PATHOLOGY OF LIVER I

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VIRAL HEPATITIS AND ALCOHOLIC LIVER DISEASE

HEPATITIS

- Hepatitis is applied to patterns of acute and chronic hepatic injuries that are produced by:

➢ Hepatotropic viruses (have a specific affinity for the liver).

➢ Other viruses such as EBV, CMV .

➢ Yellow fever

➢ Autoimmune reactions.

➢ Drugs and toxins.

Case study

- A 27-year-old man develops malaise, fatigue, and loss of appetite three weeks after a meal at café. He notes passing dark urine. On physical examination, he has mild scleral icterus and right upper quadrant tenderness. Laboratory studies show serum AST of 62 U/L and ALT of 58 U/L. The total bilirubin concentration is 3.9 mg/dL, and the direct bilirubin concentration is 2.8 mg/dL. His symptoms abate over the next 3 weeks.

LFT	Normal range
Protein	6.6-8.3 g/dL
Albumin	3.5-5.2 g/dL
Total bilirubin	0.2-1.3 mg/dL
ALT	<40 U/L
AST	<40 U/L

DIAGNOSIS

- Clinical history and examination.
- Laboratory testing.
- Biopsy.

SIGNS AND SYMPTOMS

- infection with hepatitis viruses produces a wide range of outcomes including:

❖ Acute Asymptomatic Infection:

- elevated serum transaminases or the presence of anti-viral antibodies, HAV and HBV infections, particularly in childhood.

❖ Acute Symptomatic Infection, consisting of:

- (1) an incubation period of variable length.
- (2) a symptomatic preicteric phase.
- (3) a symptomatic icteric phase.
- (4) convalescence.

❖ Fulminant Hepatic Failure:

- Occur with HBV and HAV.

❖ Chronic Hepatitis:

- persistent or relapsing hepatic disease for a period of more than 6 months.
- Possible symptoms:
- elevations of serum transaminases.
- fatigue;, malaise, loss of appetite, and bouts of mild jaundice.

❖ The Carrier State:

- A carrier is an individual who is chronically infected with a hepatropic virus and has no or subclinical evidence of liver disease.

ASSOCIATED SIGNS AND SYMPTOMS INCLUDE:

- General: fatigue (most common), malaise, mild discomfort in the right upper quadrant, anorexia
- Impaired biliary tract function: jaundice, pruritus
- Portal hypertension: gastroesophageal varices, ascites, edema, splenomegaly
- Impaired hepatocyte metabolism: spider angiomata, hepatic encephalopathy, easy bleeding / bruising

LABORATORY FINDINGS

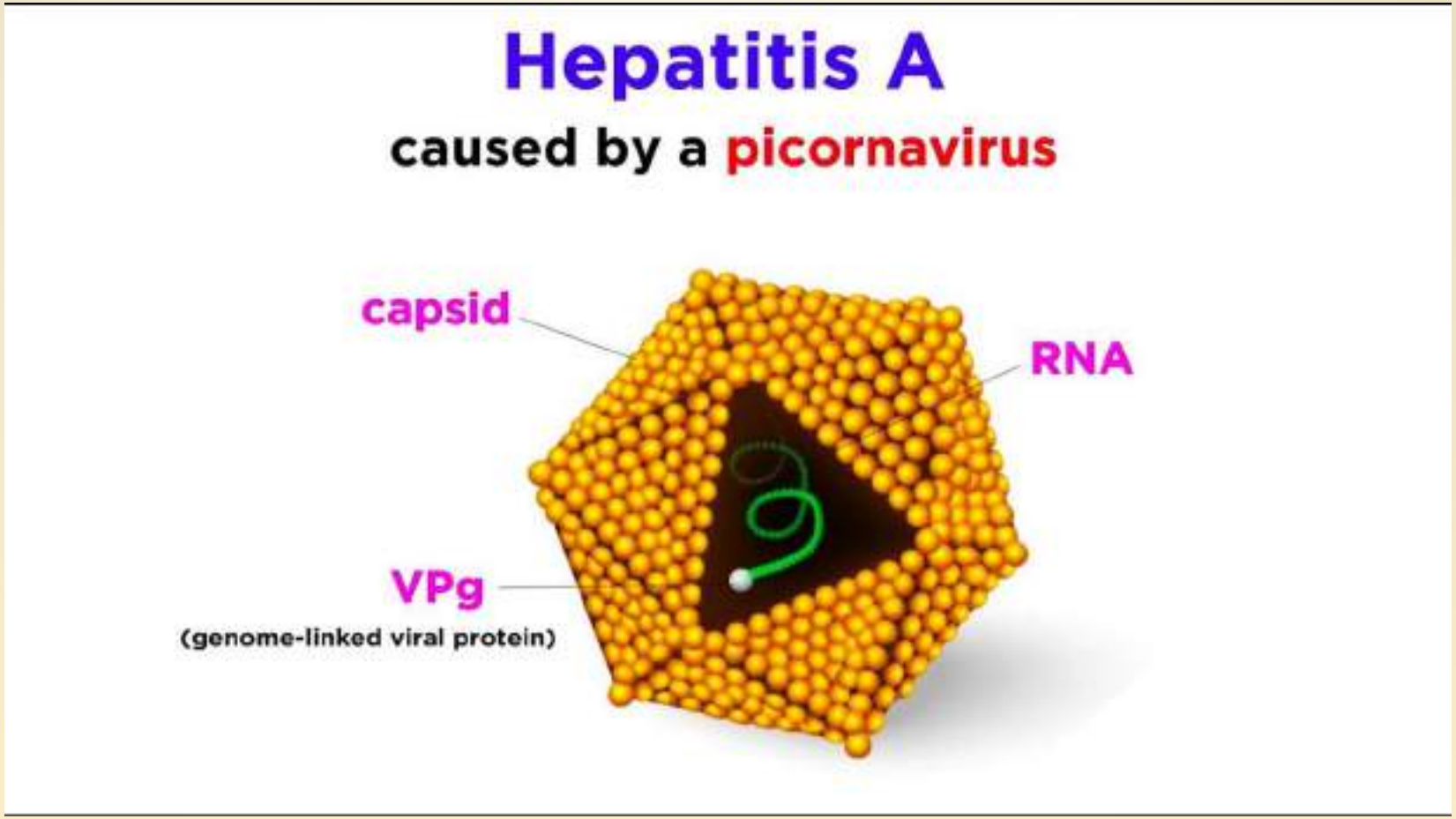
- Aminotransferase levels .
- Serological testing for hepatitis B, C and D and autoantibodies

Virus	Hepatitis A (HAV)	Hepatitis B (HBV)	Hepatitis C (HCV)	Hepatitis D (HDV)	Hepatitis E (HEV)
Viral genome	ssRNA	partially dsDNA	ssRNA	Circular defective ssRNA	ssRNA
Viral family	Hepatovirus; related to picornavirus	Hepadnavirus	*Flaviviridae*	Subviral particle in *Deltaviridae* family	Calicivirus
Route of transmission	Fecal-oral (contaminated food or water)	Parenteral, sexual contact, perinatal	Parenteral; intranasal cocaine use is a risk factor	Parenteral	Fecal-oral
Incubation period	2–6 weeks	2–26 weeks (mean 8 weeks)	4–26 weeks (mean 9 weeks)	Same as HBV	4–5 weeks
Frequency of chronic liver disease	Never	5%–10%	>80%	10% (coinfection); 90%–100% for superinfection	In immunocompromised hosts only
Diagnosis	Detection of serum IgM antibodies	Detection of HBsAg or antibody to HBcAg; PCR for HBV DNA	ELISA for antibody detection; PCR for HCV RNA	Detection of IgM and IgG antibodies, HDV RNA in serum, or HDAg in liver biopsy	Detection of serum IgM and IgG antibodies; PCR for HEV RNA

1. HEPATITIS A VIRUS (HAV).

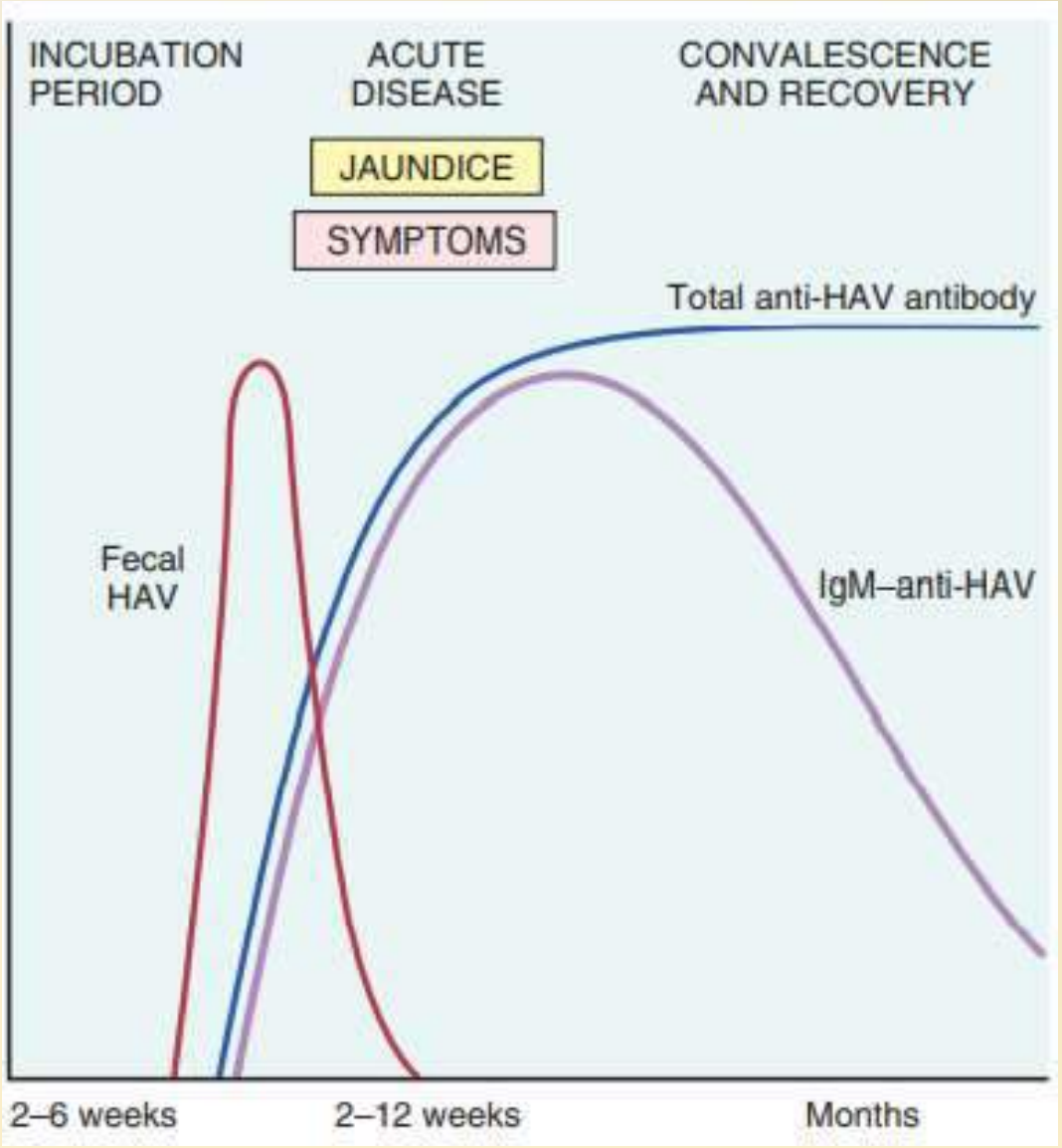
- HAV usually is a benign self-limited infection that does not cause chronic hepatitis and rarely produces fulminant hepatitis.
- incubation period of 3-6 weeks, shed in the stool for 2 to 3 weeks before and 1 week after the onset of jaundice.
- The infection associated with poor hygiene and sanitation, ingestion of steamed shellfish.
- Acute HAV tends to cause a febrile illness, jaundice and nonspecific symptoms such as fatigue and loss of appetite.

- HAV is a small, non-enveloped, positive-strand RNA picornavirus
- The cellular immune response, particularly that involving cytotoxic CD8+ T cells, plays a key role in HAV-mediated hepatocellular injury.



