Panhypopitut
Chromosomal
Trisomy 21,13,18
Toxic
TPN
Drugs
Vascular
Budd-chiari syndrome
VOD

INFECTIOUS

Generalized bacterial sepsis

Viral hepatitis

- Hepatitides A, B, C, D, E
- Cytomegalovirus
- Rubella virus

METABOLIC

Disorders of amino acid metabolism

- Tyrosinemia

Disorders of lipid metabolism

- Wolman disease
- Niemann-Pick disease (type C)
- Gaucher disease

Cholesterol ester storage disease

Disorders of carbohydrate metabolism

- Galactosemia
- Fructosemia
- Glycogenosis IV

Disorders of bile acid biosynthesis

Other metabolic defects

- α_1-Antitrypsin deficiency
- Cystic fibrosis
- Hypopituitarism
- Hypothyroidism
- Zellweger (cerebrohepatorenal) syndrome

EXTRAHEPATIC DISEASES

Biliary atresia

Sclerosing cholangitis

Bile duct stricture/stenosis

Choledochal–pancreaticoductal junction anomaly

Spontaneous perforation of the bile duct

Choledochal cyst

Mass (neoplasia, stone)

Bile/mucous plug ("inspissated bile")

INTRAHEPATIC CHOLESTASIS SYNDROMES

"Idiopathic" neonatal hepatitis

Alagille syndrome

Intrahepatic cholestasis (progressive familial intrahepatic cholestasis

TOXIC

Sepsis

Parenteral nutrition related

Cholestasis in older children

Extrahepatic

Choledochal cyst
Cholelithiasis
Inspissated syndrome
Tumors/masses

Intrahepatic

<u>Inflammation</u>
Viral hepatitis A, B, C,
acute and chronic
CMV, EBV
autoimmune
Drug induced
<u>Metabolic</u>
Wilson
Alpha one antitrypsin def.
Fructosemia
<u>Vascular</u>
Budd-chiari
VOD

Approach to infant with cholestatic jaundice

A: History

Maternal
Maternal fever or other signs of infection
Sepsis , Gram-negative bacteria (eg, E coli) causing UTI
Blood group

Full term or preterm
Idiopathic neonatal hepatitis appears to be more common among males, especially preterm or low birthweight infants

In contrast, biliary atresia occurs more commonly among females of normal weight,

- ✓ Plus sepsis and TPN common causes of cholestasis in PT
- ✓ Umblical catheterization

Onset of jaundice AND progression
Associated symptoms as vomiting, lethergy, convulsion, poor growth,
Stool and urine color
Presence of pruritus
Family history of consanguinity
affected sibling
Feeding difficulties
Blood group

Approach to infant with cholestatic jaundice

B:Clinical evaluation

Jaundice
dark urine
Pale stool
Hepatomegaly or
Hepatosplenomegaly

Fat soluble vitamines deficiency
- ✓ Signs of coagulopathy
- ✓ Signs of ricketes

Pruritis
Xanthomas
Chronic diarrhea
FTT

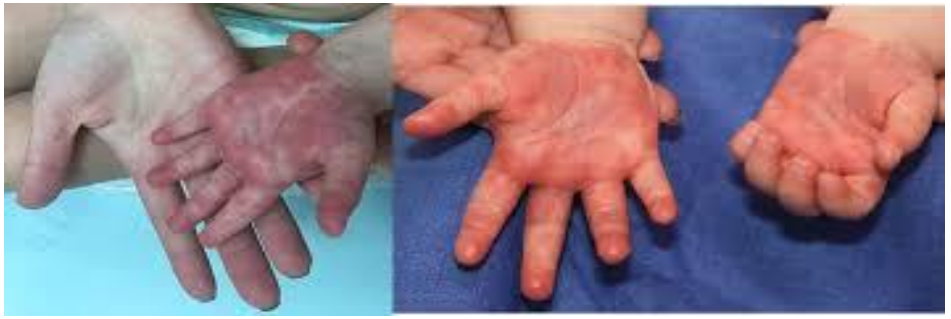
Liver
- ✓ consistency,
- ✓ contour,
- ✓ tenderness,
- ✓ presence of any masses or bruits,

as well as assessment of
Spleen size.
Documentation of the presence of ascites and any stigmata of chronic liver disease is important.

Palmar Erythema

Blotchy erythema,over thenar and hypothenar eminences and on the tips of the fingers,

Abnormal serum estradiol levels and regional alterations in peripheral circulation have been identified as possible causes.



Pruritis
Xanthomas
Chronic diarrhea and FTT

Pruritiis
retained components of bile
(probably multifactorial),

Approach to infant with cholestatic jaundice

Pruritiis

- ✓ generalized or localized (commonly palms and soles),
- ✓ worse at night,
- ✓ exacerbated with stress and heat,
- ✓ relieved by cool temperatures.
- ✓ unrelated to the degree of hyperbilirubinemia; deeply jaundiced patients can be asymptomatic.,

Chronic diarrhea and FTT

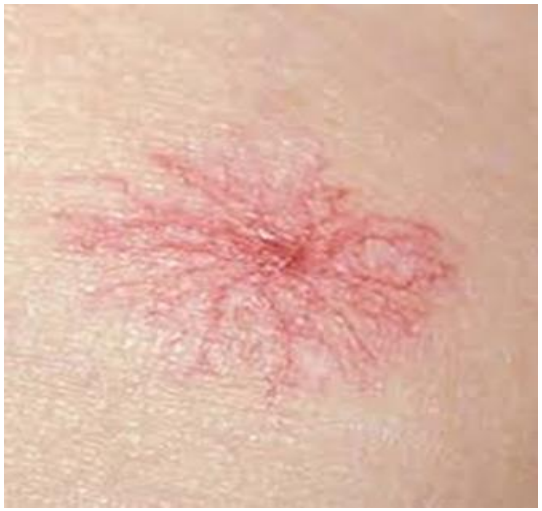
symptomatic relief by various therapeutic agents including

- ✓ bile acid-binding agents (cholestyramine),
- ✓ choleretic agents (ursodeoxycholic acid),
- ✓ opiate antagonists,
- ✓ antihistamines, and
- ✓ antibiotics.
- ✓ Plasmapheresis,
- ✓ surgical diversion of bile (partial external biliary diversion) for medically refractory pruritus.

Spider Angiomas (telangiectasias),
characterized by central pulsating arterioles from which small, wiry venules radiate,

- ✓ seen in patients with chronic liver disease;
- ✓ most prominent in the superior vena cava distribution area (on the face and chest).
- ✓ size varies between 1 and 10 mm
- ✓ they exhibit central clearing with pressure.

They reflect altered estrogen metabolism in the presence of hepatic dysfunction



Xanthomas

Brown nodules can develop, first over the extensor surfaces of the extremities; rarely, xanthelasma of the eyelids develops

The marked elevation of serum cholesterol levels (to >500 mg/dL) associated with some forms of chronic cholestasis can cause the deposition of lipid in the dermis and subcutaneous tissue.

