GENERAL PATHOLOGY

Liver and Biliary Tract

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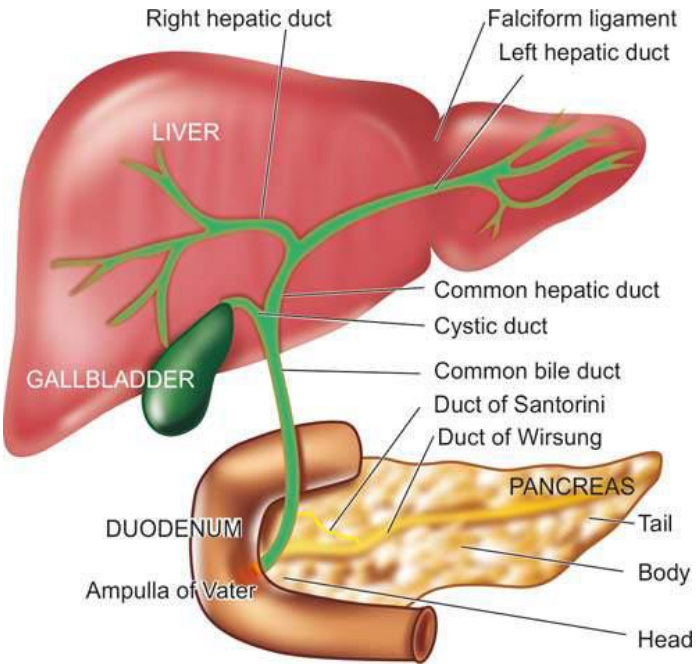
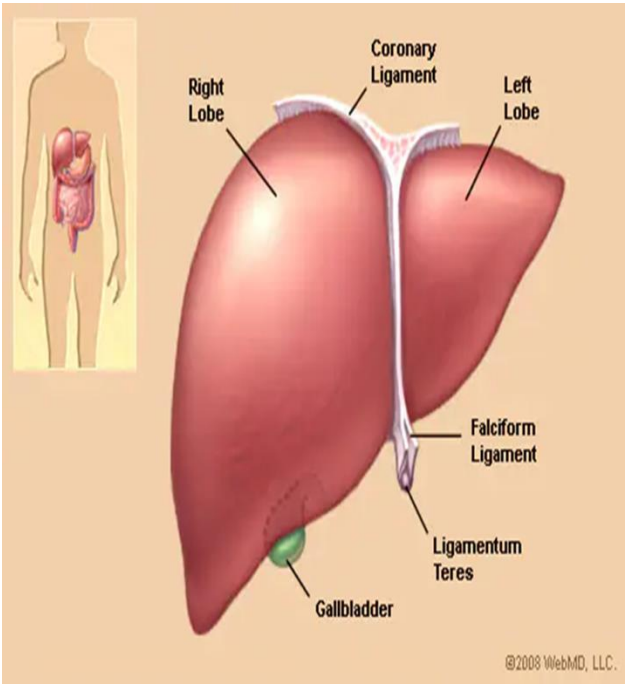
The liver is the largest organ in the body weighing 1400-1600 gm in the males and 1200-1400 gm in the females. There are 2 main anatomical lobes—right and left, the right being about six times the size of the left lobe. The right and left lobes are separated anteriorly by a fold of peritoneum called the falciform ligament، inferiorly by the fissure for the ligamentum teres, and posteriorly by the fissure for the ligamentum venosum.

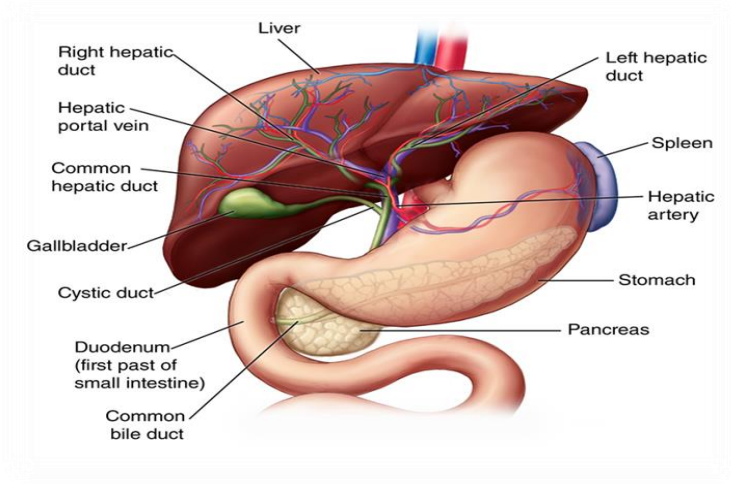


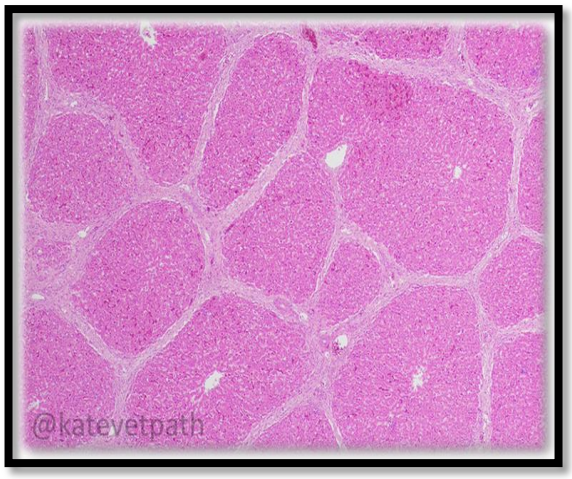


Both are made up of 8 segments that consist of 1,000 lobules (small lobes). These lobules are connected to small ducts (tubes) that connect with larger ducts to form the common hepatic duct. The common hepatic duct transports the bile made by the liver cells to the gallbladder and duodenum. There are 2 distinct sources that supply blood to the liver ،including the following:

