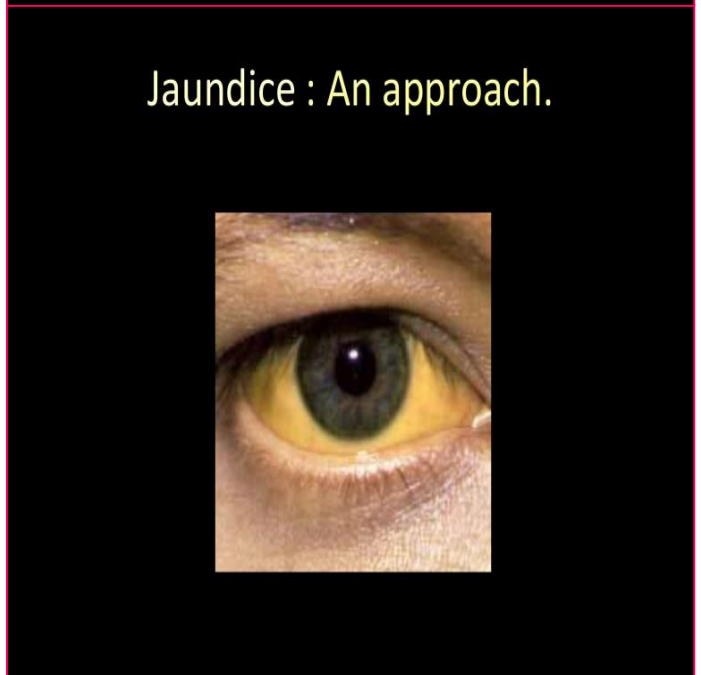
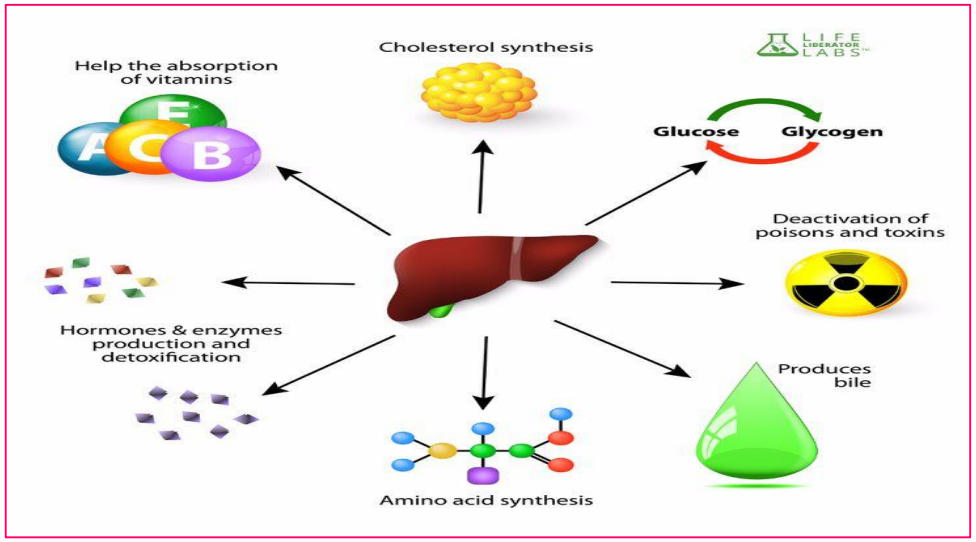
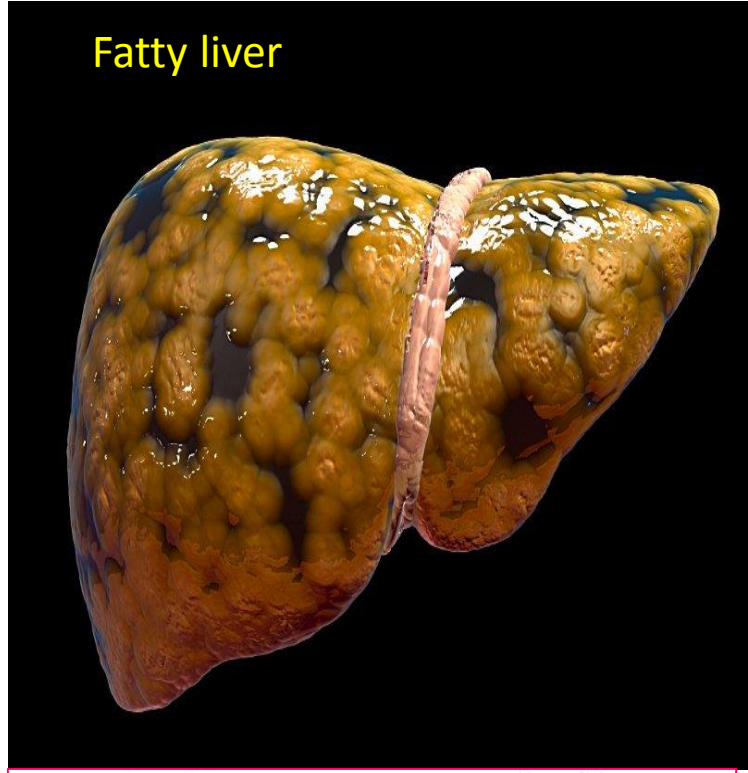
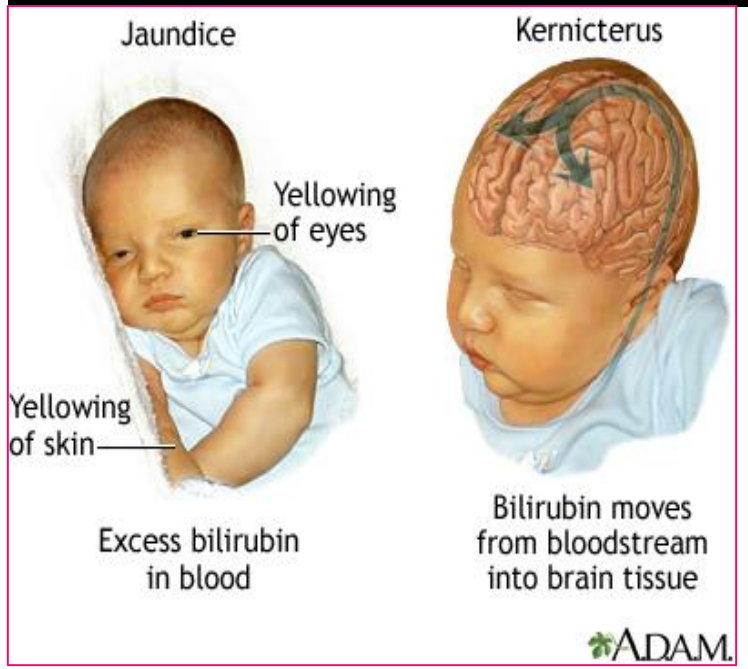




Liver Function Tests and their clinical applications

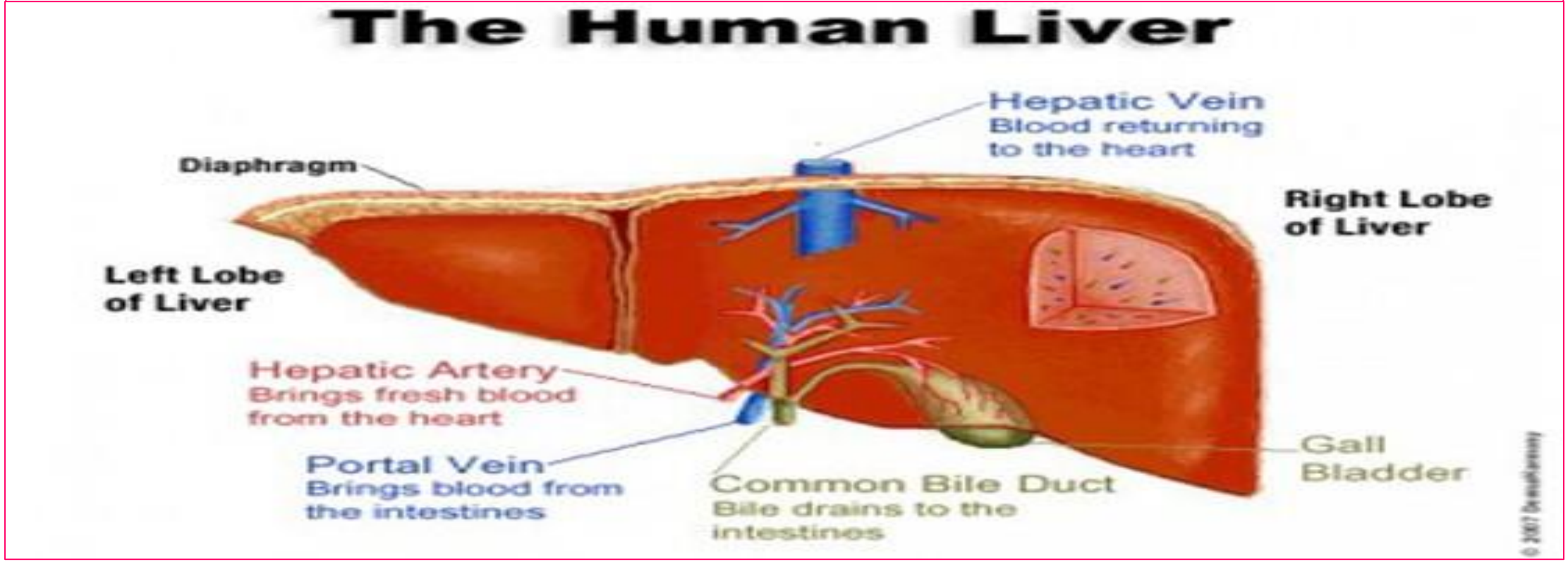
Dr. Rohini C. Sane





Liver Function Tests (LFT)

- Structure →Functions →Tests
- Definition of LFT : Tests to assess liver functions



Ultrastructure of liver

- Liver is made of lobes .
- Each lobe contains a number of lobules (functional units of Liver)
- Each lobules is made of hepatic cells .
- Hepatic cells are separated by sinusoids (vascular channels).
- The sinusoids are lined by Kupffer cells (phagocytic cells) which form part of reticuloendothelial system.
- Bile canaliculi present between hepatic cells empty into the bile ducts .

Liver Functions

❑**Synthetic functions :**

a) Protein metabolism: Synthesis of plasma proteins (albumin ,globulins ,coagulation factors :fibrinogens & prothrombin), Enzyme synthesis

b) Fat metabolism :Synthesis of cholesterol ,Triacylglycerol, fatty acids and lipoproteins

❑**Metabolic functions :**

a) Carbohydrate metabolism: Glycolysis, Glycogenesis ,Glycogenolysis ,Gluconeogenesis , Conversion of Galactose & Fructose, blood glucose regulation

b) Protein catabolism, urea cycle ,amino acid metabolism, hormone synthesis

c) Fat metabolism: fatty acid breakdown/oxidation ,cholesterol synthesis

d) Citric acid cycle , ATP synthesis

❑**Detoxifying and excretion function :**

a) Destruction of RBC & formation of bile pigments

b) Removable or excretion of drugs ,Alcohol ,hormones ,bilirubin & xenobiotics

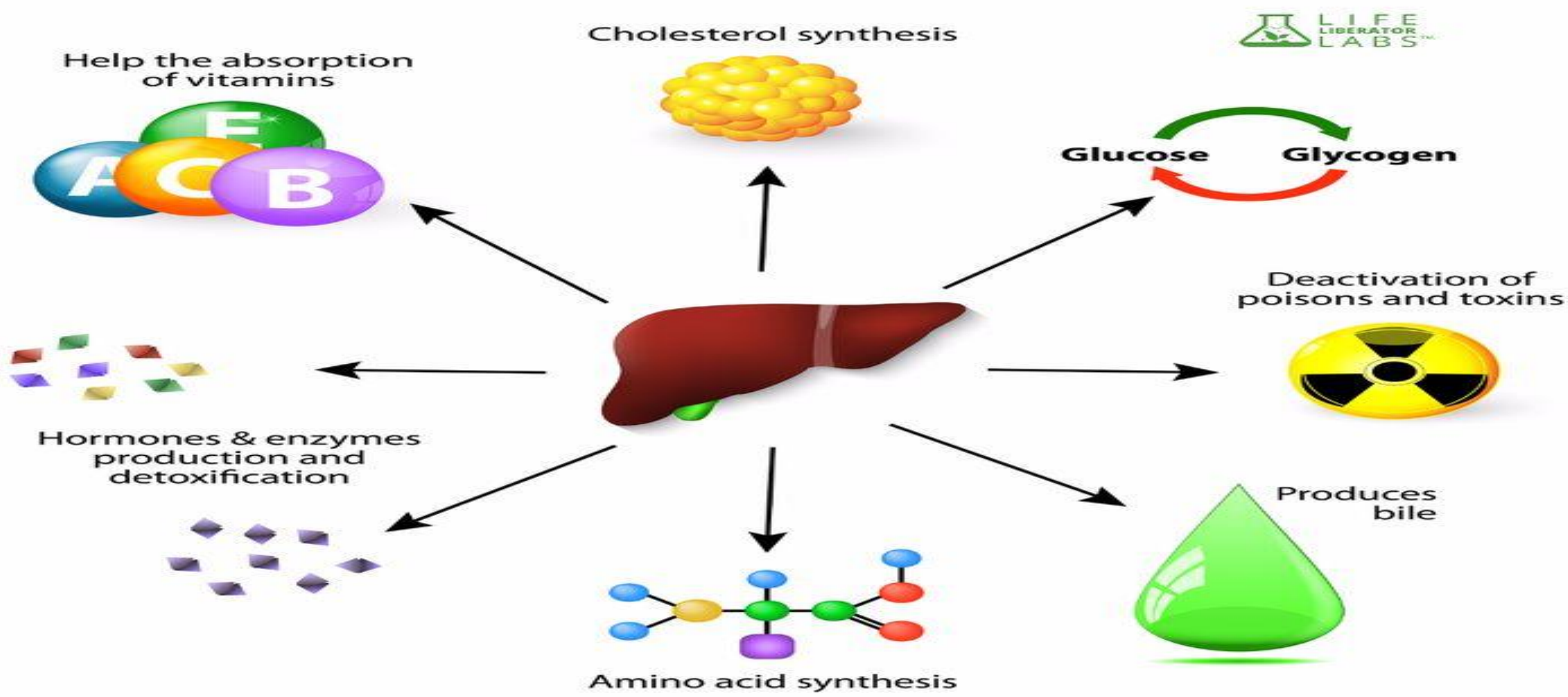
c) Conversion of ammonia to urea

d) Cholesterol -→ Production of bile salts

❑**Storage function**: Glycogen ,Iron vitamin A ,D,E, K and B12

❑**Digestion of lipids**: with the help of bile salts

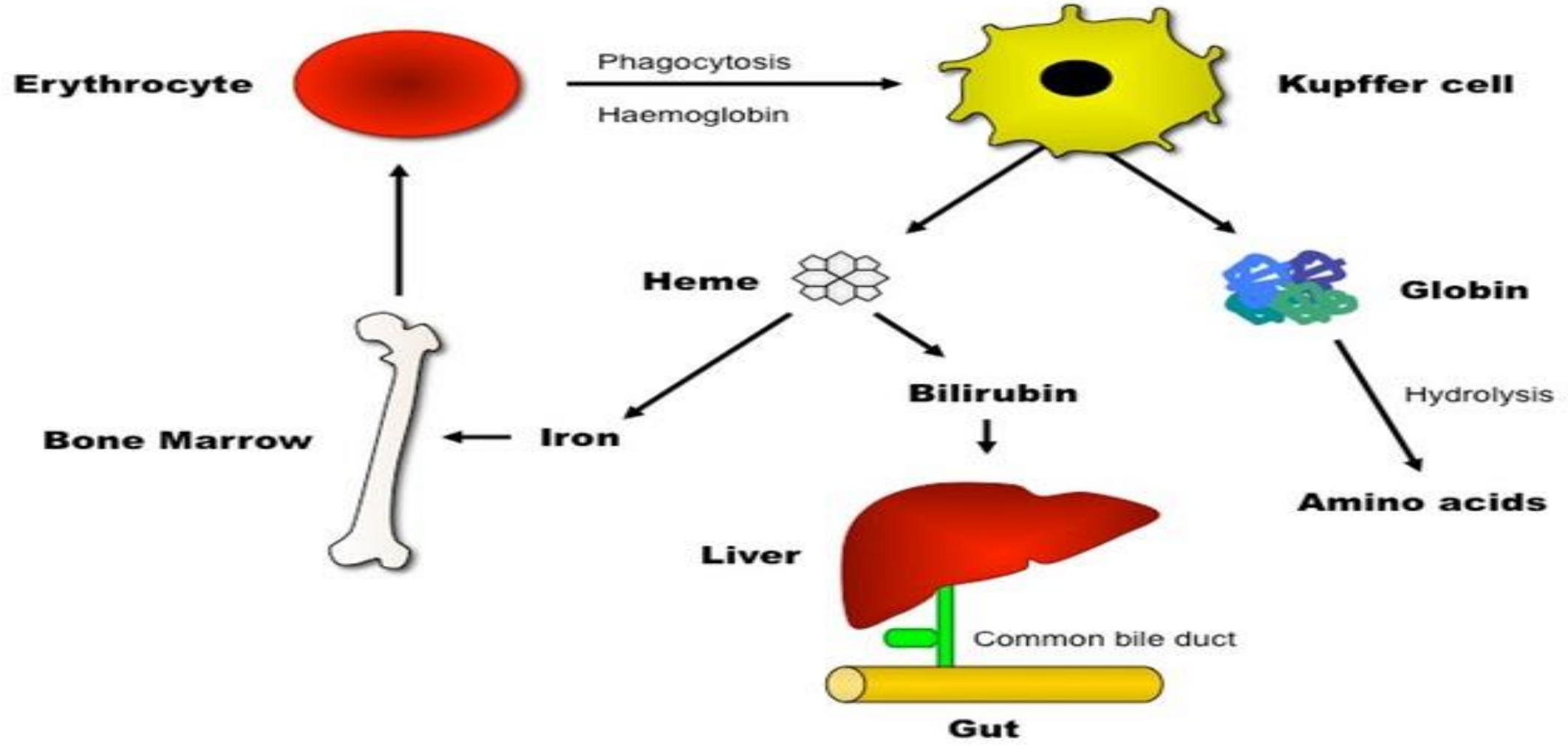
Liver Functions



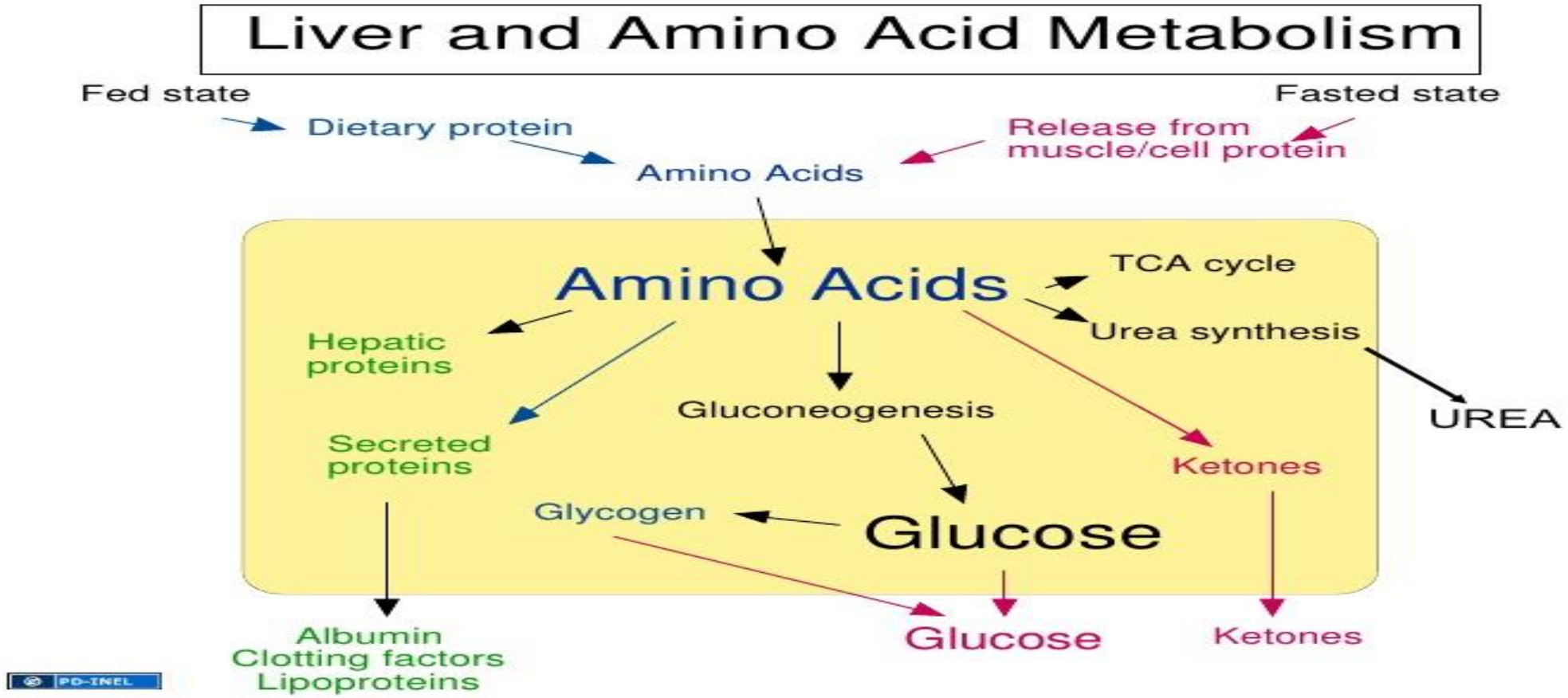
Liver Functions

1. Destruction of RBC & formation of bile pigments
2. Protein metabolism
3. Synthesis of plasma proteins ,fibrinogens & prothrombin
4. Enzyme synthesis
5. Conversion of ammonia to urea
6. Carbohydrate metabolism
7. Fat metabolism
8. Removable or excretion of drugs ,hormones & other substances
9. Detoxifying function

Liver Functions :1. Destruction of RBC & formation of bile pigments



Liver Functions : Protein metabolism: Synthesis of plasma proteins (albumin ,globulins ,coagulation factors :fibrinogens & prothrombin), Enzyme synthesis



Protein catabolism, urea cycle ,amino acid metabolism, hormone synthesis

Liver Functions : 6. Carbohydrate metabolism: Glycolysis, Glycogenesis ,Glycogenolysis ,Gluconeogenesis , Conversion of Galactose & Fructose, blood glucose regulation

Carbohydrate metabolism

Glycogenesis

Glycogenolysis

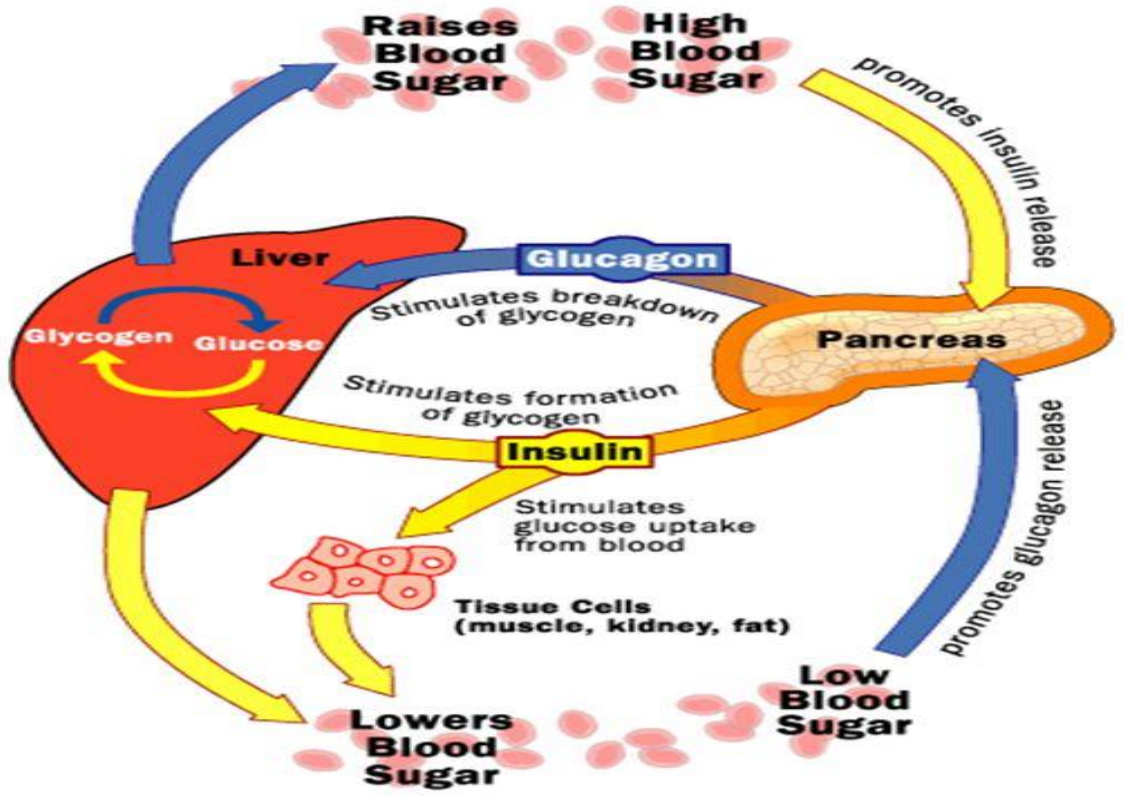
Gluconeogenesis

IMPAIRMENT

↓

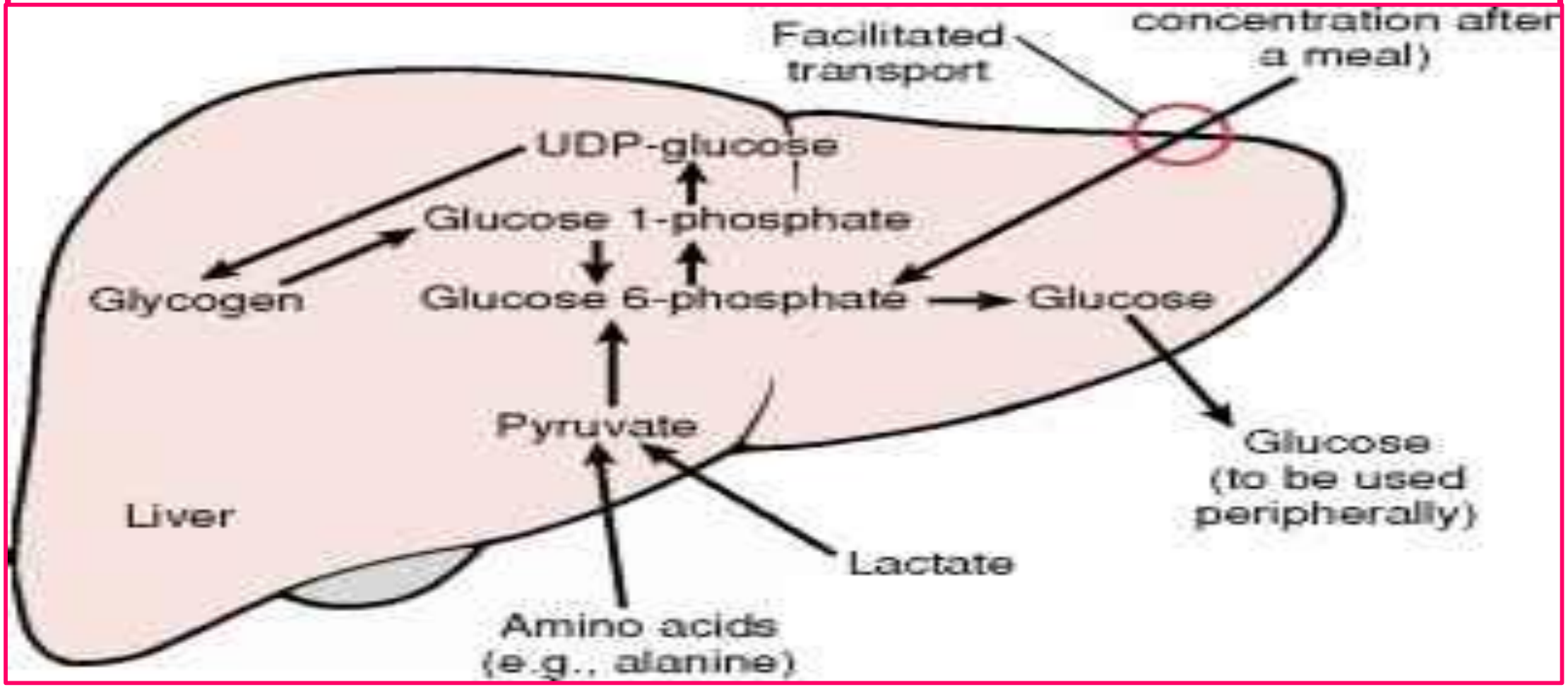
Hypoglycaemia

Glucose Intolerance



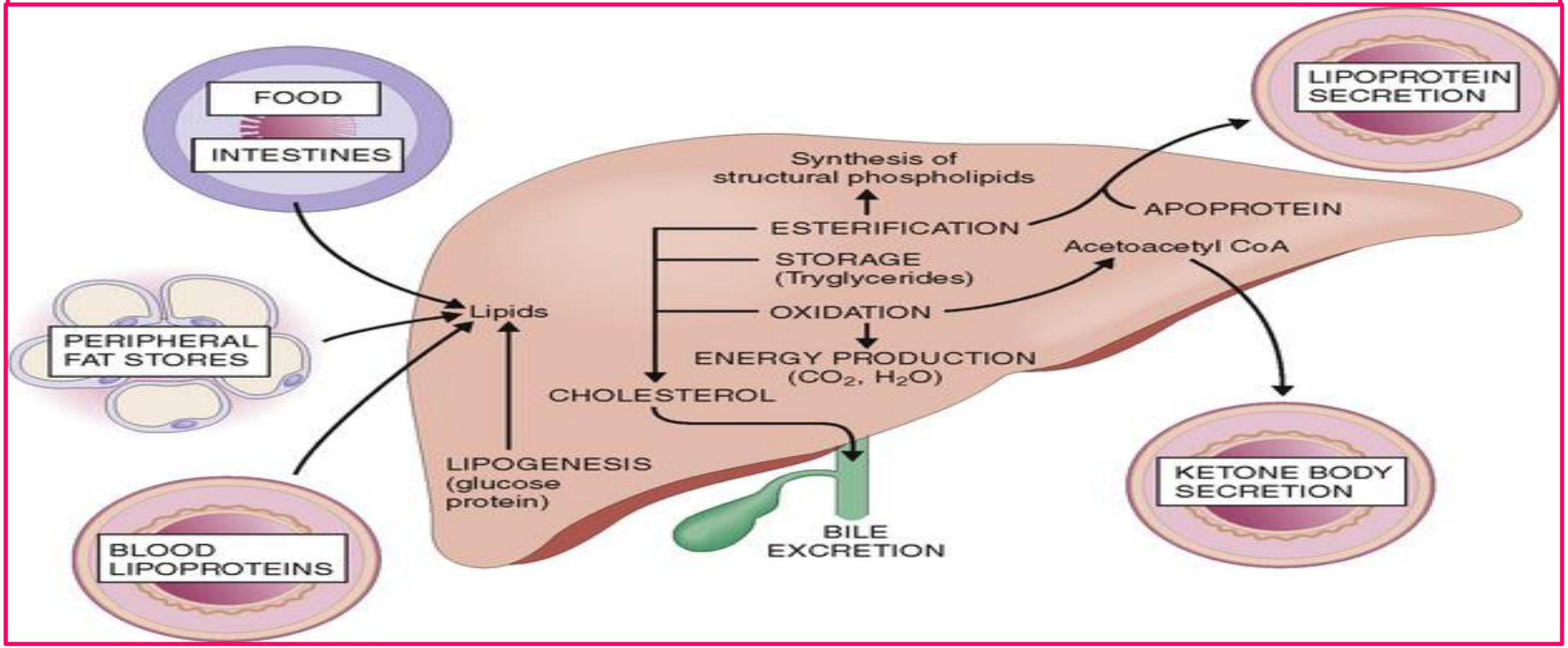
http://static.howstuffworks.com/gif/diabetes-glucose-regulation.gif

