NEET SS ANAESTHESIA TRANSPLANT ANAESTHESIA

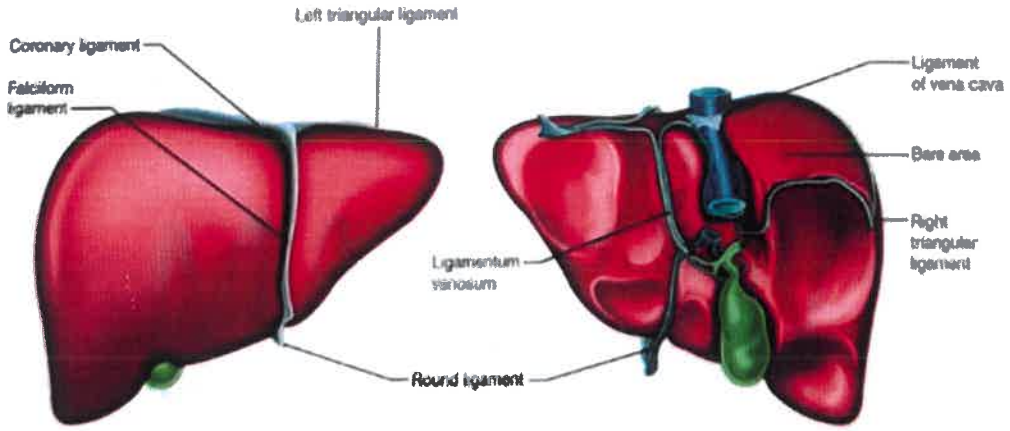
CONTENT

LIVER ANATOMY

Introduction 00:00:49

Basics :

- The human liver is the largest solid organ, comprising 2% of total body mass.
- Weight :
  - 1,500 g (600-1800).
  - Around 1.5-2% of adult body weight.
- Basic structures :
  - Coronary ligament.
  - Falciform ligament.
  - Left triangular ligament.
  - Round ligament.
  - Ligamentum venosum.
  - Ligament of vena cava.
  - Right triangular ligament.



Liver anatomy

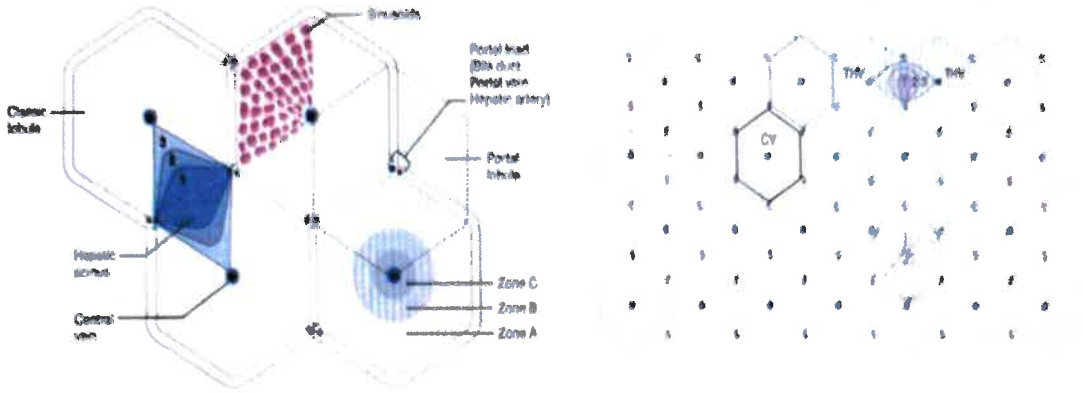
Histology :

Zones :

Hepatocytes are divided into different zones based on their proximity to the portal triad (Hepatic artery, portal vein and the bile duct).

- Zone 1 is periportal
- Zone 3 is around the central vein (Perivenous or pericentral).
- Zone 2 is in between zone 1 and zone 2 (midzone).

- Zone 3 is furthest away from the portal tracts → Receives blood with a lower oxygen tension and nutrient content.



