MODULE: CLINICAL PATHOLOGY
Unit: Hepatobiliary System

Lecturer
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UNIT OUTLINE

	No	Topic	Hours
Gall Bladder	1.	Introduction to Gall Bladder and Gall Stones	1
	2.	Cholecystitis	1
Pancreas	3.	Disorders of the Pancreas	1
Liver	4.	Introduction Manifestations and Investigations	2
	5.	Circulatory Disturbances	1
	6.	Viral Hepatitis	2
	7.	Non – Viral Hepatitis	2
	8.	Alcoholic Liver Disease and Liver Cirrhosis	1
	9.	Metabolic Liver Disease and Tumours	1
		TOTAL	**12**

Lesson 1: GALL BLADDER - INTRODUCTION AND GALL STONES

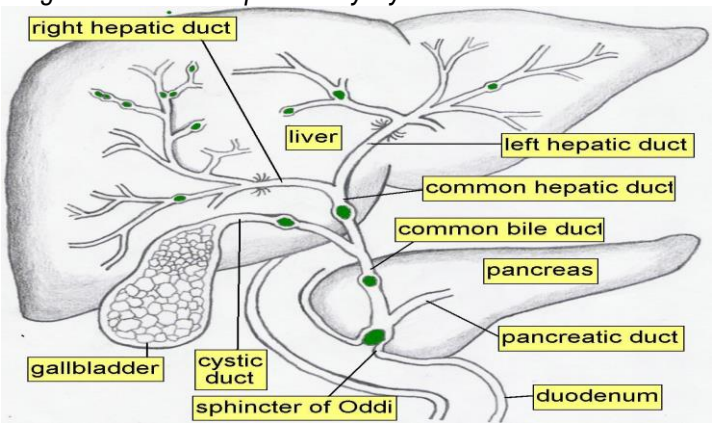
Learning Outcomes

At the end of the lesson the learner should be able to: -
1) Describe the structure and functions of the organs of the hepatobiliary system
2) Describe the pathology of gall stones
3) Investigate gall stones

1.0. INTRODUCTION – HEPATOBILIARY ANATOMY AND PHYSIOLOGY

- Hepatobiliary system includes the liver, pancreas, gallbladder and bile ducts

Diagram 1.1: The Hepatobiliary System

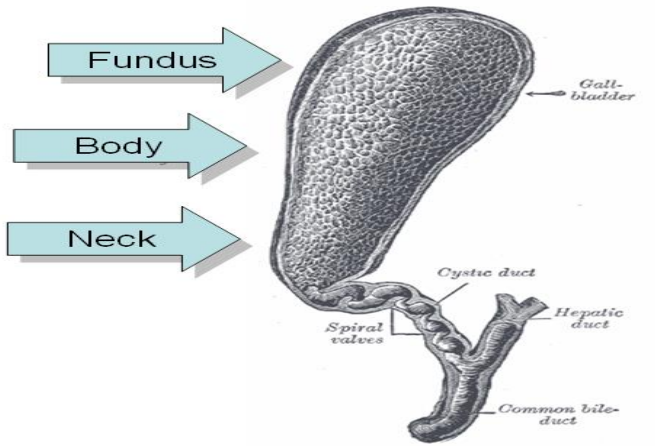


2.0. GALL BLADDER ANATOMY

Gross Anatomy

- Saclike pear-shaped 9 cm long organ attached to the inferior surface of the liver with a storage capacity of 35 – 100 ml (average 50 ml)
- Consists of the fundus, body and neck that taper into the cyst
- Stores bile produced by the liver (produces about 1-2 litres/day)

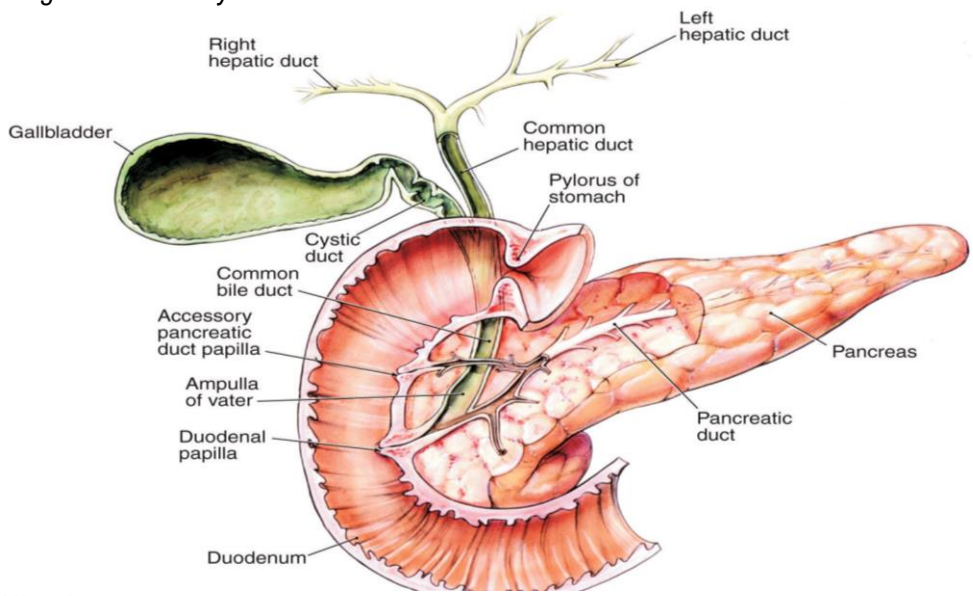
Diagram 1.2: The Gall Bladder



Biliary Ducts and Tracts

- Two hepatic ducts from the liver (one from each liver lobe) unite at the porta hepatis to form the common hepatic duct which is joined by the cystic duct from the gall bladder to form the common bile duct (CBD)
- The CBD enters the second part of the duodenum posteriorly
- In 70% cases the CBD is joined by the main pancreatic duct forming a combined opening into the duodenum (Ampulla of Vater) while in 30% cases the two open into the duodenum as separate entities
- Sphincter of Oddi is found on the duodenal portion of the CBD.

Diagram 1.3: Biliary Tracts



Histology

- Composed of 4 layers: - mucosal, smooth muscle, perivascular and serosal layer
  - i) Mucosal layer - single layer of tall columnar epithelium with numerous large permanent folds, delicate lamina propria containing capillaries and few acinar glands in the neck region
  - ii) Smooth muscle layer - external to the lamina propria and has three layers of muscles – inner longitudinal, middle oblique and outer circular.
  - iii) Perivascular layer - fibrous connective tissue interspersed with fat cells and contains arteries, veins, lymphatics, nerves and paraganglia.
  - iv) Serosal layer - covers the perivascular layer; it is on the peritoneal surface of the gall bladder; the peritoneum covers the gall bladder except where the gall bladder is embedded in the liver.

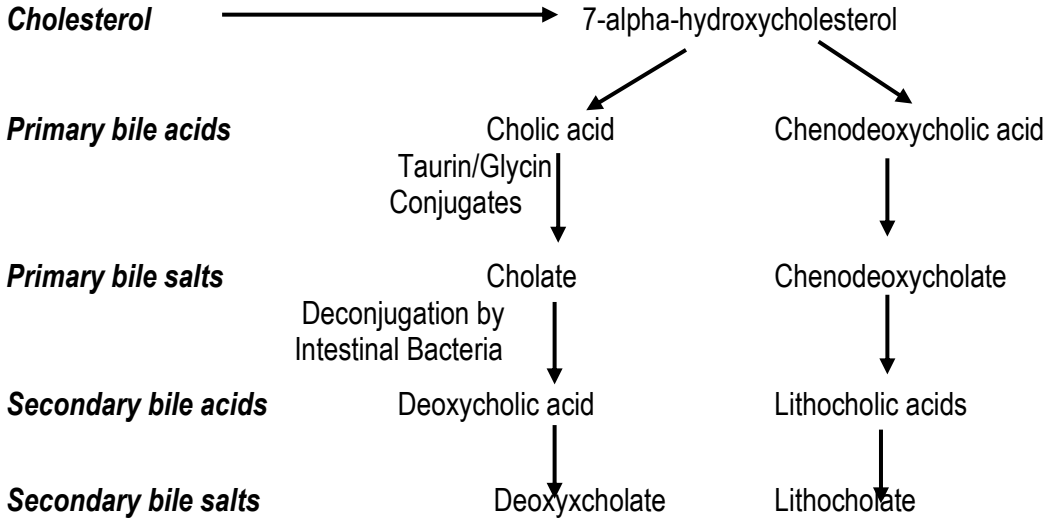
3.0. FUNCTIONS

1. Concentrate the watery bile secreted by the liver by active reabsorption of electrolytes (Na^+[major cation], Cl^- and HCO_3^-) with an iso-osmotic amount of water. Bile is delivered into the intestines for digestion and absorption of fat
2. Concentrations of non-absorbable molecules e.g. conjugated bilirubin, cholesterol and phospholipids also increase during the process of concentrating bile.
3. Bile is used in emulsification of fats in the intestines and cholesterol excretion

4.0. BILE ACIDS

- Liver produces four bile acids- two primary bile acids (cholic acid and chenodeoxycholic acid) and two secondary (deoxycholate and lithocholate).
- Primary bile acids are synthesized in the liver from cholesterol and secreted in bile as sodium salts conjugated with amino acids glycine or taurine (primary bile salts)
- Bacteria in intestinal lumen convert the primary bile acids to secondary bile salts deoxycholate and lithocholate
- Part of the secondary bile acids enters the enterohepatic circulation
- Deficiency of bile acids leads to impaired micelle formation and malabsorption of fats
- Characteristics
  i) pH of 5.7-8.6-
  ii) contents - water (85-95%), bile salts and bile acids (140-2230 mg/100 ml), bile pigment (Bilirubin – 12-70 mg/100 ml), cholesterol (97-320 mg/100 ml); inorganic ions - Sodium (145-165 mEq/L), Potassium- (2.7 -4.9 mEq/L), Chloride (88- 115 mEq/L) and Bicarbonate (27-55 mEq/L); phospholipids (mainly lecithin –140-810 mg/100 ml) and bile acids – cholic and chenodeoxycholic (synthesized in the liver from cholesterol)

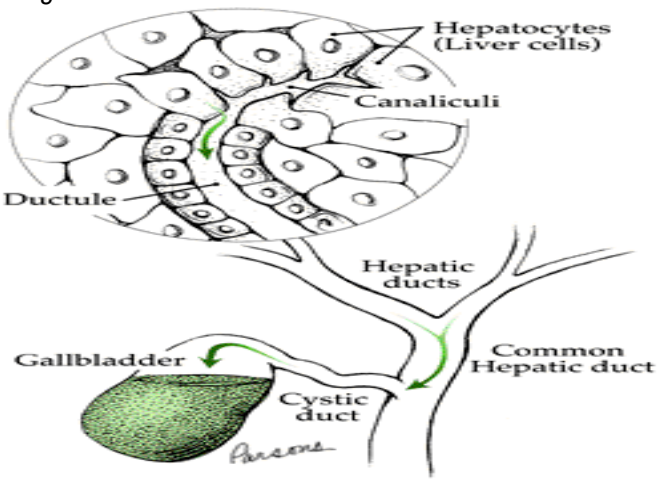
Diagram 1.4: Synthesis of Bile acids



Bile Flow

- Motility of gall bladder is influenced by *cholecystokinin hormone* secreted by the neuro-endocrine cells of the duodenum and jejunum following the presence of fats
- Biile is released into the duodenum via the ampulla of Vater following contraction of the gall bladder and relaxation of the sphincter of Oddi. Bile is the excretory route for bilirubin and drugs together with their metabolites.

Diagram 1.5: Bile Flow



5.0. PATHOPHYSIOLOGY OF GALL BLADDER DISORDERS

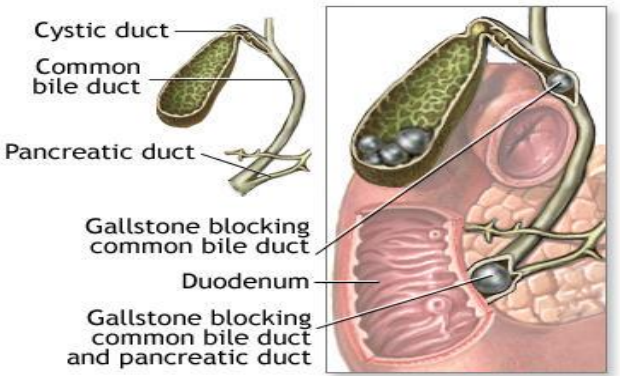
- Congenital abnormalities; Cholelithiasis (Gall stones); Cholecystitis – Acute or Chronic; Obstruction of CBD; Tumours

6.0. GALL STONES (CHOLELITHIASIS)

6.1. Introduction

- Formed from constituents of bile such as cholesterol, bile pigments and calcium salts and other organ components in varying proportions
- Sites of stone formation include the gall bladder (commonly), extrahepatic biliary tree and rarely the intrahepatic duct.

Diagram 1.6: Gallstones



6.2. Risk Factors

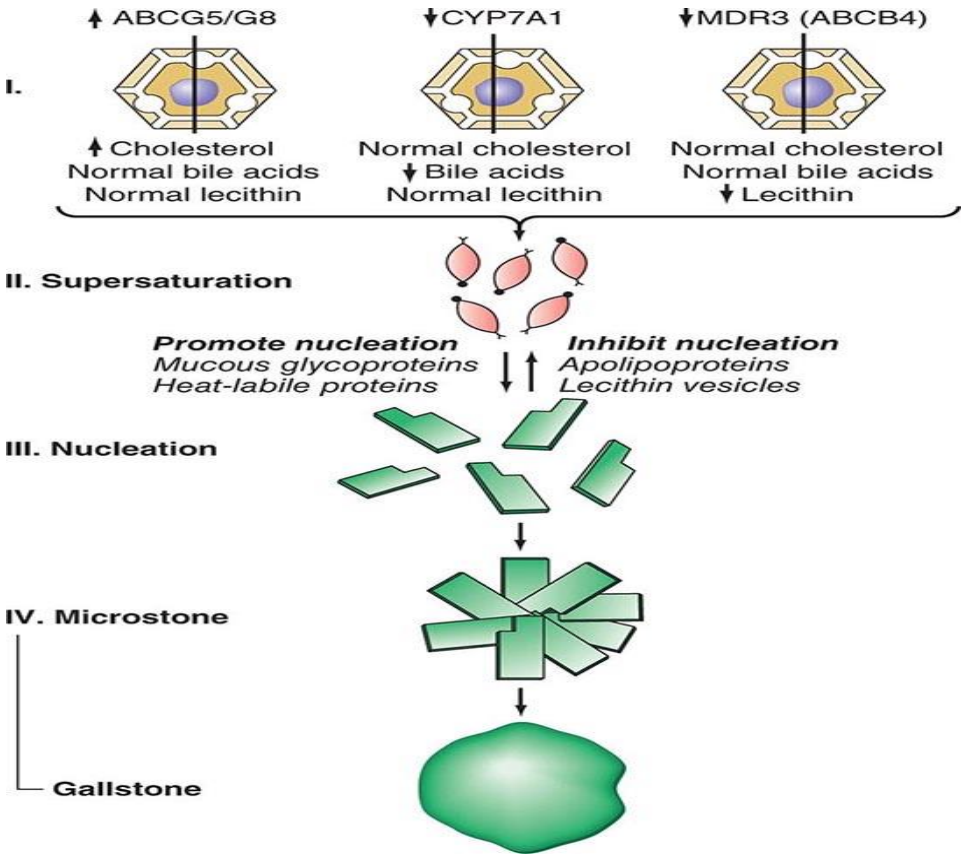
- Mnemonic of 4F's –Fat, Female, Fertile (multipara) and Forty or Fifty
- Can be ethnic-geographical, age and sex, environmental factors, acquired disorders and hereditary factors.
  i) Cholesterol stones
     - Geographical locations (Europe, America), advancing age, obesity. rapid weight gain, genetic factors (inborn errors of bile acid metabolism), sex (F: M ratio is 2:1) – female sex hormones lead to increased risk in females, during pregnancy and use of oral contraceptives, gall balder stasis, hyperlipidaemia
  ii) Pigment stones Demography – Asia, rural setups

- GIT diseases (Crohn's disease, ileal resection, and ileal bypass interrupt enterohepatic circulation), chronic haemolytic syndromes (e.g. haemolytic anaemias, cirrhosis, and hepatocellular disease), biliary infection

6.3. Pathogenesis

- Gall stone formation involves stages of supersaturation, nucleation, microstone and gallstone

Diagram 1.7: Pathogenesis of Gallstones



Cholesterol stones

- Normally cholesterol is rendered soluble by combining detergents such as water soluble bile salts and water insoluble lecithins
- Stones form when cholesterol exceeds the solubilizing capacity of bile (super saturation) and cannot remain spread in the salts and nucleates into solid crystals
- Cholesterol stones arise exclusively from the gall bladder
- Pathogenesis is determined by four major factors
  - i) Super saturation of bile with cholesterol (change in bile composition) due to increased proportion of cholesterol with decreased proportion of bile acids
  - ii) Accelerated cholesterol nucleation promoted by calcium salts
  - iii) Hypomotility of the gall bladder delays emptying of sludge or debris which promotes nucleation and thus stone formation
  - iv) Hyper secretion of mucous - the mucous traps the crystals permitting formation of stones

Pigment Stones

- Are mixtures of abnormal insoluble calcium salts of unconjugated bilirubin with inorganic calcium salts
- Component of bilirubin in the stones is low but increases when biliary infection (e.g. *Ascaris lumbricoides, Esherichia coli*, Liver flukes) leads to release of *β-glucuronidases* which hydrolyze bilirubin glucuronides

6.4. Classification

- Classified according to their composition: - pure (10%) - pure cholesterol, pigment gallstones and calcium carbonate, mixed (Laminated) gallstones (80%) or combined gallstones (10%)

	Types	Features
1.	Pure Cholesterol gallstones	• Result from the secretion of cholesterol-saturated bile by the liver • Solitary, large (≥3 cm), oval, soapy, pale yellow or almost white; float in water • Transparent and glittering crystalline surface • Incidence is high in patients taking lipid lowering drugs e.g. fibric acid derivative clofibrate
2.	Pure Pigment gallstones	• Composed of bile pigment- calcium bilirubinate • Multiple, soft mulberry-shaped, jet-black small (less than 1 cm in diameter) stones and produce no change in the gall bladder • Occur in chronic haemolytic states e.g. hereditary spherocytosis
3.	Pure Calcium	• Rare stones made of calcium carbonate • Multiple, hard grey-white, small (less than 1 cm)
4.	Mixed (Laminated) Gallstones	• Contain cholesterol, bile pigment & calcium carbonate in varying proportions and combinations • Usually have a cholesterol nucleus as a starting point • Most common gallstones (80%), multiple and multifaceted in variable sizes • Have a laminated structure with alternating dark pigment layer & pale-white layer • Usually accompanied by chronic cholecystitis
5.	Combined Gallstones	• Have a pure gallstone nucleus with mixed gallstone shell or mixed gallstone nucleus with pure gallstone shell • Usually solitary, large, smooth surfaced and accompanied with chronic cholecystitis

6.5. Clinical Features

- Clinical features are silent hence many of the gallstones are diagnosed when complications have set in however biliary pain (excruciating constant colicky pain) is a key feature. The features include pain, nausea and vomiting, jaundice, dark urine, fever and chills, light coloured stools

6.6. Investigations

1. Liver function tests - Raised serum bilirubin, Liver enzymes (raised alkaline phosphatase, moderate increase in ALT and AST and increased gamma-glutamyl transferase activity
2. Full heamogram
3. Urinalysis - bilirubinuria
4. Imaging - ultrasound, CT scan, MRCI, X-rays, ERCP, Cholescintography

6.7. Complications

- Infection/sepsis; Cholecystitis (chronic); Biliary colic; Perforation; Cholangitis (inflammation of the biliary tree); Obstruction of the common bile duct (CBD); Choledocholithiasis (gallstones pass down into the extrahepatic biliary passages and small bowel); Mucocele – distension of the gall bladder by clear, watery mucinous secretion; Biliary fistulae – formation of fistula between one part of the biliary system and the bowel or between gall bladder and skin (rare); Intestinal Obstruction (stones eroding the loop of small bowel - Gallstone ileus); Gall bladder cancer; Pancreatitis

Lesson 2: CHOLECYSTITIS

Learning Outcomes

At the end of the lesson the learner will be able to: -
1) Describe the pathophysiology and pathology of cholecystitis
2) Investigate cholecystitis

1.0. INTRODUCTION

- Cholecystitis is inflammation of the gall bladder that may be acute, chronic or acute on chronic

2.0. ACUTE CHOLECYSTITIS

- Acute inflammation of the gallbladder that primarily occurs as complication of gall stones

2.1. Pathogenesis

- Two main mechanisms - acute calculous and acalculous cholecystitis

Acute calculous cholecystitis
- Accounts for 90% of the cases, associated with obstruction in the neck of the bladder
- Commonest location of gallstone impaction is Hartman's pouch
- Obstruction causes distension followed by acute inflammation from chemical irritation
- Mucosal *phospholipases* hydrolyze luminal lecithins to toxic lysolecithins.
- Protective glycoprotein layer is disrupted lining exposing the delicate mucosal epithelial to direct action of bile salts
- Distended bladder walls release prostaglandins (fuel mucosal & mural inflammation)
- Reduced bladder motility with mechanical obstruction lead to increased intraluminal and intraductal pressure compromises blood supply to the mucosa causing ischaemia hence gall bladder mucosae necrosis (Murphy's sign)
- Secondary bacterial infection via lymphatics by *E. coli* and *Streptococcus feacalis* supervenes. Other bacteria include – *Klebsiella*, *Staphylococcus*, and *Clostridium*.

Acute acalculous cholecystitis
- Accounts for 10% cases, not associated gallstones
- Results from ischaemia due to interference with the cystic artery
- Acute a calculous will occur in post-operative patients (major non-biliary surgery), severe trauma (RTA, war injuries), severe burns, multiple organ failure, sepsis, and prolonged IV hyperalimentation and post-partum states
- Contributing factors include severe sepsis, dehydration, multiple transfusions, gall bladder stasis, torsion of the gall bladder and diabetes mellitus
- May be associated with primary bacterial infections e.g. salmonellosis, cholera and parasitic infestations.

2.2. Pathology

Gross (Macroscopic) appearance	Microscopy
Distended and tense gall bladder; swollen serosal surface is swollen, congested with haemorrhages, bright red mucosa, lumen filled with pus and green bile, pus (empyema of the gall bladder	Catarrhal inflammation (mild) and in severe cases (fibrinous, pseudomembranous, haemorrhagic and suppurative); oedema; congestion; neutrophils infiltration; necrosis and ischaemia (infarction and perforation leads to generalized peritonitis); gangrene (gangrenous cholecystitis); fibrin deposition on serosal surface is organized (causes adhesions)

2.3. Clinical Features

- Severe abdominal pain – upper abdomen; features of peritoneal irritation (muscle guarding and hyperaesthesia); tender gall bladder (Murphy's sign – right hypochondrial tenderness and rigidity, worse on inspiration); gall bladder may be palpable; slight jaundice; fever; leucocytosis with neutrophilia; restlessness, pallor, sweating and vomiting

2.4. Investigations

1. Plain abdominal radiograph (X-ray) shows gallstones
2. Cholecystography
3. Ultrasonography – shows gallstones
4. Radionuclide biliary scintigraphy
5. Raised serum amylase
6. Full heamogram shows moderate leucocytosis
7. Bilirubinuria may be present or not

2.5. Differential Diagnosis

1. Perforated peptic ulcer
2. Acute pancreatitis
3. Perforated cancer
4. Liver abscess
5. Retroperitoneal appendicitis
6. Right sided pleurisy
7. Right basal pneumonia
8. Myocardial infarction
9. Renal colic

What are the important differentiating features in these differential diagnoses?