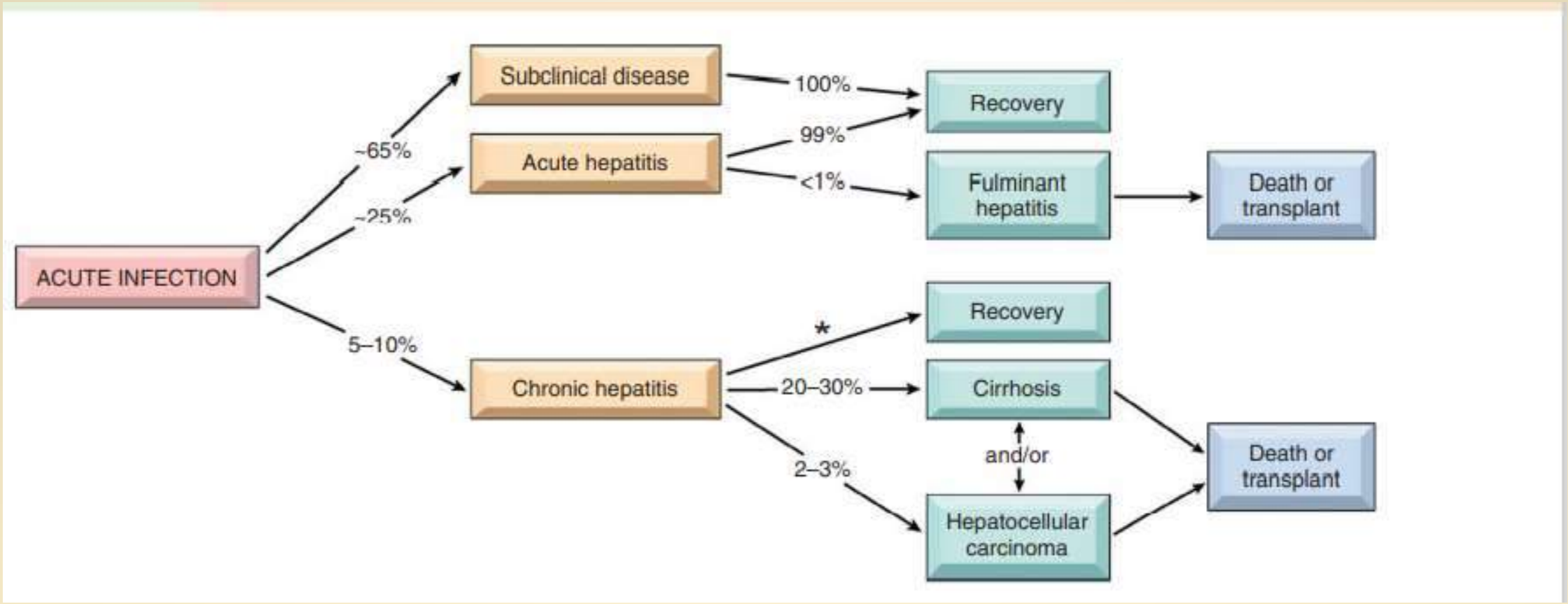
- IgM antibody against HAV appears in blood at the onset of symptoms and is a reliable marker of acute infection

The IgM response usually declines in a few months followed by the appearance of IgG anti-HAV that persists for years, often conferring lifelong immunity.

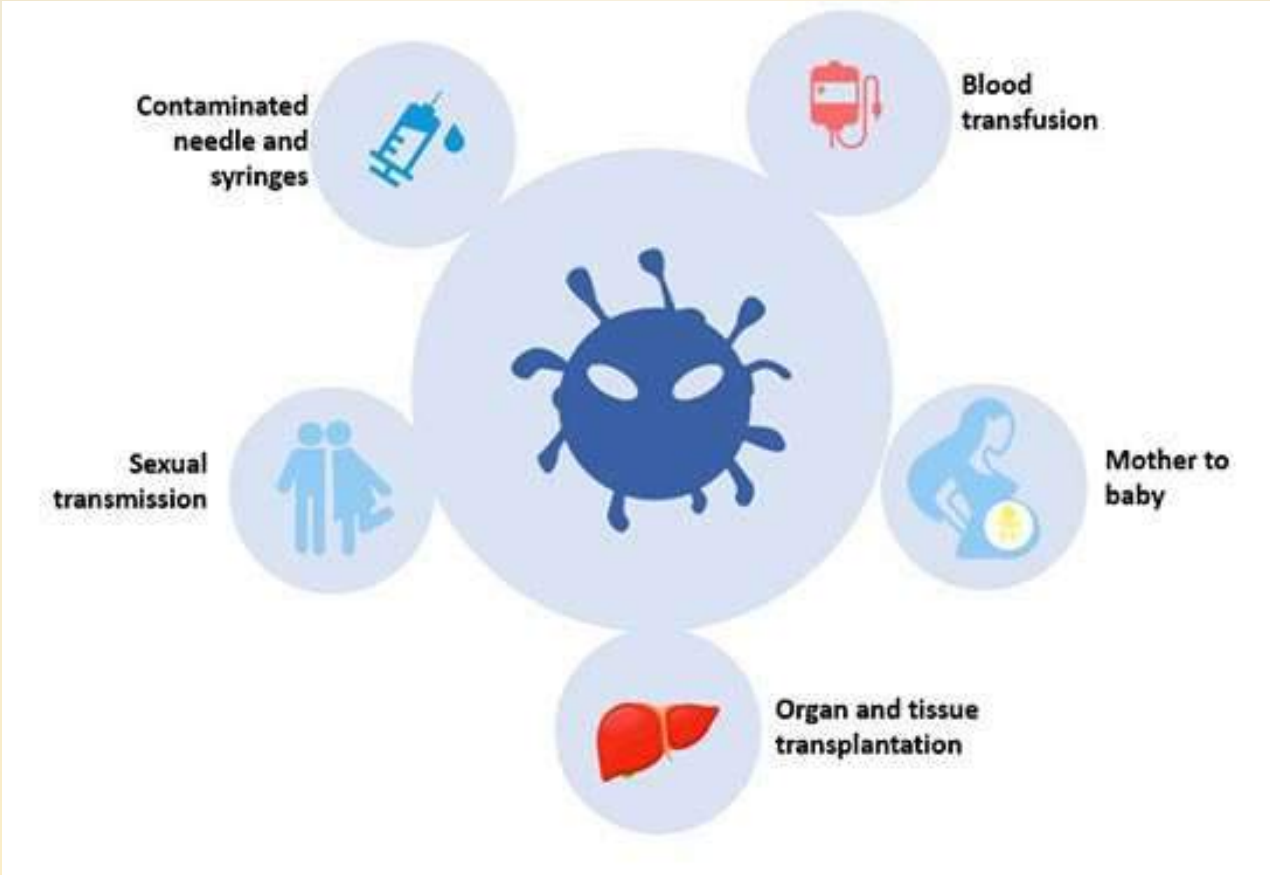


2. HEPATITIS B VIRUS (HBV)

- The outcome of HBV infection varies widely, from:
- (1) acute hepatitis with recovery and clearance of the virus.
- (2) nonprogressive chronic hepatitis.
- (3) progressive chronic disease ending in cirrhosis.
- (4) fulminant hepatitis with massive liver necrosis.
- (5) an asymptomatic "healthy" carrier state.


ACUTE INFECTION
~65%
~25%
5–10%
Subclinical disease
Acute hepatitis
Chronic hepatitis
100%
99%
<1%
*
20–30%
2–3%
Recovery
Fulminant hepatitis
Recovery
Cirrhosis
and/or
Hepatocellular carcinoma
Death or transplant
Death or transplant

TRANSMISSION OF HBV



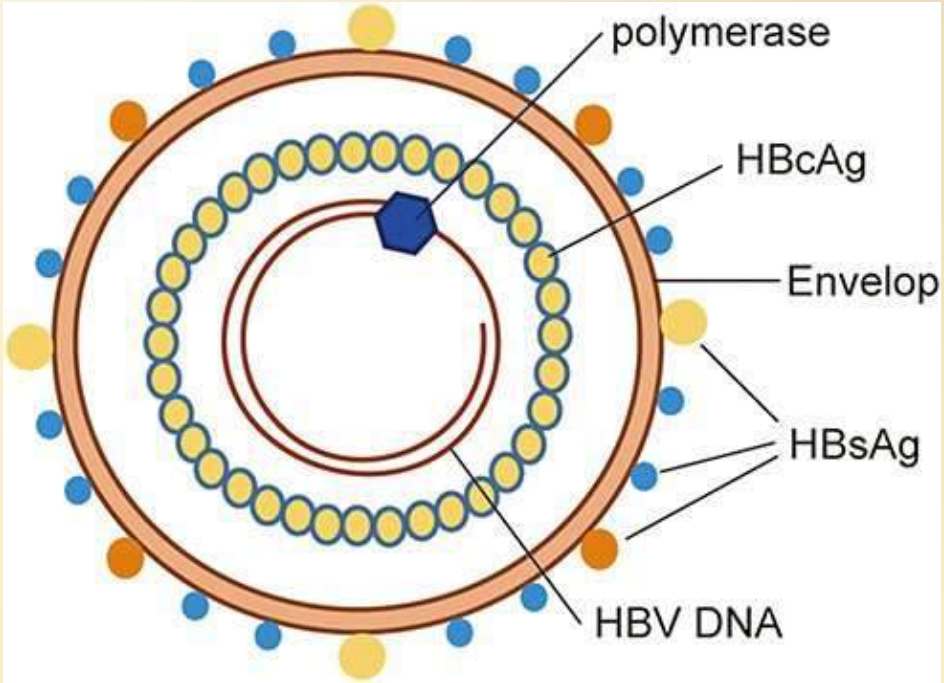
- HBV is a member of Hepadnaviridae, a family of DNA viruses.
- The HBV genome is a partially double-stranded, which encode the following proteins:

✓ Nucleocapsid "core" protein (HBcAg).

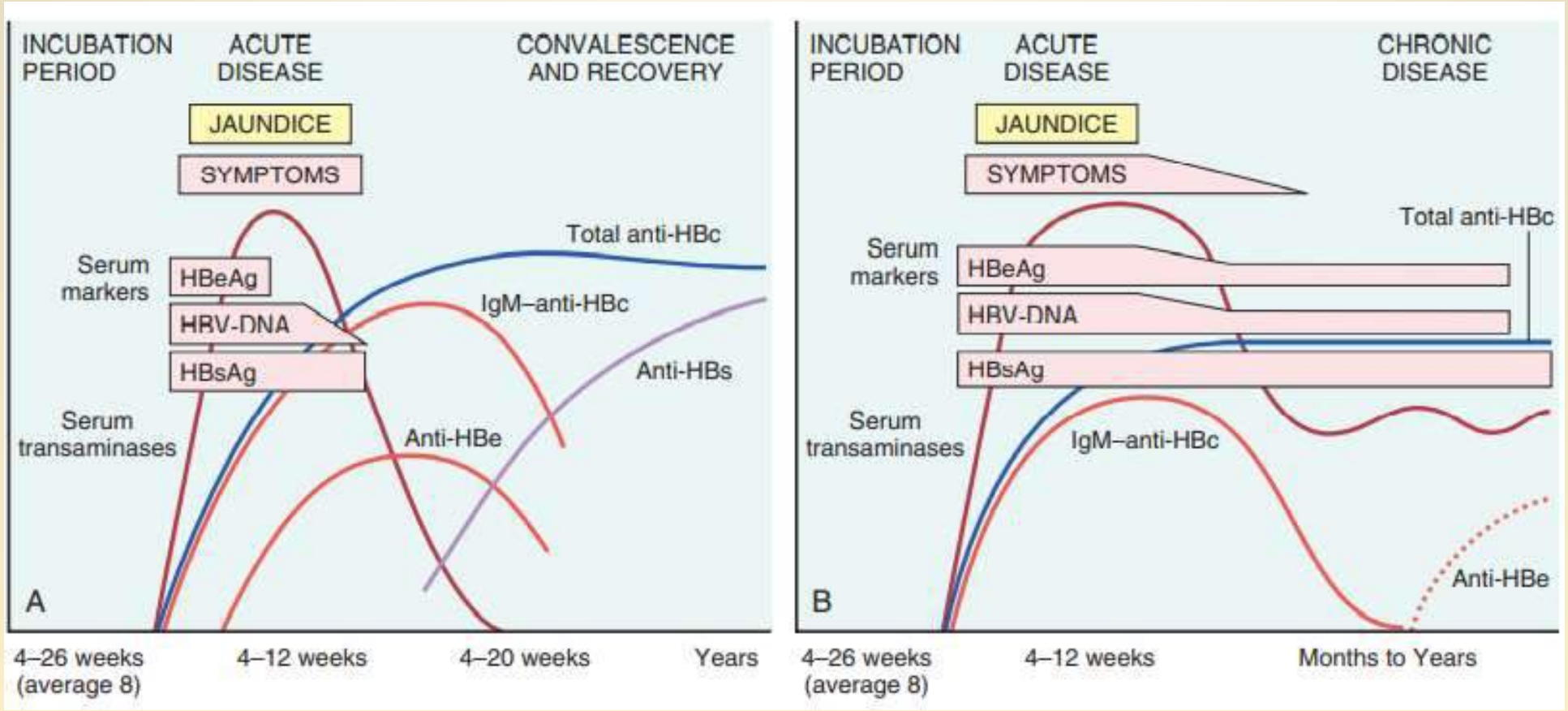
✓ Envelope glycoproteins (HBsAg).

✓ A polymerase (Pol) with both DNA polymerase activity and reverse transcriptase activity.

✓ HBx protein, which is required for virus replication.



THE COURSE OF THE DISEASE



- HBV generally is not directly hepatotoxic, and most hepatocyte injury is caused by CD8+ cytotoxic T cells attacking infected cells.

- Patient age at the time of infection is the best predictor of chronicity. In general, the younger the age at the time of HBV infection, the higher the chance of chronic infection.

