Normal liver

Anatomical Considerations

- The liver is formed of hexagonal lobules with a central vein in the center and portal triad at the corners.
- Cords or plates of liver cells are only one cell thick (detected by silver stain).
- Plates are separated by blood sinusoids lined by endothelium and contain Von-Kupffer cells.
- Hepatocytes at the periphery of the lobules facing portal tracts are called the limiting plates.
- Blood enters the liver through branches of the portal vein and hepatic artery.
- These empty into the sinusoids nearest to the portal area and so, the peripheral part of the lobule has the richest blood supply.
- The central part of the lobule has the poorest blood supply and therefore, it is most susceptible to anoxia and other types of injury.
Acinus-Lobule

1- A more physiological way to view hepatic histology is in terms of simple acinus.
2- It is a spherical structure arranged around the major branches of the portal tract. It has a terminal portal triad in its center.
3- The spherical portion of the parenchyma surrounding this is referred to as acinar zone
   (1) outside this is zone (2) and the circulatory periphery is zone (3).

Functions of the liver

- **1- Metabolism** of almost all nutrients entering the body and detoxification of toxic substances.
- **2- Storage** of most lipids and carbohydrates.
- **3- Secretion** of:
  a. Albumin
  b. Prothrombin and other coagulation factors (fibrinogen, factors V, VII, VIII, IX, X, XI, XII)
  c. Acute phase proteins (C reactive protein, serum amyloid associated)
  d. Binding and carrier proteins (transferring, ceruloplasmin).
- **4- Excretion**....of bile into the intestine. Bile contains cholesterol

Assessment of liver functions (Liver Function Tests)

- **A - Liver cell integrity**
  By measuring serum enzymes that are liberated from damaged liver cells.
  These are:-
  1- Aspartate aminotransferase (AST),
2- Alanine aminotransferase (ALT)
3- Lactic dehydrogenase (LDH).
- These enzymes are not liver specific.

**B- Hepatic secretory functions**
1- Serum albumin level...normal 3.5-5 gm/dl
2- Coagulation factors...by prothrombin time (normal 11-15 sec.).

**C- Biliary excretion tests**
1- Serum bilirubin.....increased in all types of jaundice
2- Serum alkaline phosphatase.......not specific for the liver
3- Serum Gamma Glutamyltransferase (GGT)...a specific hepatic enzyme.
- Elevation of this enzyme is a reliable test for biliary obstruction.

**Liver Cell Necrosis**

<table>
<thead>
<tr>
<th>1- Necrosis with intact framework:</th>
<th>2- Necrosis with destroyed framework</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apoptosis.</td>
<td>Pan-acinar necrosis which may be</td>
</tr>
<tr>
<td></td>
<td>a. Sub massive or</td>
</tr>
<tr>
<td>Piecemeal necrosis</td>
<td>b. Massive</td>
</tr>
<tr>
<td>Focal necrosis</td>
<td></td>
</tr>
<tr>
<td>Bridging (confluent) necrosis</td>
<td></td>
</tr>
</tbody>
</table>

**Apoptosis**

**Definition:**- single cell death

**Causes:**- * Acute viral hepatitis * Yellow fever

**Pathology**

- Cell undergoes acidophilic necrosis
- Cytoplasm is granular & dense
- Nucleus is pyknotic. When the nucleus is extruded, **Councilman body** is produced
- **S&S:** No jaundice

**Fate and complications:**- Regeneration is complete.

2- Piecemeal necrosis (Interface hepatitis)

Def.:- Apoptosis of peripheral hepatocytes resulting in moth-eaten appearance of the limiting plate. (interface hepatitis)
**Causes:** - chronic hepatitis - sub massive hepatic necrosis.

**Pathology:**
- **Gross:** No abnormality
- **M/E:** Irregular, moth eaten limiting plate
- **S&S:** no jaundice

**Fate & complications:** Regeneration is complete

3- **Focal (Spotty) necrosis**

**Def:** Necrosis of small groups of hepatocytes within the lobule.

**Causes:** Acute viral hepatitis, toxaemia, viraemia, etc.

**Pathology**
- **Gross:** Yellow dots
- **M/E:** Necrotic foci accumulate macrophages, lymphocytes, and may be neutrophils
- **S&S:** May be jaundice

**Fate & complications:** Regeneration is complete

4- **Bridging (Confluent) necrosis**

- Involves large groups of hepatocytes in more than one lobule resulting in collapse of reticulin framework of the affected lobules and connection between liver structures.
- Occurs with chronic hepatitis & sub massive hepatic necrosis
- There's collapse of the reticulin framework

**S&S:** Jaundice is always present

![Apoptosis, Piecemeal, Focal, Confleunt](image)

*Panacinar necrosis*

- It is extensive necrosis of all hepatocytes and their supporting framework in a simple acinus. Necrotic cells fragment and rupture.
- **It is caused by:** acute viral hepatitis & hepatotoxic agents e.g halothane, CCl4
- Necrosis varies from sub massive to massive. **Jaundice** is always found.
Death is due to fulminant acute hepatocellular failure.

Hepatitis
It is inflammatory process of the liver. It produces jaundice and may lead to hepatic failure.

*Acute viral hepatitis:* It is primary hepatic infection caused by specific hepatotropic viruses.

*Causative agents:* Include hepatitis A, B, (C), Delta agent, E and hepatitis G.