2.6. Complications

- Perforation (perforation); peritonitis; biliary fistula (cholecystenteric fistula); recurrent attacks; adhesions; gall bladder gangrene; cholangitis; empyema; mucocele

Explain the pathogenesis and clinical features of these complications

3.0. CHRONIC CHOLECYSTITIS

- Commonest gall bladder disease associated with gallstones
- May be insidious in onset or follow repeated attacks of acute cholecystitis

3.1. Aetiology & Pathogenesis

- It is associated with gallstones and repeated acute cholecystitis

3.2. Pathology

Gross (Macroscopic) appearance	Microscopic appearance (Histology)
Generally contracted (small) but may be normal or enlarged; shrunken with marked fibrous thickening (**Courvoisier's sign** – palpable gall bladder); thickened walls with an irregular lining, mucosal folds (intact, thickened or flattened and atrophied); lumen - contains stones and fluid (clear, turbid, or purulent)	Thickened and congested mucosa; Rokitansky-Aschoff sinuses (gland-like structures formed as a result of penetration of epithelial down growths through the muscular layer); chronic inflammation cells – lymphocytes, plasma cells and macrophages; fibrosis

Clinical features and Investigations – as acute cholecystitis

3.3. Complications

- Acute exacerbations (acute cholecystitis); pancreatitis; cholecyst-enteric fistula; gallstone ileus; ca gall bladder; mucocele; pyemia

4.0. CHOLEDOCHOLITHIASIS AND ASCENDING CHOLANGITIS

- Choledocholithiasis is the presence of stones within the biliary tree while cholangitis is bacterial infection of the bile ducts. It may be asymptomatic or symptomatic due to symptoms from obstruction, pancreatitis, cholangitis, hepatic abscess, secondary biliary cirrhosis and acute calculous cholecystitis.
- Cholangitis is associated with bacterial infection occur following obstruction to bile flow mainly due to stones in the biliary tract
- The guilty bacteria include enteric bacteria such Gram-negative aerobes – *E. coli, Klebsiella, Clostridium, Bacteroids* or *Enterobacter* and Group D streptococci
- Usually presents with fever, chills, abdominal pain and jaundice accompanied by acute inflammation of the wall of the bile ducts.

Lesson 3: DISORDERS OF THE PANCREAS

Learning Outcomes

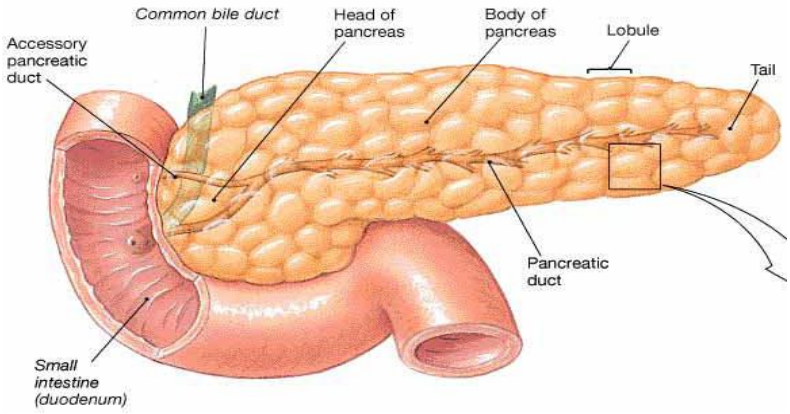
At the end of the lesson the learner will be able to: -
1) Outline the anatomy and physiology of the pancreas
2) Outline the developmental abnormalities of the pancreas
3) Describe the pathology of pancreatitis
4) Investigate pancreatitis

1.0. ANATOMY

Position
- Lies transverse within the posterior deep abdominal cavity across the upper lumbar vertebrae
- Head tucked into loop of duodenum with the tail reaching the hilus of the spleen
- Has intimate contact with organs (stomach, duodenum, transverse colon, spleen, kidneys and suprarenal glands) and blood vessels (aorta, vena cava, hepatic artery, portal vein and spleenic vessels).

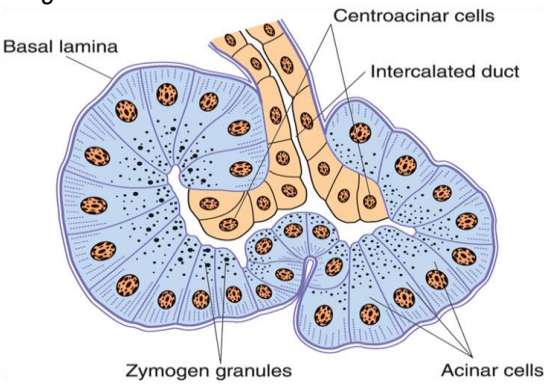
Gross
- Name pancreas is derived from the Greek word "*ankreas*" meaning "all flesh"
- Is a soft, lobulated, glandular organ with both exocrine and endocrine functions
- Divided into four parts – the head, neck, body and tail weighing 2-3 gm (neonates), 7 gm (first year), 40 gm (15 yrs), 70-150 gm in adults and length 15-25 cm

Diagram 3.1: The Pancreas



Histology
- Secretory units are small glands called acini that join to form lobules and eventually lobes
- The acinar cells synthesize the pancreatic enzymes

Diagram 4.2: The Acini



Duct system

- Main pancreatic duct (Wirsung's duct) and the common bile duct (CBD) form the ampula of Vatae before draining into the duodenum with the accessory duct (Santorini's duct) draining the anterior portion of the head of pancreas

Blood supply & Lymphatics

- Rich blood supply through branches of the celiac trunk above the neck, superior mesenteric artery below the neck and from numerous anasatomoses
- Venous drainage corresponds to arterial supply, collects into portal venous system
- Extensive lymphatic drainage.

Nerves

- By autonomic sympathetic and parasympathetic fibres
- Forms three plexuses – around acini, blood vessels and islets
- Parasympathetic is through the vagus nerve via celiac plexus and the sympathetic via greater splanchic nerves

2.0. PHYSIOLOGY

Exocrine

- Pancreatic juices contain enzymes, water and electrolytes. There are at least 22 enzymes including proteolyic enzymes (elastase, amylases), trypsin, chymotrypsin, lipase, phospholipase, carboxypeptidase, cholesteristerase, ribonuclease and deoxyribonuclease.

Endocrine

- Islet's of Langerhans secrete hormones
- Islet's of Langerhans has major cell types (beta – 70%, alpha – 20%, delta – 5 – 10% and pancreatic polypeptide cells – 1-2%) and two minor cell types (D1 cells and enterochromaffin cells).

Major Cells

- Beta cells secrete insulin, alpha cells secrete glucagons, delta cells produce somatostatin (suppresses both insulin and glucagons release)
- Pancreatic polypetides (PP) or F cells secrete pancreatic polypeptide having some gastrointestinal effects (gastrin).

Minor Cells

- D1 cells elaborate vasoactive intestinal peptide (VIP) which induces glycogenolysis and hyperglycaemia and causes secretary diarrhoea by stimulation of GIT fluid secretion
- Enterochromaffin cells synthesize serotonin

3.0. CONDITION OF THE PANCREAS

- Benign tumours; pancreatic cancer; cystic fibrosis; diabetes (to be covered in endocrine pathology); exocrine pancreatic insufficiency; hemosuccus pancreaticus or bleeding from or through the pancreatic duct; pancreatitis - acute pancreatitis and chronic pancreatitis

4.0. DEVELOPMENTAL ANOMALIES

- Congenital anomalies of the pancreas include
  1) Agenesis - is associated with other severe congenital malformations and is usually incompatible with life
  2) Hypoplasias - poor development of the pancreas

3) Annular pancreas - the pancreatic head encircles the duodenum predisposing to the risk of obstruction hence chances of recurrent pancreatitis.
4) Aberrant (or ectopic) pancreas - the pancreas may be located in the stomach, duodenum, jejunum, Meckel's diverticulum and ileum.

5.0. CYSTIC FIBROSIS

- Hereditary autosomal recessive disorder characterised by viscid secretions in all exocrine glands of the body (***mucoviscidosis***) and increased concentration of electrolytes in eccrine organs
- These secretions obstruct the passages resulting in fibrosis
- Involves multi organs and systems resulting in pancreatic insufficiency, intestinal obstruction, steatorrhoea, malnutrition, hepatic cirrhosis and respiratory complications

Pathology

Macroscopy	Microscopy
Visible cysts Fat replacement of pancreatic tissues	Architecture of pancreatic parenchyma maintained; Increased interlobular fibrosis; Atrophy of acinar ducts; Rarely – inflammation, fat necrosis; Islets of Langerhans are intact

6.0. PANCREATITIS

6.1. Introduction

- Pancreatitis is inflammation of the pancreas
- Can be acute or chronic inflammation
- Diagnostic criteria - 2 of the following 3 features
  i) Abdominal pain characteristic of acute pancreatitis
  ii) Serum amylase and/or lipase ≥3 times the upper limit of normal
  iii) Characteristic findings of acute pancreatitis on CT scan

6.2. Classification of Pancreatitis

- According to Marseilles (1963), Cambridge (1983), Revised Marseilles (1984), Atlanta International Symposium – I.A.S (1992), Aetiological or Pathological
- I.A.S (1992**) -** A clinical based classification reflecting on acute pancreatitis: - mild acute pancreatitis and severe acute pancreatitis

7.0. ACUTE PANCREATITIS

7.1. Definition

- Acute Pancreatitis is sudden inflammation of the pancreas
- Associated with necrosis of intrahepatic fat and acini

7.2. Predisposing Factors

1) Biliary tract disease – gall stones, cholecystitis
2) Excess alcohol intake
3) Abdominal surgery on the biliary tract, pancreas and stomach
4) Trauma – abdominal injuries, stab wounds
5) Metabolic disorders – hyperparathyroidism, hypervitaminosis D
6) Infections – mumps, hepatitis, Coxsackie's virus
7) Drugs – thiazide diuretics (frusemide), paracetamol overdose, high steroid doses

7.3. Aetiology

- Alcoholism and gallstones are the most important causes of acute pancreatitis
  i) Metabolic - alcoholism, hypercalcaemia, genetic, drugs (thiazide diuretics, sulfonamides, oral contraceptives, methyldopa, procainamide, furosemide)
  ii) Mechanical – pancreatic obstruction e.g. gall stones, traumatic injury/blunt, iatrogenic injury (peri-operative injury and endoscopic procedures) and periambullary tumours
  iii) Ischaemia - shock, Atheroembolism, Polyarteritis nodosa, Systemic Lupus Erythromatosus (S.L.E)
  iv) Infections - viral infections (mumps, coxsackie), *Mycoplasma pneumonia* and Blood borne bacterial infections

Most Common Causes – Mnemonic "I GET SMASHED"

I	**Idiopathic**
G	Gallstone - gallstones that travel down the common bile duct and which subsequently get stuck in the Ampulla of Vater can cause obstruction in the outflow of pancreatic juices from the pancreas into the duodenum. The backflow of these digestive juices causes lysis (dissolving) of pancreatic cells and subsequent pancreatitis
E	Ethanol (alcohol)
T	Trauma
S	Steroids
M	Mumps (paramyxovirus), other viruses (Epstein-Barr virus, Cytomegalovirus)
A	Autoimmune disease (Polyarteritis nodosa, Systemic lupus erythematosus)
S	Scorpion sting (e.g. *Tityus trinitatis*), and also snake bites
H	Hypercalcemia, hyperlipidemia/hypertriglyceridemia and hypothermia
E	ERCP (**E**ndoscopic **R**etrograde **C**holangio-**P**ancreatography - a procedure that combines endoscopy and fluoroscopy)
D	Drugs (**SAND** - steroids & sulfonamides, azathioprine, NSAIDS, diuretics such as furosemide and thiazides, & didanosine) and duodenal ulcers

7.4. Pathogenesis

- Occurs in 3 phases
  i) First phase
    - Involves a premature activation of the powerful enzyme called trypsin (normally the pancreas contains trypsin in an inactive form)
    - On release in the gut this enzyme breaks down proteins present in the food
    - Pancreatic cells are protected by presence of an inactive enzyme

  ii) Second phase
    - Activated trypsin causes inflammation within the pancreas

  iii) Third phase
    - Inflammation spreads to other organs. e.g. the lungs (ARDS)
    - Mediated by cytokines and other inflammatory mediators
    - There is activation blood coagulation or clotting factors
    - Free radicals are also released along with other chemical mediators of inflammation like cytokines (tumour necrosis factor (TNF), interleukins, arachidonic acid metabolites, platelet activator factor, leukotrienes, prostaglandins, substance P, mitogen-activated protein kinase, P-selectin or E-selectin, heat shock proteins etc.

7.5. Pathophysiology

- Destruction of pancreas is due to liberation and activation of pancreatic enzymes
  i) Enzyme production
     - Proteases such as trypsin and chymotrypsin cause proteolysis with trypsin activating the kinin system, coagulation and complement system leading to inflammation, thrombosis, tissue damage and haemorrhages
     - Lipasaes and phospholipids degrade lipids and membrane phospholipids
     - Elastases destroy the elastic tissue of the blood vessels
  ii) Activation of pancreatic enzymes due to: -
     - Obstruction of the pancreatic duct; injury of the acinar cells and poor intracellular transport of pro-enzymes
  iii) Proteolysis, Lipolysis & Haemorrhage
     - Features of acute pancreatitis - tissue proteolysis, lipolysis, haemorrhage
  iv) Necrosis
     - Periductal necrosis
        - Associated with biliary calculi and alcohol abuse
        - Main pathology is ductal inflammation and periductal necrosis e.g. gallstone pancreatitis, obstruction of pancreatic duct at Ampulla of Vater.
     - Perilobular necrosis - results from ischeamia, shock and hypotension

7.6. Pathology

Macroscopy	Microscopy
Firm swollen gland; acute peritonitis with blood stained ascitic fluid and white flecks of fat; leakage of the vasculature causes oedema	Acute inflammatory cells and inflammatory process; haemorrhage; necrosis; autodigestion of vessels by the pancreatic enzymes leads to secondary thrombosis and infarction with coagulative necrosis of the entire lobe (acute haemorrhagic pancreatitis); proteolytic destruction of the pancreatic substance

7.7. Clinical Features

- Full blown pancreatitis is a medical emergency
- Many systemic features occur due to release of toxic enzymes, cytokines and other mediators into the circulation with volatile activation of the systemic inflammatory response which results in leucocytosis, haemolysis, D.I.C, fluid sequestration, ARDS, diffuse fat necrosis, peripheral vascular collapse and shock with acute renal necrosis
- Common features
  i) Abdominal pain - sudden onset epigastric pain radiating to the back between the scapulae, difficult to relieve
  ii) Nausea and vomiting
  iii) Shock/hypovolaemia/collapse - due to loss of blood volume and electrolyte disturbances, endotoxemia and release of cytokines and vasoactive agents (bradykinin, prostaglandins, NO and PAF)
  iv) Hypocalcaemia
  v) Hyperglycaemia

7.8. Differential Diagnosis

1) Ruptured acute appendicitis
2) Perforated peptic ulcer
3) Acute cholecystitis
4) Rupture and occlusion of mesenteric vessels with bowel infraction

7.9. Diagnosis

What are the parameters and interpretation of the

1) History
2) Physical examination
3) Investigations
   - Full blood count; Renal function test; LFTs
   - Serum amylase elevated, rising serum lipase
   - Blood sugar - Hyperglycaemia, Glycosuria
   - Serum calcium - Hypocalcaemia
4) Arterial blood gases
5) Imaging - CXR, AXR, CT scan (gold standard), Ultrasound, MRI

Glasgow (Imrie) prognostic score (Mnemonic: PANCREAS)

PO2	<	60 mmHg
Age	>	55 years
Neutrophils + all WBC	>	15 x10^9/L
Calcium	<	2 mmol/L
Raised urea	>	16 mmol/L
Enzymes AST	>	200 U/L, LDH >600U/L
Albumin	<	32 g/L
Sugar, glucose	>	10 mmol/L

Balthazar Scoring

- Based on Computed Tomography Severity Index (CTSI)
- Has a maximum of 10 points (sum of the grade points and pancreatic necrosis)

Grade A: Normal CT	- 0 pts
Grade B: Focal or diffuse enlargement of the pancreas	- 1 pts
Grade C: Pancreatic gland abnormalities & peri-pancreatic inflammation	- 2 pts
Grade D: Fluid collection in a single location	- 3 pts
Grade E: Two or more fluid collections and/or gas bubbles in or adjacent	- 4 pts

Necrosis Score based on percentage of necrosis on CT

No necrosis:	0 points
0 to 30% necrosis:	2 points
30 to 50% necrosis:	4 points
Over 50% necrosis:	6 points

*********CT severity index = CT grade point + points for necrosis

Ranson's Criteria (Mnemonic WAG LA BOUCHE)

On Admission			At 48 hours After Admission	
WBC	>16000 cells/mm^3		Base deficit	>4 mEq/L
Age	>55 years		Oxygen (hypoxaemia PO_2)	<60 mmHg
Glucose	>11 mmol/L(>200 mg/dL)		Urea increase	>1.8 mmol/L
LDH (serum)	>350 IU/L		Calcium (serum)	<2 mmol/L (<8.0 mg/dL)
AST (serum)	>250 IU/L		Hct fall (cf admission level)	>10%
			Estimated sequestration of fluid	>6 L
Interpretation: Mortality rate - 0-2 (~2%), 3-4 (~15%), 5-6 (40%), 7-8 (100%)				

7.10. Complications

Local Complications

1. Pseudocysts
2. Duodenal obstruction
3. Abscess which may lead to fistulae, haemorrhage and septicaemia
4. Persistency
5. Phlegmon – a solid inflammatory mass of pancreatic tissue
6. Thrombosis
7. Spleenic artery pseudoaneurysm
8. Duodenal obstruction

Systemic Complications

1. Alimentary system
   a) Intestinal obstruction due to paralytic ileus, generalized peritonitis and mechanical obstruction following infarction of the intestines.
   b) Haemorrhage following erosion of vessels
   c) Perforation
2. Hepato-biliary system - obstructive jaundice (oedema or pseudocyst and hepatocellular jaundice
3. Metabolic – hypocalcaemia, hyperglycaemia (occasionally hypoglycaemia due to dysfunction of glucagons secreting cells), hyperlipidimia and acidosis
4. Cardiovascular system - Circulatory failure or collapse due to reduced plasma volume and diffuse vascular damage by circulating proteases and kinins.
5. Haematological - Hypercoagubility due to increased platelets and fibrinogen.
6. Renal - Renal failure due to shock, dehydration,
7. Neurological - mild confusion, delirium and coma
8. Pulmonary - Acute respiratory failure, pleural effusion, atelectasis, pneumonitis, ARDS
9. Infections – necrotic debris becomes infected with Gram negative organisms mainly
10. Cutenous changes include ecchymmosis, Cullen's sign (umbilical region) and Grey Turner's sign (flanks)

8.0. CHRONIC PANCREATITIS

8.1. Introduction

- Defined as the progressive destruction of the pancreas, which results from irreversible fibrotic destruction of the acinar and ductal tissue
- Characterized by inflammation of the pancreas with destruction of exocrine parenchyma, fibrosis and destruction of the endocrine parenchyma in late stages of the disease.

8.2. Aetiology

The associated factors are: -

1. Alcoholism 70%) – in alcohol abuse, increased protein concentration leads to increased secretions, which cause ulceration with resultant formation of scars and strictures causing atrophy and fibrosis of the pancreas.
2. Gallstones
3. High intake of precipitated fats and inspissated proteins
4. Long standing obstruction of the pancreatic duct by – pseudocyst, calculi, trauma, neoplasms
5. Calcification
6. Cytic fibrosis
7. Malnutrition
8. Familial hereditary

8.3. Pathogenesis

1) Ductal **obstruction** by **<u>concretions</u>** – substances such as alcohol increase protein concentrations in the pancreatic juice, these proteins plug up the ductal system. The ductal plugs may become calcified
2) Toxic metabolites – alcohol and its metabolites can exert toxic effects on the pancreatic acini
3) Oxidative stress – leads to generation of free radicals leading to membrane lipid oxidation
4) Necrosis-fibrosis – pancreatitis initiates a sequence of perilobular fibrosis, ductal distortion and altered pancreatic secretion

8.4. Clinical Picture

1. Reflects pathological process with pathophysiological consequences of exocrine and endocrine insufficiency
2. Severe erratic abdominal pain
3. Jaundice due to pancreatic fibrosis, oedema and gallstones
4. Hepatomegally following fatty degeneration of the liver
5. Spleenomegally resulting from portal hypertension following spleenic vein obstruction due to fibrosis
6. Gastric and oesophageal varices
7. Upper G.I.T bleeding from varices, gastric ulcers, gastritis and pseudocyts eroding duodenum.
8. Ascites
9. Steatorrhoea
10. Maldigestion
11. Hyperphagia – altered post-cibal satiety
12. Hypoglycaemia – reduced glucagons, food assimilation
13. Hyperglycaemia – reduced insulin
14. Effusion in pleural and peritoneal cavities.