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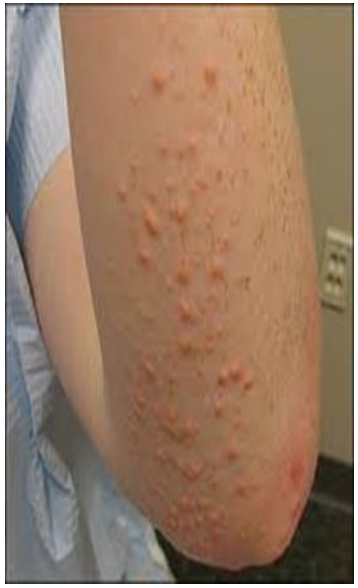
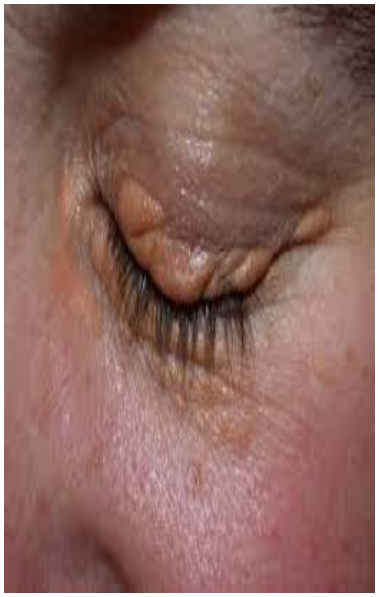
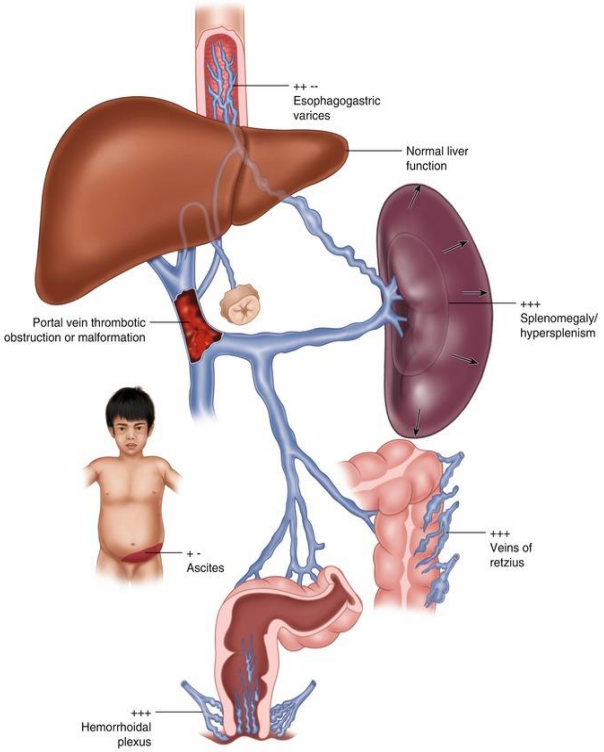




Portal hypertension

- ✓ portal pressure greater than 10 mm Hg.
- ✓ Clinically significant exists when pressure exceeds a 12 mm Hg or greater.
- ✓ Portal hypertension is the main complication of cirrhosis,
- ✓ directly responsible for 2 of its most common and potentially lethal complications: **ascites** and **variceal hemorrhage**.



Ascites
Gastrointestinal Bleeding

Encephalopathy

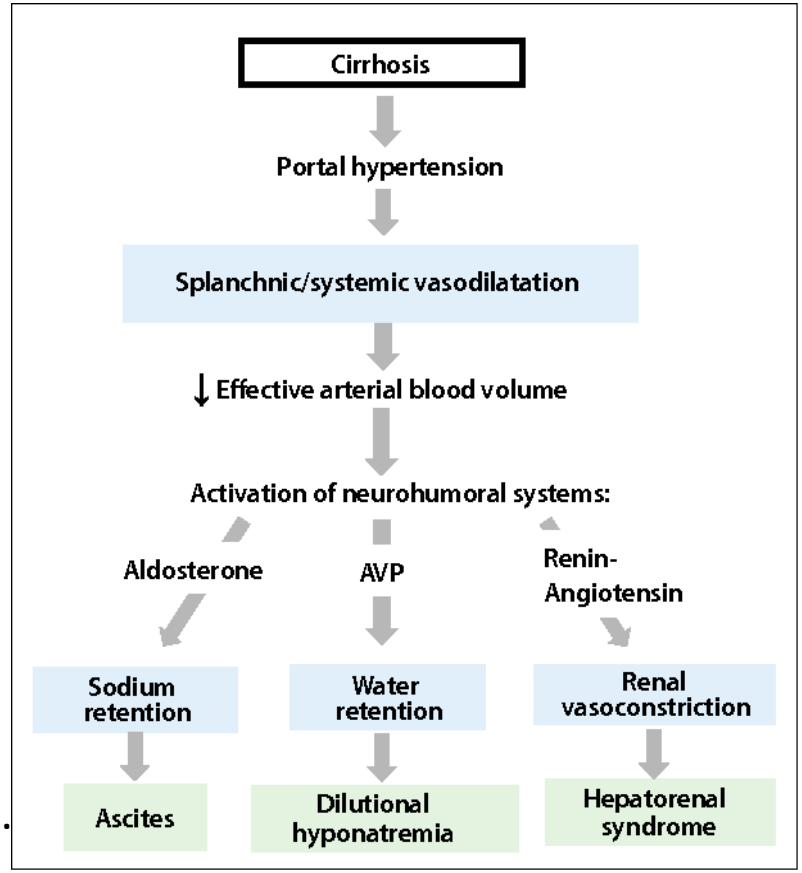
prominent form

subtle form such as deterioration of school performance, sleep disturbances, depression, or emotional outbursts.

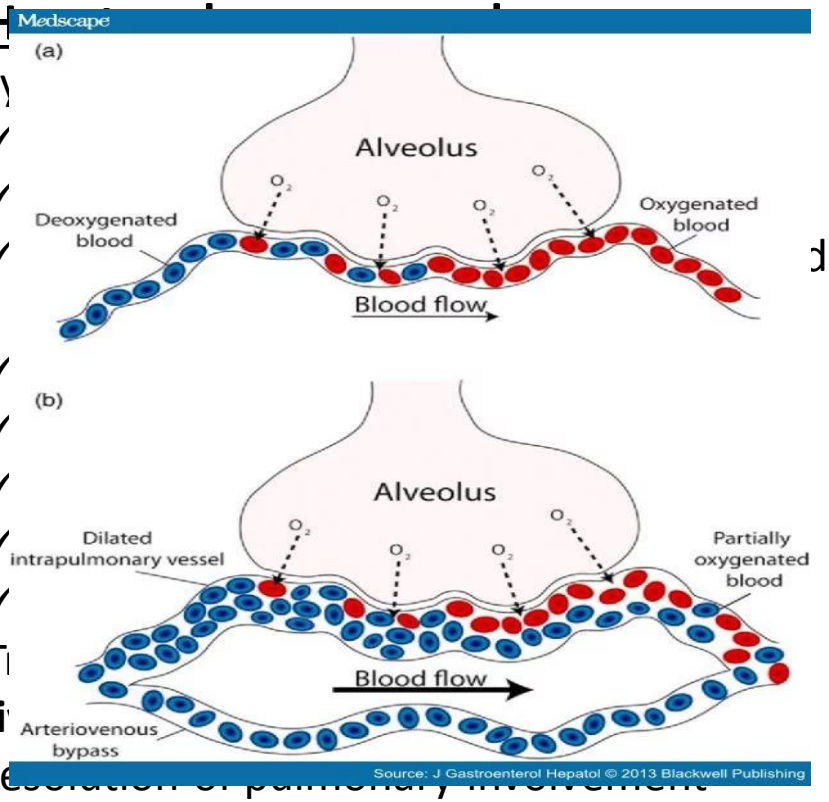
It can be recurrent and precipitated by intercurrent illness, drugs, bleeding, or electrolyte and acid-base disturbances.

Hepatorenal syndrome

The hallmark is intense renal vasoconstriction (mediated by hemodynamic, humoral, or neurogenic mechanisms).



The treatment is timely **liver transplantation**, complete renal and pulmonary recovery can be expected



usually follows.

Portopulmonary hypertension

increase in the resistance to pulmonary arterial blood flow in the setting of portal hypertension

symptoms : exertional dyspnea, fatigue, syncope, palpitations, and chest pain.