Pathogenesis:
- **Liver cell injury:** caused by
  - a. direct cytopathic effect
  - b. cytotoxic T lymphocytes.
- **Extra hepatic lesions:** caused by circulating immune complexes

Hepatitis A virus (HAV)

- **Structure:** Non enveloped RNA virus
- **Transmission:** Oro-fecal (infective hepatitis)
- **Age:** Less than 15 years
- **I.P:** 2-4 wks
- **CLP:** Mild disease - Complete recovery within 4-6 wk-
  - **Chronic hepatitis:** Not present

* Fulminant hepatitis:* Very few cases 0.1-0.4%

* Carrier state:* Not present

* HCC:* No relation

Death:* 1% of cases

Hepatitis B virus (HBV)

- **Structure** Dane particle formed of DNA core covered by a lipoprotein coat
  - **Mode of infection:** Parenteral, Sexual, Vertical transmission, close personal contact
**Age**: All ages are affected

**I.P:** 8-12 wks

**C/P**: More severe Recovery within 3-4 months.

* **Chronic hepatitis**: Found in 5% of patients. Indicated by hepatocytes having HBs Ag 6 months after the onset of the disease

**Fulminant hepatitis** More common

* **Carrier state**: 5% of cases. Their hepatocytes have ground glass cytoplasm and sanded nuclei

* **Hepatocellular carcinoma** Yes  

**Death**: 10-20% due to panacinar necrosis

---

A. Ground glass hepatocytes due to the presence of cytoplasmic hepatitis B surface antigen

B. Immunohistochemical staining using anti-Hepatitis B surface antibodies

---

**Hepatitis C Virus (HCV)**

* **Structure**: Enveloped RNA virus  

**Age**: All ages are affected

**I.P.**: Widely variable  

**C/P**: Most cases are mild.

* **Chronic hepatitis**: Found in more than 50% of patients

* **Fulminant hepatitis**: Rare  

**Carrier state**: Present

* **Hepatocellular carcinoma** yes  

**Death**: Panacinar necrosis is common in females.

---

**Hepatitis Delta agent (HD agent)**

* **Structure**: Incomplete virus formed of RNA core antigen + a coat of HBs Ag.

- **Mode of infection**: Blood born

**Age**: All ages are affected  

**I.P.**: Widely variable

- **C/P**: Most cases are mild. 

- Acute hepatitis in 2 cases:

- If associated with acute HBV or in Chronic HBV carrier
- **Chronic hepatitis** Not present

* **Fulminant hepatitis** Severe in co-infection with HBV
  
  *Carrier state*: not present  
  * **Hepatocellular carcinoma** Yes

*Death*: Panacinar necrosis is more common

**Hepatitis E virus (HEV)**

- **Structure**: RNA virus
  
  * **Mode of infection**: Oro-foecal  
  * **Age**: All ages are affected  
  * **I.P**: 3-10 wks  
  * **C/P**: Mild dis.- Severe if ass. With pregnancy.

- **Chronic hepatitis** -Not present

* **Fulminant hepatitis** Few  
  * **Carrier state**: Not present.

* **Hepatocellular carcinoma** No  
  * **Death**: few cases, 20% of pregnant females.

**Pathology of acute viral hepatitis**

- It is the same irrespective of the causative agent. It may take one of two forms.
  1. Typical viral hepatitis with focal necrosis.
  2. Acute viral hepatitis with panacinar necrosis (fulminant viral hep.) necrosis may be massive or sub massive.

1. **Typical viral hepatitis with focal necrosis**

  * **Gross**: Liver is slightly enlarged.

- Color may be red (congestion) with green areas (cholestaisis)

**M/E of Affection can be discussed under 4 main items**:-

1. **Hepatocytes**  
2. Inflammatory cellular infiltrate.
3. **Acute cholestaisis**  
4. Recovery

1. **Hepatocytes**

2. Feathery degeneration: Hepatocytes are swollen and bile stained
3. Fatty change is rare except with HCV.
4. Necrobiosis (apoptosis) ending in Councilman bodies.
5. Focal necrosis.
6. Many hepatocytes appear normal

2-Inflammatory cellular infiltrate.

Found in... 1- Portal tracts..... Lymphocytes and macrophages (mainly).
- Eosinophils and plasma (occasionally)
2- Focal lobular necrotic foci..... macrophages and lymphocytes. May be neutrophils

3) Acute cholestasis
- Due to obstruction of bile canaliculi, obstruction is caused by....
  i) Swollen, degenerated necrotic hepatocytes.
  ii) Cholangiolitis i.e. inflammation of intralobular bile canaliculi.
     - Bile canaliculi above the obstruction are dilated and filled with bile. It may form bile plugs or thrombi.
     - Intracytoplasmic bile droplets accumulate in hepatocytes (feathery degeneration) and in von-Kupffer cells
4) Recovery

- Active von Kupffer cells show hypertrophy and hyperplasia with increased phagocytosis.
- There’s increased cellularity due to increased number of von Kupffer and inflammatory cells.
- Regeneration of hepatocytes begins after 3 weeks and continues for weeks to few months. It is complete regeneration.
- The surviving hepatocytes show hypertrophy, hyperplasia and increased mitotic activity with occasional binucleated and multinucleated cells.

2-Acute viral hepatitis with panacinar necrosis (fulminant viral hepatitis)
Necrosis may be: - a- Submassive or b- Massive hepatic necrosis

a- Massive hepatic necrosis

- **Grossly:**
  1- Liver gets smaller in size (500 gm), soft, with wrinkled capsule.
  2- It is red in colour (congestion) with areas of haemorrhage.
  3- Necrosis appears as yellow patchy foci or large areas
M/E 1- Extensive hepatocyte necrosis with few surviving ones.
2- Empty reticulin framework collapses forming loose meshwork septa.
3- Portal tracts show moderate mononuclear inflammatory infiltrate

**Prognosis:**
1- Death in 80% of cases due to hepatocellular failure in 10-21 days.
2- Survivors may develop post necrotic scarring.
3- There’s no carriers due to the destruction of the viral antigens. There is long life immunity to the causative virus

b- Submassive hepatic necrosis

**Grossly:**
1- Liver gets smaller in size.
2- Necrosis appears as yellow foci which may fuse together.

**M/E:**
1- Necrosis may be confined to the center of the lobules.
2- Bridging necrosis and piecemeal necrosis are uncommon. If they are present, they indicate a more severe attack.

**Prognosis:**
1- Death due to hepatocellular failure
2- Surviving with little scarring.
3- Presence of piecemeal necrosis and/or confluent (bridging) necrosis 3-6 months after the onset of the disease indicates chronicity.

