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A HANDBOOK ON LIVER AND BILIARY DISORDER

JV'n Dr.Mona Pathak

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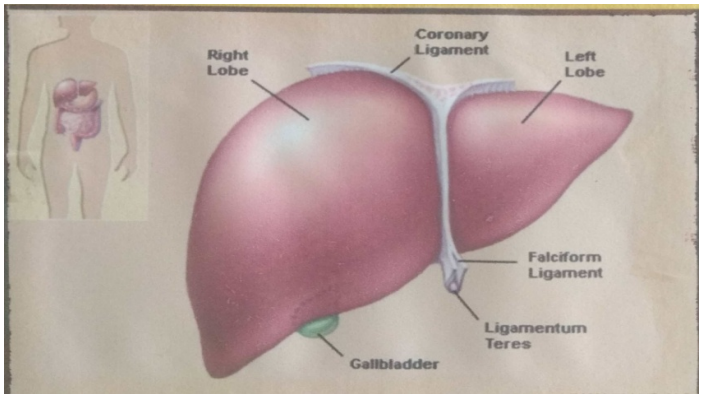
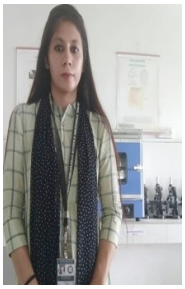


Written By
Dr.Mona Pathak
B.H.M.S., M.D.(Hom.)
Asst. Professor
Dept. of Pathology
Faculty of Homoeopathic Science
Jayoti Vidyapeeth Women's University, Jaipur.

INTRODUCTION OF AUTHOR:

Dr Mona Pathak is a MD Homoeopath. At present she is working as Assistant Prof. in Department of pathology at Faculty of Homoeopathic Science under Jayoti Vidyapeeth Women's University, Jaipur. She published various articles and write many book chapter also.



By – Jvn Dr.Mona pathak M.D (Hom)
Assitant professor department of pathology
Faculty of Homoeopathic Science
Jayoti Vidyapeeth Women's University, Jaipur.

Emai.id – drmonapathak@jvwu.ac.in

Foreward

First of I would like to give my gratitude towards our Honourable Chairperson Mam Jv'n Mithilesh Garg and our Honourable Founder and Advisor sir JV'n Vedant Garg sir for providing me an opportunity to write this book and publish in University press for the need of our students at Jayoti Vidyapeeth Women's University Jaipur.

This book is useful for the Students of BHMS, BAMS, BNYS. This book covers disorder related to liver and biliary system in short and easier way. Heapatic – biliary system is difficult to understand for student also, so in this book these topics are explained one by one for exam purpose also .

Author –

Jvn Dr.Mona Pathak

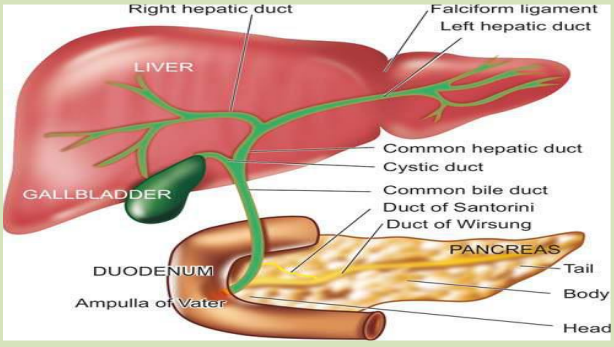
CONTENTS –

CHAPTER -1

NORMAL ANATOMY & PHYSIOLOGY OF LIVER

ANATOMY –

- 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 lobe has quadrate lobe on its inferior surface and a caudate lobe on the posterior surface. 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 fi ssure for the *ligamentum venosum.*
- The *porta hepatis* is the region on the inferior surface of the right lobe where blood vessels, lymphatics and common hepatic duct form the hilum of the liver. A firm smooth layer of connective tissue called *Glisson's capsule* encloses the liver and is continuous with the connective tissue of the porta hepatis forming a sheath around the structures in the porta hepatis.
- The liver includes a double blood supply—the portal brings the blood from the intestines and spleen, and the artery coming from the coeliac axis supplies blood to the liver. This dual blood supply provides sufficient protection against infarction in the liver. The portal vein and hepatic artery divide into branches to the right and left lobes in the porta.
- The right and left hepatic ducts also join in the porta to form the common hepatic duct. The venous drainage from the liver is into the right and left hepatic veins which enter the inferior vena cava. Lymphatics and therefore the nerve fibres accompany the hepatic artery into their branchings and terminate around the porta hepatis.



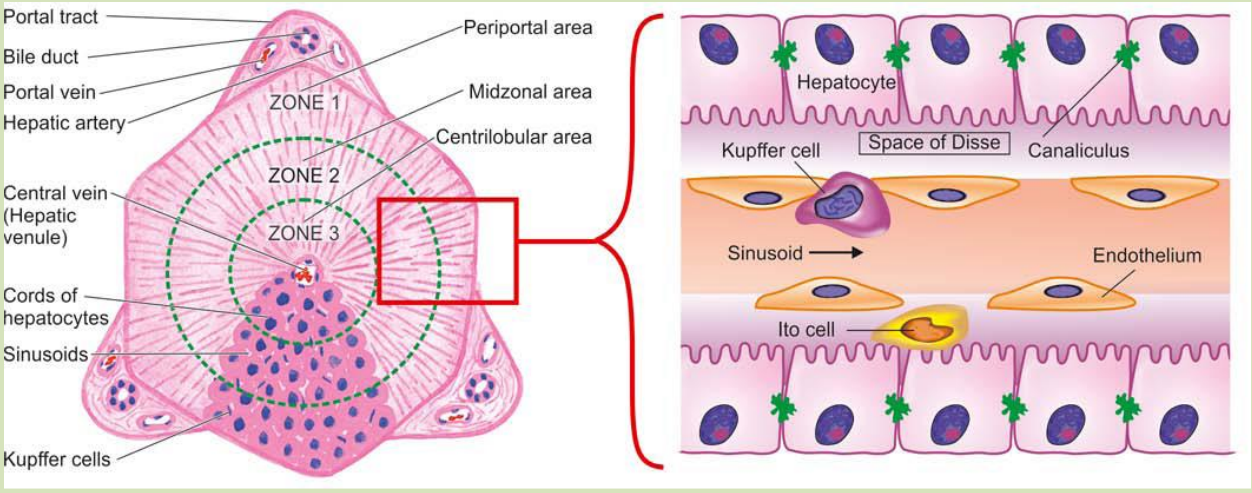
HISTOLOGY –

- The hepatic parenchyma is composed of numerous hexagonal or pyramidal *classical lobules,* each with a diameter of 0.5 to 2 mm. Each classical lobule has a central tributary from the hepatic vein and at the periphery are 4 to 5 portal tracts or triads contain ing branches of bile duct, portal vein and hepatic artery. Cords of hepatocytes and blood containing sinusoids radiate from the central vein to the peripheral portal triads.
- The *functioning lobule* or *liver acinus* as described by Rappaport has a portal triad in the centre and is surrounded at the periphery by portions of several classical lobules. However, in most descriptions on pathology of the liver, the term *lobule* is used in its classi cal form.
- The blood supply to the liver parenchyma flows from the portal triads to the central veins. Accordingly, the hepatic parenchyma of liver lobule is divided into 3 zones

1. **Zone 1** or the *periportal (peripheral) area* is closest to the arterial and portal blood supply and hence bears the brunt of all forms of toxic injury.

2. **Zone 3** or the *centrilobular area* surrounds the central vein and is most remote from the blood supply and thus suff ers from the effects of hypoxic injury.

3.**Zone 2** is the intermediate *midzonal area.*



FUNCTIONS –

The liver performs multifold functions listed below:

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

CHAPTER-2
LIVER ABSCESS

PYOGENIC LIVER ABSCESS

Most liver abscesses are of bacterial (pyogenic) origin; less often they are amoebic, hydatid and rarely actinomycotic. Pyogenic liver abscesses have become uncommon due to improved diagnostic facilities and the early use of antibiotics. However, their incidence is higher in old age and in immunosuppressed patients such as in AIDS, transplant recipients and those on intensive chemotherapy. Pyogenic liver abscesses can occur by following modes of entry:

1. ***Ascending cholangitis*** through ascending infection in the biliary tract due to obstruction e.g. gallstones, cancer, sclerosing cholangitis and biliary strictures.

2**.** ***Portal pyaemia*** by means of spread of pelvic or gastrointestinal infection resulting in portal phlebitis or septic emboli e.g. from appendicitis, empyema of gallbladder, diverticulitis, regional enteritis, pancreatitis, infected haemorrhoids and neonatal umbilical vein sepsis.

3. ***Septicaemia*** through spread by hepatic artery.

4. ***Direct infection*** resulting in solitary liver abscess e.g. from adjacent perinephric abscess, secondary infection in amoebic liver abscess, metastasis and formation of haematoma following trauma.

5. ***Iatrogenic causes*** include liver biopsy, percutaneous biliary drainage and accidental surgical trauma.