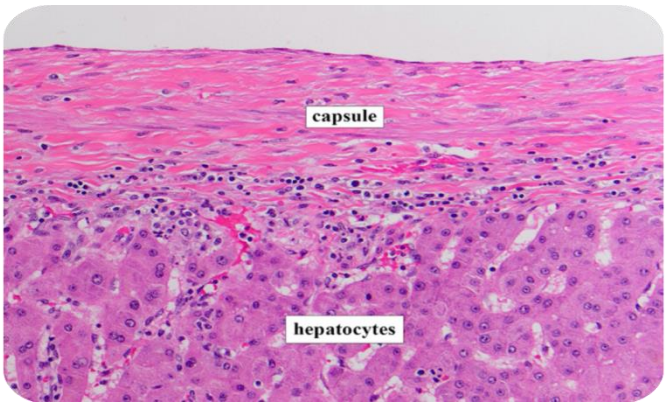
-Oxygenated blood flows in from the hepatic artery

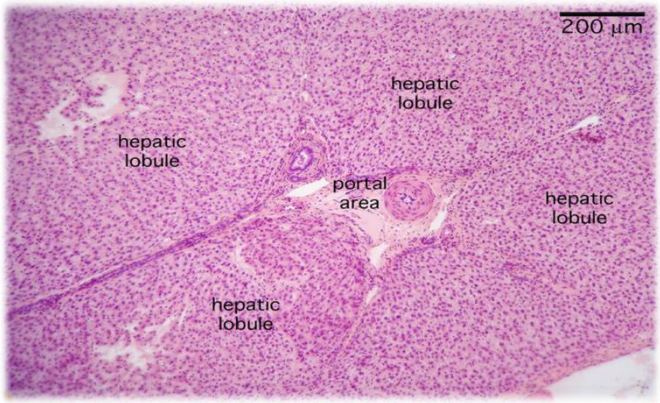
-Nutrient-rich blood flows in from the hepatic portal vein

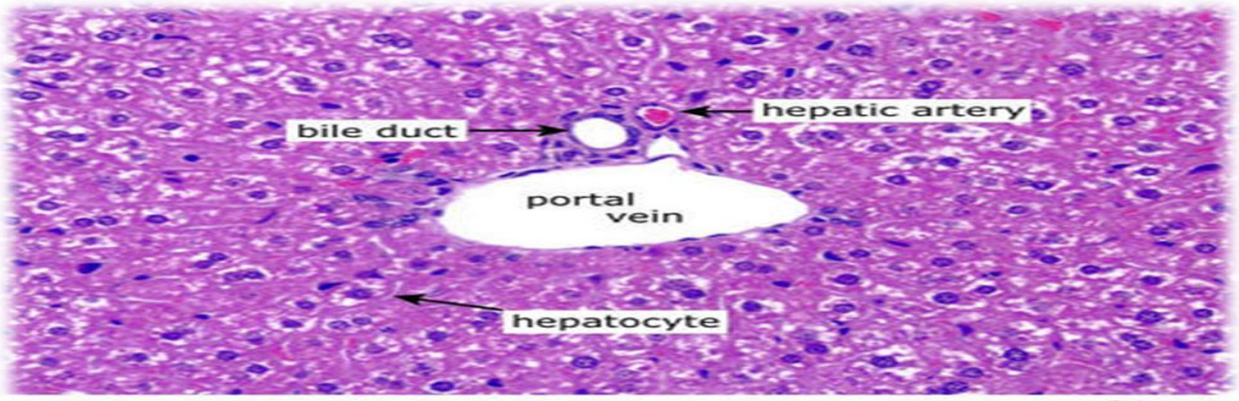




Histologically: The main hepatic cell type is the hepatocyte with its different specialized domains, such as the sinusoidal, the lateral and the canalicular. Between hepatocytes cordons there are tortuous vascular channel named sinusoids, lined by fenestrated endothelial cells allowing blood plasma freely moving from vessel to perisinusoidal space of Disse facing the hepatocytes. Resident macrophages ،such as Kupffer cells and circulating monocyte ،with lymphocytic cells ،such as NK cells, play roles in the maintenance of immune tolerance in the liver or in the activation of pro-inflammatory responses.







FUNCTIONS

1. Manufacture and excretion of bile.

2 .Manufacture of several major plasma proteins such as albumin, fibrinogen and prothrombin.

3 .Metabolism of proteins, carbohydrates and lipids.

4 .Storage of vitamins (A, D and B12) and iron.

5 .Detoxification of toxic substances such as alcohol and drugs.

Patterns of Hepatic injury

1.**Degeneration** (Ballooning ,feathery degeneration ,fat, pigments(hemosiderin, bile)

2. **Inflammation** (viral or toxic).

3. **Neoplasia** : (99% metastasis , 1% primary).

INFECTIOUS DISORDERS

The liver is almost always involved in blood –born infection such as :

- Bacterial infections (pyogenic abscesses, military tuberculosis, salmonellosis)
- Parasitic infections (malaria, amebiasis).
- Fungal infections (candidiasis).
- Viral Infections (EBV, CMV ,hepatitis)

Viral Hepatitis

Hepatitis is used to describe infection of the liver caused by hepatotropic viruses. Currently there are 5 main varieties of these viruses causing distinct types of viral hepatitis:

- **Hepatitis A virus (HAV)**, causing a faecally-spread selflimiting disease.
- **Hepatitis B virus (HBV)**, causing a parenterally transmitted disease that may become chronic.
- **Hepatitis C virus (HCV)**, previously termed non-A, non-B (NANB) hepatitis virus involved chiefly in transfusion-related hepatitis.
- **Hepatitis delta virus (HDV)** which is sometimes associated as superinfection with hepatitis B infection.