8.5. Pathology

Macroscopy	Microscopy
Enlarged, firm and nodular pancreas	Obstruction of ducts by fibrosis; metaplasia and dilatation of inter and intralobular ducts; atrophy of acinar tissue; cells in chronic inflammation

8.6. Diagnosis

1. Clinical history and physical examination
2. Demonstrate pancreatic exocrine hypofunction – vitamin B_{12}, malabsorption, secretin, reduced bicarbonate, increased fat in stool.
3. Radiological – pancreatic calcification
4. Endoscopy – ductal abnormality
5. Ultrasound
6. CT scan

Diagnosis - **TRIAD** of
1) Pancreatic calcification
2) Staetorrhoea
3) Sudden onset diabetes mellitus

Lesson 4: INTRODUCTION TO LIVER PATHOLOGY

Learning Outcomes

At the end of the lesson the learner should be able to: -

1) Outline the anatomy and physiology of the liver
2) Outline the causes and patterns of liver cell damage
3) Describe pathologic effects of liver cell damage
4) Describe the manifestations of liver disease
5) Investigate liver disease

1.0. INTRODUCTION

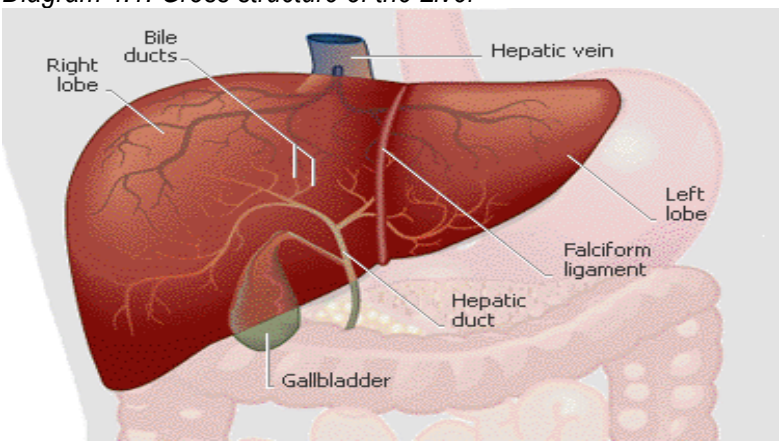
- Heaviest internal organ weighing averagely 1.5 kg (1.4 – 1.8 kg in males and 1.0 - 1.5 kg in females)
- Accounts for 2.5% of the body weight in adults and 1/8 of the body size in the foetus it takes
- Positioned immediately beneath the diaphragm in the epigastric, right and left hypochondrial regions of the abdominal cavity

2.0. ANATOMY

2.1. Gross Structure

- Has 2 major lobes (right & left) and 2 minor lobes (caudate & quadrate lobes)
- Anteriorly, the right lobe (antero-posterior diameter of 12.5 – 15 cm) separated from the small left lobe by the fulsciform ligament
- Inferiorly (on the visceral surface), the caudate lobe is near the inferior vena cave and the quadrate lobe is adjacent to the gall bladder
- Fulsciform ligament attaches the liver to the anterior abdominal wall and the diaphragm. A *ligamentum teres* (round ligament) is continuous on the free border of the *fulsciform* ligament to the umbilicus (it is a remnant of the umbilical vain).
- Porta (*porta hepaticus*) of the liver (the transverse fissure) forms the entry for the hepatic artery, portal vein, lymphatics and nerves and the exit of the hepatic ducts

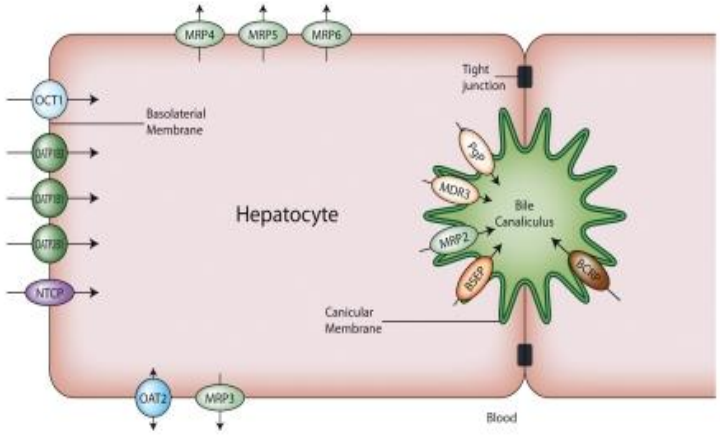
Diagram 4.1: Gross structure of the Liver



2.2. Fine Structure of the Liver

- Lobule is the basic structural and functional unit of the liver
- Liver is 1-2 cells thick because the liver cells (hepatocytes) form hepatic plates that are one to two cells thick separated by sinusoids (large capillary spaces)
- Sinusoids are lined with phagocytic Kupffer cells

Diagram 4.2: Hepatocyte



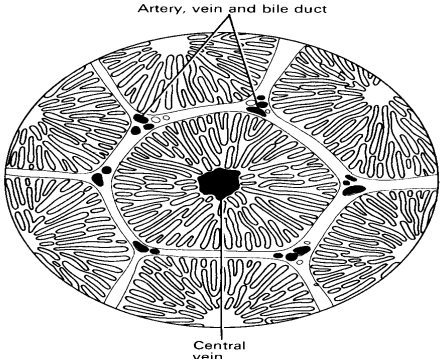
2.3. Microanatomy

- Composed of 3 structures: - portal tracts, hepatic parenchyma and hepatic outflow veins
- Portal tracts contain the branch of portal vein and artery, bile ducts, lymphatics and nerves
- Hepatocytes radiate from portal tracts towards the terminal hepatic venous radicles and sinusoids lie between and on each side of the hepatocytes

2.4. The Lobule

- Two types of lobules - triangular lobules (centred on a portal canal, divided into acini) and hexagonal lobules (fibrous portions of adjacent portal canals)
- In the middle of each lobule is a central vein and at the periphery of each lobule there are branches of the portal vein and hepatic artery
- Portal and arterial blood mixes as the blood flows through the sinusoids
- Central veins of each lobule converge to from the hepatic vein that drains blood from the liver into the inferior vena cava.

Diagram 4.3: Lobules



Hepatic sinusoids

- Unique blood vessels lined by endothelial cells and Kupffer cells
- Are irregular with a radial course in the lobules from the periphery into the central vein

2.5. Blood supply & drainage

1) The portal vein
   - Supplies 70% of the oxygen to the liver arriving from the gastro-intestinal tract loaded with products of digestion
   - Delivers blood through the hilum and feeds into the sinusoidal system

2) Hepatic artery
   - Branch of the celiac axis that runs a alongside the portal vein
   - Supplies the liver with 30% of the oxygen
   - Forms two plexuses before delivering blood into the sinusoids

3) Drainage
   - The right, middle and left hepatic vein drain the corresponding segments of the liver eventually draining into the inferior vena cava.

2.6. Bile Flow

- Bile is produced by the hepatocytes and secreted into thin channels (canaliculi)
- Canaliculi are drained at the periphery of each lobule by bile ducts that drain into hepatic ducts that carry bile away from the liver
- Blood travels in the sinusoids while bile travels in the opposite direction within the hepatic plates, blood and bile do not mix in the liver lobules.

2.7. Nervous supply

- Innervated by parasympathetic nervous system through the vagus nerve and sympathetic innervations from thoraco-lumbar nerves through the celiac ganglia.

3.0. FUNCTIONS OF THE LIVER

1) Synthesis
   a) Proteins – albumin, transport proteins, fibrinogen, prothrombin and other clotting factors
   b) Bile acids (products of cholesterol, important in fat digestion)
   c) Bilirubin
   d) Cholesterol
   e) Enzyme - AST (aspartate amino transferase), ALT (alanine amino transferase) and Alpha glutanyltransferase (α–glutanyltransferase)
2) Homeostasis/Metabolism
   a) Glucose (blood sugar) - Carbohydrates
   b) Proteins - Amino acids
   c) Fats and cholesterol
   d) Hormones - Catabolizes hormones – insulin, glucagons, oestrogen, growth hormone, glucosteroids and parathyroid hormone.
   e) Fat-soluble drugs are converted into water soluble to facilitate excretion in bile or urine.
   f) Vitamins – fat soluble – A, D, E and K
   g) Hormone and drug inactivation
3) Storage of – Vitamins, Cholesterol and Blood
4) Excretion of – Cholesterol, Bile acids, Phospholipids, Bilirubin, Drugs and Poisons e.g. pesticides, insecticides, heavy metals
5) Filter out - Poisons from the gut, nutrients such as amino acids, sugar and fats, bilirubin and bile acids, IgA and drugs
6) Defence
   a) Immunological function – the liver as a part of the R.E.S
   b) Excretion of IgA (defence against bacteria in the gut)
   c) Special macrophages (Kupffer cells)

4.0. CAUSES OF LIVER CELLS DAMAGE

4.1. Introduction

- Liver is exposed to a broad range of metabolic, toxic, microbial, circulatory and neoplastic injuries

4.2. Causes

- Microbial agents; circulatory disorders; toxic agents (drugs, chemicals); metabolic; neoplasms; trauma

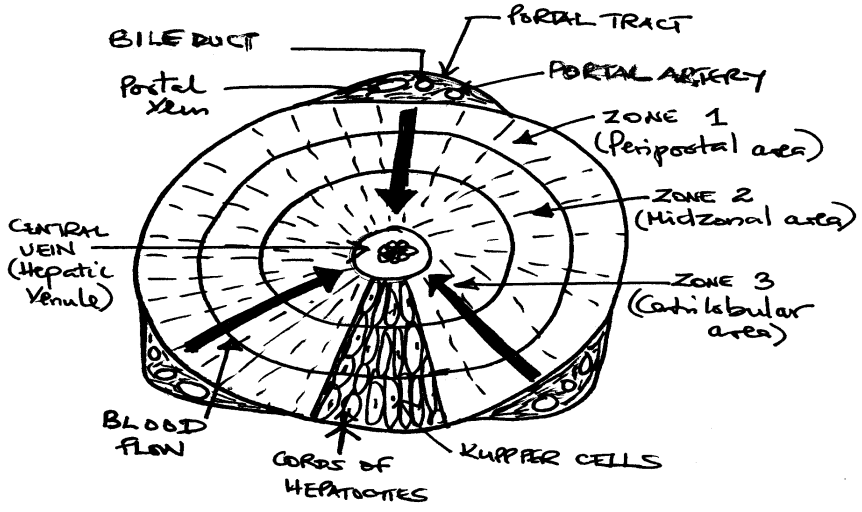
4.3. Patterns of Hepatic Injury

- Liver has narrow range of responses to injurious
- Five responses are usually seen in liver injury

1) Necrosis

- Any major injury to the liver can cause hepatocyte necrosis
- Outcome of necrosis is influenced by
  - i) Personal sensitivity to the poison
  - ii) Dosage of poison ingested
  - iii) Transfer of function – one zone becomes necrotic due to formation of toxic substances in an attempt to metabolize toxic chemicals after zone of another zone as seen in paracetamol poising
  - iv) Interference with circulation
- Types of Necrosis -
  - i) Diffuse (submassive to massive) necrosis
    - Involves all the cells in groups of lobules
    - Results from massive poisoning (drugs, industrial chemicals, mushrooms)
  - ii) Zonal necrosis
    - Centrilobular necrosis - results from ischaemic (shock, CCF, poisoning [chloroform and CCl_4]
    - Midzone necrosis - rare, seen in yellow fever and acute peritonitis
    - Periportal (peripheral) - involves the parenchyma closest to the arterial and portal blood supply, vulnerable to effects of circulating hepatotoxins e.g. phosphorus poisoning and ecclampsia

Diagram 4.4: Zones of the hepatic lobule



iii) Focal necrosis - involves small groups of hepatocytes irregularly distributed. It is usually caused by microbiologic infections – viral hepatitis, tuberculosis, typhoid fever, and fungal infections. Can also be drug induced.

2) Inflammation

- Injury to liver cells is associated with an inflammatory response (hepatitis)

3) Degeneration

- Severe damage is associated degeneration where the swollen hepatocytes have irregularly clumped cytoplasmic organelles and large clear spaces
- May be accompanied by accumulation of substances such as iron and copper or fat in the viable hepatocytes

4) Regeneration

- Liver cells are stable
- Hyperplasia and hypertrophy of liver cells occurs as a compensatory process with local and circulating growth factors playing a role
- Hepatocellular regeneration is marked by mitoses, thickening of hepatocyte cords and minimal disorganization of the parenchymal structure

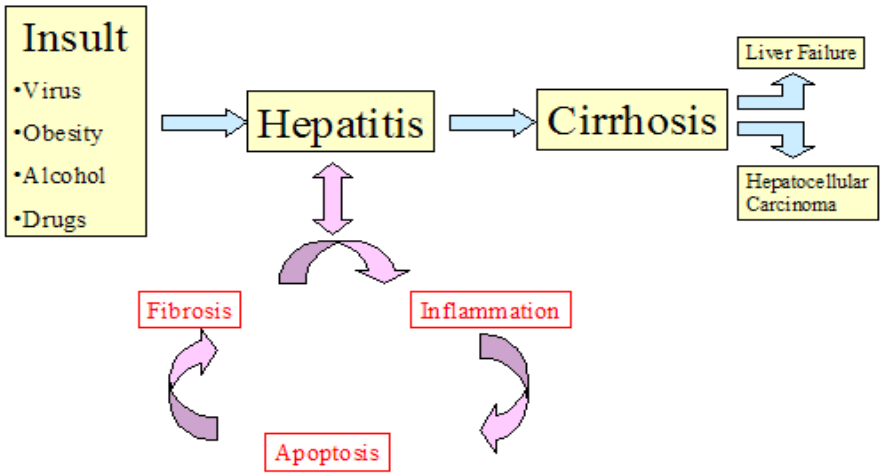
5) Fibrosis

- Fibrous tissue is formed in response to inflammation or direct toxic injury to the liver cells and it is indicative of generally irreversible hepatic damage

5.0. PATHOLOGIC EFFECTS OF DISTURBED LIVER FUNCTION

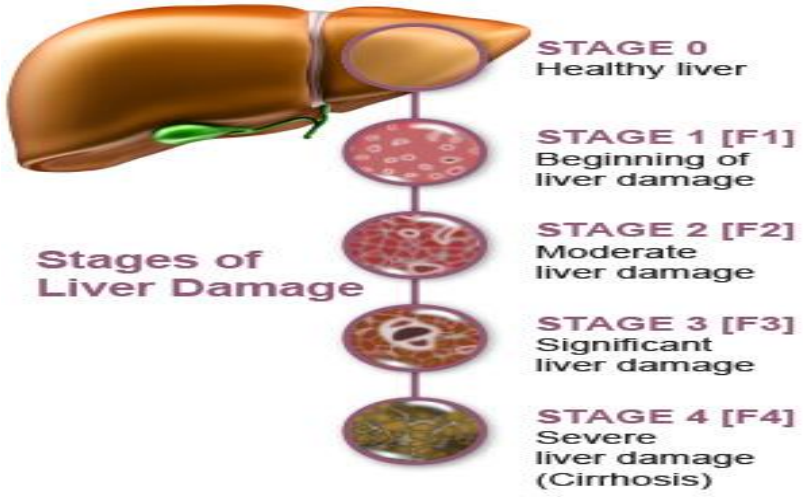
- Well expressed in two groups as hepatocellular failure (liver failure) and portal hypertension
- In hepatocellular failure, the functioning of the liver cells is below the minimal physiological state following cell damage and reduced blood supply to the liver
- Changes seen include **d**isturbed nitrogen metabolism; accumulation of bilirubin (jaundice); reduced plasma proteins; hormonal disturbances; circulatory disturbances; functional renal failure (hepato-renal syndrome)

Diagram 4.5: Effects of Disturbed Function



6.0. STAGES OF LIVER DISEASE

Diagram 4.6: Stages of Liver Disease



7.0. DISORDERS OF THE LIVER

- Include - Liver Injury, Infections, Alcoholic liver disease, Metabolic liver disease, Drug injury, Circulatory disorders and tumours

8.0. MANIFESTATIONS OF LIVER DISEASE

8.1. Introduction

- Most severe clinical consequence of liver disease is hepatic failure

> - What are the symptoms of liver disease?
> - What is the basis of the symptoms?

9.0. HEPATOCELLULAR (HEPATIC) FAILURE

9.1. Introduction

- A clinical consequence of liver disease that develops with loss of more than 80 to 90% of function (liver has a large functional reserve with marked regenerative capacity)
- A life-threatening state with severe impairment of liver function and the patients are highly susceptible to multiple organ failure
- Liver failure can be acute or chronic

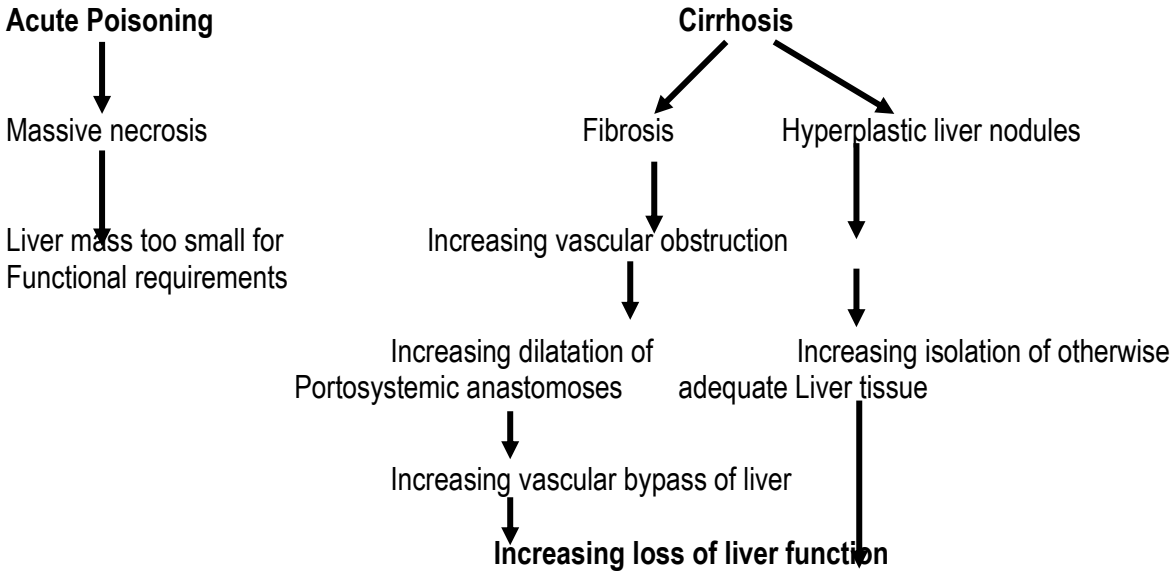
9.2. Mechanisms of Liver Failure

- Two principal mechanisms –acute poisoning and cirrhosis
  i) Acute poisoning that results in massive necrosis of liver cells leading to substantial loss
  ii) Cirrhosis of liver cells
    - Results in fibrosis and formation of hyperplastic liver nodes
    - Fibrosis causes obstruction to blood flow through the liver increasing dilatation of the portosystemic anastomoses that allow blood to by-pass the liver increasing loss of liver function
    - Hyperplastic liver nodes obstruct blood flow through the liver and isolate liver tissue causing reduction in liver cell function

9.3. Morphological Alterations

- Include massive hepatic necrosis, chronic liver disease and hepatic dysfunction without overt necrosis

Diagram 4.7: Mechanism of Liver Failure



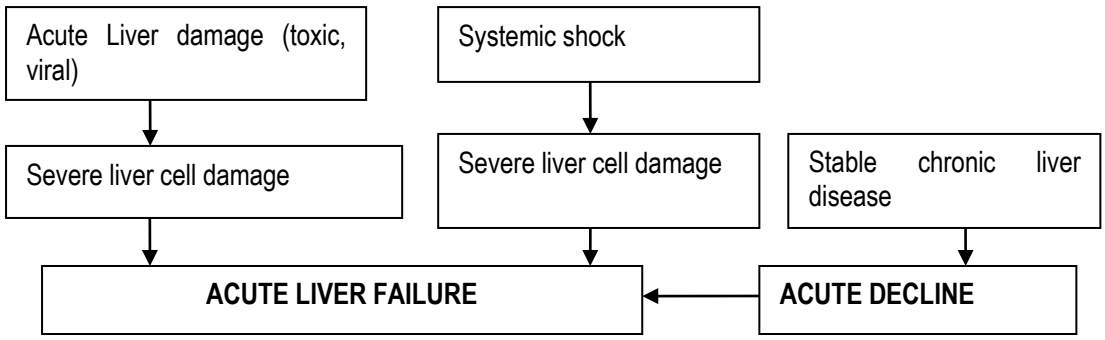
9.4. Acute Hepatocellular Failure

- Is an acute rapid onset of liver failure (less than 8 weeks) results from massive necrosis of liver cells due to poisoning and less commonly acute hepatitis
- Occurs suddenly in a previously healthy liver

Causes

1) Infections - Viral hepatitis, Yellow fever, Leptospirosis
2) Drugs - paracetamol overdose, halothane, isoniazid, NSAIDS and antidepressants
3) Toxins - chemical hepatotoxins e.g. CCl_4), aflatoxin, aminata phalloides mushrooms and bush tea
4) Alcoholic hepatitis
5) Vascular – Budd Chiari, veno-occlusive disease
6) Pregnancy complication with eclampsia
7) Physical damage e.g. irradiation

Diagram 4.8: Pathogenesis



Features of Acute Hepatocellular Failure

1. Release of enzymes (↑ AST and ↑ ALT)

2. Failure of bilirubin metabolism
3. Failure to detoxify nitrogenous compounds, circulation of excitatory amino acids
4. Failure to synthesize proteins (examples)
5. Shock

9.5. Chronic Hepatocellular Failure

- Is often secondary to cirrhosis (mainly due to interference with blood flow following distortion of the liver architecture)
- Other causes include chronic active hepatitis, and chronic cholestasis.
- Signs include finger clubbing, leukonychia; terry's nails (white proximally but distal 30% reddened by telengiectasis); palmar erythema (hyperdynamic circulation); spider naevi; duputyren's contracture; gynaecomastia; testicular atrophy; parotids enlarged; hepatomegally; bleeding tendencies; gastropathy; oesophageal varices; reduced vitamin K

9.6. Predisposing factors

- Deterioration of the patient can be very rapid with symptoms of confusion, stupor and coma setting in acutely as a result of infections, G.I.T bleeding and fluid and electrolyte imbalance
- Dramatic change in the clinical state is caused by
  i) Anoxia (due to hypovolaemia due to haemorrhage and diuresis)
  ii) Alteration in cellular metabolism (metabolic acidosis, high levels of serum lactate)
  iii) Shunting of portal venous blood away from the liver
  iv) Portal hypertension (leads to irregular perfusion resulting in anoxia)
- Main risks include - after surgery (bleeding, ascites, jaundice, and poor wound healing and high incidence of wound dehiscence) and drug use

9.7. Acute On Chronic Hepatic Failure

- Occurs as a result of decompensation of chronic liver disease
- Presents as fulminant hepatic failure (encephalopathy occurring within 8 weeks of symptoms of acute liver failure) and late onset hepatic failure (encephalopathy occurring within 9 – 26 weeks)

9.8. Complications

What are the Complications of Liver Failure?

9.9. Characteristic Signs

- Characteristic signs of **hepatocellular failure** are: -
  1) Jaundice and Cholestasis
  2) Fluid retention - Ascites and Oedema
  3) Haematological - Anaemia
  4) Hypoglycaemia
  5) Hyperkinetic circulation
  6) Acidosis
  7) Endocrine changes, gynaecomastia, hypogonadism
  8) Increased serum levels of hepatic enzymes (LD, ALT and AST)
  9) Hyperammonemia
  10) Skin changes
  11) Foetor hepaticus
  12) Portal Hypertension

1) Jaundice and Cholestasis

Introduction

- Jaundice is yellow discolouration of the sclera, mucous membrane and skin caused by increased accumulation of bilirubin or bilirubin complexes (jaundice = *icterus)*
- Bilirubin pigment has a high affinity for elastic tissue (jaundice is noticeable in tissues rich in elastin content)
- Evident clinically when the serum bilirubin level is 3 gm/dl (3 gm %) that is 50 μmol/L (30 – 60 mol/L). Normal levels of serum bilirubin are 2 – 17 μmol/L (0.3 – 1.0 gm/dl)

Bilirubin

- Major bile pigment formed as an end product of catabolism of haem-containing proteins
- Bile is excreted in stool, urine, sweat and tears. Internal organs are stained except the brain and spinal cord. In *icterus gravis neonatorum*, there is bile staining of the areas in central nervous system; the grey matter of the basal ganglia (kernicterus) and may stain the cortex.

Metabolism of Bilirubin

- Unconjugated bilirubin is produced (425 – 510 mmol, 250 – 300 gm daily) from the catabolism of haem after removal of its iron component
- Bilirubin in blood is normally almost unconjugated and bound to albumin and it is not water soluble hence does not pass into urine
- Small amount of stercobilinogen (4 mg/day) is absorbed from the bowel, passes through the liver and excreted in the urine as urobilinogen or urobilin (after further oxidation)
- Metabolism occurs in four major steps
    i) Source of bilirubin - breakdown of red blood cells
    ii) Transport of bilirubin
    iii) Hepatic phase - hepatic uptake of bilirubin, conjugation process and excretion process
    iv) Intestinal phase

Breakdown

- 80% of bile pigments are derived from the breakdown of the red blood cells (6 gm of haemoglobin is broken down daily by the spleen, bone marrow and the liver)

Transport

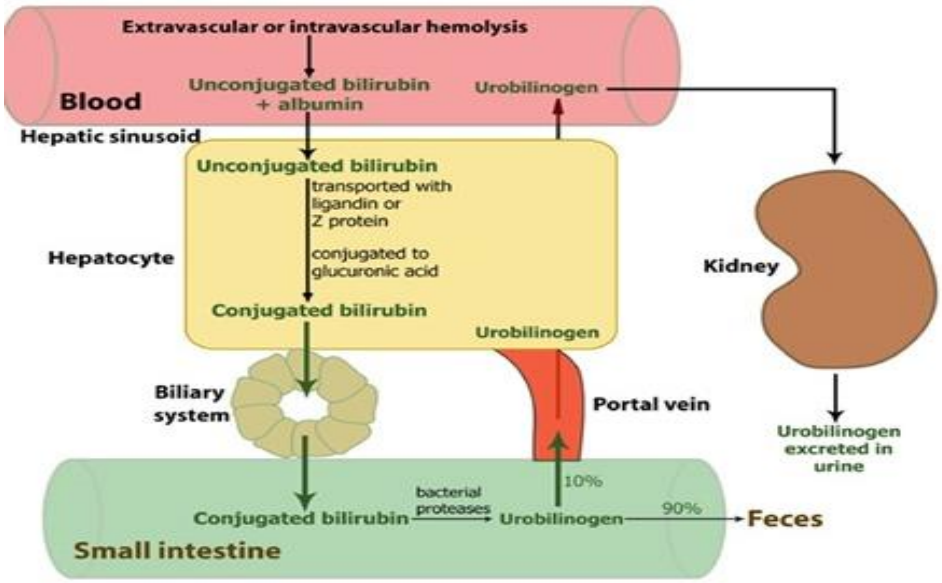
- Transported from production site to the liver bound to serum albumin (since it is virtually insoluble in aqueous solution at physiologic pH) as fat soluble, unconjugated or indirect bilirubin.