Approach to infant with cholestatic jaundice

1ST LINE INVX

- CBC
- Liver profile
- AST
- ALT
- ALP
- GGT
- BILI
- ALBUMIN
- PT, INR

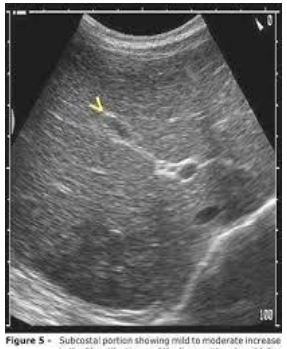


Figure 5 - Subcostal portion showing mild to moderate increase in the fiber-like tissue of the liver, with reduced biliar vesicle and thickened walls

USS

Others

- ECHO
- Fundus
- Slit lamp
- Xray vertebrae
- Hormonal assay
- Endoscopy

2ND LINE INVX

- ✓ Neonate TORCH
- ✓ Older children viral A,B,C
- ✓ Cultures blood and urine
- ✓ Metabolic screen
- ✓ Liver autoantibodies

- ✓ Hepatobiliary scintigraphy Radioisotope scaning T c99
- ✓ MRCP

Liver biopsy

General management of cholestasis

Pruritus

- ✓ Phenobarbital
- ✓ Cholestyramine
- ✓ Ursodeoxycholic acid
- ✓ Rifampicin

Nutritional management

- ✓ 120-150calories/day for infant
- ✓ MCT formula

Fat soluble vitamins A D E K

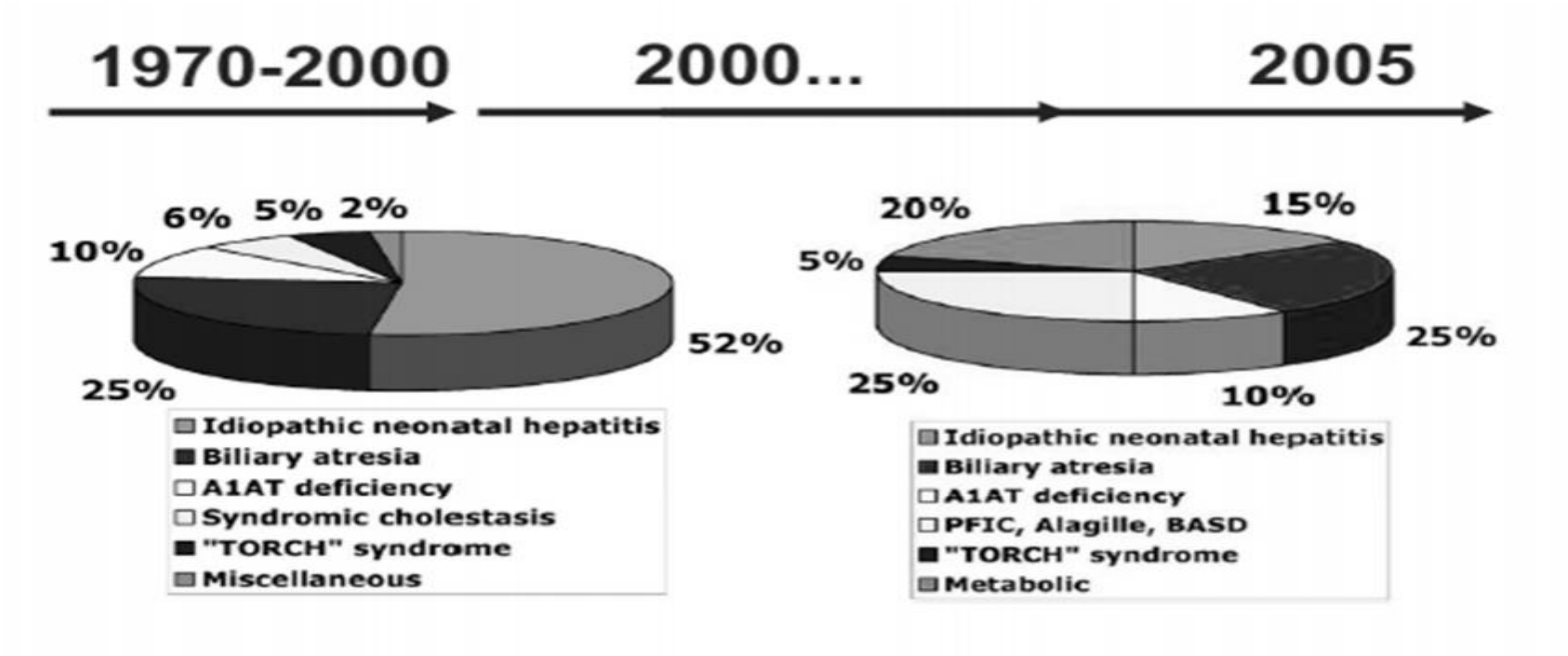
Specific treatment accordingly

Idiopathic neonatal hepatitis,

- ✓ Either a sporadic or a familial form,
- ✓ A disease of unknown cause.
- ✓ More common among males, especially preterm or low birthweight infants
- ✓ has a familial incidence of approximately 20%,
- ✓ the prognosis In sporadic cases, 60-70% recover

Intrahepatic

Familial forms, reflect a genetic or metabolic aberration; α1-antitrypsin deficiency were included in this category.



Intrahepatic

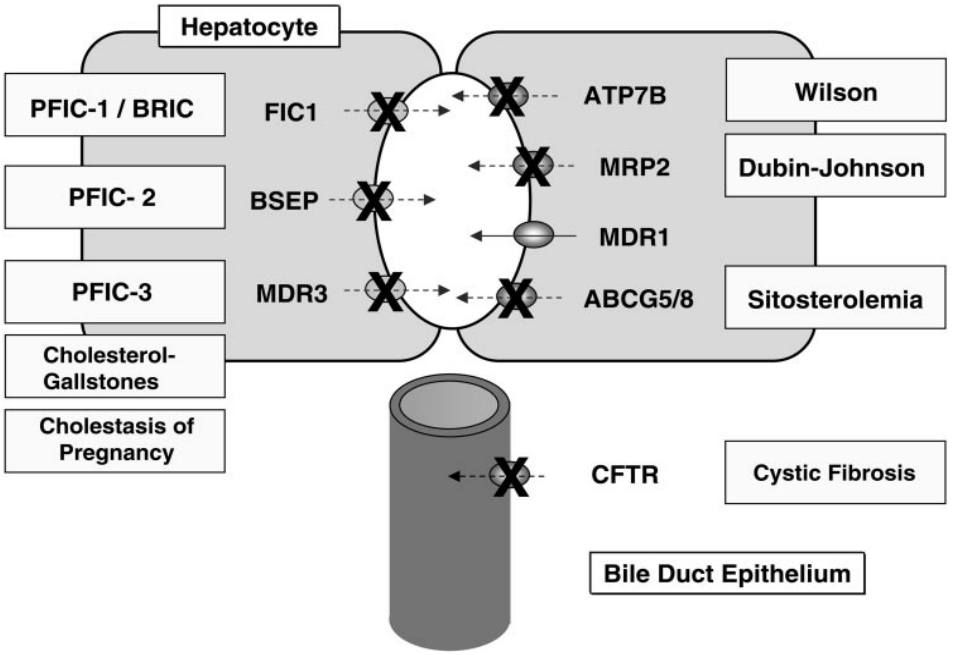
Progressive familial intrahepatic cholestasis (PFIC) type 1,2,3 AR

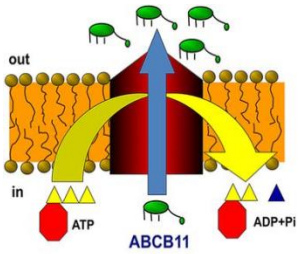
Bile Canalicular transport defect

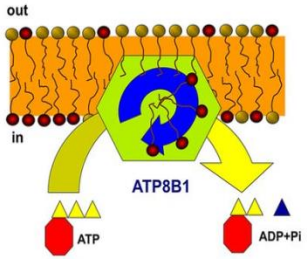
(PFIC) type 1 (Byler disease)
genetic mutation in the ATP8B1 gene on chromosome 18q21-22
encodes the protein FIC1