- **Hepatitis E virus (HEV)**, causing water-borne infection.

While HBV is a DNA virus, all other human hepatitis viruses are RNA viruses.

Hepatitis A Virus (HAV)

HAV usually is a benign self-limited infection that does not cause chronic hepatitis and rarely (in about 0.1% of cases) produces fulminant hepatitis. HAV has an incubation period of 3-6 weeks. It is typically cleared by the host immune response, so it does not establish a carrier state.

HAV is spread by ingestion of contaminated water and food and is shed in the stool for 2 to 3 weeks before and 1 week after the onset of jaundice. Thus, close personal contact with an infected individual or fecal-oral contamination accounts for most cases . Most frequently affected age group is 5-14 years; adults are often infected by spread from children.

HAV, is a small, 27 nm diameter, icosahedral non-enveloped، single-stranded RNA virus. Because HAV viremia is transient, blood-borne transmission is very rare; therefore, donated blood is not specifically screened for this virus.

Hepatitis B Virus (HBV)

The outcome of HBV infection varies widely:

1. Acute hepatitis with recovery and clearance of the virus
2. Non-progressive chronic hepatitis.
3. Progressive chronic disease ending in cirrhosis
4. Fulminant hepatitis with massive liver necrosis.
5. An asymptomatic “healthy” carrier state.

HBV has a prolonged incubation period (2–26 weeks).Unlike HAV, HBV remains in the blood during active episodes of acute and chronic hepatitis. Approximately 70% of adults with newly acquired HBV have mild or no symptoms and do not develop jaundice. The remaining 30% have nonspecific constitutional symptoms such as anorexia، fever, jaundice, and right upper-quadrant pain.

It is transmitted parenterally such as in recipients of blood and blood products، intravenous drug addicts, patients treated by renal dialysis and hospital workers exposed to blood, and by intimate physical contact such as from mother to child and by sexual contact, where it present in all physiological and pathological fluids . The disease may occur at any age.

Hepatitis C Virus (HCV):

HCV is a major cause of liver disease. Hepatitis C infection is acquired by blood trans fusions، blood products, haemodialysis, parenteral drug abuse and accidental cuts and needle-pricks in health workers. Hepatitis C has an incubation period of 20-90 days (mean 50 days). Clinically, acute HCV hepatitis is milder than HBV hepatitis but HCV has a higher rate of progression to chronic hepatitis than HBV. Persistence of infection and chronic hepatitis are the key features of HCV. Occurrence of cirrhosis after 5 to 10 years and progression to hepatocellular carcinoma are other late consequences of HCV infection. Currently, HCV is considered more important cause of chronic liver disease worldwide than HBV. HCV is a single-stranded، enveloped RNA virus.

Hepatitis D Virus (HDV):

Also called the delta agent, 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.

HDV RNA is detectable in the blood and liver at the time of onset of acute symptomatic disease.

Hepatitis E Virus (HEV)

HEV is an enterically transmitted, water-borne infection that usually produces a self-limiting disease. The virus typically infects young to middle-aged adults. A characteristic feature of HEV infection is the high mortality rate among pregnant women.The average incubation period following exposure is 4 to 5 weeks.

Clinical features and outcome of Viral hepatitis

1. Acute Asymptomatic Infection With Recovery.
2. Fulminant Hepatic Failure
3. Chronic Hepatitis.
4. The Carrier State.

Pathological features of viral hepatitis

Acute viral hepatitis:

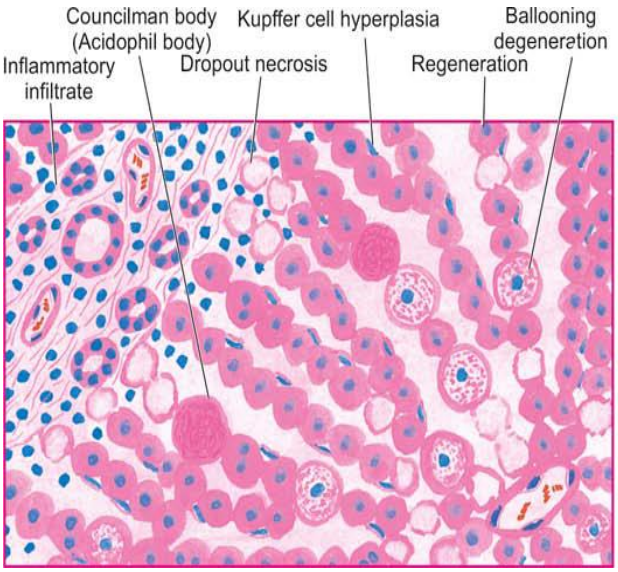
1. Hepatocellular injury : (Ballooning degeneration, Acidophilic degeneration , Dropout necrosis and Bridging necrosis) .

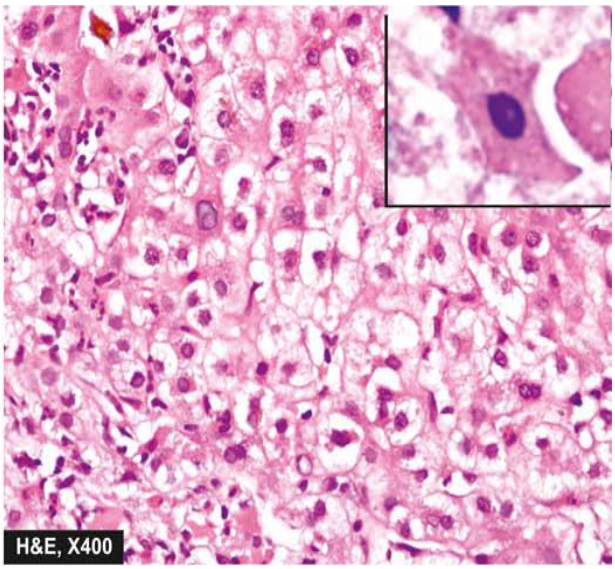
2 .Inflammatory infiltrate by mononuclear inflammatory cells, usually in the portal tracts, but may permeate into the lobules.