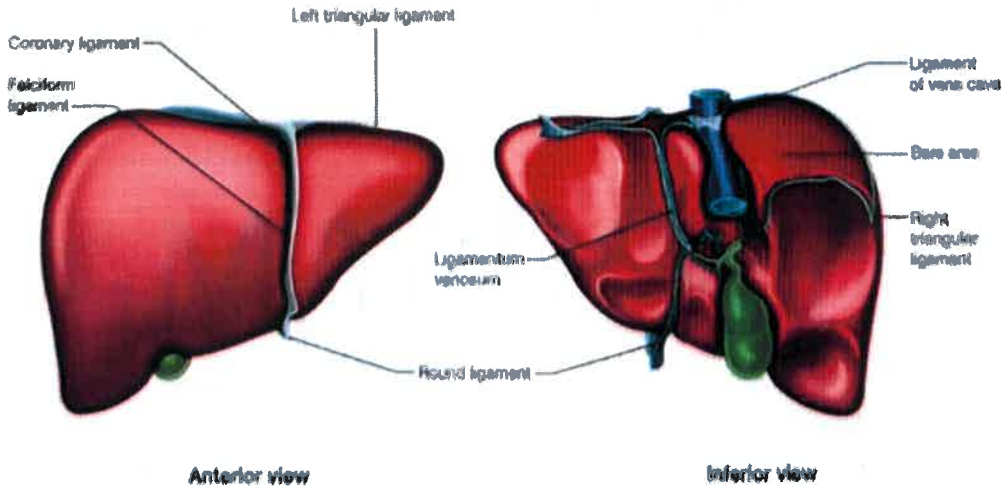
Zones of liver.

Glisson's capsule :

- Liver is covered in a thin connective tissue layer.
- Attached to the diaphragm by the coronary Ligaments.
- Anatomically, the liver has four lobes : Right, left, caudate and quadrate.

Ligaments :

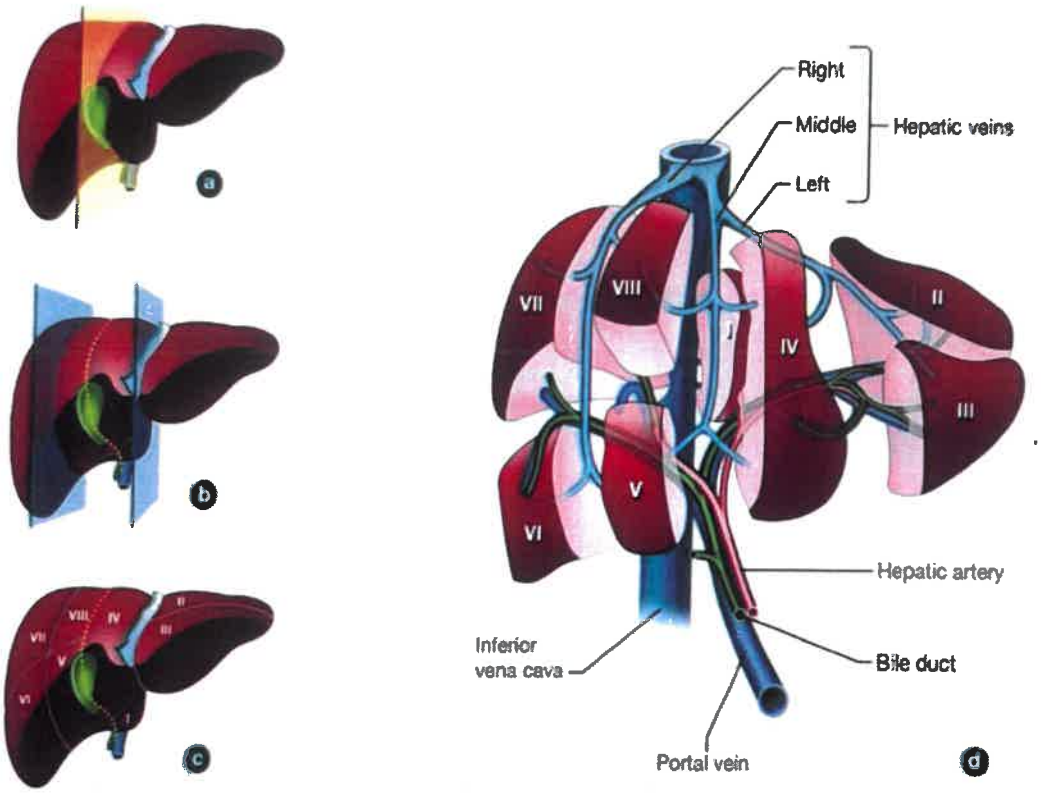
- Round ligament :
  - Remnant of left umblical vein.
  - Also known as ligamentum teres hepatis.
- Falciform ligament :
  - Divides the liver into right and left lobe.
  - Sickle shaped.



