Acute hepatitis
&
Chronic hepatitis

TUCOM
Dep. of Medicine
4th year
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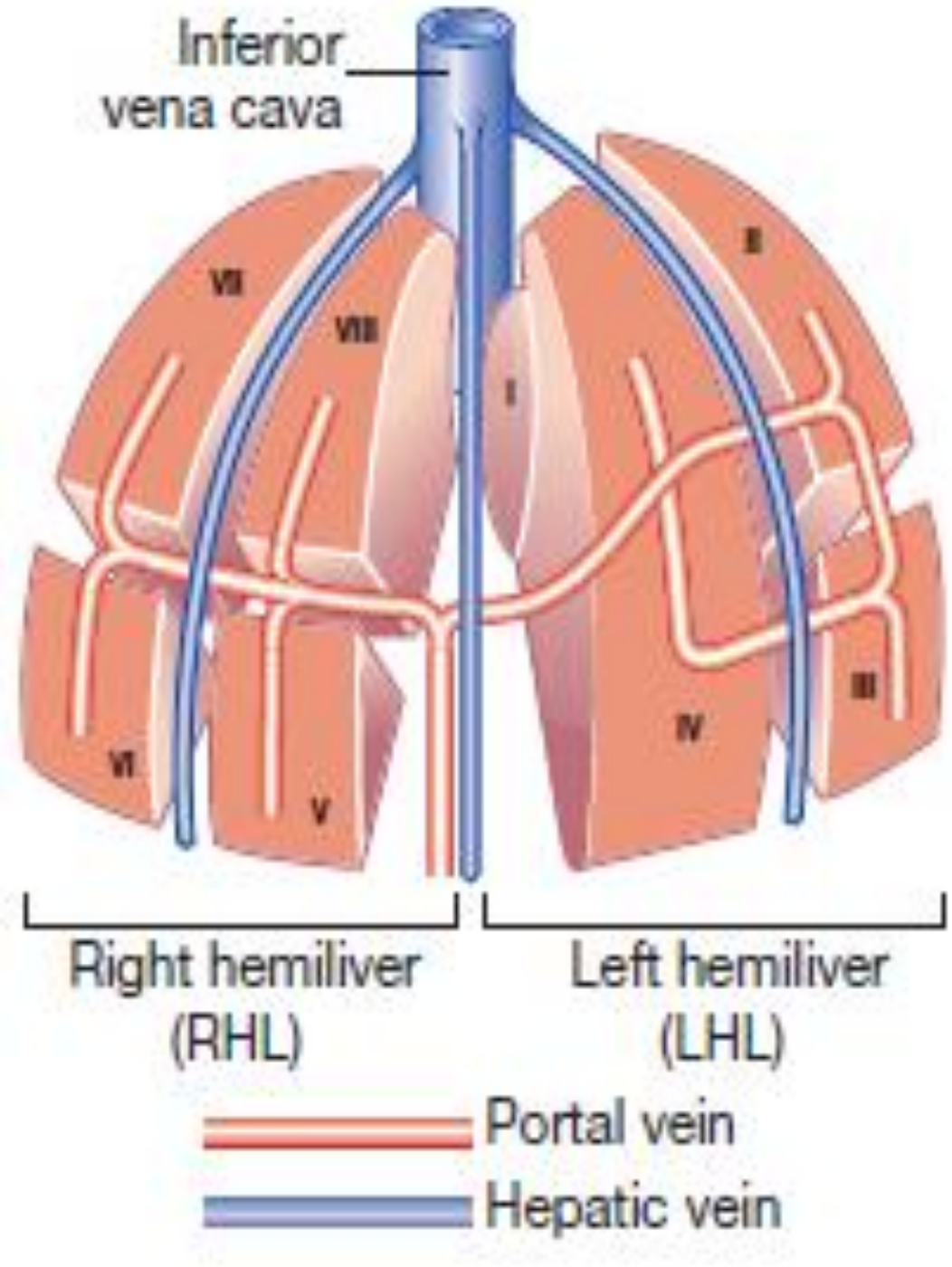
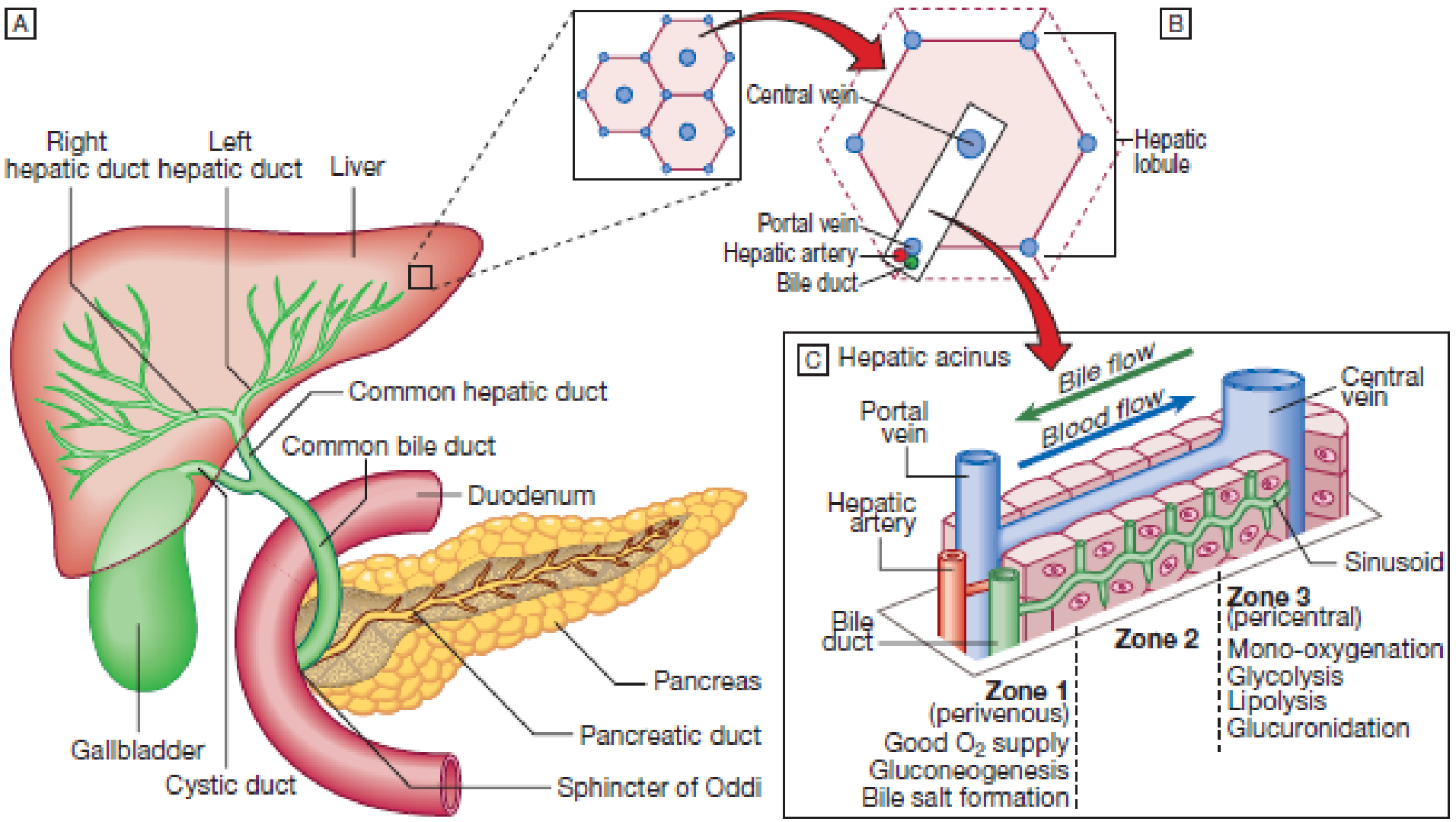
Acute hepatitis

Learning objectives:

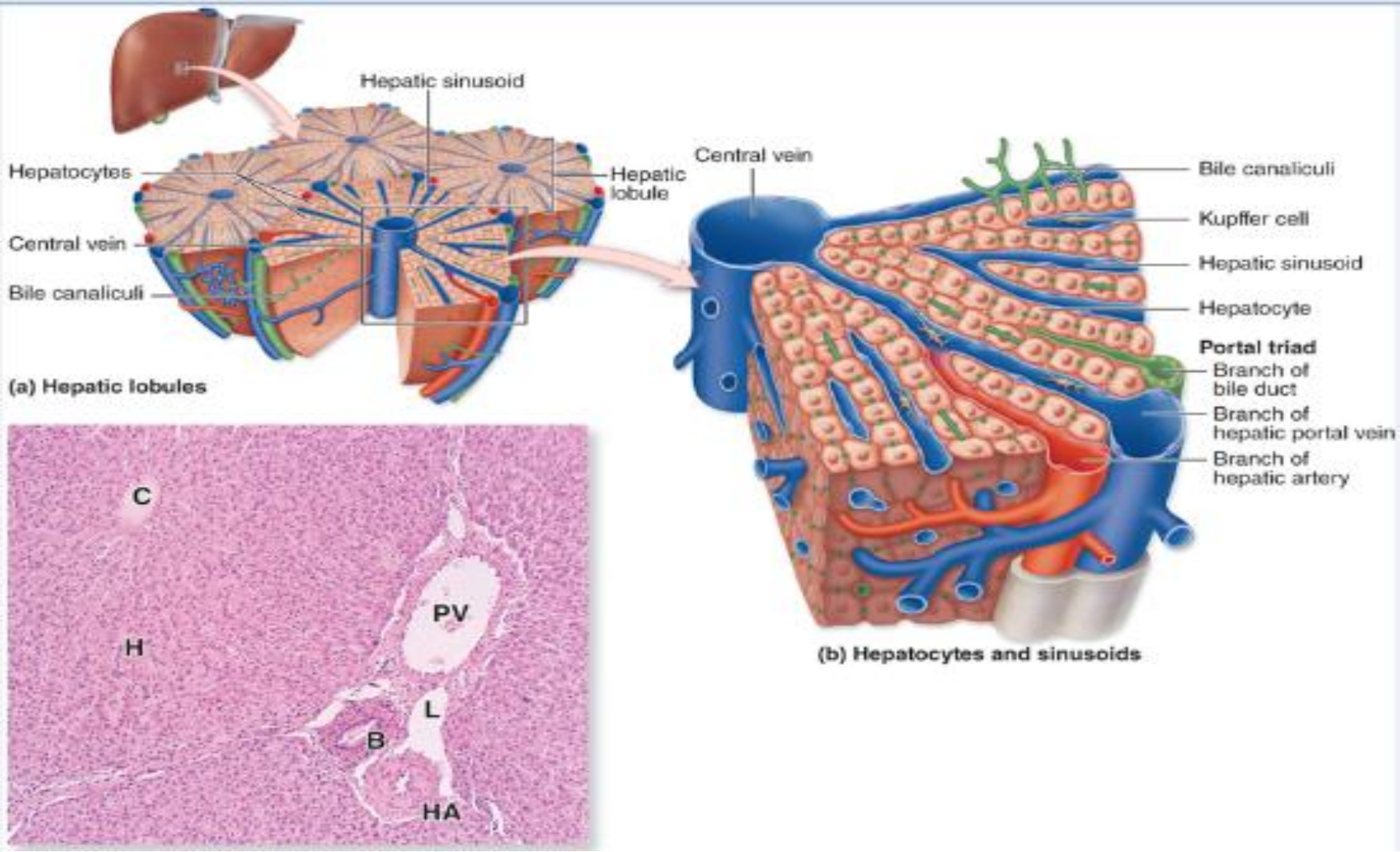
1. Define hepatitis.
2. Define the acute hepatitis.
3. List the causes of acute hepatitis.
4. Describe the various types of viral hepatitis, including viral hepatitis A, B, C, D and E.
5. Clarify the clinical features of acute viral hepatitis.
6. List the complications of acute viral hepatitis.
7. Discuss the investigations of acute viral hepatitis.
8. Identify the persons of high risk of viral hepatitis.
9. Summarize the treatment options and preventive measures of acute viral hepatitis.