3 .Kupffer cell hyperplasia: There is reactive hyperplasia of Kupffer cells many of which contain phagocytosed cellular debris, bile pigment and lipofuscin granules.

4 .Cholestasis Biliary stasis is usually not severe in viral hepatitis .

5 .Regeneration : As a result of necrosis of hepatocytes، there is lobular disarray. Surviving adjacent hepatocytes undergo regeneration and hyperplasia. If the necrosis causes collapse of reticulin framework of the lobule, healing by fibrosis follows, distorting the lobular architecture.





Chronic hepatitis:

1 .Piecemeal necrosis as periportal destruction of hepatocytes at the limiting plate .

2 .Inflammatory cell infiltration by lymphocytes, plasma cells and macrophages .

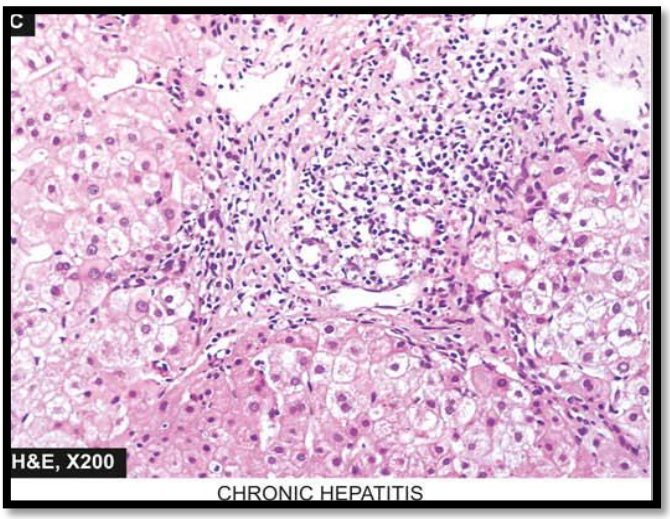
3 . Generally, the architecture of lobule is retained in mild to moderate chronic hepatitis.

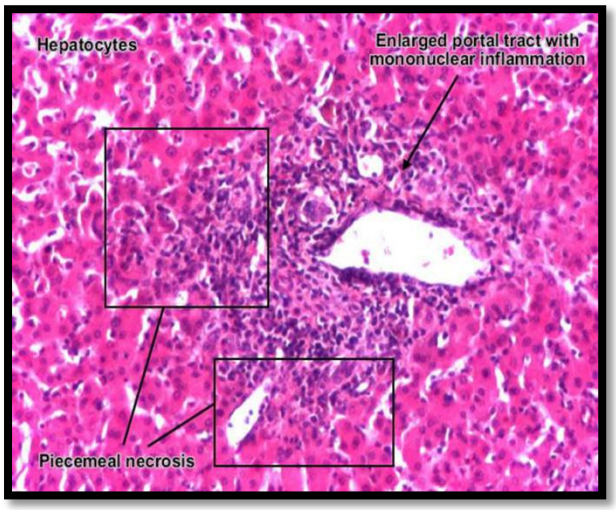
4. There are focal areas of necrosis and inflammation within the hepatic parenchyma and Scattered acidophilic bodies in the lobule.

5. Kupffer cell hyperplasia.

6. More severe form of injury shows bridging necrosis(i.e. bands of necrosed hepatocytes that may bridge portal tract-to-central vein, central vein-to-central vein, and portal tract-to-portal tract).

7. Bridging fibrosis: The onset of fibrosis in chronic hepatitis from the area of interface hepatitis and bridging necrosis is a feature of irreversible damage and liver cirrhosis.





ALCOHOLIC LIVER DISEASE

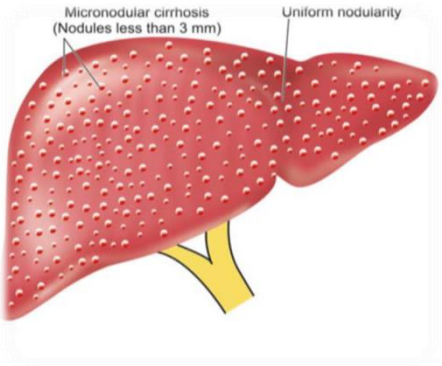
Alcoholic liver disease is the term used to describe the spectrum of liver injury associated with acute and chronic alcoholism. Excessive ethanol consumption causes more than 60% of chronic liver disease in Western countries and accounts for 40% to 50% of deaths due to cirrhosis. There are three sequential stages in alcoholic liver disease:

1.**Alcoholic steatosis** (fatty liver): Hepatocellular fat accumulation typically begins in centrilobular hepatocytes.

2.**Alcoholic hepatitis**: develops acutely, usually following a bout of heavy drinking. Repeated episodes of alcoholic hepatitis superimposed on pre-existing fatty liver are almost certainly a forerunner of alcoholic cirrhosis.

3. **Alcoholic cirrhosis**: is the most common form of lesion.

Grossly, alcoholic cirrhosis classically begins as micronodular cirrhosis (nodules less than 3 mm diameter), the liver being large, fatty and weighing usually above 2 kg. The surface of liver in alcoholic cirrhosis is studded with diffuse nodules which vary little in size, producing hobnail liver .