Hepatic Phase

- Uptake
    - Transport receptors exist on the hepatocytes sinusoids plasma membrane
    - In the cell, bilirubin is bound to ligandin (glutathione-5-transferase) and Z-protein (a fatty acid binding protein)
- Conjugation
    - Process is carried out in the liver cells
    - Free bilirubin is rendered water-soluble by conjugation with glucuronic acid in a reaction characterized by the endoplasmic reticulum enzyme *glucuronyl transferase* into bilirubin conjugates
    - There are two major conjugates: - *bilirubin diglucuronide* and *bilirubin monoglucuronide* and minor conjugates such as glycosides and xylosides. Increase in monoglucuronides follows an increase in bilirubin load, low enzyme activity and increased microsomal injury and increase in diglucuronides is enzyme induced by phenobarbitone
    - Conjugated bilirubin is water-soluble and is also referred to as direct bilirubin

- Excretion
  - Conjugated bilirubin (water-soluble bilirubin) is excreted into bile canaliculi by energy-dependent process) and passes into the bile

Diagram 4.9: Bilirubin uptake and conjugation



Intestinal phase

- In the intestines conjugated bilirubin is converted into stercobilinogen by oxidation process (a bacterial action)
- Bilirubin is then excreted in stool
- A small fraction of the stercobilinogen is reabsorbed from the gut and taken back to the liver where it is re-activated into bile (entero-hepatic circulation)
- Metabolism of bilirubin by the intestinal bacteria results in production of water-soluble urobilinogen, which is taken to the liver (entero-hepatic circulation) a small fraction of which passes the liver into the systemic circulation and eventual excretion in urine (urinary excretion)

Clinical Chemistry - The Van de Bergh reaction

- Conjugated bilirubin forms a violet colour immediately on addition of sulfanilic acid (Direct reacting bilirubin).
- The colour is intensified by unconjugated bilirubin by addition of alcohol (indirect reacting bilirubin)

Classification & Causes of Jaundice

A. Pre-hepatic (Haemolytic) Jaundice - there is increased production of bilirubin
B. Intra-hepatic Jaundice
   - ❑ Interference with hepatic uptake of bilirubin
   - ❑ Interference with conjugation and excretion of bilirubin
   - ❑ Reduced functional liver cell mass
C. Post-Hepatic (Obstructive) Jaundice - there is obstruction to flow of bilirubin

Pre-Hepatic (Haemolytic) Jaundice

- Results from increased bilirubin production which the liver will be incapable of handling
- Referred to as haemolytic jaundice because it is the process of haemolysis that destroys many red blood cells releasing excess bilirubin.

Pathology

- Can be **haemolytic** or **dyserythropoetic** in nature.
  i) Haemolytic (Acholuric) Jaundice
    - Increased RBC destruction results in increased bilirubin production from the macrophages
    - If the liver copes in a normal situation, then the result is mild or latent jaundice since a healthy liver can excrete a bilirubin load six times greater than normal before unconjugated bilirubin accumulates in then plasma. If the liver fails to cope the jaundice is quite evident
    - Unconjugated bilirubin is not water soluble therefore it does not pass into the urine hence the description acholuria
    - Features - unconjugated bilirubin, bile pigments are absent from urine (acholuria); dark (excessive pigments), increased urobilinogen
    - Causes - infections e.g. Malaria, haemoglobinopathies e.g. Sickle cell disease (SCD) and thalassaemia, drugs

  ii) Dyerythropoetic (Shunt) Hyperbilirubinaemia
    - There is ineffective and abnormal cell maturation, which that leads to early or premature destruction of erythrocyte precursors in the bone marrow
    - Familial disease e.g. pernicious anaemia and thalasasemia.

Intra-Hepatic Jaundice

- Results from the inability of the liver cells to function optimally
- Can be divided into congenital and acquired hepatic jaundice.

1) Congenital causes
   a) Interference with hepatic uptake of bilirubin (Gilbert's syndrome)
      - Familial disease of a dominant autosomal gene
      - There is unconjugated bilirubin in the absence of liver disease and overt haemolysis

   b) Interference with hepatic conjugation
      i) Physiological/neonatal jaundice - there is deficiency of *glucuronyl transferase* in the neonatal liver
      ii) Inherited defect (Criggler-Najjer syndrome)
        - There is deficiency of glucuronyl transferase
        - Increased unconjugated bilirubin
        - Two types exist - Type I (enzyme is absent) causes kernicterus and Type II (partial enzyme deficiency and reduced enzyme activity)

   c) Interference with hepatic excretion
      i) Inherited intrahepatic
        - Dubin-Johnson syndrome –partial failure of excretion and bilirubin is regurgitated into the blood
        - Rotor syndrome – total failure of excretion with accumulation of brown pigment in the liver
      ii) Acquired intrahepatic e.g. in primary biliary cirrhosis

2) Acquired causes
   a) Reduced functional hepatic cell mass
      - Occurs due to damage to the liver cells
      - Causes include -Viral (HAV, HBV, HCV, HDV, HDV); Hepatocellular toxins; Leptospirosis; Bacterial infections; Protozoal infections; Fungi – aminata toxins; Septicaemia; Snake bites; Chemicals; Cirrhosis and Hepatoma
      - Pathogenesis

- Reduced functional liver cell mass
- Poor hepatic uptake of bilirubin
- Poor conjugation of bilirubin
- Poor excretion (stasis) – intrahepatic stasis as a result of focal necrosis, swelling of liver cells and fibrosis (scarring).

b) Cholestasis
- Results from obstruction of intrahepatic bilirubin flow interfering with the process of conjugation
- Causes - drugs e.g. Chlorpromazine; infections e.g. Epstein Barr Virus (EBV), Hepatitis A, B, C; liver cirrhosis; hepatoma/tumours

c) Non-cholestatic causes (congenital)

Post-Hepatic (Cholestatic) Jaundice

- Results from obstruction (cholestasis) of bilirubin flow

i) Intrahepatic cholestasis
- Due to swelling of the hepatocytes, oedema in the parenchymal liver damage and excretory dysfunction of the bile canaliculi
- Causes - viral hepatitis; drugs; alcoholic hepatitis; cirrhosis; pregnancy; some congenital disorders

ii) Extrahepatic cholestasis
- Results from obstruction of the large duct at any point in the biliary tract to the bile canaliculi
- Causes
  1. Common duct stones
  2. Carcinoma of head of pancreas, Ampula of Vatae and bile duct
  3. Biliary stricture due to previous inflammation, ulceration by gallstones and accidental injury/iotrogenic injury.
  4. Pancreatitis and pseudocyst formation
  5. Sclerosing cholangitis
  6. Congenital malformations
  7. Round worm migration

2) Ascites
- Ascites is the accumulation of excessive volume of fluid within the peritoneal cavity (*Askitis is Greek word meaning fluid filled bag*)
- Mainly due to a combination of portal hypertension and hepatocellular failure
- Usually associated with haemodilution, oedema and decreased urine output.

3) Oedema
- Occurs as a result of hypoalbuminaemia which destabilizes osmotic (oncotic) pressure gradients at the capillaries and sodium retention due to renal effects.

4) Hypoalbuminaema
- Results from reduced synthesis due to reduction in liver cell mass

5) Anaemia
- Usually normocytic/normochromic in nature
- Occurs due to hyperspleenism, bleeding, pancytopenia; disturbances in GIT function and bone marrow depression due to toxic wastes (WHAT IS THE PATHOGENESIS OF ANEAMIA IN LIVER DISEASE)

6) Bleeding Tendencies

- Due to inadequate production of clotting factors produced in the liver i.e. fibrinogen, Factors II, V, VII, IX, X, XI, XII, XIII
- Synthesis of factors II, V, IX and X is dependent on vitamin K (steatorrhoea in liver disease leads to malabsorption of vitamin K)
- Examples - upper G.I.T bleeding, haematemesis and malena. D.I.C is associated with low fibrinogen levels and reduces platelet count.

7) Metabolic Disorders

i) Hypoglycaemia - Disordered metabolism of glucose (reduced liver storage of glycogen)
ii) Bleeding diathesis - reduced protein synthesis e.g. fibrinogen, prothrombin, factors V, VII, IX and X.
iii) Reduced elimination of endogenous oestrogen leading to gynaecomastia, testicular atrophy and spider naevi

8) Hyperkinetic Circulation

- Occurs due to peripheral vasodilatation, increased splanchic blood flow and increased cardiac output (initially)
- Increased spleenic blood flow with reduced renal blood flow causes impaired renal cortical perfusion

9) Endocrine Changes

- In the males, the changes are towards feminisation e.g. gynaecomastia and hypogonadism while in the females the changes are atrophy of gonads and breasts
- This happens due to changed end-organ sensitiveness to sex hormones.

10) Skin Changes

- The changes seen are arterial spiders" seen at the neck, face, forearms and dorsum of hands and palmar erythema especially in the thenar and hypothenar eminences "and on the pulps of fingers.

11) Feoto-Hepaticus

- It is a sweetish smell of breath whose origin appear to be the intestines due to the failure of the liver to detoxify substances absorbed from the gut.

12) Varices

- Increased venous pressure and an obstruction in portal circulation causes blood to by-pass the liver and return to the heart via the porto-systemic collateral channels (or shunts or varices) that develop where the systemic and portal circulations share capillary beds
- Sites are under the oesophageal varices, haemorrhoids, caput medusae and retroperitoneal anastomoses

i) Oesophageal varices
   - Dilated sub mucosal veins at the anastomosis at the eosophago-gastric junction
   - Collaterals develop at the lower oesophagus and upper gastric fundus between the left gastric vein (portal system) and the azygos minor vein (systemic circulation)

ii) Haemorrhoids
   - Develop at the ano-rectal junction in the lower rectum and anus between the superior haemorrhoidal vein (portal system) and the middle and inferior haemorrhoidal veins

iii) Caput medusae
   - Develops at the hilum of the liver and the umbilicus ligament between the left branch of the portal vein (portal system) and the superficial veins of the anterior abdominal wall via the para-umbilical veins (systemic circulation)

iv) Retroperitoneal anastomoses
- Seen in the retroperitoneal and portocaval anastomoses through the veins of Retzius and Sapper.

13) Spleenomegaly
- Congestive enlargement due to venous congestion, lymphoid hyperplasia and cellular infiltration

14) Hepatorenal Syndrome
- Arise as a squeal of reduced renal blood flow (effective hypovolaemia) as a consequence of systemic vasodilatation, low blood pressure and pooling of blood in the portal circulation.

15) Hepatopulmonary Syndrome
- Results from pulmonary vasodilatation with intra-pulmonary arterio-venous shunting, which causes ventilation-perfusion inequality leading to, impaired pulmonary function, finger clubbing and cyanosis.

10.0. HEPATIC ENCEPHALOPATHY

10.1. Introduction

- A life-threatening neuropsychiatric syndrome caused by liver disease commonly cirrhosis or acute liver failure
- A disorder of neurotransmission in the central nervous system (impaired mental state and neurological function) and neuromuscular transmission that may complicate hepatic failure
- Results from porto-systemic venous shunting carries un-detoxified substances to the brain resulting in a complex metabolic and organic syndrome of the brain characterized by disturbed consciousness/coma, behavioural changes, convulsions, delirium, drowsiness, neurological signs and flapping tremors
- Minor morphological changes e.g. oedema and astrocytic reaction may be encountered

10.2. Predisposing Factors

- Uraemia – spontaneous or diuretic induced; Drugs – sedatives, antidepressants, hypnotics; Increased; protein in circulation (GIT bleeding, excess dietary proteins, constipation); paracentesis (volumes >3-5L); Hypokalaemia; Infection; Trauma (including surgery); Porto-systemic shunts – surgical or systemic

Mnemonic for Predisposing Factors

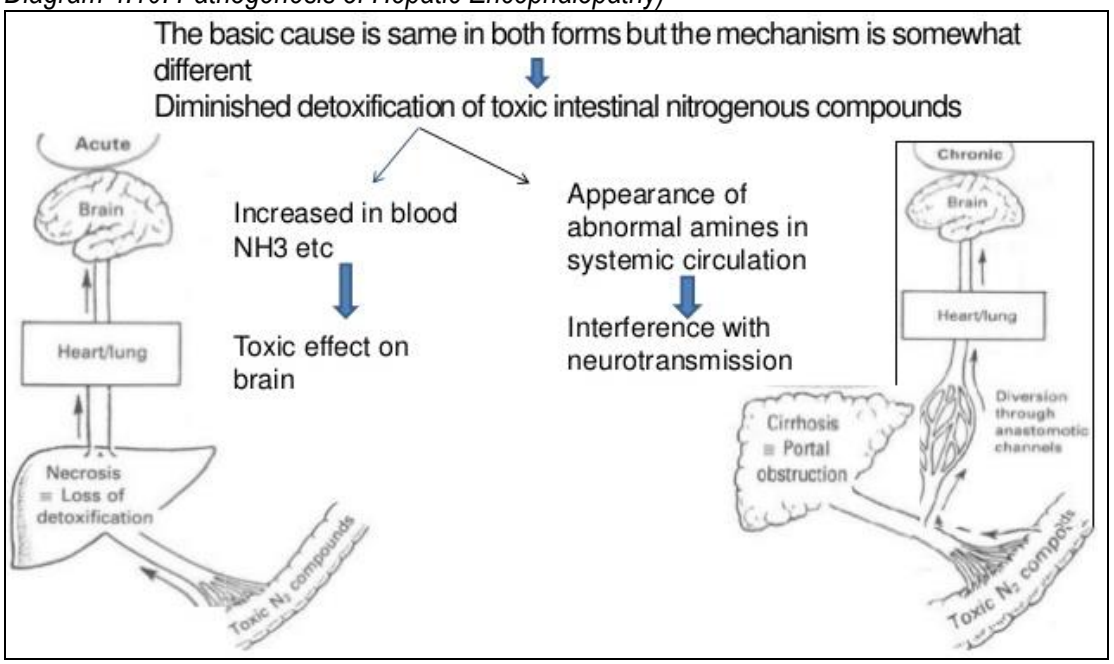
H	Haemorrhage in GIT; Hyperkalaemia
E	Excess protein in diet
P	Paracentesis
A	Acidosis; Anaemia
T	Trauma
I	Infection
C	Colon surgery
S	Sedatives

10.3. Pathogenesis

- Results from the effects of toxic products such as ammonia and other nitrogenous substances which reach the brain without being detoxified and
- In both acute and chronic states, there is diminished detoxification of toxic intestinal nitrogenous compounds

- In acute cases - increased ammonia level in blood escapes detoxification in the liver and passs through the heart/lungs to affect the brain
- In chronic states - abnormal amines appear in circulation which by-pass the liver via anastomoses to the heart/lungs reaching the brain where they interfere with neurotransmission
- There is an imbalance of excitatory and inhibitory amino acid neurotransmitters consisting of decreased excitatory neurotransmitters (glutamate and aspartate) resulting from enhanced metabolism of ammonia and increased gamma aminobutyrate (GABA) one
- Biochemical neurotoxins e.g. nitrogenous substances (ammonia) produced in the gut by bacterial action enter the systemic circulation. False transmitters e.g. octopamine, amino acids (imbalance between aromatic and branched chain amino acids) mercaptans and fatty acids.

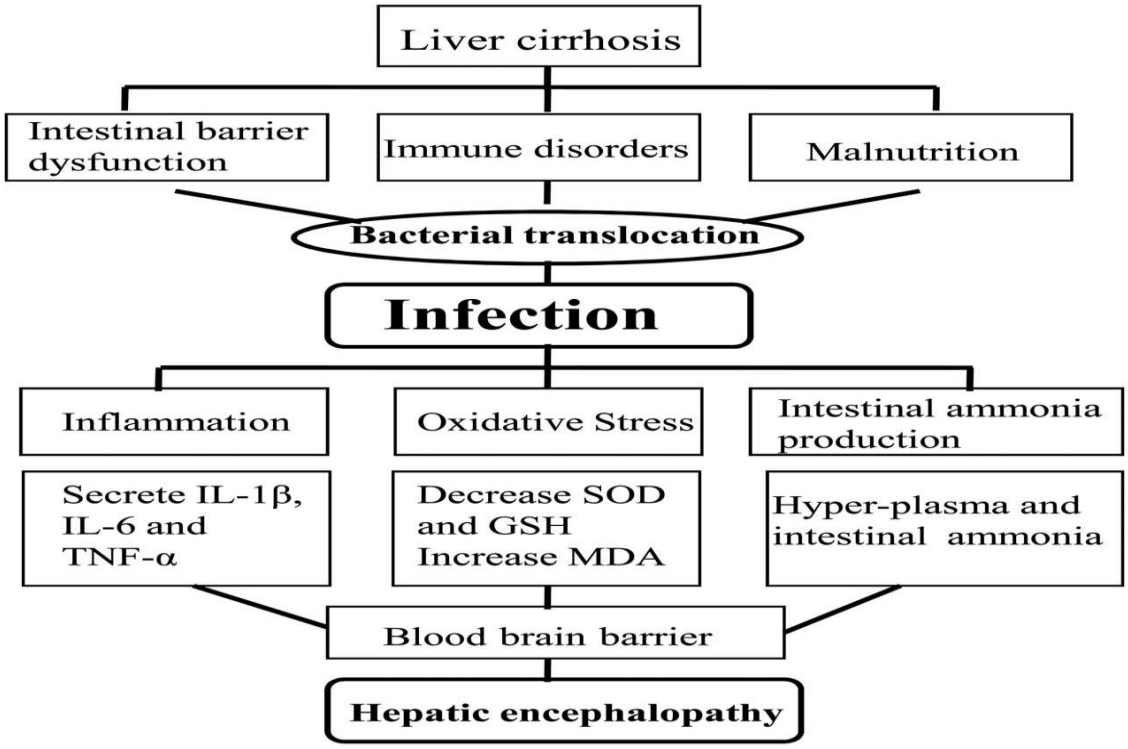
Diagram 4.10: Pathogenesis of Hepatic Encephalopathy)



10.4. Pathology

- Main pathology is cerebral oedema, structural changes and alterations in the composition of blood and the cerebral spinal fluid (CSF)
  1) Cerebral oedema
     - There is a generalized tendency to retain water and sodium due to the positive pressure ventilation used in the ICU
  2) Structural changes
     - Astrocytes become enlarged and there are changes in the vascular permeability of the blood-brain-barrier (BBB)
     - Increased sensitivity of the brain cells to a variety of agents due to interference with oxidative metals
  3) Altered Blood and CSF Composition
     - Increased nitrogenous waste products and serum levels of aromatic amino acids e.g. alanine in blood and C.S.F due to decreased deamination which reduces branched chain amino acids e.g. valine that controls neurotransmitter synthesis
     - Ammonia toxicity that leads to alteration of cerebral metabolism, depression of cerebral blood flow and increased permeability of the BBB to ammonia if alkalosis is present
     - False transmitters (GABA is the normal neurotransmitter) cross the defective BBB and there are increased binding sites for the false neurotransmitters. They increase binding sites for drugs such as barbiturates and benzodiazepines.

Diagram 4.12: Pathology of Hepatic Encephalopathy



10.5. Clinical Features

- In the acute form, severe symptoms e.g. convulsions, delirium and coma develop rapidly but in chronic conditions milder changes are encountered with coma being a late feature unless when a complication occurs
- Asterixis (involuntary jerking movements, especially in the hands, best elicited by having the patient extent the arms, dorsiflex the wrists, and spread the fingers, poor coordination), contractional apraxia, hyperreflexia and bilateral extensor plantar response, intellectual deterioration, jaundice, fetor hepaticus
- Staging
    I. Altered mood and behaviour
    II. Increasing drowsiness, confusion, slurred speech
    III. Stupor, incoherence, restlessness, significant confusion
    IV. coma

.

10.6. Staging

Stage	Abnormalities
1	Mild changes in personality and thinking, such as poor calculation ability, degraded handwriting, difficulty assembling simple figures, difficulty connecting number sequences, mild EEG abnormalities
2	Sleepiness and disruption of normal sleep, increased confusion, decreased attention span, inappropriate behaviour. EEG clearly abnormal with generalized slow waves. Increased reflexes, positive Babinski sign, ankle clonus, and asterixis are present
3	Further worsening of stage 2 abnormalities, patient asleep most of the time. Triphasic waves appear on EEG
4	Coma, extreme slowing of EEG to delta wave frequency

10.7. Diagnosis

The diagnosis is based on: _

1) History
2) Physical examination
3) Mental changes involving impairment of consciousness in a patient with other evidence of liver failure.

4) Characteristic fetor and flapping tremor (differential diagnosis: - chronic carbon dioxide retention and uraemia).
5) EEG – slowing of a wave with development of δ waves (DDX – subdural haematoma, drug or alcohol intoxication, delirium tremens, Wernicke's encephalopathy, primary psychiatric disorders, hypoglycaemia, neurological Wilson's disease)
6) Others e.g. increased blood ammonia levels.