Liver anatomy

Segmental anatomy of liver :

- Liver segmental anatomy was described by Claude Couinaud in 1954.
- Couinad segments : Total of eight independent segments.
- Each segment has its own blood supply and biliary drainage.
- Cantlie's line : Line connecting the gallbladder bed and IVC.
- Right lobe includes : Segments 5,6,7,8.
- Left lobe : Segments 2, 3, 4.
- Segment 1 : Caudate lobe (Drains into the IVC directly).



Segmental anatomy of liver.

Blood supply & microanatomy 00:18:42

Blood supply :

- Hepatopetal flow : Normal blood flow is from the portal vein through the liver.
- Hepatofugal flow : In the setting of cirrhosis and portal hypertension, blood flow reverses away from the liver.
- Liver blood supply is 25% from the hepatic artery and 75% from the portal vein.
- The liver receives approximately 25% of the resting cardiac output.

Hepatic artery :

- High-pressure/high-resistance system.

- Branch of the coeliac trunk (Branch of abdominal aorta).
- Carries oxygenated blood.
- 20%–30% of total blood supply to the liver.
- 40%–50% of total oxygen supply.
- Replaced left hepatic artery originates from left gastric artery.

Portal vein :

- Low pressure/low resistance system.
- Formed by the union of superior mesenteric vein and splenic vein behind the neck of pancreas.
- Carries oxygen-poor but nutrient-rich blood.
- 70%–80% of total blood supply.
- 50%–60% of total oxygen supply.

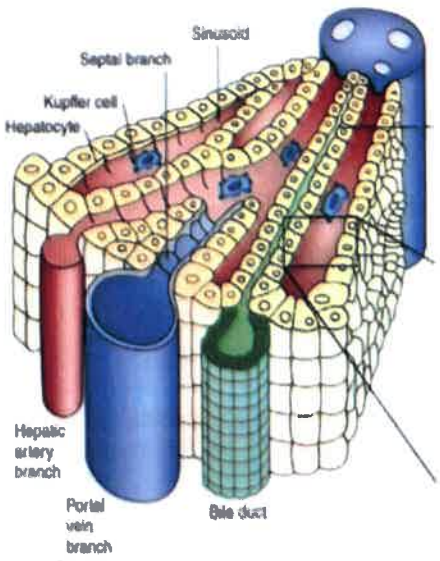
Microanatomy :

Sinusoids :

- Hepatocytes are arranged within hepatic sinusoids surrounding a central hepatic vein.
- They are bordered by interlobular portal triad consisting of a biliary duct, hepatic artery, and portal vein.

Arrangements :

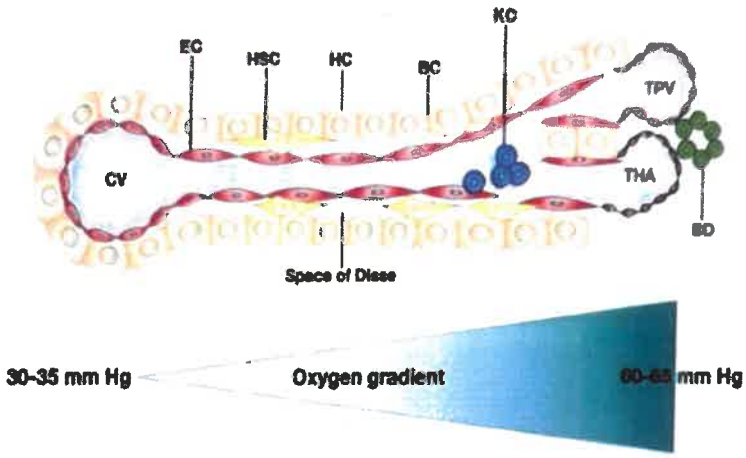
- Based on direction of blood flow.
- Hexagonal structure with the central vein in the middle and portal triad (Branches of portal vein, hepatic artery, and bile duct) in the six corners.
- The hepatic arterial and portal venous blood flows from portal triad to the central vein.
- Kupffer cells : macrophages.
- Stellate cells : Responsible for extracellular matrix production and capable of contractile function to regulate sinusoidal blood flow.



microanatomy.