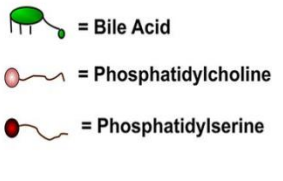
- A severe intrahepatic cholestasis.
- steatorrhea, pruritus, rickets,
- gradually developing cirrhosis,
- **low γ-(GGT) levels.**

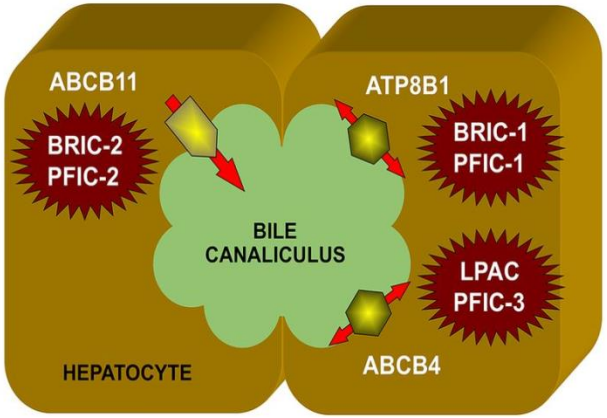
- benign recurrent intrahepatic cholestasis (BRIC) type I.

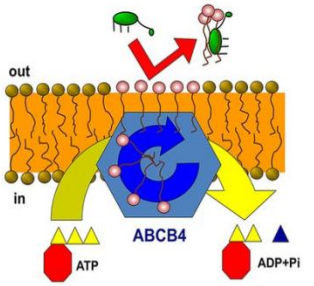












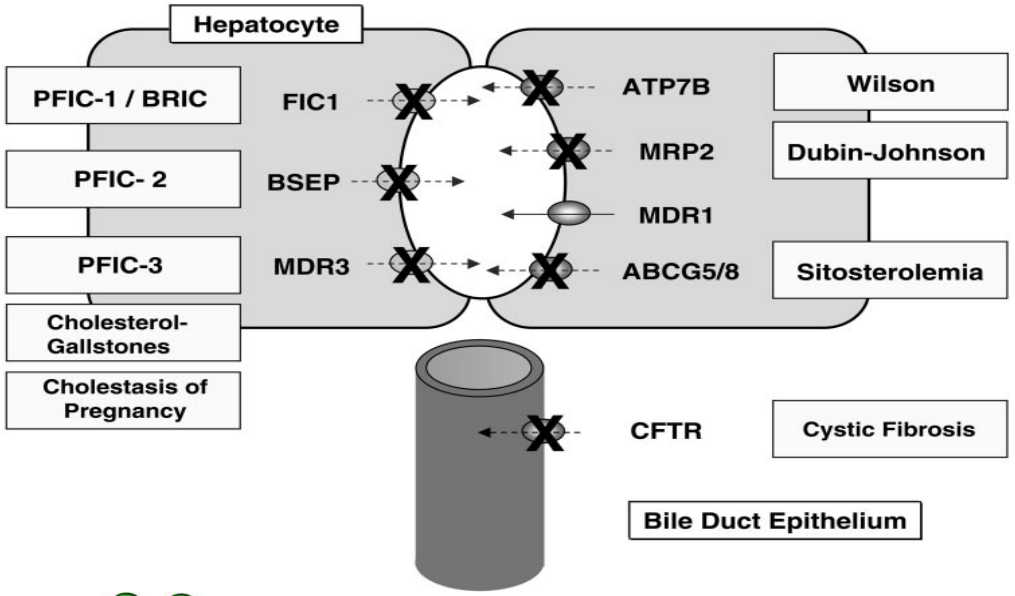
Intrahepatic

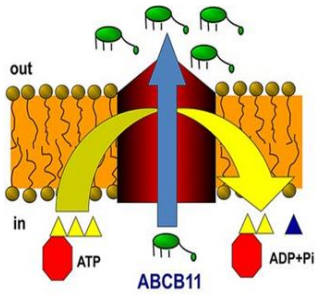
Progressive familial intrahepatic cholestasis (PFIC) **type 1,2,3 AR**
AR
Bile Canalicular transport defect

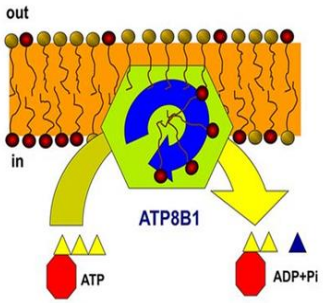
PFIC type 1 (FIC1)
PFIC type 2 *(BSEP)*

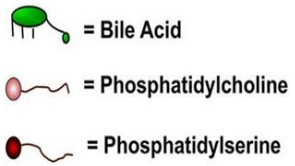
- **low γ-(GGT) levels.**

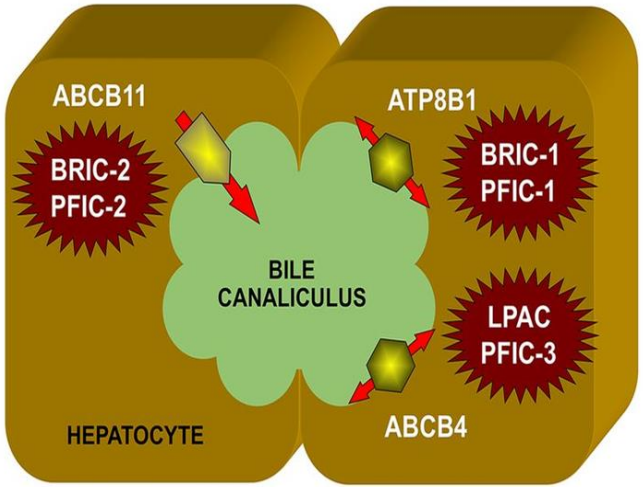
PFIC type 3 (MDR3 disease)
- ✓ **have high levels of GGT.**
- ✓ Mother had intrahepatic cholestasis during pregnancy.

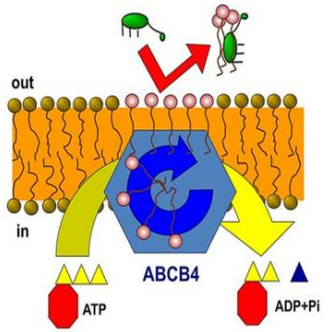




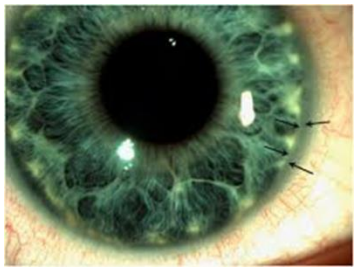








Mutations in human Jagged 1 gene (JAG1)
AD

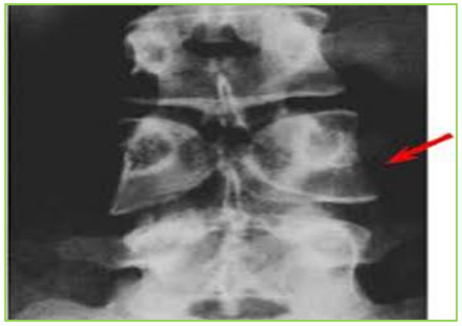


Intrahepatic

ocular abnormalities posterior embryotoxon, microcornea)

Alagille syndrome (arteriohepatic dysplasia)

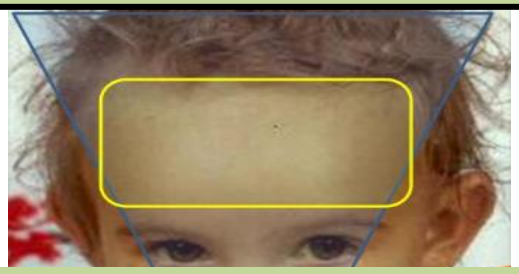
- ✓ is the most common syndrom with intrahepatic bile duct paucity.
- ✓ an absence or marked reduction in the number of interlobular bile ducts in the portal triads



butterfly vertebrae

Unusual facial: broad forehead; deep-set, widely spaced eyes; long, straight nose; and an underdeveloped mandible).