**Signs and symptoms of acute viral hepatitis**

1- Hepatic manifestations:
2- Extra hepatic manifestations:

1- Hepatic manifestations:
   - **Typical (classical) cases:**
     - Jaundice: According to its intensity
       - Non-icteric hepatitis: very mild jaundice, mild disease
     - Icteric hepatitis: jaundice is due to acute cholestasis.
   - Cholestatic viral hepatitis is characterized by more deep jaundice.
   - Fulminant viral hepatitis: hepatocellular failure.
2- Extra hepatic manifestations

**Preicteric (early) phase:** - serum sickness-like syndrome, urtcaria, skin rashes and may be polyarteritis. These manifestations subside with the appearance of jaundice

**Late in the disease:** - Vasculitis, glomerulonephritis and arthritis.
- Splenomegaly in 1/3 of cases.

* Fate of acute viral hepatitis:-
  - **Typical (classical) cases:**
    a) **Complete recovery**... anicteric cases after weeks, icteric cases after 4 wks to 4 months and cholestatic cases after months to years.
    b) **Chronicity** that may progress to cirrhosis
    c) **Chronic carriers** in whom the viral antigens are excess in hepatocytes and may reach the blood. These may have increased risk of hepatocellular carcinoma.
  - **Cases with panacinar necrosis**
    a) Death rate 70-90%.
    b) **Postnecrotic scarring may result in:** * portal hypertension
        * liver failure  * increased risk of hepatocellular carcinoma.

**Chronic Hepatitis**

*Definition:-*
  - It is the continuity of hepatitis symptomatic or biochemical (elevated enzymes or presence of viral antigens) without steady improvement for more than 6 months.

*Causes*
1. Following acute viral hepatitis (esp. HBV or HCV).
2. Drug induced (a methyl dopa & isoniaside).
3. Autoimmune (lupoid hepatitis) which is more common in females around the menopause.
4. α-1-antitrypsin deficiency, Wilson's disease and primary biliary cirrhosis
5. Many cases are of unknown causes.
*Pathogenesis:* May be an auto-immune mechanism.
*Pathology:*
- **Gross:** liver slightly enlarged - Surface may be smooth or nodular.
- **M/E:** According to Ishak score, chronic hepatitis range from very mild to severe according to the grade (degree of necrosis and inflammation) and the stage (extent of fibrosis)

1. **Necro-inflammatory changes (Grade)**
   - Considering the presence or absence and the extent of
     a. Piecemeal necrosis
     b. Lobular necrosis
     c. Lobular inflammation
     d. Portal inflammation
   - These items correlate to the activity of the lesion.
     - Each of these item is given a score number (0- 4 or0-6 ).
     - The sum of score is evaluated as minimal activity (0-3) mild activity (4-7) moderate activity (8-13) and severe activity (more than 13/18)

2. **Fibrosis (stage) :-**
   - Considering the presence and extent of fibrosis
     a. Portal fibrosis (1)
     b. Portal and periportal fibrosis (2)
     c. Septal fibrosis (3)
     d. Bridging fibrosis (4)
     e. Incomplete cirrhosis (5)
     f. Cirrhosis (6)....end stage liver lesion

**Chronic Hepatitis - Prognosis**
1- Remission especially with hepatitis C. It may be spontaneous or drug induced, it occurs with lower grades and stages of chronic hepatitis.

2- Severe disease with high mortality especially with hepatitis B or Delta agent.

3- Cirrhosis (end stage liver).

4- Hepatocellular carcinoma especially with hepatitis B.

Liver Suppuration

1- Single (solitary) abscess  Causes:
   • a- penetrating wounds  b- Secondary infected amoebic or hydatid cyst  
     c- Spread from gall bladder, subphrenic abscess or empyema.

2- Multiple abscesses  Causes:
   a- Acute ascending bacterial cholangitis and cholangiolitis due to obstruction.
   b- Suppurative phlebitis :: septic focus in the abdomen or pelvis reaches the liver Through the portal vein (portal pyaemia & portal pyelophlebitis)
   c- systemic pyaemia via hepatic artery.

Pathology:
   - Size  single abscess may reach a large size
     Multiple abscesses vary in size from microscopic to 1-3 cm. In diameter.

Abscess is acute and pus may be bile stained. It may extend to the sub diaphragm.

Complications:-
   - Rupture of the abscess leading to peritonitis.
   - Rarely, a sub diaphragmatic abscess ruptures into the thoracic cavity.
Liver cirrhosis

- It is a chronic, progressive diffuse process characterized by
  a. Hepatocellular necrosis  
  b. Replacement by fibrosis and inflammation  
  c. Hyperplasia of surviving liver cells forming regenerating nodules  
  d. Vascular derangement.
  
  All these changes lead to loss of the normal liver architecture.

Pathology of cirrhosis

Gross: - Size.. At first the liver is enlarged or of normal size. Later in the disease, it is reduced in size and weight (may be less than one kilogram).

Consistency.. Firm.

Colour.. May be yellow (fatty change), red (congestion), green (cholestasis), or pale gray (recent nodules due to absence of pigment).

Surface and cut surface.. shows regenerating nodules..

According to the size of these nodules, cirrhosis can be classified

Morphologically into:-

♣ Micronodular (regular) cirrhosis..... Small nodules 2-3 mm.in diameter.
♣ Macronodular (irregular) cirrhosis... nodules up to one cm in diameter.
♣ Mixed cirrhosis is the end stage of all types of cirrhosis.

Microscopic picture
1- **Regenerating nodules**
- Proliferated hepatocytes arranged in thick plates and separated by blood sinusoids. Central vein in abnormal sites (eccentric)
- Hepatocytes may be small, large, or binucleated

2- **Fibrosis**
- It replaces damaged hepatocytes. It develops at certain sites:
  - a-perivenular
  - b-perisinusoidal
  - c-pericellular
  - d-in relation to portal tracts.
- It may be young, cellular and highly vascular or mature with diminished vasculsarity. It encloses groups of hepatocytes, lobules or regenerating nodules.
- As a result of hepatocyte injury and fibrosis, **there's loss of normal liver architecture including the lobular and acinar pattern as well as the liver cell plates**

3- **Bile ductular proliferation:**
- Occurs in the fibrous septa. Focal choestaisis with feathery degeneration of hepatocytes occur at the margins of regenerating nodules. It becomes diffuse terminally.

4- **Inflammatory cells:**
- Lymphocytes, macrophages and plasma cells infiltrate the fibrous septa and regenerating nodules
Etiological classification of cirrhosis

- **A- Congenital** Occurs at childhood
  1- congenital syphilis
  2- Hereditary diseases:
     a. Primary idiopathic haemochromatosis
     b. Thalassemia
     c. Wilson’s disease
     d. α1-antitrypsin def.
     e. glycogen storage dis.