6. ***Cryptogenic*** from unknown causes, especially in the elderly. The commonest infecting organisms are gram-negative bacteria chiefly *E. coli;* others are *Pseudomonas, Klebsiella, Enterobacter* and a number of anaerobic organisms, bacteroides and actinomyces. abscesses are clinically characterised by pain in the right upper quadrant, fever, tender hepatomegaly and sometimes jaundice. Laboratory examination reveals leucocytosis, elevated serum alkaline phos phatase, hypoalbuminaemia and a positive blood culture.

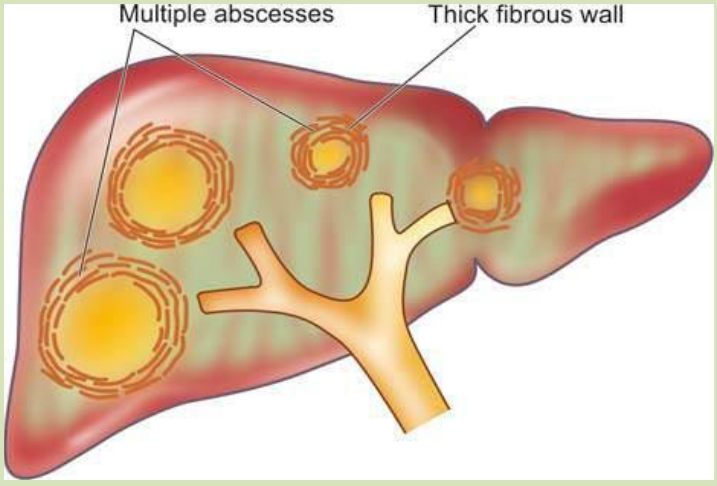
MORPHOLOGIC FEATURES –

Grossly, depending upon the cause for pyogenic liver abscess, they occur as single or multiple yellow abscesses, 1 cm or more in diameter, in an enlarged liver. The abscesses are particularly common in right lobe of the liver .

Microscopically, typical features of abscess are seen. There are multiple small neutrophilic abscesses with areas of extensive necrosis of the affected liver parenchyma. The adjacent viable area shows pus and blood clots in the portal vein, inflammation, congestion and proliferating fibroblasts.

AMOEBIC LIVER ABSCESS-

- Amoebic liver abscesses are less common than pyogenic liver abscesses and have many similar features. They are caused by the spread of *Entamoeba histolytica* from intestinal lesions.
- The trophozoite form of amoebae in the colon invade the colonic mucosa forming flask-shaped ulcers from where they are carried to the liver in the portal venous system . The patients, generally from tropical and subtropical countries, may give history of amoebic dysentery in the past.
- Cysts of *E. histolytica* in stools are present in only 15% of patients of hepatic amoebiasis. Intermittent low-grade fever, pain and tenderness in the liver area are common presenting features. A positive haemaglutination test is quite sensitive and useful for diagnosis of amoebic liver abscess.



MORPHOLOGIC FEATURES -

Grossly, amoebic liver abscesses are usually solitary and more often located in the right lobe in the posterosuperior portion. Amoebic liver abscess may vary greatly in size but is generally of the size of an orange. The centre of the abscess contains large necrotic area having reddish-brown, thick pus resembling anchovy or chocolate sauce. The abscess wall consists of irregular shreds of necrotic liver tissue.

Histologically, the necrotic area consists of degenerated liver cells, leucocytes, red blood cells, strands of connective tissue and debris. Amoebae are most easily found in the liver tissue at the margin of abscess. PAS-staining is employed to confirm the trophozoites of *E. histolytica*.

CHAPTER -3

JAUNDICE—GENERAL

Jaundice or icterus refers to the yellow pigmentation of the skin or sclerae by bilirubin . Bilirubin pigment has high affinity for elastic tissue and hence jaundice is particularly noticeable in tissues rich in elastin content. Jaundice is the result of elevated levels of bili rubin in the blood termed hyperbilirubinaemia. Normal serum bilirubin concentration ranges from 0.3-1.3 mg/dl, about 80% of which is unconjugated. Jaundice becomes clinically evident when the total serum bilirubin exceeds 2 mg/dl. A rise of serum bilirubin between the normal and 2 mg/dl is generally not accom panied by visible jaundice and is called *latent jaundice.*

NORMAL BILIRUBIN METABOLISM

Normal metabolism of bilirubin can be conveniently described under 4 main headings—source, transport, hepatic phase and intestinal phase as illustrated schematically earlier.

1. SOURCE OF BILIRUBIN -About 80-85% of the bilirubin is derived from the catabolism of haemoglobin present in senescent red blood cells. Th e destruction of effect erythrocytes at the end of their normal lifespan of 120 days takes place in the reticuloendothelial system in the bone marrow, spleen and liver. The remaining 15-20% of the bilirubin comes partly from non-haemo globin haem-containing pigments such as myoglobin, catalase and cytochromes, and partly from ineffective erythropoiesis.

2. TRANSPORT OF BILIRUBIN -Bilirubin on release from macrophages circulates as unconjugated bilirubin in plasma tightly bound to albumin. Certain drugs such as sulfonamides and salicylates compete with bilirubin for albumin binding and displace bilirubin from albumin, thus facilitating bilirubin to enter into the brain in neonates and increase the risk of *kernicterus.* Bilirubin is found in body fluids in proportion to their albumin content such as in CSF, joint eff usions, cysts etc.

3. HEPATIC PHASE -On coming in contact with the hepatocyte surface, unconjugated bilirubin is preferentially metabolised which involves 3 steps: hepatic uptake, conjugation and secretion in bile.

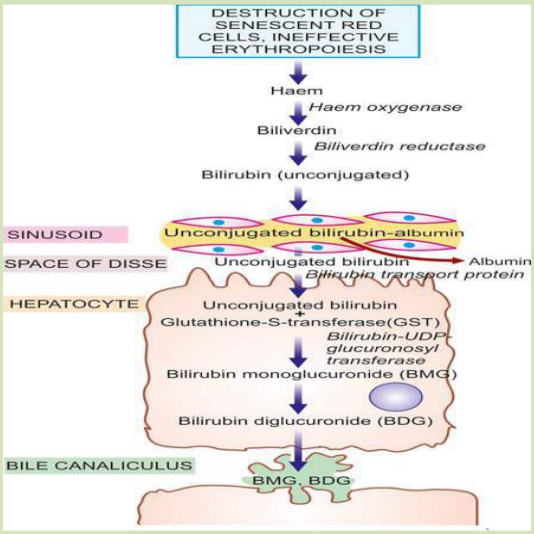
i) Hepatic uptake- Albumin-bound unconjugated bilirubin upon entry into the hepatocyte, is dissociated into bilirubin and albumin. The bilirubin gets bound to cytoplasmic protein *glutathione-S-transferase (GST)* (earlier called ligandin).

ii) Conjugation -Unconjugated bilirubin is not water-soluble but is alcohol-soluble and is converted into water-soluble compound by conjugation. Conjugation occurs in endoplasmic reticulum and involves conversion to bilirubin mono- and di -glucuronide by the action of micro somal enzyme, *bilirubin- UDP-glucuronosyl transferase* . The process of conjugation can be induced by drugs like pheno barbital.

Conjugated bilirubin is bound to albumin in two forms: reversible and irreversible. Reversible binding is similar to that of unconjugated bilirubin. However, when present in serum for a long time (e.g. in choles tasis, long-standing biliary obstruction, chronic active hepatitis), conjugated bilirubin is bound to albumin irreversibly and is termed *delta bilirubin* or *biliprotein.* This irreversible conjugated delta bilirubin is not excreted by the kidney, and remains detectable in serum for sufficient time after recovery from the diseases listed above.

iii) Secretion into bile Conjugated (water-soluble) bilirubin is rapidly transported directly into bile canaliculi by energy dependent process and then excreted into the bile.

4. INTESTINAL PHASE Appearance of conjugated bilirubin in the intestinal lumen is followed by either direct excretion in the stool as stercobilinogen which imparts the normal yellow colour to stool, or may be metabolised to urobilinogen by the action of intestinal bacteria.



TYPES OF LIVER CELL NECROSIS-

All forms of injury to the liver such as microbiologic, toxic, circulatory or traumatic, result in necrosis of liver cells. The extent of involvement of hepatic lobule in necrosis varies. Accordingly, liver cell necrosis is divided into 3 types: *diffuse* (submassive to massive), *zonal* and *focal.*

1. DIFFUSE (SUBMASSIVE TO MASSIVE) NECROSIS

When there is extensive and diff use necrosis of the liver involving all the cells in groups of lobules, it is termed diff use, or submassive to massive necrosis. It is most commonly caused by viral hepatitis or drug toxicity.