CVS abnormalities peripheral pulmonic stenosis)



Other findings : short stature, & defective spermatogenesis .

Prognosis for prolonged survival is good, but patients are likely to have pruritus, xanthomas , and neurologic complications of vitamin E deficiency if untreated.

BILIARY ATRESIA

- ✓ Most common cause of extrahepatic obstruction
- ✓ Most common cause of liver transplantion in children

Extrahepatic

Idiopathic inflammatory process
??viral infection (reovirus)
?? Immunological

- 1 in 10,000-15,000 live births.

2 types of biliary atresia (fetal and perinatal /postnatal) .

- ✓ Most patients with biliary atresia (85-90%) are normal at birth and have a postnatal progressive obliteration of bile ducts

- ✓ The embryonic or fetal-onset form manifests at birth and is associated with other congenital anomalies (situs inversus, polysplenia, intestinal malrotation, complex congenital heart disease)

Early : well infant an good weight gain
Jaundiced, hepatomegaly

Late : FTT, itching, ascitis, clubbing, hepatosplenomegaly, bleeding tendency

Differentiation of Idiopathic Neonatal Hepatitis from Biliary Atresia

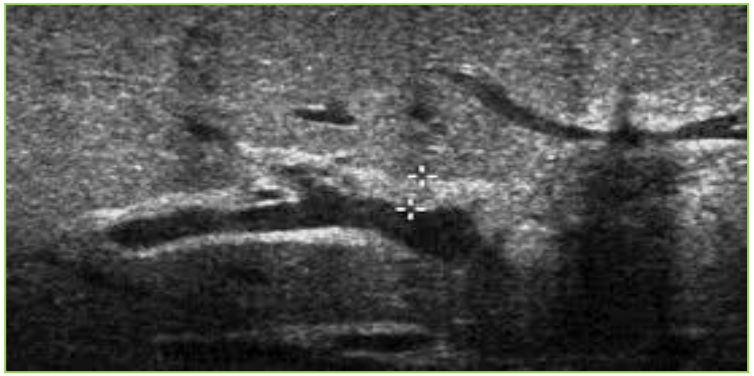
Consistently pigmented stools and the finding of bile-stained fluid on duodenal intubation excludes biliary atresia.

Persistently acholic stools is highly suggestive of biliary obstruction (biliary atresia), but patients with severe idiopathic neonatal hepatitis can have a transient severe impairment of bile excretion.

Evaluation

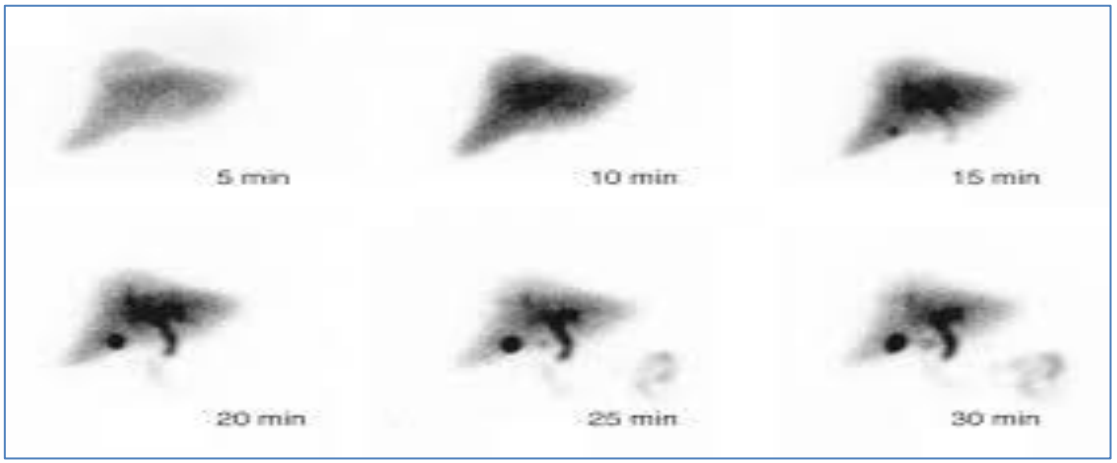
Liver function test

USS



USS in biliary atresia,
The gallbladder is either is **not** visualized or is a microgallbladder
" triangular cord sign "
Fasting at least 4 hour

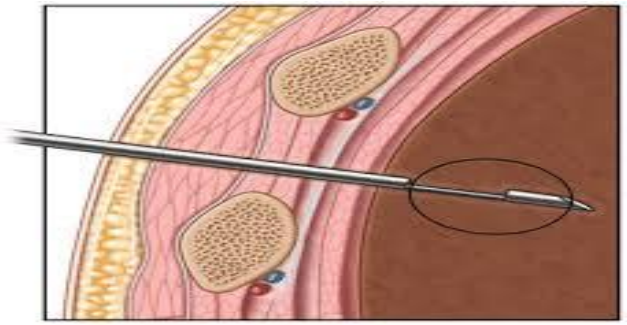
USS can detect associated anomalies such as abdominal polysplenia ,choledocal cyst



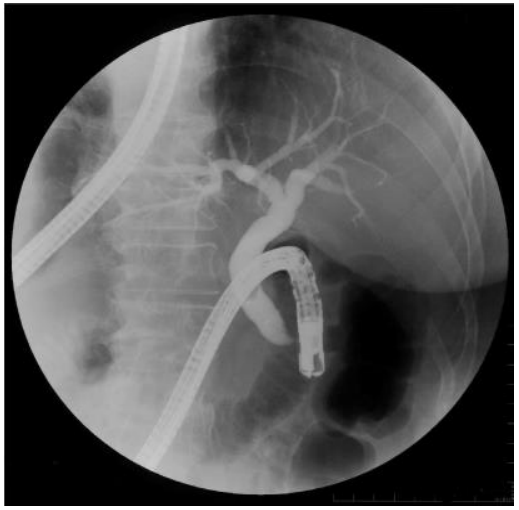
Hepatobiliary scintigraphy with technetium-labeled **i**mino**di**a**a**cetic acid derivatives **HIDA scan**

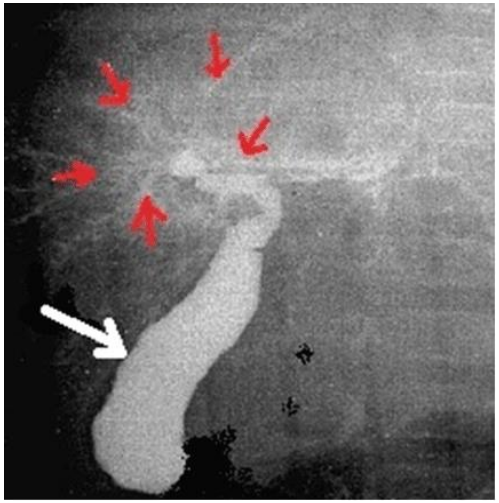
limited usefulness

- ✓ sensitive but not specific test for biliary atresia.
- ✓ need to wait for 5 days makes this procedure less practical in the evaluation of children with suspected biliary atresia.