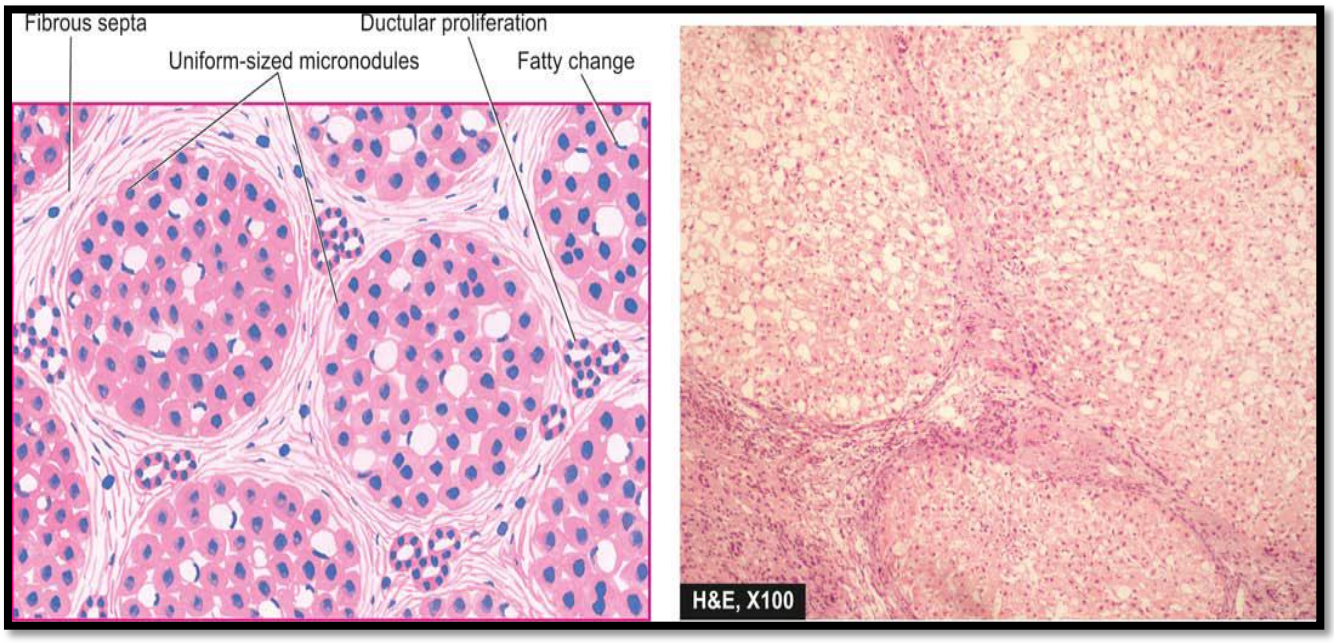
Microscopically, alcoholic cirrhosis is a progressive alcoholic liver disease. Its features include the following

i) Nodular pattern: Normal lobular architecture is effaced in which central veins are hard to find and is replaced with nodule formation.

ii) Fibrous septa: The fibrous septa that divide the hepatic parenchyma into nodules are initially delicate and extend from central vein to portal regions, or portal tract to portal tract, or both.

iii) The hepatocytes in the islands of surviving parenchyma undergo slow proliferation forming regenerative nodules having disorganized masses of hepatocytes. The hepatic parenchyma within the nodules shows extensive fatty change early in the disease. But as the fibrous septa become more thick, the amount of fat in hepatocytes is reduced.

iv) Necrosis, inflammation and bile duct proliferation.

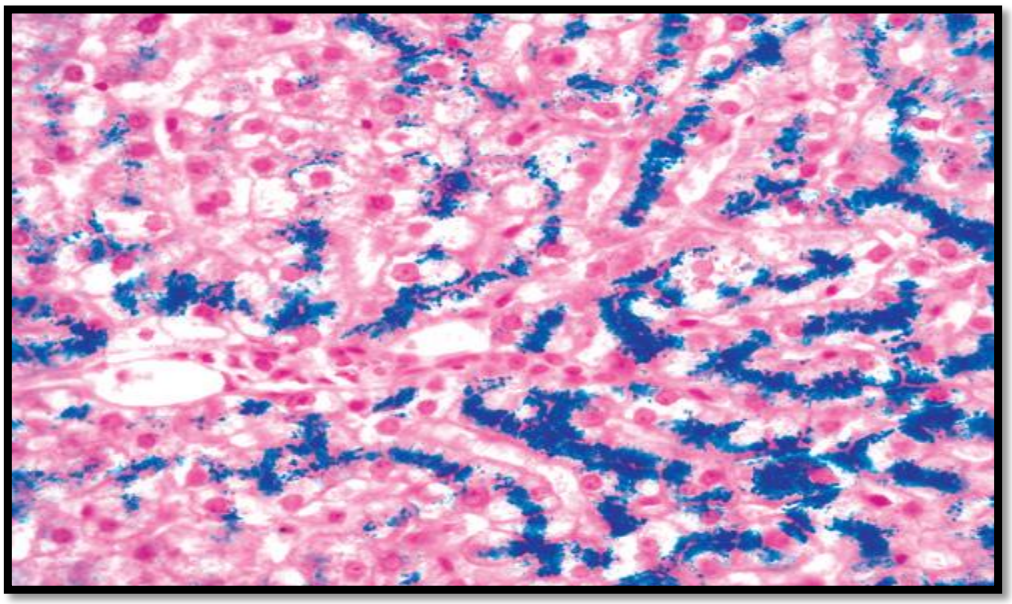


Hemochromatosis

Hemochromatosis is caused by excessive absoprtion of iron, which is primarily deposited in parenchymal organs such as the liver and pancreas, as well as in the heart، joints, and endocrine organs.