The liver is the largest organ in the body and performs many important functions. Weighing 1.2-1.5 kg. It divided into the left and right lobes --- divided into a total of eight segments (depending on blood supply) --- lobules --- The functional unit of the liver is the hepatic acinus.

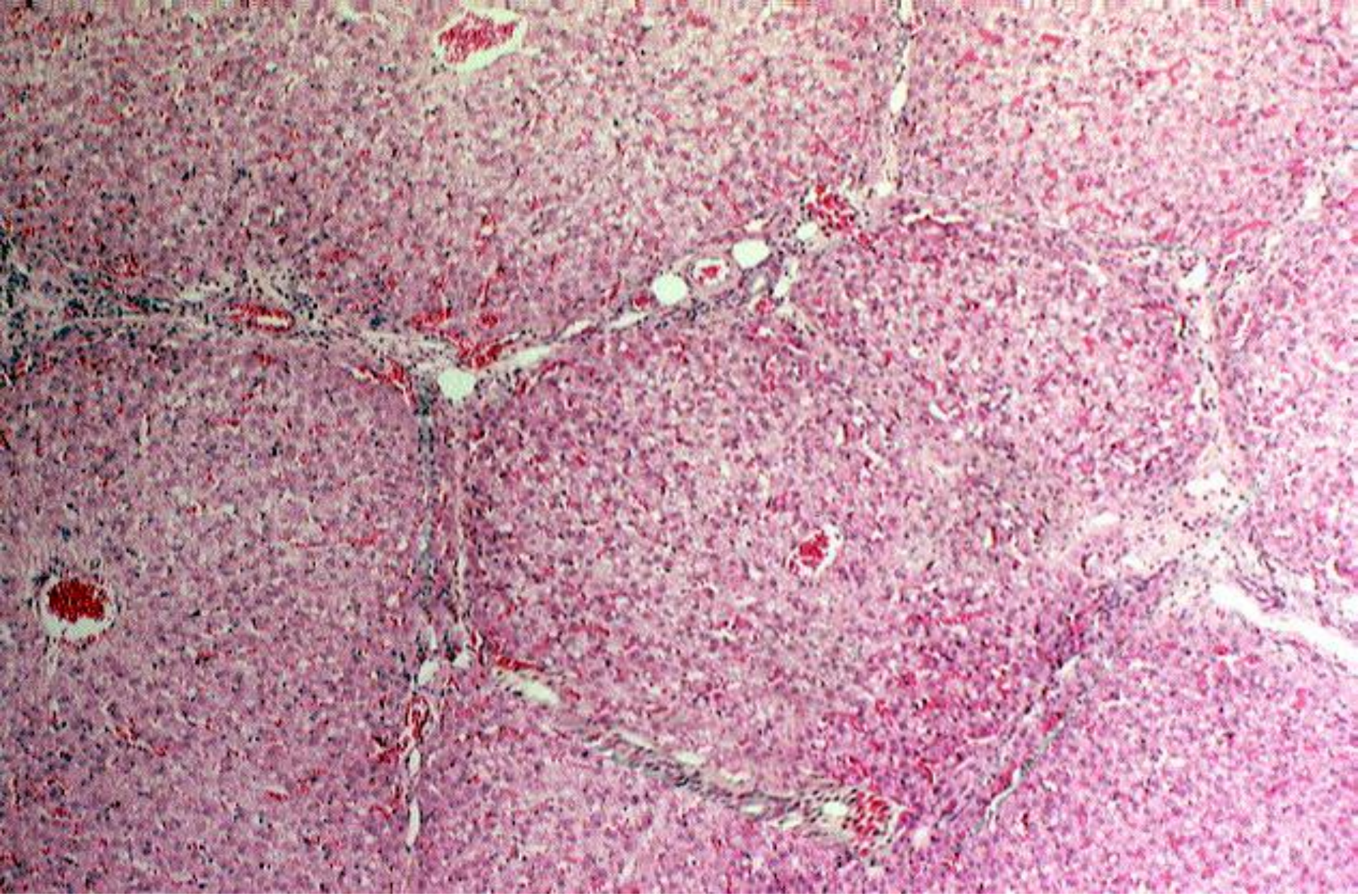




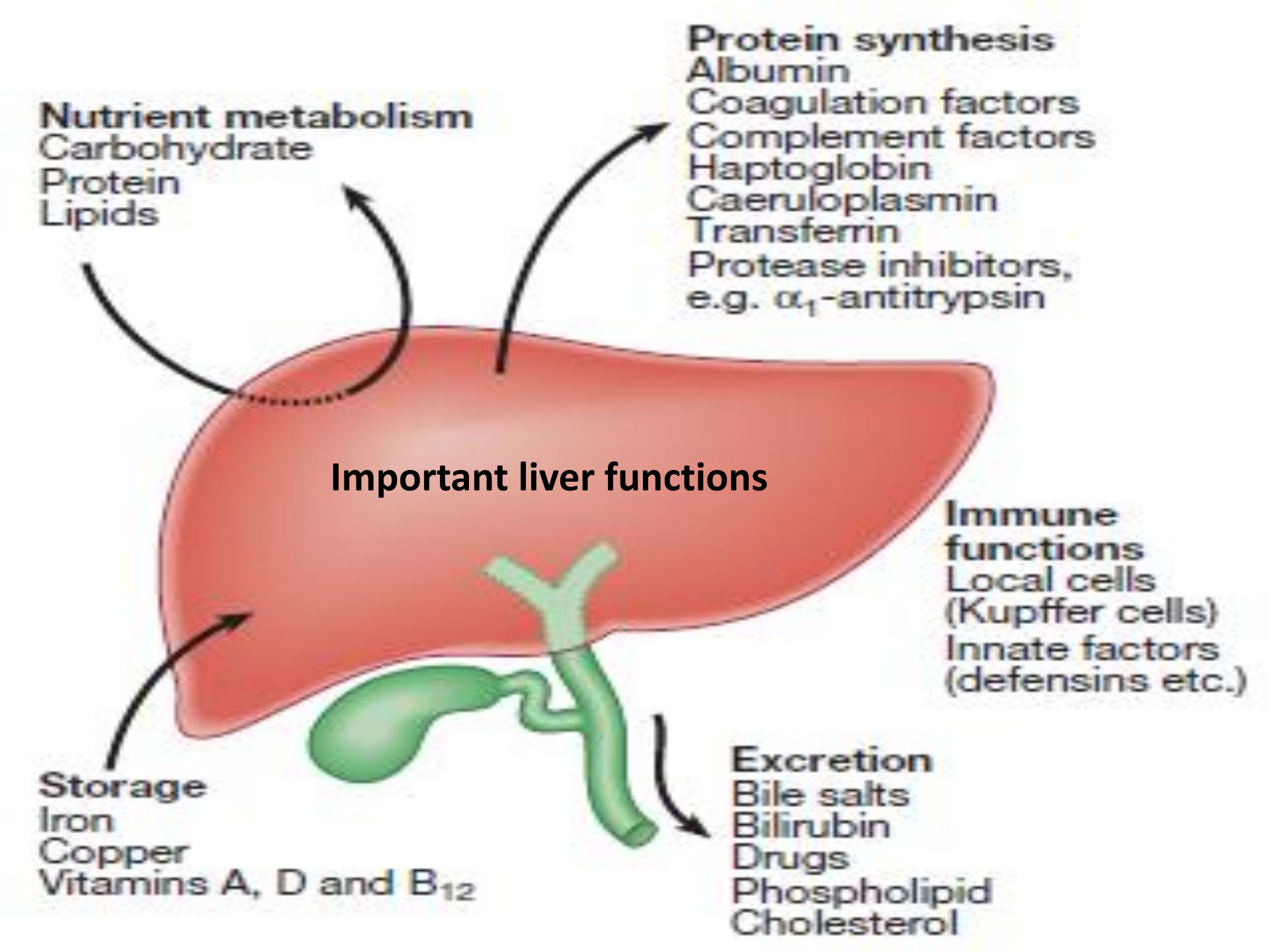
Liver structure and microstructure. A- Liver anatomy showing relationship with pancreas, bile duct and duodenum. B- Hepatic lobule. C-Hepatic acinus: is the smallest functional unit of the liver, a group of liver parenchyma that is supplied by terminal branches of the portal vein and hepatic artery and drained by a terminal branch of the bile duct.

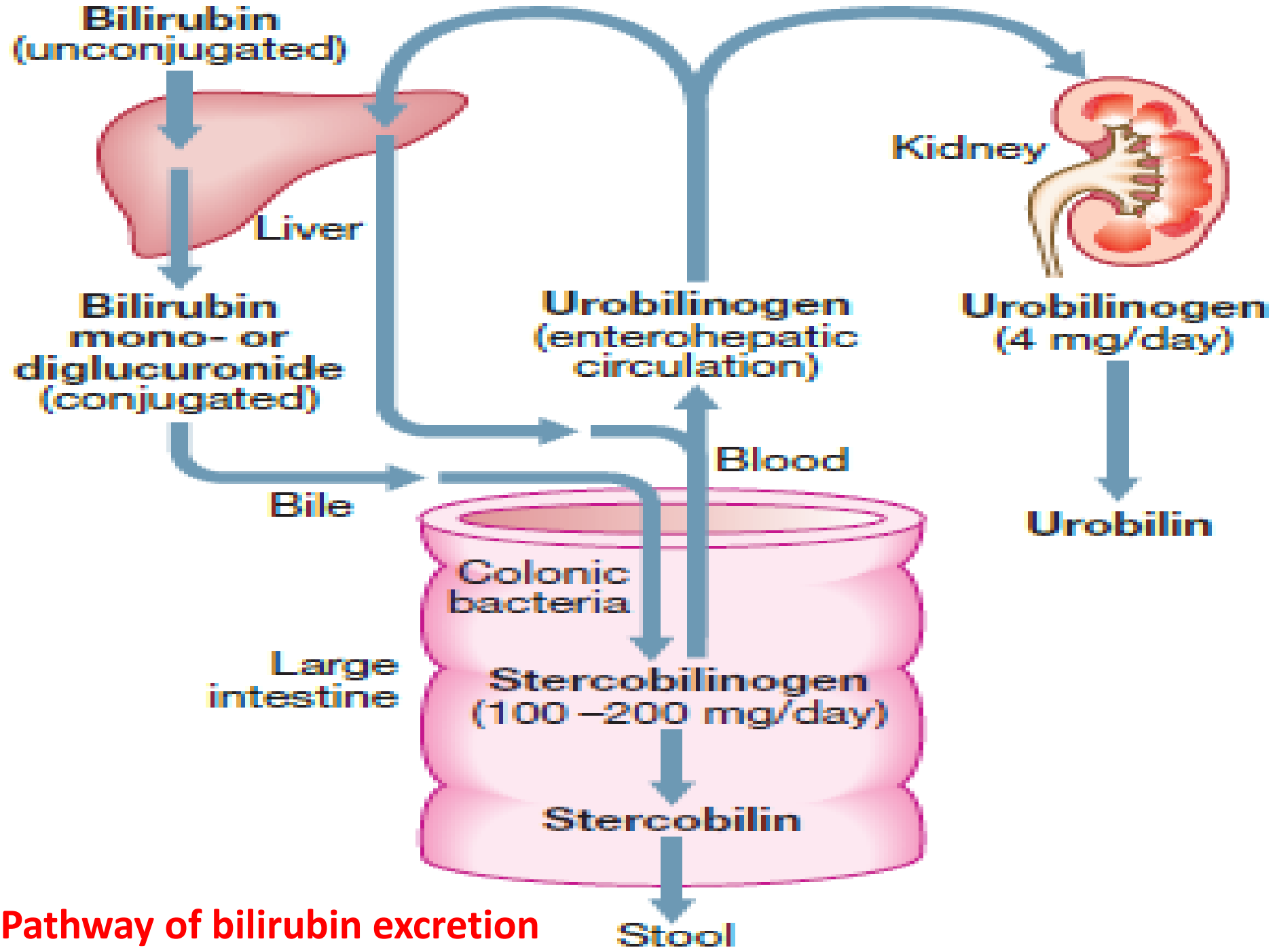


A liver segment is made up of multiple smaller units known as lobules, comprised of a central vein, radiating sinusoids separated from each other by single liver cell (hepatocyte) plates, and peripheral portal tracts. The functional unit of the liver is the hepatic acinus.