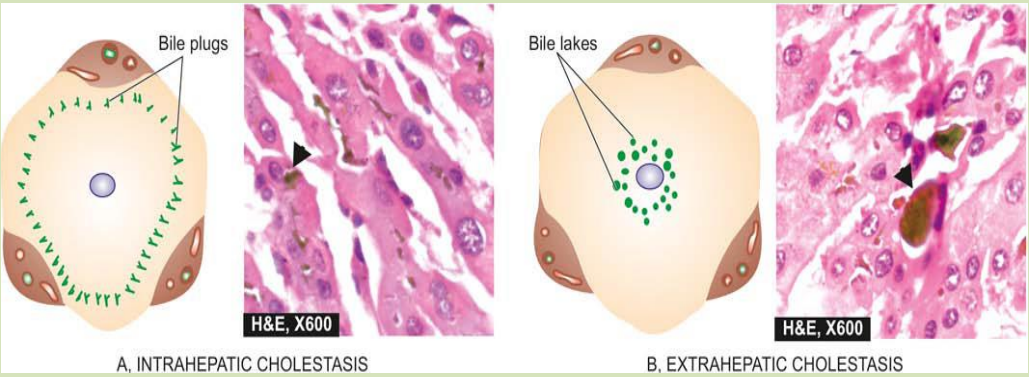
2. ZONAL NECROSIS Zonal necrosis is necrosis of hepatocytes in 3 diff erent zones of the hepatic lobule.Accordingly, it is of 3 types; each type aff ecting respective zone is caused by diff erent etiologic factors:

i) Centrilobular necrosis is the commonest type involving hepatocytes in zone 3 (i.e. located around the central vein). Centrilobular necrosis is characteristic feature of ischaemic injury such as in shock and CHF since zone 3 is farthest from the blood supply. Besides, it also occurs in poisoning with chloroform, carbon tetra chloride and certain drugs.

ii) Midzonal necrosis is uncommon and involves zone 2 of the hepatic lobule. This pattern of necrosis is seen in yellow fever and viral hepatitis. In viral hepatitis, some of the necrosed hepatocytes of the mid-zone are transformed into acidophilic, rounded Councilman bodies.

iii) Periportal (peripheral) necrosis is seen in zone 1 involving the parenchyma closest to the arterial and portal blood supply. Since zone 1 is most well perfused, it is most vulnerable to the effects of circulating hepato toxins e.g. in phosphorus poisoning and eclampsia.

2. **FOCAL NECROSIS** This form of necrosis involves small groups of hepatocytes irregularly distributed in the hepatic lobule. Focal necrosis is most often caused by microbiologic infections. These include viral hepatitis, miliary tuberculosis, typhoid fever and various other forms of bacterial, viral and fungal infections. Focal necrosis may also occur in drug induced hepatitis.



CLASSIFICATION AND FEATURES OF JAUNDICE

Based on pathophysiology, jaundice may result from one or more of the following mechanisms:

1. Increased bilirubin production
2. Decreased hepatic uptake
3. Decreased hepatic conjugation
4. Decreased excretion of bilirubin into bile

Accordingly, a simple age-old classification of jaundice was to divide it into 3 predominant types: *pre-hepatic (haemolytic), hepatic,* and *post-hepatic cholestatic.*

However, hyperbilirubi naemia due to first three mechanisms is *mainly unconjugated* while the last variety yields *mainly conjugated* hyperbilirubinaemia. The presence of bilirubin in the urine is evidence of conjugated hyperbilirubinaemia. Based on these mechanisms, the pathogenesis and main features of the two predominant forms of hyper -bilirubinaemia.

CHAPTER -4

HEPATIC FAILURE

Though the liver has a marked regenerative capacity and a large functional reserve, hepatic failure may develop from severe acute and fulminant liver injury with massive necrosis of liver cells *(acute hepatic failure)*, or from advanced chronic liver disease *(chronic hepatic failure)*. Acute hepatic failure develops suddenly with severe impairment of liver functions whereas chronic liver failure comes insidiously. The prognosis is much worse in acute hepatic failure than that in chronic liver failure.

ETIOLOGY -Acute and chronic hepatic failure result from different causes:

1.Acute (fulminant) hepatic failure occurs most frequently in *acute viral hepatitis*. Other causes are hepato-toxic drug reactions (e.g. anaesthetic agents, nonsteroidal antiinflammatory drugs, anti-depres sants), carbon tetrachloride poisoning, acute alcoholic hepatitis, mushroom poisoning and pregnancy complicated with eclampsia.

2.**Chronic hepatic failure** is most often due to *cirrhosis*. Other causes include chronic active hepatitis, chronic cholestasis (cholestatic jaundice) and Wilson's disease.

MANIFESTATIONS-

In view of the diverse functions performed by the liver, the syndrome of acute or chronic hepatic failure produces complex manifestations.

1. Jaundice -Jaundice usually reflects the severity of liver cell damage since it occurs due to failure of liver cells to metabolise bilirubin. In acute failure such as in viral hepatitis, jaundice nearly parallels the extent of liver cell damage, while in chronic failure such as in cirrhosis jaundice appears late and is usually of mild degree.

2. Hepatic encephalopathy (Hepatic coma) -Neuropsychiatric syndrome may complicate liver disease of both acute and chronic types. The features include disturbed consciousness, personality changes, intellectual deterioration, low slurred speech, flapping tremors, and finally, coma and death.. The toxic products may be ammonia and other nitrogenous substances from intestinal bacteria which reach the systemic circulation without detoxification in the damaged liver and thus damage the brain. Advanced cases of hepatic coma have poor prognosis but may respond favourably to hepatic transplantation.

3. Hyperkinetic circulation- All forms of hepatic failure are associated with a hyperkinetic circulation characterized by peripheral vasodilatation, increased splanchnic blood flow and

increased cardiac output. There is increased splenic flow but reduced renal blood flow resulting in impaired renal cortical perfusion. These changes result in tachycardia, low blood pressure and reduced renal function.

4. Hepatorenal syndrome- The term hepatorenal syndrome is applied to patients of both acute and chronic hepatic failure who develop renal failure as well, in the absence of clinical, laboratory or morphologic evidence of other causes of renal dysfunction. Hepatorenal syndrome develops in about 10% cases of acute and chronic liver diseases. The acute renal failure is usually associated with oliguria and uraemia but with good tubular function.

5. Hepatopulmonary syndrome The pulmonary changes in chronic hepatic failure such as in cirrhosis consist of pulmonary vasodilatation with intra-pulmo nary arteriovenous shunting. This results in ventilation-perfusion inequality that may lead to impaired pulmonary function, clubbing of fi ngers and sometimes cyanosis.

6. Coagulation defects Impaired synthesis of a number of coagulation factors by the diseased liver may result in coagulation disorders. These include dissemi nated intravascular coagulation (consumption coagulo pathy), thrombocytopenia and presence of fi brin degradation products in the blood.

7. Ascites and oedema -Chronic liver failure due to cirrhosis may result in portal hypertension and ascites . Decreased synthesis of albumin by the liver resulting in hypoproteinaemia and consequent fall in plasma oncotic pressure, increased hydrostatic pressure due to portal hypertension and secondary hyperaldo steronism, contribute to the development of ascites and oedema in these patients.

8. Endocrine changes -Endocrine changes may be found in association with chronic hepatic failure. The changes are more common in alcoholic cirrhosis in active reproductive life. In the male, the changes are towards feminisation such as gynaecomastia and hypogonadism. In the female, the changes are less towards masculini sation but atrophy of gonads and breasts occurs. The underlying mechanism appears to be changed end-organ sensitiveness to sex hormones in cirrhosis.

9. Skin changes -In alcoholic cirrhosis *'arterial spiders'* having radiating small vessels from a central arteriole are frequent in the vascular region drained by superior vena cava such as in the neck, face, forearms and dorsum of hands. Less frequently, *palmar erythema*, especially in the

hypothenar and thenar eminences and on the pulps of the fi ngers, is observed in chronic liver disease.

10. Foetor hepaticus -A sweetish pungent smell of the breath diseases. It appears to be of intestinal origin, possibly due to failure of the liver to detoxify sulfur-containing substances absorbed from the gut.

ETIOLOGY- The etiology of hepatic venous thrombosis in about a third of cases is unknown (idiopathic), while in the remaining cases various causes associated with increased thrombotic tendencies are attributed:

i) Polycythaemia vera

ii) Paroxysmal nocturnal haemo glo binuria

iii) Use of oral contraceptives

iv) Pregnancy and post partum state

v) Intra-abdominal cancers (e.g. hepato cellular carcinoma)

vi) Chemotherapy and radiation

vi) Myelo proliferative diseases

vii) Formation of membranous webs in the suprahepatic portion of inferior vena cava (either congenital or as a consequence of organised thrombosis).

MORPHOLOGIC FEATURES-

Grossly, the liver is enlarged, swollen, red-purple and has a tense capsule.

Histologically, the changes in sudden hepatic vein occlusion are those of centrilobular congestion, necrosis and rupture of sinusoids into the space of Disse. In slowly developing thrombosis, the changes are more chronic and include fibrosing reaction in the centrilobular zone that may progress to cardiac cirrhosis.

CLINICAL FEATURES –

Budd-Chiari syndrome is clinically characterised by either an acute form or chronic form depending upon the speed of occlusion.

1.In the *acute form*, the features are abdominal pain, vomiting, enlarged liver, ascites and mild icterus.