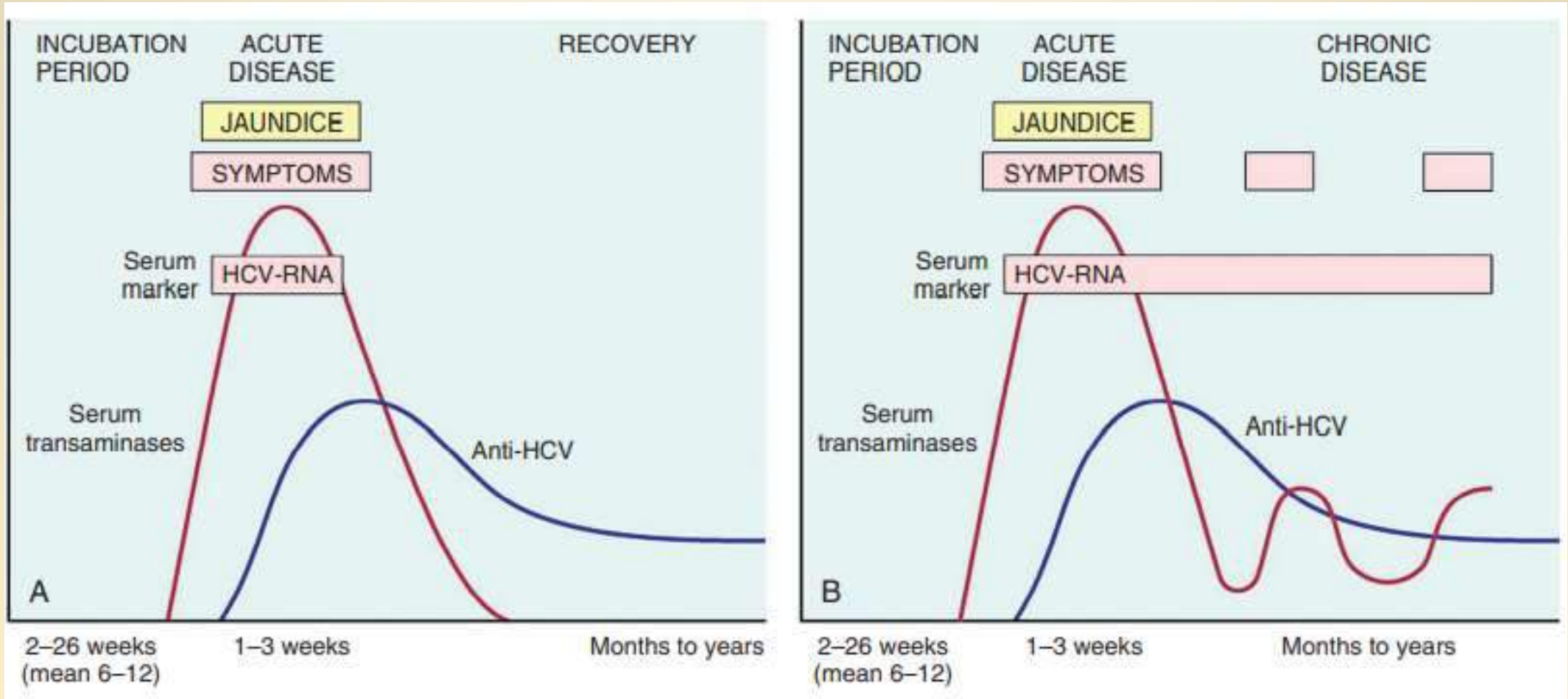
- Treatment of chronic hepatitis B with viral polymerase inhibitors and interferon can slow disease progression.

3. HEPATITIS C VIRUS (HCV)

- According to data from the Centers for Disease Control and Prevention (CDC), the most common risk factors for HCV infection are as follows:

- Intravenous drug abuse
- Multiple sex partners
- Having had surgery within the last 6 months
- Needle stick injury
- Multiple contacts with an HCV-infected individual
- Employment in the medical or dental field.
- perinatal transmission from the mother.

- HCV is a small, enveloped, single-stranded RNA virus, member of the Flaviviridae family.



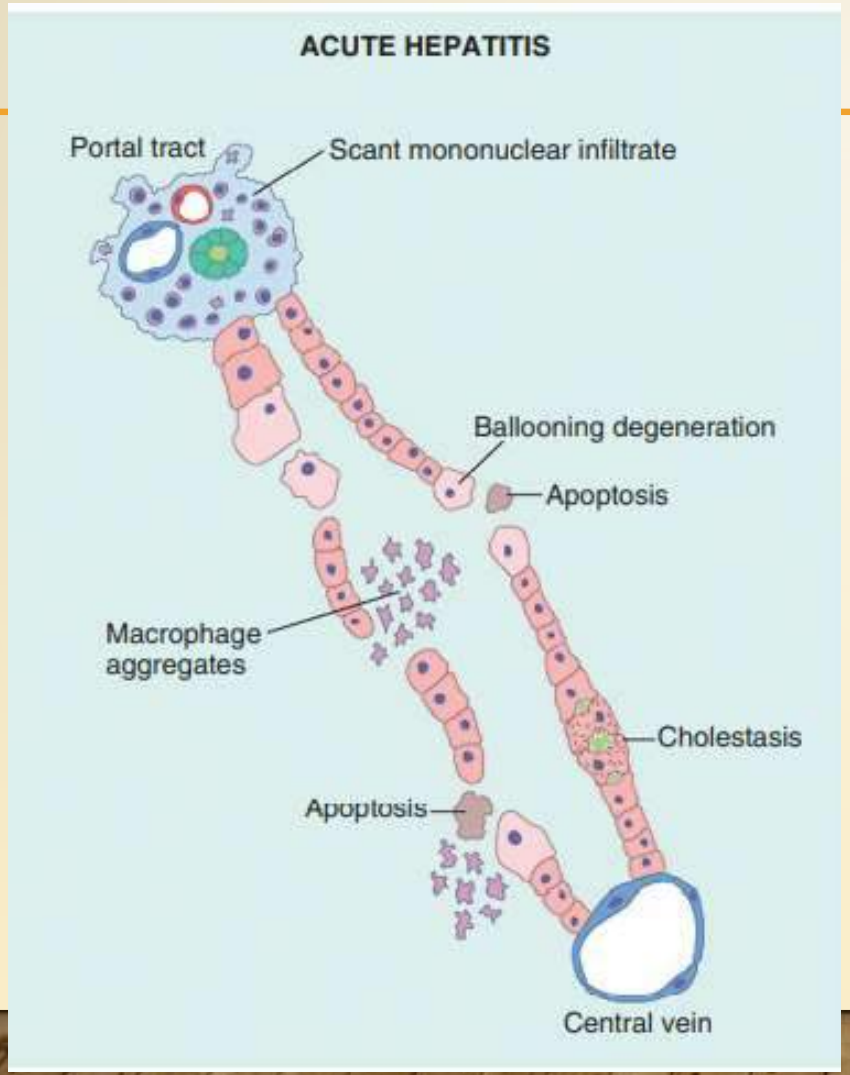
4. HEPATITIS D VIRUS (HDV)

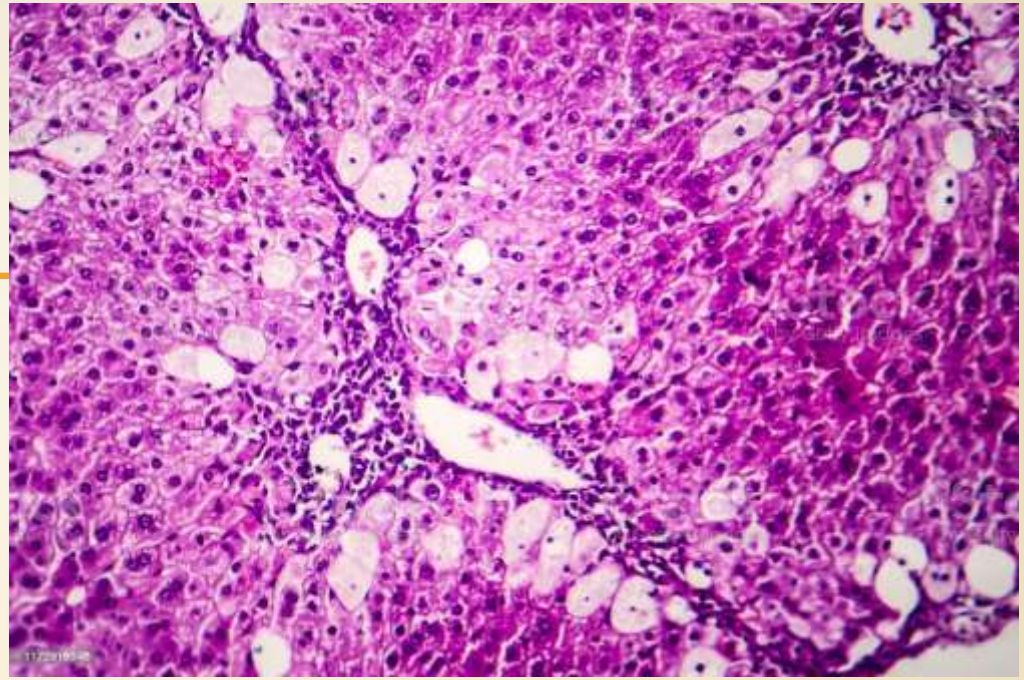
- HDV is a unique RNA virus that is dependent for its life cycle on HBV. Infection with HDV arises in the following settings:
- Coinfection by HDV and HBV.
- Superinfection of a chronic HBV carrier by HDV.

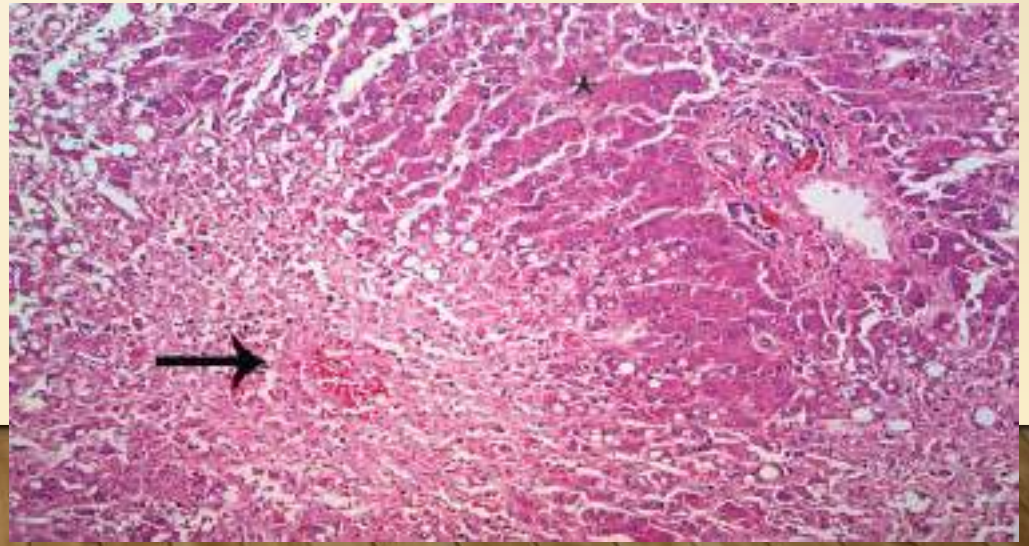
5. HEPATITIS E VIRUS (HEV)

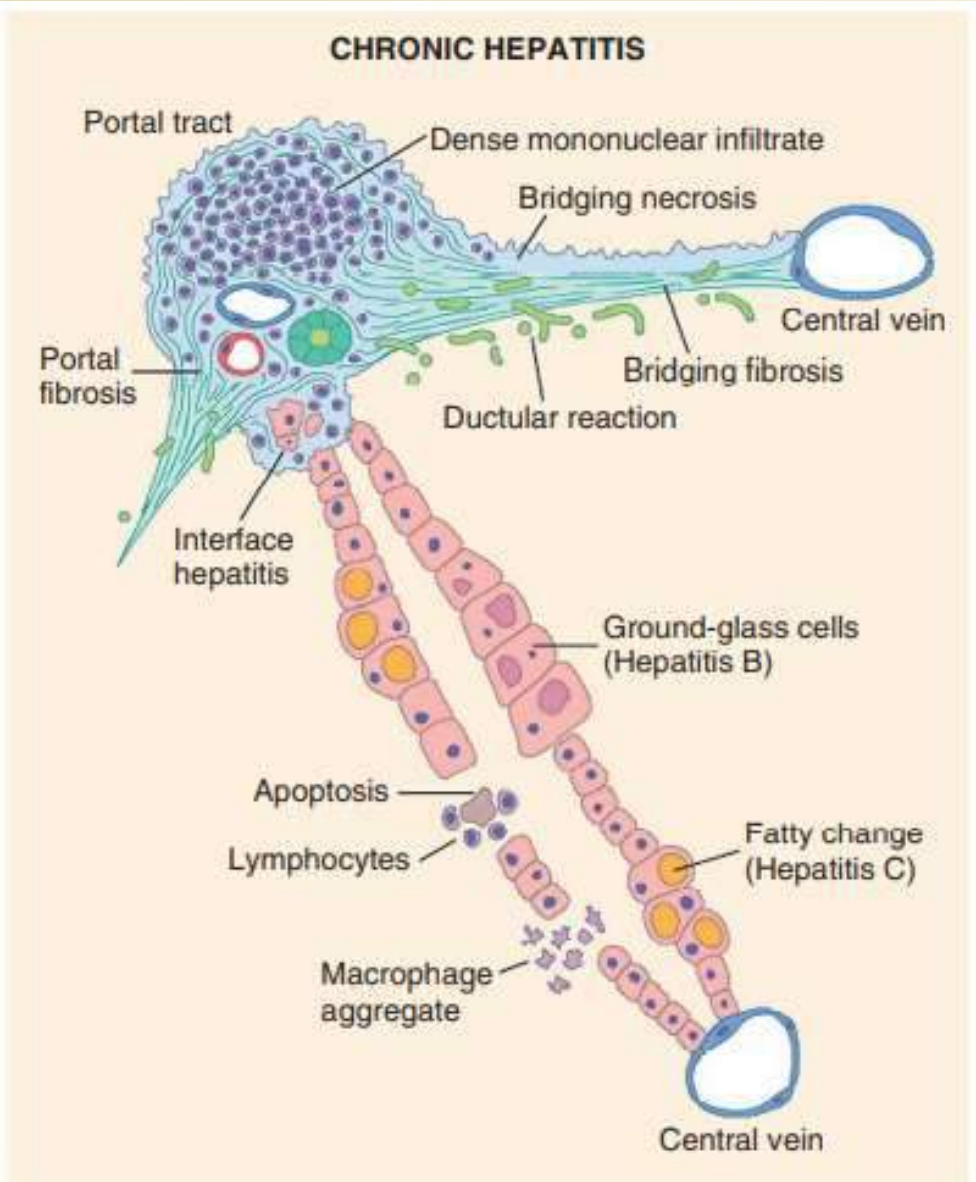
- HEV is an enterically transmitted, water-borne infection that usually produces a self-limiting disease.
- HEV is an unenveloped, positive stranded RNA virus in the Hepevirus genus.
- The virus typically infects young to middle-aged adults.
- HEV is a zoonotic disease with animal reservoirs that include monkeys, cats, pigs, and dogs.
- A characteristic feature of HEV infection is the high mortality rate among pregnant.