A lobule is a hexagonal arrangement of plates of hepatocytes radiating outward from a central vein in the center.


Protein synthesis
Albumin
Coagulation factors
Complement factors
Haptoglobin
Caeruloplasmin
Transferrin
Protease inhibitors,
e.g. α_1-antitrypsin
Nutrient metabolism
Carbohydrate
Protein
Lipids
Important liver functions
Immune functions
Local cells
(Kupffer cells)
Innate factors
(defensins etc.)
Excretion
Bile salts
Bilirubin
Drugs
Phospholipid
Cholesterol
Storage
Iron
Copper
Vitamins A, D and B_{12}



Pathway of bilirubin excretion

Laboratory Tests of Hepatic Function with (Normal Values)

1- Test of liver synthetic capacity

- Serum albumin (3.5- 5.5 mg/dL): Protein synthetic capacity (over days to weeks)
- Prothrombin time (10.5-13 sec) Protein synthetic capacity (hours to days)

2- Tests of biliary obstruction or impaired bile flow

- Serum bilirubin (0.2- 1 mg/dL) (3.4- 17.1 µmol/L): Extraction of bilirubin from blood, conjugation and excretion into bile.
- Serum alkaline phosphatase (also gamma-glutamyl transferase) (56-176 U/L).

3- Tests of hepatocellular damage

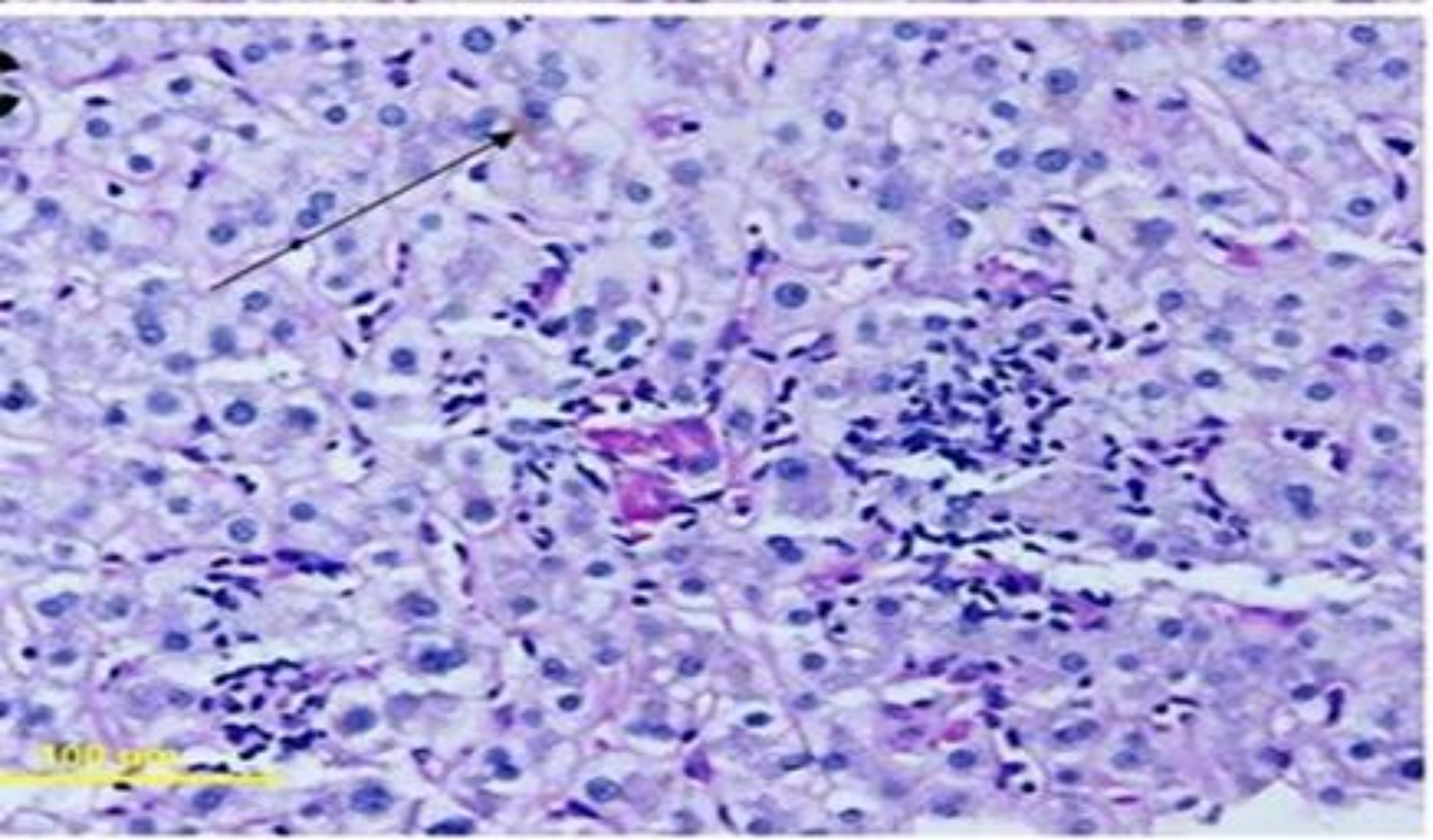
- Aspartate aminotransferase (AST) (10- 30 U/L): Release of intracellular enzyme
- Alanine aminotransferase (ALT) (5- 30 U/L): Release of intracellular enzyme

Acute hepatitis

Hepatitis: It is inflammation of the liver result from damage produced by viral, toxic, metabolic, pharmacologic, or immune-mediated attack on the liver.

Acute hepatitis: Inflammation of liver lasting less than 6 months.

Fate: Either complete resolution or rapid progression to fulminant hepatitis and acute liver failure associated with extensive necrosis and a fatal outcome or slowly progress to chronic hepatitis.



Liver Histology: Infiltration by lymphocytes in a portal tract, and the lobular parenchyma, with swelling of hepatocytes, and mild lobular disarray. A focus of Kupffer cell clustering, containing PAS-positive membrane debris and intrahepatic cholestasis (black arrow)

Causes of Acute Hepatitis

1. **Viral Hepatitis:** Common: Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, Hepatitis D virus ("delta agent") and Hepatitis E virus. Less common: Epstein-Barr virus and Cytomegalovirus. Rare: Herpes simplex and Yellow fever
2. **Alcohol**
3. **Toxins:** *Amanita phalloides* mushroom poisoning and Herbal preparations.
4. **Drugs:** Acetaminophen, Isoniazid, Halothane Phenytoin, Ketoconazole.
5. **Other:** Autoimmune hepatitis, Wilson's disease.

Amanita phalloides, is one of the most poisonous mushrooms worldwide. This species contains toxins causing liver cells death presented as gastrointestinal symptoms followed by jaundice, seizures, and coma, culminating in death.

Acute Viral Hepatitis

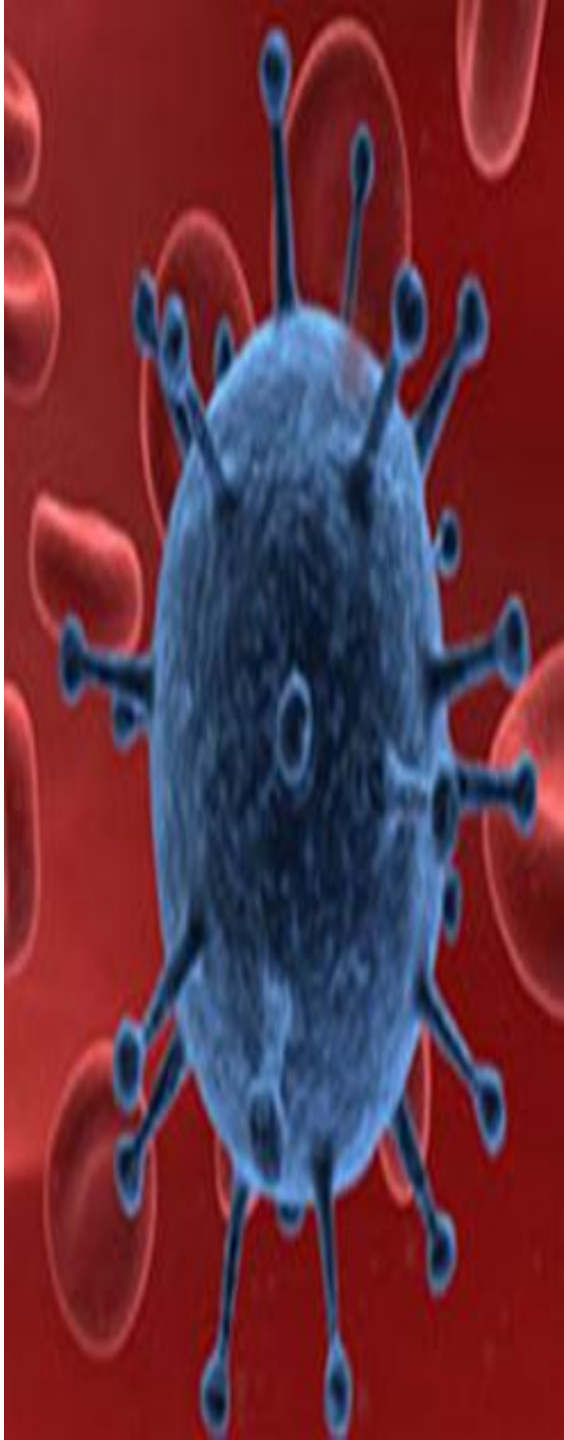
This is a common cause of jaundice

	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Group	Enterovirus picornavirus	Hepadna	Flavivirus	Incomplete virus	Calicivirus
Nucleic acid	RNA	DNA	RNA	RNA	RNA
Size (diameter)	27 nm	42 nm	30-38 nm	35 nm	27 nm
Incubation (weeks)	2-4	4-20	2-26	6-9	3-8
Transmission	Fecal-oral, waterborne or foodborne	Parenteral inoculation, sexual and vertical	Similar to HBV, but vertical Transmission uncommon, poor sexual transmission	Similar to HBV	Similar to HAV
Carrier state	No	Yes	No	Yes	No
Chronic infection	No	Yes 10% in Horizontal. 90% in Vertical trans.	Yes. Common (80%)	Yes. Common	No
Prevention					
Active	Vaccine	Vaccine	No	Prevented by	No
Passive	Immune serum globulin	Immune serum globulin	No	hepatitis B vaccination	No

Hepatitis A virus (HAV):

belongs to the picornavirus group of enteroviruses. HAV is highly infectious and is spread by the faecal–oral route. Infected individuals, who may be asymptomatic, excrete the virus in faeces for about 2–3 weeks before the onset of symptoms and then for a further 2 weeks or so. Infection is common in children but often asymptomatic. Infection is also more common in areas of overcrowding and poor sanitation.

HAV antigen is only present in the blood transiently during the incubation period. Anti-HAV of IgM type present in the blood at the onset of the clinical illness and is diagnostic of an acute HAV infection



Hepatitis B virus:

is one of the most common causes of chronic liver disease and hepatocellular carcinoma worldwide. Approximately one-third of the world's population have serological evidence of past or current infection with hepatitis B and approximately 350–400 million people are chronic HBs Ag carriers. The virus, also called a Dane particle. Humans are the only source of infection.

Serology:

Hepatitis B surface antigen (HBsAg): HBsAg is an indicator of active infection, and a negative test for HBsAg makes HBV infection very unlikely. The persistence of HBsAg for longer than 6 months indicates chronic infection.

Antibody to HBsAg (anti-HBs): usually appears after about 3–6 months and persists for many years or perhaps permanently. Anti-HBs implies either a previous infection, in which case anti-HBc (IgG type) is usually also present, or previous vaccination, in which case anti-HBc is not present.