- Pit cells : Lymphocytes.
- Venous drainage of the liver is through the hepatic veins directly into the inferior vena cava (IVC).

- The perisinusoidal space of Disse : The space separating the sinusoids from hepatocyte.
- Bile is produced by hepatocytes and secreted into biliary canaliculi via canals of Hering.



Cross section of portal triad.

Zones :

- Zone 1 :
  - Periportal (Zone 1) hepatocytes are the major sites of aerobic metabolism, and process such as glycogen synthesis and sulfation.
  - Blood supply is the highest and is susceptible to damage by blood-borne toxins and infection.
- Zone 3 :
  - Perivenous (Zone 3) hepatocytes are the major sites of anaerobic metabolism, glycolysis and glucuronidation.
  - Zone 3 hepatocytes are most sensitive to hypoxia.
  - Zone 3 is closer to the central vein.
  - This area is higher in CYP 450 levels but gets the least blood supply and is susceptible to ischaemia.
- Zone 2 or intermediate zone.

HEPATIC BLOOD FLOW

Liver receives 25% of resting cardiac output.
It receives 20% of resting oxygen consumption.
And 10-15% of total blood volume (Liver and splanchnic circulation).

Dual blood supply :

- Hepatic artery : 25% hepatic artery.
- Portal vein : 75% portal vein.
- Oxygen delivery is equivalent : 50%.

Total hepatic blood flow (THBF) :

THBF = PBF+ HABF

- PBF : Portal Blood Flow.
- HABF : Hepatic Artery Blood Flow.

Facts :

- Portal vein acts as a valveless capacitance vessel
- Hepatic artery :
  - Resistance vessel
  - Hepatic artery blood flow depends on systemic arterial pressure & flow.
- Liver acts as an autologous reservoir of blood.

Factors effecting hepatic blood flow 00:03:56

Types :

i. Intrinsic :
   a. Hepatic artery buffer response (HABR).
   b. Myogenic autoregulation.
   c. Metabolic control.

iv. Extrinsic :
   a. Neural.
   b. Humoral.

Intrinsic :

Hepatic arterial buffer response (HABR) :

- When the portal blood flow decreases the hepatic artery blood flow is upregulated so that the total hepatic blood flow remains constant.
- THBF = PBF+ HABF.
- Hepatic artery flow changes according to portal flow.
- It has an inverse relationship.
- mediated by adenosine (Causes vasodilatation).
- Endotoxins & splanchnic vasoconstriction can abolish HABR.
- This inverse relationship is called the hepatic arterial buffer response.
- The hepatic artery "buffers" changes in portal venous flow to maintain a steady state.

Adenosine wash out hypothesis :

- Elevations in portal venous flow wash out locally produced adenosine, thereby decreasing hepatic arterial flow.
- Adenosine : Vasodilator.

Volatile anesthetics and HABR :

- HABR is preserved by isoflurane, sevoflurane & desflurane.
- Volatile anesthetics : Decrease MAP and CO.
- Hepatic artery blood flow is decreased by halothane and enflurane through direct vasoconstriction.

metabolic control :

- Decrease in O_2 content or pH of portal venous blood, there is increase hepatic arterial blood.
- Post prandial hyperosmolarity increases blood flow.
- myogenic autoregulation : Vascular smooth muscle stretch during hypertension to protect the liver.

Extrinsic :

Neural :

- Parasympathetic and sympathetic nerves regulates vascular tone.
- Blood volume is shifted to systemic circulation.
- Hepatic artery has alpha 1, a 2 & beta a receptors.
- Portal vein has only alpha.

Humoral :

- Glucagon : Causes hepatic artery vasodilation.
- Angiotensin II : Causes vasoconstriction.
- Vasopressin : Used in portal HTN, reduces portal venous pressure.

Hepatic blood flow measurement 00:12:30

Clearance technique :

- Based on 'Ficks principle'.
- Rate of disappearance of a substance that is exclusively cleared by liver.
- High extraction ratio : ICG, propranolol, lidocaine.
- Dual cholate test :
  - measures the clearance of cholate, a bile salt.
  - Given in both oral and intravenous form.

Indicator dilution technique :

- Can measure hepatic blood flow even in the setting of liver dysfunction.
- Hepatic blood flow can then be calculated by creating indicator dilution curves.
- The substance used should be resistant to hepatic clearance.
- Used as a research tools.