- **B- Acquired**
  1- Cryptogenic (10-50%).
  2- Alcoholic (30-70%)
  3- Post viral (15-20%)
  4- Biliary cirrhosis (16%) primary or secondary.

---

A. **Congenital Cirrhosis**

- **Primary idiopathic haemochromatosis:** An inborn error of iron metabolism resulting in hepatic iron overload with destruction of hepatic cells resulting in liver cirrhosis

* **Wilson’s disease:** “Hepato-lenticular degeneration”
It is an inborn error of copper metabolism “autosomal recessive”. It leads to deposition of copper in tissues at certain sites.

1- Limbus of the cornea greenish brown coloration (Kayser Fleisher ring)
2- Basal ganglia of the brain.
3- Liver Acute and chronic hepatitis, then micronodular which passes to macronodular cirrhosis

\[\text{Wilson’s Disease}\]

* \text{α-1-antitrypsin defiency}:- It is a rare genetic disease which causes:-

a. Pulmonary emphysema.

b. Liver affection in the form of chronic hepatitis, macronodular cirrhosis and rarely, hepatocellular carcinoma.

- The liver contains PAS positive inclusions representing α-1-antitrypsin.

B- Acquired cirrhosis

1- Alcoholic (nutritional, Laennec’s) cirrhosis:-

Incidence: - Common in western countries, ♂ > ♀, 40-70 years. Affects 10-20 % of alcohol abuse persons.

*Pathology:-
- **Gross:** Liver is at first enlarged (fatty change), then return to normal size and lastly, it becomes slightly reduced in size (1.2 kg or more).
- Cirrhosis is micronodular then macronodular then mixed.

**M/E**

- **a. Hepatocytes:** show fatty change that decreases progressively.
  - Few hepatocytes show increased intracytoplasmic haemochromatosis.
- **b. Fibrous septa:** show - Regular margins between it and regenerating nodules.
  - Moderate lymphocytic infiltrate.
  - Slight bile ductular proliferation.

*Prognosis:* It progresses slowly over few years.

![Alcoholic cirrhosis](image)

2- **Post viral (post hepatitic) cirrhosis (15-20%)**

*Incidence:* Affects ♂♀ Any age.

*Cause:* Viral hepatitis (mostly HBV or HCV)

Acute hepatitis → chronic hepatitis → cirrhosis.

*Pathology*

- **Gross:** - Liver is shrunken (1kg). - Fatty change is absent (except with HCV).
  - Cirrhosis is mixed.
- **M/E:** - *Hepatocytes*... show degeneration, necrosis...etc as other types of cirrhosis.

*Fibrous septa* - They are thick and immature (more cellular and vascular).

- Irregular margins (piece meal necrosis).
- Heavy lymphocytic infiltrate.

*Prognosis:* More rapid course than alcoholic cirrhosis.

Hepatocellular carcinoma is more liable to occur

3- **Biliary cirrhosis (16%)**
- It is due diffuse chronic cholestaisis (obstruction of the biliary flow) leading to damage and scarring all over the liver. Two types are known
  1. Primary biliary cirrhosis and
  2. Secondary biliary cirrhosis.

- **Primary biliary cirrhosis**
  - **Definition:** It is destructive chronic inflammation of intrahepatic bile ductules and small ducts leading to micronodular cirrhosis.
  - **Incidence:** Typically affects middle aged women.
    Patients present with fatigue, pruritis and eventually, jaundice.
  - **Cause:** Autoimmune. Patients have autoantibodies directed against mitochondrial enzymes (AMA).
  - **Pathology:**
    - **Gross:** Liver is enlarged, dark green in color (cholestaisis).
    - Cirrhosis is micronodular.
    - **M/E:**
      1. Early, portal tracts show lymphocytes and plasma cell infiltrate the bile ducts and destroy them.
      2. Granulomatous inflammation surrounding the damaged and inflamed bile ducts is the hallmark of (PBC).
      3. Cholestatic changes such as bile ductular proliferation, periportal Mallory’s hyaline and increased copper in periportal hepatocytes.
      4. In the end stage disease, micro nodular cirrhosis occurs and the inflammatory changes subside.

---

**Primary biliary cirrhosis**

-1- 
-2- 
-3- 
-4-
Secondary biliary cirrhosis:

**Definition:** It is extra hepatic (surgical) cholestasis due to prolonged extra hepatic major bile duct obstruction.

**Causes** - Obstruction of hepatic or common bile duct by:
- Congenital biliary atresia.
- Pressure by enlarged LN or tumor.
- Carcinoma of the bile duct, ampulla of Vater or pancreatic head.

**Effects of obstruction:**
- **Complete obstruction** leads to back pressure all over the biliary tract.
  - Damage by inspessated bile.
- **Incomplete obstruction** leads to acute suppurative cholangitis and cholangiolitis.

**Pathology:**
- **Gross:** Liver is enlarged, dark green in colour (cholestatis).
  - Cirrhosis is micronodular.
- **M/E:** Cholestasis allover the biliary tree.
- Feathery degeneration leading to necrosis of hepatocytes. Aggregations of such necrotic cells lead to bile infarcts.
- Bile lakes are formed within hepatic substance due to rupture of biliary tract system.
- Portal tracts show inflammatory reaction in the form of edema, neutrophils, lymphocytes plasma cells and macrophages.
- May be ascending cholangitis and cholangiolitis

**Primary sclerosing cholangitis**
- A chronic liver disease of immunological origin affecting large intrahepatic and extrahepatic bile ducts.
- Affects males younger than 40 years and in 70% of cases it is associated with ulcerative colitis.
- There is segmental fibrosis of bile ducts resulting in obstruction and secondary biliary cirrhosis.
- Incidence of cholangiocarcinoma is about 10%.
- Treatment is liver transplantation

![Primary ascending cholangitis](image)

**Effects of liver cirrhosis**
- I-Loss of hepatocytes + disruption of portal circulation leading to 1- hepatocellular failure
- II- Obstruction of portal circulation leading to 2- portal hypertension.
- III- liver cell hyperplasia leading to 3- hepatocellular carcinoma
I- hepatocellular failure
It is the ultimate fate of many liver diseases. It may be either acute or chronic.