The hepatitis B core antigen (HBc Ag): is not found in the blood, but antibody to it **(anti-HBc)** appears early in the illness. Anti-HBc is initially of IgM type (reveal an acute HBV infection) while IgG antibody appearing later.

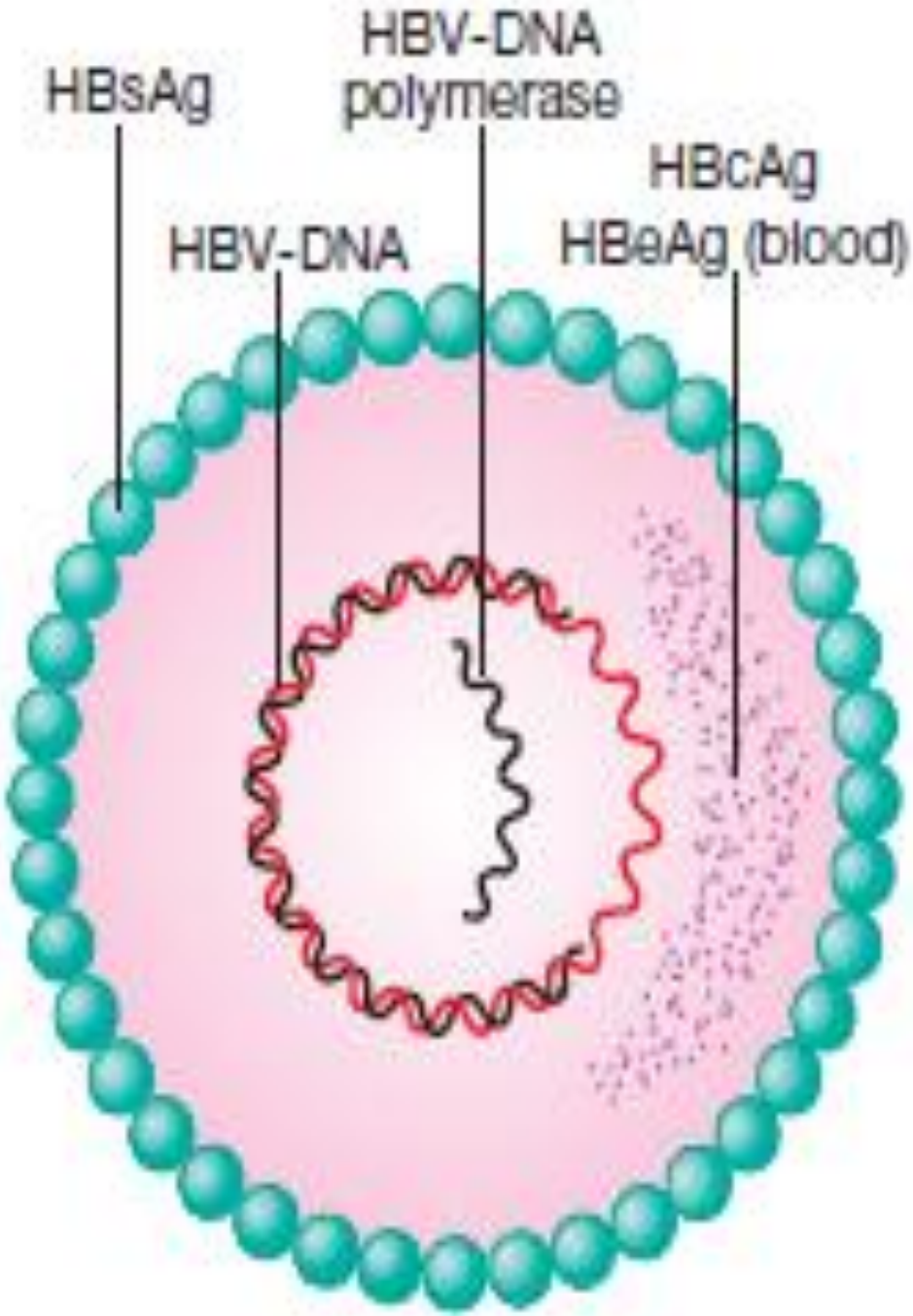
The hepatitis B e antigen (HBe Ag): appears only transiently at the onset of the illness and is followed by the production of antibody (anti-HBe). The Hbe Ag reflects active replication of the virus in the live and more likely to be highly infectious.

Viral load: HBV-DNA can be measured by PCR in the blood. Viral loads are usually in excess of 10^5 copies/ml in the presence of active viral replication.

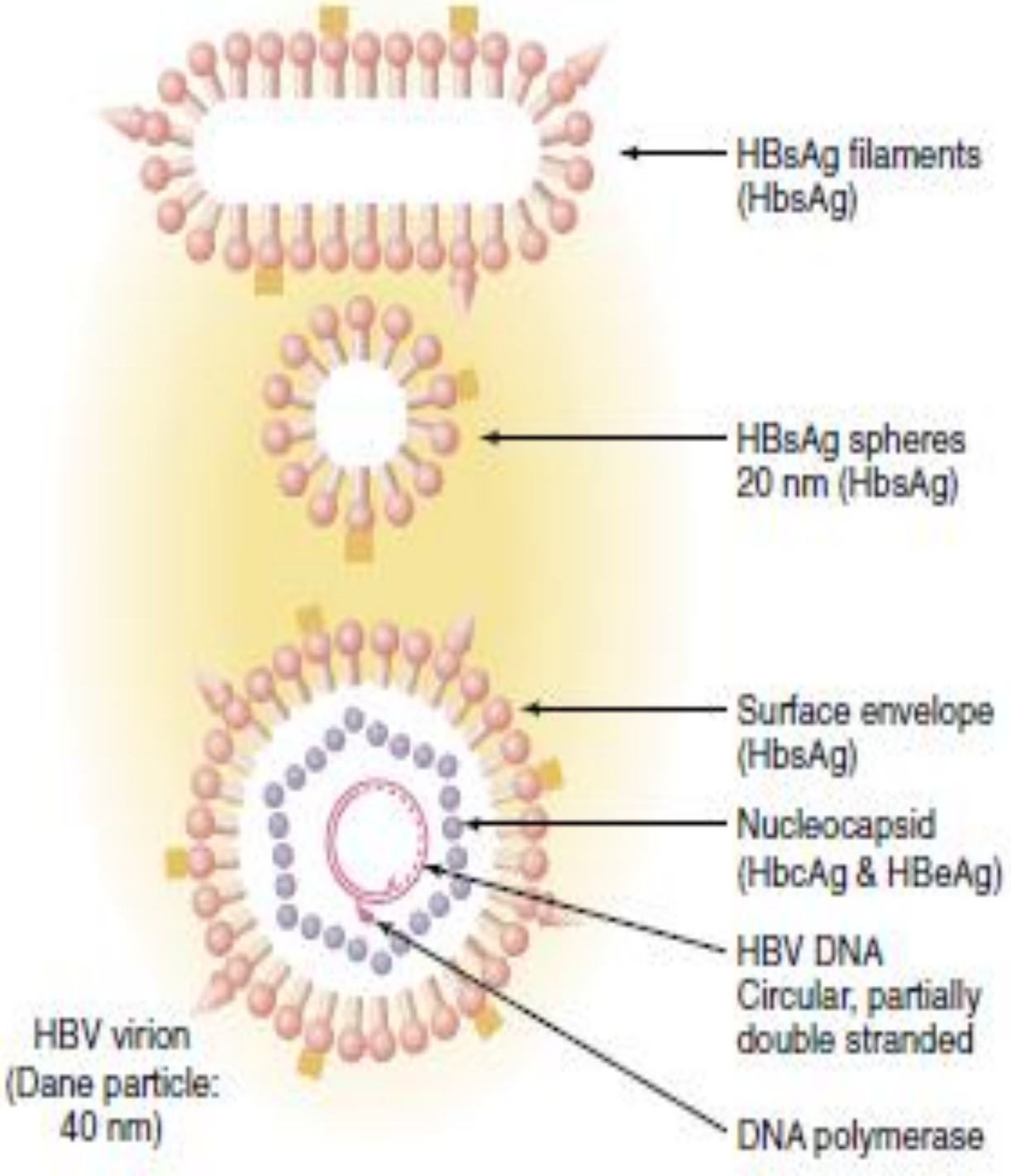
Chronic HBV infection is marked by the presence of HBsAg and anti-HBc (IgG) in the blood. Usually, HBeAg or anti-HBe is also present.

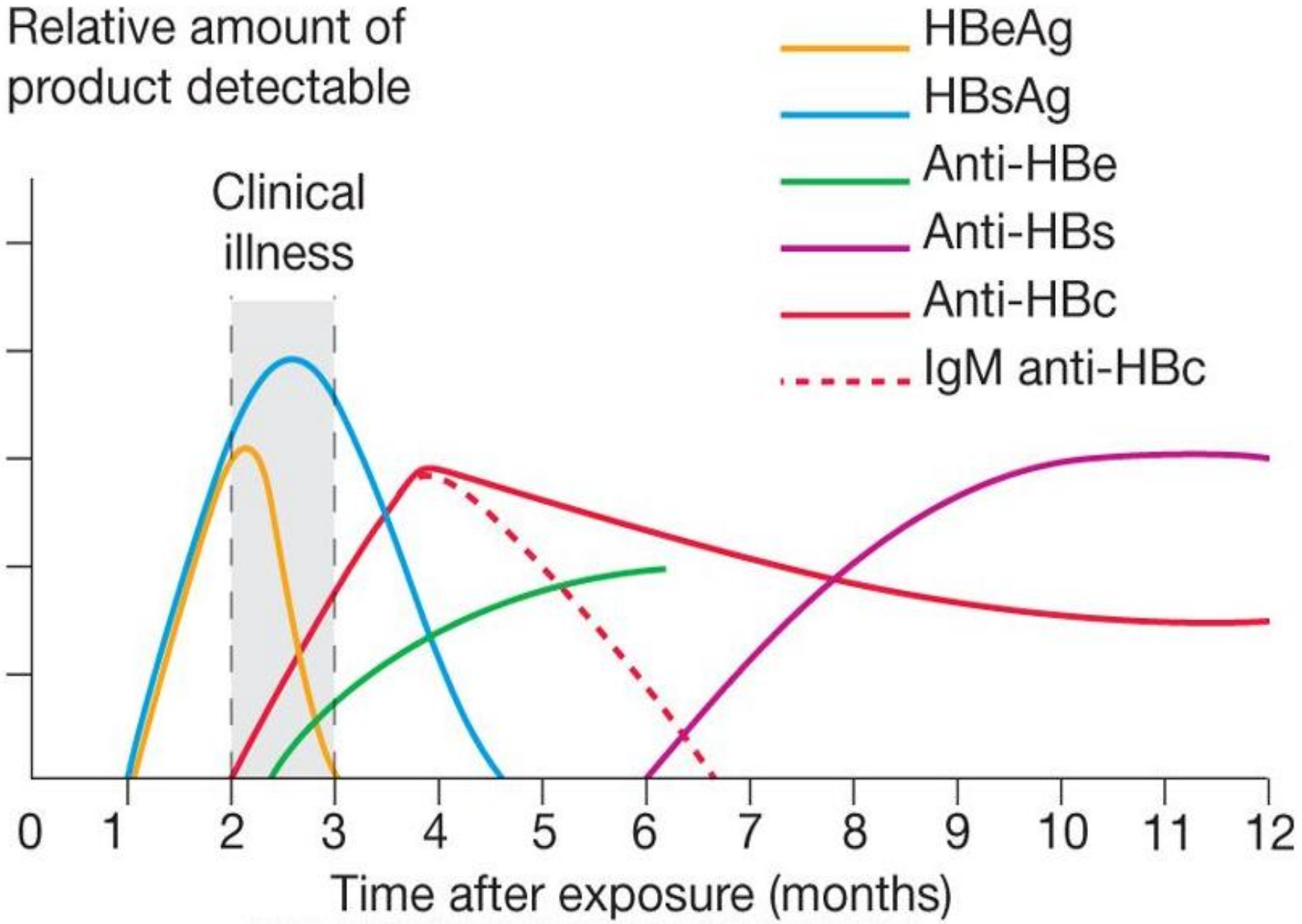
Chronic carrier state: in which HBsAg persists in serum, HBeAg is negative or no detectable viral replication (PCR $<10^4$ viral copies/mL)

Schematic diagram of hepatitis B virus. Hepatitis B surface antigen (HBsAg) is a protein that makes up part of the viral envelope. Hepatitis B core antigen (HBcAg) is a protein that makes up the capsid or core part of the virus (found in the liver but not in blood). Hepatitis B e antigen (HBeAg) is part of the HBcAg that can be found in the blood and indicates infectivity



Schematic diagram of hepatitis B virus (HBV)- related particles in serum and the associated antigens. The spheres and filaments consist of only hepatitis B surface glycoproteins (HBsAg), they are 20 nm in diameter. The complete virion (Dane particle: 40 nm diameter).