Liver Functions : 6. Carbohydrate metabolism

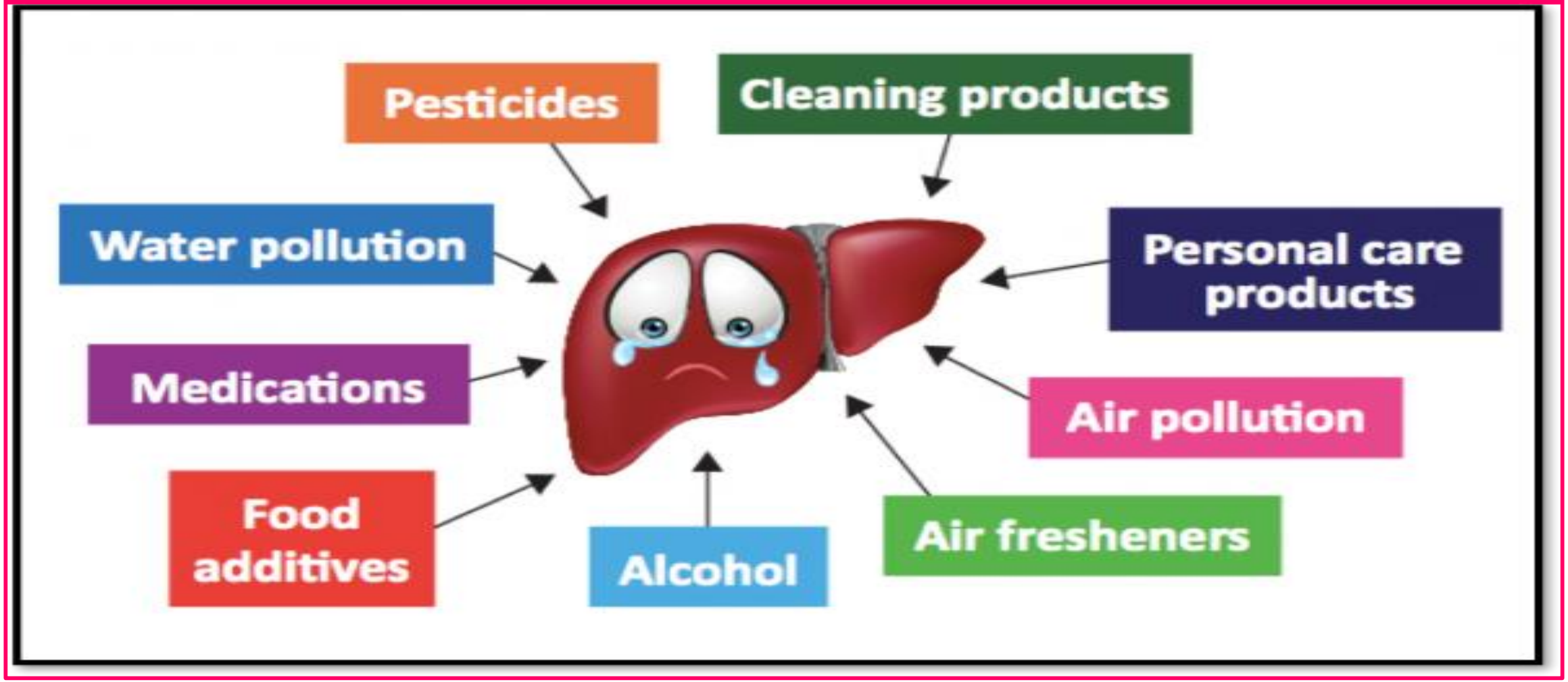


Liver Functions : 7. Fat /Lipid metabolism :Synthesis of cholesterol ,Triacylglycerol, fatty acids and lipoproteins

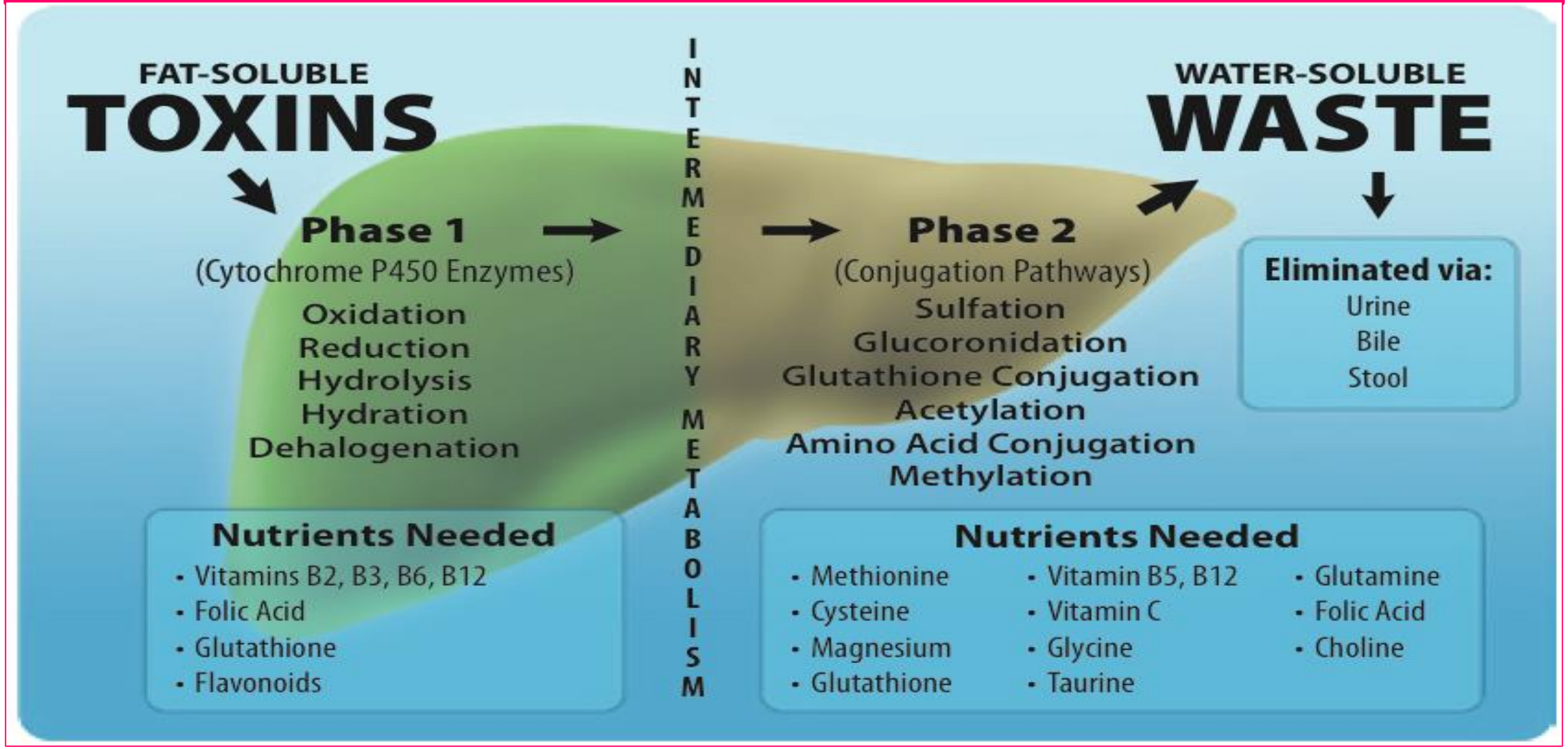
Fat metabolism: fatty acid breakdown/oxidation ,cholesterol synthesis



Liver Functions : 8. Removable or excretion of drugs ,hormones & other substances



Liver Functions : 9. Detoxification



Classification of Liver Functions

Function of the Liver

Metabolism / Detoxification

- Metabolizes products of digestion
- Glucose regulation
- Vitamin storage
- Metabolizes drugs
  - Some of the common drugs used in Dentistry
  - Ethanol.
- Breaks down bilirubin

Synthesis and Secretion

- Components of clotting factors
- Cholesterol, triglyceride synthesis
- Bile production
- Other proteins and hormones

Storage and Filtration of Blood

- Acts as a blood reservoir
- Contains phagocytic cells
- Part of the reticuloendothelial system.

Clinical Applications of Liver Function Tests

1. Degree of parenchymal cell damage
2. Differentiate type of liver diseases : Jaundice, hepatitis ,obstructive, cirrhosis , hepatoma, (an undiagnosed chronic illness)
3. Judge the prognosis of patient
4. Evaluate the response to the treatment e.g. therapy with statins to check hepatotoxicity , therapy for coagulation disorders

Classification of Liver Function Tests:1

❖**A :Classification based on biochemical findings :**

➢**Group I (tests based on Liver excretory function)**

1. Serum Bilirubin :Van der Bergh reaction (total ,conjugated)
2. Serum Bilirubin : Icteric index
3. Urine bilirubin and bile salts
4. Urine urobilinogen & fecal stercobilinogen
5. Urine urobilin & fecal stercobilin

Classification of Liver Function Tests:2

❖**A: Classification based on biochemical findings :**

➢**Group II (Liver enzyme panel tests: biomarkers for Liver injury and or cholestasis)**

1. Alkaline phosphatase (ALP)
2. Serum glutamate pyruvate transaminase (SGPT)
3. Serum glutamate oxalate transaminase (SGOT)
4. Gamma Glutamyl Transferase(GGT)
5. Serum isocitrate dehydrogenase
6. Choline esterase
7. 5 ‘ nucleotidase

Classification of Liver Function Tests:3

❖**A:Classification based on biochemical findings :**

➢**Group III (tests based on Liver synthetic function)**

Plasma protein concentration :

1. serum : Total protein , albumin , globulin ,serum A:G ratio & fibrinogen concentration
2. Flocculation test
3. Amino acid in blood & urine

Test for blood coagulation

1. Prothrombin time determination

Classification of Liver Function Tests:4

❖**A: Classification based on biochemical findings :**

➢**Group IV (tests based on Liver specific function)**

1. Alpha -1 antitrypsin (AAT)
2. Alpha fetoprotein(AFP) as LFT
3. ceruloplasmin
4. Ferritin

Classification of Liver Function Tests:5

❖**B :Classification based on clinical aspects :**

➢**Group I (markers for Liver dysfunction)**

1. Serum Bilirubin :Van der Bergh reaction (total ,conjugated)
2. Serum Bilirubin : Icteric index
3. Urine bilirubin and bile salts
4. Urine urobilinogen & fecal stercobilinogen
5. Urine urobilin & fecal stercobilin
6. Serum : Total protein , albumin , globulin ,serum A:G ratio
7. Prothrombin time determination
8. Blood Ammonia ,when indicated

Classification of Liver Function Tests:6

❖**B :Classification based on clinical aspects :**

➢**Group II (markers for Hepatocellular injury)**

1. Serum glutamate pyruvate transaminase (SGPT)
2. Serum glutamate oxalate transaminase (SGOT)

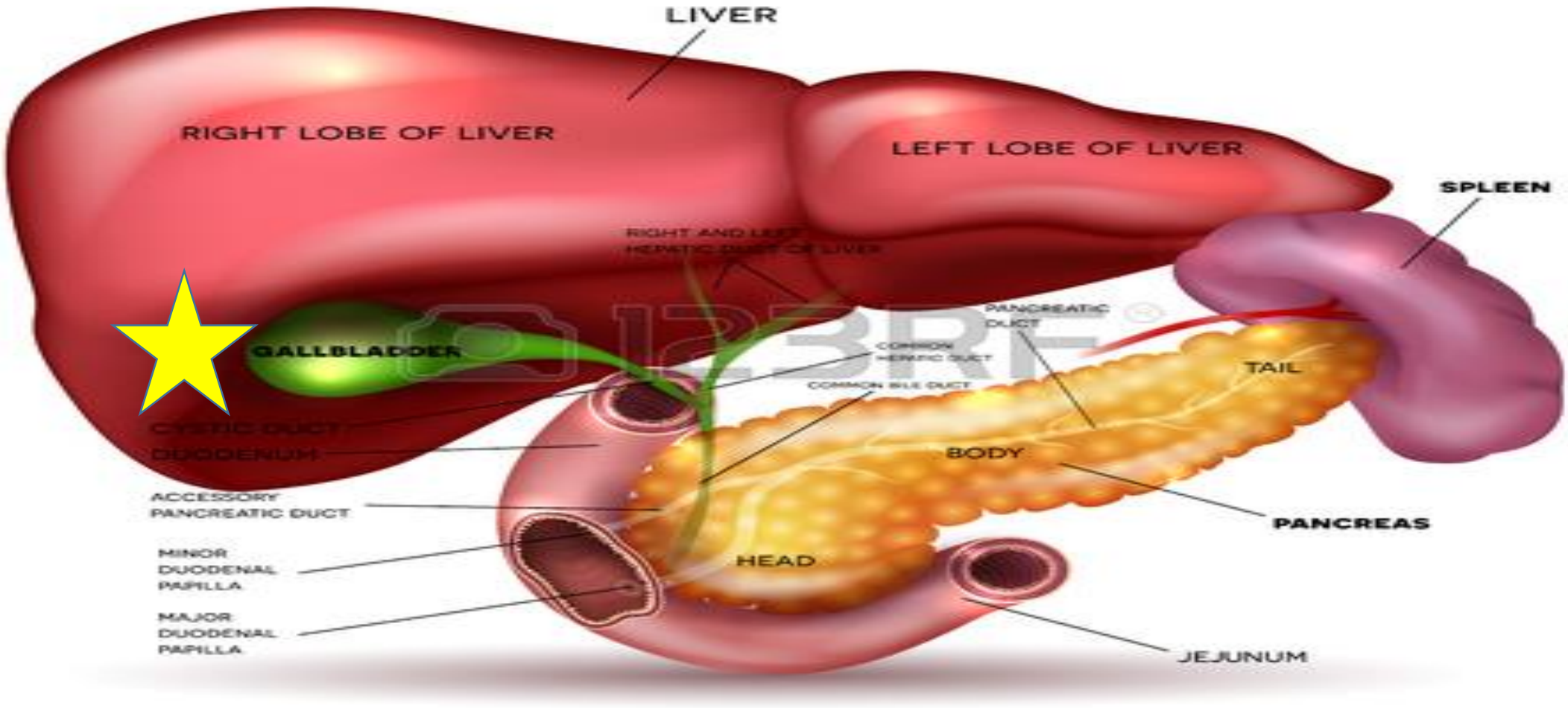
Classification of Liver Function Tests:7

❖**B :Classification based on clinical aspects :**

➢**Group III (markers for cholestasis)**

1. Alkaline phosphatase (ALP)
2. Gamma Glutamyl Transferase(GGT)

Liver function tests based upon bile pigment metabolism



Liver function tests based upon bile pigment metabolism

- Excretory function of liver can be assessed measurement of plasma bilirubin
- Unconjugated bilirubin is increased due excessive hemolysis or defective conjugation.
- Conjugated bilirubin is increased when excretory functions of liver are impaired .

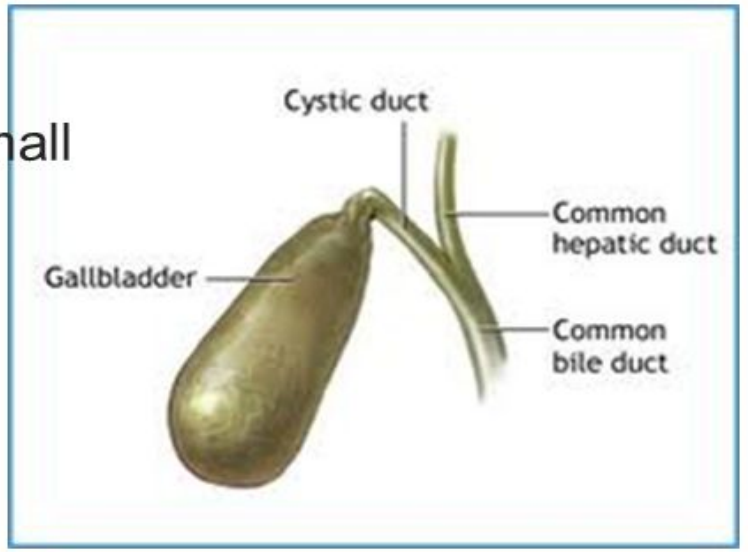
Bile

- About one litre of bile is secreted by hepatic parenchymal cells into bile canaliculi from where it passes through the intrahepatic ducts and enters the intestine through the common bile duct.
- Function of the gall bladder : absorbs water ,electrolyte and concentrates the bile.
- Presence of partially digested food in the intestine stimulates gall bladder contraction by cholecystokinin and emptying of bile into the duodenum

Liver function tests based upon bile pigment metabolism

Gallbladder

Stores bile between meals, reabsorbs water to concentrate bile, and contracts to release bile into small intestine



Functions of Bile Salts

-Aid digestive enzymes

-Break down fat globules into smaller droplets (emulsification)

-Then they mix with water so the fat molecules can be digested more effectively

Secretion of bile

Sight /taste smell of food →gastric juice

↓

cholecystokinin

↓

Bile

↓ bile duct

duodenum

Composition of bile

Components of bile include :

Bile acids are present as bile salts

Primary Bile acids : cholic acids and chenodeoxycholic acids

Secondary Bile acids : deoxycholic acids, lithocholic acid

Bile acids are conjugated by the liver to form water bile salts →sodium and potassium **glycocholate/taurocholate.**

Bile salts : are reabsorbed from the intestines into the portal blood and then transported to the liver and reexcreted into bile . (enterohepatic circulation)

Bile pigments : bilirubin ,biliverdin and small amount of coproporphyrin

Other Components: Cholesterol ,Lecithin , Electrolytes , fatty acids, Alkaline phosphatase

Functions of bile

Absorption of fat : bile Salts help in fat absorption by

1. lowering the surface tension
2. emulsification of fats in intestine
3. formation of micelles with cholesterol and phosphatidylcholine
4. activation of lipases in the intestine
5. Neutralization of acidic chyme from stomach
6. Excretion of bile acids bile pigments ,cholesterol ,drugs, toxins and inorganic substances such as Zinc ,copper and Mercury

Formation & Excretion Of Bile Pigments

Liver

Fragmentation of RBC

↓ **reticuloendothelial system**

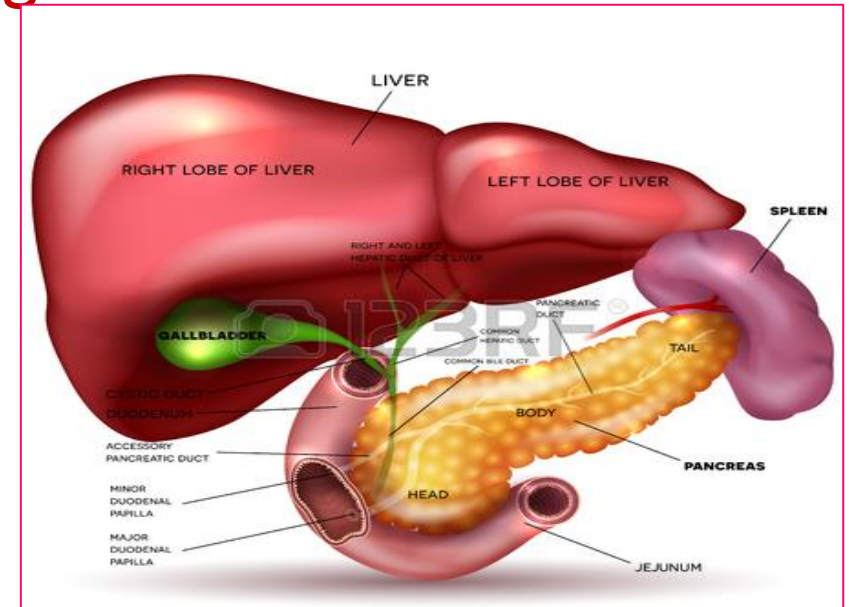
Free bilirubin (protein bound)

↓

Bilirubin glucuronides (conjugated)

↓ **bile duct**

Urobilinogen



Conjugated bilirubin

↓

Urobilinogen

↓

Stercobiilinogen

↓

Stercobilin **intestine**

Kidney

Urobilinogen

↓

Urobilin

↓

Urine

Liver function tests based upon bile pigment metabolism

Bilirubin Metabolism- Biochemical tests for jaundice

1. Serum Bilirubin :Van der Bergh reaction
2. Serum Bilirubin : Icteric index
3. Urine bilirubin and bile salts
4. Urine urobilinogen & fecal stercobilinogen
5. Urine urobilin & fecal stercobilin

Liver function tests based upon bile pigment metabolism

- **Chief constituents of bile related with LFT :**

1. Bile salts
2. Bile pigments
3. Cholesterol

- **LFT in Serum based upon bile pigment metabolism:**

a) Serum Bilirubin & Biliverdin → Diazo sulphanalic Test /Van Der Bergh Test
b) Estimation of Serum Cholesterol
c) Icteric Index

- **LFT in Urine and stool:**

i. Urine Bilirubin : Gmelin's Test's / Fouchet's Test
ii. Urobilinogen and Fecal Stercobilinogen → Erhlich's Test
iii. Urobilin & Fecal Stercobilin → Schlesinger's Test

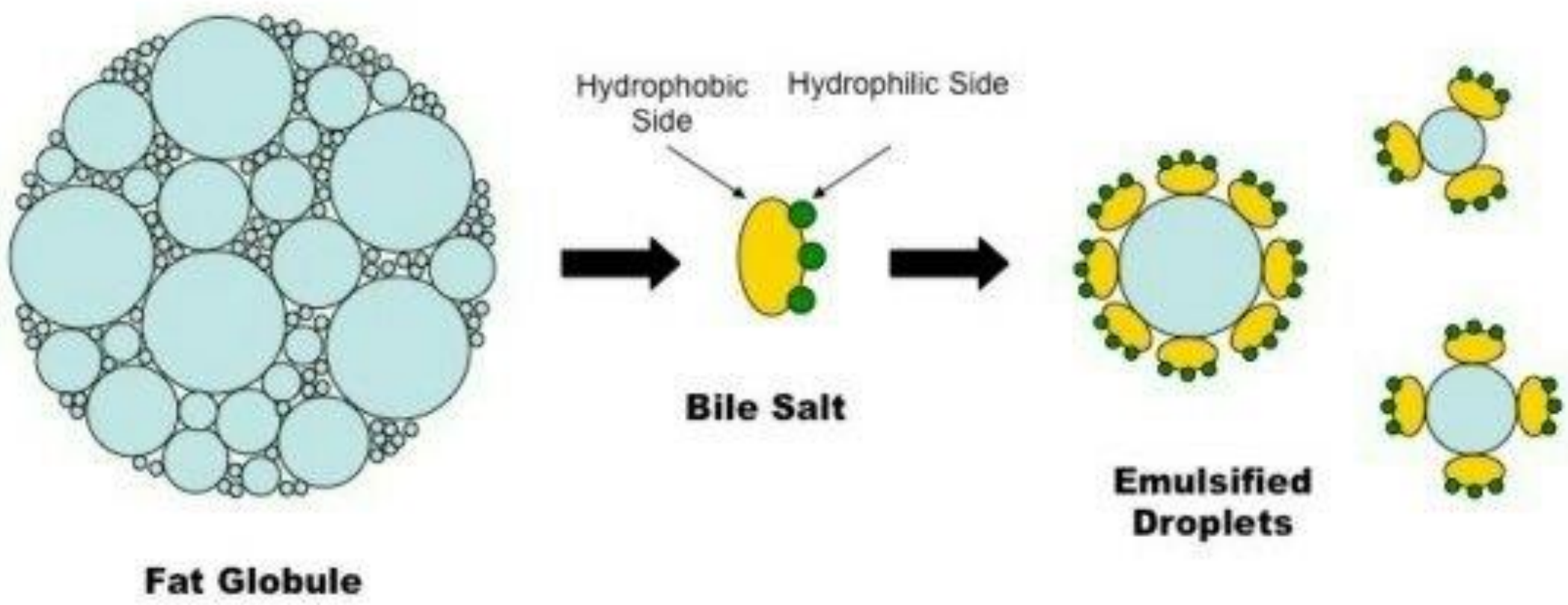
Bile Salts : Sodium Glycocholate and Taurocholate

Bile Salts : Sodium Glycocholate and Sodium Taurocholate

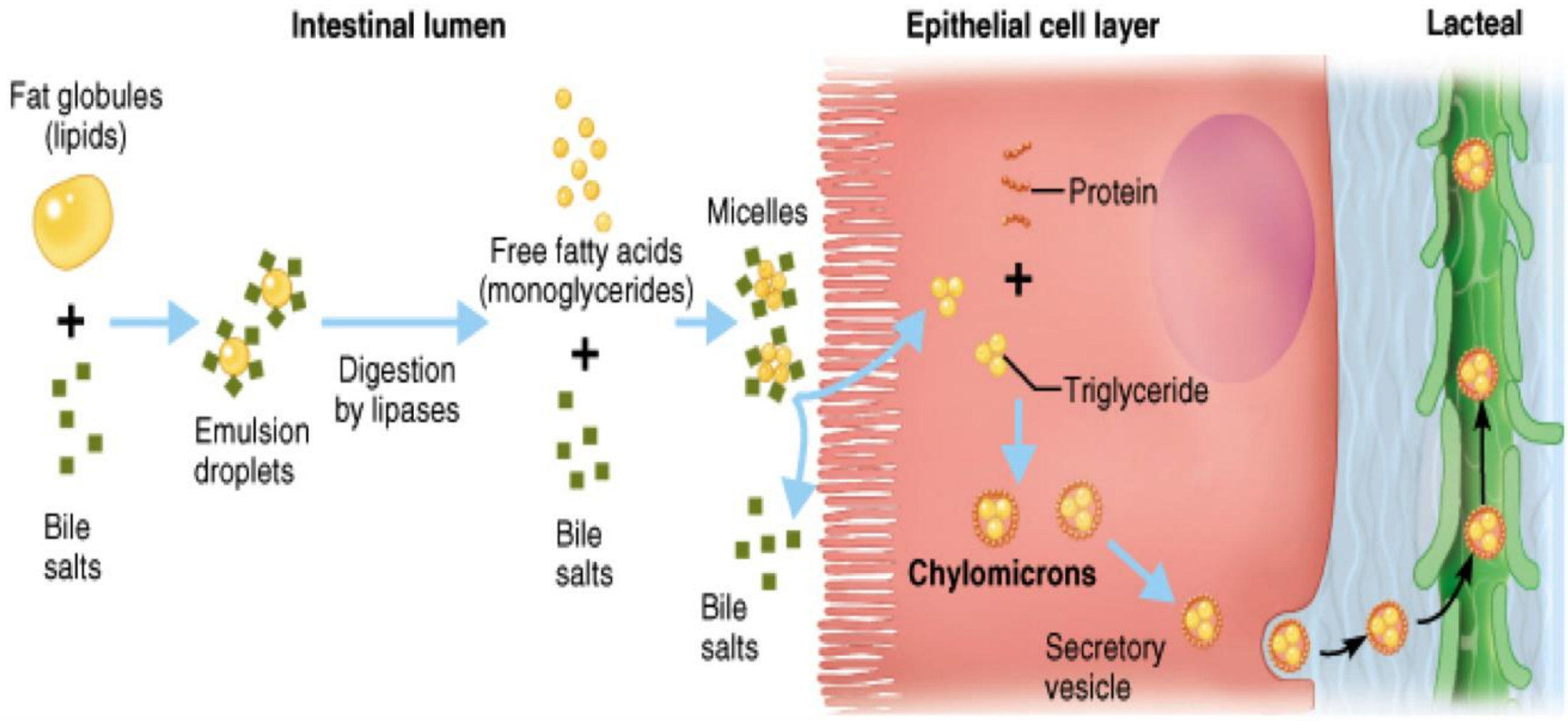
Functions of Bile Salts :