* Signs and symptoms: - 1- Jaundice: - Hepatotoxic
2- Hepatic encephalopathy: - It results from inability of the liver to detoxify the neurotoxic nitrogenous bacterial products bacterial products of the gut (ammonia) which is absorbed, cross the portal to the systemic circulation to reach the brain where it ...
*Causes of hepatic encephalopathy :-
   i. Massive liver cell damage.
   ii. Increased nitrogenous load due to high protein diet or GIT hemorrhage.
   iii. Porto-systemic anastomosis especially porto - caval. In this case, portal blood passes to the hepatic vein prior to its detoxification in the liver
*Signs and Symptoms of hepatic encephalopathy: -
They are related to raised blood ammonia level, they include:-
1- Psychiatric disturbances, 2- flabby tremors,
3- disturbances of consciousness and finally 4- coma and death.

3-Coagulation defects:- Due to :-
a. defective hepatic synthesis of clotting factors (prothrombin, factors VII, IX, and X. abnormal factors are produced.
b. Thrombocytopenia due to splenomegaly
c. DIC due massive liver cell necrosis

4-Acute liver failure.....show in addition a. fever ... and b. foeter hepaticus.

5-Chronic liver failure Shows in addition
   i. Ascitis and edema    ii. Hypothermia
   iii. Hyperestrenism: due to failure of estrogen degradation in the liver. This leads to  a. Hypogonadism in both sexes.
       b. palmer erythema due to local vasodilatation of blood vessels of the skin of the palms of the hands.
  
c. Spider angiomas consisting of a central pulsating dilated arteriole from which small vessels radiate. They are found in the skin of the face, neck and arms (areas drained by the superior vena cava)
d. Testicular atrophy and gynecomastia in males.
e. Menstrual irregularities, secondary amenorrhea and breast atrophy in females

Jaundice

* Definition: - It is generalized tissue staining with bilirubin particularly skin and sclera. The color ranges from yellow to deep orange: This occurs when serum bilirubin exceeds 2 mg/dl (normal serum bilirubin is up to 1.0 mg/dl).

Types of jaundice
<table>
<thead>
<tr>
<th>Pathogenesis</th>
<th>Hemolytic (acholuric)</th>
<th>Obstructive (cholic)</th>
<th>Hepatotoxic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increased: unconjugated Bilirubin</td>
<td>Increased: conjugated Bilirubin</td>
<td>increased both conjugated and unconjugated Bilirubin</td>
</tr>
<tr>
<td>Serum bilirubin</td>
<td>Mild increase (2 mg/dl)</td>
<td>Mild, moderate or severe.</td>
<td>Variable</td>
</tr>
<tr>
<td>Urinary bilirubin</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Urinary urobilinogen</td>
<td>Increased (dark urine)</td>
<td>Absent</td>
<td>Variable</td>
</tr>
<tr>
<td>Foecal stercobilinogen</td>
<td>Increased</td>
<td>Absent (Clay colored Variable stool)</td>
<td>Variable</td>
</tr>
<tr>
<td>Steatorrhea Vit K deficiency</td>
<td>Absent</td>
<td>Present (malabsorption of fat and fat sol. Vitamins)</td>
<td>Variable</td>
</tr>
</tbody>
</table>

**II-Portal hypertension**

*Definition:* It is elevation of the portal venous pressure (normal 7 m.m Hg).

*Causes:* 1- Presinusoidal 2- Sinusoidal 3- Postsinusoidal
Presinusoidal:

a. Massive splenomegaly and increased splenic blood flow.
b. Portal vein obstruction by thrombosis or outside pressure.
c. Portal venular obstruction at the portal tracts e.g. by fibrosis, granuloma or chronic hepatitis.

Sinusoidal:

Cirrhosis due to perisinusoidal fibrosis

Postsinusoidal:

a. Alcoholic hepatitis leading to perivenular fibrosis.
b. Cirrhosis leading to interference with the blood flow and to arterio-venous anastomosis resulting in increased venous blood pressure.
c. Venocclusive diseases of the liver caused by some drugs & plant toxins. It results in progressive fibrous occlusion of the hepatic venules and vein radicals.
d. Budd-Chiari syndrome: It is hepatic vein thrombosis. 30% of cases have no apparent cause. It produces portal hypertension and hepatomegaly. It is fatal if not treated.
e. obstruction of major hepatic vein by tumors.
f. Right sided heart failure and constrictive pericarditis

Effects of portal hypertension:

A. Ascitis: It is intraperitoneal accumulation of serous fluid which is a Transudate. It causes abdominal distension.

Causes:
a. Increased hydrostatic pressure in the portal venous system.
b. Decreased albumin synthesis in the liver.....decreased colloid osmotic pressure of plasma.
c. Sodium and water retention due to secondary hyperaldosteronism and ADH secretion.
d. Leakage of hepatic lymph through the hepatic capsule due to hepatic vein obstruction.

- **B. Splenomegaly:** - It results from chronic venous congestion.
  - The spleen is 1 kg. in weight with capsular adhesions.
  - It shows Gamma Gandi nodules. - There may be hypersplelenism.

- **C. Porto-Systemic venous anastomosis:** - Present in the following sites
  * Esophageal varices... Rupture of these vessels is the main cause of death.
  * Around the umbilicus “Caput meduci”. * Ano -rectal vessels.

### III. Tumors of the liver

- **I- Benign:** - a. Epithelial: - i. liver cell adenoma
  - ii. Bile duct adenoma and cystadenoma.
  - b. Mesenchymal: - Cavernous haemangioma.

- **II Malignant:**
  1. Primary
  2. Secondary

- **1. Primary:**
  - A. Epithelial: - Hepatocellular carcinoma. - Cholangiocarcinoma
  - Mixed hepatocarcinoma.
  - B. Mesenchymal: - Angiosarcoma & Lymphoma
C. Mixed: - Hepatoblastoma.

- 2- Secondary: - Carcinoma  - Sarcoma  - Lymphoma & leukemia

**Benign tumors of the liver...**

- *Liver cell adenoma:*
  - Occurs in young females. Related to oral contraceptives. - Encapsulated. - Formed of groups of hepatocytes which may produce pseudocanaliculi and bile. - Highly vascularized, liable for rupture with internal hemorrhage

- *Cavernous hemangioma:*
  - Common. - Usually superficial. - Single or multiple, less than 2 cm. in diameter.