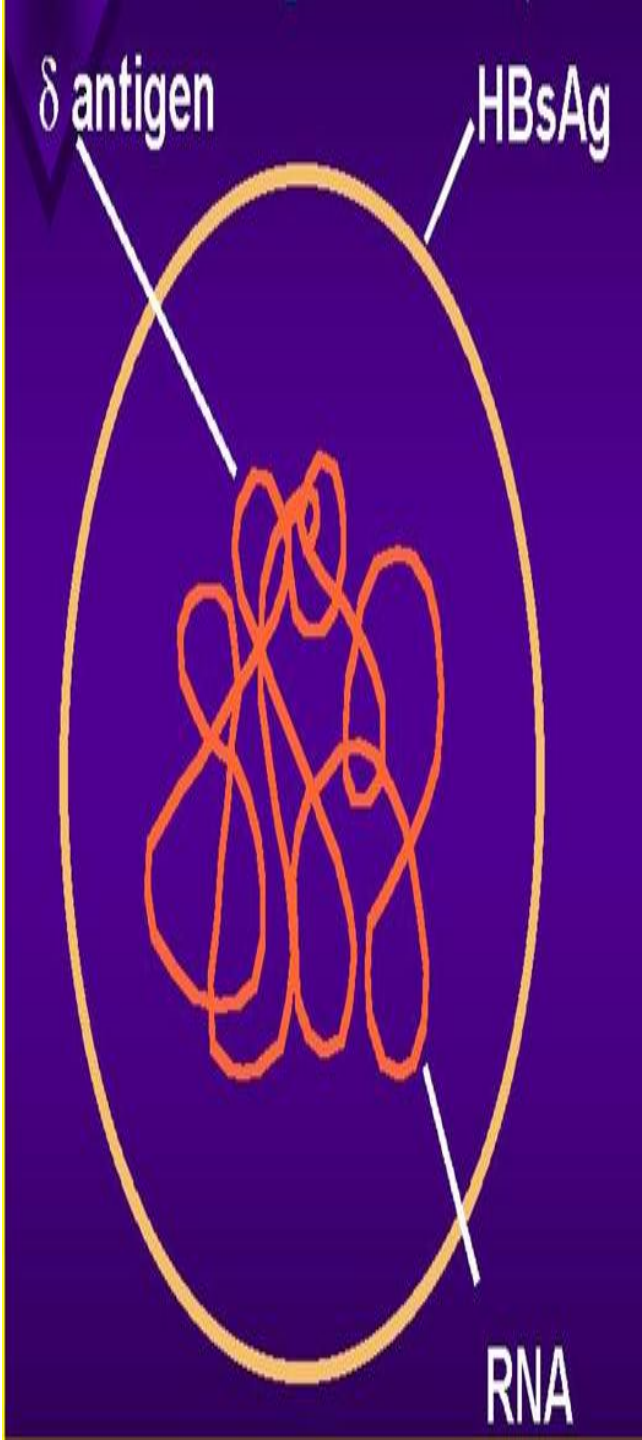
Serological responses to hepatitis B virus infection. (HBsAg = hepatitis B surface antigen; anti-HBs = antibody to HBsAg; HBeAg = hepatitis B e antigen; anti-HBe = antibody to HBeAg; anti-HBc = antibody to hepatitis B core antigen)

23.42 How to interpret the serological tests of acute hepatitis B virus infection

Interpretation	HBsAg	Anti-HBc IgM	Anti-HBc IgG	Anti-HBs
Incubation period	+	+	–	–
Acute hepatitis				
Early	+	+	–	–
Established	+	+	+	–
Established (occasional)	–	+	+	–
Convalescence				
(3–6 months)	–	±	+	±
(6–9 months)	–	–	+	+
Post-infection	–	–	+	±
Immunisation without infection	–	–	–	+

+ Positive; – negative; ± present at low titre or absent.

The hepatitis D (Delta) virus (HDV): is an RNA-defective virus that has no independent existence; it requires HBV for replication and has the same sources and modes of spread. It can infect individuals simultaneously with HBV or can superinfect those who are already chronic carriers of HBV. HDV contains a single antigen to which infected individuals make an antibody (anti-HDV) initially IgM (acute infection) and later IgG (chronic infection when it remain in high level).

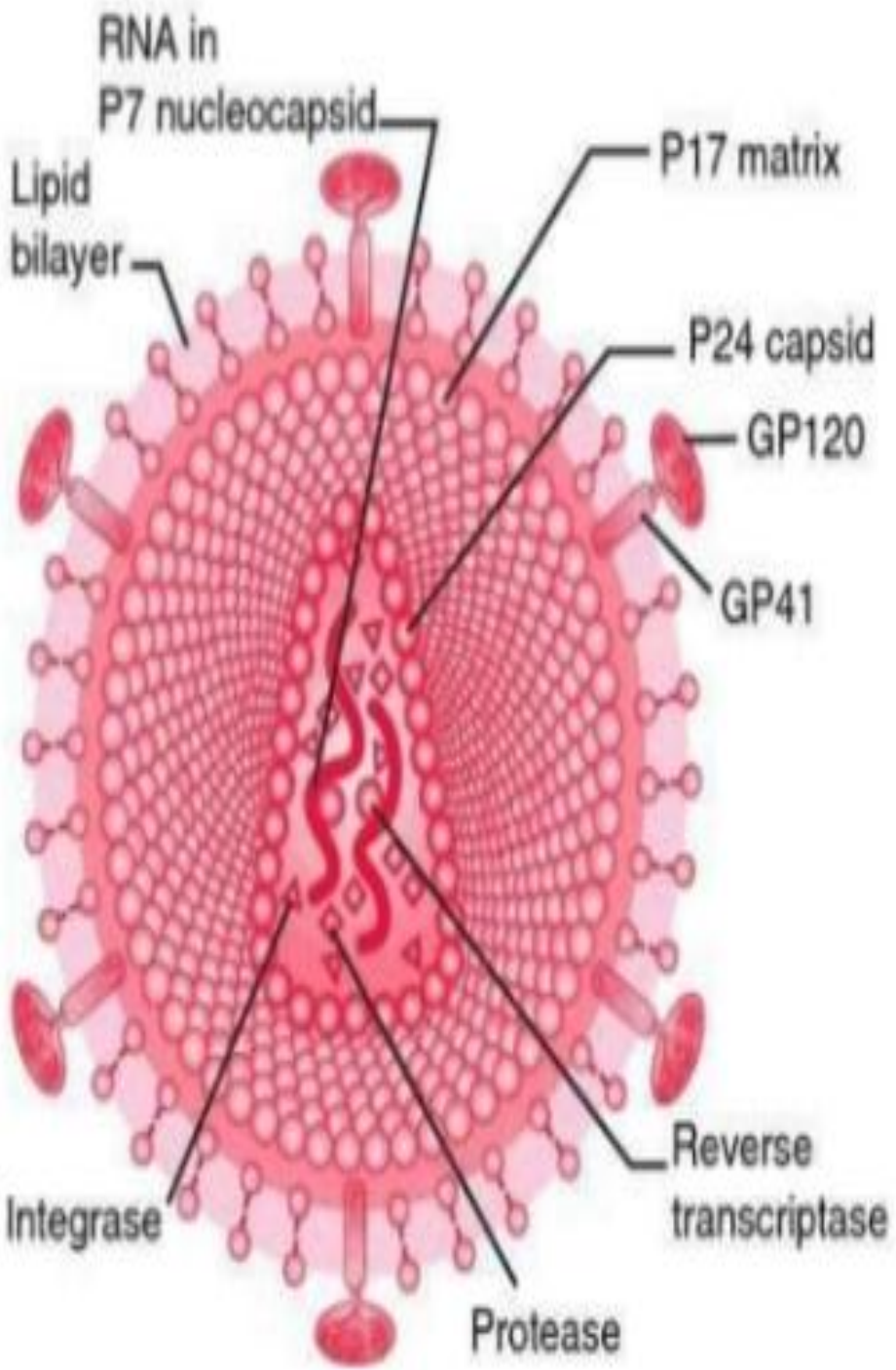


Hepatitis C

- Acute symptomatic infection with hepatitis C is rare. 80% of individuals exposed to the virus will become chronically infected and 20% of them develop liver cirrhosis within 20 years. Risk factors for progression to cirrhosis include male gender, immunosuppression (such as co-infection with HIV), prothrombotic states and heavy alcohol misuse.
- Hepatitis C RNA can be identified in the blood as early as 2-4 weeks after infection. Active infection is confirmed by the presence of serum hepatitis C RNA in anyone who is antibody positive.
- Anti-HCV antibodies persist in serum even after viral clearance, whether spontaneous or post-treatment.

Hepatitis E

- The clinical presentation and management of hepatitis E are similar to that of hepatitis A.
- Hepatitis E differs from hepatitis A in that infection during pregnancy is associated with the development of acute liver failure, which has a high mortality.
- In acute infection, IgM antibodies to HEV are positive.

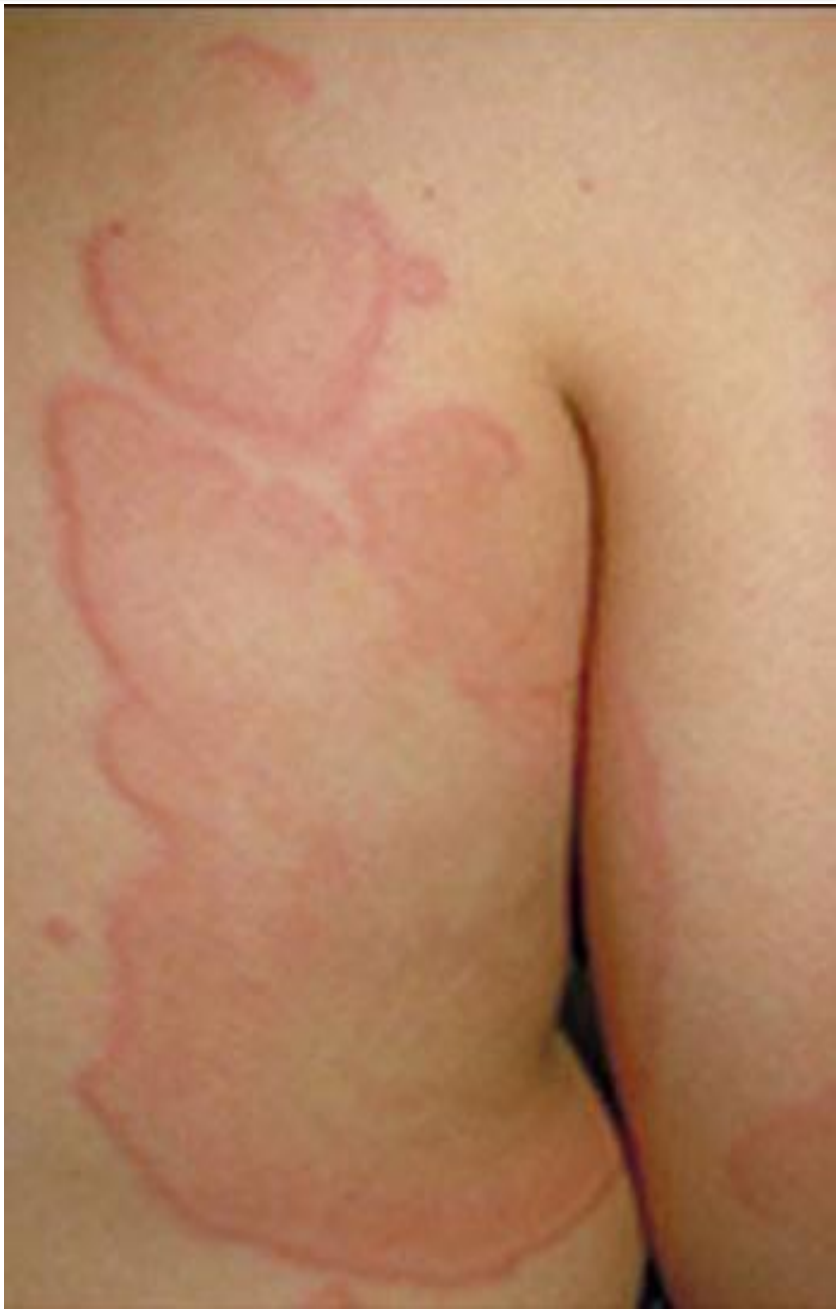


Clinical features of viral hepatitis

1-Prodromal phase: Which last for several days and characterized by malaise, fatigue, anorexia, nausea, vomiting, myalgia, headache, and mild fever.