1. Hereditary hemochromatosis (Primary) : an inherited disorder, result from mutation in HFE gene.
2. Acquired hemochromatosis (Secondary) : occurs as a consequence of parenteral administration of iron , ineffective erythropoiesis, cases with thalassemia and myelodysplastic syndromes.

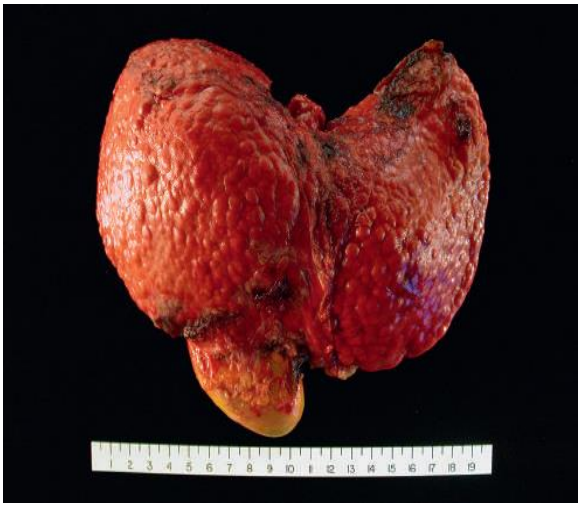
   The morphologic changes in severe hemochromatosis are characterized principally by (1) Tissue deposition of hemosiderin in many organs such as liver، pancreas, myocardium, pituitary gland, adrenal gland, thyroid and parathyroid glands, joints, and skin.
   (2) cirrhosis .
   (3) pancreatic fibrosis.
   - In the liver, iron becomes evident first as golden-yellow hemosiderin granules in the cytoplasm of periportal hepatocytes, which can be histochemically stained with **Prussian blue** .
   - With increasing iron load, there is progressive deposition in the rest of the lobule, the bile duct epithelium, and Kupffer cells. At this stage, the liver typically is slightly enlarged and chocolate brown.

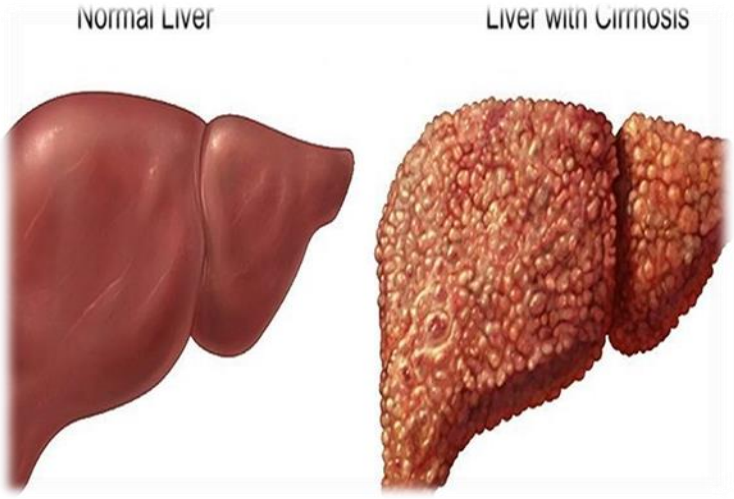


CIRRHOSIS

Cirrhosis is the end-stage of chronic liver disease & is defined by three characteristics:

1-Bridging fibrous septae in the form of delicate or broad bands of fibrosis that link portal tracts with one another and portal tracts with centrilobular veins.
2 .Parenchymal nodules containing regenerating hepatocytes encircled by fibrosis. with diameters varying from very small micronodules to large macronodules.
3 .Disruption of the architecture of the entire liver.



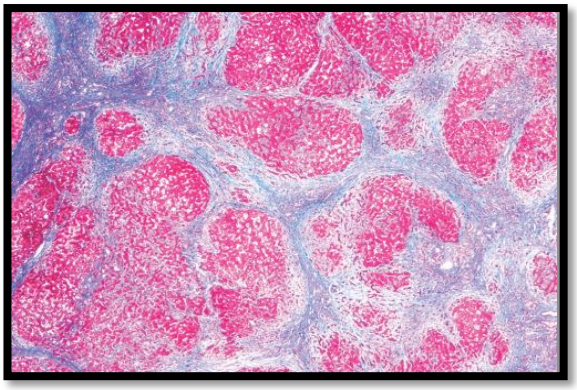


Classification of cirrhosis

The only satisfactory classification of cirrhosis is based on the underlying etiology. The established causes of cirrhosis:
1 .Alcoholic liver disease (70% in Western countries)
2. Viral hepatitis (a very common cause in our country).
3. Biliary diseases
4.Primary hemochromatosis
5. Wilson disease
6. al-Antitrypsin deficiency
7. Cryptogenic cirrhosis

Pathogenesis of cirrhosis

The central pathogenetic processes in cirrhosis are progressive fibrosis and reorganization of the vascular microarchitecture of the liver. In cirrhosis, types I and III collagen are deposited in the lobule, creating delicate or broad septal tracts. New vascular channels in



the septae connect the vascular structures in the portal region (hepatic arteries and portal veins) and terminal hepatic veins.
In cirrhosis death is usually due to one or more of the following:

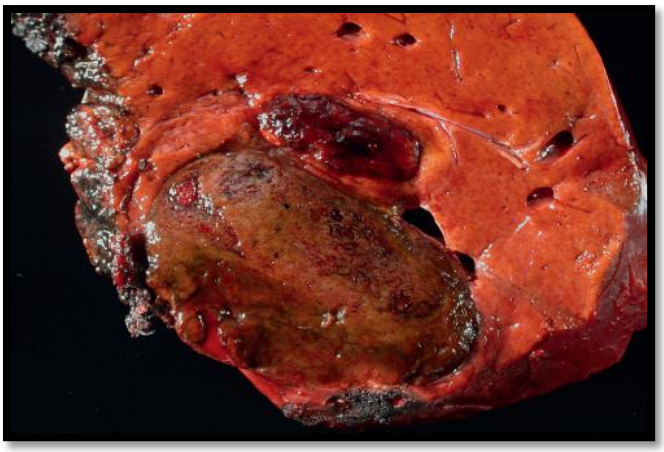
1. Progressive liver failure.
2. Portal hypertension related complications
3. The development of hepatocellular carcinoma

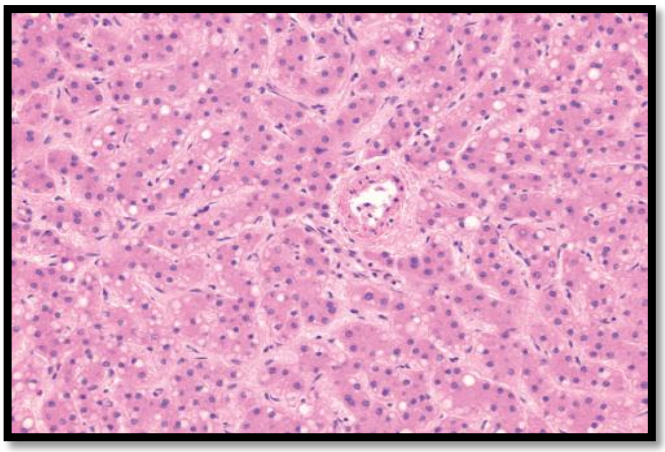
Thick bands of collagen separate rounded cirrhotic nodules.

Benign Tumors

Cavernous hemangiomas : are most common benign lesions of the liver . These well-circumscribed lesions consist of vascular channels and intervening stroma. They appear as discrete red-blue, soft nodules, less than 2 cm in diameter, often directly beneath the capsule.

Hepatic (liver cell) Adenoma : usually occurs in women of childbearing age who have used oral contraceptive steroids, and it may regress on discontinuance of hormone use. The tumor is yellow-tan, well demarcated nodules, up to 30 cm in diameter and is often located beneath the capsule.It is composed of sheets and cords of cells that may resemble normal hepatocytes with prominent arteries and veins.





Hepatocellular Carcinomas (HCC)

The incidence (generally 5% of all cancers) varies widely in different areas of the world. More than 85% of cases occur in countries with high rates of chronic HBV infection e.g. Asian and African countries.

Pathogenesis:

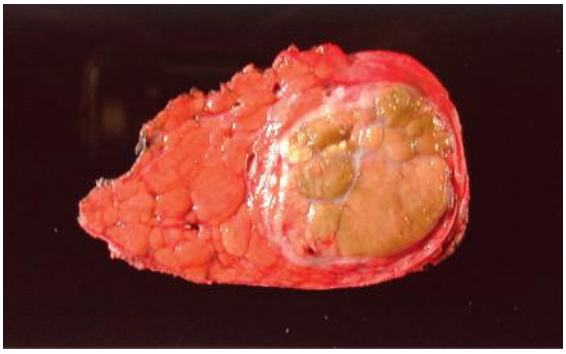
Three major etiologic associations have been established:

1. Infection with HBV or HCV
2. Alcoholic cirrhosis
3. Aflatoxin exposure,substances made by a fungus that contaminates peanuts, wheat, soybeans, ground nuts, corn, and rice is a major risk factor for liver cancer

Gross features:

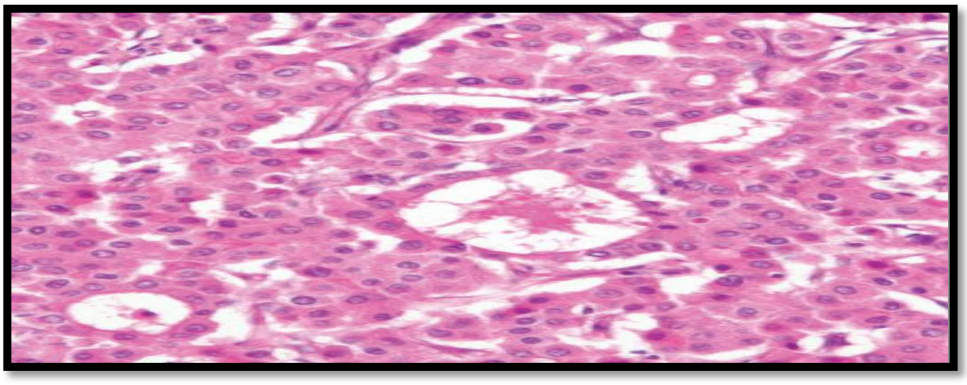
There are three gross forms of HCC.

1. **Unifocal** , usually a massive tumor
2. **Multifocal** , i.e. made of variably sized nodules
3. **Diffusely infiltrative**, i.e. permeating widely and sometimes involving the entire liver.



Microscopic features:

1. HCCs range from well-differentiated to poorly differentiated lesions. In well differentiated HCC the neoplastic hepatocytes are arranged in broad trabeculae which are separated by sinusoids.
2. Central necrosis in the broad trabeculae may produce a pseudoglandular Pattern.
3. Poorly differentiated tumors are composed of large multinucleate anaplastic tumor giant cells.
4. In the better differentiated variants, globules of bile may be found within the cytoplasm of cells and in pseudocanallouli between cells.
5. Mallory bodies may be found within the cytoplasm of the neoplastic cells.
6. HCC displays scant connective tissue stroma (that is why it is soft in consistency



GALLBLADDER DISEASES

Cholelithiasis (Gallstones)

Gallstones trouble up to 20% of adult populations and are mainly of two types :

1. Cholesterol stones: composed of crystalline cholesterol monohydrate (80%)
2. Pigment stones : composed predominantly of bilirubin calcium salts (20%).