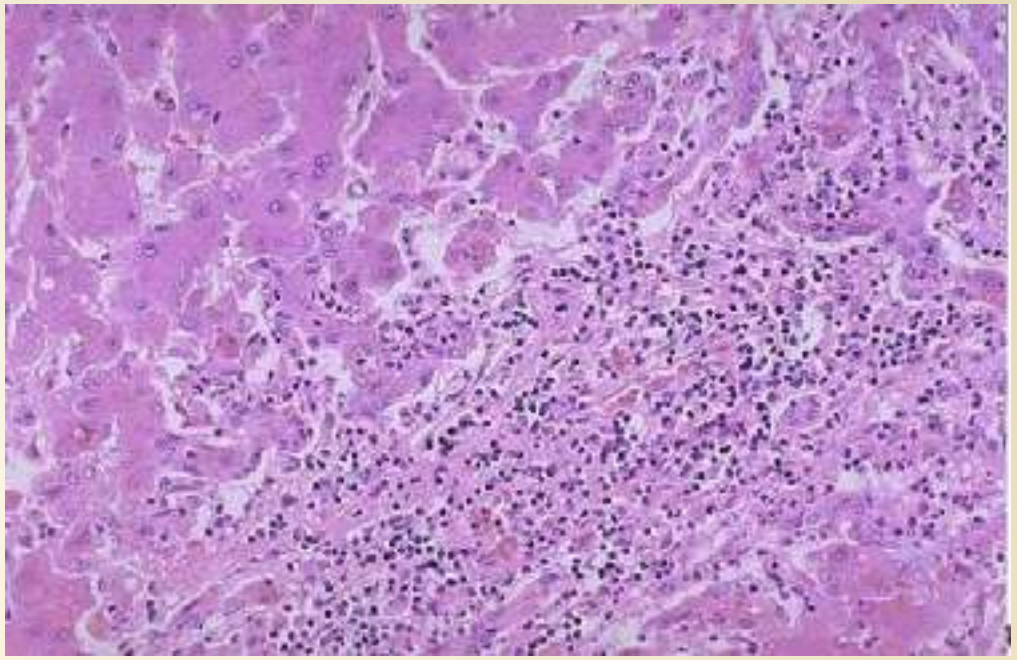
III. BIOPSY.


ACUTE HEPATITIS
Portal tract
Scant mononuclear infiltrate
Ballooning degeneration
Apoptosis
Macrophage aggregates
Cholestasis
Apoptosis
Central vein






CHRONIC HEPATITIS
Portal tract
Dense mononuclear infiltrate
Bridging necrosis
Central vein
Portal fibrosis
Bridging fibrosis
Ductular reaction
Interface hepatitis
Ground-glass cells (Hepatitis B)
Apoptosis
Lymphocytes
Fatty change (Hepatitis C)
Macrophage aggregate
Central vein



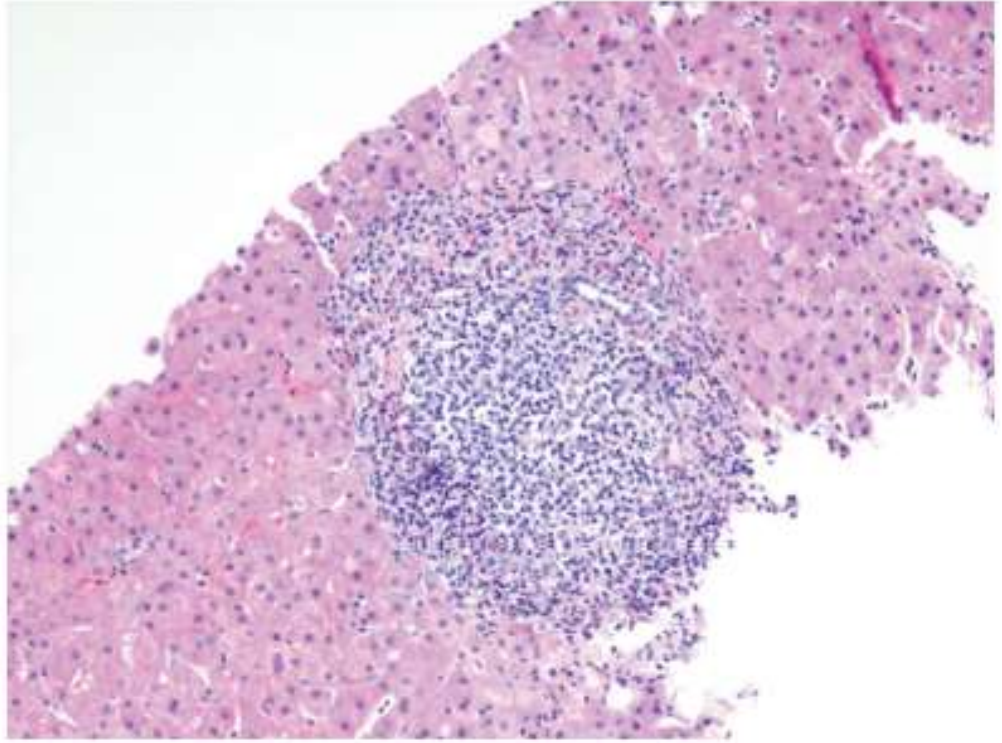


Fig. 16.15 Chronic viral hepatitis due to HCV, showing characteristic portal tract expansion by a dense lymphoid infiltrate.

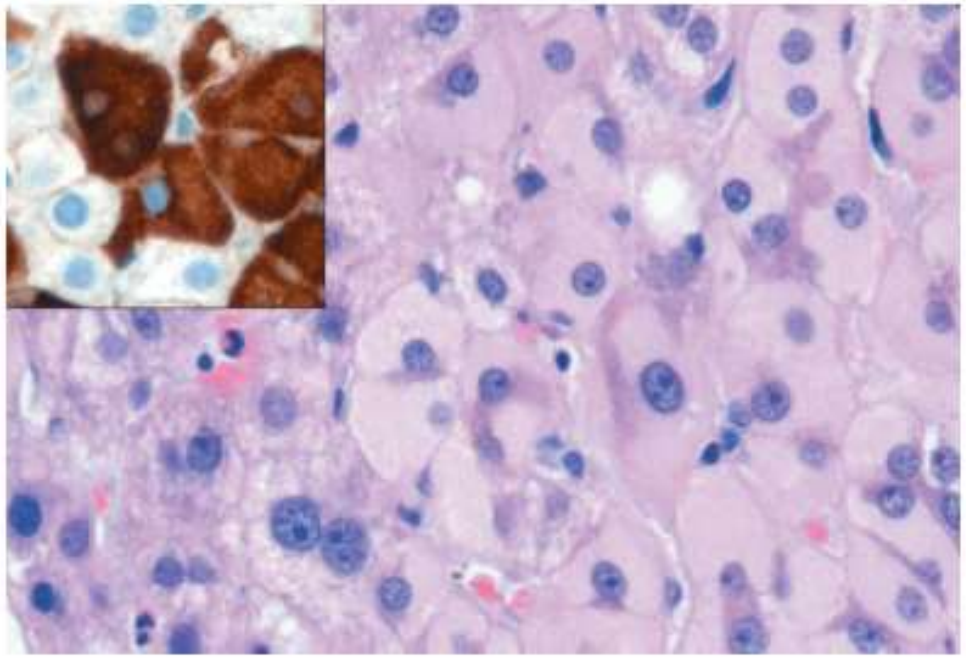
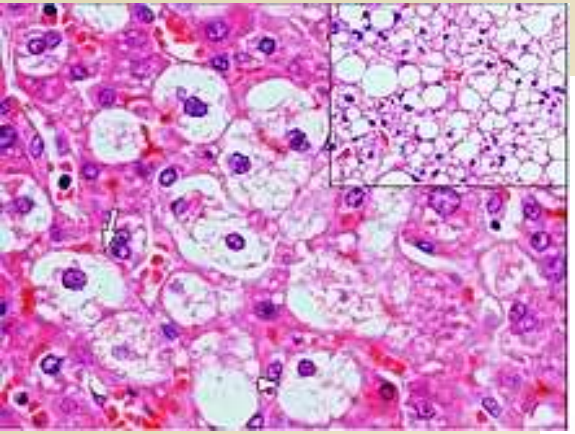
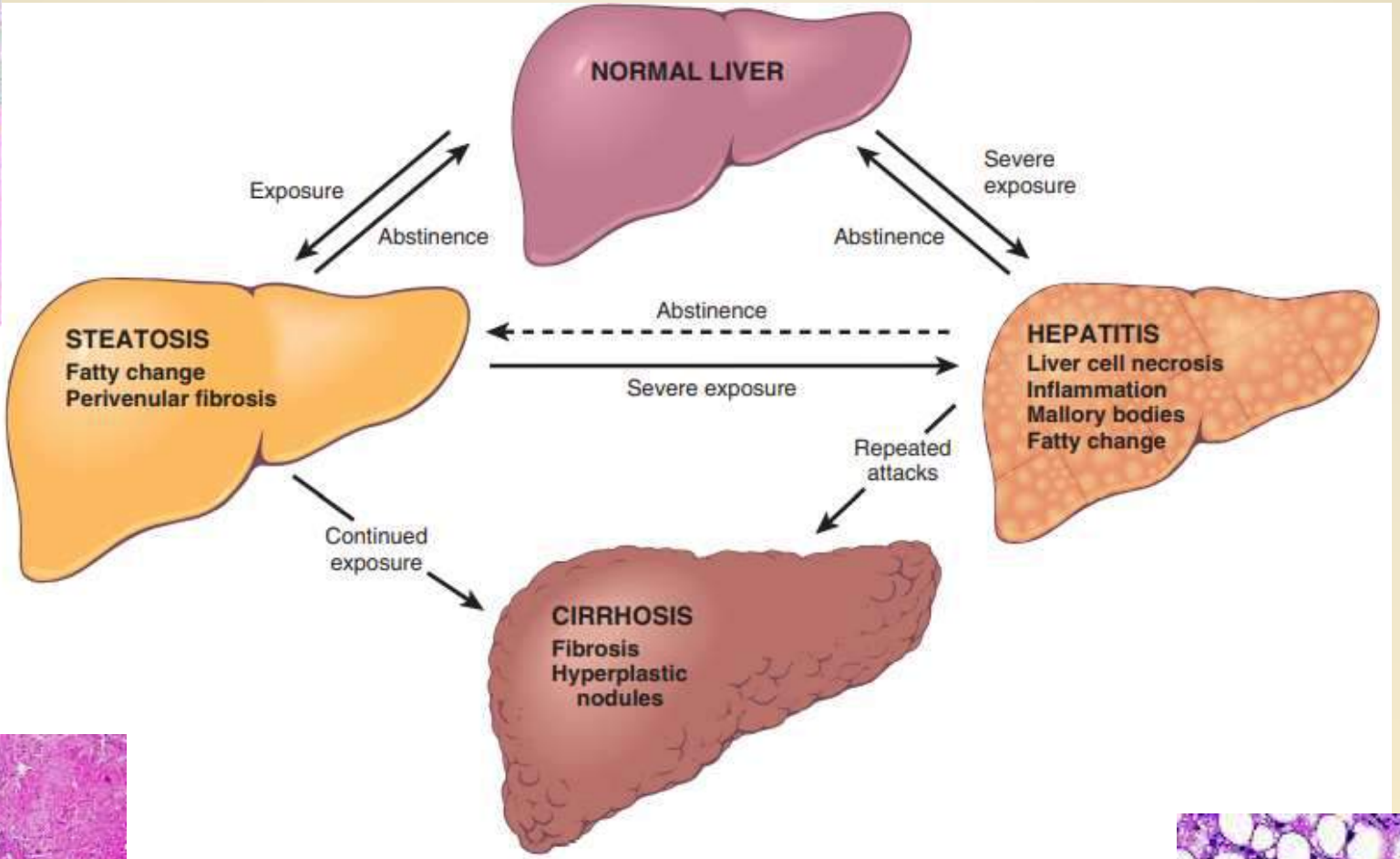


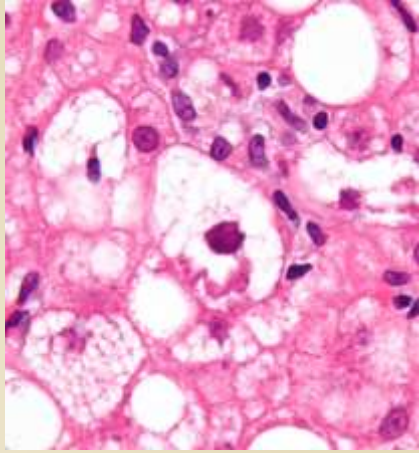
Fig. 16.14 Ground-glass hepatocytes in chronic hepatitis B, caused by accumulation of hepatitis B surface antigen. Hematoxylin-eosin staining shows the presence of abundant, finely granular pink cytoplasmic inclusions; immunostaining *(inset)* with a specific antibody confirms the presence of surface antigen *(brown)*.