**Malignant tumors of the liver...**

- *Haemangio (angiosarc.)* Related to Vinyl chloride, chronic arsenic poisoning & thorotrast.
  - *Hepatoblastoma:*
    - A rare embryonal tumors of childhood.
    - A mixed tumors formed of epithelial and mesenchymal elements.

**Primary liver carcinoma**

- 1- Hepatocellular carcinoma:

**Definition:** Primary carcinoma formed of cells resembling hepatocytes.

**Incidence** 80-85% of 1ry malignant liver tumors.* In high incidence areas (Africa & Ascia) it affects young adults.*In low incidence areas (USA & Europe), it occurs after 50 years. *Males >females
**Predisposing factors**

1. HBV.
2. Regenerating nodules of cirrhosis
3. Diet:
   a. poor protein and vitamins
   b. Experimentally, Aflatoxin B1 produces mycotoxin that contaminates badly stored food & cereals.
   c. Azo dyes
   d. Nitrosamines.
4. Hormones e.g. estrogen and androgen.

![Image of liver sections]

**Primary liver carcinoma**

**Gross**

- A. May take one of three forms:
  1. Single large, well defined mass with areas of haemorrhage and necrosis.
  2. Multiple small nodules scattered all over the liver sparing its periphery.
  3. Diffuse infiltration of the entire liver.
- B. Tumor tissue is yellow-white and may be bile stained (green).

**M/E**

1. **Well differentiated carcinoma:**
   - Tumor cells resemble hepatocytes.* They are arranged in trabeculae separated by sinusoids & pseudoglandular
   - Bile may be present.

![Image of liver cells]

Well differentiated hepatocellular carcinoma

2. **Poorly differentiated carcinoma:**
   - Large anaplastic cells
   - May be bi or multinucleated giant cells or clear cell type.
   - Stroma is scanty and poorly vascular.
3. **Fibrolamellar carcinoma:** cords of polygonal cells with acidophilic cytoplasm. They are separated by lamellated fibrous stroma.

**Spread**
1. Direct… in the liver
2. Lymphatic to L.N of porta hepatic

- **S&S**
  1. Silent hepatomegaly.
  2. Rapid increase in size of a cirrhotic liver with hemorrhagic ascitis.
  3. Paraneoplastic syndrome
  4. Increased level of a fetoprotein (1000 ng/ml)

- **Prognosis**
  - Poor, most patients die within one year from liver cell failure or metastasis. 5 years survival rate is 5%.

**Cholangiocarcinoma (bile duct adenocarcinoma)**

**Definition:**
Primary carcinoma formed of cells resembling biliary tract epith. It arises from intrahepatic biliary tree

**Incidence:** 5-20 % of primary malignant liver tumors. Males = females.

**Predisposing factors:**
1. Liver flukes in the Far East.
2. It may be associated with cirrhosis
3. Primary sclerosing cholangitis

**Gross:**
- A. As hepatoma, it may be single mass, multiple tumors or diffuse liver infiltration.
B. C/S is green due to biliary obstruction. Tumor tissue is yellow-white.
- Large tumors have areas of hage and necrosis
M/E: * Usually, it is a well differentiated adenocarcinoma.
* Tumor cells resemble biliary epithelium.
* Stroma is abundant and fibrous (desmoplastic)

Spread, S&S and prognosis: As hepatocellular carcinoma, distant spread is uncommon.

Secondary (metastatic) tumors of the liver
Metastatic Cancer Is the Most Common Malignant Tumor of the Liver.
Reaches the liver by:
- Direct ... from gall bladder, stomach and colon.
- Lymphatic spread....from lungs & breast.
- Blood spread.....x. Portal vein from the GIT (stomach, colon, pancreas)
  x. Hepatic artery....from primary and secondary lung tumors & malignant melanoma.

Gross: Marked hepatomegaly, distorted liver.
- Surface shows central umbilication (central depression due to necrosis).
- Liver is green due to intrahepatic cholestasis caused by pressure of the tumor over bile duct radicals causing its obstruction.
- Secondaries vary in size and color according to its primary e.g black in malignant melanoma.
- C/S shows multiple tumor nodules allover the organ including its periphery (unlike primary tumors).
- Rarely, secondaries are represented by one or two masses.
- Liver failure is rare (sufficient reserve of hepatic tissue is present).

**Extrahepatic Biliary Tract**

**Gall bladder**

Normal gall bladder

- **Cholecystitis**

It is inflammation of the gall bladder. It may be acute or chronic.

In 80-90% of cases, it is associated with gall stones (Calcular cholecystis).

*Causes and pathogenesis:-*

1. **Obstruction of cystic or common bile duct:-**
   - By stones, strictures, pressure from the outside, tumors etc.
   - Obstruction concentration of bile chemical irritation of the gall bladder
Secondary bacterial infection  stone formation  trauma to the wall of gall bladder  more infection.

2- Secondary bacterial infection:

- Usually by intestinal commensals E.coli, streptococcus fecalis…. They reach the gall bladder by lymphatics.  (S.typhi reaches the gall bladder after systemic infection).

Acute cholecystitis

- May be catarrhal, suppurative, hemorrhagic or gangrenous.

**Grossly:** - Gall bladder is enlarged edematous and fiery red in color.
- Wall is edematous, hyperemic, may show abscesses or gangrenous dark brown or green or black foci which may perforate.
- Serous covering show fibrinosuppurative inflammation and exudation.
- Mucosa is edematous, hyperemic and ulcerated.
- If associated with stones, obstruction results in accumulation of pus leading to Empyema of the gall bladder.

**Fate:** - Healing by fibrosis and adhesions.  - Chronicity.

**Complications:**
- Pericholecystic abscess.
- Rupture leading to acute peritonitis.
- Ascending suppurative cholangitis and liver abscess

Chronic cholecystitis

May follow Acute cholecystitis or starts chronic. Gall stones are usually present.
- **Grossly:**—

1. If associated with obstruction:
   - Gall bladder is dilated.    - Wall may be thickened or thinned out.
   - Contents may be clear, turbid or purulent.