Percutaneous liver biopsy is the most valuable procedure in the evaluation of neonatal hepatobiliary diseases





Exploratory laparotomy and direct cholangiography

Hepatoportoenterostomy (Kasai) procedure

The success rate for establishing good bile flow after the Kasai operation is (90%) if performed **before 8 wk** of life.

early referral and prompt evaluation of infants with suspected biliary atresia is important

Complication

Ascending cholangitis

Need for transplantion later

Metabolic Diseases of the Liver

DISORDERS OF CHO METABOLISM
Galactosemia
Fructosemia
Glycogen storage diseases

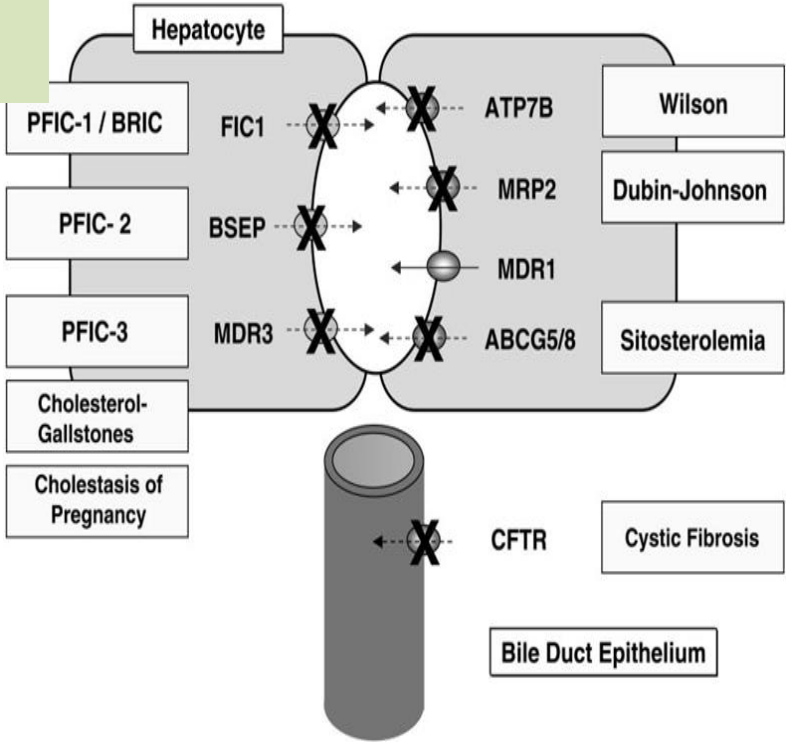
DISORDERS OF BILE ACID METABOLISM
Defects in bile acid synthesis

MISCELLANEOUS
α_1-Antitrypsin deficiency
Cystic fibrosis

DISORDERS OF A AND PROTEIN METABOLISM
Hereditary tyrosinemia type I & type II
Inherited urea cycle enzyme defects
Maple serum urine disease

DISORDERS OF LIPID METABOLIS
Familial hypercholesterolemia
Gaucher disease
Niemann-Pick

DISORDERS OF BILIRUBIN METABOLISM
Crigler-Najjar (Type I, Type II)
Gilbert disease
Dubin-Johnson syndrome
Rotor syndrome



Clinical Manifestations That Suggest the Possibility of Metabolic Disease

- ✓ Recurrent vomiting, failure to thrive,
- ✓ Fulminant hepatic failure,
- ✓ Hypoglycemia, organic acidemia, lactic acidemia,
- ✓ hyperammonemia, bleeding (coagulopathy)
- ✓ Developmental delay/psychomotor retardation, hypotonia,
- ✓ progressive neuromuscular deterioration, seizures, myopathy, neuropathy
- ✓ Cardiac dysfunction/failure
- ✓ Unusual odors
- ✓ Cataracts