11.0. INVESTIGATIONS IN LIVER DISEASE

- Meant to evaluate hepatocyte integrity, biliary excretory function and hepatocyte function
- Aims of Investigations
  i) Detect hepatic abnormality
  ii) Measure severity of liver damage
  iii) Define structural effects on the liver
  iv) Identify the specific cause
  v) Investigate possible complications

1) BLOOD TESTS

a) Liver Function Tests (LFTs)

i) Bilirubin (serum bilirubin)

- Elevation of direct bilirubin (hyperbilirubinaemia) occurs if the cause of the problem is outside the liver e.g. gallstones
- Indirect bilirubin is elevated in hepatocellular disease and excessive haemolysis
- Normal values of total bilirubin are from 0.3 to 1.0 mg/dL (3 to 22 *mmol/L)*

ii) Coagulation tests

- Increased Prothrombin time (PT) – normal = 11 to **13.5 seconds**
- Blood test that measures how long it takes blood to clot
- A *prothrombin time* test can be used to screen for bleeding abnormalities.

iii) Serum proteins

- Hypoalbuminaemia (
- *Normal serum* protein *level* is 60 to 80 gm/l. *Albumin* makes up 35 to 50 gm/L

iv) Serum Enzyme Assays

a) Alanine Aminotransfarase (ALT) – Normal values 0 –35 IU
   - Also, called SGPT (*Serum glutamic pyruvic transaminase)*
   - ALT is a cytosolic enzyme present in the liver
   - Increased in conditions of liver cell inflammation or death
   - Most sensitive marker for liver cell damage.

b) Aspartate Aminotransfarase (AST) – Normal values 0 – 35 IU
   - Also called SGOT(*serum glutamic-oxaloacetic transaminase***)**
   - AST is a mitochondrial enzyme released from heart, liver, skeletal muscle and kidney
   - Reflects damage to the hepatic cell
   - May be elevated in other conditions such as myocardial infarct (heart attack).
   - Not as specific to liver disease as ALT

c) Alkaline phosphotase (Normal values - 3 – 13 kA[1] units/dl[2] or 25 – 85 IU[3]/dl)
- An enzyme associated with the biliary tract
- Produced by tissues such bone, liver, intestines and placenta
- *Causes of raised alkaline phosphatase - biliary tract damage and inflammation – primary biliary cirrhosis; Liver disease – alcoholic hepatitis; Gall stones; Renal damage; Intestinal damage; Bone disease; Pregnancy*

d) **Gamma Glutamic Transpeptidase** (γ–GT- GGT)
- Liver is the primary source, also produced by the bile ducts
- Serum levels parallel those of alkaline phosphatase hence it is used to confirm the raised level of alkaline phosphatase is of hepatobiliary nature.
- Causes of raised γ–GT (GGT) include liver disease/toxins, bile duct disease, medications and alcohol.

b) Immunological Tests

Viral markers
- Antinuclear antibody in chronic active hepatitis or antibodies to specific aetiologic Hepatitis B surface antigen (HBsAg); Hepatitis B core antigen (HBcAg); Hepatitis Be antigen (HBeAg); Amoeba antibodies (in amoebic liver abscess)

Immunoglobulins
- IgA is predominant in bile and is raised in liver cirrhosis
- IgG is markedly raised in chronic active hepatitis
- IgM in primary biliary cirrhosis

c) Haematological Tests – TBC(FHG)
a. Normocytic normochromic anaemia (upper GIT bleeding from peptic ulcer or varices)
b. Hypochromic microcytic (chronic blood loss from portal hypertensive gastropathy, peptic ulcers due to iron deficiency)
c. Macrocytes associated with alcohol abuse
d. Leucopoenia and thrombocytopenia may complicate portal hypertension and hyperspleenism
e. Leucocytosis – associated with cholangitis, alcoholic hepatitis and hepatic abscess
f. Erythrocytosis – in hepatocellular carcinoma
g. Thrombocytosis – GIT haemorrhage and hepatocellular carcinoma

d) Biochemical (Metabolic) Tests
i) Hyponatraemia
ii) Serum urea
iii) Serum cholesterol (normal 130 – 230 gm/dl), phospholipids and triglycerides,
iv) Blood glucose level
v) Serum ammonia

2) URINE TESTS
i) Urobilinogen - Urobilinogen is normally excreted in urine
ii) Bromsulphalein (BSP) excretion - BSP is a dye that is removed from the circulation by the same mechanisms as bilirubin
iii) Bile acids (bile salts) - Primary bile salts are formed from cholesterol in the liver cells.

[1] King-Armstrong
[2] Deci-Litre
[3] International Units

3) IMAGING

i) Plain abdominal X-rays
ii) Barium studies
iii) Ultrasounds
iv) CT scans
v) Cholangiography
vi) Arteriography
vii) EEG

4) ENDOSCOPY

i) Endoscopy
ii) Sigmoidoscopy

5) BIOPSY

- Biopsy is taken for histology especially in cases of tumours
- Can be done by fine needle aspiration or laparoscopy
- Main complications are abdominal and/or shoulder pain, bleeding and biliary peritonitis.

What are the key parameters in the investigations above?
Explain the significance of each investigation

Lesson 5: CIRCULATORY DISORDERS OF THE LIVER

Learning Outcomes

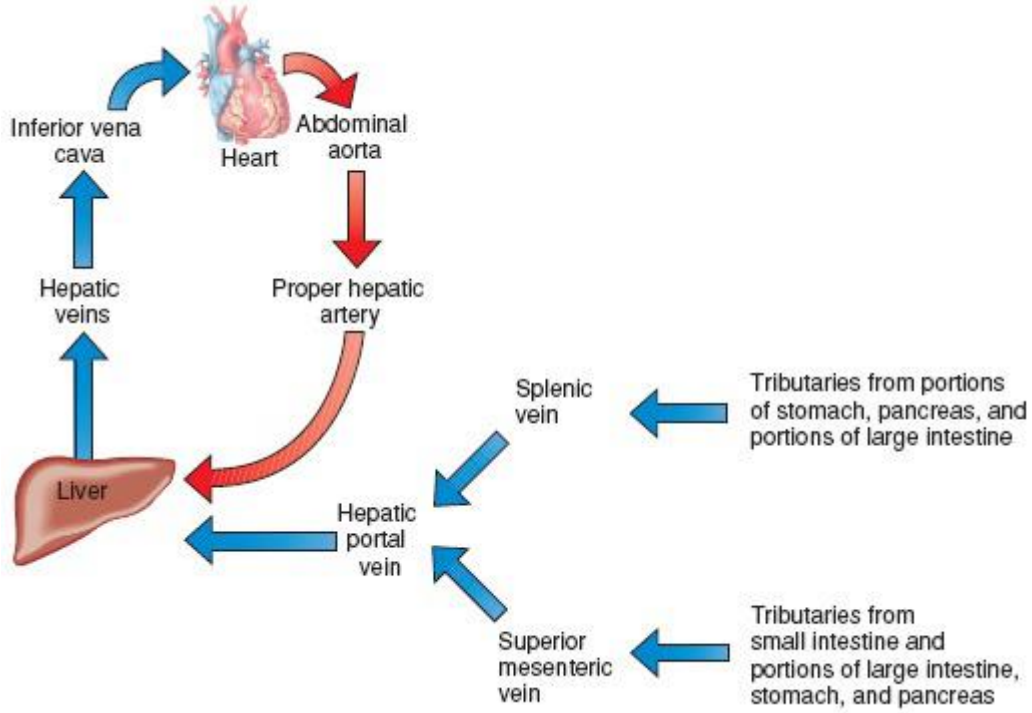
At the end of the lesson the learner should be able to: -

1. Outline causes of circulatory disturbances to the liver
2. Discuss the effects of circulatory disturbances in the liver
3. Explain the clinical consequences of hepatic circulatory disturbances
4. Discuss the pathology of portal hypertension
5. Describe the clinical effects of portal hypertension

1.0 INTRODUCTION

- Blood flow through the liver is enormous with the total hepatic blood flow at 1.5 litres/minute of which 75% is from the portal vein (with 85% oxygen saturation compared to 95% arterial oxygen saturation) and 25% from the hepatic artery.
- Mixing of the blood occurs in the sinusoids and with this enormous flow, circulatory disturbances produce a profound effect on the liver.

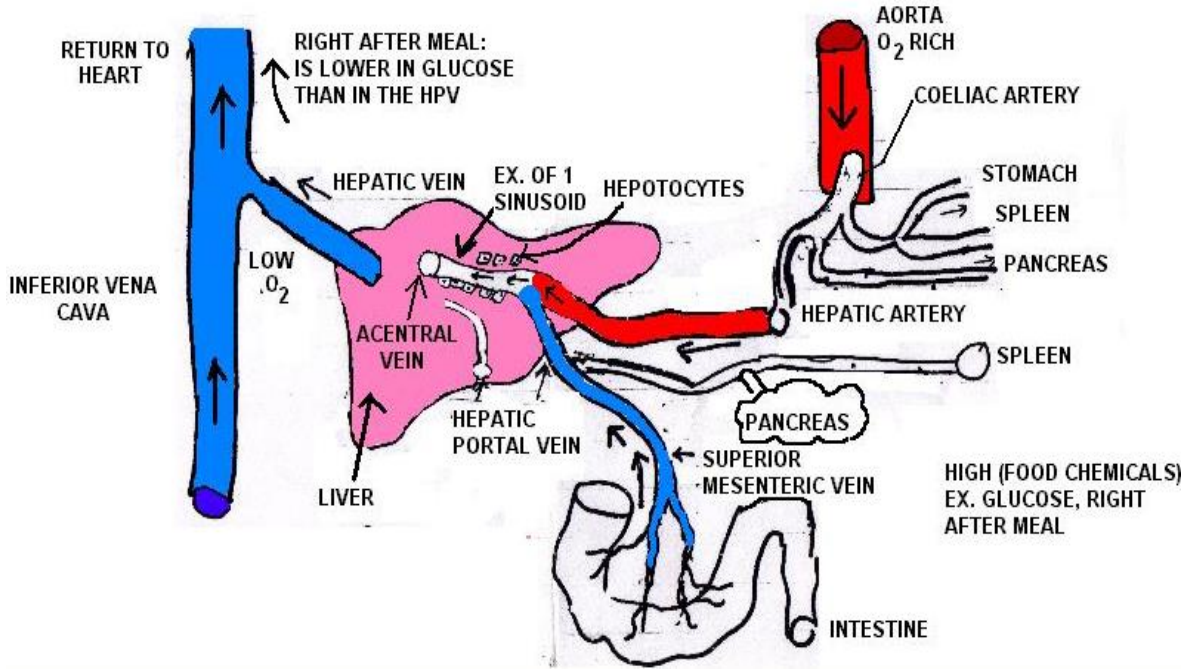
Diagram 5.1: Portal Blood Circulation



2.0 CLASSIFICATION AND CAUSES

- The disorders of circulation that can occur in the liver include: -
  1. Impaired blood flow into the liver
     a. Local disorders - Hepatic arterial+ obstruction and portal venous obstruction
     b. Systemic disorders - shock and venous congestion (Congestive cardiac failure)
  2. Impaired blood flow through the liver
     a. Intrahepatic
     b. Extrahepatic
  3. Hepatic venous outflow obstruction

Diagram 5.2: Classification and Causes



3.0 IMPAIRED BLOOD FLOW INTO THE LIVER

- Occurs due to hepatic artery obstruction and portal vein obstruction
- Hepatic arterial obstruction is a rare occurrence and liver infarcts are rare

4.0 HEPATIC ARTERY OBSTRUCTION

- Causes **-** thrombo-embolism, neoplasia, accidental ligation of the main hepatic artery, Infarction as seen in polyarteritis nodosa and acute bacterial endocarditis and sepsis causing infarcts

5.0 PORTAL VENOUS OBSTRUCTION

- Obstruction of the portal blood flow may occur within the liver (intrahepatic) or outside the liver (extra-hepatic)
- Obstruction may occur in the hepatic veins, hepatic sinusoids, intrahepatic portal vein branches and the portal vein.
- The normal pressure in the portal circulation is 5 – 10 mmHg (average of 7 mmHg). Obstruction to the portal blood flow leads to increased pressure in the system (portal hypertension).

Causes

1) Intrahepatic
   - Hepatic cirrhosis (commonest), tumour invasion (primary and secondary), congenital hepatic fibrosis, schistosomiasis and acute hepatitis (viral and alcoholic – causes sinusoidal compression)
2) Extrahepatic
   - Intra-abdominal cancers, intra-abdominal sepsis, direct tumour invasion, myeloproliferative disorders, thrombosis e.g. after upper abdominal surgery, splenectomy

6.0 SYSTEMIC DISEASE

- Circulatory disturbances of the liver may result from systemic disease. Acute circulatory failure (shock) leads to impaired perfusion of the liver cells causing liver cell necrosis that provokes an acute inflammatory reaction with migration of polymorphs and increased serum amintransfarases.
- Venous congestion in congestive cardiac failure leads to enlargement and congestion of the liver (tender hepatomegaly). There is death of liver cells as a result of hypoxia and compression by the dilated sinusoids. Eventually nodular regeneration is witnessed.

7.0 IMPAIRED BLOOD FLOW THROUGH THE LIVER

Intrahepatic

- Cirrhosis; Physical occlusion – sickle cell disease; D.I.C; Necrosis; Secondary tumours (breast, lymphoma, malignant melanoma)

8.0 HEPATIC VENOUS OUTFLOW OBSTRUCTION

- There is obstruction in the major hepatic veins
- In the normal liver, no anatomises exist between the hepatic vein and portal vein however they do occur in liver cirrhosis
- Obstruction of the hepatic vein leads to Budd-Chiari syndrome (hepatic vein thrombosis) and hepatic veno-occlusive disease.

Hepatic vein thrombosis (Budd-Chiari syndrome)

- There is slow development of thrombosis of the hepatic vein and the adjacent inferior vena cava.

Causes

1. Idiopathic (1/3 of the cases)
2. Increased tendency to thrombosis in states such as - Polycythaemia vera, Oral contraceptives, Pregnancy and postpartum state, Intra-abdominal tumours, Chemotherapy, Radiation and Myeloproliferative disease
3. Congenital webs

Clinical features

1) In acute form – abdominal pain, vomiting, enlarged liver, ascites, mild ice
2) In chronic form – tender hepatomegaly, ascites and features of portal hypertension.

Pathology

Gross (macroscopic) appearance	Microscopic appearance
Liver is enlarged, congested and swollen with a tense capsule it is and red-purple in colour	Congestion; necrosis; thrombosis; rupture of sinusoids; fibrosis (may progress to cardiac cirrhosis)

Hepatic Veno-occlusive disease

- Hepatic veno-occlusive disease comprises of intimal thickening, stenosis and obliteration of hepatic veins (resembles Budd-Chiari syndrome but there is no thrombosis in the veins)
- It is associated with anti-neoplastic drugs and immunosuppressive therapy.

9.0 PORTAL HYPERTENSION

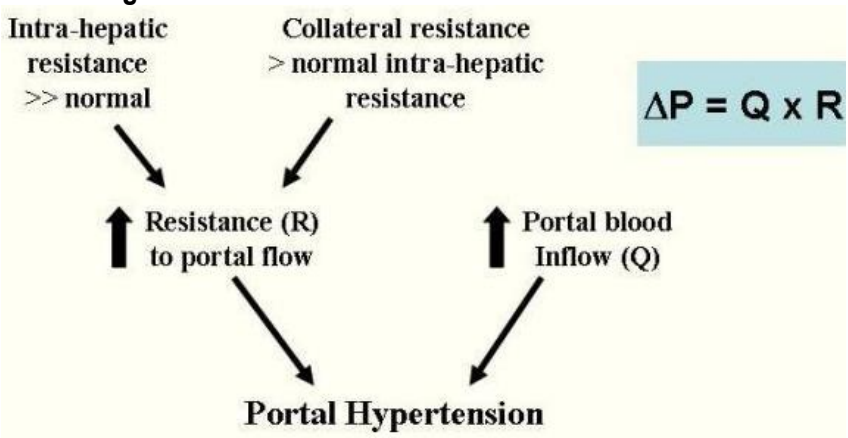
9.1. Introduction

- Portal hypertension is increase in resting portal venous pressure above 12 mmHg. (Normal is 5 – 10 mmHg with an average of 7 mmHg)
- It results from obstruction to blood flow in the portal system anywhere along portal system course either within the liver (intrahepatic) or outside the liver (extrahepatic)
- The portal veins have no valves thus obstruction anywhere in the system leads an increase in pressure.

9.2. Causes (Major Causes)

1) Pre-hepatic (Presinusoidal) - portal vein thrombosis – idiopathic, portal sepsis, malignancy, pancreatitis and blood disorders; neoplastic obstruction of portal vein; myelofibrosis; congenital absence of portal vein
2) Intra-hepatic (Sinuisoidal) - cirrhosis; portal tract fibrosis; metastatic tumours; polycystic disease of the liver; budd-chiari syndrome; hepatic veno-occlusive disease; diffuse granulomatous disease; extensive fatty change
3) Post-hepatic (postsinuisoidal) - congestive heart failure; constrictive pericarditis; hepatic veno-occlusive disease; budd-chiari syndrome

9.2 Pathogenesis



9.3. Classification

- Based on the site of obstruction of blood flow giving three main types: -
  i) Pre-hepatic (before blood reaches the hepatic sinusoids),
  ii) Intra-hepatic and
  iii) Post-hepatic

What are the causes of portal hypertension?

9.4. Major Sequalae of Portal Hypertension

- Four major effects of portal hypertension include

1) **Ascites**

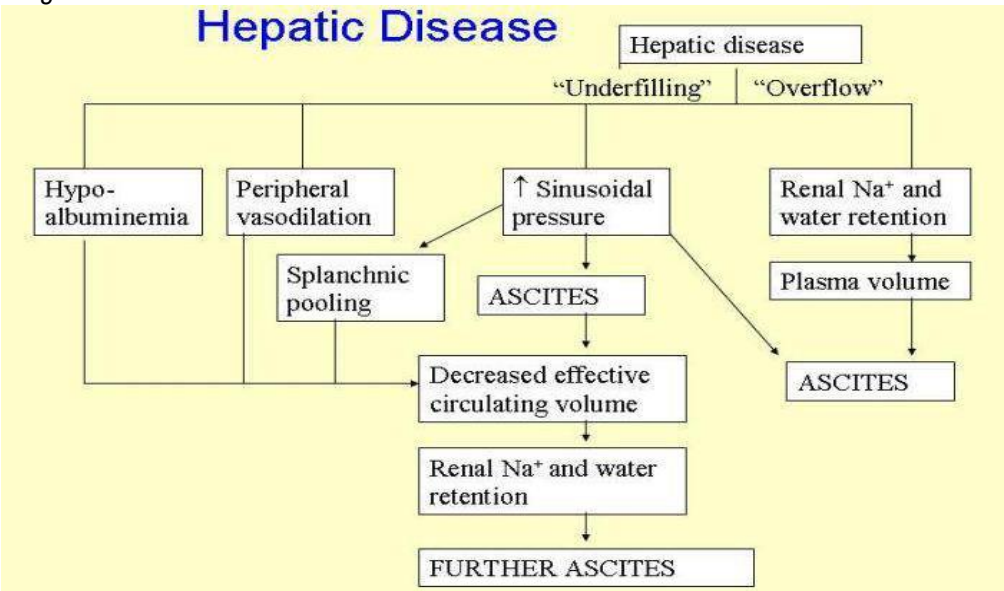
- This is accumulation of excessive volume of fluid in the peritoneal cavity. It is clinically detectable when more than 500 ml of fluid has accumulated in the peritoneal cavity.

Pathogenesis

A. Local factors
   a) Portal hypertension – has a role to play in combination with other factors
   b) Increased hepatic lymph formation – increased intra-sinusoidal pressure stimulates hepatic lymph formation that weeps through the liver surface

B. Systemic factors
   a) Decreased plasma colloid oncotic pressure following hypoalbuminaemia resulting from impaired hepatic synthesis of plasma proteins and loss of albumin into the peritoneal cavity.
   b) Hyperaldosteronism – increased aldosterone secretion and impaired hepatic metabolism and excretion of aldosterone.
   c) Impaired renal excretion – reduced renal excretion and excess release of antidiuretic hormone causes renal retention of sodium and water.

Diagram 5.3: Ascites Formation



2) **Varices**

- Varices are the collateral channels or porto-systemic shunts. Increased venous pressure and obstruction in portal circulation causes blood to by-pass the liver and return to the heart via the porto-systemic collateral channels (or shunts or varices) that develop where the systemic and portal circulations share capillary beds

a) Oesophageal varices

- Are dilated sub mucosal veins. An anastomosis exists at the eosophago-gastric junction. The collaterals develop at the lower oesophagus and upper gastric fundus between the left gastric vein (portal system) and the azygos minor vein (systemic circulation). These can also be called oesophageal-gastric varices.

b) Haemorrhoids

- These develop at the ano-rectal junction in the lower rectum and anus between the superior haemorrhoidal vein (portal system) and the middle and inferior haemorrhoidal veins. This anastomosis has a different structure hence it rarely bleeds.

c) Caput medusae

- Develops at the hilum of the liver and the umbilicus ligament between the left branch of the portal vein (portal system) and the superficial veins of the anterior abdominal wall via the para-umbilical veins (systemic circulation)

d) Retroperitoneal anastomoses

- Retroperitoneal anastomoses are seen in the retroperitoneum and porto-caval anastomoses through the veins of Retzius and Sappey

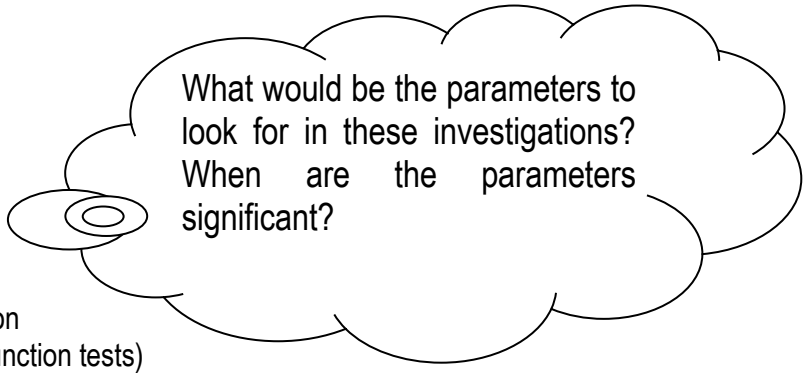
3) **Splenomegaly**

- The enlargement is referred to as congestive spleenomegally
- The enlargement could be due to venous congestion, lymphoid hyperplasia and cellular infiltration. The spleen may weigh 500 – 1000 gm.

4) **Hepatic encephalopathy**

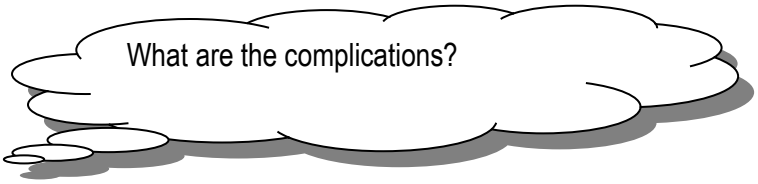
- Porto-systemic venous shunting carries un-detoxified substances to the brain resulting in a complex metabolic and organic syndrome of the brain characterized by disturbed consciousness, neurological signs and flapping tremors.

9.5 Investigations



1. Endoscopy
2. Sigmoidoscopy
3. Barium meal
4. Liver biopsy
5. Ultra sound
6. CT scan
7. Hepatic vein catheterisation
8. Liver biochemistry (liver function tests)
9. Full heamogram
10. Other specific investigations that target the specific causes.

9.6 Complications



Lesson 6: VIRAL HEPATITIS

Learning Outcomes

At the end of the lesson the learner should be able to: -
1. Outline the causes of liver infection
2. Describe the pathology of hepatitis
3. Investigate hepatitis

1.0 INTRODUCTION - HEPATITIS

- An inflammatory lesion of the liver with diffuse involvement of the liver cells
- Hepatitis can be acute or chronic in nature
- Classification of hepatitis in aetiological based
  - i) Infections - Viral hepatitis; Fungal – Histoplasma; Helminthic; Protozoa – Cryptosporidium, Toxoplasmosis (T. gondii); Bacterial - M. tuberculosis, Leptospirosis; Rickettsial - Q. Fever (Rickettsia burnetii)
  - ii) Autoimmune disorders
  - iii) Drug reactions
  - iv) Alcohol

2.0 ACUTE HEPATITIS

- Acute hepatitis has similar clinical features and histological appearances on histology irrespective of the cause

3.0 VIRAL HEPATITIS

- Acute inflammation of the liver causes by viruses and is characterized by diffuse hepatitis with widespread liver cell necrosis.

3.1 Aetiology

1. Hepatotropic viruses
   - Hepatitis A virus (HAV); Hepatitis B virus (HBV); Hepatitis C virus (HCV); Hepatitis D (delta) virus (HDV); Hepatitis E virus (HEV); Hepatitis F virus (HFV); Hepatitis G virus (HGV)
2. Non-Hepatotropic viruses
   - Cytomegalovirus (CMV –neonates, immuno-compromised patients); Arbovirus (Yellow fever); Herpes simplex in the immuno-compromised individuals; Herpes zooster in the immuno-compromised individuals; Epstein Barr virus (EBV) – infectious mononucleosis; Ebola virus; Coxsackie virus

3.2 Pathology of Viral Hepatitis

- Hepatocellular damage is an essential feature
- Cellular reaction is predominantly lymphocytic and monocytic derived by the viral antigens rather than chemical mediators of classical inflammation

Macroscopic appearance
- i) Swelling (hepatomegally) - elicited on clinical examination and imaging
- ii) Gross appearance – swollen, reddish liver with an oedematous capsule surface exuding serous fluid.
- iii) Widespread hepatitis leads to shrinking of liver with a wrinkled capsule.
- iv) Regenerative hyperplasia in surviving areas

Microscopic appearance

i) Cellular infiltration with lymphocytes, plasma cells and macrophages
ii) Evidence of hepatocellular injury and cell death.