2. If not associated with obstruction:
   - Gall bladder is contracted, wall is markedly thickened.

3. Serosa is smooth with fibrous adhesions. Draining lymph nodes are enlarged.

4. Wall is thickened, opaque and gray-white with red tinge.

5. Mucosa is gray-red with ulcerations and pouches.

6. Stones are usually present.

![Image of gall bladder](image1.png)

* **M/E:**— Chronic non-specific inflammation in all layers.

- Adenomatosis of the gall bladder (cholecystitis glandularis proliferans):

- It is the presence of gland-like structures formed by dipping of the lining mucosa in between the muscle coat. It is a benign lesion.

- May be squamous metaplasia (especially in the presence of stones).

* **Complications:**— Acute attacks.

**Colesterolosis of the gall bladder**

-It is patchy deposition of cholesterol esters in the wall of the gall bladder within mucosal macrophages. It results from disturbance of cholesterol metabolism.

* **Grossly:**—

   - Strawberry gall bladder or yellowish mucosal flecking.
- Lipid polypoid nodules which may detach.
- Cholesterol stones in 1/3 of cases.

Cholelithiasis (Biliary calculi)
- These are insoluble material found within the biliary tract and are formed of bile constituents (cholesterol, bile pigments and calcium salts).

* Incidence: - ♂ < ♀ - Above 40 years.
* Sites: - Gall bladder, extra hepatic biliary tract. Rarely, intrahepatic biliary tract.

*Predisposing factors:-
  1- Change in the composition of bile.
  2- Stasis.
  3- Infection.

1- Change of the composition of bile:-

A. Lithogenic bile:- It is the disturbance of the ratio between cholesterol and lecithin or bile salts. Lecithins & bile salts keep cholesterol in solution and prevents its precipitation.

*Causes of lithogenic bile:
  a. Primary (unexplained).
  b. Excessive cholesterol excretion in bile (supersaturation) due to
     - Hypercholesterolaemia which may be hereditary or the 4 F (Female, Forty, Fatty, Fertile).
     - Drugs as clofibrate and exogenous estrogen.
     - High intake of calories (obesity).
c. Low lecithin secretion or deficiency of bile acids due to
- Hereditary or acquired defective synthesis of lecithin.
- Increased absorption from inflamed gall bladder.
- Excessive loss due to impaired intestinal absorption (ileal disorders).

B. Increased concentration of bilirubin in bile: “pigment stones”
   a. Haemolytic diseases (hereditary or acquired).
   b. Cirrhosis.

C. Hypercalcaemia: Calcium carbonate stones.

2. Stasis
   a. Increases bile concentration and b. favors infection.

3. Infection
   - Causes active absorption of bile salts resulting in precipitation of cholesterol.
   - Provides a nucleus for stones (bacteria, mucous, epithelium, fibrin).

* Pathogenesis
  i. Nucleation or initiation of stone formation:
     - The nidus may be cholesterol “due to supersaturation” Bacteria, parasite RBCs or mucous.
  ii. Acceleration:
     When the stone remains in the gall bladder, other constituents are added to the nidus to form the stone.

Types and characters of gall stones

Cholesterol    bile pigment    calcium carbonate    mixed stone
<table>
<thead>
<tr>
<th>Pure stones (10%)</th>
<th>Mixed stones (80%)</th>
<th>Compound stones (10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>Usually solitary</td>
<td>Multiple</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>May reach 3cm</td>
<td>&lt;1cm</td>
</tr>
<tr>
<td><strong>Shape</strong></td>
<td>Rounded or oval</td>
<td>Irregular</td>
</tr>
<tr>
<td><strong>Surface</strong></td>
<td>Smooth or granular</td>
<td>Smooth</td>
</tr>
<tr>
<td><strong>Color</strong></td>
<td>Pale-yellow-white</td>
<td>Dark brown to jet black</td>
</tr>
<tr>
<td><strong>C/S</strong></td>
<td>Cholesterol crystals “specules” radiating from the centre</td>
<td>Homogenous</td>
</tr>
<tr>
<td><strong>Consistency</strong></td>
<td>Soft</td>
<td>Friable or hard</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>Light weight</td>
<td></td>
</tr>
<tr>
<td><strong>Specific gravity</strong></td>
<td>Low specific gravity</td>
<td></td>
</tr>
<tr>
<td><strong>Gall bladder</strong></td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>
*Effects of gall stones:-
- Silent in 50% of cases.
- Movement of stone & its impaction biliary colic.

* Complications of gall stones:-
- Predispose to infection.
- Chronic irritation leading to
  a. Ulceration
  b. Squamous metaplasia & carcinoma.

Obstructive effects:-
A Cystic duct:- leading to mucocoel or empyema that can rupture leading to peritonitis.
b. Common bile duct: - leading to obstructive jaundice, ascending cholangitis and secondary biliary cirrhosis.
c. Ampulla of Vater:- leading to acute hemorrhagic pancreatic necrosis.
d. Intestinal obstruction:- if gall stones perforate into the intestine, they reach the ileum leading to gall stone ileus.
Tumors of extra hepatic biliary tract

- **Benign:** very rare, papilloma, fibroma, lipoma.

- **Malignant:** Cholangiocarcinoma
  1. Carcinoma of the gall bladder.
  2. Carcinoma of extra hepatic bile ducts including ampulla of Vater.

**Carcinoma of gall bladder**

- **Incidence:** Uncommon - Old age 70-75 years-♀:♂ 3:1
- **Predisposing factors:** Gall stones leading to chronic irritation 60-90%
- **Chemicals**
- **N/E site** Fundus. - Infiltrating, fungating or papillary cystadenocarcinoma

- **M/E** - Adenocarcinoma which may be mucoid leading to pseudomyxoma peritonei.
- **Squamous cell carcinoma** Or adenoacanthoma from squamous metaplasia

**Spread**
- Direct... to the liver leading to obstructive jaundice.
- Lymphatic... to lymph nodes of the porta hepatice
- Blood..... Rare

**Prognosis** Poor..5 years survival rate is 3%

**Carcinoma of extra hepatic bile ducts including ampulla of Vater.**

- Less common than gall bladder ♂ >♀
- Liver flukes.-Biliary calculi may predispose to it.
- **Sites....** Lower & upper ends of common bile duct
- Tumor is small.-Gall bladder may be enlarged.
- **M/E:** Adenocarcinoma.- Papillary cystadenocarcinoma. -Mucin may be produced.
Normal Considerations:

The pancreas is a mixed endocrine and exocrine gland linked to the second part of the duodenum.