Arthritis and urticaria (serum sickness) due to immune complex deposition, may be present in 5 to 10% of cases of acute hepatitis B and C.

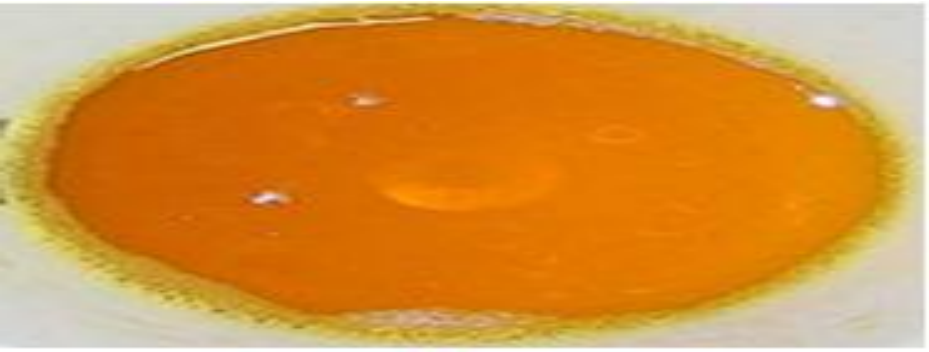
Taste and smell alteration.



2- Icteric phase: Jaundice appear after few days to 2 weeks.

- Dark urine and pale stools.
- Improvement in the patient's well-being.
- Splenomegaly is found in about one-fifth of patients.

Anicteric phase: Symptoms without jaundice.



Dark urine

Pale stool

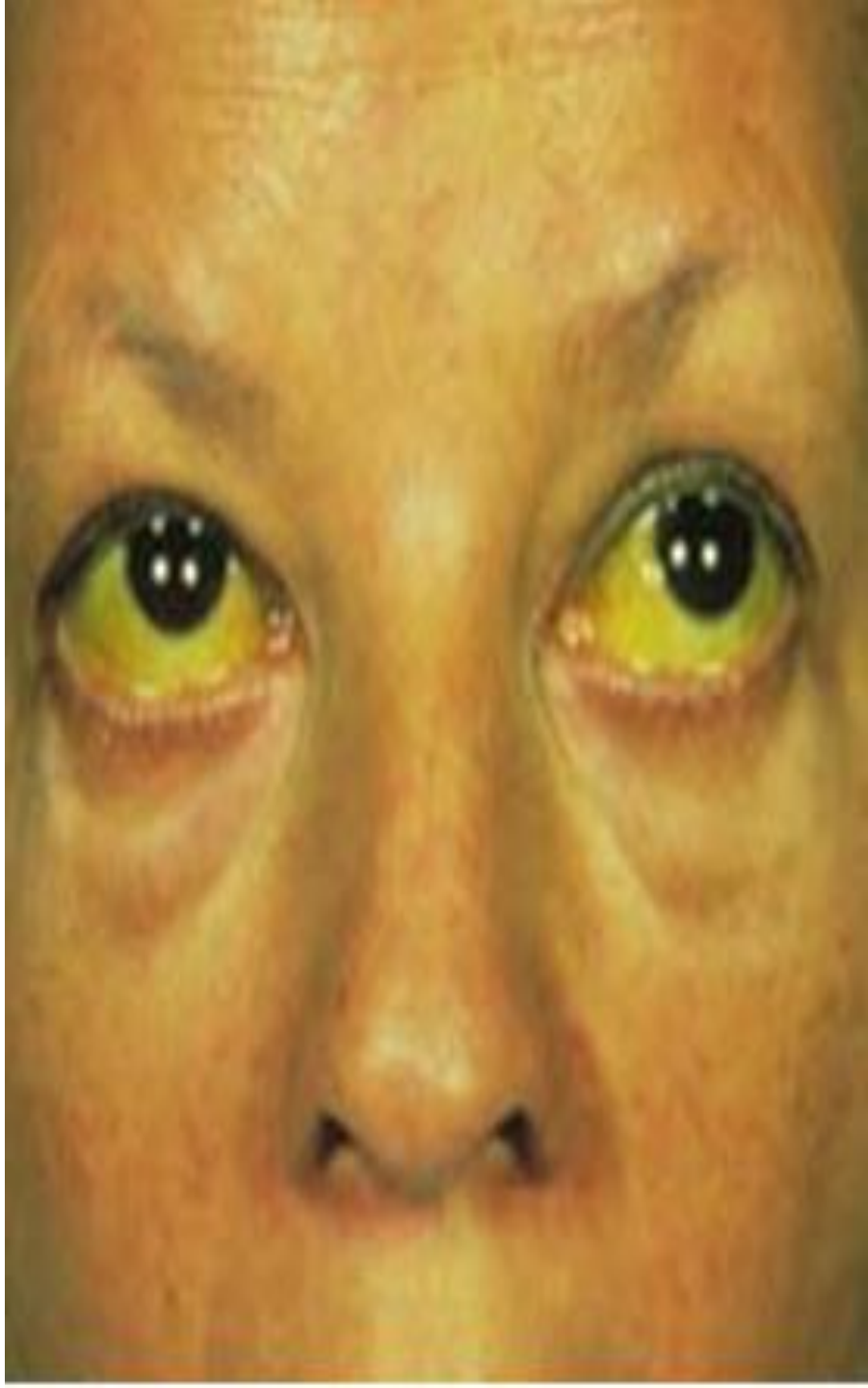
Laboratory:

1. Aminotransferases (ALT & AST) serum levels rise to greater than 20- 100 fold normal.
2. An elevated serum bilirubin (>2.5 to 3.0 mg/dL) or higher than 20 mg/dL.
3. Serum alkaline phosphatase when it rise to more than three times of normal levels indicate cholestatic hepatitis.
4. Prolongation of the prothrombin time in sever hepatitis.
5. Serological tests confirm the aetiology of the infection.

3-Recovery phase: Gradual resolution of symptoms and laboratory values

Complications

1. Cholestatic hepatitis.
2. Acute liver failure.
3. Chronic hepatitis.
4. Aplastic anemia.
5. Relapsing hepatitis.



Management

1- Supportive treatment:

- Rest
- Maintenance of hydration and adequate dietary intake.
- Alcohol should be avoided.
- Hospitalization if severe nausea and vomiting or deterioration of liver function.
- Drugs such as sedatives and narcotics should be avoided.
- Elective surgery should be avoided.
- Acute hepatitis C: Pegylated interferon- α may prevent the development of chronic infection
- Vitamin K indicated if prolonged cholestasis.

2- Liver transplantation: Very rarely indicated, when the patient developed acute liver failure.

Chronic Hepatitis

Learning objectives:

1. Define chronic hepatitis.
2. List the causes of chronic hepatitis.
3. Summarize the classification of chronic hepatitis.
4. Describe the various types of chronic viral hepatitis including hepatitis B, C and D.
5. Summarize the other forms of chronic hepatitis including nonalcoholic steatohepatitis, autoimmune hepatitis and metabolic (genetic) hepatitis.
6. Interpret laboratory test results in chronic hepatitis.
7. Discuss treatment options of chronic hepatitis.

Chronic Hepatitis

Defined as a hepatic inflammatory process lasting more than 6 months.

Causes of Chronic Hepatitis:

1. **Viral Hepatitis: B, C and Hepatitis B with superimposed hepatitis D.**
2. **Alcoholic hepatitis.**
3. **Nonalcoholic steatohepatitis.**
4. **Drugs and Toxins: Methyldopa, Nitrofurantoin, Amiodarone, Captopril, Propylthiouracil.**
5. **Autoimmune hepatitis**
6. **Genetic and Metabolic Disorders: Wilson's disease, and α_1-Antitrypsin deficiency.**

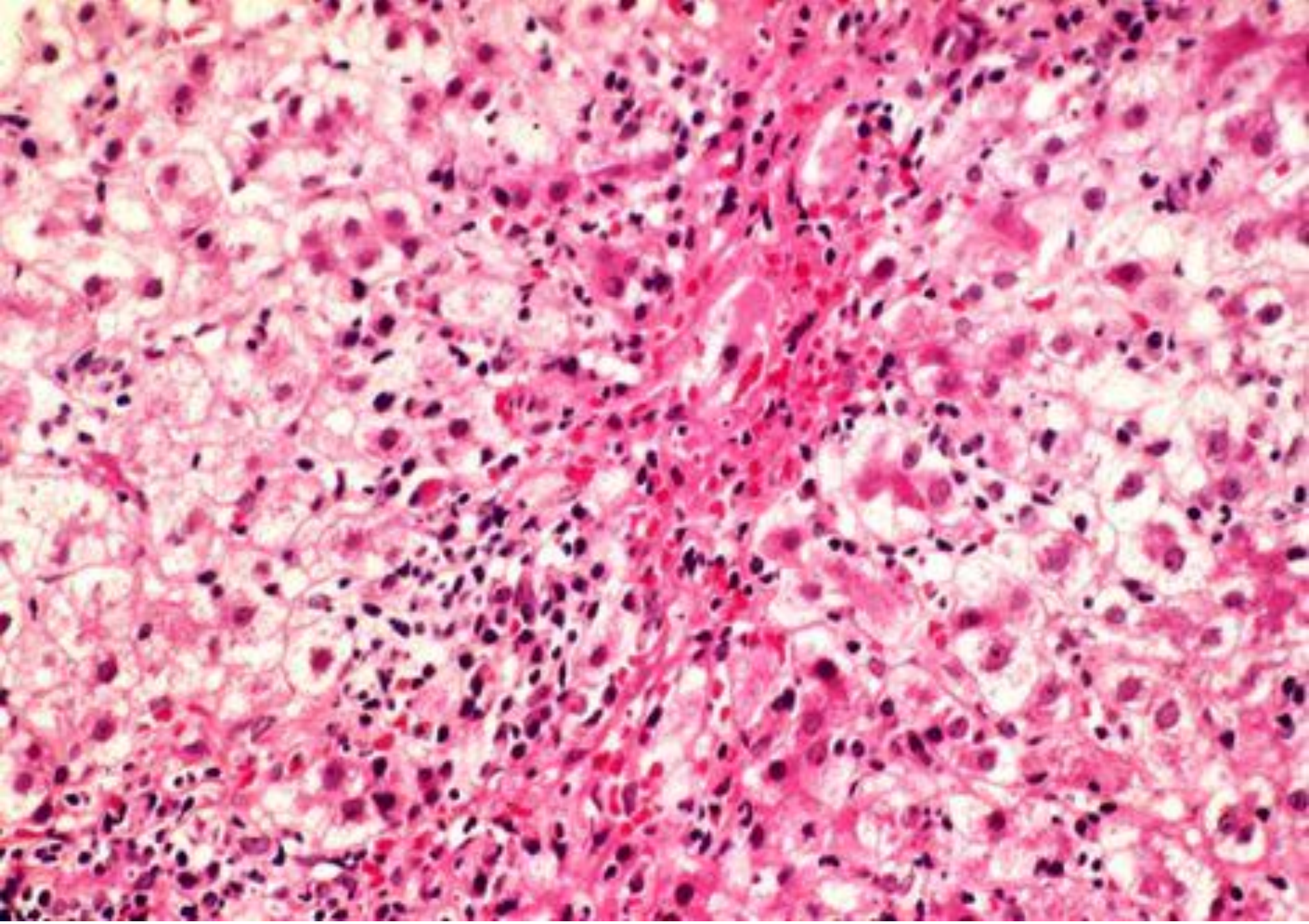
Classification

1-Initial classification: which depend on histopathology only:

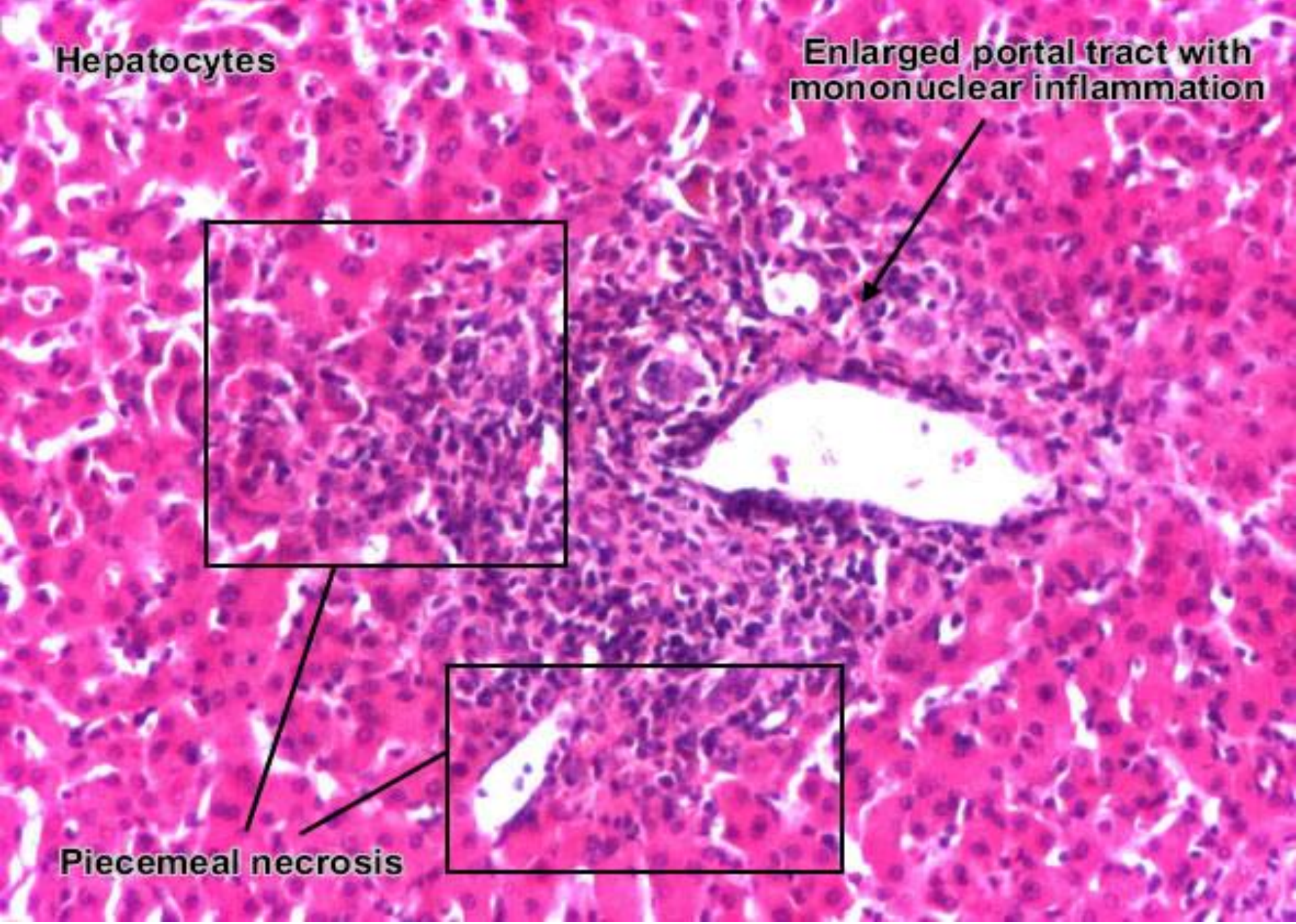
A. **Chronic persistent hepatitis: inflammatory activity confined to portal areas -- good prognosis.**
B. **Chronic lobular hepatitis: inflammatory activity and necrosis scattered throughout the lobule -- good prognosis.**
C. **Chronic active hepatitis: inflammation that spilled into the adjacent lobule associated with necrosis and fibrosis, which progress to cirrhosis and liver failure.**

2-Recent classification: which depend on:

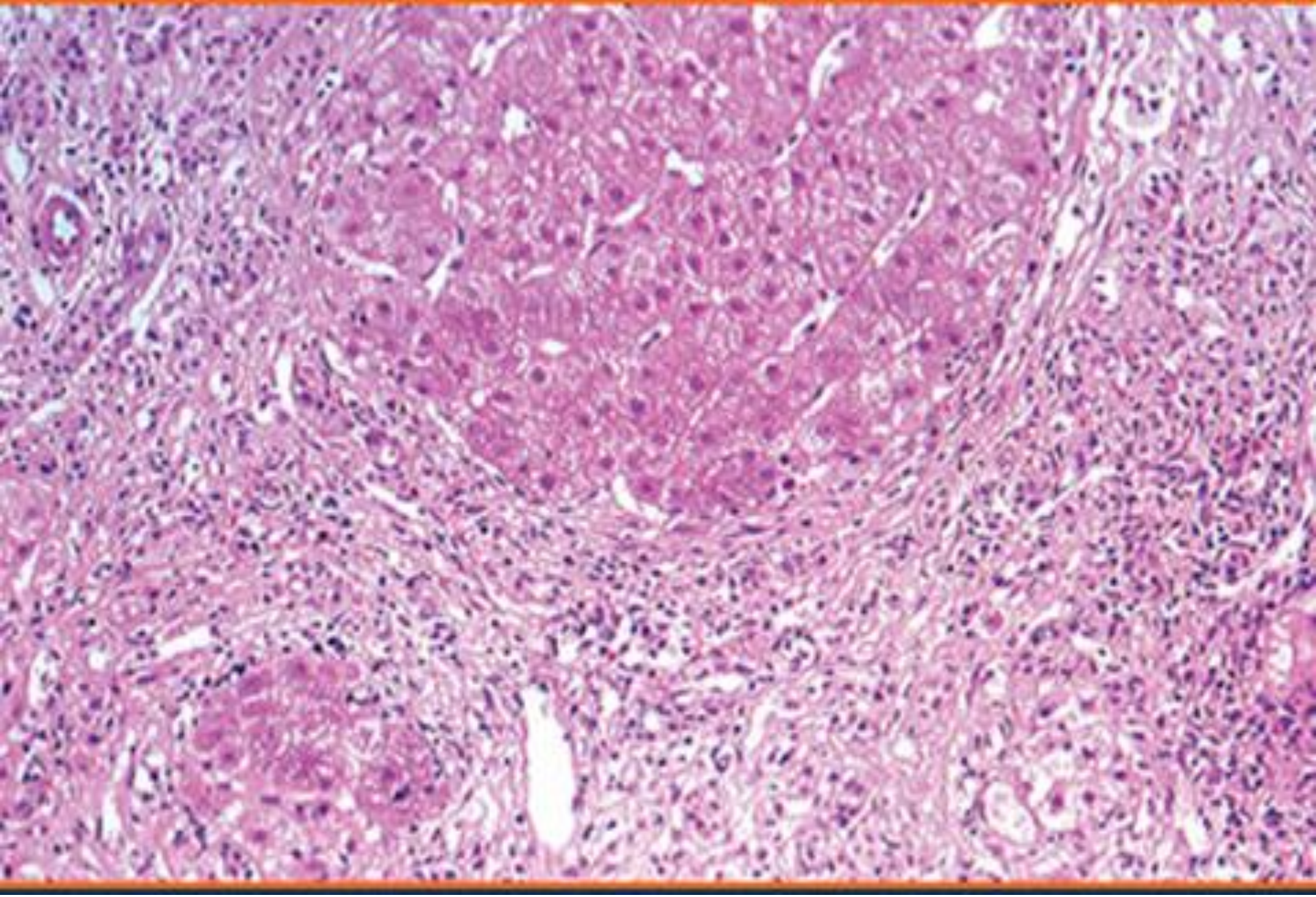
A. **Etiologic agent**
B. **Grade of injury (numbers and location of inflammatory cells)**
C. **Stage of disease (degree and location of fibrosis)**



Chronic persistent hepatitis: inflammatory activity confined to portal areas.



Chronic lobular hepatitis; inflammatory activity and necrosis scattered throughout the lobule



Chronic active hepatitis; inflammation that spilled into the adjacent lobule associated with necrosis and fibrosis.

Chronic hepatitis B

Route of transmission: Horizontal transmission (10%): Injection drug use, infected unscreened blood products, tattoos/acupuncture needles, sexual. Vertical transmission (90%): From HBs Ag positive mother.

Clinical features: Asymptomatic, fatigue, jaundice, malaise and anorexia, may progress to liver failure.

Extrahepatic features: arthralgias and arthritis, glomerulonephritis, and vasculitis , due to immune complexes deposition.

Invx; Aminotransferases elevated. HBs Ag +ve, HBe Ag +ve, and anti-HBc IgG Ab +ve.

Treatment: Indicated when there is: high viral load in the presence of active hepatitis, as demonstrated by elevated serum transaminases and/or histological evidence of inflammation and fibrosis.

The goal of antiviral therapy is to achieve an sustained virologic response (SVR), defined as undetectable HCV RNA levels (aviremia) 6 months after treatment discontinuation.

1- Nucleoside/nucleotide antiviral agents act by inhibiting the reverse transcription of pre-genomic RNA to HBV-DNA

- **Lamivudine: it is effective, but long-term therapy is often complicated by the development of HBV-DNA polymerase mutants (e.g. the 'YMDD variant'), which lead to viral resistance.**
- **Entecavir and tenofovir: Monotherapy with entecavir or tenofovir is substantially more effective than lamivudine in reducing viral load in HBeAg-positive and HBeAg-negative chronic hepatitis.**

2- Interferon-alfa: it acts by augmenting a native immune response. In HBeAg-positive chronic hepatitis, 33% lose e antigen after 4–6 months of treatment,

3- Liver transplantation: postliver transplant prophylaxis with direct-acting antiviral agents and hepatitis B. immunoglobulins

Chronic Hepatitis D

- Chronic hepatitis B plus D has similar clinical and laboratory features to those seen in chronic hepatitis B alone, but more severe chronic hepatitis or cirrhosis.
- Preventing hepatitis B effectively prevents hepatitis D.
- Anti-HDV IgG titer is high.

Chronic Hepatitis C

- 80% will become chronically infected

Clinical features:

- Similar to chronic hepatitis B, fatigue common, but jaundice is rare.
- **Extrahepatic features:** Essential mixed cryoglobulinemia, Sjögren's syndrome, lichen planus and porphyria cutanea tarda.
- Progress to cirrhosis and hepatocellular carcinoma.

Invx: Presence of serum hepatitis C RNA in anyone who is antibody-positive. Liver histology degree of liver fibrosis

- **Molecular analysis:** There are six common viral genotypes. Genotype 1 was less easy to eradicate than genotypes 2 and 3 with traditional pegylated interferon alfa-/ribavirin-based treatments.