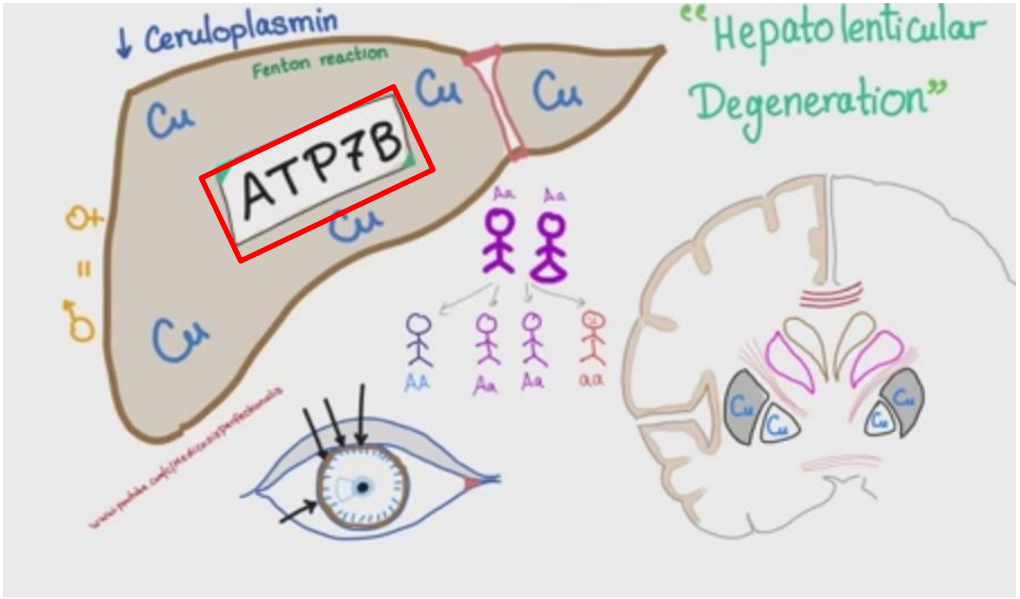
Galactosemia

AR

Chloestatic jaundice ,vomiting ,hypoglycemia and convulsion, cataract

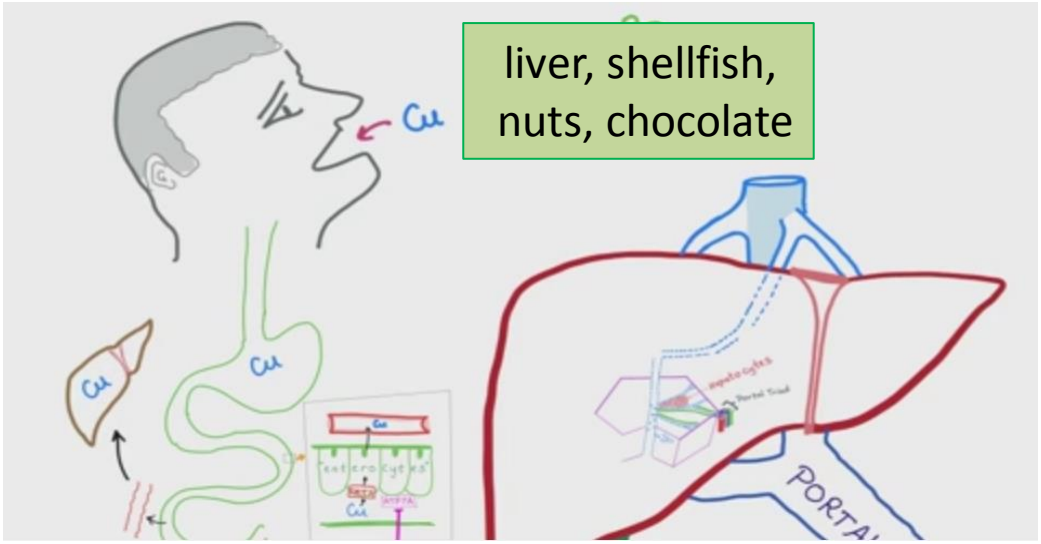
Treatment : soya based formula

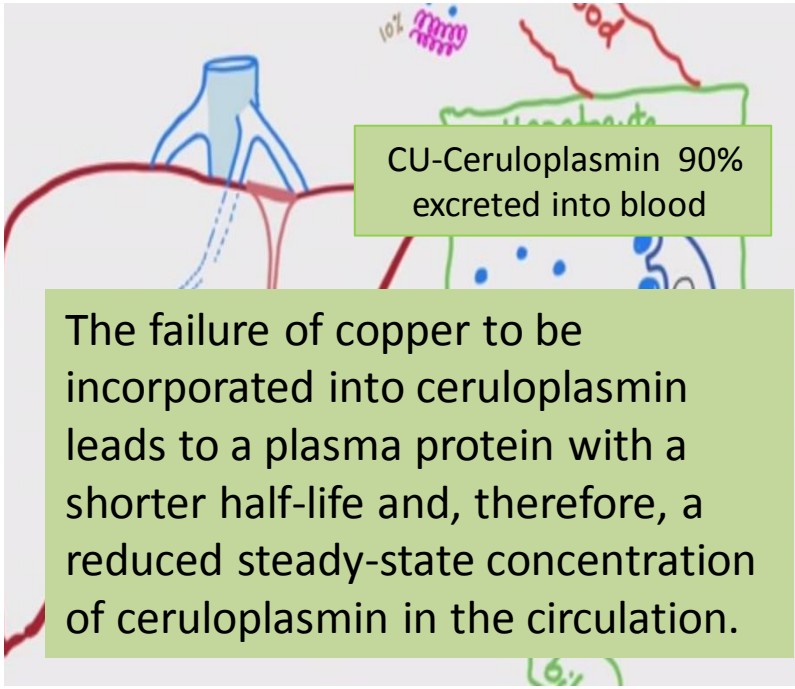
Wilson Disease (hepatolenticular degeneration)



1 in 30,000 to 1 in 50,000 births worldwide

degenerative changes in the brain, liver disease, and Kayser-Fleischer rings in the cornea





The failure of copper to be incorporated into ceruloplasmin leads to a plasma protein with a shorter half-life and, therefore, a reduced steady-state concentration of ceruloplasmin in the circulation.

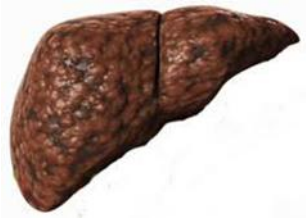
CLINICAL MANIFESTATIONS

Kayser-Fleischer rings
present in 95% of patients with neurologic symptoms
absent in 50% young patients with hepatic Wilson d

After 20 yr of age, neurologic symptoms predominate

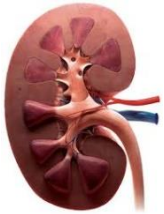
liver disease may precede neurologic manifestations by as much as 10 yr

Any patient presenting with any form of liver disease, particularly if older than 5 yr of age should be investigated for the possibility of Wilson disease



Neurologic disorders
intention tremor,
dysarthria,
rigid dystonia,
Parkinsonism,
choreiform movements,
deterioration in school performance,
or behavioral changes.

Hepatic disorder
- ✓ Asymptomatic hepatomegaly (with or without splenomegaly),
- ✓ acute hepatic failure
- ✓ subacute or chronic hepatitis,
- ✓ Cryptogenic cirrhosis, portal hypertension, ascites, edema, variceal bleeding,or other effects of hepatic dysfunction (delayed puberty, amenorrhea,coagulation defects)



Coombs-negative hemolytic anemia may be an initial manifestation

Renal Fanconi syndrome and progressive renal failure

Unusual manifestations include arthritis, pancreatitis, and endocrinopathies (hypoparathyroidism).

Wilson disease should be considered in children and teenagers with

- ✓ unexplained acute or chronic liver disease,
- ✓ neurologic symptoms of unknown cause,
- ✓ acute hemolysis,
- ✓ psychiatric illnesses, behavioral changes,
- ✓ Fanconi syndrome

- ✓ Ceruloplasmin levels is decreased
- ✓ urinary copper excretion is increased

Hepatic copper accumulation is the hallmark of Wilson disease

- ✓ measurement of hepatic parenchymal copper concentration is the method of choice for diagnosis.

Liver transplantation is curative

Diet

- ✓ restrict dietary copper intake to <1 mg/day.
- ✓ Foods such as liver, shellfish, nuts, and chocolate should be avoided.

continued administration,
urinary copper levels can become normal,
marked improvement in hepatic
improvement in neurologic function
disappearance of Kayser-Fleischer rings.

Zinc has also been used b/c ts ability to impair the gastrointestinal absorption of copper.

Drugs

Chelation therapy is managed with oral administration of d-penicillamine or triethylene tetramine dihydrochloride (Trien, TETA, trientine)

α1-ANTITRYPSIN DEFICIENCY

mutation in the SERPINA1 gene
an autosomal recessive disorder.

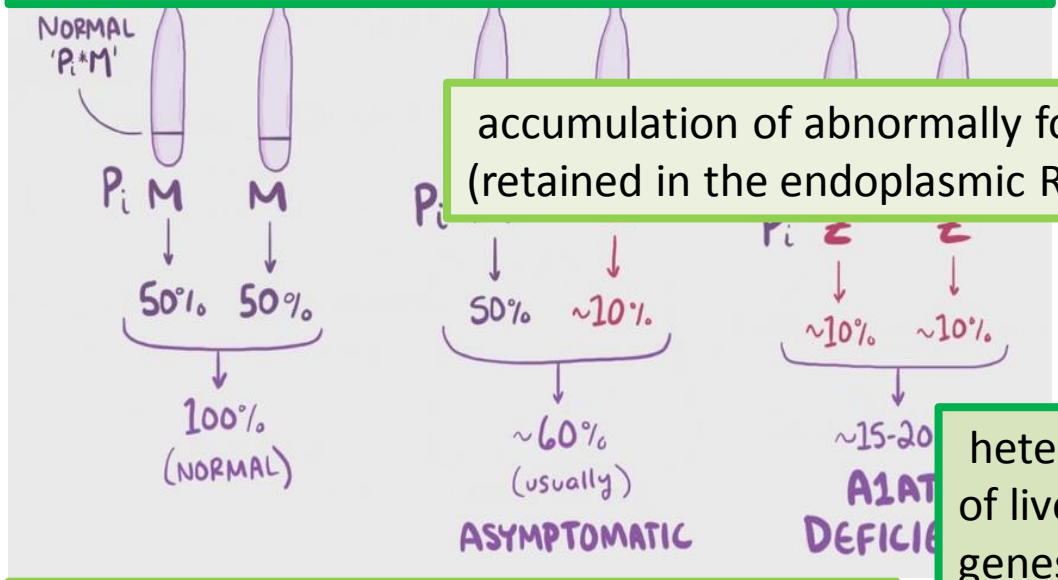
α1-Antitrypsin, a protease inhibitor synthesized by the liver

PI protects lung alveoli from destruction by neutrophil elastase

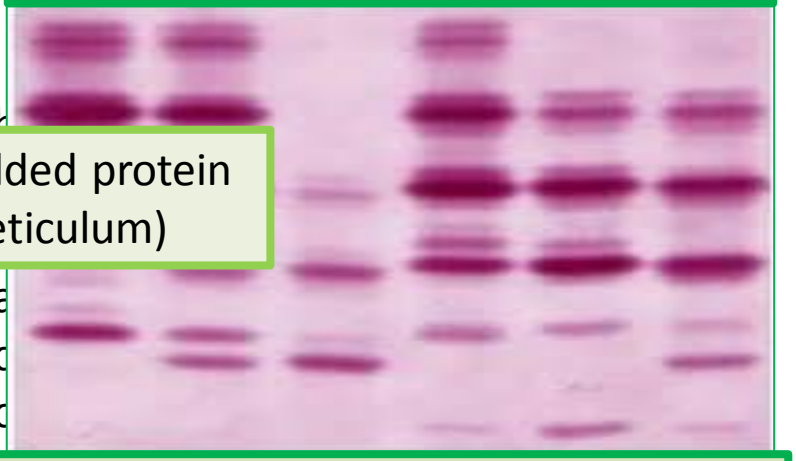
The most common allele of the protease inhibitor (Pi) system is M, and the normal phenotype is PiMM

α1-Antitrypsin is present in more than 20 different codominant alleles, only a few of which are associated with defective protease inhibitors.