2. In the more usual *chronic form*, the patients present with pain over enlarged tender liver, ascites and other features of portal hypertension. The acute form of illness leads to acute hepatic failure and death, whereas in chronic form the patient may live for months to a few years

CHAPTER -5

VIRAL HEPATITIS

The term viral 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 chiefl y 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. Though a number of other viral diseases such as infection with Epstein-Barr virus (in infectious mononucleosis), arbovirus (in yellow fever), cytomegalovirus, herpes simplex and several others aff ect the liver but the changes produced by them are nonspecific; the term 'viral hepatitis' is strictly applied to infection of the liver by the hepatitis viruses.

ETIOLOGIC CLASSIFICATION

Based on the etiologic agent, viral hepatitis is currently classified into 6 etiologic types—hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E and hepatitis G. The contrasting features of major types are presented in

Hepatitis A

- Infection with HAV causes hepatitis A (infectious hepatitis). Hepatitis A is responsible for 20-25% of clinical hepatitis in the developing countries of the world but the incidence is much lower in the developed countries.
- Hepatitis A is usually a benign, self-limiting disease and has an incubation period of 15-45 days. The disease occurs in epidemic form as well as sporadically.
- It is almost exclusively spread by faeco-oral route.The spread is related to close personal contact such as in overcrowding, poor hygienic and sanitary conditions. Frozen and stored contaminated foods and water have been blamed in many epidemics.
- Most frequently affected age group is 5-14 years; adults are often infected by spread from children.

PATHOGENESIS –

Hepatitis A virus is present in the liver and replicates there. It is present in the liver, bile, blood and stools in the pre-icteric incubation period but viraemia andviral shedding in stool is diminished after jaundice appears.Evidence that hepatitis caused by HAV has an immunologic basis comes from demonstration of following antibodies acting as serum markers for hepatitis A infection .

1. *IgM anti-HAV antibody* appears in the serum at the onset of symptoms of acute hepatitis A.
2. *IgG anti-HAV antibody* is detected in the serum after acute illness and remains detectable indefinitely. It gives lifelong protective immunity against reinfection with HAV.

Hepatitis B

- Hepatitis B (serum hepatitis) caused by HBV infection has a longer incubation period (30-180 days) and 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.
- The disease may occur at any age. HBV infection causes more severe form of illness that includes: acute hepatitis B, chronic hepatitis, progression to cirrhosis, fulminant hepatitis and an asymptomatic carrier stage.
- HBV plays some role in the development of hepatocellular carcinoma as discussed .

PATHOGENESIS –

There is strong evidence linking immune pathogenesis with hepatocellular damage:

i) Since a carrier state of hepatitis B without hepatocellular damage exists, it means that HBV is not directly cytopathic.

ii) It has been observed that individuals with defect or deficiency of cellular immunity have more persistent hepatitis. B disease instead of clearing HBV from their blood.

iii) In support of cell-mediated mechanism in hepatocellular damage by HBV comes from observation that viral antigens (in particular nucleocapsid proteins HbcAg and HbeAg) are attacked by host cytotoxic CD8+T lymphocytes.

iv) The host response of CD8+T lymphocytes by elaboration of antiviral cytokines is variable in different individuals and that determines whether an HBV-infected person recovers, develops mild or severe disease, or progresses to chronic disease.

Hepatitis C

- The diagnosis of this major category of hepatitis was earlier made after exclusion of infection with other known hepatitis viruses in those times and was initially designated non-A, non-B(NANB) hepatitis. However, now it has been characterised and is called hepatitis C.
- Hepatitis C infection is acquired by blood transfusions, blood products, haemodialysis, parenteral drug abuse and accidental cuts and needle-pricks in health workers. About 90% of post-transfusion hepatitis is of hepatitis C type. About 1-2% of volunteer blood donors and up to 5% of professional blood donors are carriers of HCV.
- 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 conse quences of HCV infection. Currently, HCV is considered more important cause of chronic liver disease worldwide than HBV.
- **PATHOGENESIS**- HCV induces hepatocellular injury by cellmediated immune mechanism is supported by the following:

  i) It is possible that the host lymphoid cells are infected by HCV.

  ii) HCV-activated CD4+ helper T lymphocytes stimulate CD8+ T lymphocytes via cytokines elaborated by CD4+ helper T cells.

  iii) The stimulated CD8+T lymphocytes, in turn, elaborate antiviral cytokines against various HCV antigens.

  iv) Further support to this T- cell mediated mechanism comes from the observation that immune response is stronger in those HCV-infected persons who recover than those who harbor chronic HCV infection.

  v) There is some role of certain HLA alleles and innate immunity in rendering variable response by different hosts to HCV infection.

vi) Natural killer (NK) cells also seem to contribute to containment of HCV infection.

vii) In as subset of patients, there is crossreactivity between viral antigens of HCV and host autoantibodies to liver-kidney microsomal antigen (anti-LKM) which explains the association of autoimmune hepatitis and HCV hepatitis

Hepatitis D

Infection with delta virus (HDV) in the hepatocyte nuclei of HBsAg-positive patients is termed hepatitis D. HDV is a defective virus for which HBV is the helper. Thus, hepatitis D develops when there is concomitant hepatitis B infection. With coinfection, acute hepatitis D may range from mild to fulminant hepatitis but fulminant hepatitis is more likely in such simultaneous delta infection. Chronicity rarely develops in coinfection.

PATHOGENESIS –

HDV, unlike HBV, is thought to cause direct cytopathic effect on hepatocytes. However, there are examples of transmission of HDV infection from individuals who themselves have not suffered from any attack of hepatitis, suggesting that it may not be always cytopathic..

Hepatitis E

- Hepatitis E is an enterically-transmitted virus, previously labelled as epidemic or enterically transmitted variant of non-A non-B hepatitis. The infection occurs in young or middle-aged
- individuals, primarily seen in India, other Asian countries, Africa and central America.
- The infection is generally acquired by contamination of water supplies such as after monsoon flooding. However, compared with HAV, secondary person-to-person infection does not occur with HEV. Thus HEV has some common epidemiologic features with HAV.
- HEV infection has a particularly high mortality in pregnant women but is otherwise a self-limited disease and has not been associated with chronic liver disease.

CLINICO-PATHOLOGIC SPECTRUM-

Among the various etiologic types of hepatitis, evidence linking HBV and HCV infection with the spectrum of clinico pathologic changes is stronger than with other hepatotropic viruses. The

typical pathologic changes of hepatitis by major hepatotropic viruses are virtually similar. HAV and HEV, however, do not have a carrier stage nor cause chronic hepatitis. The various clinical patterns and pathologic consequences of different hepatotropic viruses can be considered under the following headings:

i) Carrier state

ii) Asymptomatic infection

iii) Acute hepatitis

iv) Chronic hepatitis

v) Fulminant hepatitis (Submassive to massive necrosis) In addition, progression to cirrhosis (p and association with hepatocellular carcinoma areknown to occur in certain types of hepatitis which are discussed separately later.

I. Carrier State

An asymptomatic individual without manifest disease, harbouring infection with hepatotropic virus and capable of transmitting it is called carrier state. There can be 2 types of carriers:

1. An *'asymptomatic healthy carrier'* who does not suffer from

2. An *'asymptomatic carrier with chronic disease'* capable of transmitting the organisms.

As stated before, hepatitis A and E do not produce the carrier state. Hepatitis B is responsible for the largest number of carriers in the world, while concomitant infection with HDV more often causes progressive disease rather than an asymptomatic carrier state.

There is geographic variation in incidence of HBV carrier state: while in normal population in US and western Europe it is less than 0.5%, its prevalence is much higher in Asian and tropical countries (5-20%). An estimated 2-3% of the general population are asymptomatic carriers of HCV.

MORPHOLOGIC FEATURES **-**Carriers of HBV may or may not show changes on liver biopsy.

 Healthy HBV carriers may show no changes or minor- hepatic change such as presence of fi nely granular, groundglass, eosinophilic cytoplasm as evidence of HBsAg.

 Asymptomatic carriers with chronic disease may show changes of chronic hepatitis and even cirrhosis.

II. Asymptomatic Infection-These are cases who are detected incidentally to have infection

with one of the hepatitis viruses as revealed by their raised serum transaminases or by detection of the presence of antibodies but are otherwise asymptomatic.

III. Acute Hepatitis-

The most common consequence of all hepatotropic viruses is acute inflammatory involvement of the entire liver. In general, type A, B, C, D and E run similar clinical course and show identical pathologic findings.Clinically, acute hepatitis is categorised into 4 phases: incubation period, pre-icteric phase, icteric phase and posticteric phase.

1. **Incubation period –**

It varies among different hepatotropic viruses: for hepatitis A it is about 4 weeks (15-45 days); for hepatitis B the average is 10 weeks (30-180 days); for hepatitis D about 6 weeks (30-50 days); for hepatitis C the mean incubation period is about 7 weeks (20-90 days), and for hepatitis E it is 2-8 weeks (15-60 days). The patient remains asymptomatic during incubation period but the infectivity is highest during the last days of incubation period.

2. Pre-icteric phase -This phase is marked by prodromal constitutional symptoms that include anorexia, nausea, vomiting, fatigue, malaise, distaste for smoking, arthralgia and headache. There may be low-grade fever preceding the onset of jaundice, especially in hepatitis A. The earliest laboratory evidence of hepatocellular injury in pre-icteric phase is the elevation of transa minases.