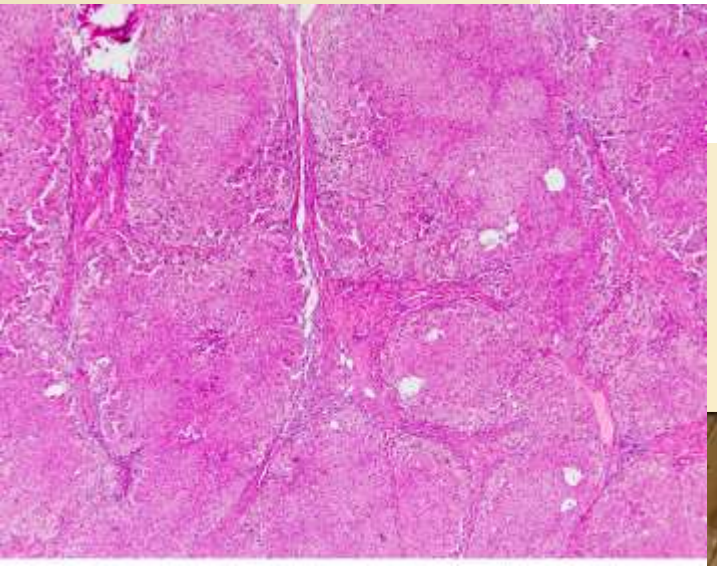
ALCOHOLIC LIVER DISEASE

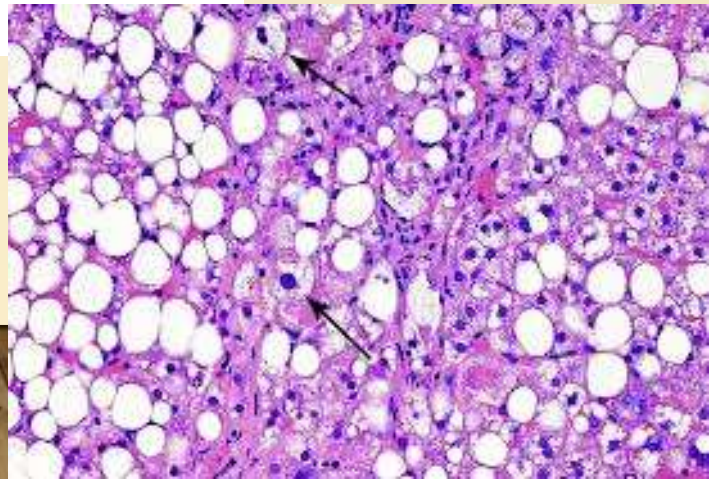
- Excessive ethanol consumption causes more than 60% of chronic liver disease in Western countries and accounts for 40% to 50% of deaths due to cirrhosis.
- Short-term ingestion of as much as 80 g of ethanol per day generally produces mild reversible hepatic changes.
- Chronic intake of 40 to 80 g/day is considered a borderline risk factor for severe injury.
- women are more susceptible than men to hepatic injury??



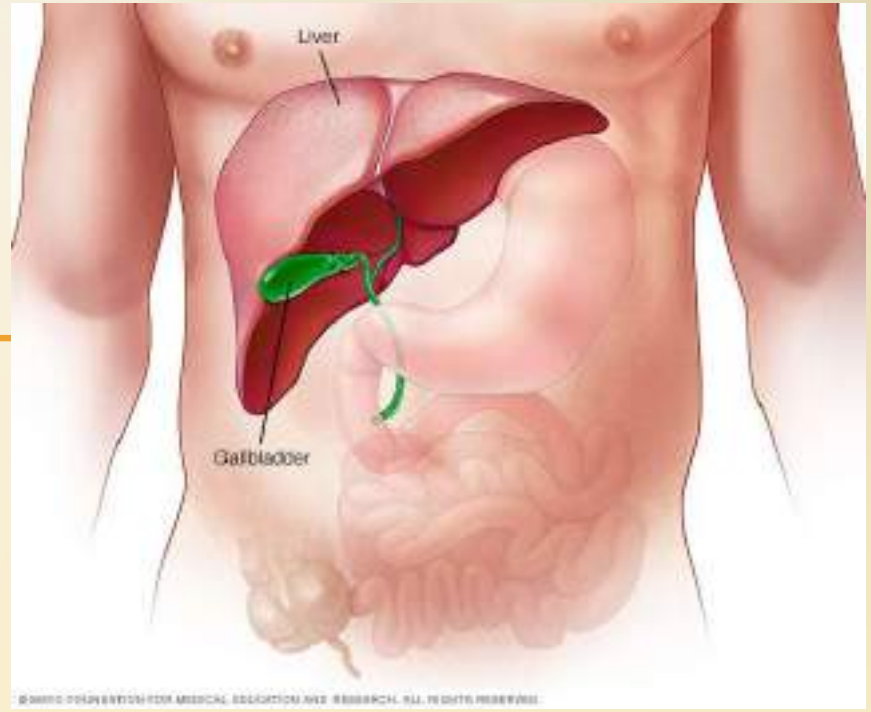

NORMAL LIVER
Exposure
Abstinence
Severe exposure
Abstinence
STEATOSIS
Fatty change
Perivenular fibrosis
Abstinence
Severe exposure
HEPATITIS
Liver cell necrosis
Inflammation
Mallory bodies
Fatty change
Repeated attacks
Continued exposure
CIRRHOSIS
Fibrosis
Hyperplastic nodules





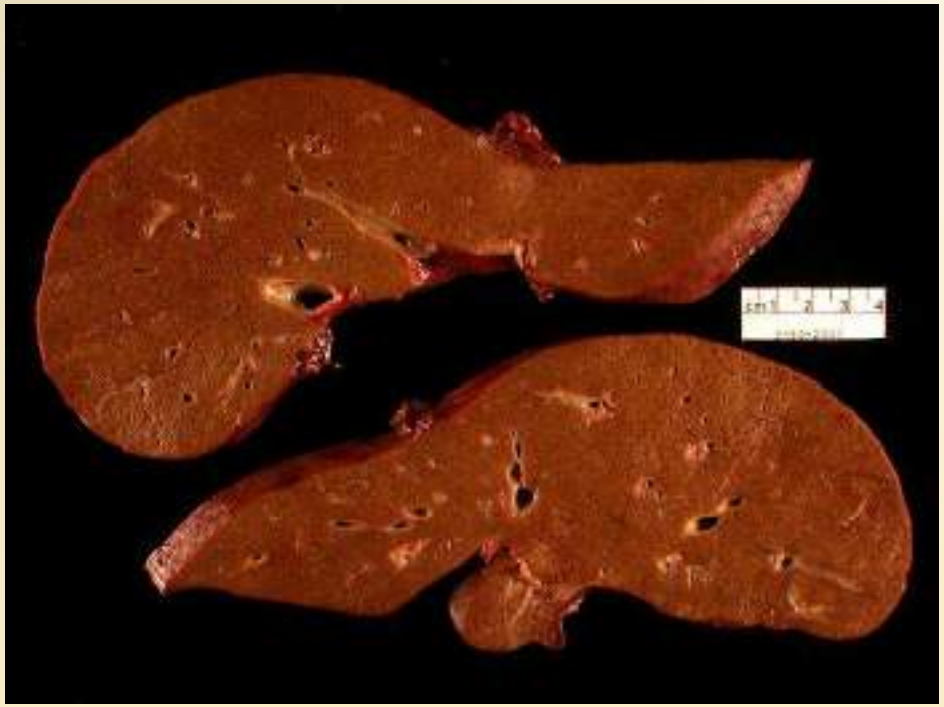


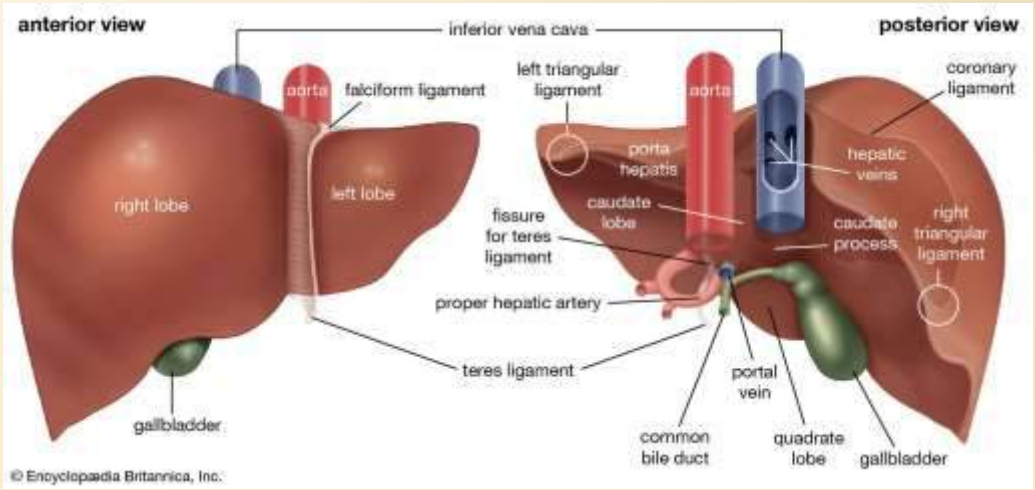
CIRRHOSIS AND CHOLESTASIS



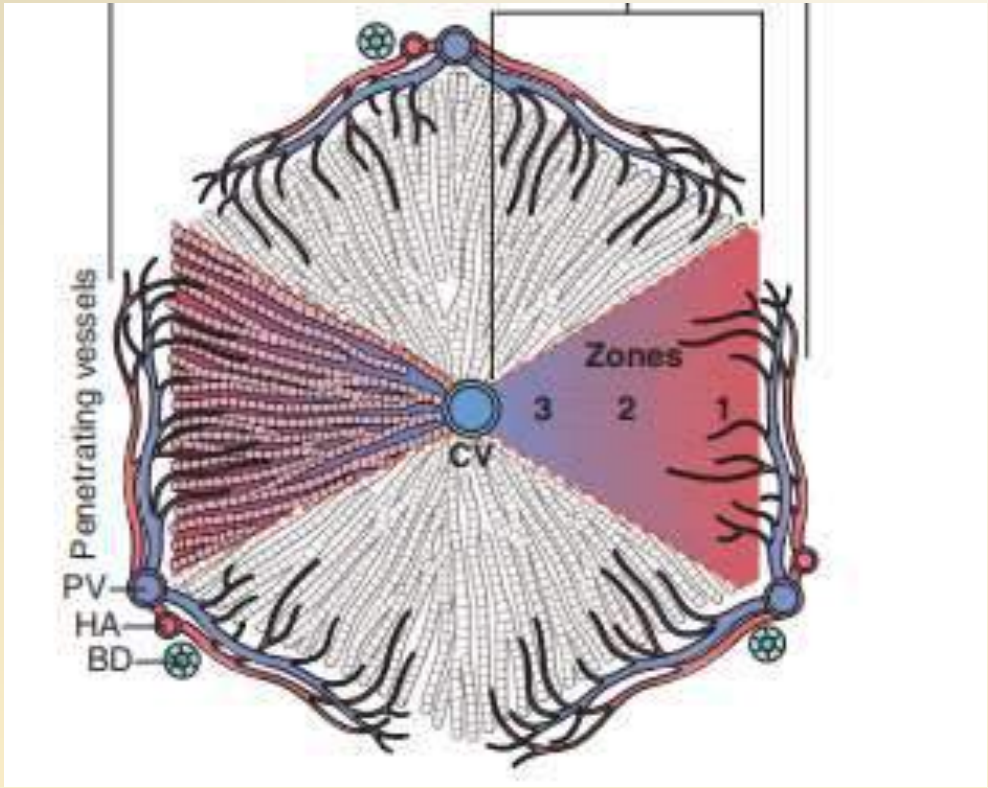
- The normal adult liver weighs 1400 to 1600 gm. It has a dual blood supply, with the portal vein providing 60% to 70% of hepatic blood flow and the hepatic artery supplying the remaining 30% to 40%.

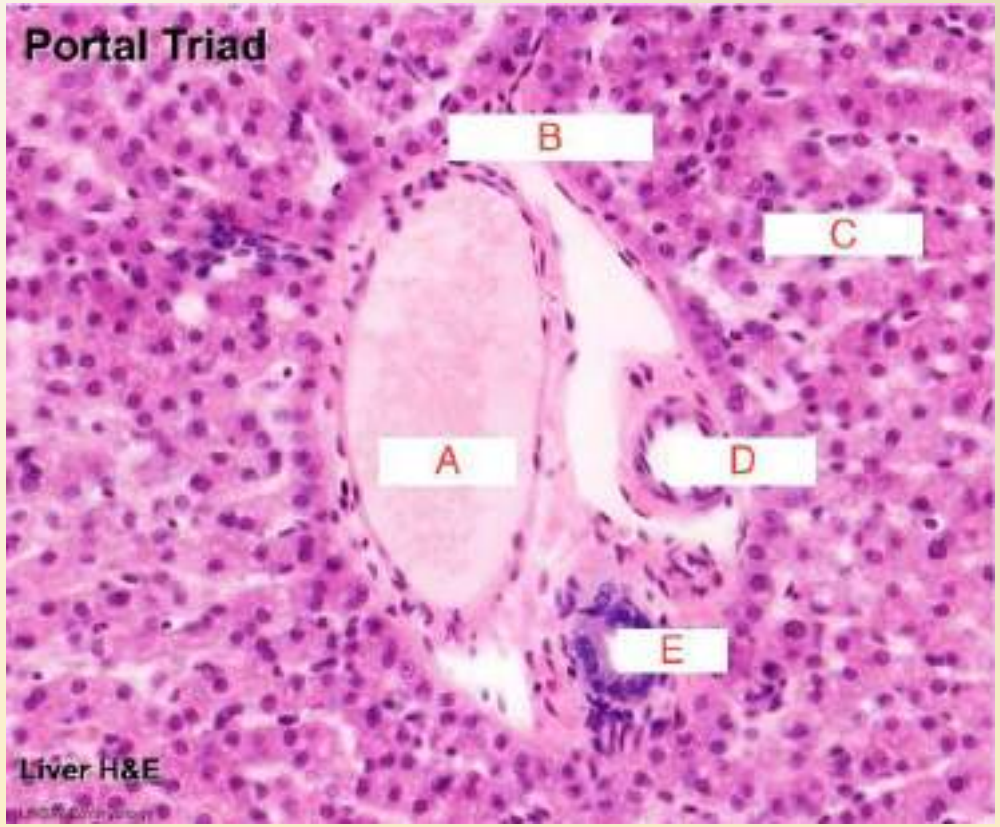
- Portal tract?