1. Emulsification & digestion of lipids
2. Absorption of fat soluble vitamin K /E /D
3. Cholesterol solubility

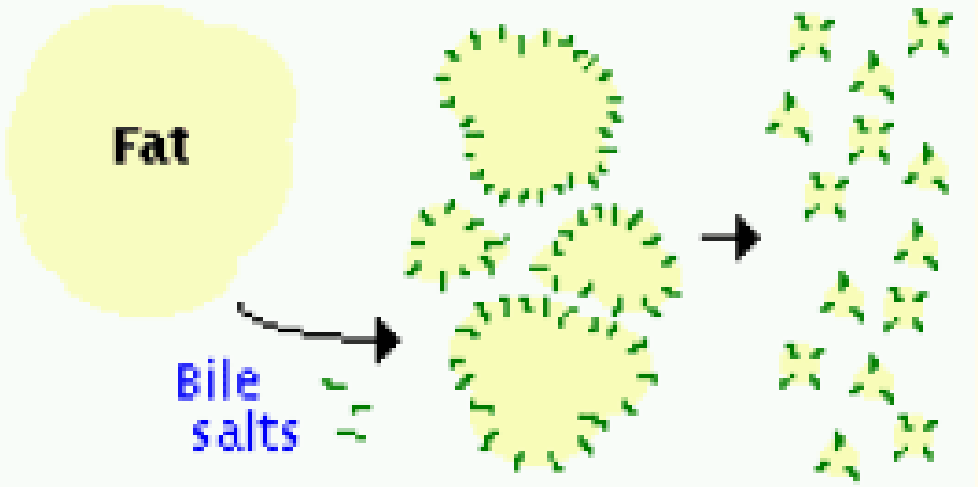
Functions of Bile Salts :1. Emulsification & digestion of lipids

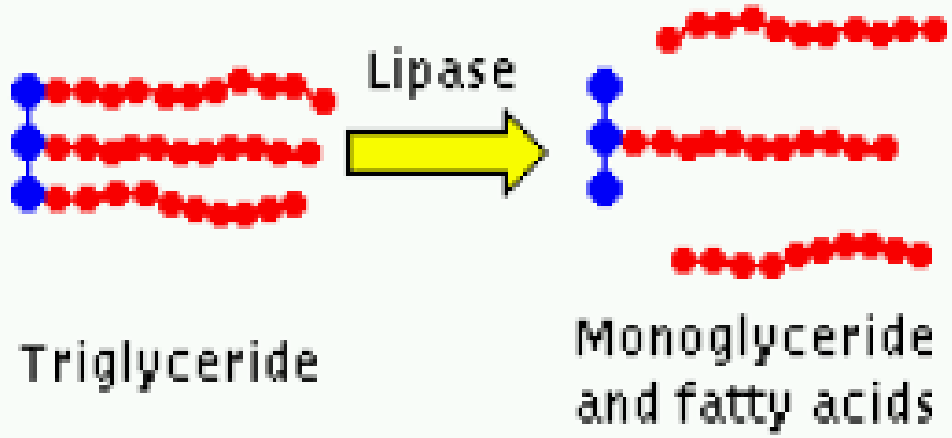


Functions of Bile Salts :Absorption of fat soluble vitamin K /E /D



Functions of Bile Salts : Cholesterol solubility





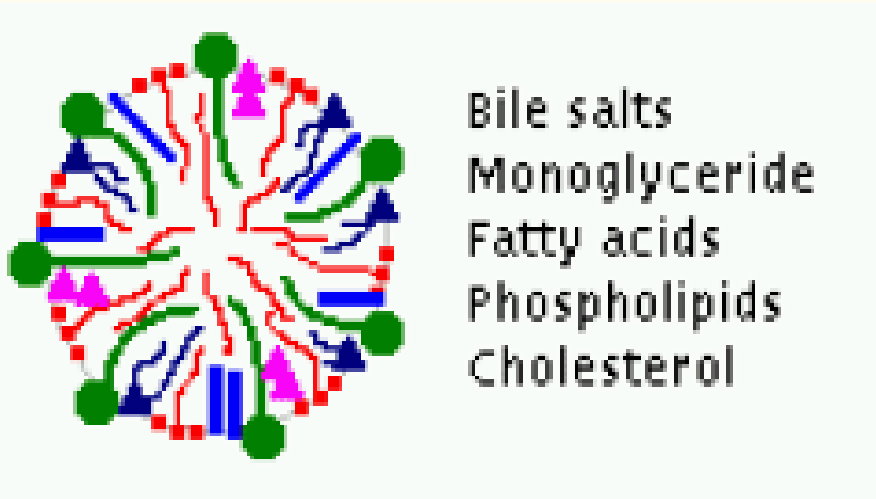
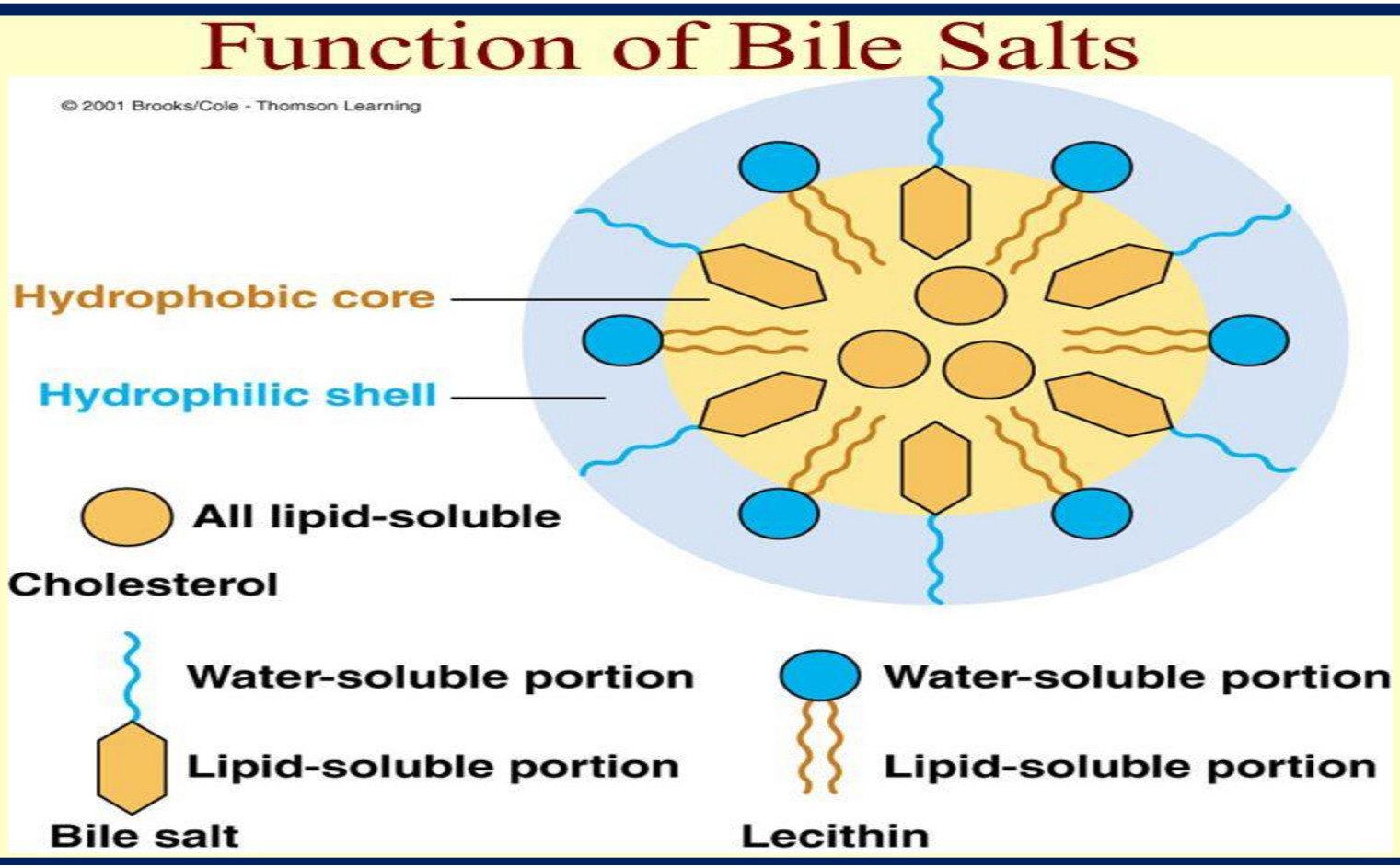
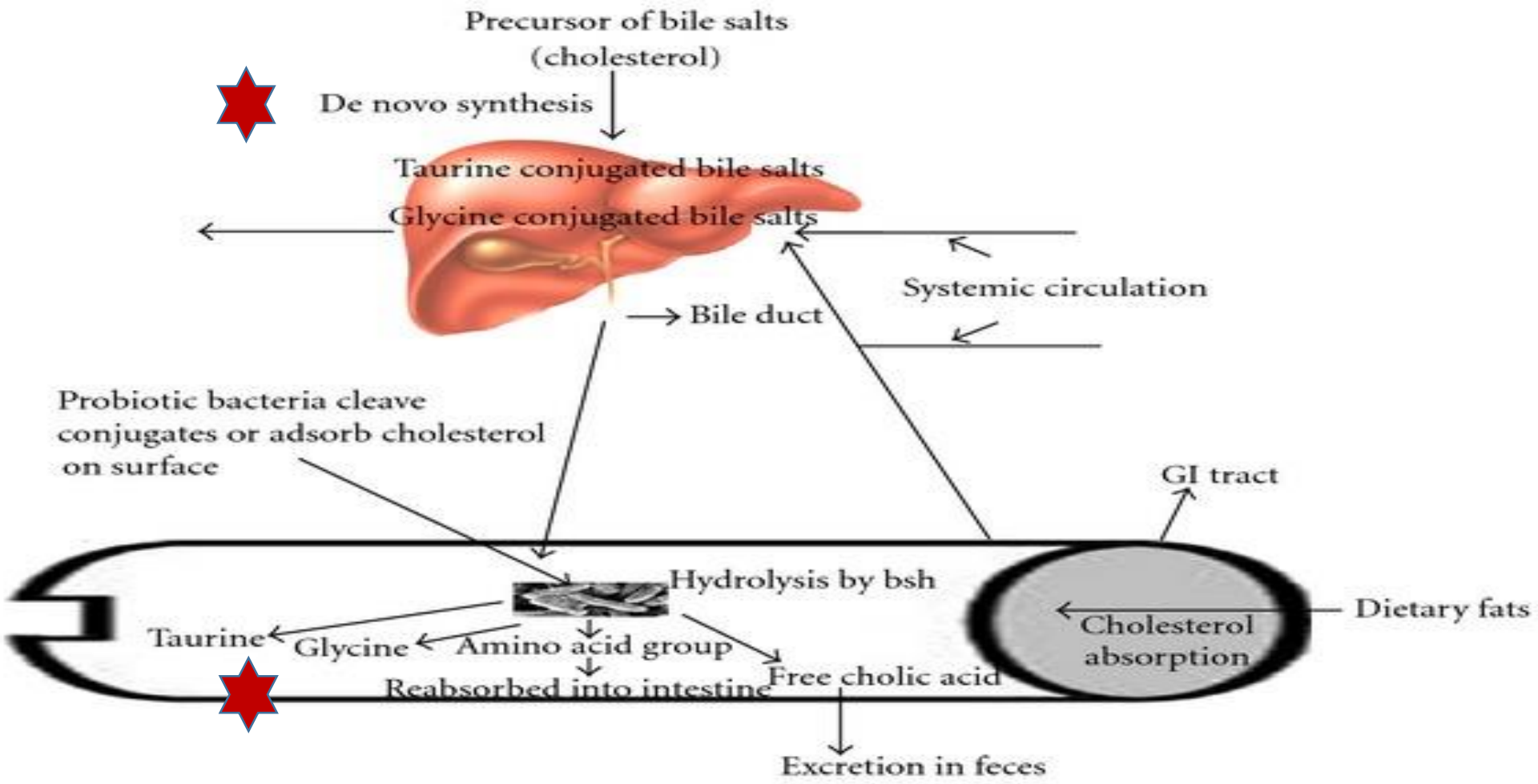


Fig: Emulsification, Hydrolysis and Micelle Formation

Functions of Bile Salts : Cholesterol solubility



Bile Salts and Cholesterol



Liver function tests for Bile Salts

1. Hay’s Sulphur Powder Test (most commonly used)
2. Petenkofer ’s Test
3. Oliver Peptone’s Test

Hay's Sulphur Powder Test for urinary bile salts detection in Jaundice

Detection of bile salts in urine

- Hay's surface tension test

- The property of bile salts to lower the surface tension is utilized in this test .
- Fresh urine at room temperature taken in a conical glass tube is sprinkled on the surface particles of sulphur.
- If bile salts are present, sulphur particles sink to the bottom because of lowering of surface tension by bile salts.
- If sulphur particles remain on the surface of urine, bile salts are absent.
- Thymol (used as a preservative) gives false positive test.

Hay's Sulphur Powder Test for urinary bile salts detection in Jaundice

Test for Bile salts

In the control, sulphur powder remains immiscible with the underlying liquid. In the positive test, the sulphur powder sinks to the bottom.

Interpretation: Bile salts and bile pigments are present in urine in obstructive jaundice.

Control for comparison

Positive test

Van der Bergh Test : Liver Function Tests based upon Bile Pigment Metabolism

- Serum + Van der Bergh reagent →violet complex → Direct bilirubin / Conjugated bilirubin =[A]
- Serum + Alcohol *+ Van der Bergh reagent →violet complex → Direct + Indirect bilirubin = Total bilirubin= [B]
- *Alcohol solubilizes proteins of free /indirect bilirubin
- Total bilirubin [B] - Conjugated bilirubin [A]= Indirect bilirubin

Mechanism of Van der Bergh Tests

Van den Bergh Test for Bilirubin

- It is a specific test for for identificaion of increased serum bilirubin levels.
- Normal serum gives a negative van den Bergh reaction.
- Mechanism of the reaction:

Van den Bergh reagent is a mixture of equal volumes of sulfanilic acid (in dilute HCl)& sodium nitrite.

- Principle:

Diazotised sulfanilic acid reacts with bilirubin to form a purple coloured azobilirubin.

- Direct and indirect reactions:

Unconjugated Bilirubin is insoluble in water while the conjugated bilirubin is soluble.

Van der Bergh Tests: Liver Function Tests based upon Bile Pigment Metabolism in serum

Van den Bergh reaction

1-This is a reaction between **bilirubin and Ehrlich diazo reagent** giving a **reddish purple** compound.

2- **Conjugated bilirubin** reacts directly with the reagent. Thus it is called: **direct bilirubin**

3- **Unconjugated bilirubin** does not react with the reagent directly except after addition of methyl alcohol. Thus it may be called: **indirect bilirubin**

Van der Bergh Test results

Plasma Bilirubin

- Normal plasma bilirubin: 0.2–0.8 mg/dl.
- Unconjugated bilirubin: 0.2–0.6 mg/dl.
- Conjugated bilirubin: 0–0.2 mg/dl.
- If the plasma bilirubin level exceeds 1mg/dl, the condition is called hyperbilirubinemia.
- Levels between 1 & 2 mg/dl are indicative of latent jaundice.

Comparison of Direct and Indirect Bilirubin

Parameter	Direct Bilirubin	Indirect Bilirubin
Normal serum Bilirubin concentration (physiological)	(0 - 0.4 mg %)	0.2- 0.8 mg %
Significant increase in serum Bilirubin levels observed in	Obstructive jaundice	Hemolytic &Hepatic jaundice Hepatitis

Comparison of Free Bilirubin and Conjugated Bilirubin

	Free Bilirubin	Conjugated Bilirubin
1.	Bilirubin + Albumin	Bilirubin + Glucuronides
2 .	water insoluble	water insoluble
3.	cannot be filtered	filtered at glomerulus
4.	Indirect reaction with Diazo reagent	Direct reaction with Diazo reagent
5.	Increased concentration in hemolytic jaundice	Increased concentration in hepatic /obstructive jaundice

Direct and indirect bilirubin in differentiation of Jaundice

- **Indirect positive** - **Hemolytic jaundice**
- **Direct positive** - **Obstructive jaundice**
- **Biphasic** - **Hepatic jaundice**
- **Bilirubin in urine:**
- **The conjugated bilirubin, being water soluble, is excreted in urine.**
- **Unconjugated bilirubin is not excreted.**
- **Bilirubin in urine can be detected by Fouchet's test or Gmelin's test.**

Gmelin's and Fouchet's test in urine : Liver function tests based upon bile pigment metabolism

- Type of Urinary bilirubin is a conjugated bilirubin.

1. **Gmelin's test :**

Urine in Kahn's tube layer it with conc HNO_3 → rock the test tube to achieve maximum contact between two layers→ play of colors at junction of two layers (**yellow –bilirubin** /green –biliverdin /red –bilifushchin / violet - bilicyanin)

2. **Fouchet's test:**

Urine + Barium chloride + Magnesium sulphate → bile pigments adsorbed on Barium sulphate →filter sing Whatman's filter paper →add Fouchet's reagent * →pista green color

* Trichloro acetic acid of Fouchet's *reagent causes de-adsorption of bilirubin from Magnesium sulphate & Ferric chloride – oxidizes **bilirubin** into **biliverdin** .

Interpretation of Fouchet's test

Fouchet's Test

- Bilirubin in urine implies increased serum direct bilirubin and excludes hemolysis as the cause

- Bile pigments adhere to the precipitate of barium sulphate.

- On addition of Fouchet's reagent, ferric chloride in the presence of trichloroacetic acid oxidises yellow colour bilirubin to green colour biliverdin and blue coloured cyanobilirubin forming pista green colour.

Gmelin's test in urine : Liver function test based upon bile pigment metabolism

Tests for bile pigments

74

2) Gmelin's test

Principle: Nitric acid oxidizes Bilirubin to Biliverdin giving different colors from green to violet.

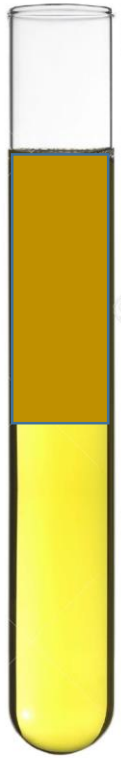
Procedure: To about 5 ml of concentrated HNO_3 in a test tube, add an equal volume of urine carefully so that the two liquids do not mix.

At the junction of two liquids **various colored rings (Green, blue, red, violet** etc.) will be formed.

Bilirubin –yellow ,Biliverdin –green ,Bilifuschin –Red , Bilicyanin -violet

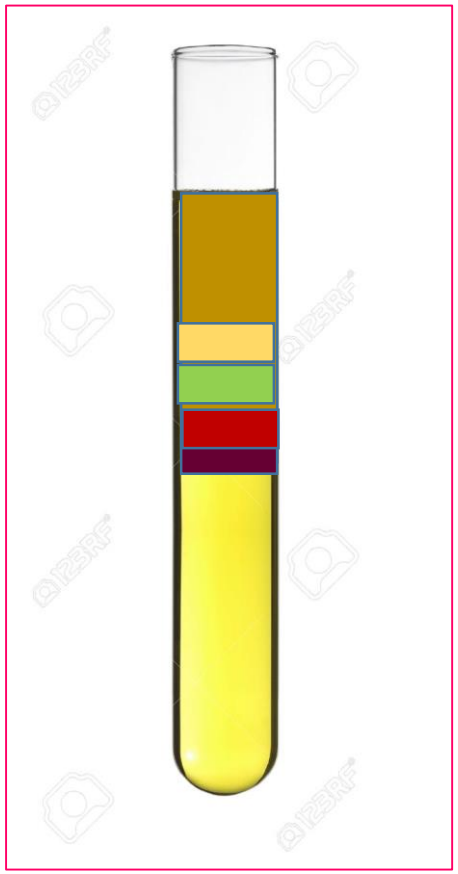
Gmelin's test in urine : Liver function test based upon bile pigment metabolism

Gmelin's Test



← URINE→

← CONC HNO_3→



Bilirubin –yellow ,Biliverdin –green ,Bilifuschin –Red , Bilicyanin -violet

Fouchet's test in urine : Liver function test based upon bile pigment metabolism

Urine analysis – Chemical Characteristics

Abnormal Constituent	Name of the Test	Associated Clinical Conditions	Characteristics
Bile salts	Hay's test	Viral hepatitis Alcoholic hepatitis Toxic hepatitis Drug induced hepatitis Obstructive jaundice	
Bile pigments	Fouchet's test	pista green color→	

Ehrlich's test : Liver function tests based upon bile pigment metabolism

❑**Synthesis of urobilinogen in human body:**

Bilirubin

↓ reduction (intestinal bacteria)

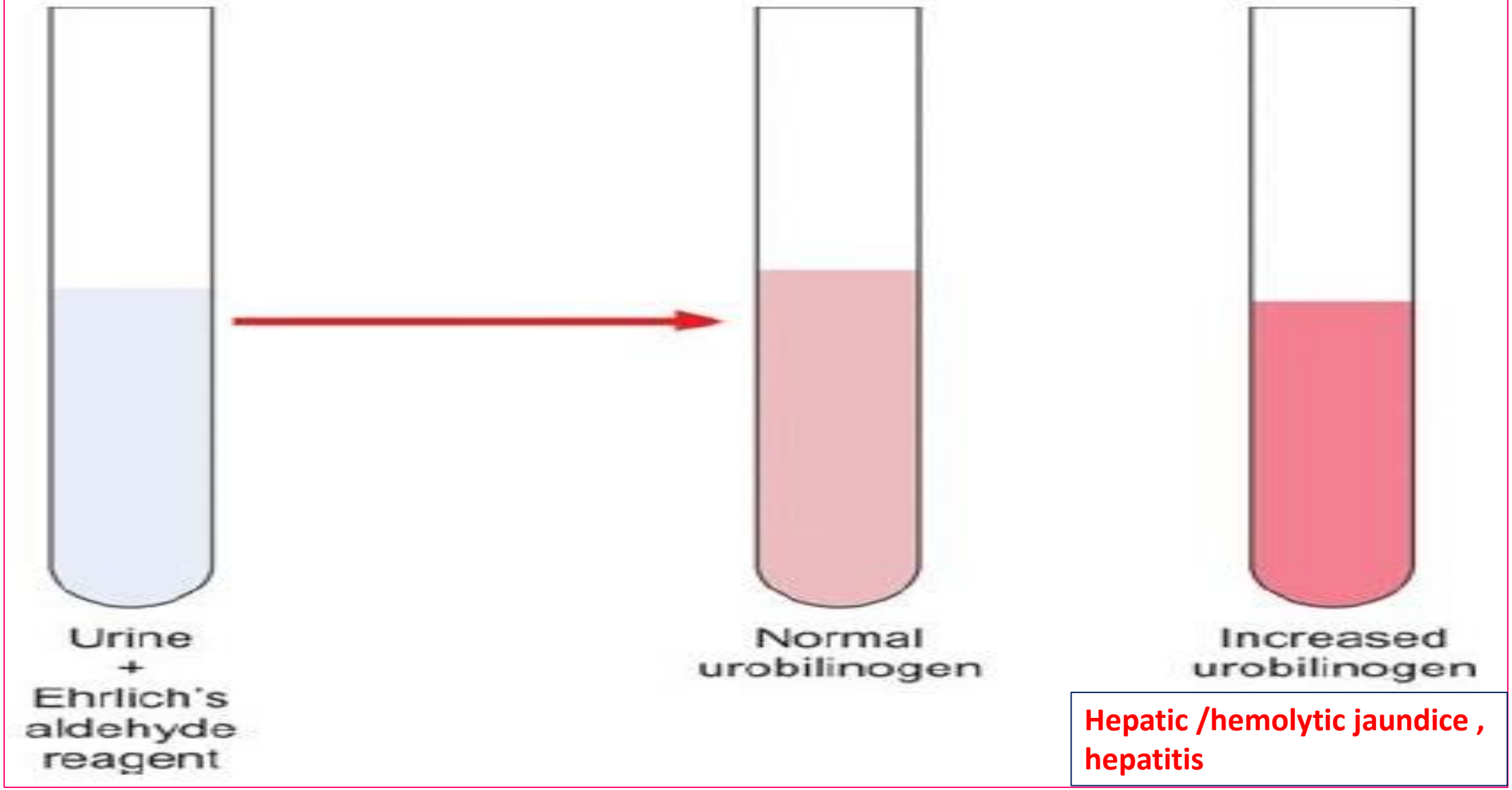
Urobilinogen

❑Ehrlich's test for Urobilinogen detection :

Urine +Dimethyl amino benzaldehyde →pink color

Ehrlich's test results	Interpretation
Faint pink	Normal
No red color	Obstructive jaundice
District red color	Hepatic /hemolytic jaundice ,hepatitis

Ehrlich's test : Liver function tests based upon bile pigment metabolism



Hepatic /hemolytic jaundice , hepatitis

Ehrlich's reagent for Urobilinogen detection :

Urobilinogen

- Test- ehrlich test

  In 5 ml of urine add 0.5 ml of Ehrlich's reagent(HCl 20 ml, d/w 80 ml, p-dimethylaminobenzaldehyde 2 gm). Allow to stand for 5 min. development of pink colour indicates +test.

- Causes-hemolytic jaundice, early hepatitis, hepatocellular jaundice.

Principle of Ehrlich's test for Urobilinogen detection :

Test for Urobilinogen

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Ehrlich's test

Principle: The test for urobilinogen is based on the Ehrlich Aldehyde Reaction.

P-dimethylaminobenzaldehyde in an acid medium with a color enhancer reacts with urobilinogen to form a pink-red color.

The optimum temperature for testing is 22° - 26°C.

Ehrlich's test for fecal Urobilinogen detection

Fecal urobilinogen - Normal about 300mg.

Increased in Hemolytic jaundice in which color of feces is dark.

In Obstructive jaundice urobilinogen is not excreted through feces and the color is the feces is pale.

Schlesinger's test : Liver function test based upon bile pigment metabolism

❖Synthesis of urobilin in human body

Urobilinogen

↓ auto oxidation

Urobilin

❖Schlesinger's test for Urobilin detection:

1.Zinc acetate +alcohol → mix

2. Urine + iodine → mix

①+② →filter →**green fluorescence**

Schlesinger's test results	Interpretation
No green fluorescence	Obstructive jaundice
green fluorescence	Hemolytic jaundice

Icteric index :Liver function test based upon bile pigment metabolism

Icteric index

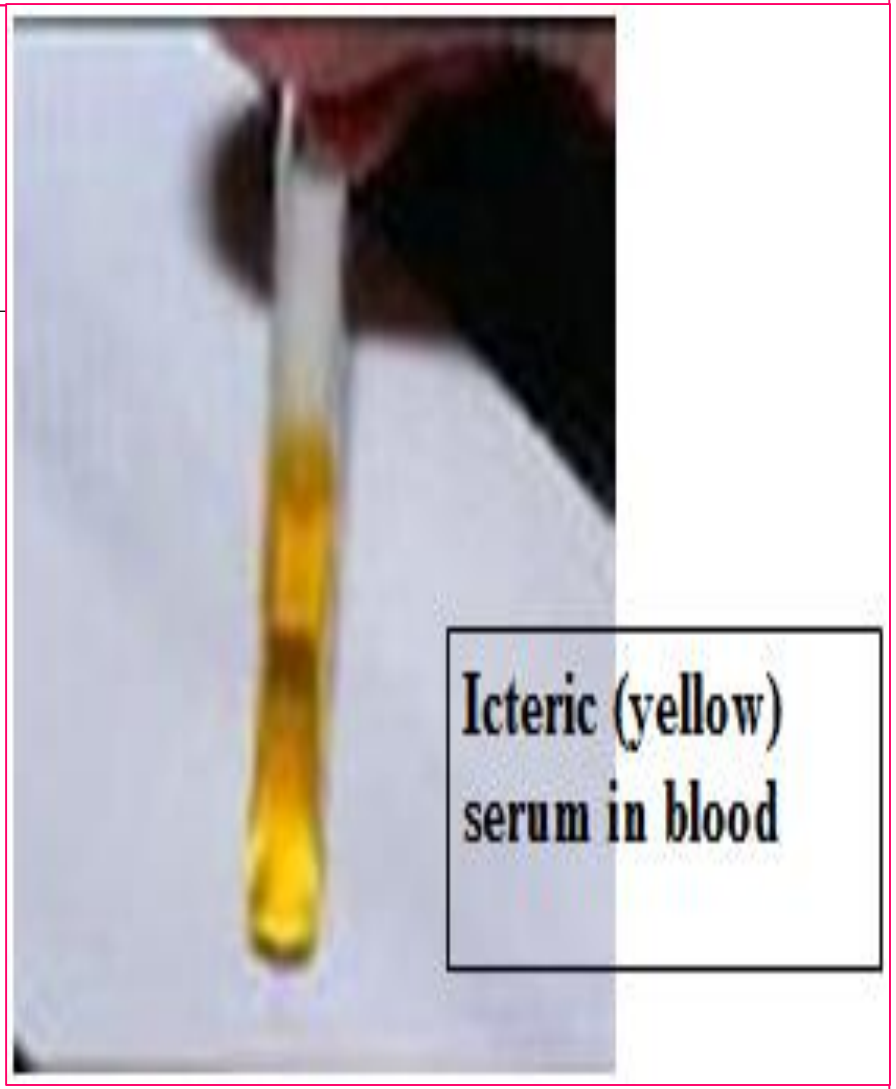
Potassium dichromate solution (0.01 %)

$$\text{Icteric index} = \frac{\text{volume of diluted serum}}{\text{volume of serum used}}$$

Normal value = 1-6 units

Latent jaundice =6 -14 units

Clinical jaundice = > 15 units



Icteric index :Liver function test based upon bile pigment metabolism

รูปที่ 2 icteric serum

Icteric serum
(Bilirubin concentration)

1+ = 2.5 mg/dl

2+ = 5.0 mg/dl

3+ = 10.0 mg/dl

4+ = 20.0 mg/dl

Jaundice

Jaundice : An approach.