Z allele predisposes to clinical deficiency; patients with liver disease are usually PiZZ homozygotes and have serum α1-antitrypsin levels (~10-20% of N)



accumulation of abnormally folded protein (retained in the endoplasmic Reticulum)



heterozygotes PiZ-, PiSZ, PiZI are not a cause of liver disease alone but can act as modifier genes, increasing the risk of progression in other liver disease such as nonalcoholic fatty liver disease and hepatitis C.

The null phenotype : complete absence of any protein and causes only lung disease

In affected patients, the course of liver disease is also highly variable.

Infants with liver disease are indistinguishable from “idiopathic”neonatal hepatitis,

Jaundice, acholic stools, and hepatomegaly are present in the 1st wk of life, but the jaundice usually clears in the 2nd-4th mo. Complete resolution , persistent liver disease, or the development of cirrhosis can follow.

Older children can present with asymptomatic hepatomegaly or manifestations of chronic liver disease or cirrhosis, with evidence of portal hypertension

Emphysema is not typically observed in children but an increased risk for developing asthma is reported

Therapy is supportive; liver transplantation has been curative

Autoimmune hepatitis

Chronicity is determined by
- ✓ duration of >3-6 mo or by
- ✓ evidence of chronic hepatic decompensation AND physical stigmata of chronic liver disease

chronic hepatic inflammatory process manifested by
- ✓ elevated s. aminotransaminase concentrations,
- ✓ serum autoantibodies, and/or
- ✓ Hypergammaglobulinemia

The severity is variable;
- ✓ only biochemical evidence of liver dysfunction, or
- ✓ stigmata of chronic liver disease, or
- ✓ can present in hepatic failure.

CLINICAL MANIFESTATIONS

Patients can be **asymptomatic** or have fatigue, malaise, behavioral changes, anorexia, and amenorrhea, sometimes for many months before jaundice or stigmata of chronic liver disease are recognized

jaundice
mild to moderate in severe cases.

The liver may be tender and slightly enlarged but might not be felt in patients with cirrhosis.
The spleen is commonly enlarged.

In 25-30% of patients with autoimmune hepatitis, particularly children, the illness **mimics acute viral hepatitis**

Extrahepatic manifestations can include

- ✓ arthritis
- ✓ vasculitis
- ✓ Nephritis
- ✓ Thyroiditis
- ✓ Coombs-positive anemia, and
- ✓ rash

- ✓ patients' initial clinical features reflect cirrhosis
- ✓ ascites,
- ✓ bleeding,
- ✓ esophageal varices,
- ✓ or hepatic encephalopathy).

Table 362-2 Classification of Autoimmune Hepatitis

VARIABLE	TYPE 1 AUTOIMMUNE HEPATITIS	TYPE 2 AUTOIMMUNE HEPATITIS
Characteristic autoantibodies **ANA** **ASMA** **ALKMA**	Antinuclear antibody* Smooth-muscle antibody* Antiactin antibody† Autoantibodies against soluble liver antigen and liver-pancreas antigen‡ Atypical perinuclear antineutrophil cytoplasmic antibody	Antibody against liver-kidney microsome type 1* Antibody against liver cytosol type 1* Antibody against liver-kidney microsomal type 3
Geographic variation	Worldwide	Worldwide; rare in North America
Age at presentation	Any age	Predominantly childhood and young adulthood
Gender of patients	Female in ~75% of cases	Female in ~95% of cases
Association with other autoimmune diseases	Common	Common§
Clinical severity	Broad range, variable	Generally severe
Histopathologic features at presentation	Broad range, mild disease to cirrhosis	Generally advanced
Treatment failure	Infrequent	Frequent
Relapse after drug withdrawal	Variable	Common
Need for long-term maintenance	Variable	~100%

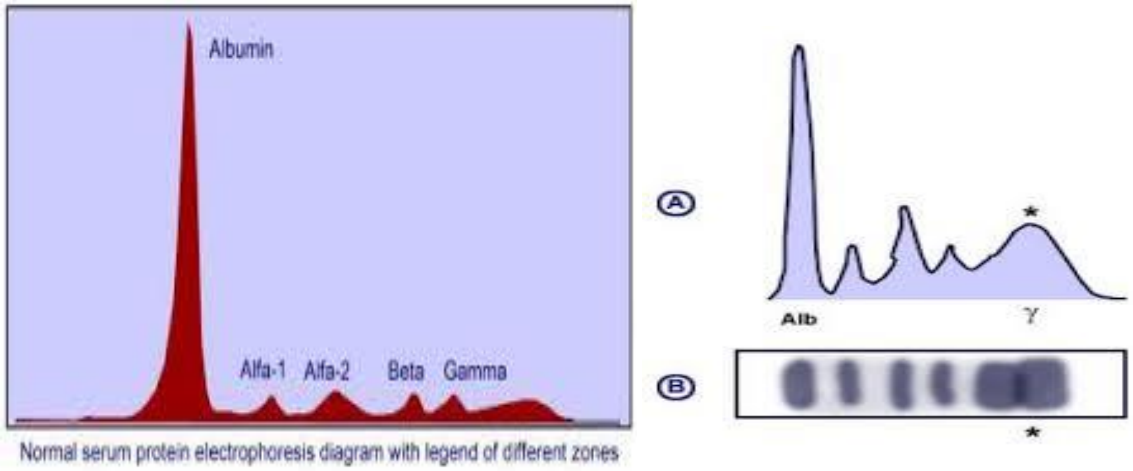
LABORATORY FINDINGS

related to the severity of presentation.
In many asymptomatic cases, serum aminotransferase ranges between 100 - 300 IU/L, whereas levels in excess of 1,000 IU/L can be seen in symptomatic

S. bilirubin concentrations may be normal in mild cases but are commonly 2-10 mg/dL in more severe cases.

PT is prolonged,
A normochromic normocytic anemia, leukopenia, and thrombocytopenia *become* more severe with the development of portal hypertension and hypersplenism.

Serum γ-globulin levels can show marked polyclonalelevations.
Hypoalbuminemia is common



Normal serum protein electrophoresis diagram with legend of different zones

autoantibodies
20% of patients with apparent autoimmune hepatitis might not have autoantibodies at presentation.

LIVER BIOPSY

TREATMENT
Prednisone, with or without azathioprine or 6-mercaptopurine

Liver transplantation has been successful in patients with end-stage or fulminant liver disease associated with autoimmune hepatitis

Disease recurs after transplantation in approximately 30% of patients

Table 362-1 | Disorders Producing Chronic Hepatitis

Chronic viral hepatitis
- Hepatitis B
- Hepatitis C
- Hepatitis D

Autoimmune hepatitis
- Anti-actin antibody positive
- Anti–liver-kidney microsomal antibody positive
- Anti-soluble liver antigen antibody-positive
- Others (includes antibodies to liver-specific lipoproteins or asialoglycoprotein)
- Overlap syndrome with sclerosing cholangitis and autoantibodies
- Systemic lupus erythematosus
- Celiac disease

Drug-induced hepatitis

Metabolic disorders associated with chronic liver disease
- Wilson disease
- Nonalcoholic steatohepatitis
- α_1-Antitrypsin deficiency
- Tyrosinemia
- Niemann-Pick disease type 2
- Glycogen storage disease type iv
- Cystic fibrosis
- Galactosemia
- Bile acid biosynthetic abnormalities

- ✓ isoniazid,
- ✓ Methyldopa
- ✓ nitrofurantoin
- ✓ sulfonamides.

Thank you