Direct measurements :

- USG probes or electromagnetic probes.
- Radiological methods :
  - Doppler ultrasonography can show diminished portal flow and portal venous flow reversal.
  - Contrast CT, MRI.
  - Elastography : Fibrosis.

Note :

Halothane hepatitis :

- Halothane undergoes metabolism by the liver more than any other volatile anaesthetic.
- The breakdown products are trifluoroacetic acid and trifluoroacetic chloride.
- Bind to proteins in the liver, where they are recognized by the immune system as antigens.
- The resulting immune response is known as halothane hepatitis.

- Results in fulminant hepatic necrosis, fatal in 50% to 75% of cases.
- multiple exposures increase the likelihood of this response.
- Halothane hepatitis is 10 to 20 times more prevalent in adults than in the pediatric population.

Pharmacokinetics 00:01:00

Bioavailability :

- Drugs administered intravenously have 100% bioavailability because original form of the drug reaches the systemic circulation unchanged.
- First pass metabolism : When taken orally, the intestines and liver absorb and process drugs thereby decreasing the effective dose that enters systemic circulation.

Drug metabolism :

Xenobiotics :

- Drugs/natural and synthetic substances → metabolised by the liver.
- Goal : To render the compounds more hydrophilic → Renal elimination of the modified drug or its metabolites occurs easily.

Phases of drug metabolism :

2 main phases : Phase 1 & Phase 2.

Occurs alone or in combination.

Phase 1 :

- Alter existing functional groups to make the molecule more polar, thereby increasing its water solubility.
- Phase 1 enzymes consist of cytochrome P450 (CYP superfamily) of enzymes that hydrolyze, oxidize, or reduce the parent compound.

Phase 2 :

- Act primarily to conjugate polar compounds & increase their hydrophilicity.
- These enzymes can be inhibited & inducible.
- Glucuronation, acetylation, sulfation, methylation.

Phase 3 :

- Involve the excretion of compounds into bile by molecular transporters.
- Molecular transporters : multidrug resistance protein, cystic fibrosis transmembrane conductance regulator and multidrug resistance related protein, ATP binding cassettes (ABC).

Clinical significance :

- Absence or dysfunction of these phase I or II enzymes can result in hyperbilirubinemia and encephalopathy.
- Gilbert's syndrome : mutation in bilirubin-UGT that leads to reduced conjugation of bilirubin with glucoronide and unconjugated hyperbilirubinemia.
- Depletion of molecules involved in conjugation reactions can result in liver injury.
- Acetaminophen toxicity : Relative depletion of glutathione and accumulation of N-acetyl-p-benzoquinone-imine (NAPQI), the unconjugated toxic acetaminophen by-product.
- Zone 3 damage → Necrosis.
- Cytochrome 2C19 (CYP 2C19) is the enzyme that activates the prodrug of clopidogrel and the enzyme that metabolizes proton pump inhibitors : Competition for this enzyme causes a decreased activation of clopidogrel and an increased risk of acute coronary syndrome.

Conjugation :

- Phase II biotransformation reaction.
- The activated drugs are conjugated with polar species such as glutathione, sulphate, glycine, or glucoronic acid to render them water-soluble and easily excretable by the kidneys.

Drug clearance :

Hepatic drug clearance depends on three factors :

- The intrinsic ability of the liver to metabolize a drug (Presence of the appropriate drug metabolizing enzyme).
- Hepatic blood flow.
- Extent of binding of the drug to blood components (Albumin).

Extraction ratio :

- Substances that undergo significant first-pass elimination are said to have a high extraction ratio.
- Elimination of these drugs is largely determined by hepatic blood flow.
- Liver removes the entire drug entering liver in one pass.

Low extraction ratio :

- Drugs that require a prolonged time for biotransformation : Have a low extraction ratio.

- Such drugs are often protein bound in the circulation.
- Not readily available to drug metabolizing enzymes in the liver

Common anaesthetic drugs :

High Clearance (high extraction ratio that is blood flow dependent)	Intermediate Clearance	Low Clearance (low extraction ratio that is blood flow independent)
Morphine	Aspirin	Warfarin
Lidocaine	Quinine	Phenytoin
Propofol	Codeine	Rocuronium
Propranolol	Nortriptyline	Methadone
Fentanyl	Vecuronium	Diazepam
Sufentanil	Alfentanil	Lorazepam

Note :

- Drugs with a high intrinsic clearance : Eg : Lignocaine, opioids, etomidate, and propofol have a hepatic clearance dependent on hepatic blood flow.
- They are unaffected by enzyme induction because of the already high extraction ratio.