Pathogenesis and Risk Factors

The majority of individuals with gallstones (80 %) have no identifying risk factors

Contributory risk factors include :

1 .**Age and gender**: the incidence of gall stones increases with age in that only 5% of the population younger than age 40 but 25% of those older than 80 years develop stones. The prevalence in women is about twice as high as in men.

2. **Ethnic and geographic**: gallstones are more prevalent in Western industrialized societies and uncommon in developing ones.

3. **Heredity family history** imparts increased risk.

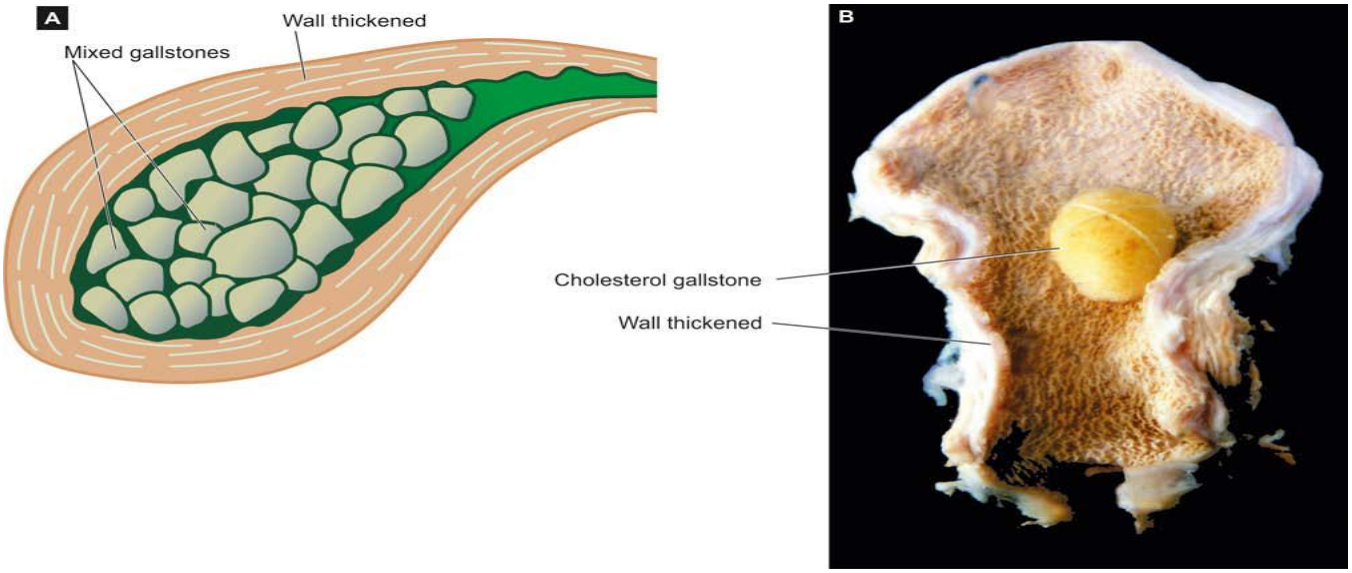
4 **Environment**: estrogenic influences, including oral contraceptives and pregnancy, increase hepatic cholesterol uptake and synthesis, leading to excess biliary secretion of cholesterol.

5. **Obesity, rapid weight loss.**

Cholecystitis

This may be acute, chronic, or acute superimposed on chronic, and almost always occurs in association with gallstones. Its epidemiologic distribution closely parallels to that of gall stones.

Chronic Cholecystitis : may be the sequel to repeated bouts of acute cholecystitis, but in most instances it develops de novo, it is almost always associated with gallstones but these do not seem to have a direct role in the initiation of inflammation.



Pathological feature

1-The changes are extremely variable and sometimes minimal.

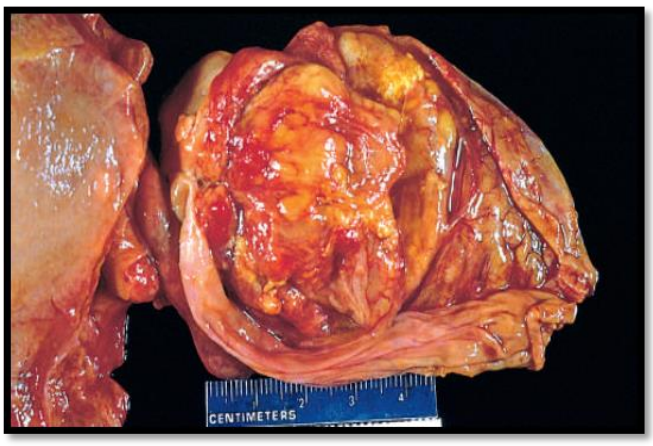
2-The mere presence of stones within the gallbladder, even in the absence of acute inflammation, is often taken as sufficient justification for the diagnosis.

3-The gallbladder may be contracted, of normal size, or enlarged.

4-The submucosa and subserosa are often thickened from fibrosis.

TUMORS

Carcinoma of Gallbladder is the most frequent malignant tumor of the biliary tract.



Gross features

The cancer is either exophytic (fingating) or infiltrative growth .

Microscopic features

-Well- to poorly differentiated infiltrative adenocarcinomas that is sometimes papillary .

-By the time gallbladder cancers are discovered most have invaded the liver directly and many have extended to the cystic duct and adjacent bile ducts and lymph nodes.