Jaundice

- **Jaundice :**Yellowish tint to body tissue(sclera ,skin , and mucus membrane) because of increased bilirubin content in extra –cellular fluid (total serum bilirubin > 2 mg %)

❖**Causes** of **Jaundice**

1. increased destruction of RBC with rapid release into blood: hemolytic Jaundice/pre hepatic Jaundice/retention jaundice – characterized by elevated levels of plasma unconjugated bilirubin

2. obstruction of bile duct :obstructive (post hepatic Jaundice)/regurgitation jaundice -characterized by elevated levels of plasma conjugated bilirubin

3. dysfunction of liver cells : hepatic Jaundice

4. Physiological : Physiological neonatal Jaundice

Hemolytic /Pre hepatic /Retention jaundice

❖Hemolytic /Pre hepatic /Retention jaundice - characterized by elevated levels of plasma unconjugated bilirubin

- Unconjugated bilirubin : protein bound and water insoluble ,it is not excreted in the urine therefore referred as acholuric jaundice.

❖**Causes of Hemolytic /Pre hepatic /Retention jaundice :**

1. Hemolytic /Pre hepatic jaundice
2. Defective hepatic uptake of bilirubin
3. Decreased conjugation of bilirubin
4. Neonatal (physiological) jaundice

Decreased conjugation of bilirubin

❖Decreased conjugation of bilirubin due to :

1. Decrease in functioning live cell mass as in chronic hepatitis and cirrhosis
2. Defect in conjugation of bilirubin as in familial unconjugated hyperbilirubinemia such as:

a) Crigler- Najjar syndrome in which there is complete absence (type I) or deficiency (type II) of UDP glucuronyl transferase activity. Plasma bilirubin levels are less than 20mg/dL (345 μmols /L) in type I but do not exceed 20mg/dL (345 μmols /L)in type II. Phenobarbital administration is effective in type II but not in type I .

b) Gilbert syndrome , a common form of familial jaundice in which Plasma bilirubin levels are between 1.2 and 2.5mg/dL (20- 40 μmols /L) due to defective hepatic uptake and conjugation of bilirubin.

c) Acquired deficiency of UDP glucuronyl activity due to :

i. Hypothyroidism ,which delays maturation of this enzymes

ii. Drugs such as novobiocin that inhibits UDP glucuronyl transferase activity

iii. Presence of pregnane -3 β-20α diol ,an inhibitor of UDP glucuronyl transferase in breast (breast milk jaundice)

Hemolytic /Pre hepatic jaundice

❖Hemolytic /Pre hepatic jaundice: excessive hemolysis with overproduction of bilirubin occurs in :

1. Congenital erythrocyte abnormalities (e.g. hemoglobinopathies- ,sickle cell anemia , glucose -6 phosphate dehydrogenase –G6PD deficiency)
2. Ineffective erythropoiesis (e.g. pernicious anemia)
3. Incompatible blood transfusion
4. Infections by hemolytic organisms such as plasmodium species- (causative agent for malaria)
5. Drugs (e.g. Sulphonamide ,salicylates)that displace bilirubin from plasma albumin

Defective hepatic uptake of bilirubin

- Defective hepatic uptake of bilirubin due to :

1. Sepsis
2. Prolonged fasting
3. Drugs such as flavaspidic acids seed in treatment of tapeworm infestation that compete with bilirubin for binding to ligandin .

Obstructive/ post hepatic /regurgitation jaundice

- Obstructive / post hepatic / regurgitation jaundice): is characterized by increase in plasma conjugated bilirubin and appearance of bilirubin in urine (choleric jaundice).
- Amount of bilirubin entering in the intestine is reduced→ decreased formation of urobilin → pale stools

Causes of Obstructive/ post hepatic /regurgitation jaundice

❖ **Causes of Obstructive/ post hepatic /regurgitation jaundice include :**

1. Impaired hepatic excretion of bilirubin
2. Cholestasis (Obstruction to bile flow)

Impaired hepatic excretion of bilirubin

❖Impaired hepatic excretion of bilirubin is observed in :

- Extensive liver cell damage as in hepatitis and cirrhosis with impaired in uptake ,conjugation and excretion of bilirubin. Plasma bilirubin dose not exceed 20 mg/ dL (345 μmol/L).Plasma ALP activity is normal ,while AST and ALT raised . Cholelithiasis is present and prothrombin time is prolonged.
- Familial conjugated hyperbilirunaemia such as **Dubin-Johnson syndrome** in which conjugation of bilirubin is normal but hepatic secretion of conjugated bilirubin into the bile is defective . The condition is associated with accumulation of brown pigment with staining properties of lipofuscin and abnormal coproporphyrin excretion.

Cholestasis

❖Cholestasis (Obstruction to bile flow) that may be

- Intrahepatic Cholestasis due to impaired bile secretion from hepatocytes into the bile canaliculi caused by

1. Drugs(chlorpromazine ,oral contraceptive ,methyltestosterone)
2. Alcohol
3. Primary biliary cirrhosis
4. inflammation of biliary tract
5. Carcinoma of the bile duct
6. Cystic fibrosis

- Extrahepatic Cholestasis due to

a) Congenital atresia of main bile ducts
b) bile duct stricture after surgery
c) Gallstones in the common bile duct or Ampulla of Vater
d) Carcinoma of head of the pancreas

Characteristics of cholelithiasis

- Obstruction to bile flow referred to as **cholestasis.**
- Cholestasis (Obstruction to bile flow) is characterized by :

1. Increase in ALP activity
2. High plasma bilirubin levels of 50 mg/dl (862 μmols /L)
3. Prothrombin deficiency and hemorrhage due to malabsorption of vitamin K
4. Hypercholesterolemia due to deceased cholesterol excretion in bile

Direct and indirect bilirubin in differentiation of Jaundice

- **Indirect positive** - **Hemolytic jaundice**
- **Direct positive** - **Obstructive jaundice**
- **Biphasic** - **Hepatic jaundice**
- **Bilirubin in urine:**
- **The conjugated bilirubin, being water soluble, is excreted in urine.**
- **Unconjugated bilirubin is not excreted.**
- **Bilirubin in urine can be detected by Fouchet's test or Gmelin's test.**

Physiological (neonatal) jaundice

❖**Physiological jaundice** (neonatal jaundice):is characterized by excessive hemolysis combined with an immature hepatic system for uptake ,conjugation, and secretion of bilirubin.

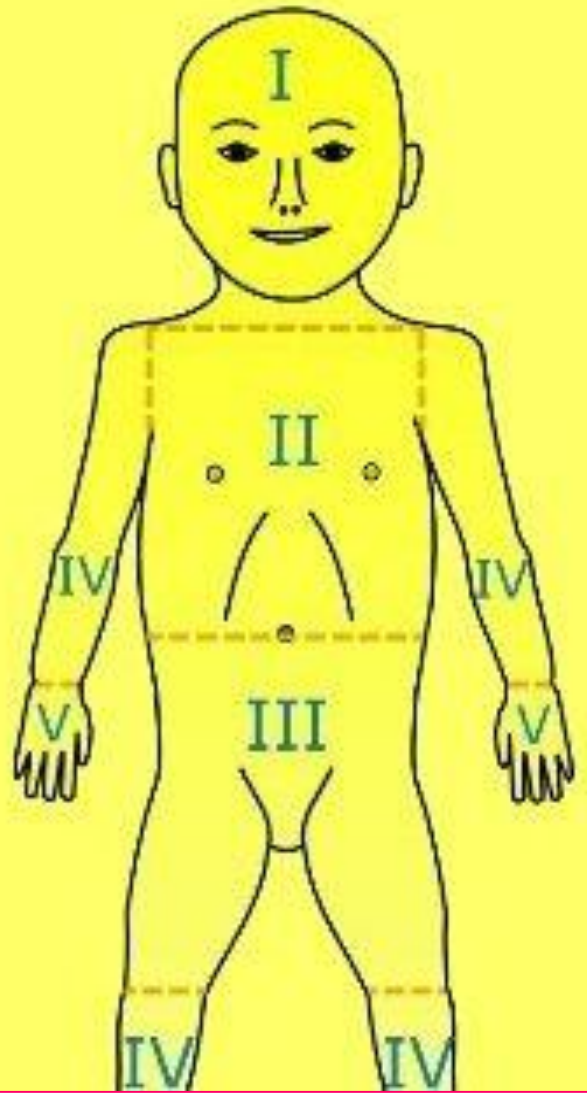
❖ develops within 48hrs.

❖**Causes** of **Physiological jaundice** :

1. Enzyme system involved in conjugation of bilirubin (UDP glucuronyl transferase) is lacking /defective.
2. Destruction of excessive fetal hemoglobin→ increase in plasma unconjugated bilirubin (30 mg/dL-517 μmols /L) that can penetrate the blood –brain barrier, leading to hyper bilirubinemic toxic encephalopathy (kernicterus) eventually leading to brain damage or death.

➢Condition can be treated by phenobarbital administration or by exposure to visible light which promotes hepatic excretion of unconjugated bilirubin.

Physiological verses pathological jaundice

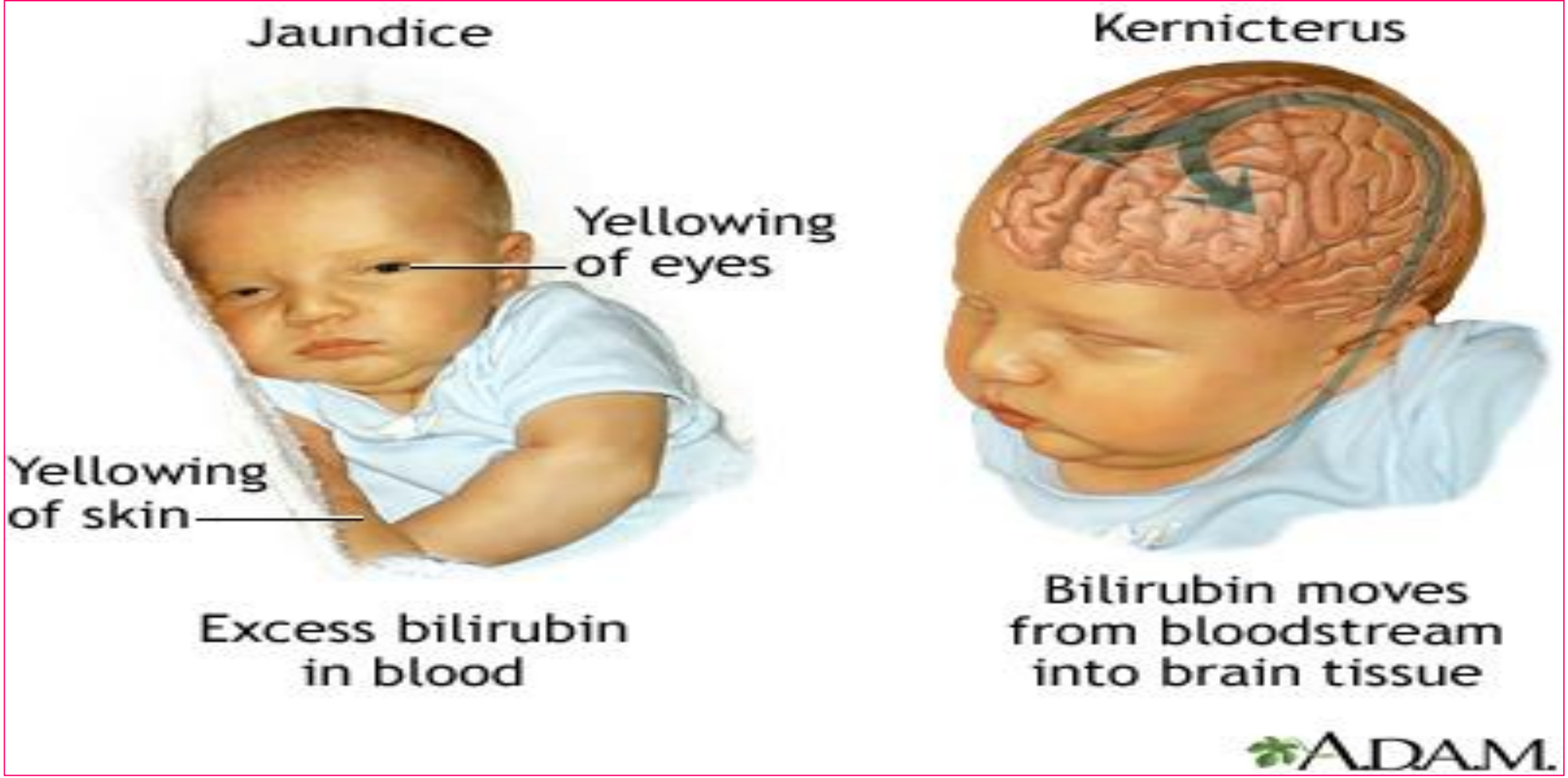


	PHYSIOLOGICAL	PATHOLOGICAL
STARTS @	After 4 days	1st or 2nd Day
BILIRUBIN	< 20mg/dl	> 20mg/dl
KERNICTERUS	Rare	Common
RESOLVES	Early	Late

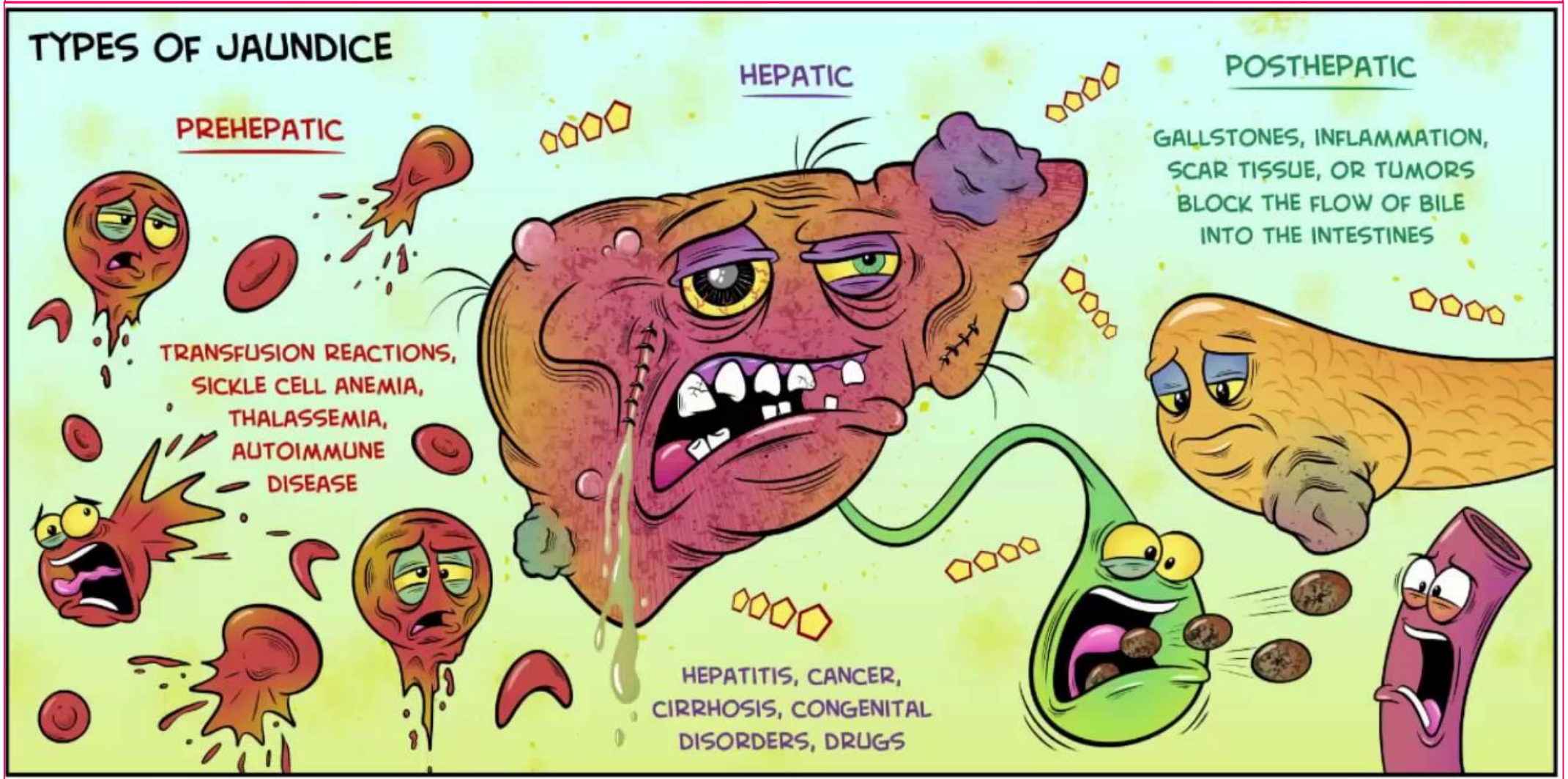
Comparison of physiological and pathological neonatal jaundice

PHYSIOLOGICAL NEONATAL JAUNDICE	PATHOLOGICAL NEONATAL JAUNDICE
Appears after 24 hours.	Appears within 24 hours.
Increase bilirubin < 5mg/dl	Increase bilirubin > 5mg/dL per day at the rate of 0.2mg/dL per hour
Clinically not detectable after 14 days.	Jaundice persist after 14 days.
Disappears without treatment.	Need treatment according to the cause.

Physiological jaundice



Causes of Jaundice



Comparison of types of Jaundice

	Hemolytic /prehepatic jaundice	Hepatic (hepatocellular) jaundice	Obstructive jaundice
Causes	**hemolysis of RBC** –drugs and toxins ,malaria ,incompatible blood transfusion , hemoglobinopathies, antibodies ,Gilbert or CN Syndrome	**hepatic cells affected** –infection ,viral hepatitis, toxin ,liver poison/toxic hepatitis ,intrahepatic cholestasis	**obstruction to flow of bile-** gallstones ,tumors ,strictures ,narrowing of bile duct as a result of surgery/carcinoma of pancreas , extrahepatic cholestasis
Liver function	**Normal**	**Abnormal**	**Normal**
Serum Bilirubin (Van Der Bergh Test)	free or unconjugated bilirubin increased /indirect positive (2-5 mg %)	conjugated/direct or unconjugated-biphasic Positive (50 mg%)	conjugated/direct positive (20 mg%)
Fouchet 's test (urine bilirubin)	Negative	Positive (+)	Positive (+ + +)
Urobilinogen (urine) (Ehrlich test)	Increased /positive	Increased /normal	Negative /clay color stool
Urobilin (Urine) Schlesinger Test)	increased/positive	varied	negative
Bile Salts (Urine) Hay's Test	negative	positive (+)	positive (+ +)

Comparison of retention and regurgitation Jaundice

	Hemolytic /prehepatic /retention jaundice	Obstructive/ post hepatic /regurgitation jaundice
Serum Bilirubin (Van Der Bergh Test)	free or unconjugated bilirubin increased /indirect positive (2-5 mg %)	Conjugated bilirubin/direct positive (20 mg%)
Total Serum Bilirubin	Increased	Increased
unconjugated bilirubin	Increased	-
Conjugated bilirubin	-	Increased
Fouchet 's test (urine bilirubin)	Negative (unconjugated bilirubin bound to albumin is water insoluble and not filtered by glomerulus)	Positive (+++) conjugated bilirubin is water soluble
Urobilinogen (urine) (Ehrlich test)	Increased /positive	Negative /normal in viral hepatitis and cirrhosis .Absent in extrahepatic cholestasis because bilirubin doesn't enter the intestine
Urobilinogen (fecal) (Ehrlich test)	Increased /positive	Low in viral hepatitis and cirrhosis .absent in extrahepatic cholestasis → clay color stool
Urobilin (Urine) Schlesinger Test)	increased/positive	negative
Bile Salts (Urine) Hay's Test	negative	positive (++)present in cholelithiasis

Liver Function Tests based upon Protein Metabolism

- Synthetic function of Liver can be assessed by estimating plasma proteins and prothrombin time.

Liver Functions based upon Protein Metabolism

❖Liver Functions based upon Protein Metabolism:

1. All the plasma proteins except immunoglobulins are synthesized by liver viz albumin ,globulins ,fibrinogen

Serum **albumin** is the most important protein synthesized by liver and reflects the extent of functioning liver cell mass.

Turnover rates of **haptoglobin** and **transferrin** are lesser than albumin therefore **u**sef**u**l to identify recent changes in liver functions.

2. Deamination

3. Transamination

Liver Function Tests Based Upon Protein Metabolism

Plasma protein concentration

1. Plasma albumin ,globulin & fibrinogen concentration
2. Flocculation test
3. Amino acid in blood & urine

Test for blood coagulation

1. Prothrombin time determination

Test for enzyme derived from liver

1. Serum Alkaline phosphatase
2. Serum glutamate oxalate transaminase (SGOT)
3. Serum glutamate pyruvate transaminase (SGPT)
4. Serum isocitrate dehydrogenase
5. Serum Choline esterase
6. Serum 5 ‘ nucleotidase

Determination of glutamine in CSF

Estimation of plasma protein concentration : Liver Function Tests Based Upon Protein Metabolism

1. **Estimation of plasma protein concentration is based on chemical composition:**

A. Peptide bonds:

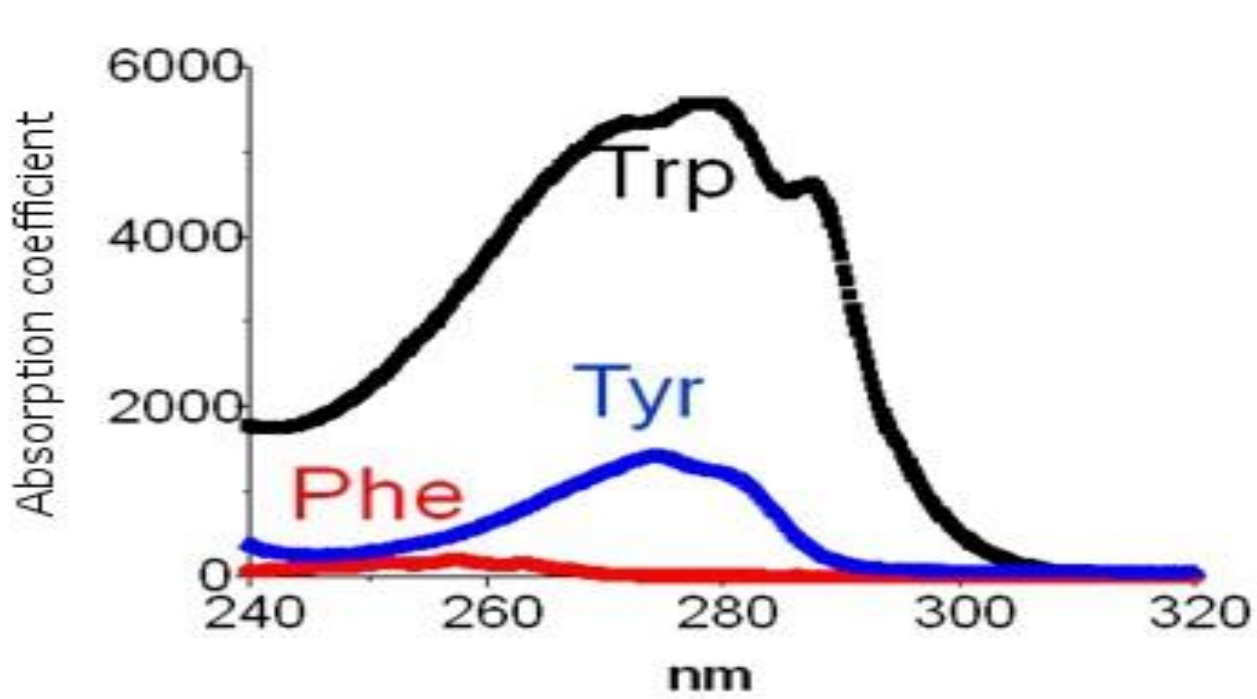
i. Biuret method :–peptide bond of proteins +copper (Cu^{2+}) + alkaline p H – violet color complex

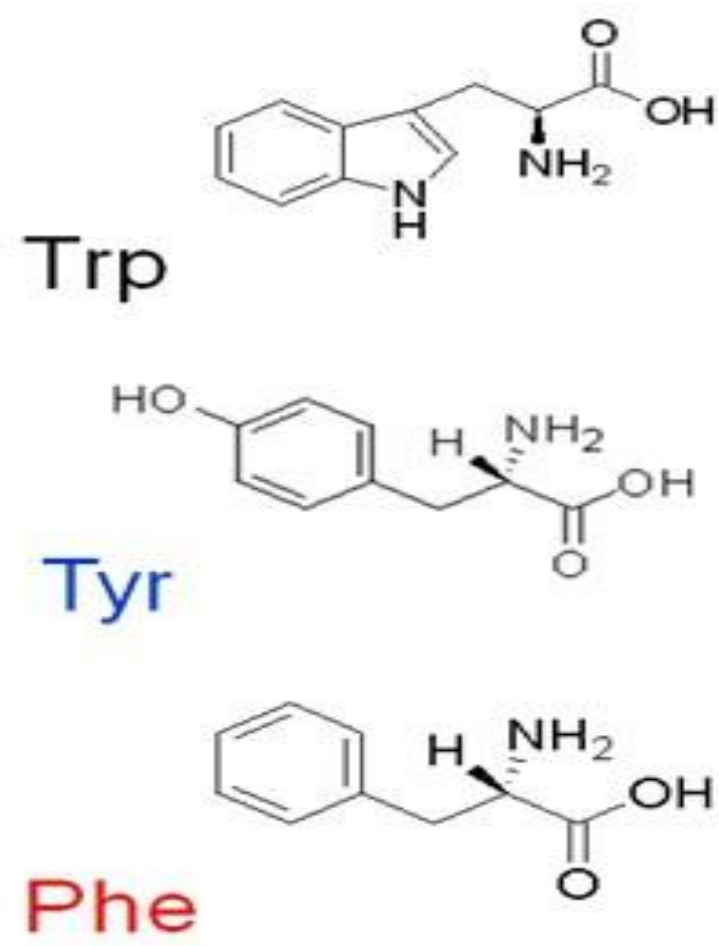
ii. Ultra- violet absorption by peptide bond :Spectrophotometer

micro gram protein = (optical density 215- optical density 225)x144

B. Nitrogen content :weight contribution in protein by nitrogen 16%(kjeldhal method for N content) =weight of protein =N X 6.25

Ultra- violet absorption by peptide bond





Biuret Test :Liver Function Tests Based Upon Protein Metabolism

Tasks and Laboratory Experiments

Proteins

- **Biuret Test**
- The Biuret Reagent is made of sodium hydroxide and copper sulfate. The blue reagent turns violet in the presence of proteins, and the darker the purple color, the more protein is present.