Models of liver anatomy





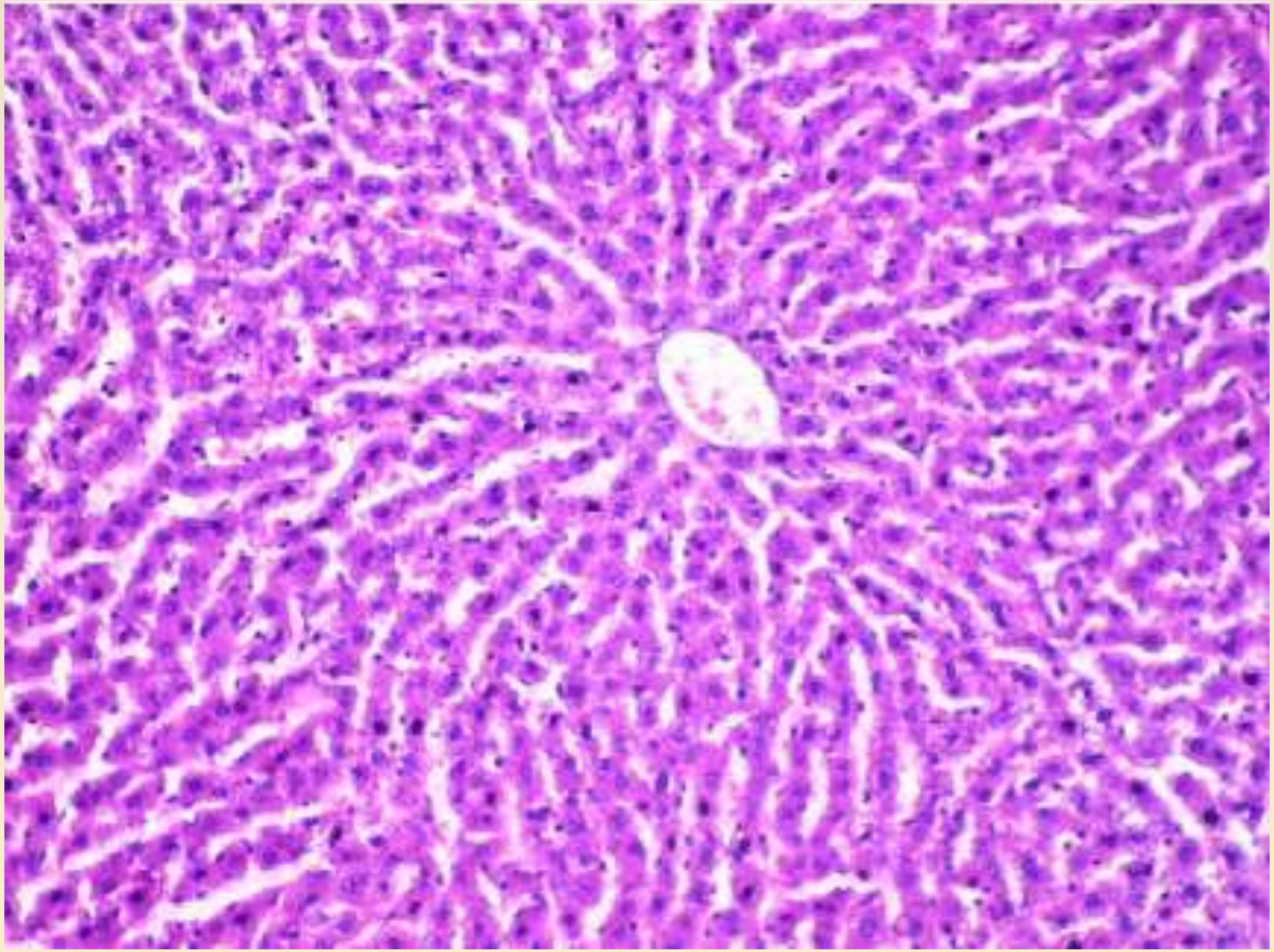


Table 16.1 Laboratory Evaluation of Liver Disease

Test Category	Blood Measurement*
Hepatocyte integrity	Cytosolic hepatocellular enzymes† *Serum aspartate aminotransferase* (AST) *Serum alanine aminotransferase* (ALT) Serum lactate dehydrogenase (LDH)
Biliary excretory function	Substances normally secreted in bile† *Serum bilirubin* *Total*: unconjugated plus conjugated *Direct*: conjugated only Urine bilirubin Serum bile acids Plasma membrane enzymes (from damage to bile canaliculus)† *Serum alkaline phosphatase* *Serum γ-glutamyl transpeptidase (GGT)*
Hepatocyte function	Proteins secreted into the blood *Serum albumin*‡ *Prothrombin time (PT)*‡ *Partial thromboplastin time (PTT)*‡ Hepatocyte metabolism Serum ammonia‡ Aminopyrine breath test (hepatic demethylation)‡

- The major hepatic diseases can be classified as:

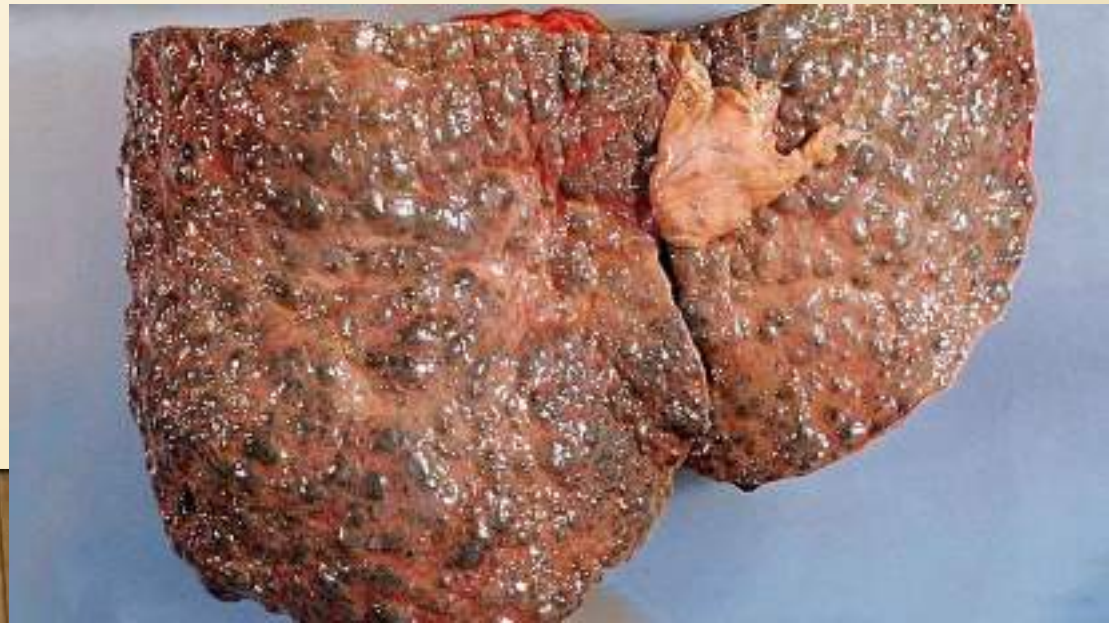
- 1. primary:
- viral hepatitis.
- alcoholic liver disease.
- nonalcoholic fatty liver disease (NAFLD).
- Cirrhosis.
- hepatocellular carcinoma (HCC).

- 2. secondary:
- cardiac disease.
- disseminated cancer.
- extrahepatic infections

CIRRHOSIS

- Cirrhosis is the morphologic change most often associated with chronic liver disease; it refers to the diffuse transformation of the liver into regenerative parenchymal nodules surrounded by fibrous bands.

- The leading causes include:
  - chronic hepatitis B, C.
  - non-alcoholic fatty liver disease (NAFLD).
  - alcoholic liver disease
  - Drug induced liver injury
  - Cryptogenic (idiopathic) cirrhosis



PATHOPHYSIOLOGY

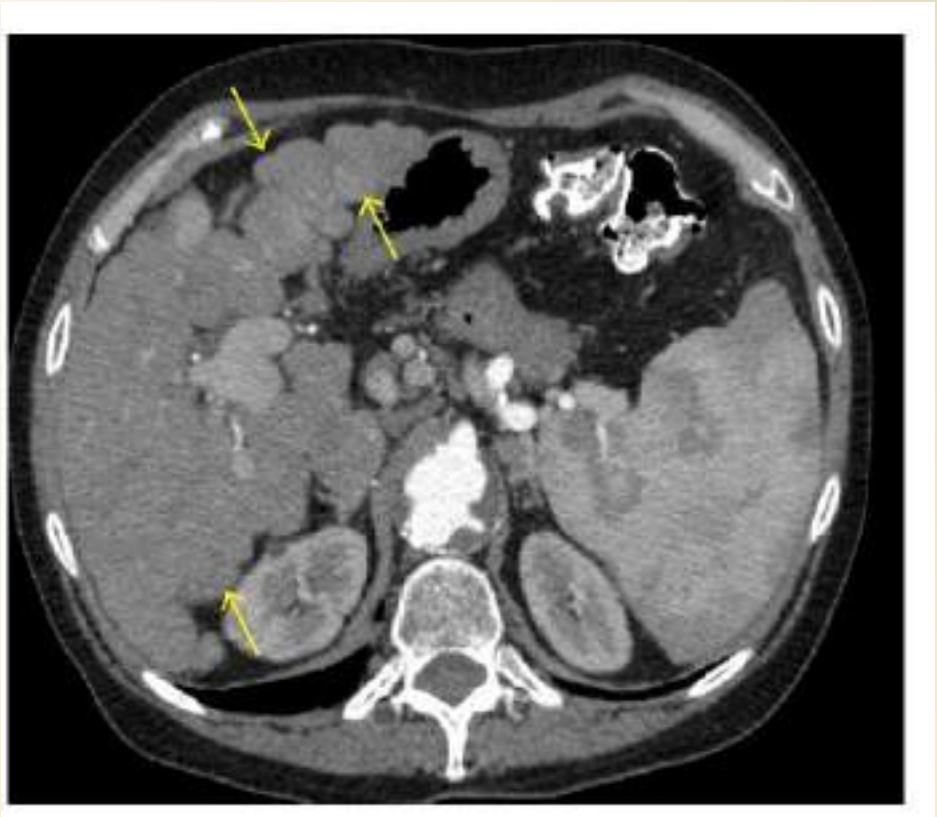
- Combination of processes :

Fibrosis: excessive production of collagen type I / III by hepatic stellate cells

Regeneration of hepatocytes through proliferation of progenitor cells of the ductular reaction

DIAGNOSIS

- 1. Liver function test.
- 2. Radiology.
- 3. Biopsy

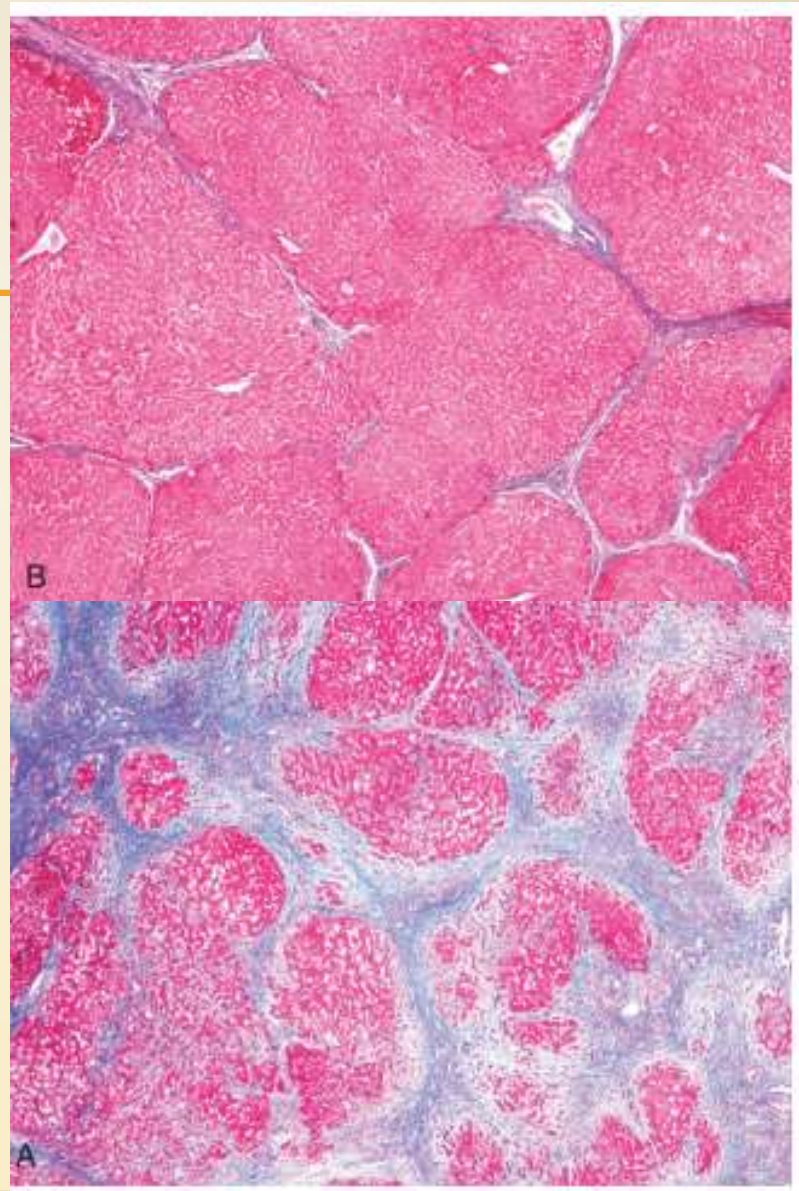


HISTOPATHOLOGY

*diffuse transformation of the entire liver into regenerative parenchymal nodules surrounded by fibrous bands.