What biochemical changes can be seen at all stages of liver disease?

3.3 Clinico-Pathologic Spectrum

- Can be considered as: -
  1) The carrier state
  2) Asymptomatic infection
  3) Acute hepatitis
  4) Chronic hepatitis
  5) Fulminant hepatitis (sub-massive to massive necrosis)
  6) Liver cirrhosis (to be considered later)
  7) Hepatocellular carcinoma (to be considered later)

I. The Carrier State

- Individuals have no manifestation of the disease and capable of transmitting it.
- Two types of carrier states - asymptomatic healthy and asypmtomatic carrier with chronic disease
- HBV has the highest incidence of carrier states
- Factors that accelerate the incidence of carrier states are early age of infection and impaired immunity
- Recognized by detection of HbsAg in the serum

II. Asymptomatic Infection

- Detected incidentally as revealed by raised serum transaminases

III. Acute Hepatitis

- Most common consequence resulting in acute inflammation of the liver with involvement of the entire liver
- Types A, B, C, D and E run a similar clinical course
- Has 4 phases - incubation period, pre-ecteric, icteric and post-icteric phase.
  a) Incubation Period
     - Patient is asymptomatic but infectivity is highest during the last days of incubation period
     - ICP - Hepatitis A – 4 weeks (15-45 days); Hepatitis B – 10 weeks (30-180 days); Hepatitis C – 7 weeks (42-56 days); Hepatitis D – 6 weeks (30-50 days); Hepatitis E – 2-8 weeks (15-60 days)
  b) Pre-icteric Phase
     - Precedes onset of jaundice
     - Prodromal constitutional symptoms such as nausea, anorexia, vomiting, fatigue, malaise, athralgia, distaste for smoking and headache
     - Evidence of hepatocellular damage is elevation of serum ALT, AST.
  c) Icteric Phase
     - There is clinical jaundice and constitutional symptoms disappear
     - Other features include dark coloured urine (due to bilirubinuria), clay-coloured stools (due to cholecystitis), pruritus (due to elevated serum bile acids), weight loss, tender hepatomegaly and deranged liver function tests
  d) Post-icteric Phase
     - Lasts 1-4 weeks and is followed by clinical and biochemical recovery in 2-12 weeks.
     - Recovery phase is prolonged in HBV and HCV

IV. Chronic Hepatitis

- Is a chronic inflammatory hepatic disease continuing for more than six months
- Factors increasing the vulnerability of a patient of viral hepatitis to develop chronicity are the impaired immunity and the extremes of age
- Aetiology
  i) Hepatitis viruses - HBV (most important), HCV, HDV and HGV
  ii) Drugs – methyldopa, isoniazid, nitrofurantoin and sulphonamides
  iii) Chronic alcoholism
  iv) Metabolic disease - Wilson's disease
  v) Autoimmune diseases - rheumatoid arthritis, Sjogren's syndrome, ulcerative colitis and thyroiditis
  vi) Idiopathic

Classification

- Two main types - chronic persistent hepatitis and chronic
  i) Chronic persistent hepatitis
    - Benign self-limiting condition where there is delayed recovery from an attack of acute viral hepatitis
    - Pathological changes include inflammation with expansion of portal tracts and cellular infiltration (mononuclear cells), necrosis and the architecture is usually preserved
  ii) Chronic active (aggressive) hepatitis
    - Involves the portal tracts and hepatic parenchyma
    - Usually leads to cirrhosis and has a wide spectrum of clinical features
    - Pathological Changes inflammation with abundant monocellular infiltration, necrosis and fibrosis with scarring (from the necrosis)

4.0 HEPATITIS A (INFECTIOUS HEPATITIS)

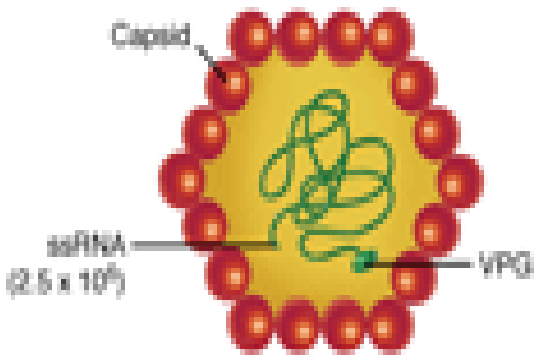
4.1 Introduction

- Hepatitis A is an RNA virus of the pircona group which is naturally acquired benign, self-limiting disease with and ICP of 2 – 4 weeks (up to 45 days)
- Common in low socio-economic areas occurring sporadically or in epidemics
- Transmission is feaco-oral route through fingers, food and drink.

4.2 The Hepatitis A Organism (Structure)

- HAV is a small, 27nm diameter, non-enveloped single-stranded RNA virus of the Picorna virus family, genus enterovirus (same family as the poliovirus)

Diagram 8.1: Structure of HAV



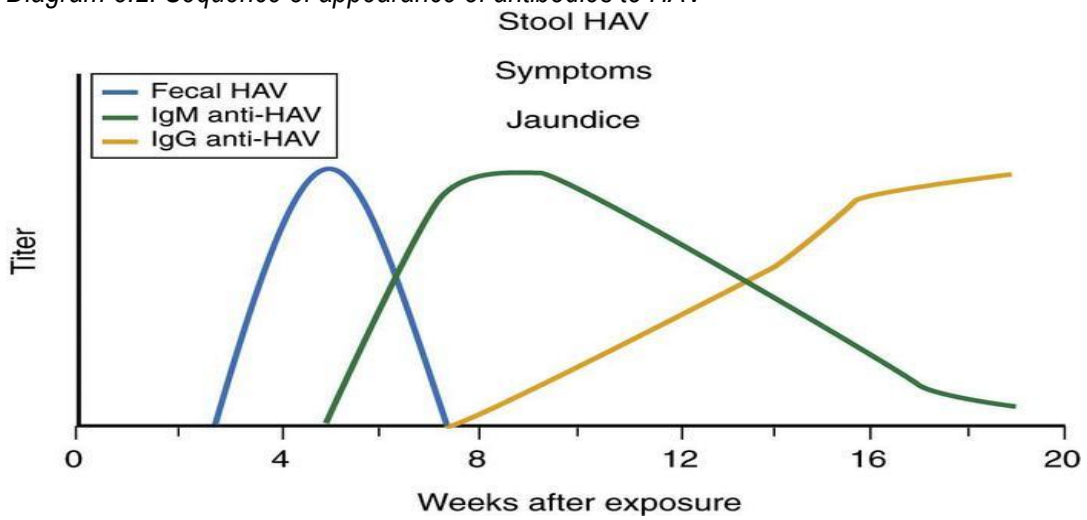
4.3 Pathogenesis

- Virus replicates within the liver cells and is excreted in stool
- Present in the liver cells, bile, stool and blood during the incubation period and pre-icteric phase diminishing after the onset of jaundice
- HAV is excreted in faeces of infected persons for about two weeks before onset of illness and for up to seven days after the onset of illness
- Patients are maximally infectious before the onset of jaundice
- Faeces and blood become infected 3-4 weeks after exposure and remain infective for three weeks.

4.4 Immunology

- HAV evokes a strong antibody response and a rapid rise in IgM antibody titre occurs at the onset of the illness and lasts for 3-6 months
- IgG antibodies are present in high titres from clinical onset and lasts for life (protective immunity against re-infection)
- In stool HA Ag (hepatitis A antigen) can be found
- Viral markers IgM anti-HAV antibody appears in the serum at the onset of symptoms. IgG anti-HAV antibody is detected in the serum after IgM antibody and give the lifelong immunity against re-infection

Diagram 8.2: Sequence of appearance of antibodies to HAV



4.5 Pathology

- Widespread cellular damage (centrilobular necrosis) with the hepatocytes are swollen, granular and later shrink leaving a scar in case of cell death
- Portal tracts are enlarged and may become continuous with central veins
- Severe damage causes massive necrosis causing fulminant hepatic failure and stasis

4.6 Investigations

a) Liver biochemistry (liver function tests) - Increased serum bilirubin, urobilinogen and AST
b) Haematological tests – leucopenia, relative lymphocytosis, prolonged prothrombin time (PT), anaemia and increased ESR
c) Viral markers - increased IgG anti-HAV and IgM anti-HAV antibodies
d) Liver biopsy (what will you see?)
e) Ultrasound (what do you expect?)

Complications

What are the complications of HAV infection?

5.0 HEPATITIS B (SERUM) HEPATITIS

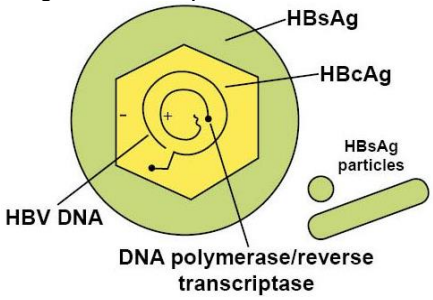
5.1 Introduction

- HBV is a *DNA virus of the Hepadna group* present worldwide affecting all ages
- Has a longer incubation period of 30-180 days
- Transmitted parenterally
- Risk groups **(6Hs) –** Homosexuals, Haemophiliacs, Health workers, Heroin drugs), Haemodialysis and Homes (e.g. prisons)
- Found in body secretions such as saliva, semen and vaginal secretions.
- HBV causes a severe form of illness – acute hepatitis B, chronic hepatitis, fulminant hepatitis, cirrhosis, asymptomatic carrier state and has a role in development of hepatocellular carcinoma

5.2 Structure

- Hepadna virus (DNA virus) with marked hepatotropism
- HBV shows three types of particles the spheres (small particles of 20 nm diameter), tubules (20 nm diameter and 100 nm long) and Dane particles (large 42 nm diameter)
- The Dane particle is spherical and it is partially single-stranded and partially double-stranded
- Has an outer surface envelop of protein, carbohydrate and lipid and an inner hexagonal core

Diagram 8.3: Hepatitis B Virus



5.3 Pathology

- As for HAV

5.4 Immunology & Serology

- Immuno-pathogenic mechanism causing hepatocellular damage
- Explained through three main mechanisms namely immunological markers, cellular immunity (delayed hypersensitivity) and immune-complex mediated tissue injury.
- A number of immunological markers are found in the serum and hepatocytes and indicate the presence of HBV infection

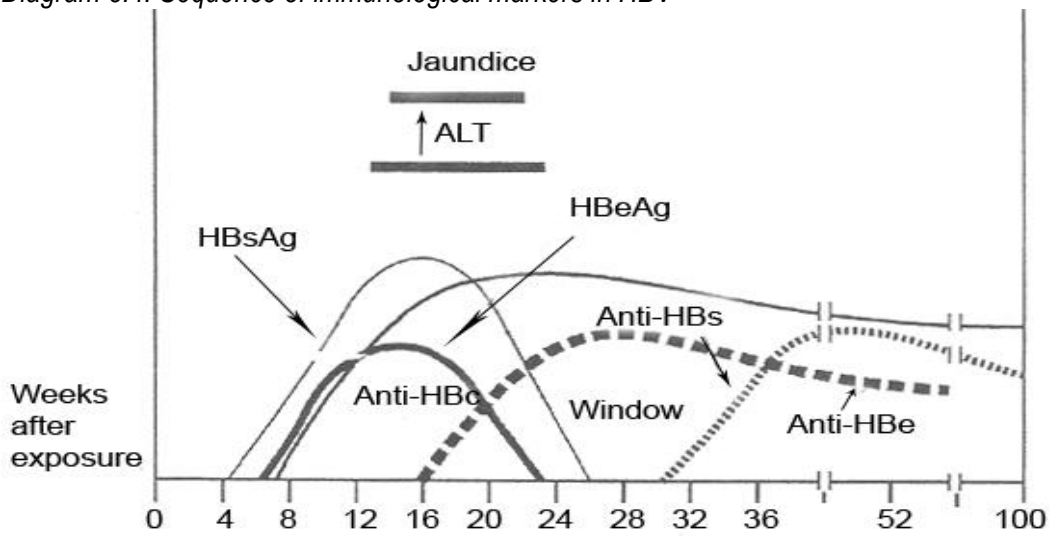
HbsAg (Hepatitis B surface antigen)

- Produced in the liver cell cytoplasm and appears in blood within the prodromol phase up to one week after the onset of symptoms
- Seen 2-8 weeks before biochemical evidence of liver damage/jaundice.
- Levels start to come down after the onset of symptoms and persist after the illness up to 3 –6 months
- Cleared from the circulation during the convalescence and an antibody against it developed
- Forms the basis for screening carriers (carriers do not develop the antibody) and its persistence for more than six months implies a carrier state

Anti-HBs

- Antibody to **HbsAg** and appears late (3 months after onset) and the response may be both IgM and IgG type

Diagram 8.4: Sequence of immunological markers in HBV



HbeAg (Hepatitis B e antigen)

- Derived from core protein and appears at the same time as HbsAg
- Present transiently (3-6 weeks) during the acute attack disappearing at the peak of the illness and its persistence beyond 10 week is indicative of development of chronic liver disease and a carrier state
- Precedes increase in ALT (SGOT)

Anti-HBe

- Antibody to HBeAg that appears in blood after the Ag has disappeared (it starts appearing as the Ag reduces but it is detectable after the Ag has disappeared)
- Anti-e indicates a relatively low infectivity of serum

HbcAg (Hepatitis B Core Antigen)

- Derived from the core protein and it is found in the cell nuclei and not in serum
- Cannot be detected in the blood

Anti-HBc

- An IgM or IgG antibody to HBcAg and usually appears 2-4 weeks after appearance of the HbcAg (just after the clinical symptoms have set in)
- IgM anti-HBc persists for 4-6 months and is later followed by IgG anti-HBc
- IgM indicates recent acute HBV infection and IgG suggests infection in the remote past
- Antibody is not a reliable indicator for HBV since it does not disappear from the blood (it persists after recovery).

Cellular Immunity (Delayed Hypersensitivity)

- Features of hepatocellular damage result from cell-mediated immune mechanism and not direct damage by the virus
  i) Absence of hepatocellular damage in HBV infected carrier state
  ii) Presence of sensitised T-lymphocytes at sites of liver cell damage
  iii) Patients with depressed cell-mediated immunity easily progress from acute to chronic hepatitis.

Immune-complex mediated mechanism

- There is formation of circulating immune-complexes by combination of HbsAg and anti-HBs resulting in activation of the complement system that causes tissue destruction.
- This may explain the extra-hepatic manifestations of HBV infection e.g. serum sickness-like syndrome, glomerulonephritis and polyarteritis nodosa.

5.5 Clinical Patterns

- Hepatitis B infection causes 5 clinical patterns of infection namely: -
  i) Acute self-limiting hepatitis
     - Illness is self-limiting in which patients recover after an illness with jaundice, malaise and anorexia
     - Develop lifelong immunity and is the most common outcome
  ii) Fulminant acute hepatitis
     - Very rare and causes massive necrosis of liver cells

  iii) Chronic hepatitis
     - Affects 5 – 10% and may recover or progress to cirrhosis
     - Due to failure to eliminate HBV from the liver associated with or without active viral replication
  iv) Asymptomatic carrier state
     - May develop chronic hepatitis
  v) Clinically inapparent asymptomatic infection
     - Sub-clinical form that may progress to carrier state or chronic hepatitis

5.6 Investigations

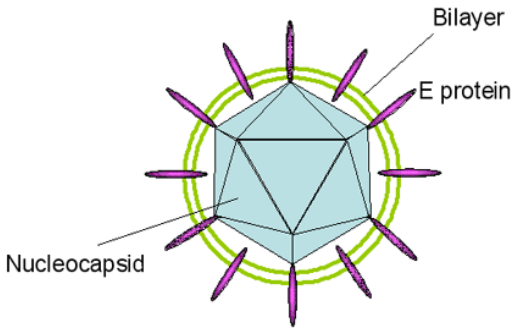
As for HAV

6.0 HEPATITIS C

6.1 Introduction

- Single-stranded, enveloped RNA flavivirus with an incubation period of 20-90 (mean 50 days, 2 months) days that produces serologic and virologic markers.
- Clinically similar to HBV
- Previously referred to as Hepatitis Non-A Non-B infection
- Acquired by blood transfusions, blood products, haemodialysis, parenteral drug abuse and accidental cuts and needle pricks in health workers
- An important cause of post-transfusion hepatitis.

Diagram 8.5: HCV



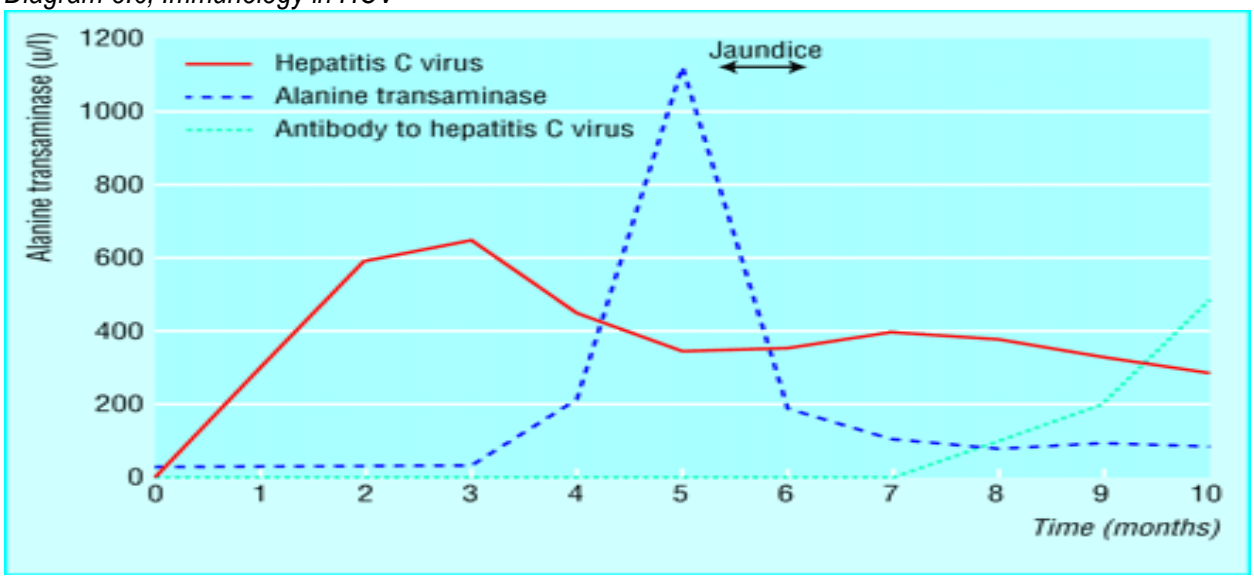
6.2 Pathogenesis

- Unclear but thought to be an immunologic mechanism and cell destructive replication or both.

6.3 Clinical Features

- Acute form it is milder than HBV but has a higher rate of progression to chronic hepatitis as persistency and chronicity are its key features
- An important cause of chronic liver disease than HBV
- In the long run, it is associated with cirrhosis and hepatocellular carcinoma.
- Clinical features are as others in addition to extrahepatic features of arthritis and agranulocytosis
- Diagnosis involves detection of antibodies to HCV and HCV RNA in blood by PCR tests

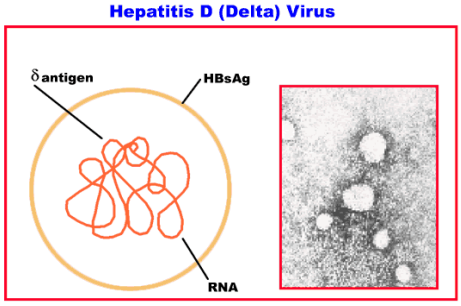
Diagram 8.6; Immunology in HCV



7. HEPATITIS D (DELTA) HDV HEPATITIS

- HDV is a defective RNA virus for which HBV virus is a helper hence the infection occurs with concomitant HBV infection, which can be a co-infection (being simultaneous with HBV) or super-infection (infect a chronic HBV carrier)
- High-risk groups are intravenous drug abusers, homosexuals, transfusion recipients and health acre workers.

Diagram 8.7: HDV



- In co-infection, the picture ranges from mild to fulminant and chronicity is rare but in super-infection with incubation period of 30-35 days chronic HBV infection worsens with appearance of severe acute

fulminant attacks, progression of carriers' state and acceleration towards cirrhosis. Hepatocellular carcinoma is less common in HbsAg carriers with HDV infection.

- HDV is a small single-stranded RNA particle that is double shelled with the inner shell containing HbsAg and the inner one the delta antigen
- Produces markers that are of IgG and IgM
- Pathogenesis is unclear but it is thought to be direct cytopathic effect on the hepatocytes.

8. HEPATITIS E VIRUS HEPATITIS (HEV)

- An enterically transmitted virus with the infection being generally acquired by contamination of water supplies but compared to HAV person-to-person infection does not occur
- The transmission is faecal-oral route.
- HEV is a single-stranded non-enveloped RNA virus that produces anti-HEV antibodies that are of both IgM and IgG class

9. HEPATITIS G (HGV) HEPATITIS

- Hepatitis G virus (HGV) is a single stranded RNA virus
- A blood-borne infection that can cause acute and chronic hepatitis
- Infection found in blood donors and is transmitted by blood transfusion

SELF-ASSESSMENT - TASK

Complete the following table to illustrate the features (differences) of various types of Viral Hepatitis.

	Feature	HAV	HBV	HCV	HDV	HEV	HGV
1.	Agent						
2.	RNA or DNA virus						
3.	Viral particle						
4.	Genome						
5.	Morphology						
6.	Spread						
7.	Incubation period						
8.	Antigen(s)						
9.	Antibodies						
10.	Severity						
11.	Vaccine						
12.	Chronic hepatitis						
13.	Carrier state						
14.	Hepatocellular carcinoma						
15.	Prognosis						

Lesson 7: NON-VIRAL HEPATITIS

Learning Outcomes

At the end of the lesson the learner should be able to: -
1) Discuss the pathology of non-viral infections of the liver

1.0 INTRODUCTION

- Liver may be infected by several non-viral microbes including bacteria – (several microbes), protozoa (amoebiasis, malaria, visceral leishmaniasis) and helminthic infection (ascaris; schistosoma; liver flukes; hydatid disease)

2.0 BACTERIAL HEPATITIS

2.1. Pyogenic Liver Abscess

Incidence
- Is higher in old age, in immunosuppressed patients

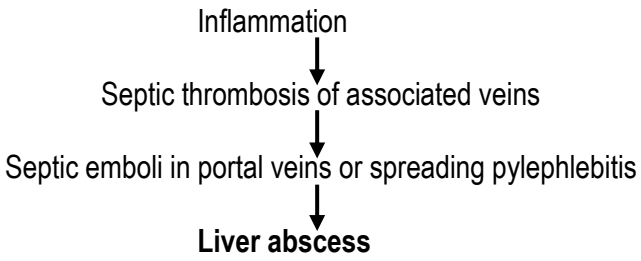
Organisms
- Gram-negative organisms - E. coli, Pseudomonas, Klebsiella and Enterobacter, S. milleri; Anaerobic organisms; Bacteroids; Actinomyces

Mode of Entry (Infection)
1. Ascending cholangitis – extension of infection from the biliary tract due to obstruction e.g. galls stones, cancer and biliary stenosis.
2. Portal pyaemia (suppurative pyelophebitis) - by spread of pelvic or gastrointestinal infection causing pyephlebitis or septic emboli e.g. from appendicitis, empyema of gall bladder, diverticulitis, regional enteritis, pancreatitis, infected haemorrhoids and neonatal umbilical sepsis.
3. Haematogenous
   - Portal vein (mesenteric infections) – anaerobes, Streptococci, Bacteroids
   - Hepatic artery (bacteraemia/septicaemia)
4. Direct infection – this may follow infection from an adjacent perinephric abscess, secondary infection in amoebic liver abscess, following haematoma formation after trauma.
5. Iatrogenic causes - may occur after procedures such as liver biopsy, biliary drainage and accidental surgical trauma
6. Cryptogenic - unknown causes especially in the elderly.