3. Icteric phase -The prodromal period is heralded by the onset of clinical jaundice and the constitutional symptoms diminish. Other features include dark-coloured urine due to bilirubinuria, clay-coloured stools due to cholestasis, pruritus as a result of elevated serum bile acids, loss of weight and abdominal discomfort due to enlarged, tender liver.

4. Post-icteric phase The icteric phase lasting for about 1 to 4 weeks is usually followed by clinical and bio –chemical recovery in 2 to 12 weeks. The recovery phase is more prolonged in hepatitis B and hepatitis C. Up to 1% cases of acute hepatitis may develop severe form of the disease (fulminant hepatitis); and 5-10% of cases progress on to chronic hepatitis.

MORPHOLOGIC FEATURES

Grossly, the liver is slightly enlarged, soft and greenish.

Histologically, the changes are as follows **.**

1. Hepatocellular injury Th ere may be variation in the degree of liver cell injury but it is most marked in zone 3 (centrilobular zone):

i) Mildly injured hepatocytes appear swollen with granularcytoplasm which tends to condense around the nucleus *(ballooning degeneration).*

ii) Others show acidophilic degeneration in which the cytoplasm becomes intensely eosinophilic, the nucleus becomes small and pyknotic and is even tually extruded from the cell, leaving behind necrotic, acidophilic mass called *Councilman body* or *acidophil body* by the process of apoptosis.

iii) Another type of hepatocellular necrosis is *dropout necrosis* in which isolated or small clusters of hepatocytes undergolysis.

iv) *Bridging necrosis*

2. Inflammatory infiltrate There is infiltration by mononuclear infl ammatory 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 phago cytosed cellular debris, bile pigment and lipofuscin granules.

4. Cholestasis Biliary stasis is usually not severe in viral hepatitis and may be present as intra cytoplasmic bile pigment granules.

5. Regeneration As a result of necrosis of hepato cytes, there is lobular disarray.

The above histologic changes apply to viral hepatitis by various types of hepatotropic viruses in general, and by HBV in particular.

IV. Chronic Hepatitis

Chronic hepatitis is defined as continuing or relapsing hepatic disease for more than 6 months with symptoms along with biochemical, serologic and histopathologic evidence of inflammation and necrosis. Majority of cases of chronic hepatitis are the result of infection with hepato tropic viruses—hepatitis B, hepatitis C and combined hepatitis B and hepatitis D infection. However, some non-viral causes of chronic hepatitis include: Wilson's disease, □-1-antitrypsin deficiency, chronicalcoholism, drug-induced injury and autoimmune diseases. The last named gives rise to *autoimmune or lupoid hepatitis* which is characterised by positive serum autoantibodies (e.g. antinuclear, anti-smooth muscle and anti-mitochondrial) and a positive LE cell test but negative for serologic markers of viral hepatitis.

MORPHOLOGIC FEATURES -The pathologic features are common to both HBV and HCV infection and include the following lesions **.**

1.Piecemeal necrosis -Piecemeal necrosis is defined as peri-portal destruction of hepatocytes at the limiting plate (*piecemeal* = piece by piece). Its features in chronic hepatitis.

i) Necrosed hepatocytes at the limiting plate in periportal zone.

ii) Interface hepatitis due to expanded portal tract by infiltration of lymphocytes, plasma cells and macrophages.

iii) Expanded portal tracts are often associated with proliferating bile ductules as a response to liver cell injury.

2. Portal tract lesions -All forms of chronic hepatitis are characterised by variable degree of changes in the portal tract.

i) Inflammatory cell infiltration by lymphocytes, plasma cells and macrophages .

ii) Proliferated bile ductules in the expanded portal tracts.

iii) Additionally, chronic hepatitis C may show lymphoid aggregates or follicles with reactive germinal centre and infiltration of inflammatory cells in the damaged bile duct epithelial cells.

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

i) There are focal areas of necrosis and inflammation within the hepatic parenchyma.

ii) Scattered acidophilic bodies in the lobule.

iii) Kupffer cell hyperplasia.

iv) 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).

v) Regenerative changes in hepatocytes in cases of persistent hepatocellular necrosis.

vi) Cases of chronic hepatitis C show moderate fatty change.

vii) Cases of chronic hepatitis B show scattered groundglass hepatocytes indicative of abundance of HBsAg in the cytoplasm.

4. Bridging fibrosis -The onset of fibrosis in chronic hepatitis from the area of interface hepatitis and bridging necrosis is a feature of irreversible damage.

i) At first, there is periportal fibrosis at the sites of inter face hepatitis giving the portal tract stellate-shaped appearance.

ii) Progressive cases show bridging fibrosis connect ing portal tract-to-portal tract or portal tract-to-central vein traversing the lobule.

iii) End-stage of chronic hepatitis is characterised by dense collagenous septa destroying lobular architecture and forming nodules resulting in postnecrotic cirrhosis.

CLINICAL FEATURES –

The clinical features of chronic hepatitis are quite variable ranging from mild disease to picture of cirrhosis.

i) **Mild chronic hepatitis** shows only slight but persistent elevation of transaminases ('transaminitis') with fatigue, malaise and loss of appetite.

ii) Other cases may show mild **hepatomegaly, hepatic tenderness and mild splenomegaly.**

iii) Laboratory findings may reveal prolonged pro- thrombin time, hyperbilirubinaemia, hyperglobulinaemia and markedly elevated alkaline phosphatase.

iv) Systemic features of circulating immune complexes due to HBV and HCV infection may produce features of immune complex vasculitis, glomerulonephritis and cryoglobulinaemia in a proportion of cases.

V. Fulminant Hepatitis (Submassive to Massive Necrosis)-

Fulminant hepatitis is the most severe form of acute hepatitis in which there is rapidly progressive hepato cellular failure. Two patterns are recognised—*submassive necrosis* having a less rapid course extending up to 3 months; and *massive necrosis* in which the liver failure is rapid and fulminant occurring in 2-3 weeks.Fulminant hepatitis of either of the two varieties can occur from viral and non-viral etiologies:

 Acute viral hepatitis accounts for about half the cases, most often from HBV and HCV; less frequently from combined HBV HDV and rarely from HAV. However, HEV infection is a serious complication in pregnant women

 Non-viral causes include acute hepatitis due to drug toxicity (e.g. acetaminophen, non-steroidal anti-infl amatory drugs, isoniazid, halothane and anti-depressants), poisonings, hypoxic injury and massive infiltration of malignant tumours into the liver.

MORPHOLOGIC FEATURES- Grossly, the liver is small and shrunken, often weighing 500-700 gm. The capsule is loose and wrinkled. The sectioned surface shows diffuse or random

involvement of hepatic lobes. There are extensive areas of muddy-red and yellow necrosis (previously called *acute yellow atrophy)* and patches of green bile staining.

Histologically, two forms of fulminant necrosis are distinguished—submassive and massive necrosis **.**

1.In **submassive necrosis,** large groups of hepatocytes in zone 3 (centrilobular area) and zone 2 (mid zone) are wipedout leading to a collapsed reticulin framework. Regeneration in submassive necrosis is more orderly and may result in restoration of normal architecture.

2. In **massive necrosis,** the entire liver lobules are necrotic. As a result of loss of hepatic parenchyma, all that is left is the collapsed and condensed reticulin framework and portal tracts with proliferated bile ductules plugged with bile. Inflammatory infiltrate is scanty. Regeneration, if it takes place, is disorderly forming irregular masses of hepatocytes. Fibrosis is generally not a feature of fulminant hepatitis.

CHAPTER-6

OTHER INFECTIONS AND INFESTATIONS

Apart from viral hepatitis, the liver is aff ected by infections with bacteria, spirochaetes and fungi and is involved in some parasitic infestations. Some common examples of such conditions are described below.

CHOLANGITIS-

Cholangitis is the term used to describe inflammation of the extrahepatic or intrahepatic bile ducts, or both. There are two main types of cholangitis—pyogenic and primary sclerosing.

While primary sclerosing cholangitis is discussed later with biliary cirrhosis (page 610), pyogenic cholangitis is described below.

Pyogenic Cholangitis-

Cholangitis occurring secondary to obstruction of a major extrahepatic duct causes pyogenic cholangitis. Most commonly, the obstruction is from impacted gallstone; other causes are carcinoma arising in the extrahepatic ducts, carcinoma head of pancreas, acute pancreatitis and inflammatory strictures in the bile duct. Bacteria gain entry to the obstructed duct and proliferate in the bile. Infection spreads along the branches of obstructed duct and reaches the liver, termed *ascending cholangitis.* The common infecting bacteria are enteric organisms such as *E. coli, Klebsiella* and *Enterobacter.*

MORPHOLOGIC FEATURES **-**The affected ducts show small beaded abscesses accompanied by bile stasis along their course and larger abscesses within the liver. The abscesses are composed of acute infl am matory cells which in time are replaced by chro nic infl ammatory cells and enclosed by fibrous capsule.