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Serum Proteins in normal and abnormal liver function(dysfunction)

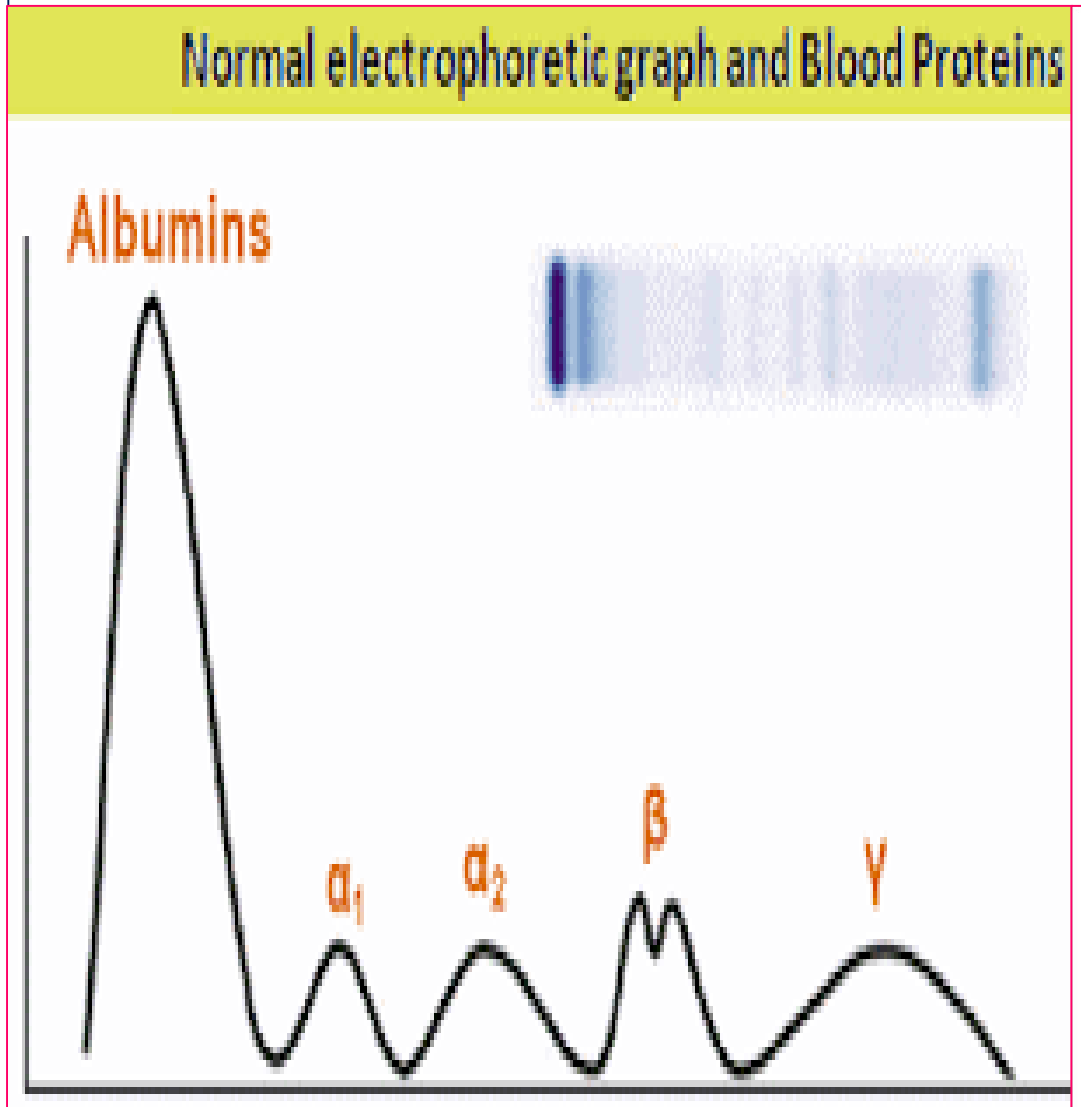
Serum protein type	Concentration (physiological)
Total serum protein	6.5-7.5gm%
Serum albumin	3.5-5gm %
Serum globulin	2.5-3.5gm %
Serum fibrinogen	200-500 mg%
Albumin /globulin(A/G)	2:1 to 1.5: 1

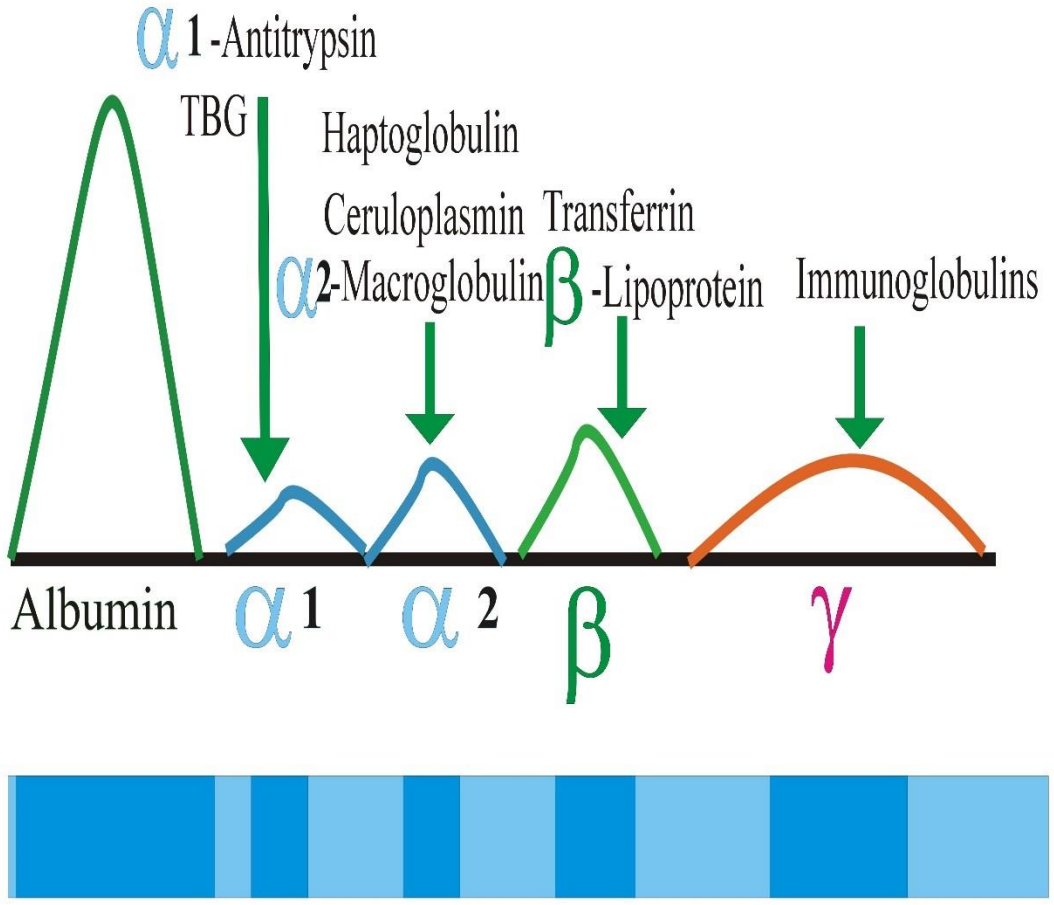
Chronic liver diseases → Serum albumin (half life 20 days) decreases
Cirrhosis → hypoalbuminemia and hyperglobulinemia→ A/G deceases

Normal Serum protein electrophoretic pattern

	Percentage (%)	g /dl
Serum Albumin	55-65	3.5 -.4.7
Serum α 1 globulins	2- 4	0.2 - 0.3
Serum α 2 globulins	6-12	0.4 - 0.9
Beta globulins	8-12	0.5 – 1. 0
Gamma globulins	12-22	0.7 – 1. 5

Protein electrophoretic pattern in normal liver function





Protein electrophoretic pattern in liver dysfunction

Protein electrophoresis

- Cirrhosis :
  - ↓↓albumin,
  - ↓alpha-1,alpha-2 & beta band
  - ↑ polyclonal immunoglobulins: IgG & IgA (beta-gamma bridging pattern)
- Autoimmune hepatitis:
  - -↓ albumin
  - -↑↑ polyclonal IgG
- Primary biliary cirrhosis:
  - -↑ polyclonal IgM

Serum Protein pattern in liver dysfunction

Serum protein type	Pattern in liver diseases
Serum Albumin content	Decreased → edema (< 2.5 gm%)
Serum globulins	increased
fibrinogen	Decreased
A: G ratio	< 1.5 : 1

Abnormal protein electrophoretic patterns in liver diseases

Liver disease	Abnormal protein electrophoretic pattern
Acute hepatitis	Pre albumin reduced
Cirrhosis	Albumin reduced, gamma globulins increased
Hepatocellular disease	Alpha- 1 globulins reduced (parallel to albumin)
Biliary obstruction	Alpha- 2 globulins ,beta globulins increased

The rise in gamma globulins will have wide base ,suggestive of polyclonal gammopathy .

Serum globulins

- Serum globulins : constitute immunoglobulins
- Immunoglobulins : produced by beta lymphocytes
- Alpha and beta globulins : synthesized by hepatocytes
- Gamma globulins in serum : increased in Cirrhosis ,chronic active hepatitis

immunoglobulin	Normal levels serum (mg/dl)
IgG	700- 1600
IgM	40-230
IgA	70-400
IgD	0 -8
IgE	0-3.8 microgram /dl

Serum globulins in **liver diseases**

- Gamma globulins in serum : increased in Cirrhosis ,chronic active hepatitis

Liver disease	Increased levels of serum
Auto immune hepatitis	**IgG**
Primary Biliary Cirrhosis	**IgM**
Alcoholic liver disease	**IgA**

Autoantibodies in Autoimmune hepatic disorders

❖Commonly encountered **Autoantibodies in Autoimmune hepatic disorders are :**

1. Antinuclear antibodies
2. Double stranded DNA
3. smooth muscle (actin) antibodies
4. antimitochondrial antibodies
5. Asialoglycopotein antibodies

Autoantibodies in Autoimmune hepatic disorders

- Auto immune chronic hepatitis is due to defective suppressor T cells leading to synthesis of Autoantibodies against hepatocytes surface antigens .
- High titers of antimitochondrial antibodies are seen in primary biliary cirrhosis.
- Anti smooth muscle antibodies and antinuclear antibodies are seen chronic active hepatitis .
- Increase in globulins (IgM/IgG) → decrease in A:G ratio

LFT in Autoimmune hepatitis

Parameter	Cases not active in state	active /advanced state
Serum bilirubin	Normal	3-10 mg %
Serum Albumin	Normal	Decreased
Serum Globulin	< 2.5 g %	> 2.5 g %
Serum ALP	Normal	Increased
Serum Transaminases	< 100 U /L	100- 1000 U /L
PT	Prolonged	Prolonged
Autoantibodies Auto immune hepatitis	ANA	ANA, smooth muscle antibodies

Flocculation tests as Liver Function Tests based upon Protein Metabolism

PRINCIPLE : The stability of protein in solution (serum) in presence of precipitating agents depend upon A/ G ratio .

1. Thymol turbidity test

Thymol decreases solubility of lipids & dispersion of beta & Gamma globulin

Saturated thymol solution + serum → 30 mins turbidity of test solution is compared with standard solution of concentration 10mg/100ml

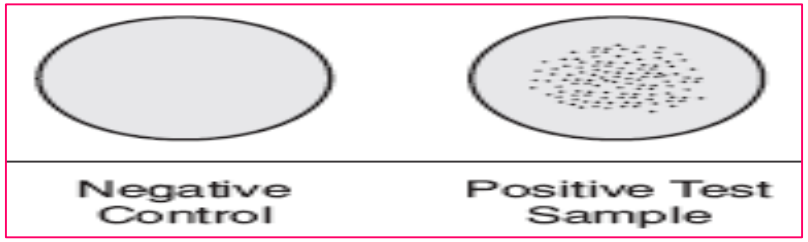
slight turbidity (0-4 units) : observed in normal /obstructive jaundice

Increased turbidity – increased in globulins → observed in infective hepatitis

2. Serum colloidal gold test

3. Serum colloidal test

4. Zinc sulphate test



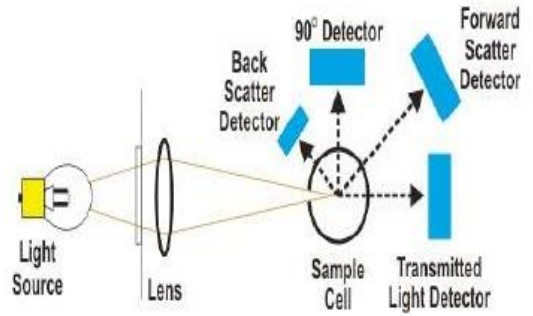
Positive flocculation test suggest increase in gamma globulin & lipoprotein observed in liver diseases ,kala azar ,multiple myeloma

Comparison of Turbidometry and Nephelometry

THEORY

Scattered light may be measured by

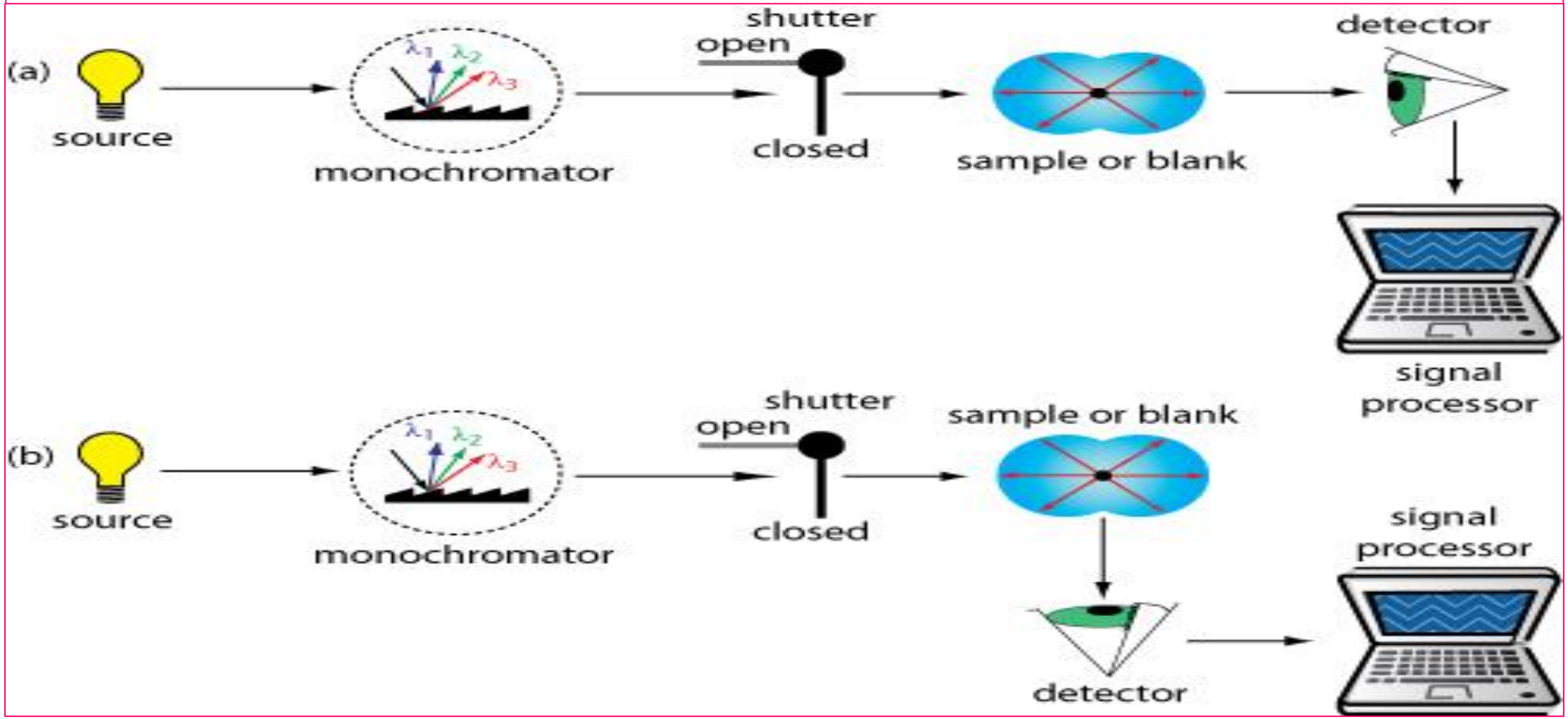
- Turbidimetry
- Nephelometry
- In turbidimetry, the intensity of light transmitted through the medium, the unscattered light, is measured.



DIFFERENCE BETWEEN NEPHELOMETRY AND TURBIDIMETRY

Nephalometry	Turbidimetry
1. Mercury arc lamp	1. Tu / Du lamp is used
2. Rectangular cuvette used	2. Semi octagonal cuvette
3. Scattered light is measured	3. Light transmitted is measured
4. Measured at 90 deg	4. Measured in straight line
5. PMT is detector	5. Photocell is detector

Comparison of Turbidometry and Nephelometry



Prothrombin time as LFT

- Prothrombin time : time required for clotting to take place in citrated plasma in which optimum quantity of thromboplastin & calcium have been added. (Principle of assay → Blood Clotting (Morawitz Theory)
- Prothrombin time increases in hepatic & obstructive jaundice .

Blood Clotting (Morawitz Theory)

Prothrombin

↓ CALCIUM ,THROMBOPLASTIN, FACTOR V ,VII,X, VIT K

Thrombin

↓

Fibrinogen →→ Fibrin (Clot)

Test procedure of **Prothrombin time** (PT)

❖Test procedure of **Prothrombin time** – (PT)

0.1 ml plasma + 0.1ml Thromboplastin + .025 M CaCl2→ mix and incubate at 37^0 C→ Clot formation

❖Interpretation of test results :

a. Normal range for prothrombin time → 11- 14 sec
b. Hepatitis : >14 sec
c. Obstructive jaundice : increased (reversed by parenteral administration of vitamin K . Unavailability of bile salts →decreased absorption of vitamin K → decreased prothrombin synthesis→ prolonged Prothrombin time

❑**Prothrombin Index=** PT of control/PT OF PATEINTS X100 =70-100%

Interpretation of Prothrombin time as LFT

Prothrombin :

1. **synthesized by liver**
2. **Half life 6 hrs. therefore indicates present function of liver**
3. **Prolonged Prothrombin time: only when liver loses 80 % of its reserve capacity.**

PROTHROMBIN TIME

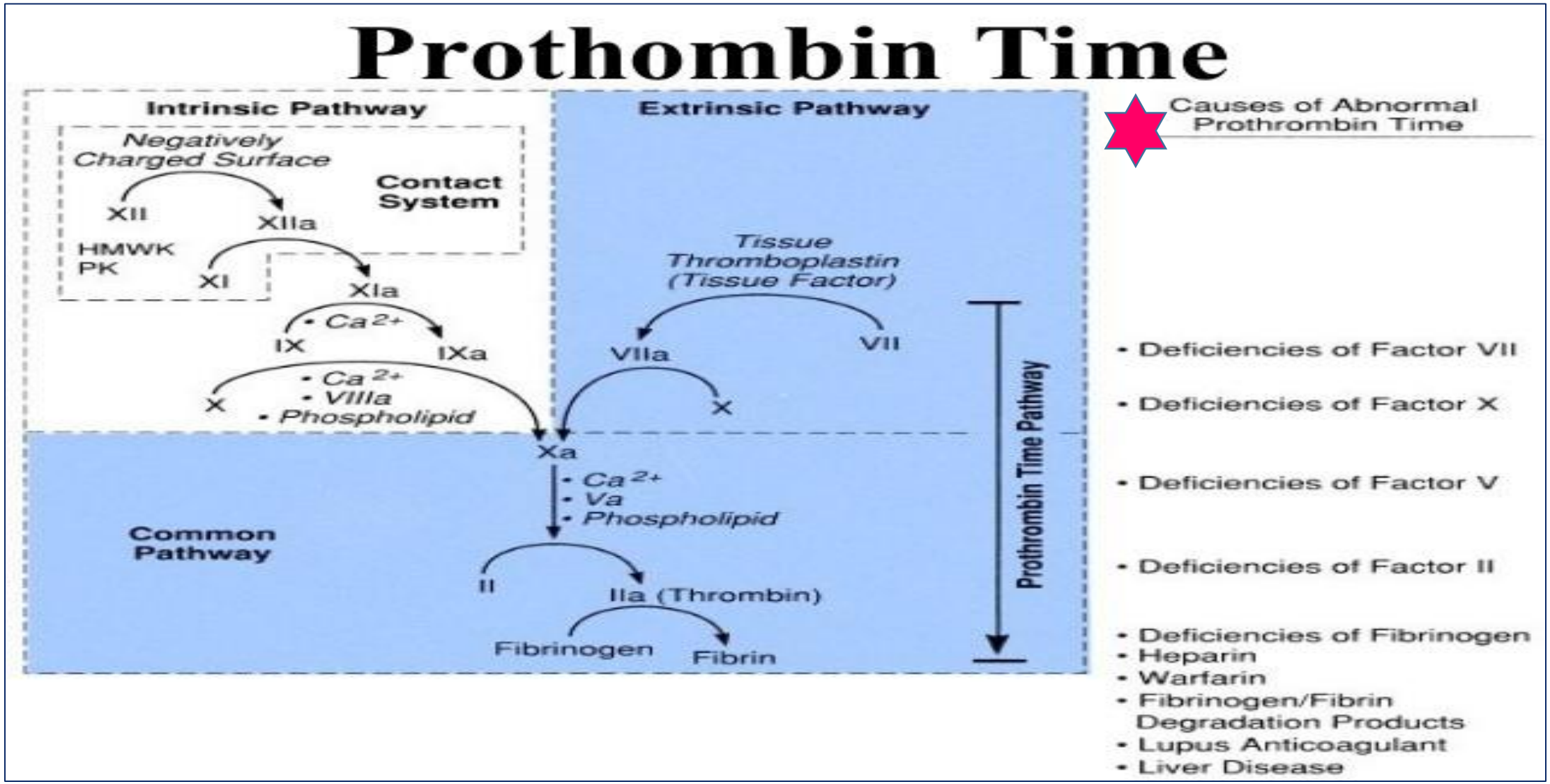
- Measures Effectiveness of the Extrinsic Pathway

NORMAL VALUE

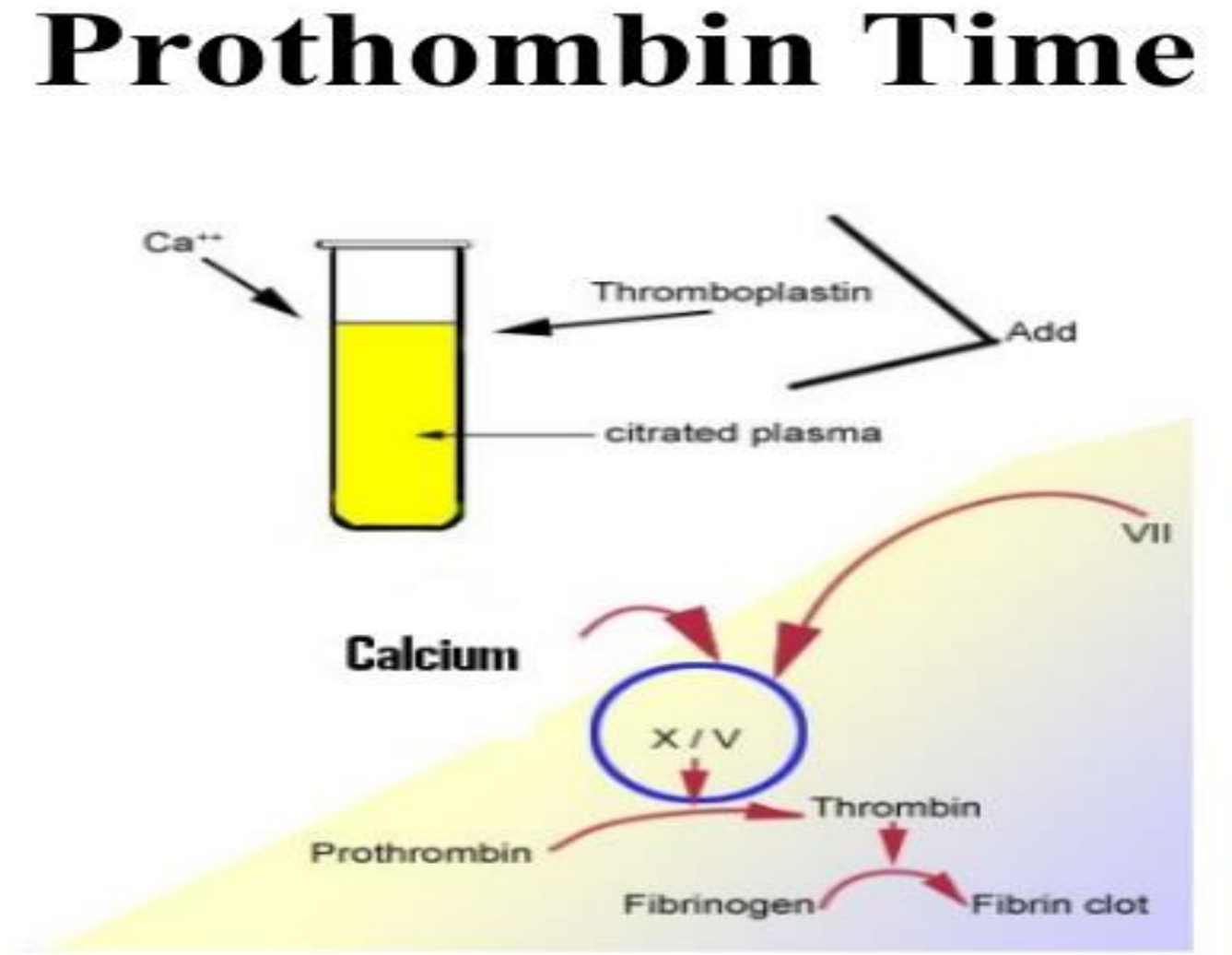
10-15 SECS

11-16 sec depends.....

Blood Clotting



Prothrombin time as LFT



Comparison of Prothrombin time of Hepatic verses Obstructive Jaundice

Hepatic jaundice	Obstructive jaundice
1.Liver cell damaged	Liver cell normal
2. Lack of synthesis of Prothrombin , factor VII ,IX ,X is due to hepatocyte damage	Lack of synthesis of prothrombin is due to unavailability of vitamin K
3. **Prolonged Prothrombin time:** Reversed by VITAMIN K parenteral administration	**Prolonged Prothrombin time** :Cannot be reversed by VITAMIN K supplementation

Enzymes in liver diseases

- **Enzymes in liver diseases are classified into two groups:**

1. Those indicating hepatocellular damage → increase in functional plasma enzymes & decrease in non functional plasma enzymes
2. Those indicating cholestasis (obstruction)

Enzymes in liver diseases-increase in functional plasma enzymes &

Functional plasma enzyme	Normal concentration
SGPT/ALT/Alanine amino transferase	10 -35 IU /L
SGOT/AST/Aspartate amino transferase	< 35 IU /L
Alkaline phosphatase	40- 125 IU /L
5’ Nucleotidase	2 -10 IU /L

Non -Functional plasma enzyme –Choline esterase: 40-80 U /L

Enzymes in liver diseases: SGPT and SGOT

- SGPT : increases in liver diseases (also in muscle & kidney diseases) ,infective hepatitis , primary & secondary hepatic cancer ,obstructive jaundice (200 -300 IU / l)
- Myocardial infarction : 2-20 fold increase in SGOT

❑Principle of SGPT and SGOT assay :

- Alpha Keto Glutarate + L –Alanine → L –Glutamate +Pyruvate
- Alpha Keto Glutarate + L –Aspartate → L –Glutamate + OAA(→ Pyruvate)
- Amount of Pyruvate α Enzyme concentration
- Pyruvate + DNPH (Dinitrophenyl Hydrazine) →Hydrozone of Pyruvic Acid

❖Sustained increase in plasma transaminases for more than 6 months indicates chronic liver disease .

SGPT in liver diseases

❖SGPT **in liver diseases :**

- Acute hepatitis : > 1000 units
- Hepatic diseases :Elevation in SGPT is more than SGOT
- The degree of elevation in SGPT reflects the extent of hepatocellular damage.
- Lowering of transaminases indicate recovery ,but sudden fall from very high may indicate poor prognosis
- Alcoholic liver disease : SGOT > SGPT , SGOT : SGPT ratio >2,mild elevation in SGPT

SGOT : SGPT ratio

SGOT : SGPT ratio > 2
Alcoholic hepatitis
Hepatitis with cirrhosis
Non alcoholic steatohepatitis (NASH)
Liver metastasis
Myocardial infarction
Erythromycin treatment

Low SGOT : SGPT ratio (higher ALT)
Acute hepatocellular injury
Toxic exposure
Extrahepatic obstruction(cholestasis)

Liver diseases and Transaminases

Liver diseases	Transaminases
Parenchymal liver cell damage	Plasma ALT and AST increased
Viral /toxic hepatitis	Plasma ALT and AST increased (increase in ALT > AST –where the cytoplasm sustains major damage)
Cirrhosis	increase in Plasma AST > ALT (where the cytoplasm and mitochondrial membrane are damaged)
Chronic active hepatitis	ALT and AST normal or slight increased
Cholestasis*	Plasma ALT and AST slight increased
Alcoholic hepatitis	Plasma ALT :AST ratio reversed

Cholestasis* : ALP and GGT increased

Alkaline Phosphatase in Obstructive liver disease

❑**Alkaline Phosphatase(ALP) :**

1. **is a maker of** Obstructive **liver disease.**
2. Bile duct Obstruction induces synthesis of Alkaline Phosphatase by biliary tract epithelial cells
3. Significant elevation in serum Alkaline Phosphatase → suggestive of cholestasis / hepatic carcinoma/hepatitis with inflammatory edema producing obstruction/primary biliary cirrhosis .
4. Progressive increase in ALP is characteristic of malignancy.
5. has 6 isoenzymes.
6. hepatic isoenzyme originates from lining of the bile canaliculi and sinusoidal surfaces of hepatocytes .
7. Regan isoenzyme : or carcinoplacental isoenzyme : a isoenzyme closely resembling placental form is seen in 15% cases of hepatic carcinoma (also seen in lung /intestinal carcinoma).

Enzymes in liver diseases : Alkaline Phosphatase

❑ **Alkaline Phosphatase activity** (ALP) **:** Hydrolysis of monophospharic ester for calcification of bone (increase in synthesis of alkaline Phosphatase in liver diseases)

❑**Principle of Alkaline Phosphatase estimation King & Armstrong Method:**

Disodium Phenyl Phosphate + Serum Alkaline Phosphatase (pH 10) → Phenol + Inorganic Phosphate

Phenol + Amino Antipyrine → **Brown Color** (α conc. of ALP)

❑**Interpretation of Alkaline Phosphatase estimation King & Armstrong Method:**

- Normal Range Serum Alkaline Phosphatase : 3-13 KA
- INCREASED Serum Alkaline Phosphatase : Obstructive Jaundice > Hepatitis
- Hepatoma → INCREASED Serum Alkaline Phosphatase ,impaired BSP , normal conjugated bilirubin

Gamma Glutamyl Transferase: Enzymes in liver diseases

❖**Gamma Glutamyl Transferase** (GGT)= **Gamma Glutamyl Transpeptidase : transfers Gamma Glutamyl residues to substrate . (e.g. Synthesis of Glutathione in human body**)

❖GGT is predominately located in the endoplasmic reticulum of the cells of the hepatobiliary tract.