Pathogenesis

- Takes two main forms – ascending infection and septic embolism arising from suppurative lesions in the abdominal cavity

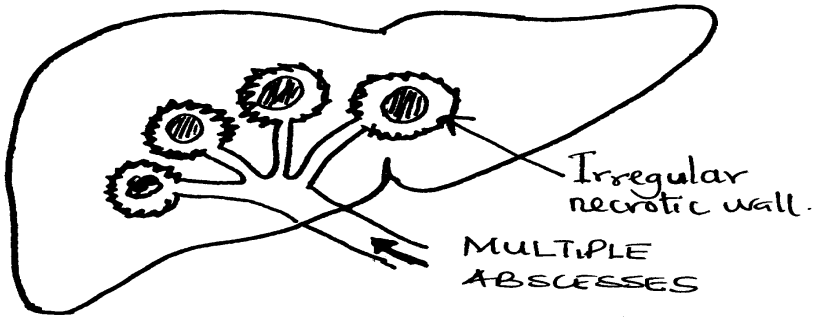
Diagram 7.1: Illustration of pathogenesis of pyogenic liver abscess



Pathology

Gross appearance (Macroscopic)	Microscopic appearance
An enlarged liver; Single or multiple abscesses	Necrosis; Inflammation; Congestion; Proliferating fibroblasts

Diagram 9.2: Pyogenic Liver Abscess



Clinical Features

- High swinging fever (±rigors and sweating); RUQ pain ± radiating to the shoulder; cough ± pleuritic pain; PUO; Signs - pain in the right upper quadrant; fever; tender hepatomegaly, Durban sign +ve (pressure in the 6th intercostals space elicits tenderness due to stretching of the liver capsule); jaundice (±) and laboratory features; - Leucocytosis, Elevated serum alkaline phosphates, Hypoalbuminaemia, Positive blood culture

Differential Diagnosis
1. Amoebic liver abscess
2. Hydatid
3. Choledochal cysts
4. Necrotic colorectal metastasis

Investigations
1. Abdominal U/S or CT scan
2. U/S guided Needle Aspiration
3. CXR (raised right diaphragm and lung collapse or an effusion at the base of the right lung)
4. TBC/FBC

2.2. Hepatic Tuberculosis

- TB liver occurs as a result of **miliary dissemination** from primary complex or from chronic adult pulmonary tuberculosis
- Patients have unexplained fever, jaundice, hepatomegally or hepatospleenomegally
- There is central caseous necrosis with destruction of liver framework.
- Diagnosis is by liver biopsy where tubercles are seen in the parenchyma. Z-N staining for AFB is confirmatory.

2.3. Actinomycosis

- *Actinomycosis israeli* is as anaerobic commensal in the G.I.T. infection around the appendix extends to the liver by the portal system when an individual's immunity is compromised.

2.4. Spirochaetal Infections

Syphilis
- Syphilis of the liver may be seen in congenital and acquired syphilis

- Caused by *Trepanoma pallidum*
- In congenital syphilis, there is diffuse interstitial pericellular fibrosis and ischaemic atrophy of hepatocytes
- In acquired syphilis, there is diffuse hepatitis, granuloma formation (in secondary syphilis) and hepatic gummas (in tertiary syphilis)
- Healing occurs with extensive scarring producing gross distortion of the liver (hepar lobatum).

Leptospirosis

- *Leptospira icterohaemorrhagic* is a spirochete that penetrates human skin or enters the body via the respiratory or oral route
- It has an incubation period of 10-15 days
- Common in sewer workers, agricultural workers and fish handlers
- Causes Weil's disease that presents with conjunctivitis, renal tubular damage, haemorrghic tendencies, jaundice, focal myocardial/skeletal muscle necrosis and mild lymphocytic meningitis
- Causes cell degeneration, focal necrosis, cholestasis and haemorrhage.

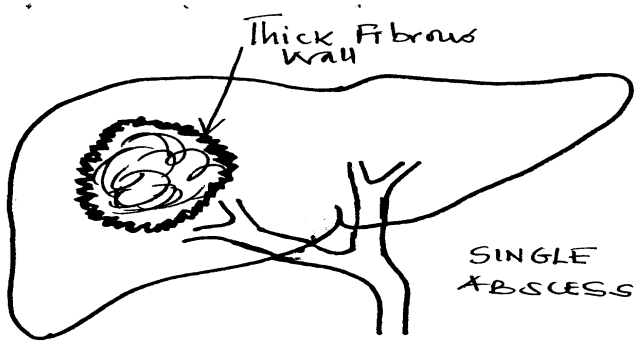
3.0 PROTOZOAL HEPATITIS

3.1. Amoebic Liver Abscess

Aetiology

- Spread of *Entamoeba histolytica* from intestinal lesions in 50% cases

Diagram 9.3: Amoebic Liver Abscess



Pathogenesis

- Amoebic trophozoites emerge from the vegetative form in the colon and invade the bowel, forming flask-shaped ulcers from where they enter a portal venous radical and carried to the liver where they multiply rapidly and destroy the parenchyma after blocking blood vessels and causing infarction necrosis resulting in a large single abscess located in the right lobe (due to a rich blood supply) although multiple abscesses may occur in advanced diseases.

Clinical Features

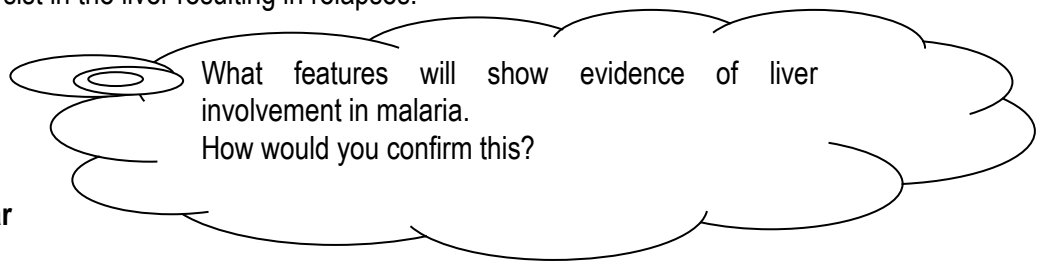
- History of amoebic dysentery; intermittent low grade fever; pain and tenderness in the liver area; tender hepatomegally and positive agglutination test (a very sensitive test)

Pathology

Gross appearance (Macroscopic	Histology/Microscopic appearance
Solitary abscess of variable size located in the right lobe in postero-superior position; Centre of the abscess contains large necrotic area with reddish-brown thick pus (anchovy or chocolate sauce)	Liver has a necrotic area with degenerated liver cells, red blood cells, leucocytes, strands of connective tissue and leucocytes

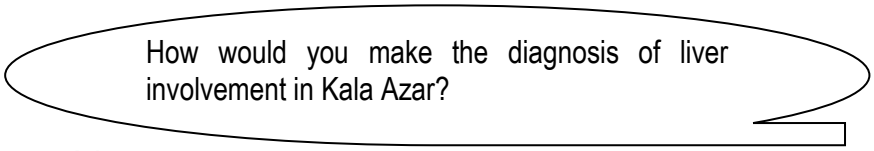
3.2. Malarial Parasites

- Initially develops within the hepatocytes and may persist for years
- In the erythrocytic phase colonized red blood cells are phagocytosed by Kuppfer cells, which show marked hypertrophy and hyperplasia
- The hepatocytes contain abundant dark brown granules of malarial parasite (haemozoin). *P. vivax* and *P. ovale* persist in the liver resulting in relapses.



3.3. Kala-Azar

- *L. donovani* causes hyperplasia of the Kuppfer cells



4.0 HELMINTHIC HEPATITIS

4.1. Hydatid Disease (Echinococcosis)

Aetiology & Pathogenesis

- Results from infection by the larval stage of the dog tapeworm *Echinococcus granulosus*
- Man, acquires the infection by handling dogs as well as eating contaminated vegetables
- The ova ingested by man is removed from the chitinous[4] wall by the effect of gastric juices and passes through the intestinal mucosa from they are carried to the liver by portal venous system eventually getting trapped in the hepatic sinusoids where they develop into a hydatid cyst
- The ova that fail to be trapped by the liver reach the pulmonary capillary blood via the right side of the heart forming pulmonary hydatid cysts
- Others reach the brain, spleen, bone and muscles.

Pathology

- Hydatid cysts grow slowly and may attain a diameter of over 10 cm
- E. granulosus causes unilocular hydatid cysts while E. multilocularis results in multilocular or alveolar cyst in the liver. Hydatid sand is a grain-like material composed of numerous scolices present in hydatid fluid
- Hydatid fluid contains antigenic proteins which when liberated into the circulation gives rise to eosinophilia or may cause anaphylaxis
- The cyst has three zones namely – the pericyst, ectocycst and endocyst

i) Pericyst

- Outer host inflammatory reaction consisting of fibroblastic proliferation, mononuclear cells, eosinophils and giant cells
- It later develops into a dense fibrous capsule, which may calcify.

ii) Ectocyst

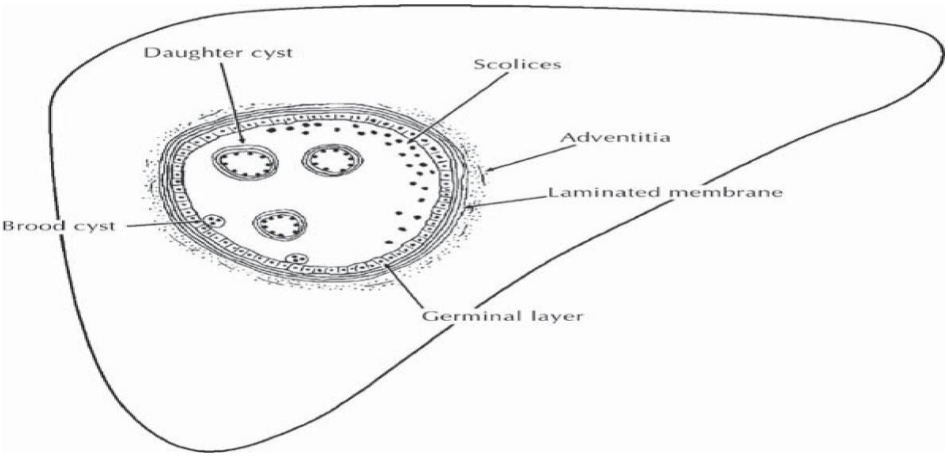
- Forms the intermediate layer composed of characteristic acellular, chitinous, laminated hyaline material.

[4] A hard outer covering

iii) Endocyst

- Inner germinal layer bearing daughter cells (blood-capsules) and scolices projecting into the lumen.

Diagram 9.4: Hydatid cyst in the liver



- The complications of hydatid cyst include rupture (into peritoneal cavity, lungs and bile ducts), secondary infection and allergy due to sensitisation.

Diagnosis

What are the anticipated findings in these situations?

- History
- Physical examination
- Blood – peripheral blood eosinophilia
- Radiological examination
- Serological tests – indirect haemoagglutination test and Casoni test[5].

1.0 SCHISTOSOMIASIS

S. mansoni and *S. japonicum* affect the liver producing hepatic fibrosis that eventually leads to portal hypertension.

2.0 ASCARIASIS

Ascariasis lumbricoides causes direct invasion of the common bile duct producing obstruction and cholangitis.

Clinical Problems

With specific examples, **DISCUSS** the effects of infections on the liver. State the specific investigations indicating confirmatory indicators. Also, do explain how the microbes gain access to the liver. What happens to the liver defence systems?

[5] Hypersensitivity reaction to an intradermal injection of hydatid antigen

Lesson 8: ALCOHOLIC LIVER DISEASE AND LIVER CIRRHOSIS

Learning Outcomes

At the end of the lesson the learner should be able to: -
1. Describe the pathogenesis and pathology of liver cirrhosis and alcoholic liver disease.
2. Explain the complications of liver cirrhosis and alcoholic liver disease
3. Investigate liver cirrhosis and alcoholic liver disease

1.0 ALCOHOLIC LIVER DISEASE (ALD)

1.1 Introduction

- Alcohol toxicity occurs due to the **ethanol and its metabolites**
- Presence of high iron levels in some wines and beers may have an effect
- ALD describes liver injury due to **acute or chronic alcoholism**
- Spectrum of injury includes alcoholic steatosis (fatty liver), alcoholic hepatitis and alcoholic cirrhosis
- Short term ingestion of 80 grams of alcohol (8 beers) over one to several days produces mild reversible liver changes such as fatty liver while intake of 80 grams of alcohol daily pauses the risk of severe hepatic injury
- Daily ingestion of 160 grams or more for 10 – 20 years results in severe liver injury

1.2 Metabolism of Ethanol

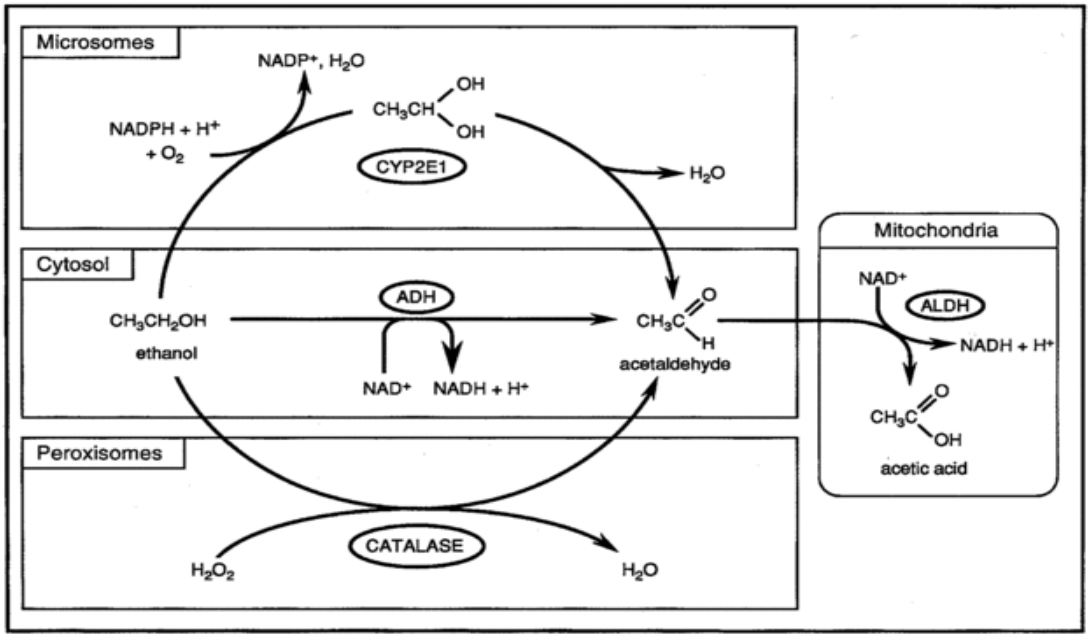
- One gram of alcohol yields 7 calories but alcohol cannot be stored hence it has to be oxidised in the liver
- Ethanol is rapidly absorbed from the stomach and small intestines with the absorption being reduced by food
- 95% of ethanol is metabolised in the liver to acetaldehyde and acetate and the 5% is excreted as ethanol in urine and breath
- Urine concentration is 1.3 times that of blood with the breath:blood ratio at 1:2300.
- Metabolism of ethanol to acetate involves a two-step enzymatic process involving two enzymes: **alcohol dehydrogenase** (ADH) and **acetaldehyde dehydrogenase** (ALDH) in the mitochondria of the hepatocytes. This accounts for 90% of ethanol metabolism with the remaining 10% being oxidised elsewhere in the body.

i) First Step
- Ethanol is catabolised to acetaldehyde (toxic and may cause membrane damage and cell necrosis)
- At the same time the co-factor nicotinamide dinucleotide (NAD), which is a hydrogen acceptor, is reduced to NADH
- This reaction occurs via three pathways
  a) Cytosol (ADH enzyme)
  b) Smooth endoplasmic reticulum (MEOS)
  c) Microsomal ethanol oxidising system and peroxisomes (H_2O_2).

ii) Second step
- Occurs in the mitochondria
- Acetaldehyde is converted to acetate (acetic acid)
- Most of the acetate is oxidised to carbon dioxide and water or converted by the citric acid cycle to other compounds e.g. fatty acids
- NAD is reduced to NADH increasing the NADH:NAD redox ratio

- The changes in oxidation-reduction process include
  a) Increased hepatic fatty acid synthesis and reduced fatty acid oxidation resulting in accumulation of fats in the liver (fat is then esterified to glycerides)
  b) Impairs carbohydrate resulting in hypoglycaemia and lactic acidosis
  c) Impairs protein metabolism

Diagram 10.1: Ethanol Metabolism



Key: ADH – alcohol dehydrogenase
ACDH – acetaldehyde dehydrogenase
NAD – nicotinamide adenine dinucleotide
NADH – reduced NAD

1.3 Aetiology

1. Drinking patterns
   - Quantity and duration (daily intake of 80 gm of any alcohol for at least 10 years is likely to cause cirrhosis)
   - The alcohol content dictates the liver damage
2. Malnutrition
   - Absolute or relative malnutrition of proteins and vitamins contributes to evolution of cirrhosis; Calories from alcohol displace other nutrients; Chronic gastritis; Pancreatitis
3. Infections - intercurrent bacterial infections accelerate the course of the disease
4. Genetic factors - rate of ethanol metabolism is under genetic control and is affected when there is alteration in the enzyme systems – MEOS and ADH.

1.4 Pathogenesis

- Liver injury due to alcohol consumption results in morphologic lesions of fatty liver, alcoholic hepatitis and alcoholic cirrhosis through the following mechanisms.
  i) Ethanol is directly toxic to microtubules, mitochondria and membrane and leads to a fatty liver
  ii) Ethanol metabolites e.g. acetaldehyde is toxic to cytoskeleton and cell membrane causing hepatocellular necrosis
  iii) Free radicals - Oxidation of ethanol produces free radicals that attack the membrane and proteins
  iv) Increased redox ratio - Increased NADH:NAD ration produces increased lactacte:pyruvate ratio leading to lactic acidosis, fatty change, collagen formation and impaired gluconeogenesis and

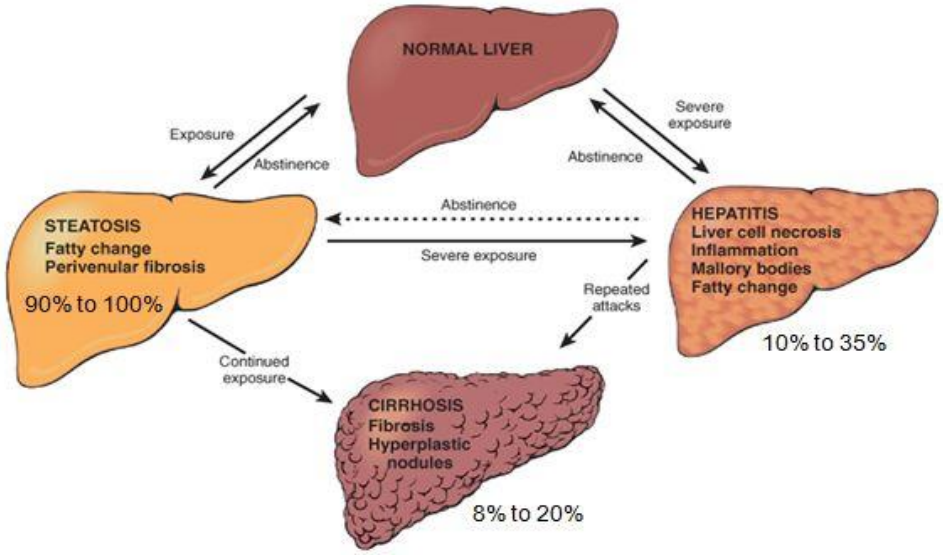
altered steroid metabolism. Lactic acidosis is associated with reduced renal secretion of uric acid. Reduced gluconeogenesis (from amino acids) results in hypoglycaemia.

v) Retention of liver cell water and proteins - Alcohol inhibits secretion of newly synthesized proteins by the liver encouraging retention of water in the liver cells causing swelling of liver cells – hepatomegally.
vi) Hypoxia - Due to increased demand for oxygen leading to hypoxia eventually hepatocellular necrosis
vii) Increased liver fat - from dietary sources and excess mobilization from the adipose tissue or increased hepatic synthesis.
viii) Immunological mechanism - Cell-mediated immunity is impaired in alcoholic liver disease and ethanol has a direct immunologic attack on hepatocytes.
ix) Fibrogenesis and inflammation - The major stimulus is liver cell necrosis and the mediators of inflammation (lymphokines and monokines)

1.5 Pathophysiology

- Alcoholic liver disease is a chronic disorder featuring **steotosis**, **hepatitis**, **progressive fibrosis**, **cirrhosis** and marked disruption of vascular perfusion of the liver.

Diagram 5.2: Alcoholic Liver Disease



- The pathophysiology entails: -
  1) Hepatocellular steatosis (fatty accumulation) due to: -
     a. Shunting of substances from catabolism to lipid biosynthesis due to excess generation of reduced NADH (NADH + H^+) by enzymes *alcohol dehydrogenase* and *acetaldehyde dehydrogenase*
     b. Impaired synthesis of lipoproteins
     c. Increased peripheral catabolism of fat
  2) Alcohol induced hepatic metabolism of methionine due to reduced intrahepatic glutathione levels results in increased sensitization of liver cells to oxidative injury
  3) Induction of cytochrome P-4590 (CYP2E1) which results in increased catabolism of alcohol in the ER which increases the rate of conversion of other drugs such as acetaminophen to toxic metabolites. There is also membrane damage
  4) Direct damage of liver cells on microtubular and mitochondrial function as well as alteration of membrane fluidity.
  5) Acetaldehyde is a major intermediate metabolism of alcohol metabolism and induces lipid perioxidation. Produces some substances that disrupt the cytoskeleton and membrane function

6) There is formation of new proteins that cause an immunological reaction resulting in inflammation and immune mediated hepatocellular injury
7) Alcohol as food displaces other nutrients leading to malnutrition and vitamin deficiencies (vitamin B12), impaired digestive function due to chronic gastric and intestinal mucosal damage and pancreatitis.
8) Alcohol induces release of endothelins which are vasoconstrictor substances resulting in reduced hepatic sinusoidal perfusion and hence regional hypoxia
9) Alcohol induces release of bacterial endotoxins from the gut into the portal circulation where they induce inflammation in the liver

2.0 ALCOHOLIC STEATOSIS (FATTY LIVER)

- Fatty liver disease (steatosis) is the build-up of excess fat in the liver cells. Fatty liver may cause no damage, but sometimes the excess fat leads to inflammation of the liver (steatohepatitis) which causes liver damage. The risk factors most commonly linked to fatty liver disease are overweight (BMI of 25-30), obesity (BMI above 30), diabetes and elevated triglyceride levels.
- Potential pathophysiologic mechanisms
  i) Decreased mitochondrial fatty acid beta-oxidation
  ii) Increased endogenous fatty acid synthesis or enhanced delivery of fatty acids to the liver
  iii) Deficient incorporation or export of triglycerides as very low-density lipoprotein (VLDL)

Gross appearance
- The liver is enlarged, yellow, greasy and firm

Microscopy
- Microvesicular and macrovesicular fat droplets
- Cellular infiltration with lymphocytes, macrophages and giant cells.