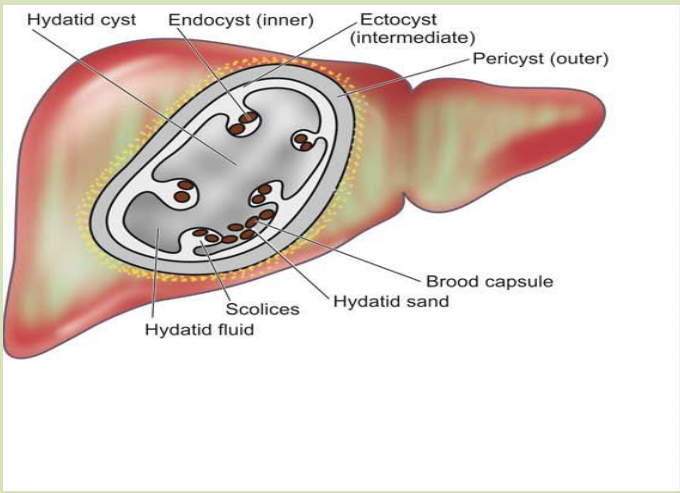
HEPATIC TUBERCULOSIS-

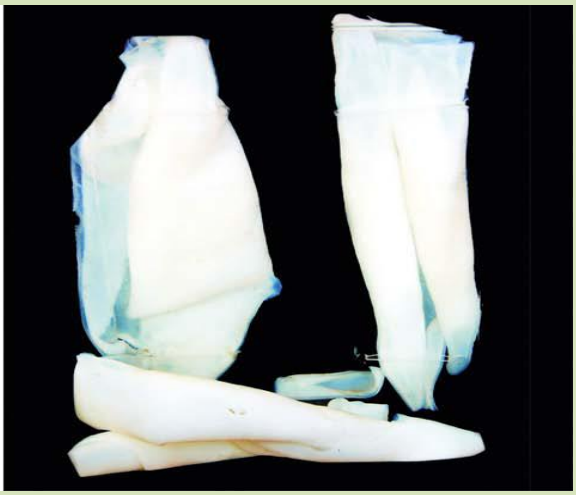
Tuberculosis of the liver occurs as a result of military dissemination from primary complex or from chronic adult pulmonary tuberculosis. The diagnosis is possible by liver biopsy. Th e patients may have unexplained fever, jaundice, hepatomegaly or hepatosplenomegaly. There may be elevated serum alkaline phosphatase levels and hyperglobulinaemia.

MORPHOLOGIC FEATURES- The basic lesion is the epithelioid cell granuloma characterised by central caseation necrosis with destruction of the reticulin framework and peripheral cuff of lymphocytes . Ziehl-Neelsen staining for AFB or culture of the organism from the biopsy tissue is confirmatory. Rare lesions consist of tuberculous cholangitis and tuberculous pylephlebitis.

HYDATID DISEASE (ECHINOCOCCOSIS)-

- Hydatid disease occurs as a result of infection by the larval cyst stage of the tapeworm, *Echinococcus granulosus.* The dog is the common defi nite host, while man, sheep and cattle are the intermediate hosts. The dog is infected by eating the viscera of sheep containing hydatid cysts.
- The infected faeces of the dog conta minate grass and farmland from where the ova are ingested by sheep, pigs and man. Thus, man can acquire infection by handling dogs as well as by eating contaminated vegetables.
- The ova ingested by man are liberated from the chitinous wall by gastric juice and pass through the intestinal mucosa from where they are carried to the liver by portal venous system. These are trapped in the hepatic sinusoids where they even tually develop into hydatid cyst.
- About 70% of hydatid cysts develop in the liver which acts as the first filter for ova. However, ova which pass through the liver enter the right side of the heart and are caught in the pulmonary capillary bed and form pulmonary hydatid cysts. Some ova which enter the systemic circulation give rise to hydatid cysts in the brain, spleen, bone and muscles.
- The disease is common in sheep-raising countries such as Australia, New Zealand and South America. The *uncomplicated hydatid cyst* of the liver may be silent or may produce dull ache in the liver area and some abdominal distension.





MORPHOLOGIC FEATURES –

Hydatid cyst grows slowly and may eventually attain a size over 10 cm in diameter in about 5 years. *E. granulosus* generally causes unilocular hydatid cyst while *E. multilocularis* results in multilocular or alveolar hydatid disease in the liver.

The cyst wall is composed of 3 distinguishable zones—

outer *pericyst,* intermediate characteristic *ectocyst* and inner *endocyst* **.**

1. Pericyst is the outer host infl ammatory reaction consisting of fibroblastic proliferation, mononuclear cells, eosinophils and giant cells, eventually deve loping into dense fibrous capsule which may even calcify.

2. Ectocyst is the intermediate layer composed of characteristic acellular, chitinous, laminated hyaline material.

3. Endocyst is the inner germinal layer bearing daughter cysts (brood-capsules) and scolices projecting into the lumen.

Hydatid sand is the grain-like material composed of numerous scolices present in the hydatid fluid. Hydatid fluid, in addition, contains antigenic proteins so that its liberation into circulation gives rise to pronounced eosinophilia or may cause anaphylaxis.

CHEMICAL AND DRUG INJURY

HEPATIC DRUG METABOLISM –

The liver plays a central role in the metabolism of a large number of organic and inorganic chemicals and drugs which gain access to the body by inhalation, injection, or most commonly, via the intestinal tract.

The liver cells via P-450 cytochrome and cytochrome reductase enzyme systems. Other steps involved in the drug metabolism are its conjugation with an endogenous mole cule, its active transport from the hepatocytes and ultimately its excretion in the bile or in urine depending upon the molecular weight of the substance. A number of risk factors predispose an individual to hepatic drug injury such as pre-existing liver disease, ageing, female sex and genetic inability to perform a particular bio transformation.

HEPATOTOXICITY-

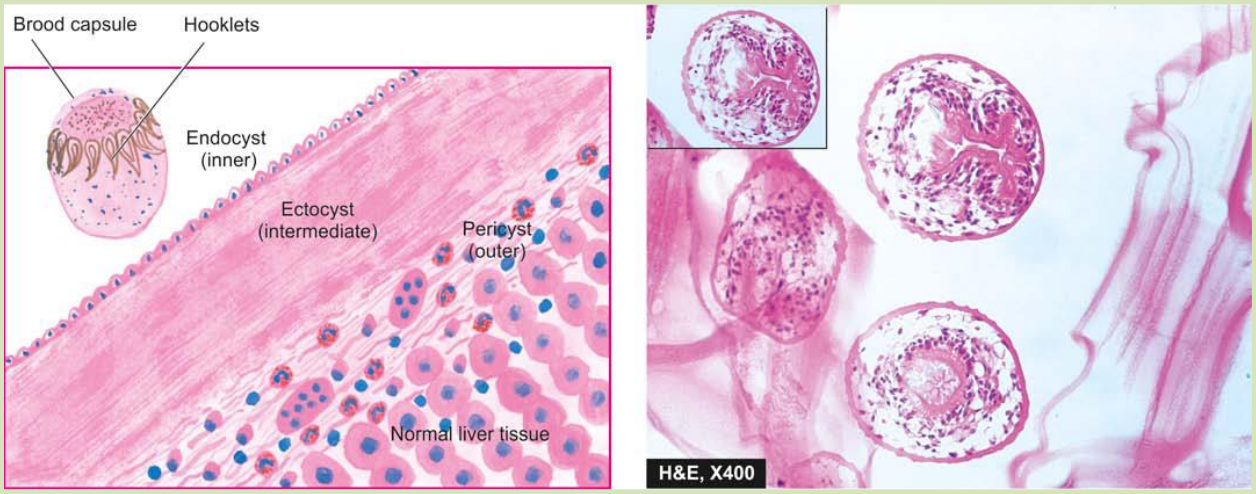
- Toxic liver injury produced by drugs and chemicals may virtually mimic any form of naturally-occurring liver disease. In fact, any patient presenting with liver diseaseor unexplained jaundice is thoroughly questioned about history of drug intake or exposure to chemicals.
- Hepatotoxicity from drugs and chemicals is the commonest form of iatrogenic disease. Severity of hepatotoxicity is greatly increased if the drug is continued after symptoms develop.

- Among the various *inorganic compounds* producing hepatotoxicity are arsenic, phosphorus, copper and iron. *Organic agents* include certain naturally-occurring plant toxins such as pyrrolizidine alkaloids, mycotoxins and bacterial toxins.

- The synthetic group of organic compounds are a large number of medicinal agents. In addition, exposure to hepatotoxic compounds may be occupational, environmental or domestic that could be accidental, homicidal or suicidal ingestion. In general, drug reactions affecting the liver are divided into two main classes:

1. **Direct or predictable,** when the drug or one of its metabolites is either directly toxic to the liver or it lowers the host immune defense mechanism. The adverse effects occur in

most individuals who consume them and their hepatotoxicity is dose-dependent e.g. carbon tetrachloride.