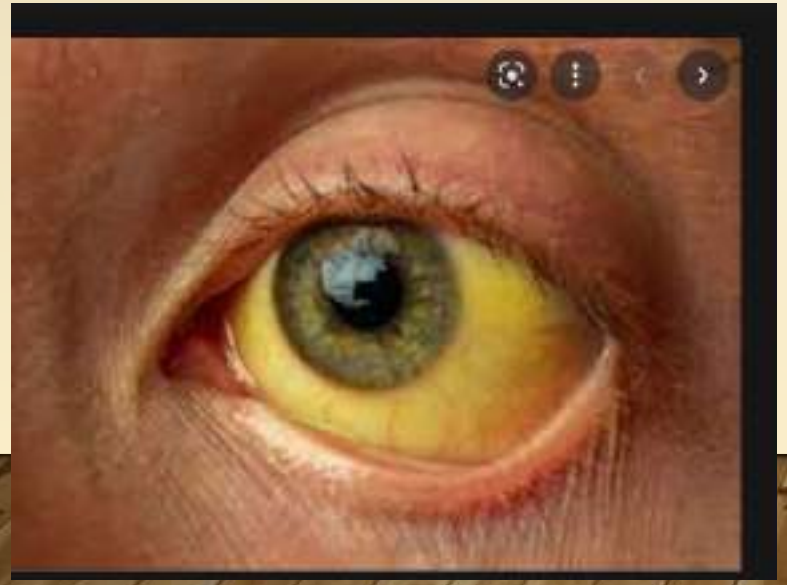
* ductular reactions.

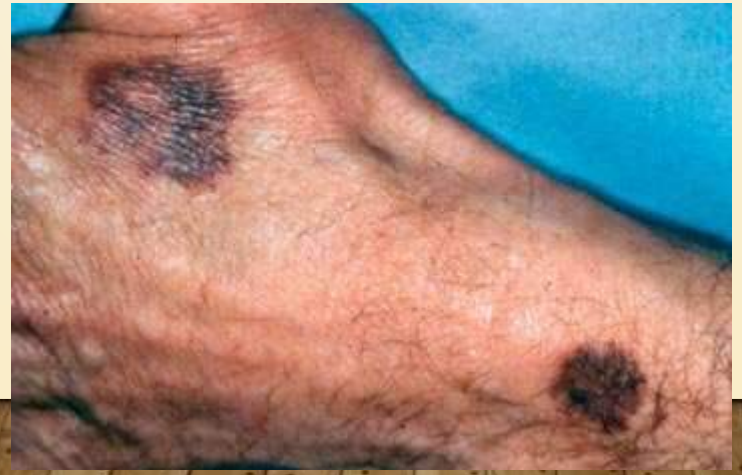
* (Masson trichrome stain) highlights these fibrous septa.

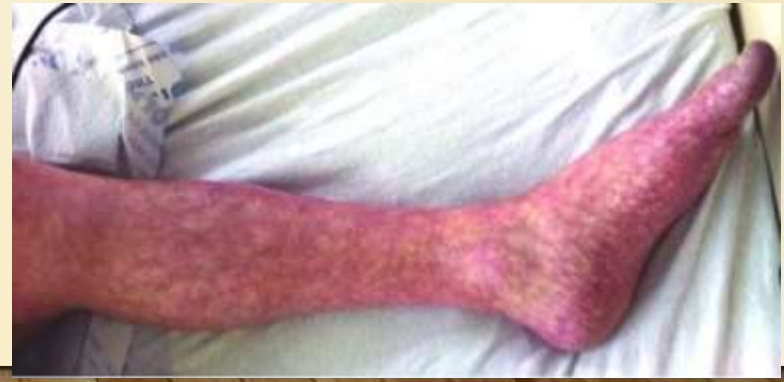


CLINICAL FEATURES

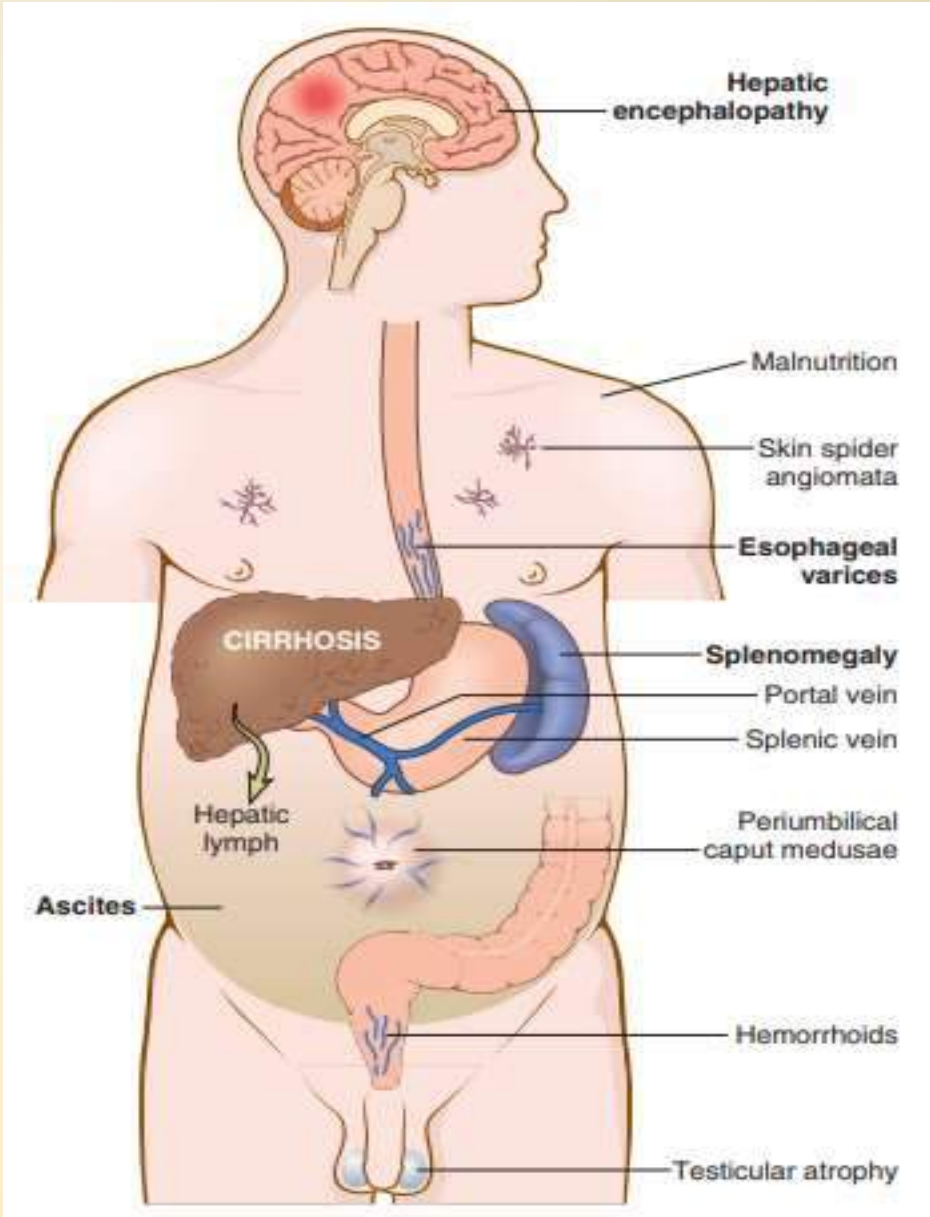
- 1. 40% of individuals with cirrhosis are asymptomatic until the most advanced stages of the disease.
- 2. Non specific symptoms such as anorexia, weight loss, weakness.
- 3. signs and symptoms of liver failure e.g Jaundice, encephalopathy, and coagulopathy.
- 4. Pruritus, portal hypertention (intrahepatic vascular resistance).





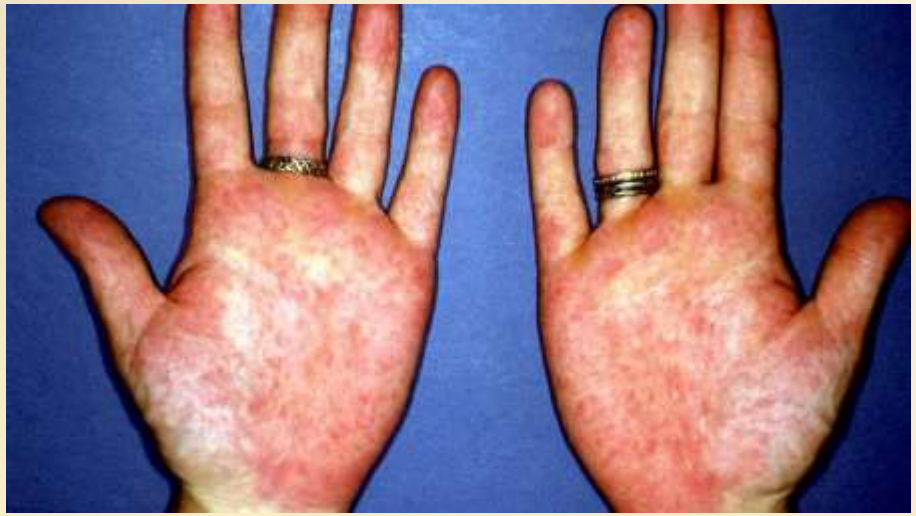


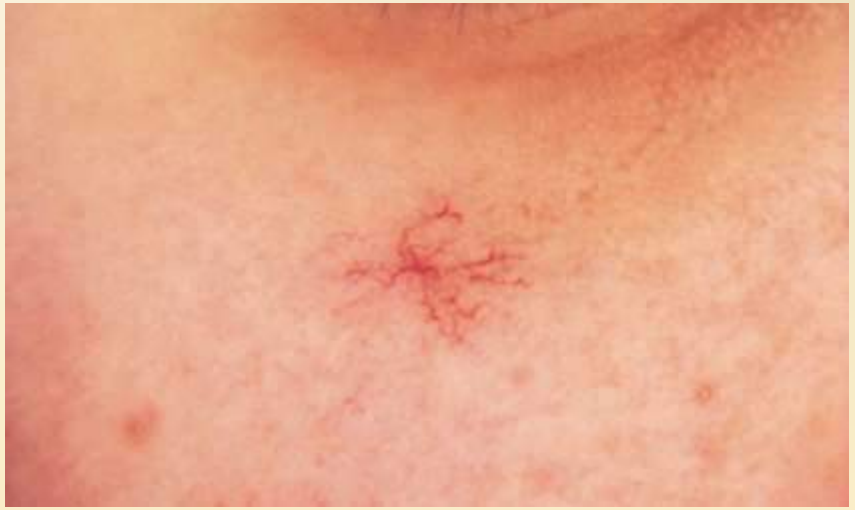
Major clinical consequences of portal hypertension in the setting of cirrhosis.