3.0 ALCOHOLIC HEPATITIS

Develops acutely following a bout of heavy drinking and repeated episodes of hepatitis and fatty change are front-runners of alcoholic cirrhosis.

Histology
1) Hepatocellular necrosis
2) Mallory bodies or alcohol hyaline – eosinophilic intracytoplasmic inclusions
3) Inflammatory response with fibrosis

4.0 LIVER CIRRHOSIS

4.1. Introduction

- A chronic irreversible disease of the liver in which the normal architecture of the entire liver is destroyed by deposition of connective tissue and formation of regenerated nodules
- Also, be defined as a diffuse process characterized by fibrosis and a conversion of normal architecture into structurally abnormal nodules.
- Liver cirrhosis has **four major features** namely: -
  i) Involvement of the entire liver
  ii) Distortion of normal lobular architecture of liver parenchyma
  iii) Formation of nodules separated by irregular band of fibrosis
  iv) Hepatocellular necrosis.

- Results from long continued loss of liver cells and persistent inflammation accompanied by fibrosis and compensatory hyperplasia
- Architectural distortion that occurs in liver cirrhosis interferes with blood flow through the liver
- Death results from hepatocellular failure or portal hypertension or both.

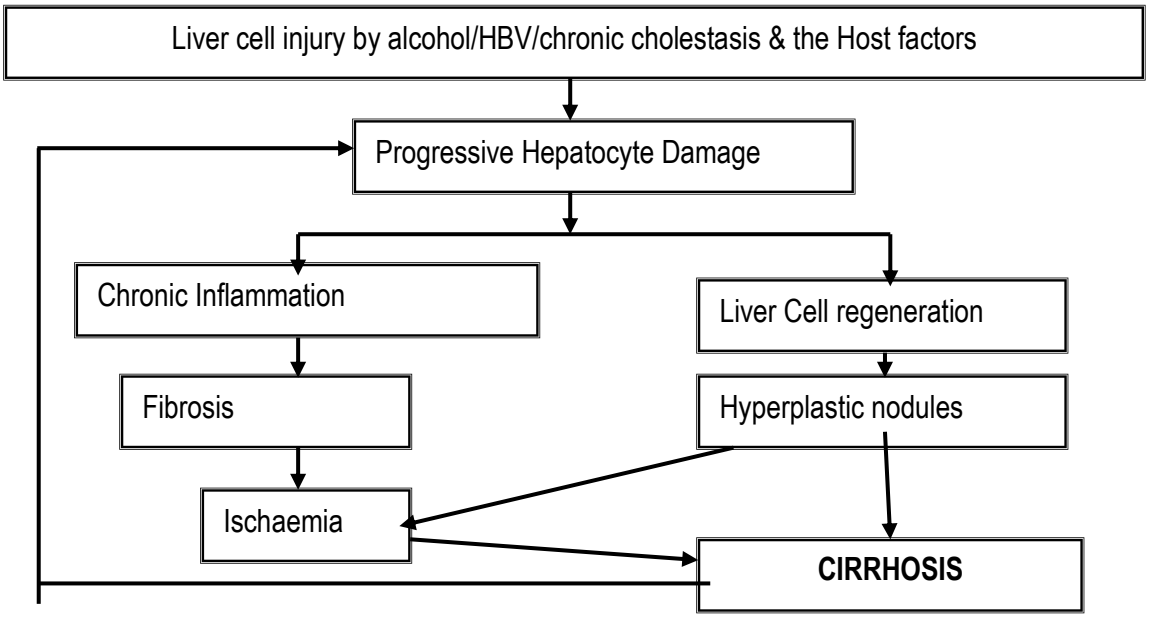
4.2. Aetiology

1. Alcohol
2. Infections – HBV, HCV, *Schistosoma mansoni*
3. Cryptogenic – unknown
4. Autoimmune disorders - chronic active hepatitis (CAH) and primary Biliary cirrhosis
5. Drugs/toxins – Alcohol, Methyldopa, Isoniazid, Methotraxate
6. Metabolic - Wilson's disease, Porphyria
7. Biliary obstruction – Atresia, Gall stones, Strictures
8. Vascular - chronic right heart failure, Budd-Chiari syndrome and veno-occlusive disease
9. Miscellaneous - Neonatal hepatitis syndrome, Acidosis

4.3. Pathogenesis

- Principal pathogenic processes in cirrhosis are progressive fibrosis and reorganization of vascular microarchitecture of the liver
- Cirrhosis is an end stage of chronic liver disease characterized by formation of bridging fibrous septae across the portal tracts, parenchymal nodules made of proliferating hepatocytes circle by fibrosis and disruption of hepatic architecture.
- Pathogenesis of liver cirrhosis involves four main phenomena that lead to architectural distortion of the liver cell patterns
- The processes include hepatocellular necrosis, inflammation, fibrosis and nodule formation

Diagram 5.3: Pathogenesis of liver cirrhosis



a) Hepatocellular Necrosis

- Cirrhosis is initiated by hepatocellular necrosis resulting from lesions causing continued destruction of hepatocytes leading to collapse of the normal lobular pattern of the liver and initiates a chronic inflammatory reaction that is continued and persistent
- May also result from the ensuing ischaemia courtesy of compromised blood supply.

b) Inflammation

- Continued necrosis of liver cells triggers off a chronic inflammatory process, which is more productive that exudative thus resulting in progressive replacement fibrosis and hyperplasia of the liver cells.

c) Fibrogenesis (Fibrosis)

- Results from increased synthesis of collagen and an increased number of collagen-producing cells.
- Sources of excess collagen are peripheral sinusoidal satellite cells
- May be portal-central, portal-portal or both and leads to proliferation of fat-storing cells
- Cells underlying the sinusoidal epithelium are transformed into myofibroblasts and fibriocytes. Monokines and lymphokines are believed to play some role in this process.

d) Regenerative Nodules

- Emanate from compensatory proliferation of hepatocytes and hyperplasia of the liver cells in a process driven by possibly the growth factors and hormonal imbalance.

4.4. Classification of Cirrhosis

- Cirrhosis can be classified on the basis of **morphology** and **aetiology**.

a) Morphologic Classification

- Based on the size of the nodules formed
- Three morphologic types of cirrhosis: - micronodular, macronodular and mixed.

b) Micronodular Cirrhosis

- Nodules are uniformly small and regular, less than 3 mm in diameter
- Diffuse involvement of all liver lobules
- It is seen in portal cirrhosis, nutritional cirrhosis and Laennec's cirrhosis.
- Indicates impaired capacity for regrowth seen in alcoholism, malnutrition, severe anaemia and old age.

c) Macronodular Cirrhosis

- Nodules of variable sizes (larger than 3 mm in diameter)
- Irregular pattern with marked regeneration
- Seen in post-necrotic or post-hepatic situations

d) Mixed Cirrhosis

- Exhibits both micronodular and macronodular characteristics
- Some portal tracts and central veins are spared
- Seen in the late stages of cirrhosis and it depends on the degree of continued liver damage and the regeneration capacity of the liver.

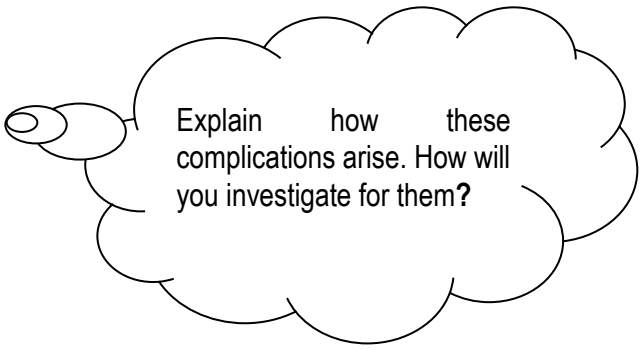
4.5. Pathology

Macroscopy	Microscopy
• Liver size may be normal or enlarged otherwise it shrinks • Surface of the liver is diffusely nodular	• Nodules show loss of normal architecture • Portal tracts and hepatic veins have lost their regular spacing • Liver cell atrophy and loss

4.6. Complications of Liver Cirrhosis

1. Portal hypertension

2. Progressive hepatic failure
3. Development of hepatocellular carcinoma.
4. Chronic relapsing pancreatitis.
5. Steatorrhoea
6. Gall stones.
7. Infections
8. Haematologic derangements.
9. Cardiovascular complications
10. Musculoskeletal abnormalities
11. Endocrine disorders
12. Hepatorenal syndrome



5.0 ALCOHOLIC LIVER CIRRHOSIS

5.1. Introduction

- Affects more males than females with peak incidence being 35-55 years
- Liver size is slightly reduced due to fatty change
- Associated with chronic active hepatitis, piecemeal necrosis, inflammatory cell infiltration and bile duct proliferation
- An irreversible lesion and patients die from complications such as portal hypertension, bleeding and infections.

Child-Turcotte-Pugh Classification for Severity of Cirrhosis

Clinical and Lab Criterias	Points*		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time Seconds prolonged International normalized ratio	 <4 <1.7	 4-6 1.7-2.3	 >6 >2.3

***Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)**
Class A = 5 to 6 points (least severe liver disease)
Class B = 7 to 9 points (moderately severe liver disease)
Class C = 10 to 15 points (most severe liver disease)

5.2. Pathology

Gross (macroscopic) appearance

- Early pattern is micronodular and later a mixed picture or macronodular with nodules of 1 cm in diameter that may not be yellow as they lack lipid.
- Liver architecture is replaced by small regenerating nodules (1-3 mm diameter), which are yellow due to lipid content.
- Loss of acinar architecture

Microscopy

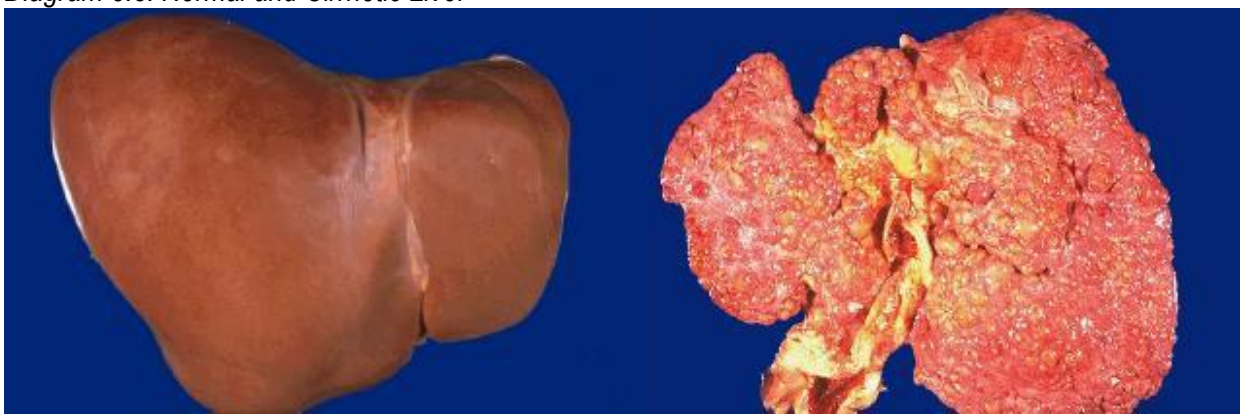
- Liver cell architecture destroyed by formation of large amounts of connective tissue
- Hepatocytes show regenerative changes
- Light lymphocytic infiltration
- Presence of Mallory bodies, giant mitochondria and increased iron storage – features that differentiate alcoholic cirrhosis form other aetiologies.

6.0 POST-VIRAL (POST-HEPATIC) CIRRHOSIS

6.1. Introduction

Post-viral cirrhosis affects more females than males with peak incidence being in the younger ages. The liver is usually smaller compared to alcoholic cirrhosis. It has a poor prognosis as a result of rapid development of portal hypertension, hepatocellular failure and increased incidence of liver cell carcinoma.

Diagram 5.3: Normal and Cirrhotic Liver



6.2. Pathology

Gross (macroscopic) appearance

- The cirrhosis is macronodular

Microscopic appearance

- Normal architecture is not completely lost
- Fatty infiltration is slight or absent
- Heavy lymphocytic infiltration indicating continuing activity

Lesson 9: METABOLIC LIVER DISEASE AND TUMOURS

Learning Outcomes

At the end of the lesson the learner should be able to: -

1) Describe the effects of tumours of the liver
2) Investigate patients with tumours of the liver
3) Explain the effects of metabolic liver diseases
4) Investigate patients with metabolic liver diseases

1.0 DRUG INDUCED LIVER DISEASE

1.1. Introduction

- The liver plays a big role in metabolism of drugs, organic & inorganic chemicals.
- Drugs and chemicals gain entry into the body by inhalation, injection and most commonly via the intestinal tract
- Drug induced hepatic injury is a common iatrogenic disease
- Clinico-pathological spectrum ranges from mild effects to massive necrosis & cell death.

1.2. Classification

- Drugs can cause hepatocellular damage or cholestasis
- Classification may also be based on liver cells (hepatotoxicity) type that is affected i.e. intrinsic toxicity or direct acting toxicity
- Drug injury can lead to hepatocellular injury and necrosis, hepatitis, fibrosis, cirrhosis, cholestasis and neoplasia

1.3. Hepatotoxicity

- Hepatotoxicity forms the commonest form of iatrogenic disease
- Drug reactions affecting the liver can be classified into two main classes
  i) Type I (Direct or predictable) Reactions
     - Occur in most individuals taking the drug and it is dose related
     - It lowers the host immune defence mechanism
  ii) Type II (Indirect or unpredictable or Idiosyncratic) Reactions
     - Occur in only a small number of especially sensitive subjects taking the drug
     - Not dose related and the drug acts or its metabolites act as haptens inducing hypersensitivity reactions in the host.

1.4. Pathologic Changes

Are based on two large categories - **acute liver disease** and **chronic liver disease**

Table 1: Classification of Hepatic Drug Reactions

Pathologic Changes	Agents
Acute liver disease	
2. Zonal necrosis	Carbon tetrachloride, Acetaminophen, Halothane
3. Massive necrosis	Halothane, acetaminophen, methyldopa

4.	Fatty change	Tetracycline, salicylates, methotraxate, ethanol
5.	Hepatitis	Methyldopa, isoniazid, halothane, ketaconazole
6.	Granuloma formation	Sulphonamides, methyldopa, quinidine allopurinol
7.	Cholestasis	Oral contraceptives, sex hormones, chlorpromazine, nitrofurantoin
8.	Veno-occlusive Diease	Cytotoxic drugs and radiotherapy
9.	Hepatic/portal Vein thrombosis	Oral contraceptives

Chronic liver disease

1.	Fibrosis-cirrhosis	Methotraxate
2.	Focal nodular hyperplasia	Vinyl chloride, Vitamin A, Sex hormones
3.	Adenoma	Sex hormones
4.	Hepatocellular carcinoma	Sex hormones, Anabolic streroids

2.0 AUTOIMMUNE HEPATITIS

3.0 TUMOURS OF THE LIVER

1.0 INTRODUCTION

- May result from a number of situations and cause epigastric fullness and discomfort
- May also be detected on routine physical examination or radiological studies necessitated by other indications.

2.0 NODULAR NEOPLASMS

- Solitary or multiple nodules such as **focal nodular hyperplasia** and **nodular regenerative hyperplasia** may develop in a non-cirrhotic liver
- Focal nodular hyperplasia is well demarcated and poorly encapsulated. It is common mainly during the young-middle age affecting more females than males.
- Nodular regenerative hyperplasia forms spherical nodules and is associated with portal hypertension and affects the entire liver

3.0 BENIGN NEOPLASMS

- The common benign neoplasms are **cavernous haemangiomas** (blood vessel tumours) and **liver cell (hepatic) adenomas** which develop from hepatocytes. Liver cell adenomas occur in young females with history of prolonged use of oral contraceptives.
- Liver cell adenomas are significant clinically because: -
  i) They present as intrahepatic mass that can be mistaken for hepatocellular carcinoma

ii) Subcapsular adenomas have the tendency to rupture especially during pregnancy (cause of oestrogen stimulation)
iii) May harbour hepatocellular carcinoma

4.0 MALIGNANT TUMOURS

The liver and lungs are visceral organs commonly affected by secondary (metastatic) tumours.

PRIMARY TUMOURS

Primary tumours may arise from hepatocytes (**hepatocellular carcinoma**) or bile duct (**cholangiocarcinomas**). Hepatoblastoma and angiosarcomas are rare.

HEPATOCELLULAR CARCINOMA (HEPATOMA)

1.0 INTRODUCTION

Hepatoma the most common primary tumour of the liver occurring 4-6 times more common in males than females. The peak incidence is in 5th to 6th decades of life. The tumour supervenes on cirrhosis especially the macronodular type.

2.0 AETIOLOGY

- Unknown but the associated factors are: -

1. HBV and HCV
2. Cirrhosis
3. Alcohol
4. Mycotoxins, Aflatoxins e.g. *Aspergillus flavus* (produced by moulds)
5. Chemical carcinogens e.g. butter-yellow (food additives)
6. Miscellaneous - prolonged immunosuppressive therapy in renal transplant patients, haemochromatosis, tobacco smoking and parasitic infestations e.g. schistosomiasis

3.0 PATHOGENESIS

Three major associations' namely **viral infection** (HBV, HCV), **chronic alcoholism** and **food contaminants** (aflatoxin)

4.0 PATHOLOGY

Macroscopic (Gross) appearance

- Enlarged liver with a nodular/massive tumour that is a well-defined large size mass with central necrosis and haemorrhagic with irregular bile staining
- Nodular type is hard, scarred, deformed liver studded with multiple whitish-greyish or dark green irregular nodules
- Massive variety forms a large tumour mass in the right lobe with multiple smaller growths left.

Microscopy

- Tumour cells closely resemble the hepatocytes and the cells are arranged in nodules of varying sizes with the cells in cords and trabecular of varying thickness. Areas of necrosis are seen.

5.0 CLINICAL FEATURES

- Ill-defined upper abdominal pain; malaise; fatigue; weight loss; abdominal mass; abdominal fullness; GIT/oesophageal variceal bleeding
- On examination jaundice, fever, palpation (hepatomegaly, irregularity and nodularity)
- Laboratory – increased serum -feto proteins (DDx – cirrhosis, massive liver necrosis, chronic hepatitis, normal pregnancy, foetal distress or death, foetal neural defects such as ancephaly and spina bifida)

6.0 STAGING

7.0 PROGRESS AND DEATH

Natural course of hepatocellular carcinoma is progressive enlargement of the primary mass which results in impaired hepatic function or metastasis first to the lungs and then to other sites.

Causes of Death

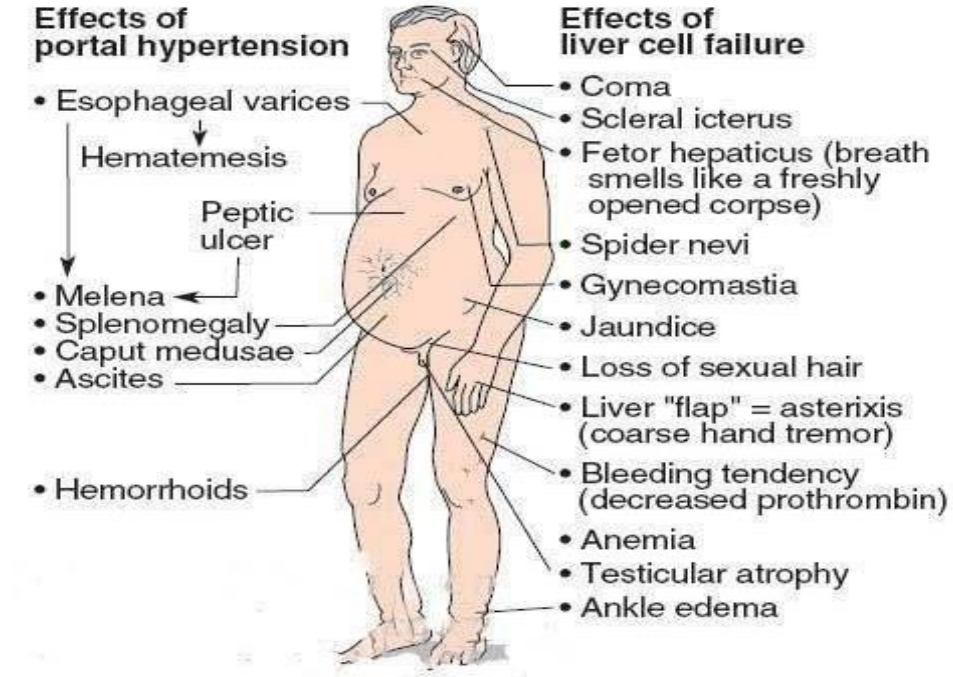
1) Cachexia
2) GIT/oesophageal variceal bleeding
3) Liver failure with hepatic coma
4) Rupture of the tumour with fatal haemorrhage

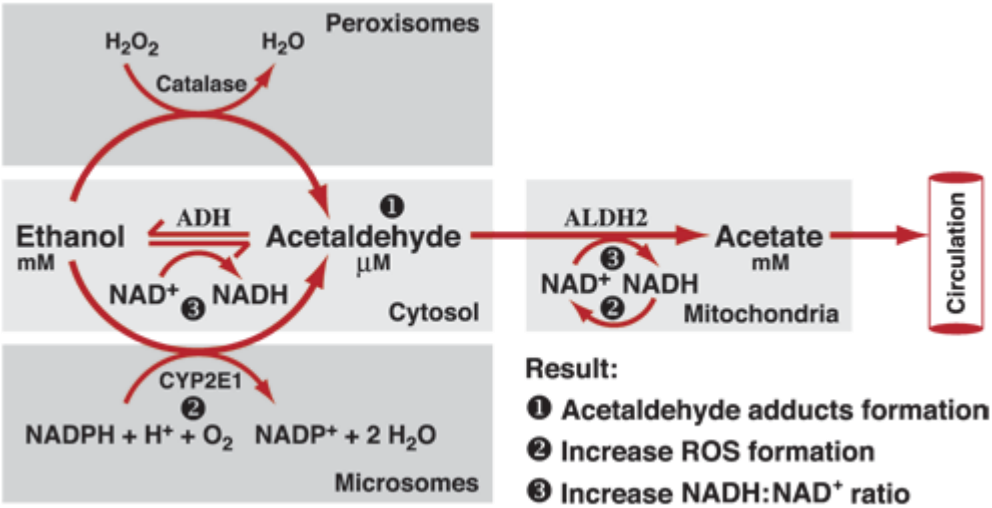
8.0 INVESTIGATIONS

- Blood counts; Endoscopy; Liver function tests; Renal function tests; Abdominal X-ray; Untrasound; CAT scan; Biopsy

Secondary (Metastatic) Tumours

Metastatic tumours of the liver are more common than the primary neoplasia. Most common hepatic metastases are those of the breast, lung and colon. Others include leukaemias and lymphomas


Effects of portal hypertension
• Esophageal varices
Hematemesis
Peptic ulcer
• Melena
• Splenomegaly
• Caput medusae
• Ascites
• Hemorrhoids
Effects of liver cell failure
• Coma
• Scleral icterus
• Fetor hepaticus (breath smells like a freshly opened corpse)
• Spider nevi
• Gynecomastia
• Jaundice
• Loss of sexual hair
• Liver "flap" = asterixis (coarse hand tremor)
• Bleeding tendency (decreased prothrombin)
• Anemia
• Testicular atrophy
• Ankle edema


Peroxisomes
H2O2
H2O
Catalase
Ethanol
mM
ADH
Acetaldehyde
µM
NAD+
NADH
Cytosol
ALDH2
Acetate
mM
NAD+ NADH
Mitochondria
Circulation
CYP2E1
NADPH + H+ + O2
NADP+ + 2 H2O
Microsomes
Result:
❶ Acetaldehyde adducts formation
❷ Increase ROS formation
❸ Increase NADH:NAD+ ratio