Cytochrome P450

00:28:15

Features :

- Group of enzymes, predominantly in liver.
- metabolism of various drugs.
- Involved in phase I reactions.
- CYP 450 are proteins containing haem as a co-factor.
- The term P450 is from the spectrophotometric wavelength absorption maxima for the enzyme in the reduced state (450 nm).
- Drug-drug interactions can result in the induction or inhibition of CYP450 enzymes.
- CYP450 enzymes are located throughout the body.
- Highly concentrated within the smooth endoplasmic reticulum of hepatocytes within the liver.
- Liver, gut and Kidneys.

Importance in anaesthesia :

- CYP 2E1 : mainly responsible for oxidative metabolism of volatile anaesthetics.
- CYP 3A : IV anaesthetics.
- Polymorphism : Genetic mutations that give rise to enzymes with different abilities to metabolise drugs.
- The expression of CYP450 enzymes varies between populations and will influence drug metabolism and response.
- Inducers increase the expression level of CYP450 enzymes resulting in increased metabolism of drugs.
- Reduces the therapeutic concentration.
- Therefore, potential changes in drug concentration may cause treatment failure.
- Expression and function of Phase I & II enzymes are reduced in neonates.
- Activities of few CYP450 enzymes are increased in women compared to men
- Genetic polymorphism.

CYP450 inducers :

- Anticonvulsants : Phenytoin, carbamazepine, phenobarbitone.
- Steroids : Dexamethasone, prednisolone, glucocorticoids.
- Antibiotics : Rifampicin, griseofulvin.
- Others : Nicotine, alcohol, cigarette smoke, St John's Wort.

CYP450 inhibitors :

- Inhibitors prevent the CYP450 enzymes from working or reduce the rate of an enzyme-catalysed reaction.
- This decreases drug metabolism in the body and increases the potential for toxicity.
- Azoles : Ketoconazole, fluconazole.
- Antibiotics : Sulfonamides, metronidazole, ciprofloxacin, chloramphenicol, macrolides, isoniazid.
- Cimetidine.
- Omeprazole.
- Sodium valproate.
- Grapefruit.

Note :

Phase I biotransformations :

- CYP3A4 is the single most important enzyme.
- 40% to 45% of all CYP mediated drug metabolism.

morphine metabolism :

- Glucuronidation
- morphine is metabolised to morphine-3-(inactive) and morphine-6- glucoronides (Active).

LIVER FUNCTION TESTS

Introduction 00:00:36

Basic interpretation :

- AST is more sensitive than ALT to liver damage.
- Reduction in albumin concentration is more likely to be as a result of protein catabolism than decreased synthesis.
- ALP increases occur with biliary tract dysfunction.

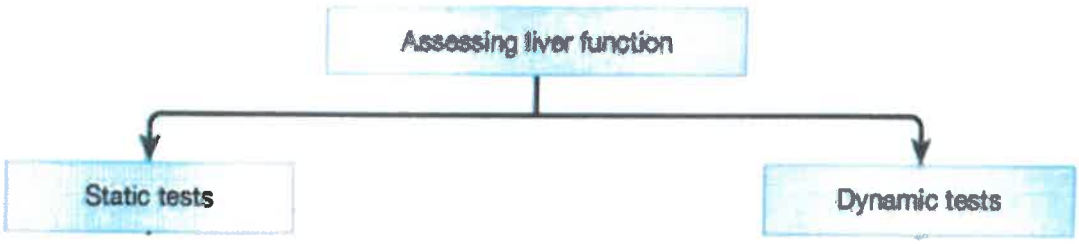
Functions of liver :