❖**Normal serum level of GGT : 10 -30 U/ L**

❖(GGT)→ increases in cholestasis ,post hepatic obstruction

- **Gamma Glutamyl Transferase** (GGT)→ increases in chronic alcoholism and increase is parallel to alcohol intake .GGT is increased in alcoholics even when other LFT are within normal limits.

In liver diseases ,GGT elevation parallels to that of ALP and sensitive to biliary tract disease .

❖Disadvantage : non-specific and can be induced by drugs and alcohol

Enzymes in liver diseases : Gamma Glutamyl Transferase

❖**Normal serum level of Gamma Glutamyl Transferase(GGT) : 10 -30 U/ L**

❖**conditions associated with elevated GGT are:**

1. Chronic alcoholism
2. Infective hepatitis
3. Myocardial infarction
4. Renal failure
5. Chronic obstructive pulmonary disease
6. Diabetes Mellitus
7. NASH(non alcoholic steatohepatitis)

❖**Gamma Glutamyl Transferase** (GGT) has 11 isoenzymes .

5’ nucleotidase:Enzymes in liver diseases

- 5’ nucleotidase = nucleotide phosphatase (NTP) : serum level of NTP is elevated in hepatobiliary disease and its estimation is specific for obstructive liver disease (moderately increased in hepatitis) .
- **Normal serum level of** 5’ nucleotidase **: 2-10 U/ L**
- Principle of 5’ nucleotidase estimation :

5 ‘ end of nucleotide is hydrolyzed by 5’ nucleotidase (optimum pH 7.5)

e.g. Adenosine 5 ‘ P → Adenosine + Inorganic P

- Alkaline phosphatase (interferes with estimation of NTP) is inactivated by Nickel.
- Unlike ALP , serum level of 5’ nucleotidase is unelated with osteoblastic activity therefore is unaffected by bone diseases .
- It is a maker enzyme for plasma membranes and seen as an ecto-enzyme. (enzyme present on plasma membrane)

Pseudocholinesterase

- Pseudocholinesterase or type II Acetylcholine esterase :

1. Non specific and can hydrolyze acyl esters
2. Synthesized by liver cells
3. Non functional plasma enzyme
4. Activity deceases in liver diseases

Amino acids in blood & urine

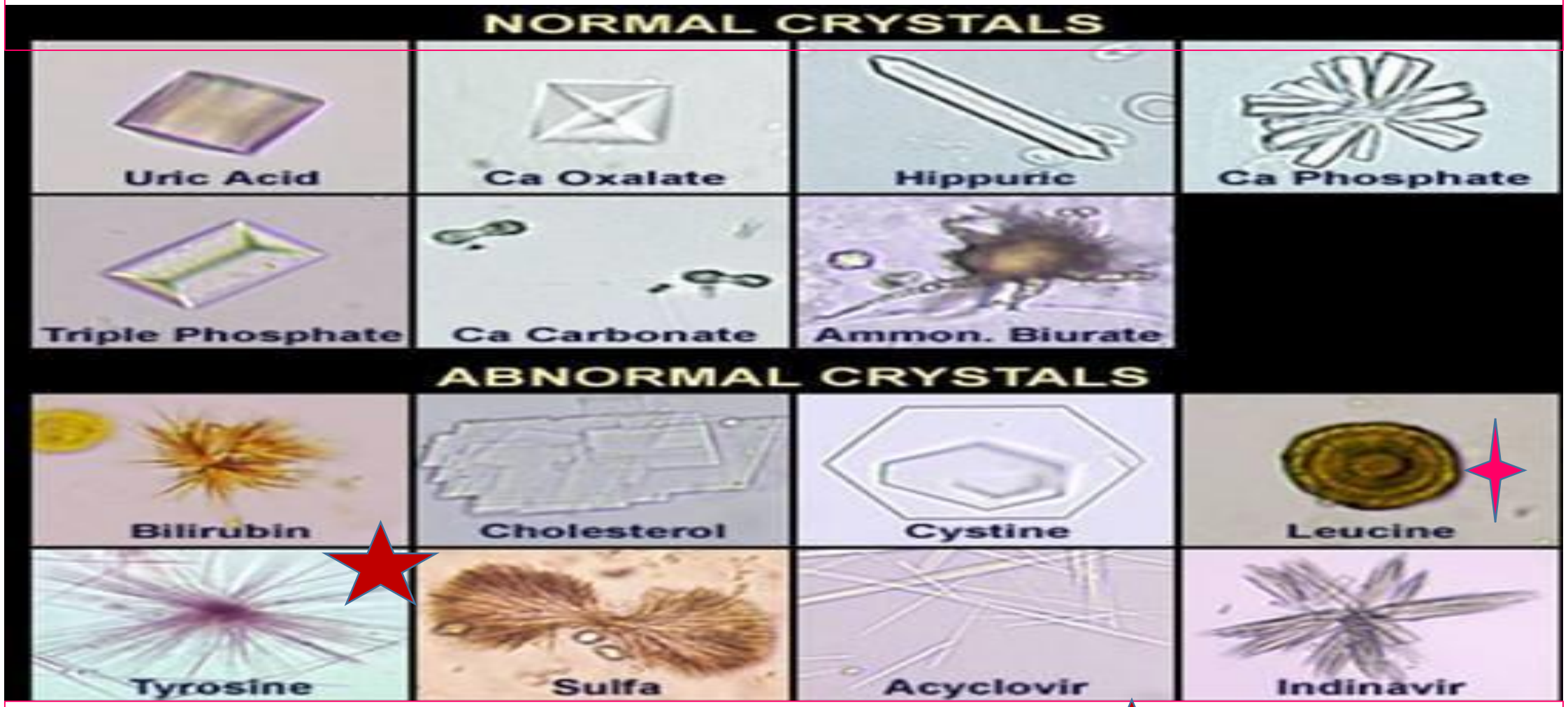
❖Causes of aminoaciduria

1 . Overflow –observed in liver diseases ,genetic cause(Serum amino acid levels are normal/ high)

2. **renal** – renal diseases ,heavy metal poisoning (Serum amino acid levels are normal)

- ❑**Tyrosine crystals** : soluble in acid /alcohol ,needle shaped
- ❑**Leucine crystals** : yellow spherical ,insoluble in acids ,soluble in alcohol

Urinary Tyrosine and Leucine crystals



Tyrosine crystals : soluble in acid /alcohol ,needle shaped

Leucine crystals : yellow spherical ,insoluble in acids ,soluble in alcohol

Diagnostic tests for aminoaciduria

SCREENING TESTS FOR AMINOACIDURIAS

GUTHRIES BACTERIAL INHIBITION TEST

FERRIC CHLORIDE TEST

DINITROPHENYL HYDRAZINE (DNPH) TEST

ESTIMATION OF BLOOD PHENYLALANINE & LIVER PHENYLALANINE HYDROXYLASE ACTIVITY

- Chromatography
- Spectrofluorimetric methods

Comparison of LFT in types of Jaundice

Test	Hemolytic Jaundice	Obstructive Jaundice	Hepatic Jaundice
SGPT	Normal	Raised slightly	Raised markedly
ALP(40 -125 /L)	Normal	Raised (10-12times)	Raised(2-3 times)
Thymol flocculation test	Negative	Negative	Positive
5’ nucleotidase Not affected by bone diseases –Paget disease	5-17 IU /ml		

Alpha fetoprotein(AFP) as LFT

❖Alpha fetoprotein(AFP) :

1. Normal component of fetal blood
2. Disappears after birth within few weeks
3. Normal serum AFP : up to < 1 year → 3ng/ml ,adult male/female →15 ng/ml
4. Mild elevation : suggestive of chronic hepatitis /cirrhosis
5. A tumor maker :Significant increase serum AFP hepatocellular carcinoma ,germ cell tumor ,teratoma of ovary
6. Elevated AFP levels in maternal serum : fetal neural tube defects/fetal death /multiple fetuses
7. Low AFP levels in maternal serum : fetal Down syndrome

Ceruloplasmin (Cp) as LFT

❖ **Ceruloplasmin (Cp) as LFT :**

1. Synthesized by Hepatic parenchymal cells and small part by lymphocytes
2. Normal serum **Ceruloplasmin (Cp)** : 20-60 mg/dl
3. Elevated serum levels Ceruloplasmin (Cp): active Hepatitis, Biliary Cirrhosis, hemochromatosis, obstructive Biliary disease
4. Decreased **Ceruloplasmin (Cp): Wilson's hepatocellular degeneration**

Transthyretin (Prealbumin)

❖**Transthyretin (Prealbumin) :**

1. Synthesized by liver
2. Major function : transport of thyroxine and triiodothyronine
3. Normal serum **Transthyretin (Prealbumin)** : 20-40 mg/dl
4. A useful parameter to assess the hepatic function in early in the course of liver disorders

Alpha -1 antitrypsin (AAT)

❖Alpha-1 antitrypsin (AAT) :

1. Synthesized and secreted by liver
2. Major function : inactivates proteases (elastase and collagenase)
3. has got multiple alleles
4. PiZZ allele: characterized by defective enzyme activity→ prone for developing **liver cirrhosis**
5. Normal serum Alpha -1 antitrypsin (AAT) : 90-200 mg/dl (0.9-2 g/L)

Haptoglobin as LFT

❖**Haptoglobin:**

1. Synthesized and secreted by liver
2. Major function :transports free hemoglobin to reticuloendothelial system
3. Free hemoglobin freely filtered at glomerulus and hemoglobin bound to haptoglobin not filtered at glomerulus (retained in circulation)
4. Exaggerated hemolysis : hemoglobin bound to haptoglobin is degraded by reticuloendothelial system → rapid depletion of haptoglobin from circulation
5. Turnover rates of **haptoglobin** and **transferrin** are lesser than albumin therefore **u**sef**u**l to identify recent changes in liver functions .
6. Normal serum **Haptoglobin** : 30-200 mg/dl (0.3-2 g/L)
7. Low serum **Haptoglobin :** seen in hepatocellular liver disease (deficient synthesis) and in hemolytic disease (increased ate of degradation)
8. **Acute phase reactant** : high levels of serum haptoglobin :seen in inflammatory process, infections , trauma ,myocardial infarction

Glutamine in CSF (Indirect Liver Function Test)

❑Synthesis of Glutamine by brain cells to detoxify ammonia :

Glutamate + Ammonia + Glutamate Synthetase* →Glutamine

➢Glutamate synthetase* decreases in liver diseases therefore concentration of ammonia increases leading to ammonia toxicity.

❑Principle of estimation of Glutamine in CSF

Glutamine

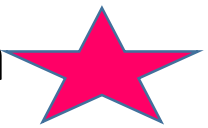
↓ dilute acid boil at 100 ^{0} c

Estimation of Ammonia

❑Interpretation of estimation of Glutamine in CSF:

Normal range **of Glutamine in CSF →6-14** mg/ dl

Glutamine in CSF is elevated in Infectious hepatitis, Hepatic coma



Interpretation of Glutamine in CSF (Indirect Liver Function Test)

Condition	Levels of Glutamine in CSF
Normal (physiological)	8 -18 mg%
★ Infectious hepatitis	16-28 mg%
★ Hepatic coma	30-60 mg%
Suggestive of critical conditions	> 40 mg %

Interpretation of Glutamine in CSF is more reliable than CSF ammonia.

Glutamine in CSF (Indirect Liver Function Test)

CSF Glutamine

- Produced by brain cells from ammonia and α-ketoglutarate to remove toxic ammonia
- Indirect test for the presence of excess ammonia in the CSF
- Normal: 8 to 18 mg/dL
  - Elevated in liver disease
  - Elevated in children with Reye syndrome
  - Disturbance of consciousness when glutamine levels are more than 35 mg/dL
- More reliable than direct CSF ammonia

Liver Function Tests

❖**Liver function tests based upon carbohydrate metabolism**

1. Galactose tolerance test
2. Fructose tolerance test

❖**Liver function tests based upon lipid metabolism**

1. Serum total ,free & ester cholesterol
2. Fecal fat

❖**Test for detoxifying function**

1.Hippuric acid estimation in urine & serum

❖**Test for excretion of foreign substances**

1. Bromosulphthalein test

LFT based on Carbohydrate Metabolism

❑Functions of liver in Carbohydrate metabolism

1. Glycolysis
2. Glycogenesis
3. Glycogenolysis
4. Gluconeogenesis
5. Conversion of Galactose & Fructose

❖ Liver is the only organ which carries out function of Galactose & Fructose uptake.

Galactose Tolerance test as LFT

- Metabolic function of liver can be assessed by ability of the liver to metabolize galactose .

Galactose Tolerance test as LFT

- **Procedure of Galactose Tolerance Test**

1. 40 gm of Galactose given orally (or 350 mg of Galactose /body kg weight as 25-30 % IV solution
2. Blood samples : fasting & every half hourly over period of two hours

- Normal Serum Galactose → 0-100 mg%
- In normal individual →3 gm of Galactose appear in urine within 4hrs after oral supplementation , and blood levels declined progressively and each fasting levels by 2 hrs.
- In Liver diseases (Cirrhosis ,Hepatitis): galactose utilization decreased

1. Urinary excretion of Galactose > 3gms
2. Blood Galactose > 500 mg%

Bromosulphthalein Test as LFT based on Excretory functions

- Liver performs function of excretion of drugs & dyes.

❑Test procedure of Bromosulphthalein Test :

Intravenous injection of Bromosulphthalein dye -5mg /body kg weight as 5 % solution

❑Advantages of Bromosulphthlein dye:

1.Safe to use in humane body

2. Detection easier as it gives –purple color in alkaline medium

Test results→

Time (minutes)	Dye retained in normal conditions (%)	Dye retained in liver diseases (%)
30	10	
45	7	50
60	0	

LFT associated with detoxification

- The liver is involved in detoxification of xenobiotics by the action of monooxygenase followed by conjugation to form polar compounds ,water soluble compounds that can be excreted in the bile or urine.
- Detoxification function of Liver can be assessed by

1. Estimating hippuric acid synthesis test
2. Blood Ammonia
3. Aminopyrine breath test

LFT associated with detoxification

❑Mechanisms of detoxification in Liver involve

1. Conjugation: Conjugates using Glycine ,Cysteine , Sulphuric Acid ,Glucuronic Acid, Acetic Acid & Methyl Group
2. Methylation
3. Oxidation
4. Reduction
5. Hydrolysis

Hippuric Acid Test: LFT associated with detoxification

1. Hippuric acid & Glycine synthesis by hepatocytes
2. Conjugation with Glycine by hepatocytes
3. Excretion of Hippuric acid by kidney
4. Liver & kidney function hand in hand for detoxification.

Hippuric Acid Test: LFT associated with detoxification

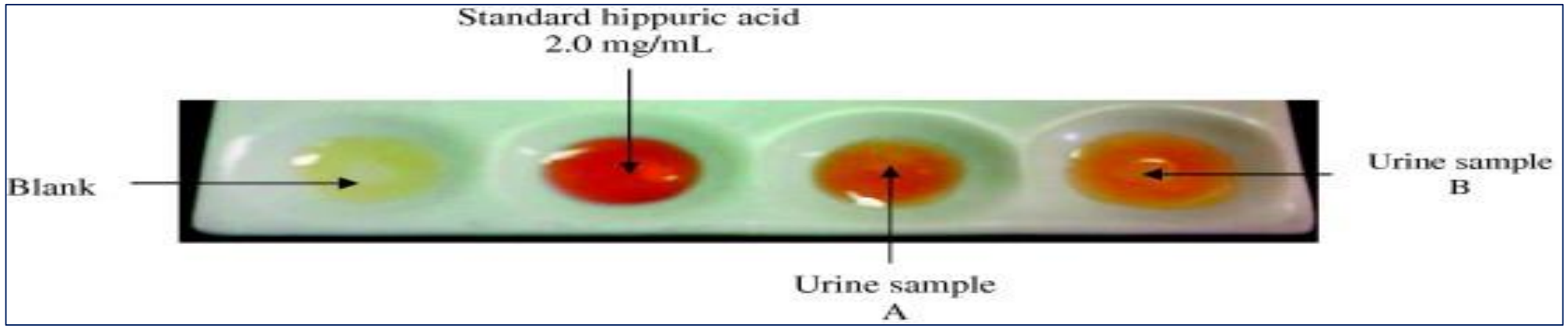
❑Hippuric Acid :

Benzoic Acid(Toxic)+ Glycine →Hippuric Acid

8 gm Benzoic acid consumed in diet → 3gm Hippuric acid in urine

❑Steps of Hippuric Acid Test :

1. Precipitation of Hippuric acid with Ammonium sulphate
2. Dissolve precipitate in water
3. Titration with NaOH



Hippuric Acid Test: LFT associated with detoxification

Tests based on Detoxifying capacity of liver

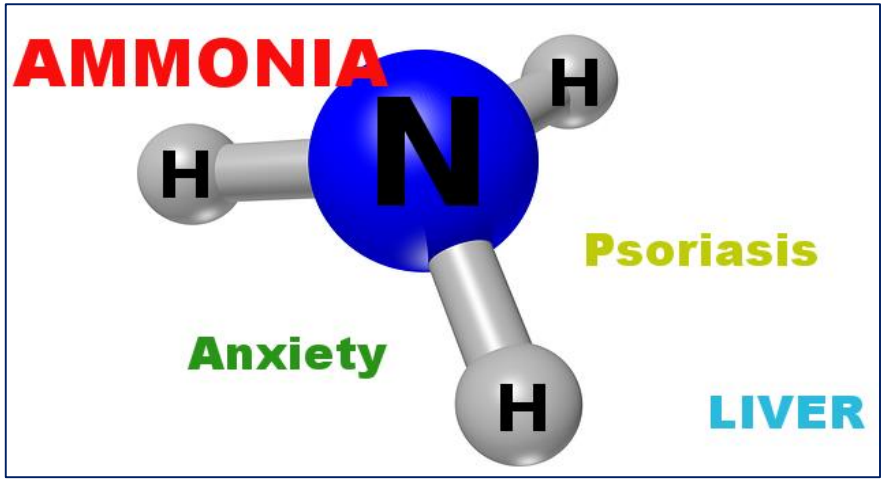
- Hippuric acid test
- Hippuric acid synthesis → assess detoxification function
- Benzoic acid + Glycine = Hippuric acid
- Procedure:

  - 6g sodium benzoate dissolved in 250ml water is given orally 2hrs after light breakfast and after emptying bladder
  - Urine is collected for next 4 hours
  - Amount of hippuric acid excreted is estimated
  - Normal: > 4.5 g of hippuric acid (60% of sodium benzoate)
  - Abnormal: < 3g indicates hepatic dysfunction

Estimation of Blood Ammonia as LFT

- **Blood Ammonia : is an index of urea synthesis by liver.**
- Sources of ammonia in human body :

1. Transamination & deamination
2. Nitrogenous material by bacterial action in gut
3. Kidney hydrolysis of glutamine by glutaminase
4. Pyrimidine catabolism



Estimation of Blood Ammonia as LFT

❖**Estimation of Blood Ammonia** by Micro Diffusion Method :

Blood (arterial) + K2 CO3 →Ammonia released → titration with HCL

❖**Interpretation of Estimation of Blood Ammonia**

Normal range **of Blood Ammonia** →15-45 microgram/100 ml

Elevated of Blood Ammonia:

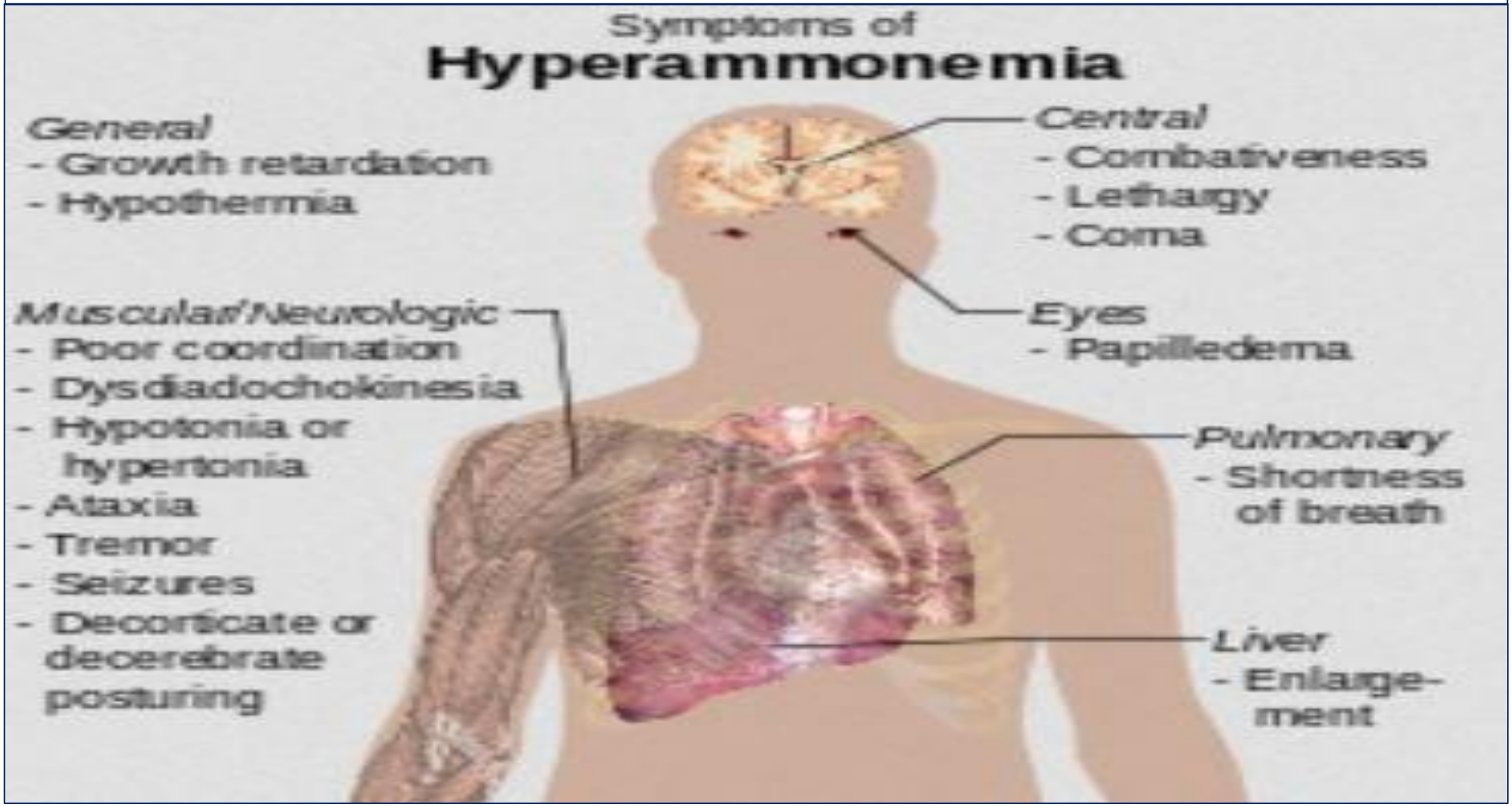
a. Cirrhosis (250 microgram /100ml) and or
b. Development of collateral circulation→ portocaval anastomosis
c. Parenchymal hepatic disease

❖**Increased** blood **Ammonia** → Hepatic coma due to CNS complications

❖Estimation of Blood Ammonia may be helpful to exclude or diagnose hepatic failure in patients with unexplained stupor and coma .

- blood **Ammonia estimation is i**ndicated neonates suspected to have urea cycle disorders and in organic acidurias) .

Manifestation of Ammonia toxicity



Estimation of Blood Ammonia as LFT

-Blood Ammonia

- An ammonia test measures the amount of ammonia in the blood. Most ammonia in the body forms when protein is broken down by bacteria in the intestines . The liver normally converts ammonia into urea, which is then eliminated in urine.

- Ammonia levels in the blood rise when the liver is not able to convert ammonia to urea. This may be caused by cirrhosis or severe hepatitis.

- For this test, a blood sample may be taken from either a vein or an artery.

Normal range

Adults:	9.5-49 mg/dL	7-35 mmol/L)
Children:	40-80 mg/dL	28-57 mmol/L
Newborns:	90-150 mg/dL	64-107 mmol/L

Precautions for serum /plasma ammonia estimation

- Fasting arterial blood sample
- Use vacutainers ,blood to be withdrawn until it is full
- Partial filling allows entry of air
- Glutamine in the specimen is a source of ammonia contamination → this can be avoided by placing the sample in ice and centrifuging to separate to plasma /serum
- Carry out assay as soon as possible
- EDTA / heparin can be used as anticoagulants
- Enzymatic assay (with Glutamate dehydrogenase is done by photometry or by ammonia selective electrode)

Ammonia Tolerance Test

❑**Test procedure of Ammonia Tolerance Test** :

12 hours overnight fast

↓10gms of ammonium citrate given orally

Blood samples –fasting and every 30 mins over period of 150 mins

❑**Interpretation of Ammonia Tolerance Test** :

Normal –marginal increase in serum ammonia

Cirrhosis – significant increase in serum ammonia (200-300 micrograms/100ml)

Ammonia Tolerance Test

Ammonia

Ammonia Tolerance Test:

1. 12 hour fast – red top tube
2. NH_3Cl capsules 45 mg/lb max dose 3g PO
3. 30 minutes later – red top tube

Increase should be <32%

100% sensitive for PSS

DO NOT GIVE NH_3Cl if resting ammonia elevated

- Can induce HE

Aminopyrine breath test

- Aminopyrine breath test: involves measurement of $^{14}CO_2$ formed from [^{14}C]methyl labeled aminopyrine in liver by N-demethylation .
- In liver diseases such as cirrhosis and hepatitis ,the amount of $^{14}CO_2$is decreased .