Anatomically, it is formed of three parts: head, body, and tail.

- The exocrine portion is formed of acini and ducts. Acini secrete pancreatic digestive enzymes which include:
  - Proteolytic enzymes e.g. trypsin and chemotrypsin.
  - Lipolytic enzymes e.g. lipase and phosphatase.
  - Glycolytic enzymes e.g. Amylase.

Microscopically,

The exocrine pancreas consists of acini that are arranged in lobules. Each lobule is drained by a central duct and is surrounded by fibrous stroma containing the feeding blood vessels.

- The duct system of the pancreas consists of small ducts draining the lobules which then converge to large ducts that ultimately form the main pancreatic duct. The terminal portion of the main pancreatic duct fuses with the common bile duct forming a common biliary-pancreatic duct which opens in the muscular wall of the duodenum at the Ampulla of Vater which is guarded by sphincter of Oddi.
Acute hemorrhagic pancreatitis
- It is an acute inflammatory process caused by enzymatic-mediated destruction of pancreatic and peri-pancreatic tissue.
- It results from inappropriate activation of pancreatic digestive enzymes inside the ducts and acini of exocrine pancreas.
- Activated enzymes act on the pancreatic cells which lead to additional release of digestive enzymes into the interstitial and peripancreatic tissue and blood vessels.
- **Incidence:** Common in middle aged females more than males.
- **Causes:**
  - Most common causes: Include *Gall stones* and *Alcohol abuse*.
  - Less common causes: Include *Viruses* (e.g. mumps)

Drugs (sulfonamides and contraceptives) - Trauma.

**Pathogenesis:**
- Obstruction of the terminal portion of the pancreatic duct ➔ Reflux of bile into the pancreatic duct ➔ increased pressure inside the ducts
- Reversal of the bile flow backwards into the acini ➔ Activation of the pancreatic lyric enzymes into small ducts and acini ➔ Rupture of damaged acinar cells ➔ Release of digestive enzymes into the interstitial space and peri-pancreatic tissue ➔ Auto digestion of proteins, lipids and carbohydrates components of cells of the pancreas, peripancreatic tissue and blood vessels.

**Gross:**
- Pancreas: enlarged with focal haemorrhage and necrosis.
- Per pancreatic tissue and momentum: Fat necrosis with formation of fat soaps and calcification. These foci appear chalky-white.
- Peritoneal cavity: Ascitis. The ascetic fluid resembles chicken broth (turbid, haemorrhagic with fat globules).
**Microscopically:**

1. Necrosis of pancreatic acini, ducts and blood vessels. In these anatomic sites, the component cells lose their outlines and nuclei.
2. Fat necrosis:- Fat cells become indistinct and lose their internal structures. The entire field appears bluish due to deposition of calcium salts.
3. Haemorrhage:- Blood infiltrates the tissues.
4. Acute inflammation:- Neutrophils invade the necrotic tissue. In later stages, neutrophils are replaced by macrophages and the entire area undergoes fibrosis.

**Signs and Symptoms:**

- Acute abdomen followed by shock. Jaundice in less than 50% of cases.
- Increased serum amylase and lipase.

*Complications:*

1. Chemical peritonitis.
2. Endotoxic shock due to release of intestinal bacterial endotoxins into the circulation.
3. Suppurative infection of pancreas and peritoneum.
4. Pancreatic pseudocyst: liquefied areas -due to impaired drainage- contain pancreatic juice and necrotic debris. They may be walled off by fibrous tissue and the contents become calcified. Pseudocysts usually occur in lesser sac but may be in the pancreas.

*Prognosis:*

- Mortality rate is 10-50% due to shock, abdominal sepsis and adult respiratory distress syndrome.
**Chronic pancreatitis**

- It is progressive pancreatic damage produced by repeated acute mild attacks ending in months or years - by fibrosis of acini more than islets resulting in pancreatic insufficiency.

- **Incidence:**
  
  Usually affects middle aged males than females.

- **Pathology:**

  * Grossly: – a. Pancreas is enlarged and firm.
    
    b. C/S shows a smooth grey appearance with loss of the normal lobulation.
    
    c. Calcification and ductal dilatation may be seen.

  *M/E:* a. Early: Patchy fibrosis, later on fibrosis becomes confluent.
  
    b. Fibrosis affects exocrine more than endocrine pancreas.
  
    c. There may be calcification and ductal dilatation.

- **Complications:**  
  
  a. Recurrent mild jaundice.
  
  b. Secondary chronic malabsorption syndrome.
  
  c. Diabetes mellitus

**Tumors of the exocrine pancreas**

**Carcinoma:**

**Incidence:** – More common in males. Affects older ages (more than 50 years.)

**Grossly:** – Site: In descending order of frequency

a.*Head (60-65%)  

b.* Entire pancreas 20%

c.*Body (15%).  
d.*Tail (5%).

Tumor grey-white, hard gritty mass.

Occasionally, it is cystic (cystadenocarcinoma).
Tumors of the exocrine pancreas

M/E: - - It is usually an adenocarcinoma-may be mucin secreting. It may be with abundant fibrous stroma.

Effects:-

1. Cancer head: obstructs common bile duct or Ampulla of Vater leading to progressive obstructive jaundice (early diagnosis) with marked dilatation of the gall bladder (50%) according to Courvoisier's law. Tumor may also obstruct the duodenum.

2. Cancer body and tail: remains silent for sometimes and so, it may reach a large size at the time of discovery.

* Spread: -

- Local spread: to retroperitoneal structures as vertebral column, diaphragm, kidney, and adrenals. It may invade adjacent structures as spleen but involvement of the biliary system is late.
- Blood spread: to the liver, lungs, bone... etc.

Signs and Symptoms: - It may be associated with migrating thrombophlebitis (Traussau's sign), phlebothrombosis, peripheral neuropathy and myopathy.

Prognosis: - 5 years survival rate is 2%.