Treatment:

- **Until 2011,** the treatment of choice was dual therapy with pegylated interferon-alfa, given as a weekly subcutaneous injection, together with oral ribavirin, a synthetic nucleotide analogue. efficacy of these agents was poor (12 months) treatment. 40% SVR.
- **Since 2011,** new classes of direct-acting antiviral agents (DAAs) have been developed. **Initially,** DAAs were added to interferon-/ ribavirin-based regimens. **Recently,** however, combinations of DAAs have increasingly been used in 'interferon-free' regimens.

Example of interferon-free regimens:

- 12 weeks of treatment with oral sofosbuvir plus ledipasvir plus ribavirin can achieve a 99% SVR in treatmentof genotype 1 patients.
- Sofosbuvir plus velpatasvir achieves similar results and is pan-genotypic.
- **Liver transplantation:** should be considered when complications of cirrhosis occur. recurrence of cirrhosis no longer happen, as modern antiviral therapy post-transplant achieves excellent results

Non-alcoholic steatohepatitis

Most common in persons who are overweight, diabetes, and hyperlipidemia.

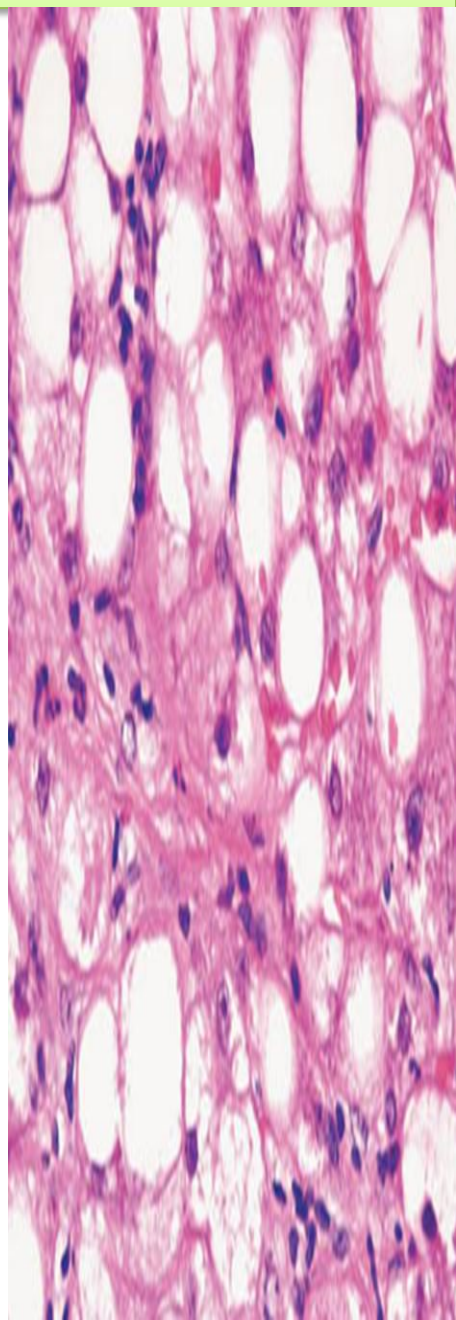
Clinical features:

- Asymptomatic: As abnormal LFTs.
- Complication: Cirrhosis, variceal haemorrhage or hepatocellular carcinoma.

U/S: liver will appear bright.

Liver biopsy: fat deposition is usually macrovesicular, neutrophil infiltration and fibrosis.

Treatment: Weight reduction. Vitamin E (as an antioxidant). Lipid-lowering agents with bezafibrate or gemfibrozil. Drugs that improve insulin resistance like metformin or insulin-sensitising agents, in particular glitazones, may be helpful.



Autoimmune hepatitis

- It is an immune-mediated liver injury
- Association with other autoimmune diseases like Hashimoto's thyroiditis or rheumatoid arthritis
- Hypergammaglobulinaemia and autoantibodies
- Young women
- Usually Insidious, with fatigue, anorexia, jaundice, fever, arthralgia, amenorrhoea and vitiligo.
- One-quarter of patients the onset is acute, resembling viral hepatitis, but resolution does not occur.
- Signs of chronic liver disease, especially spider naevi and hepatosplenomegaly, can be present.

Investigations: Antinuclear antibodies, anti-smooth muscle antibody and antimicrosomal antibodies (anti-LKM) are positive. Increase IgG level.

Treatment:

- glucocorticoids is life-saving in autoimmune hepatitis, Initially, prednisolone (40 mg/day) is given orally.
- Maintenance therapy reduced-dose prednisolone (below 5–10 mg/day) with azathioprine (1.0–1.5 mg/kg/day).
- Newer agents, such as mycophenolate mofetil (MMF), are increasingly being used.

GENETIC AND METABOLIC HEPATITIS

- Wilson's disease and α_1-antitrypsin deficiency
- Before the age of 35 years
- Family history of liver disease

Wilson's disease

Wilson's disease is a rare, autosomal recessive disorder of copper metabolism that is caused by a variety of mutations in the gene ATP7B on chromosome 13. Total body copper is increased, with excess copper deposited in, and causing damage to, several organs.

- **Hepatic disease** occurs predominantly in childhood and early adolescence. acute hepatitis, recurrent hepatitis, hepatitis with massive haemolysis, fulminant liver failure, chronic hepatitis, cirrhosis.
- **Neurological** damage causes basal ganglion syndromes and dementia which tends to present in later adolescence.
- **Others** include renal tubular damage and osteoporosis.
- **Kayser-Fleischer rings** the most important single clinical clue to the diagnosis and can be seen in 60% of adults.

Diagnosis:

low serum caeruloplasmin is the best single laboratory clue to the diagnosis. **High free serum copper concentration. High urine copper excretion** of greater than 0.6 µmol/24 hrs and a **very high hepatic copper content**

Treatment:

The copper-binding agent penicillamine is the drug of choice. Liver transplantation is indicated for fulminant liver failure or for advanced cirrhosis with liver failure

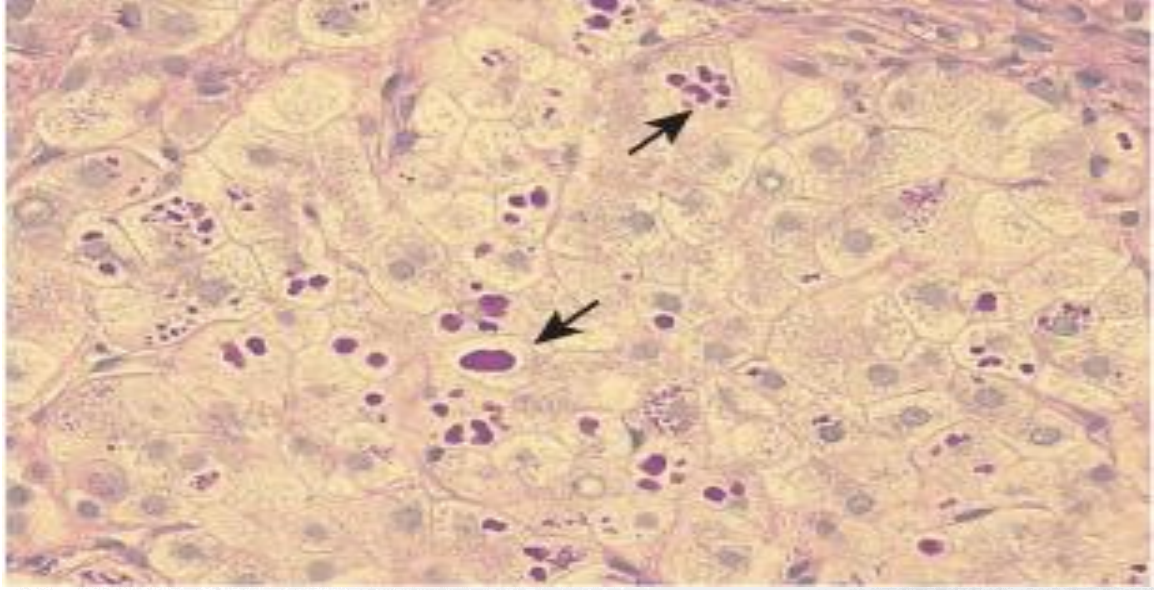
Kayser-Fleischer rings at the junction of the cornea and sclera

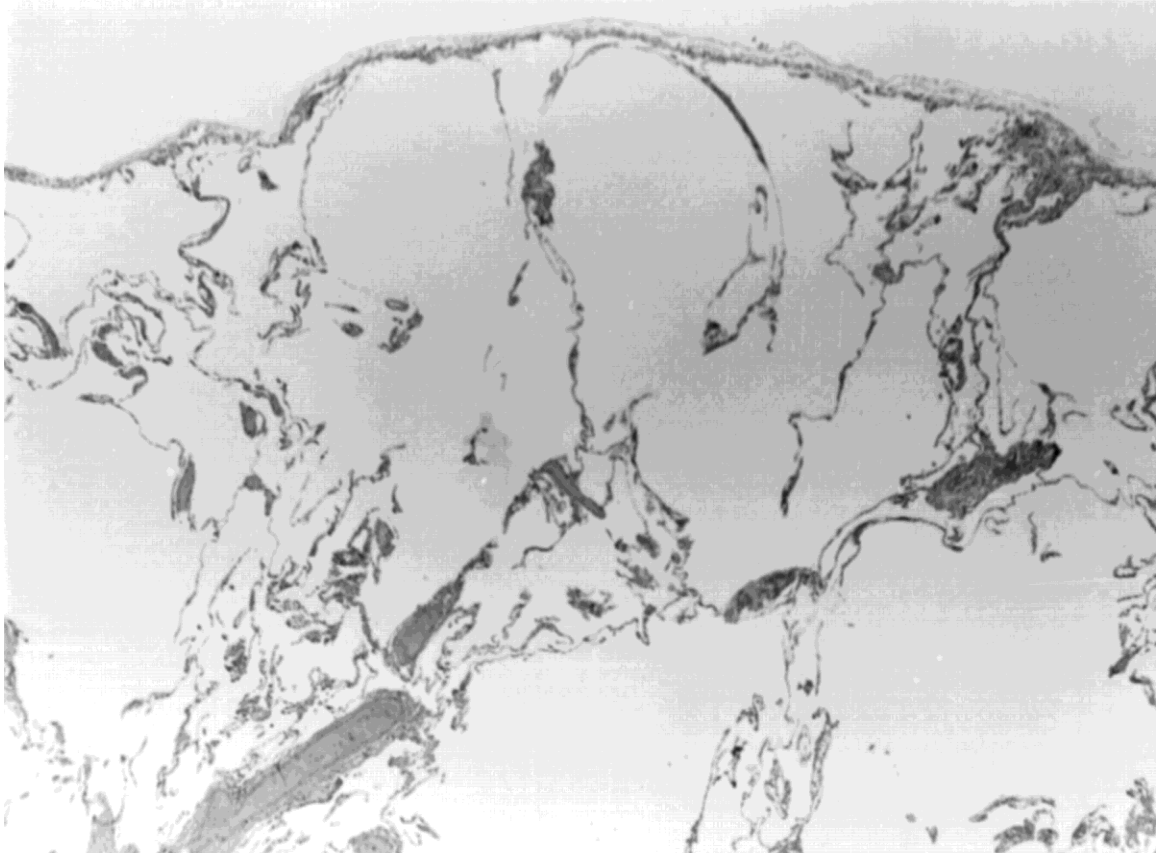
Alpha$_1$-antitrypsin deficiency

- **Alpha$_1$-antitrypsin (α_1-AT)** is a serine protease inhibitor (Pi) produced by the liver. It's gen located on **chromosome 14**. Which described as medium (M), slow (S), and very slow (Z). Homozygous individuals (PiZZ) have low plasma α_1-AT concentrations, these forms cannot be secreted into the blood by liver cells because it is polymerized within the endoplasmic reticulum of the hepatocyte, that leads to hepatic and pulmonary disease.
- Liver disease includes chronic hepatitis and cirrhosis in adults, and in the long term hepatocellular carcinoma. Lung disease including emphysema in adult life.

Diagnosis is made from the low plasma α_1-AT concentration and the PiZZ genotype.

No specific treatment is available; Life style modification: correct obesity, stop smoking and alcohol. Treat the complications of CLD. Liver transplantation if end stage liver dis.





Thanks