Estimation of cholesterol :Function of liver associated with fat metabolism

❑One of the function of liver associated with fat metabolism:

- Synthesis & esterification of cholesterol

Liebermann's Burchard's Reaction : LFT associated with fat metabolism

- Function of liver –synthesis & esterification of cholesterol
- Principle of Liebermann Burchard's Test :

Cholesterol + Acetic anhydride + H_2SO_4 → Green color complex

- Normal range of serum Total cholesterol → (150-250 mg%)
- Normal range of Serum Free Cholesterol → 30% (20-40% = 30-60mg%)
- Normal range of Serum Ester Cholesterol →70 % (60 -80% =90 -190 mg %)
- Normal value of Free /ester Cholesterol ratio → 1:4
- Obstructive jaundice →(> 250 mg%) Hypercholesterolemia

No change in Free /Ester Cholesterol ratio

- Infective Hepatitis → Total serum Cholesterol normal / decreased and

Increase in Free /Ester Cholesterol ratio (as conc. Ester Cholesterol decreases)

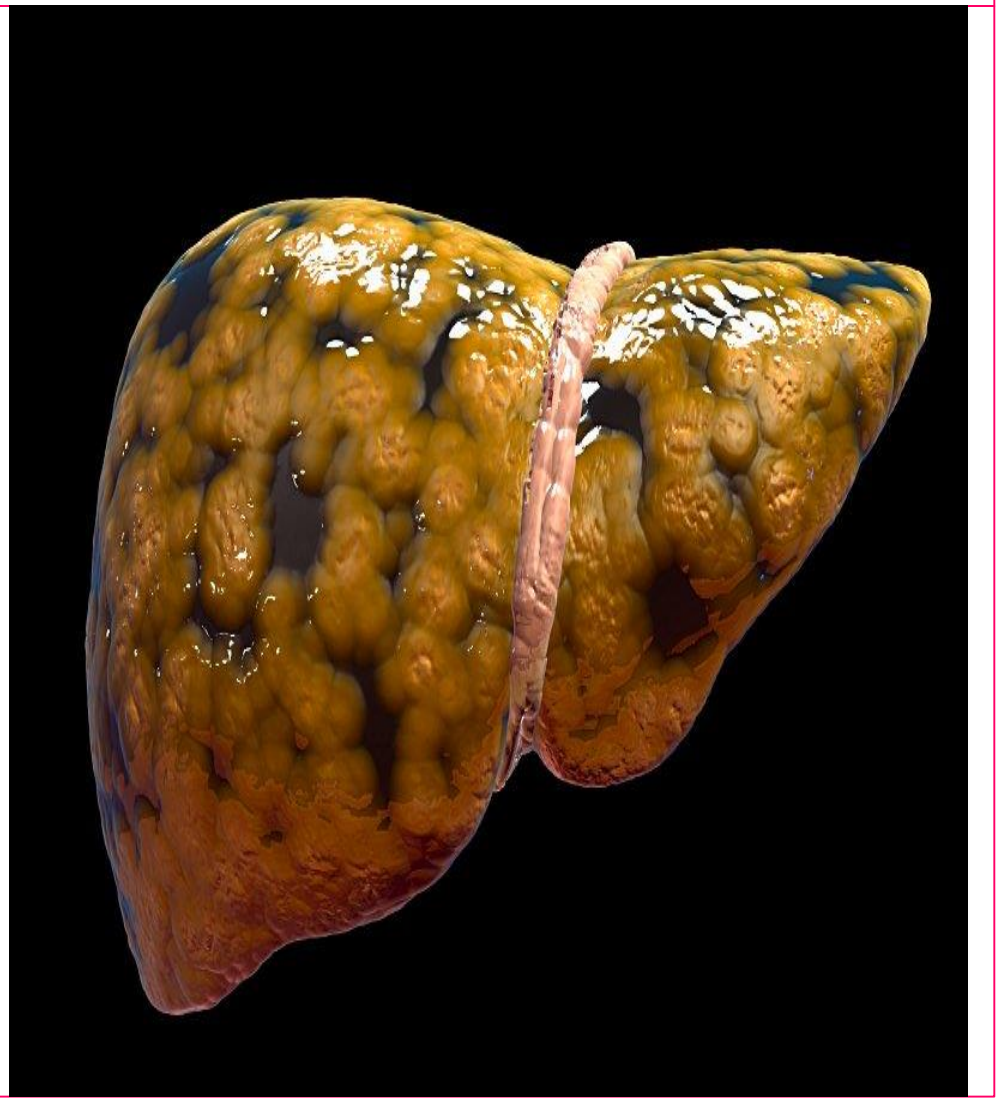
Fatty liver

❖**Causes of Fatty liver**

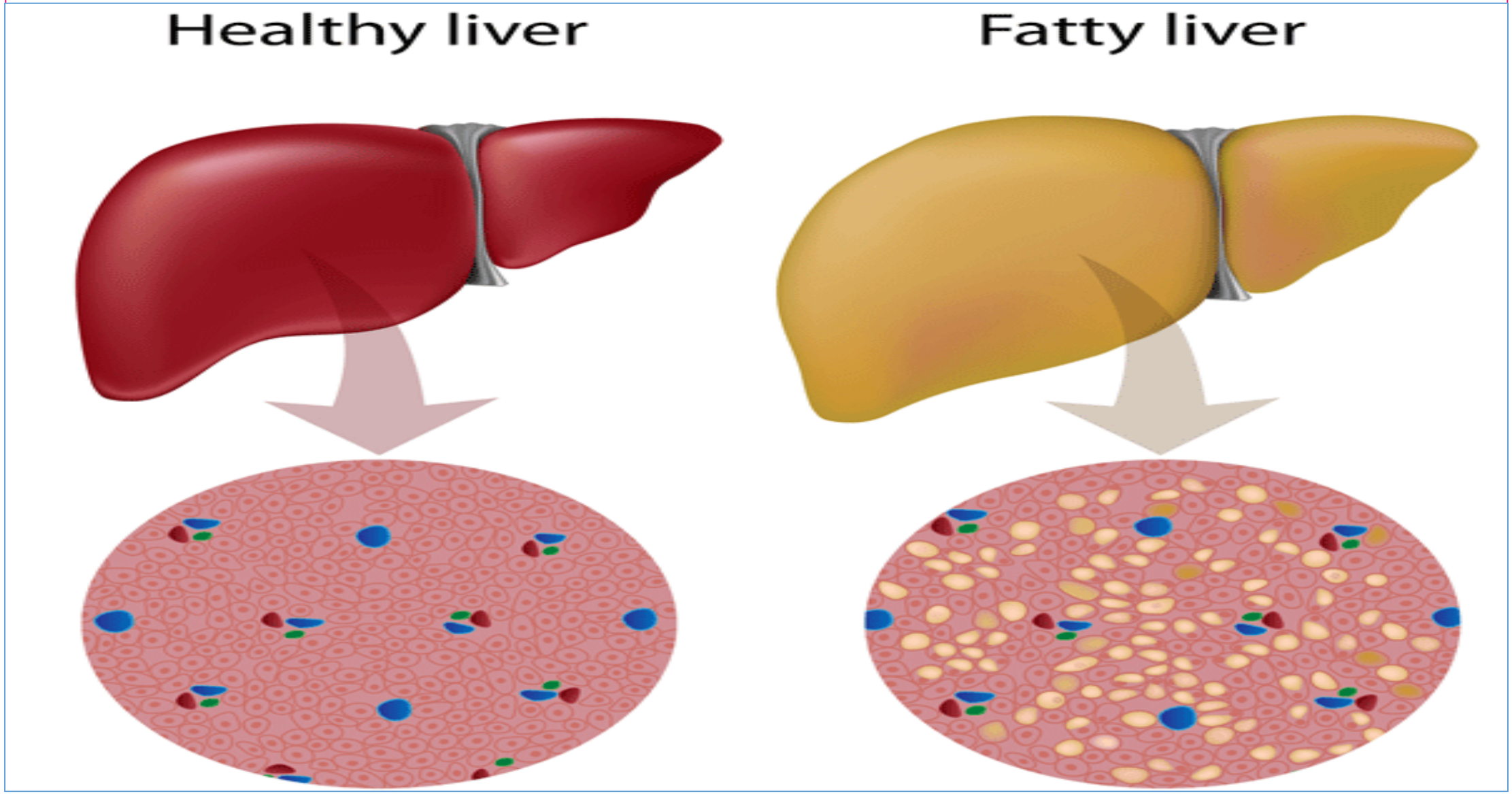
1. Abnormal fat formation
2. Excessive transport of lipids to liver
3. Impaired transport of fats from liver

❖**Conditions associated with Fatty liver**

a. Starvation
b. Diabetes Mellitus
c. Kwashiorkor
d. Pancreatomy
e. Excessive consumption of alcohol
f. Infections
g. Toxins



Fatty liver



Causes of cholestatic liver disease

Extrahepatic

- **Cholelithiasis** (stones in gallbladder)
- Carcinoma of head of pancreas
- Chronic pancreatitis
- Biliary strictures
- Portal lymphadenopathy
- Liver flukes infestation

Intrahepatic

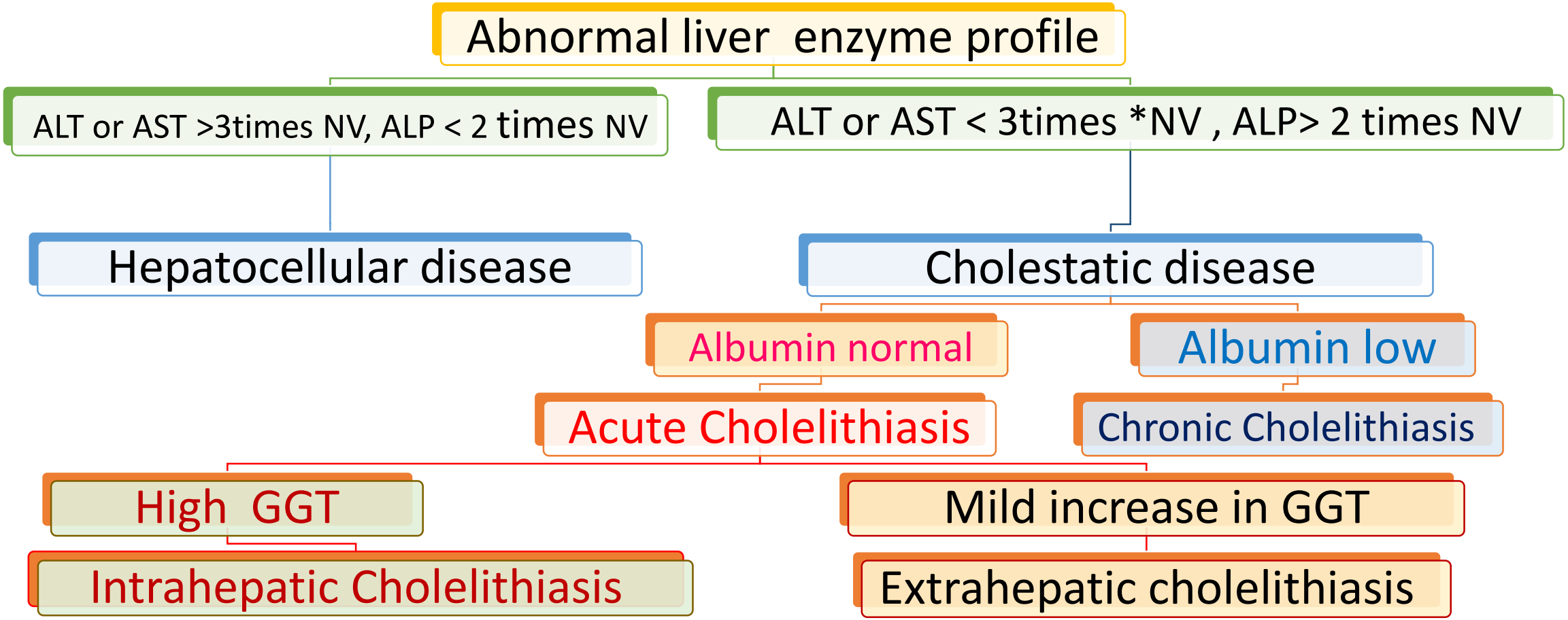
- Alcoholic cirrhosis
- **Primary biliary cirrhosis**
- (NASH)*
- Protoporphyrias
- Viral Hepatitis
- Dubbin-Johnson syndrome

Drugs

- Androgens
- Chlorpromazine
- Erythromycin
- Cyclosporine
- Captopril
- Phenytoin
- Nitrofurantoin
- Chlorpropamide

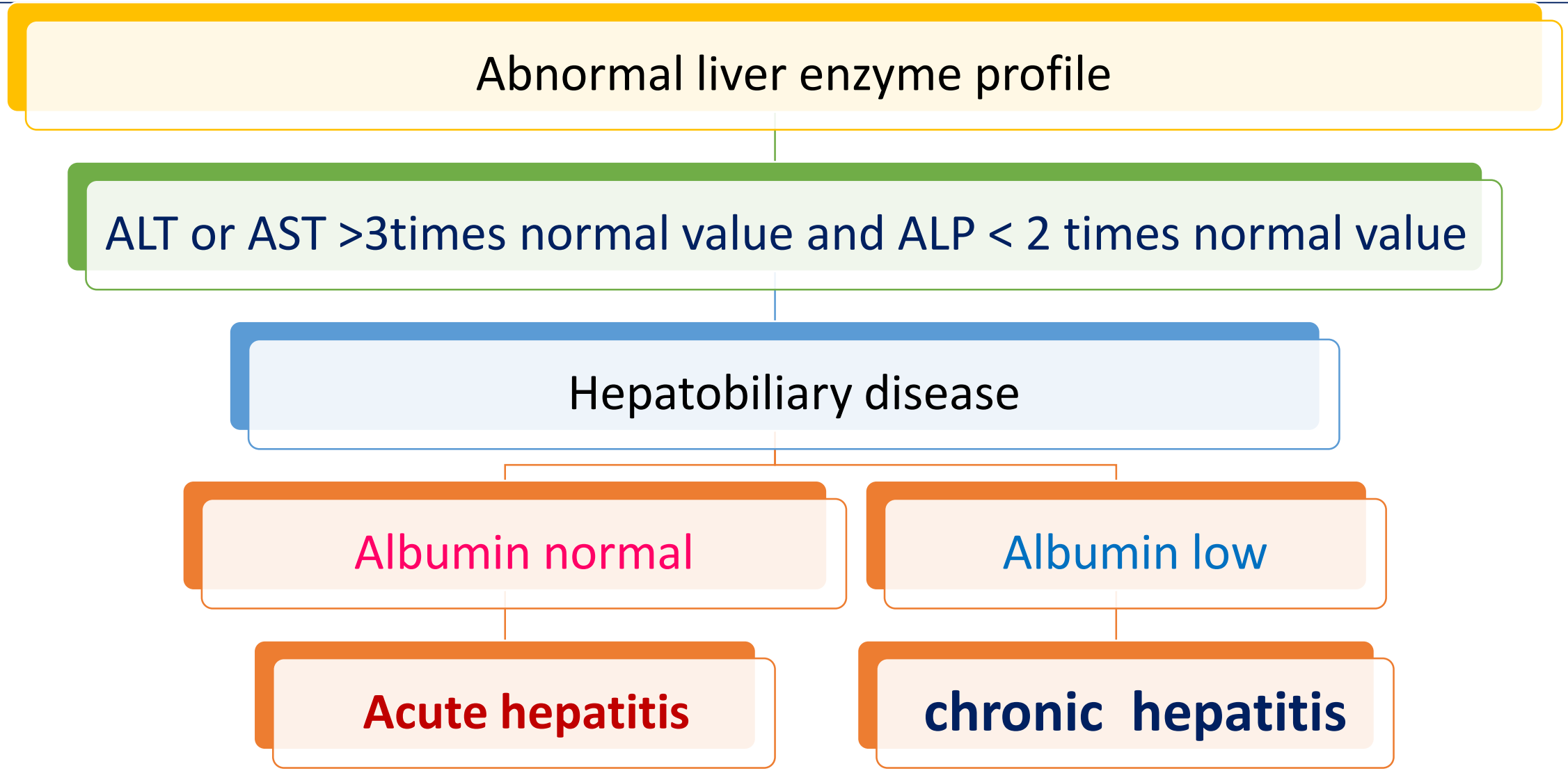
* Non- alcoholic steatohepatitis

Differential diagnosis of Extrahepatic and Intrahepatic cholestatic liver disease based on enzyme profile



*NV =normal value

Differential diagnosis of chronic and acute hepatitis based on enzyme profile



Chronic hepatitis

❖**Chronic hepatitis refers to a group of disorders characterized by Chronic hepatic inflammation .**

❖**Types of Chronic hepatitis:**

a) Chronic persistent hepatitis

b) Chronic lobular hepatitis

c) Chronic active hepatitis

Comparison of Types of Chronic hepatitis

Chronic persistent hepatitis	Chronic lobular hepatitis	Chronic active hepatitis
A benign ,asymptomatic condition that dose not progresses to cirrhosis	Foci necrosis and inflammation in liver lobules that progresses to cirrhosis	Hepatic necrosis , lobular inflammation ,fibrosis that progresses to cirrhosis→ liver failure and death
Slight increase in plasma transaminases	increase in plasma transaminases	increase in plasma transaminases (AST >ALT as the disease progresses)
		Hyperbilirubinemia (and jaundice) increase in plasma IgG levels ,low plasma albumin

Characteristics of cholestasis

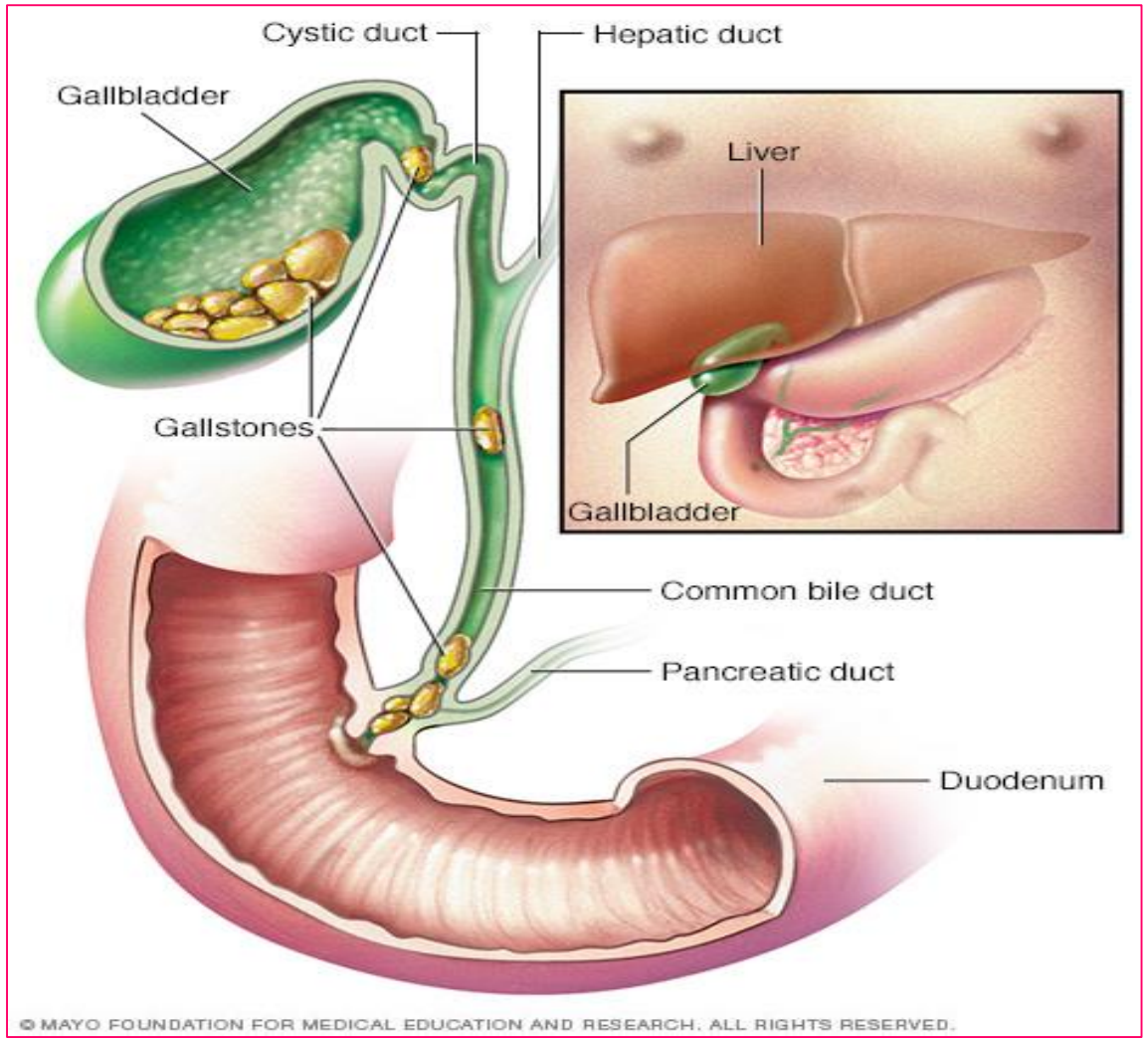
- Obstruction to bile flow referred to as **cholestasis.**
- Characteristics of cholelithiasis include :

1. Increase in plasma ALP activity
2. high plasma bilirubin levels of 50 mg/dl(862 μmols/L)
3. Prothrombin deficiency and hemorrhage due to malabsorption of vitamin K → prolonged Prothrombin time (parental administration of vitamin K corrects the abnormality)
4. Hypocholesteremia due to increased cholesterol excretion in bile

Gall stone formation

- Gall stones are crystalline structures formed by concentration or accretion of the bile constituents that may be cholesterol stones ,mixed stones or pigment stones.
- Gall stone formation : there is precipitation of bile salts * , bile pigments ** & cholesterol *** due to abnormal Free / esterified cholesterol ratio
- Bile salts * : water soluble
- bile pigments** : sparingly soluble in water
- cholesterol *** : Insoluble in water
- Gall stone formation →obstructive jaundice

Gall stones


Cystic duct
Hepatic duct
Gallbladder
Liver
Gallstones
Gallbladder
Common bile duct
Pancreatic duct
Duodenum
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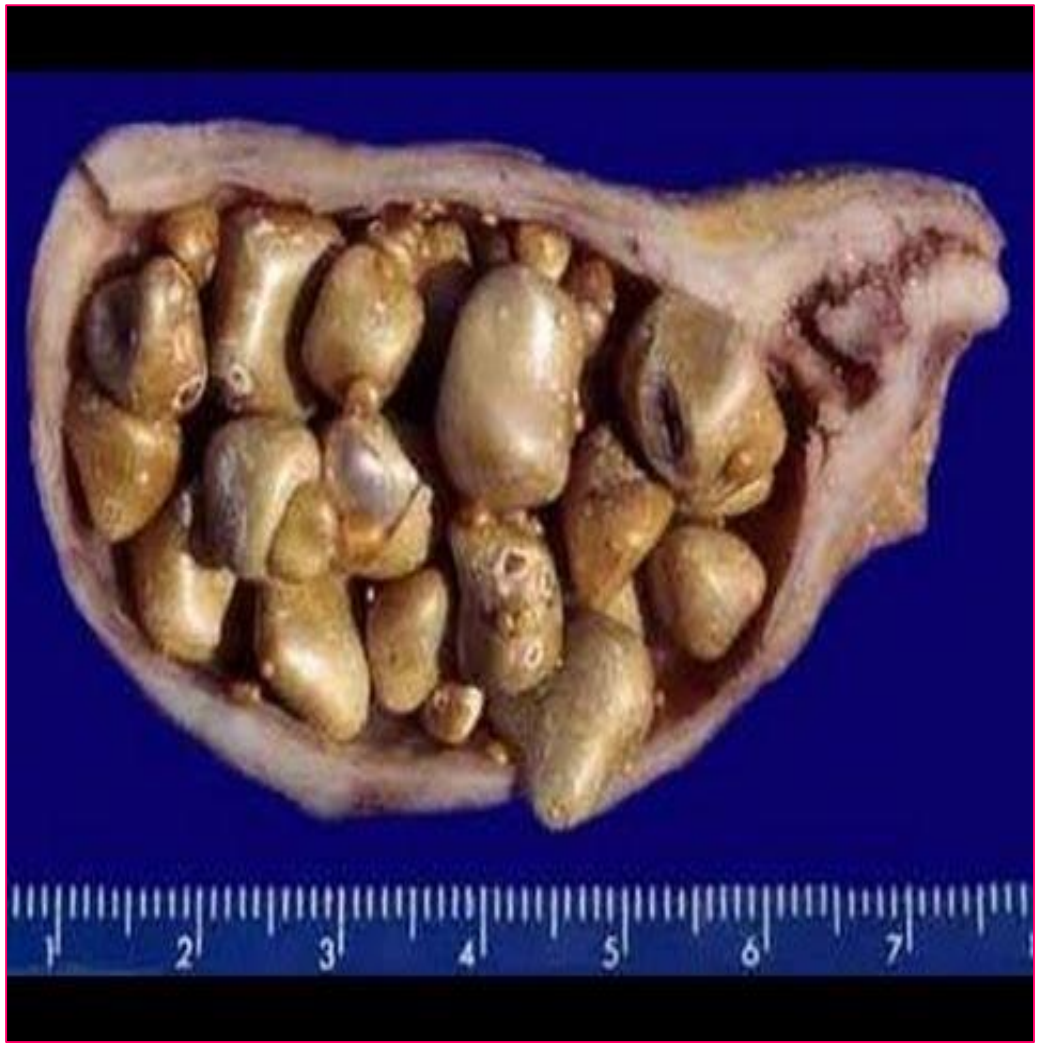
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Cholesterol and mixed stones

- **Cholesterol and mixed stones:**

1. account for 80% of total stones
2. more prevalent in westerns countries
3. are made up of Cholesterol monohydrate (> 70%),calcium salts ,bile acids ,bile pigments ,proteins ,fatty acids and phospholipids
4. occur due to supersaturation of bile with cholesterol as a result of

a) Obesity and high caloric diets

b) Increased activity of HMG –CoA reductase ,or decreased activity of 7α hydroxylase with decreased formation of bile acids with cholesterol

c) decreased secretion of bile salts and phospholipids

d) Hypolipidemic drugs such as clofibrate that increase cholesterol secretion in bile

Gall stone analysis for presence of cholesterol

Salkowski and Liebermann Burchard's Test: LFT associated with fat metabolism

Detection of Steroids

1.Salkowski's Test

B A

2. Libermann Burchard's Test

A B

Pigment Gall stones

- **Pigment Gall stones :**

1. are more prevalent in oriental countries, especially in Asia
2. are composed of calcium bilirubinate and small amount of cholesterol (<10%)
3. occur in association with

a) Biliary tree infections

b) Chronic hemolytic state (hereditary spherocytosis) in which increased hemoglobin breakdown results in overproduction of bilirubin and increased bilirubin secretion

Consequences and treatment of gall stones

❖Consequences of gall stones :

a) acute or chronic cholecystitis

b) Obstructive jaundice due to obstruction of the common bile duct

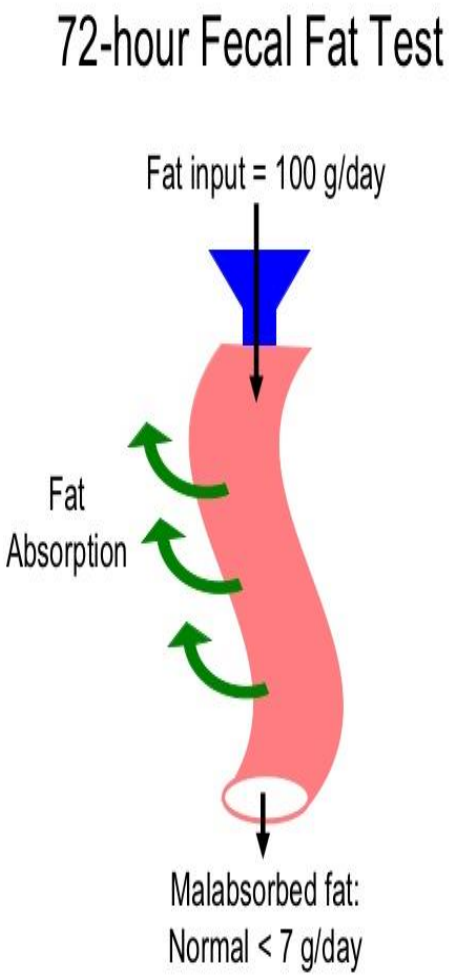
❖Treatment of gall stones :

a) Cholecystectomy (surgical removal of the gall bladder).

b) Oral administration of the bile acids ,choledeoxycholic acid and urodeoxycholic acid →to dissolve gallstones by reducing the relative saturation of bile with cholesterol.

c) Shock wave lithotripsy to shatter gallstones with into tiny fragments and enable passage through cystic duct.

Fecal fat :suggestive of hepatobiliary disease



Investigations:

Specific:

Tests of fat absorption:

Quantitative fecal fat

Patient should be on daily diet containing 80-100 grams of fat.

Fecal fat estimated on 72 H collection.

6 grams or more of fat/day is abnormal.