2. **Indirect or unpredictable or idiosyncratic,** when the drug or one of its metabolites acts as a hapten and induces hypersensitivity in the host. In many instances, drug hepatotoxicity is associated with appearance of autoantibodies to liver-kidney microsomes (i.e. anti-LKM2) directed against cytochrome P450 enzyme.

   The hepato -toxicity by this group does not occur regularly in all individuals and the effects are usually not dose-related e.g. acetaminophen. A simplified clinic pathologic classification of important hepatic drug reactions and the agents causing them is presented in **.**

   The changes produced by hepatotoxic agents may vary from mild, which are diagnosed only by elevated serum transaminases, to instances of massive necrosis and death. The pathologic changes by hepatotoxins include 2 large categories:

1. *Acute liver disease* characterised by cholestasis, hepatocellular necrosis, fatty change, granulomatous reaction or vascular disease.
2. *Chronic liver disease* characterised by variable degree of fi brosis, cirrhosis or neoplasia.

CHAPTER -7

STRUCTURE AND FUNCTION OF BILIARY SYSTEM

NORMAL STRUCTURE

ANATOMY-

- The gallbladder is a pear-shaped organ, 9 cm in length and has a capacity of approximately 50 ml. It consists the *fundus, body* and *neck* that tapers into the cystic duct.
- The two hepatic ducts from right and left lobes of the liver unite at the porta hepatis to form the common hepatic duct which is joined by the cystic duct from the gallbladder to form the common bile duct.
- The common bile duct enters the second part of the duodenum posteriorly. In about 70% of cases, it is joined by the main pancreatic duct to form the combined opening in the duodenum *(ampulla of Vater).* In 30% cases, the common bile duct and the pancreatic duct open separately into the duodenum.
- The common bile duct in its duodenal portion is surrounded by longitudinal and circular muscles derived from the duodenum forming *sphincter of Oddi.*

HISTOLOGY- Histologically, the gallbladder, unlike the rest of gastrointestinal tract, lacks the muscularis mucosae and submucosa. The wall of the gallbladder is composed of the following 4 layers:

1. Mucosal layer: It has a single layer of tall columnar epithelium which is thrown into permanent folds that are larger and more numerous in the neck of the gallbladder.

2. Smooth muscle layer: External to the lamina propria are smooth muscle bundles in layers inner longitudinal, middle oblique, and outer circular.

3. Perimuscular layer: Outer to the muscle layer is a zone of fibrous connective tissue with some interspersed fat cells.

3. **Serosal layer:** The perimuscular layer is covered by serosa on the peritoneal surface of the gallbladder. The peritoneum the gallbladder except in the region of gallbladder fossa where it is embedded in the liver. The *extrahepatic bile ducts* are also lined by tall columnar epithelium that overlies the lamina propria. It is surrounded by dense layer of fibromuscular tissue.

FUNCTIONS –

The main function of the gallbladder is to store and concentrate the bile secreted by the liver and then deliver it into the intestine for digestion and absorption of fat. The concentrating ability of the gallbladder is due to its absorptive mucosal surface that has numerous folds. Normally, the liver secretes approximately 500 ml of bile per day and the gallbladder concentrates it 5-10 times. The motility, concentration and relaxation of the gallbladder are under the influence of a peptide hormone, cholecystokinin, released from neuroendocrine cells of the duode num and jejunum.

CHAPTER -8

BILIARY SYSTEM DISORDER

CONGENITAL ANOMALIES-

Several uncommon congenital anomalies of the biliary system have been described. These include: agenesis, duplication and heterotopic tissue. However, *congenital cystic lesions* of the bile ducts (as also of the liver) are more frequently diagnosed. These conditions include: congenital intrahepatic biliary dilatation (Caroli's disease), choledochal cysts, polycystic liver disease and congenital hepatic fibrosis. All of them may be complicated by malignant change.

CHOLELITHIASIS (GALLSTONES) -

Gallstones are formed from constituents of the bile (viz. cholesterol, bile pigments and calcium salts) along with other organic components. Accordingly, the gallstones commonly contain cholesterol, bile pigment and calcium salts in varying proportions. They are usually formed in the gallbladder, but sometimes may develop within extrahepatic biliary passages, and rarely in the larger intrahepatic bile duct.

RISK FACTORS

The incidence of gallstones varies markedly in different geographic areas, age, gender, diet and various other risk factors. These factors which largely pertain to cholesterol stones can be summed up in the old saying that gallstones are common in 4F's acronym for—*'fat, female, fertile (multipara)* and *forty'.* Some of the risk factors in lithogenesis are explained below:

1. Geography Gallstones are quite prevalent in almost the entire Western world. American Indians have the highest known prevalence. Black Africans and popu lations in the Eastern world are relatively free of cholelithiasis.

2. Genetic factors -There is increased frequency of gallstones in first-degree relatives of patients with cholelithiasis. Patients of gallstones disease have increased secretion of dietary cholesterol in bile than in non-gallstone patients inspite of high-cholesterol diet. Recently, mutation in *CYP7A1* gene has been found that results in deficiency of enzyme, cholesterol 7-hydroxylase, which has a role in bile acid synthesis.

3. Age -There is steady increase in the prevalence of gallstones with advancing age which may be related to increased cholesterol content in the bile. The incidence increases above the age of 40 and presentation of disease is usually in the 50s and 60s.

4. Sex -Gallstones are twice more frequent in women than in men. In the United States, autopsy series have shown gallstones in about 20% of women and 8% of men above the age of 40. The incidence is higher in multiparous women than in nulliparous women.

5. Drugs -Women on oestrogen therapy or on birth control pills have higher incidence of gallstone.

6. Obesity -Obesity is associated with increased cholesterol synthesis and its excretion resulting in higher incidence of gallstones in obese patients.

7. Diet- Deficiency of dietary fi bre content is linked to higher prevalence of gallstones. A moderate consumption of alcohol, however, seems to protect against gallstones.

8. Gastrointestinal diseases-Certain gastrointestinal disorders such as Crohn's disease, ileal resection, ileal bypass surgery etc are associated with interruption in entero hepatic circulation followed by gallstone formation.

9. Factors in pigment gallstones- All the above factors apply largely to cholesterol stone.

TYPES OF GALLSTONES

As stated before, gallstones contain cholesterol, bile pigment and calcium carbonate, either in pure form or in various combinations. Accor dingly, gallstones are of 3 major types

1. PURE GALLSTONES -They constitute about 10% of all gallstones. They are further divided into 3 types according to the component of bile forming them. These are as under

i) Pure cholesterol gallstones: They are usually solitary, oval and fairly large (3 cm or more) fi lling the gallbladder. Their surface is hard, smooth, whitish-yellow and glistening.On cut section, the pure choles terol stone shows radiating glistening crystals. It may result in deposition of cholesterol within the mucosal macro phages of the gallbladder producing *cholesterolosis* which is an asymptomatic condition**.** Pure cholesterol stones are radiolucent but 10- 20% of them have calcium carbonate in them which renders them opaque.

ii) Pure pigment gallstones: These stones composed primarily of bile pigment, calcium bilirubinate, and contain less than 20% cholesterol. They are generally multiple, jet-black and small (less than 1 cm in diameter). They have mulberry like external surface. Th ey are soft and can be easily crushed. The gallbladder usually appears uninvolved.

iii) Pure calcium carbonate gallstones: They are rare. Calcium carbonate gallstones are usually multiple, grey-white, small (less than 1 cm in diameter), faceted and fairly hard due to calcium content. They, too, do not produce any change in the gallbladder wall.

2. MIXED GALLSTONES -Mixed gallstones are the most common (80%) and contain more than 50% cholesterol monohydarate plus an admixture of calcium salts, bile pigments and fatty acids. They are always multiple, multifaceted so that they fit together and vary in size from as tiny as sand-grain to 1 cm or more in diameter. On section, they have distinct laminated structure with alternating dark pigment layer and pale-white layer revealing different combinations of cholesterol, bilirubin pigment and calcium carbonate, laid down in layers at different times **.** Mixed gall stones are invariably accompanied by chronic cholecystitis.

3. COMBINED GALLSTONES -They comprise about 10% of all gallstones. Combined gallstones are usually solitary, large and smooth-surfaced. It has a *pure gallstone nucleus* (cholesterol, bile pigment or calcium carbonate) and outer shell of mixed gallstone; or a *mixed gallstone nucleus* with pure gallstone shell Combined gallstones, too, are associated with chronic cholecystitis.

CLINICAL MANIFESTATIONS AND COMPLICATIONS-

In about 50% cases, gallstones cause no symptoms and may be diagnosed by chance during investi gations for some other condition *(silent gallstones).* The future course in such asymptomatic silent cases is controversial, most surgeons advocating chole cystec tomy while physicians advising watchful waiting. Follow-up studies, however, show that only about 10% of such cases develop symptoms. Symptomatic gallstone disease appears only when complications develop.

These are as under

1. Cholecystitis The relationship between cholelithiasis and cholecystitis is well known but it is not certain which of the two comes first. Th e patients with gallstones develop symptoms due to cholecystitis which include typical biliary colic precipitated by fatty meal, nausea, vomiting, fever alongwith leucocytosis and high serum bilirubin.