5. Hyperestrogenemia:

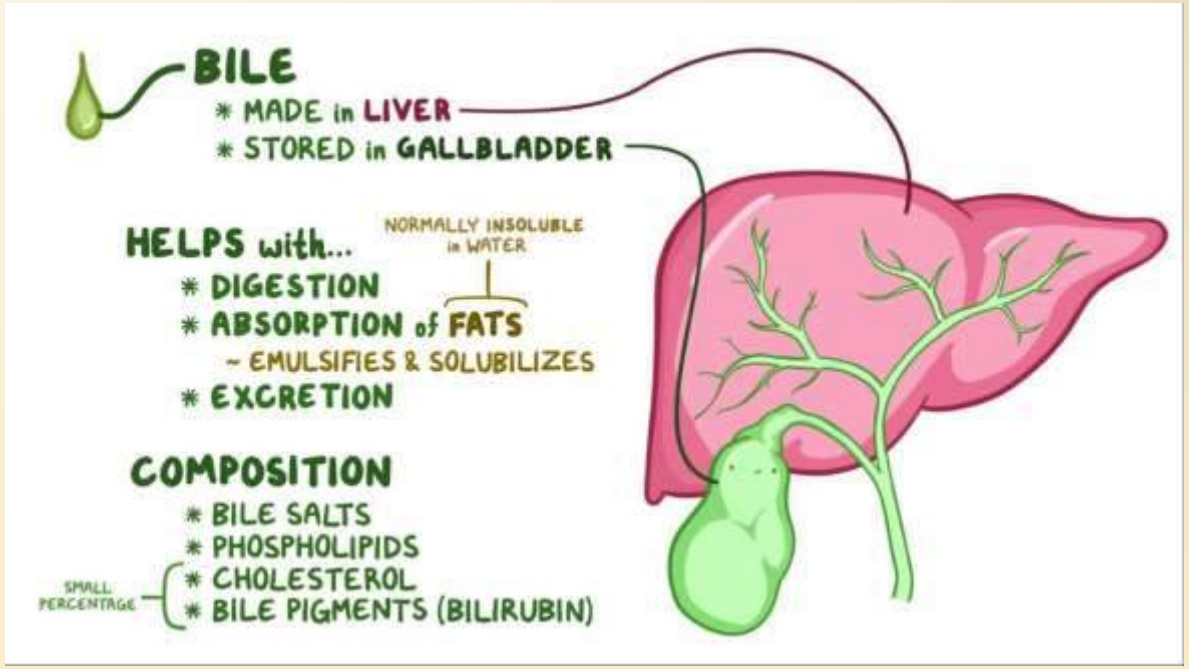
- due to impaired estrogen metabolism in male patients with chronic liver failure can give rise to palmar erythema (a reflection of local vasodilatation) and spider angiomas of the skin. Such male hyperestrogenemia also leads to hypogonadism and gynecomastia.
- 6. hepatocellular carcinoma (HCC).





CHOLESTASIS

- Cholestasis is a condition caused by extrahepatic or intrahepatic obstruction of bile channels or by defects in hepatocyte bile secretion.



- Patients may have :

➢Jaundice.

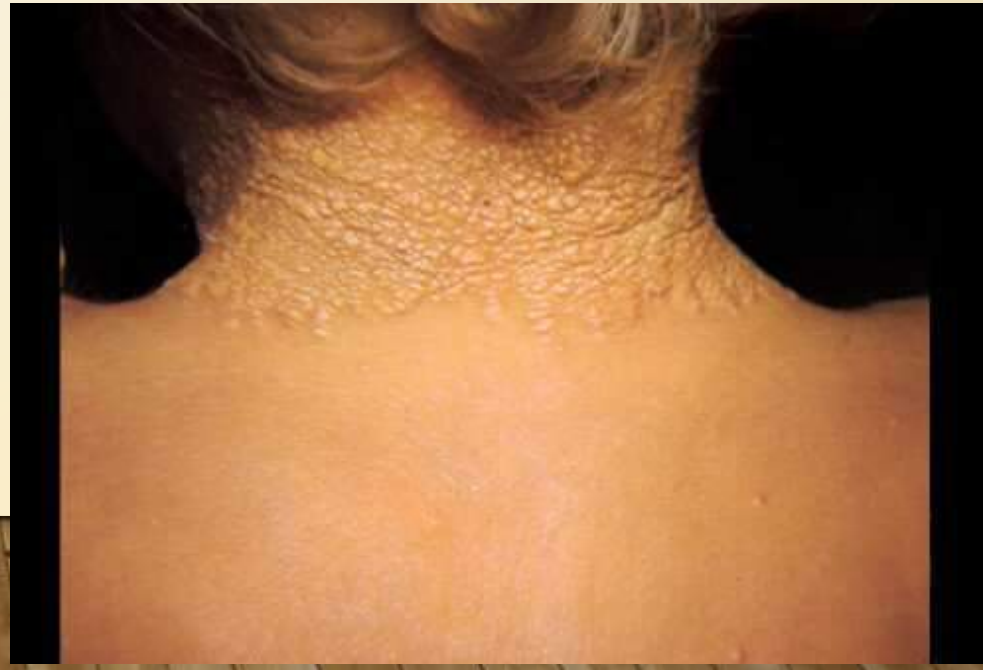
➢Pruritus.

➢skin xanthomas (focal accumulation of cholesterol).

➢symptoms related to intestinal malabsorption, including nutritional deficiencies of the fat-soluble vitamins A, D, or K.

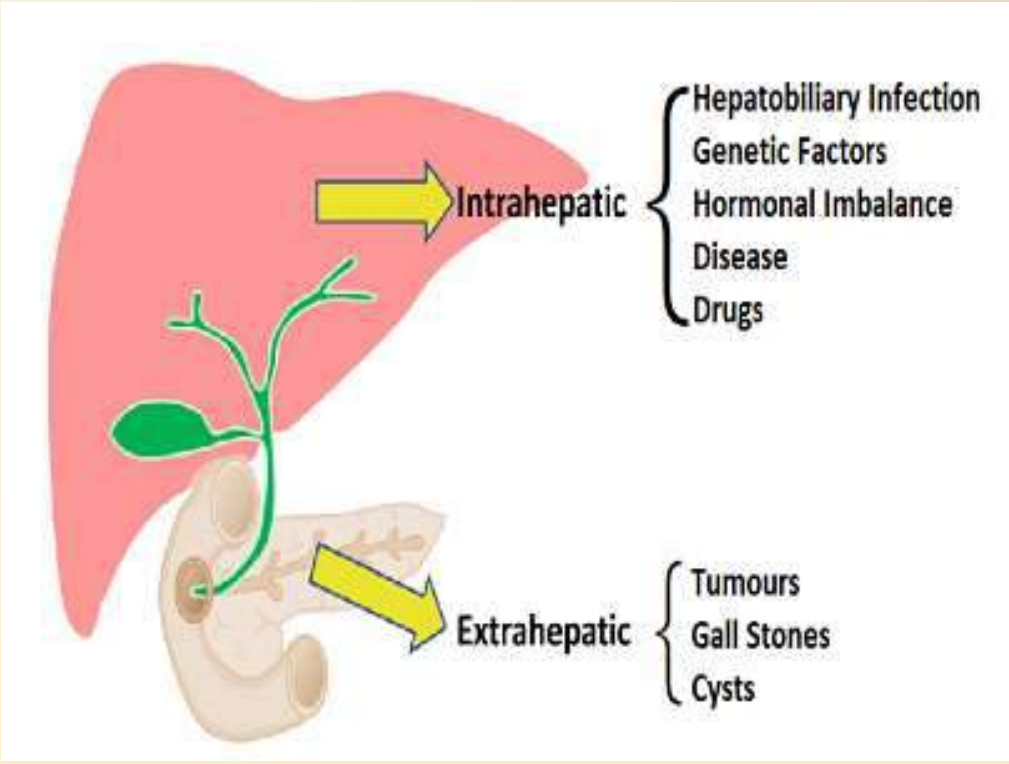
Lab:

elevated serum alkaline phosphatase and γ-glutamyl transpeptidase (GGT),



CAUSES

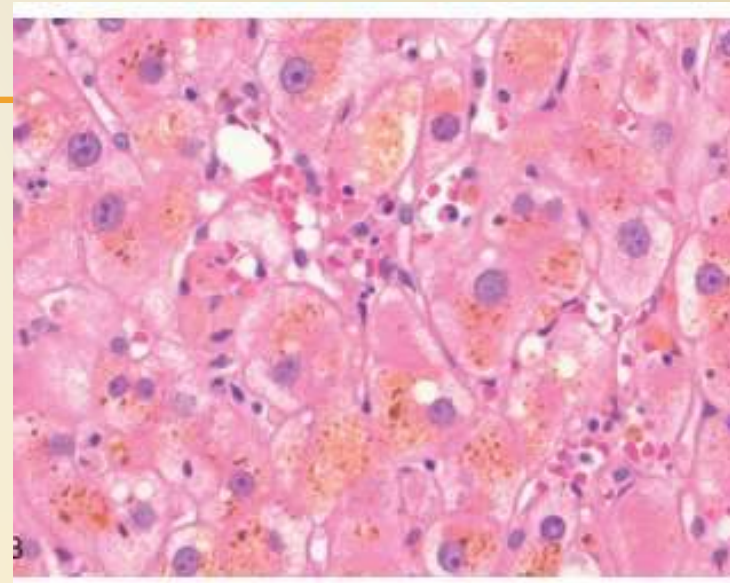
- Most typically seen in biliary disease (primary sclerosing cholangitis, primary biliary cirrhosis) .
- drug induced liver injury.
- pregnancy.
- benign familial recurrent cholestasis



PATHOPHYSIOLOGY

- Bile is produced in hepatocytes and flows as follows:
- hepatocyte canaliculi → canals of Hering → bile ductules → interlobular bile ducts → larger bile ducts → duodenum
- Injury or obstruction at any point along biliary flow can lead to cholestasis

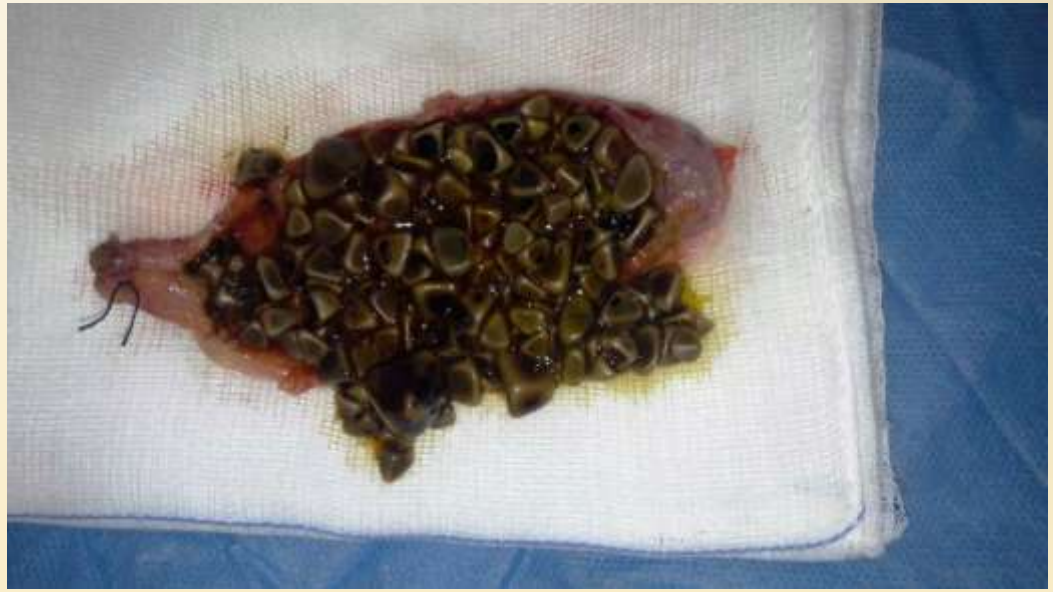
HISTOPATHOLOGY



- accumulation of bile pigment within the hepatic parenchyma.
- Rupture of canaliculi leads to extravasation of bile, which is quickly phagocytosed by Kupffer cells.
- feathery degeneration:
- Droplets of bile pigment accumulate within hepatocytes, give them foamy appearance

CAUSES: A. BILE DUCT OBSTRUCTION.

- The most common cause of bile duct obstruction in adults is:
- extrahepatic cholelithiasis.
- malignant obstructions.
- postsurgical strictures.
- Obstructive conditions in children include :
- biliary atresia.
- cystic fibrosis.
- choledochal cysts.

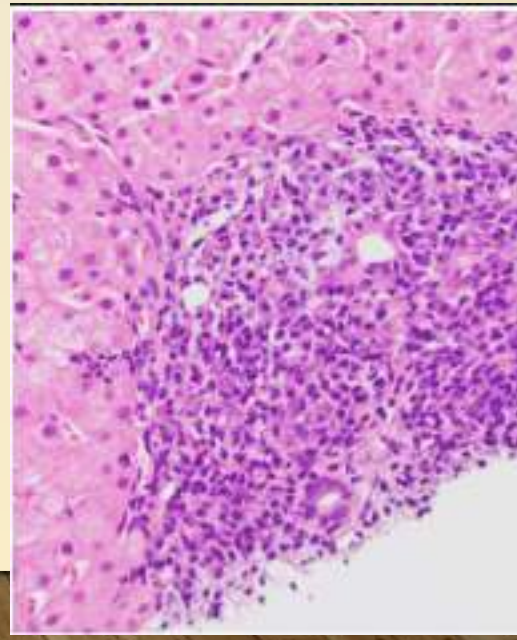


B. NEONATAL CHOLESTASIS

- Prolonged conjugated hyperbilirubinemia in the neonate, termed neonatal cholestasis.
- The major conditions causing it are:
- (1) cholangiopathies, primarily biliary atresia .(complete or partial obstruction of the extrahepatic biliary tree that occurs within the first 3 months of life.)
- (2) a variety of disorders causing conjugated hyperbilirubinemia in the neonate, collectively referred to as neonatal hepatitis

C. PRIMARY BILIARY CHOLANGITIS.

- autoimmune disease (Anti-mitochondrial antibodies) whose primary feature is nonsuppurative, inflammatory destruction of small- and medium-sized intrahepatic bile ducts.
- **Occur in** middle-age women, with a female-to-male ratio of 6:1. Its peak incidence is between 40 and 50 years of age.
- **Histology:**
- Dense lymphocytic infiltrate in portal tracts with granulomatous destruction and loss of medium sized interlobular bile ducts, focal and variable within the liver



D. PRIMARY SCLEROSING CHOLANGITIS

- Primary sclerosing cholangitis (PSC) is characterized by inflammation and obliterative fibrosis of intrahepatic and extrahepatic bile ducts, leading to dilation of preserved segments.

- Classic finding is "onion skin" fibrosis around affected bile ducts