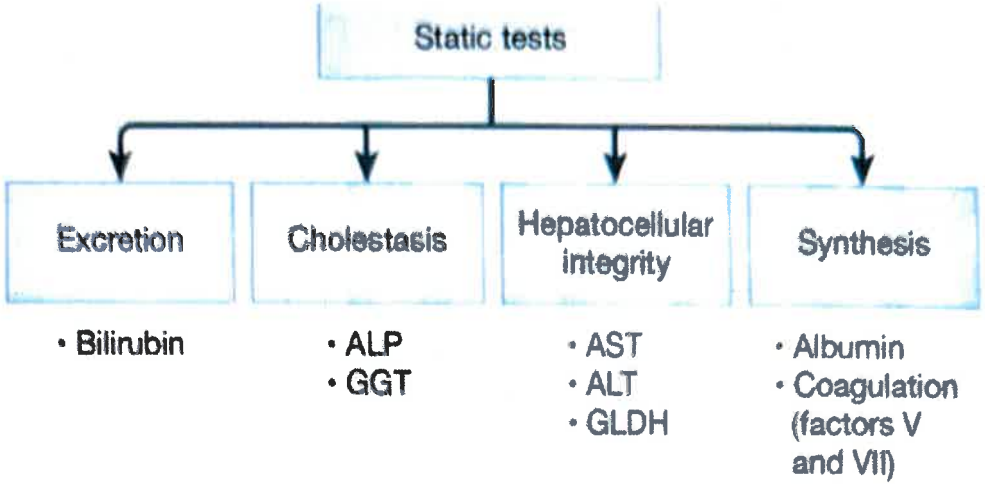
- Multi functional organ.
- metabolic functions : Carbohydrate, lipids, proteins, minerals and vitamins.
- Excretory function : Bile pigments, bile salts → Bile → Intestine.
- Detoxification : Ammonia → Urea, antibiotic metabolism.
- Protective function : Kupffer cells.
- Storage function : Glycogen, Vitamin A, D, B_{12}.
- Synthetic functions : Plasma proteins → Albumin, prothrombin, hormones.
- Conjugates bilirubin with glucuronic acid to form water soluble bilirubin that is excreted in bile.
- Production of cholesterol and lipoproteins.
- Vitamin K dependent coagulation factors (II, VII, IX, and X).

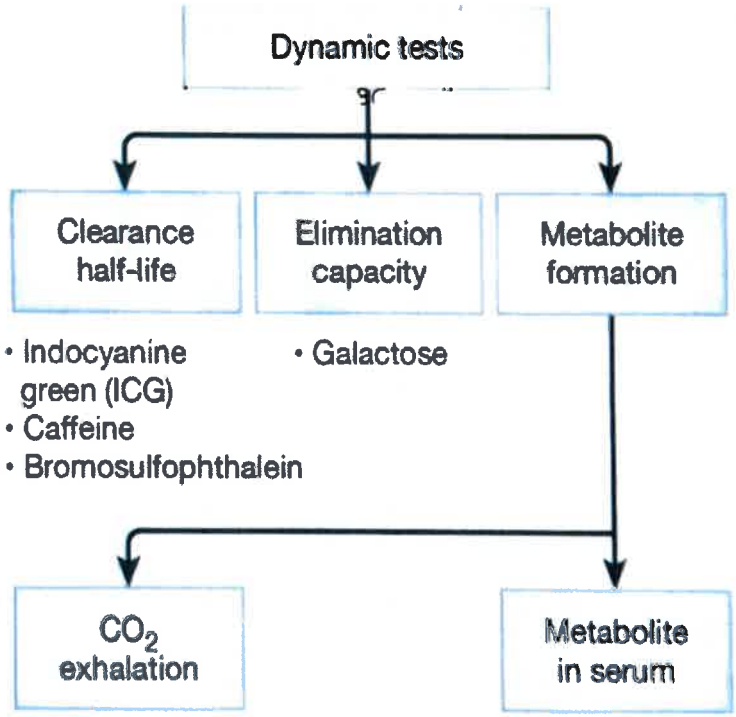
Tests of liver function 00:05:22

1. Clinical findings.
2. Radiological studies.
3. Laboratory :

- Static.
- Dynamic : measures functional pathways.







Test		Normal values	Purpose
Total bilirubin	mg/dL	< 2.0	Conjugation, excretion
Conjug. bilirubin	mg/dL	< 15% of total bilirubin	
ALT/SGPT	IU/L	< 40	Enzymes released by liver cell injury/death
AST/SGOT	IU/L	< 40	
Alk. phosphatase		Varies by method	Enzymes released by biliary injury or obstruction
GGT	IU/L	< 35	
Albumin	g/dL	3.5 - 5.5	Synthetic function
Prothrombin time	INR	0.9 - 1.2	