2. Choledocholithiasis- Gallstones may pass down into the extrahepatic biliary passages and the small bowel, or less often they may be formed in the biliary tree. Patients with gallstone in the common bile duct frequently develop pain and obstructive jaundice. Fever may develop due to bacterial ascending cholangitis.

3. Mucocele and empyema -Mucocele or hydrops of the gallbladder is distension of the gallbladder by clear, watery mucinous secretion resulting from impacted stones in the neck of the gallbladder. When it gets infected empyema is formed.

4. Biliary fistula -An uncommon complication of cholelithiasis is formation of fi stulae between one part of the biliary system and the bowel, and rarely between the gallbladder and the skin.

5. Gallstone ileus A gallstone in the intestine may be passed in the faeces without causing symptoms. Occasionally, however, gallstones in the intestine may cause intestinal obstruction called gallstone ileus.

6. Pancreatitis Obstructive cholecystasis may result in acute pancreatitis.

7. Gallbladder cancer Th ere is a small and doubtful risk of development of cancer of the gallbladder in cases with cholelithiasis.

CHOLECYSTITIS:

Cholecystitis or inflammation of the gallbladder may be acute,chronic, or acute superimposed on chronic. Though chroniccholecystitis is more common, acute cholecystitis is a surgical emergency.

ACUTE CHOLECYSTITIS-

In many ways, acute cholecystitis is similar to acute appendicitis.The condition usually begins with obstruction, followed by infection later.

ETIOPATHOGENESIS- Based on the initiating mechanisms, acute cholecystitis occurs in two types of situ ations—*acute calculous* and *acute acalculous cholecystitis.*

1.**Acute calculous cholecystitis** -In 90% of cases, acute cholecystitis is caused by obstruction in the neck of the gallbladder or in the cystic duct by a gallstone. The commonest location of impaction of a gallstone is in Hartmann's pouch. Obstruction results in distension of the gallbladder followed by acute inflammation which is initially due to chemical irritation. Later, however, secon dary bacterial infection, chiefly by *E. coli* and *Streptococcus faecalis,* supervenes.

2. **Acute acalculous cholecystitis** -The remaining 10% cases of acute cholecystitis do not contain gallstones. In such cases, a variety of causes have been assigned such as previous nonbiliary surgery, multiple injuries, burns, recent childbirth, severe sepsis, dehydration, torsion

of the gallbladder and diabetes mellitus. Rare causes include primary bacterial infection like salmonellosis and cholera and parasitic infestations.

MORPHOLOGIC FEATURES- Except for the presence or absence of calculi, the two forms of acute cholecystitis are morphologically similar.

Grossly, the gallbladder is distended and tense. The serosal surface is coated with fibrinous exudate with congestion and haemorrhages. The mucosa is bright red. The lumen is filled with pus mixed with green bile. In calculous cholecystitis, a stone may get impacted in the neck or in the cystic duct. When obstruction of the cystic duct is complete, the lumen is filled with purulent exudate and the condition is known as *empyema of the gallbladder.*

Microscopically, wall of the gallbladder shows marked inflammatory oedema, congestion and neutrophilic exudate. There may be frank abscesses in the wall and gangrenous necrosis with rupture into the peritoneal cavity *(gangrenous cholecystitis).*

CLINICAL FEATURES -The patients of acute cholecystitis of either type have similar clinical features. They present with severe pain in the upper abdomen with features of peritoneal irritation such as guarding and hyperaesthesia. The gallbladder is tender and may be palpable. Fever, leucocytosis with neutrophilia and slight jaundice are generally present. Early cholecystectomy within the first three days has a morta lity of less than 0.5% and risk of complications such as perforation, biliary fi stula, recurrent attacks and adhesions is avoided.

However, medical treatment brings about resolution in a fairly large proportion of cases though chances of recurrence of attack persist.

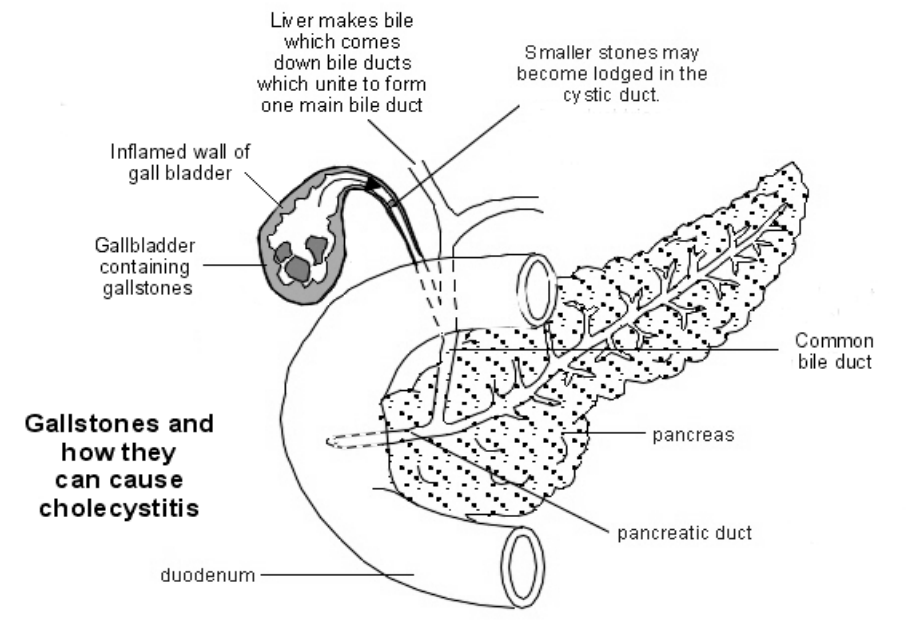
CHRONIC CHOLECYSTITIS -

Chronic cholecystitis is the commonest type of clinical gallbladder disease. There is almost constant association of chronic cholecystitis with cholelithiasis.

ETIOPATHOGENESIS –

The association of chronic cholecystitis with mixed and combined gallstones is virtually always present. However, it is not known what initiates the inflammatory response in the gallbladder wall. Possibly, supersaturation of the bile with cholesterol predisposes to both gallstone

formation and inflammation. In some patients, repeated attacks of mild acute cholecystitis result in chronic cholecystitis.



TYPE FREQUENCY COMPOSITION GALLBLADDER

CHANGES

APPEARANCE

1. ***Pure gallstones*** 10% i) Cholesterol Cholesterolosis Solitary, oval, large, smooth, yellow white;on C/S radiating glistening crystals.

ii) Bile pigment No change Multiple, small, jet-black, mulberryshaped; on C/S soft black.

iii) Calcium carbonate No change Multiple, small, grey-white, faceted; C/S hard

2. ***Mixed gallstones*** 80% Cholesterol, bile pigment and calcium carbonate in varying combination Chronic cholecystitis Multiple, multifaceted, variable size, on C/S laminated alternating darkpigment layer and pale-white layer

3. ***Combined gallstones***

10% Pure gallstone nucleus with mixed gallstone shell, or mixed gallstone mnucleus with pure gallstone shell Chronic cholecystitis Solitary, large, smooth; on C/S central nucleus of pure gallstone with mixed shell or vice versa.

MORPHOLOGIC FEATURES Grossly, the gallbladder is generally contracted but may be normal or enlarged The wall of the gallbladder is thickened which on cut section is grey-white due to dense fibrosis or may be even calcifi ed. Th e mucosal folds may be intact, thickened, or flattened and atrophied. The lumen commonly contains multiple mixed stones or a combined stone.

Histologically, the features are as under

1. Thickened and congested mucosa but occasionally mucosa may be totally destroyed.
2. Penetration of the mucosa deep into the wall of the gallbladder up to muscularis layer to form *Rokitansky,Aschoff 'sinuses.*
3. Variable degree of chronic infl ammatory reaction, consisting of lymphocytes, plasma cells and macrophages, present in the lamina propria and subserosal layer.
4. Variable degree of fi brosis in the subserosal and subepithelial layers. A few morphologic variants of chronic chole cystitis are considered below:

Cholecystitis glandularis, when the mucosal folds fuse together due to infl ammation and result information of crypts of epithelium buried in the gallbladder wall.

 Porcelain gallbladder is the pattern when the gallbladder wall is calcified and cracks like an egg-shell.

 Acute on chronic cholecystitis is the term used for the morphologic changes of acute cholecystitis superimposed on changes of chronic cholecystitis.

CLINICAL FEATURES Chronic cholecystitis has ill-definedand vague symptoms. Generally, the patient—*a fat, fertile, female of forty or fi fty,* presents with abdo minal distension or epigastric discomfort, especially after a fatty meal. There is a constant dull ache in the right hypochondrium and epigastrium and tenderness over the right upper abdomen. Nausea and Flatulence are common. Biliary colic may occasionally occur due to passage of stone into the bile ducts. Cholecystography usually allows radiologic visualisation of the gallstones.

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Contact Us:

University Campus Address:

Jayoti Vidyapeeth Women's University

Vadaant Gyan Valley, Village-Jharna, Mahala Jobner Link Road,

Jaipur Ajmer Express Way, NH-8, Jaipur- 303122, Rajasthan (INDIA)

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