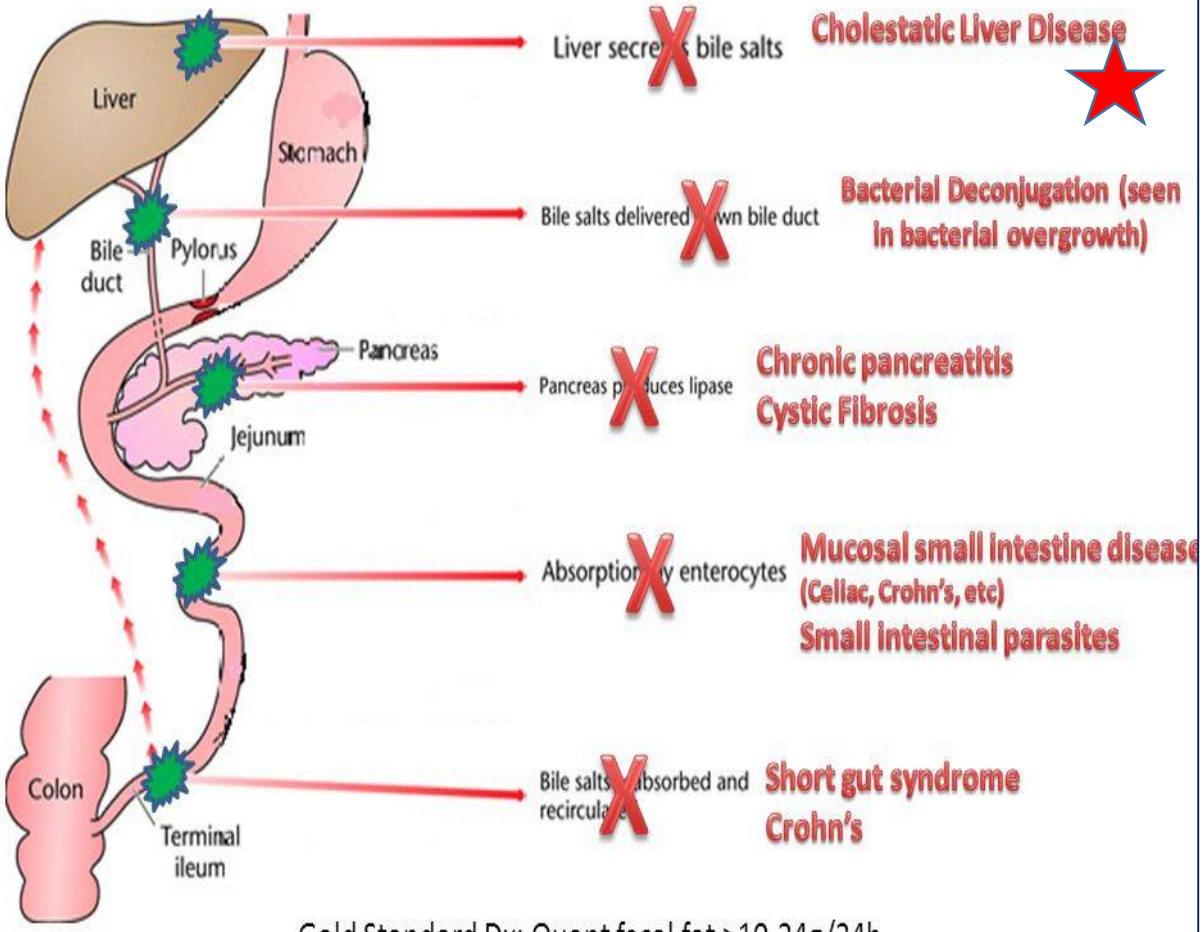
May be due to: - Pancreatic

- Small intestinal

- Hepatobiliary disease

Fecal fat :LFT associated with fat metabolism

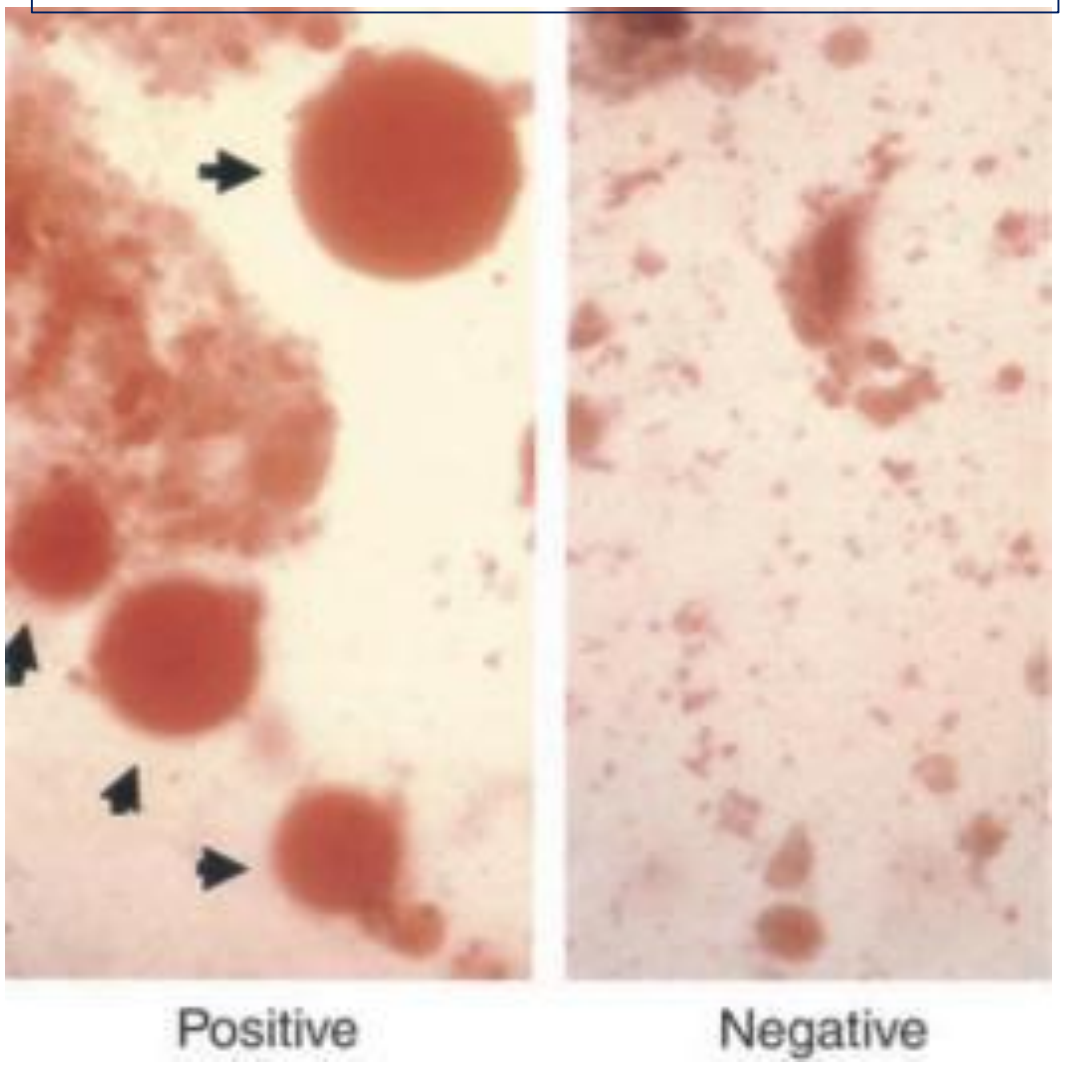
Mal Fat Absorption



Gold Standard Dx: Quant fecal fat >10-24g/24h

Remember: ADEK Deficiencies

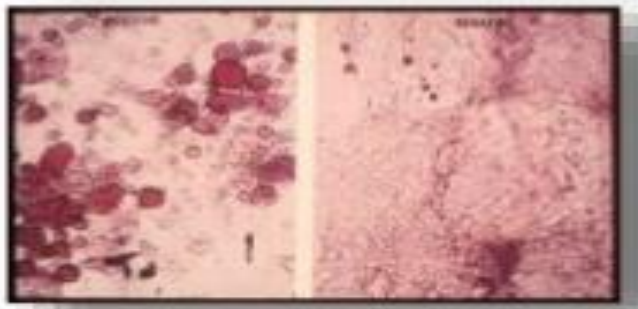
Staining for Fecal fat detection



Quantitative tests for Fecal fat :LFT associated with fat

Tests for steatorrhea

- Quantitative test
  - 72hr stool fat collection – gold standard
    - > 6gm/day – pathologic
    - P'ts with steatorrhea - >20gm/day
    - Modest elevation in diarrheal disease (may not necessarily indicate Malabsorption)
- **Qualitative tests**
  - **Sudan III stain**
    - Detect clinically significant steatorrhea in >90% of cases
  - Acid steatocrit – a gravimetric assay
    - Sensitivity – 100%, specificity – 95% , PPV – 90%
  - NIRA (near infra reflectance analysis)
    - Equally accurate with 72hr stool fat test
    - Allows simultaneous measurement of fecal fat, nitrogen, CHO



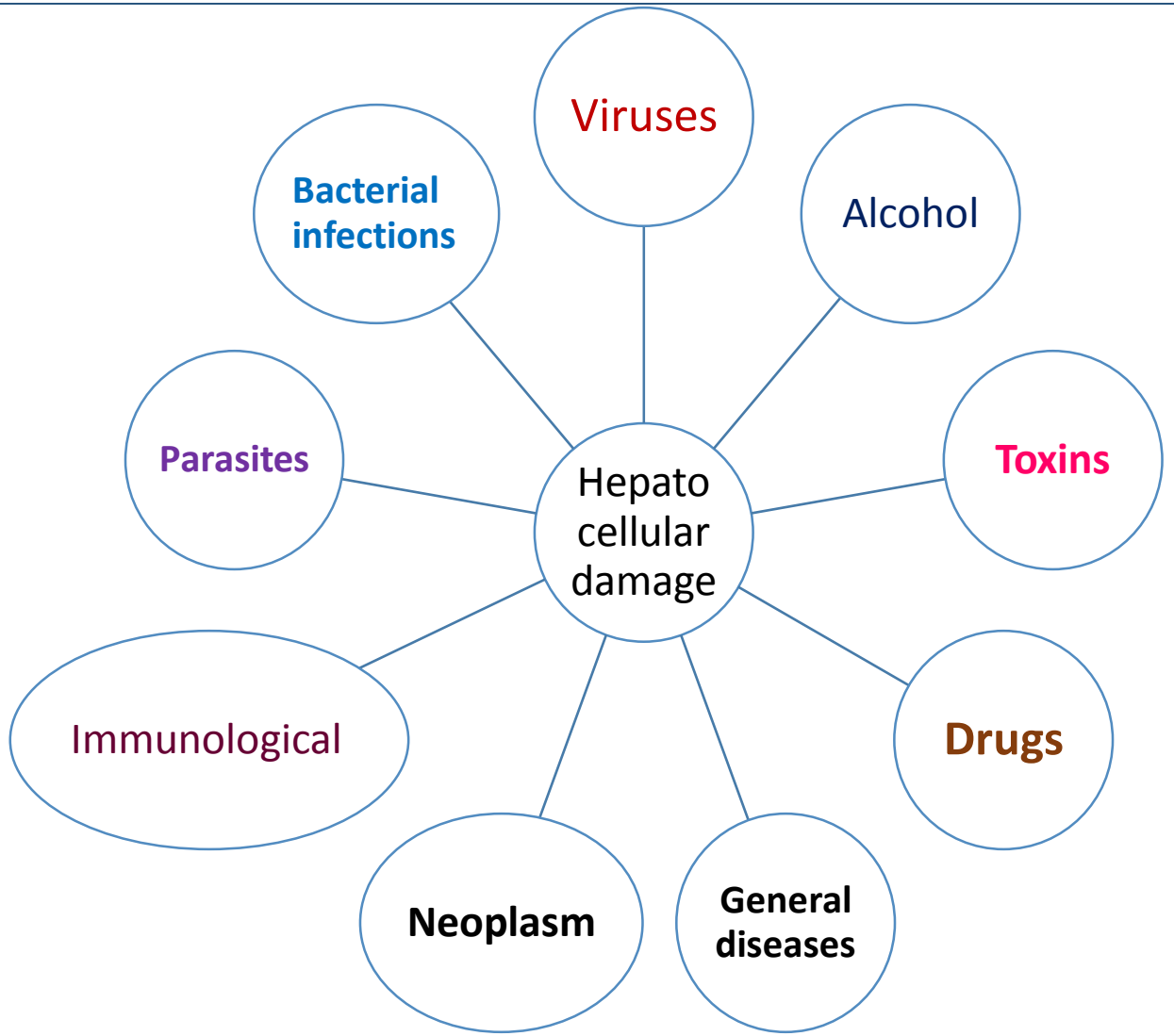
Viral Hepatitis

Type of Viral Hepatitis	Diagnosis (Type of antibody in serum)	Transmission of Viral Hepatitis
Hepatitis A	Anti –HAV IgM	Fecal- oral route ,food and water borne infections
Hepatitis B acute	HBsAg (viral surface antigen) , internal components of the virus(HBcAg), Anti- HBc IgM	Percutaneous ,sexual or perinatal
Hepatitis B chronic	HBsAg , Anti-HBeAg ,HBV DNA	Percutaneous ,sexual or perinatal
Hepatitis C	Anti- HCV and HCV RNA	Percutaneous ,intravenous drug user
Hepatitis D (delta)	HBsAg and Anti-HDV	Percutaneous in HBsAg +ve , intravenous drug user
Hepatitis E	Anti- HEV IgM and IgG	water borne epidemic

Markers of Hepatitis B infection

Type of antibody in serum	Significance
HBsAg	Surface antigen. indicates acute infection .Persistence for more than six months→ means chronic infection
HBeAg ,	Viral replication ,high infectivity
Anti-HBsAg antibody	Indicates immunity
Anti-HBeAg antibody	Resolution of acute infection
Anti- HBc IgM antibody	acute infection
HBV DNA	used to assess viral load

Causes of hepatocellular damage



Causes of hepatocellular damage

Viruses: HAV,HBV,HCV ,Herpes, Adenovirus
Immunological: Autoimmune hepatitis, NASH
Bacterial infections :TB, Leptospirosis , Brucella , Abscesses
Parasites: Helminths , Amebiasis , Plasmodia , Leishmania
General diseases: Wilson's disease ,Porphyria ,Amyloidosis ,Sarcoidosis, AAT deficiency
Neoplasm: hepatocellular carcinoma, metastatic liver disease, Lymphomas
Alcohol
Toxins: carbon tetrachloride ,chloroform ,Arsenic, Aflatoxin, mushroom
Drugs: Salicylates ,Tetracyclines ,Methotrexate ,Isoniazid ,Rifampicin ,Methyldopa

Clinical features of Acute liver failure

Liver :loss of metabolic functions, decreased gluconeogenesis →hypoglycemia, decreased lactate clearance →lactic acidosis ,decreased Ammonia clearance →hyperammonemia , decreased synthetic capacity →coagulopathy ,Portal Hypertension

Lungs : Adult respiratory distress syndrome

Heart :subclinical myocardial injury

Kidney: frequent dysfunction or failure

Brain: Hepatic encephalopathy ,cerebral edema ,intracranial hypertension

Adrenal gland : inadequate glucocorticoid production contributing hypotension

Bone marrow: frequent suppression(common in viral diseases)

Circulating leucocytes : impaired function contributing sepsis

Portal Hypertension

- The entire venous drainage of gastrointestinal tract, the spleen ,the pancreas and gallbladder constitutes portal circulation with a pressure of 5 mm of Hg .Any obstruction in the course of portal circulation will cause **Portal Hypertension.**
- **Causes of Portal Hypertension:**

1. **Presinusoidal-**e.g. portal vein thrombosis
2. **Sinusoidal-**e.g. cirrhosis
3. **Post sinusoidal-**e.g.-hepatic vein thrombosis

Effects of Portal Hypertension

- **Effects of Portal Hypertension include :**

1. Due to increase in pressure ,veins of portal system get dilated (varices) .Liver becomes more dependent on arterial blood flow from hepatic artery.
2. Portosystemic shunting leads to deterioration of the metabolic functions of the liver.
3. Hyperestrogenism is manifested as testicular atrophy, gynecomastia and palmer erythema.
4. Failure of detoxification ammonia by urea synthesis leads to Hyperammonemia and hepatic encephalopathy .
5. Decrease in albumin synthesis leads to hypoalbuminemia which predispose to oozing of fluid into peritoneal cavity causing **Ascites** .
6. Diminished synthesis of clotting factors predisposes to bleeding.

Ascites

❖ **Ascites :**

a) is due to effusion of serous fluid into the abdominal cavity.

b) is a common presenting feature of cirrhosis.

c) Is accompanied by peripheral edema.

d) may be due causes not related to any pathology of liver.

e) Ratio of serum Albumin : ascetic fluid Albumin is > 1.1 → indicates portal hypertension as a cause of **Ascites.**

Pathogenesis of Ascites

Scarring of liver

↓

Increased resistance to blood flow

↓

Hypoalbuminemia → decreased colloidal intravascular pressure → oozing of protein rich fluid into the intraperitoneal spaces → increased intraperitoneal colloidal pressure

↓

decreased central blood pressure

↓

Decreased renal perfusion→ activation of renin angiotensin system→ sodium and water retention

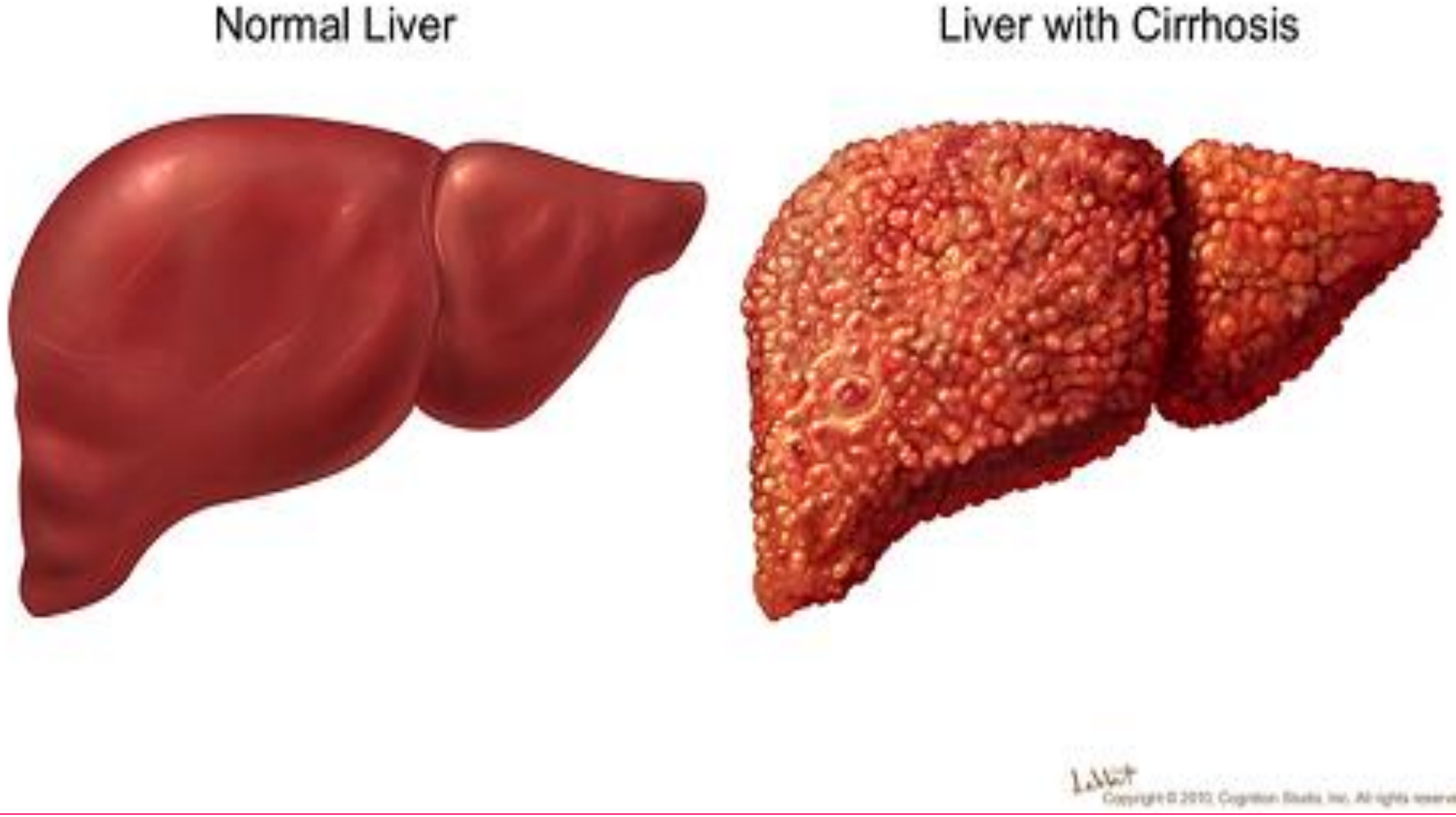
↓

Further fluid escapes into the peritoneal cavity

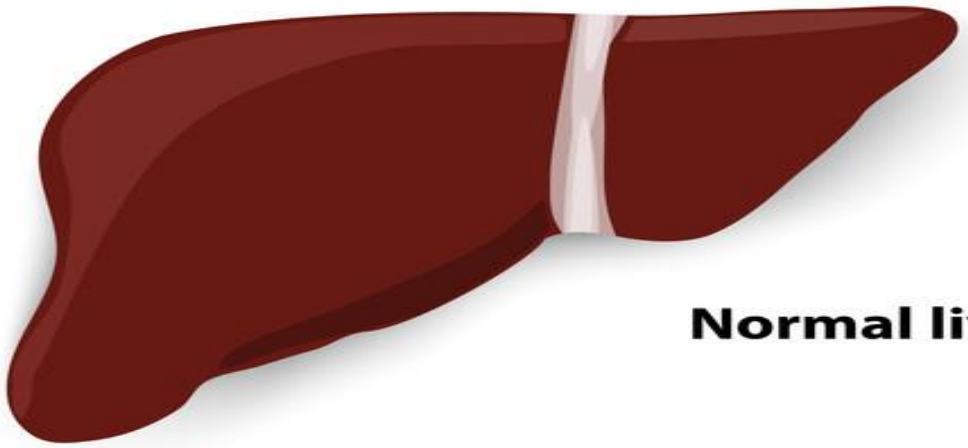
Cirrhosis

- **Cirrhosis : is the result of many inflammatory and metabolic diseases of liver. It is characterized by fibrosis and disorganization of hepatic architecture.**

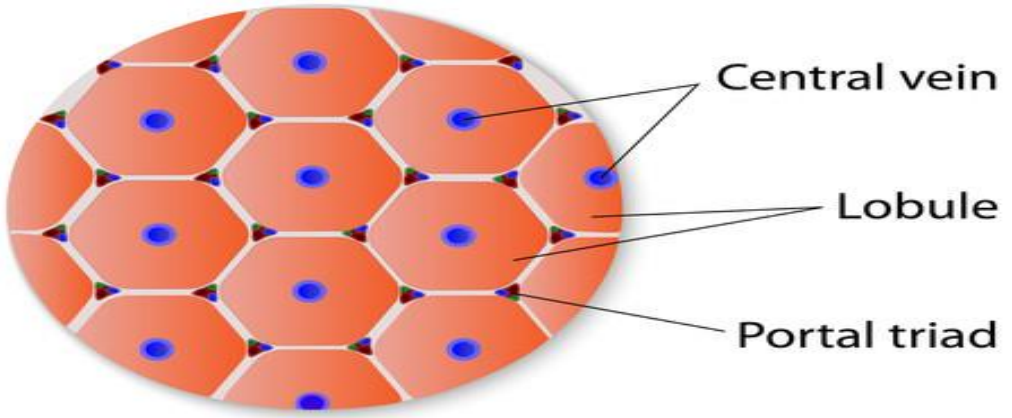
Cirrhosis

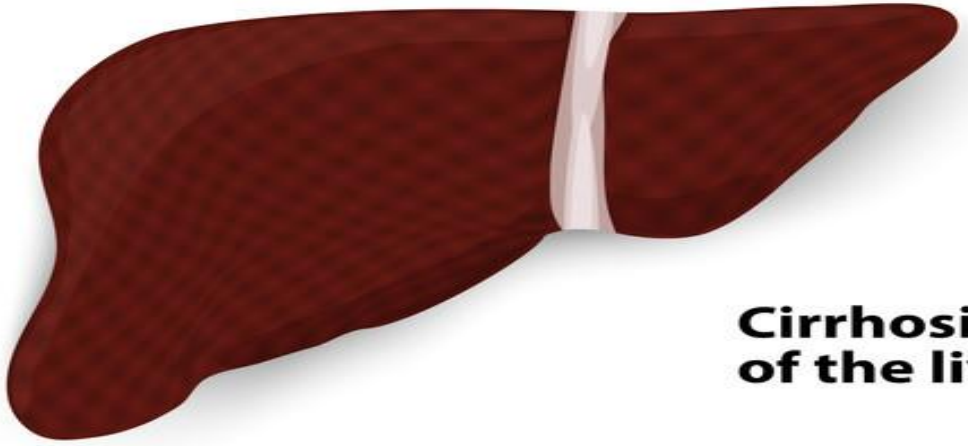


Cirrhosis

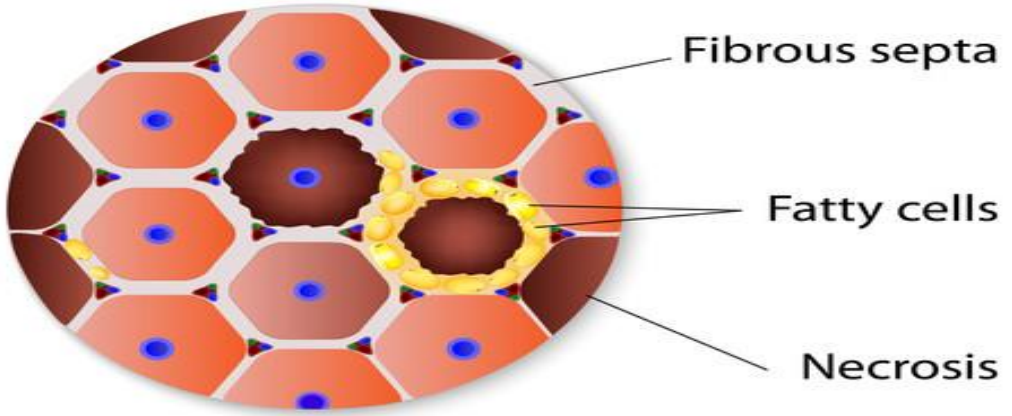


Normal liver





Cirrhosis
of the liver



Causes of Cirrhosis

❖**Causes** of **Cirrhosis include :**

1. Alcoholism (most common cause)
2. Chronic active hepatitis
3. Viral hepatitis
4. Toxins
5. Drugs
6. Hemochromatosis
7. Wilson’s disease

Clinical manifestations of Cirrhosis

❖**Clinical manifestations of Cirrhosis:**

1. Nausea
2. Vomiting
3. Anorexia
4. diarrhea
5. Fatigue
6. Fever
7. Jaundice

Consequences of Cirrhosis

❖**Consequences of Cirrhosis include:**

1. Distortion of normal hepatic architecture due to **fibrosis**
2. Disruption of hepatic blood supply by regeneration of nodules of hepatocytes with increased pressure in portal vein and portal hypertension
3. Loss of functioning liver cell mass leading to **Jaundice**
4. Accumulation of fluid in peritoneal cavity (**ascites**) ,hepatic encephalopathy and **edema**
5. Glucose intolerance and central hyperventilation resulting in **respiratory alkalosis**
6. **Hepatocellular failure** and primary Hepatocellular carcinoma in advanced cases
7. **Renal failure** in the end –stage alcoholic cirrhosis
8. Hormonal disturbances leading to **feminization** of males ,gynecomastia ,deceased body hair, **impotence** and testicular atrophy

Biochemical findings in Cirrhosis:1

❖ **Biochemical findings in Cirrhosis:**

➢ **Bile pigments:**

1. Normal or slightly increased plasma bilirubin
2. Absence of bilirubin in the urine
3. Excessive urinary excretion of urobilinogen

➢ **Plasma enzymes :**

1. Increase in plasma AST greater than that of ALT
2. Moderate increase in plasma ALP and GGT

➢ Decreased synthesis of prothrombin and other vitamin K dependent clotting factors leading to coagulopathy and prolonged prothrombin time

➢ **Plasma proteins :**

1. Decreased plasma albumin that contributes to edema
2. hyperglobulinemia
3. Increased synthesis of IgG and IgA
4. Characteristic serum protein electrophoretic pattern of β-γ **fusion**

➢ **Procollagen type III peptide measurement is useful in monitoring fibrosis**

Biochemical findings in Cirrhosis:2

❖ **Biochemical findings in Cirrhosis:**

➢ **Minerals**

1. Dilutional Hyponatremia in patients with ascites
2. Hypokalemia due to increased urinary loss
3. Prerenal azotemia
4. Hypomagnesemia and Hypophosphatemia due to dietary deficiency and increased urinary loss

Management of Cirrhosis

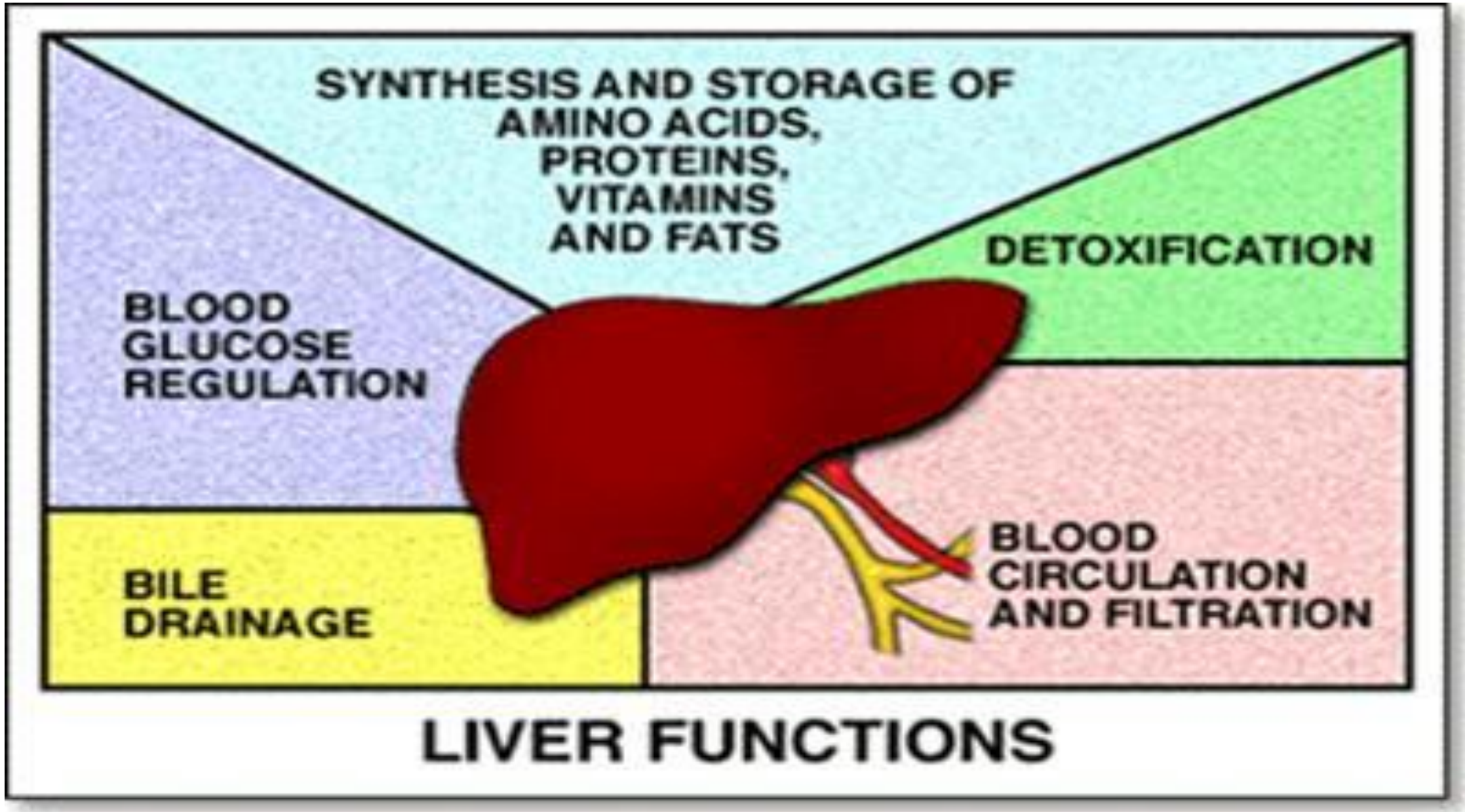
❖ **Management of Cirrhosis include**

1. Avoidance of alcohol
2. Maintenance of caloric intake
3. Maintenance of fluid and electrolyte balance
4. Management of ascites by sodium restriction
5. Management of hepatic encephalopathy controlling gastrointestinal bleeding ,restricting dietary proteins
6. Neomycin treatment to control toxin production by intestinal bacteria

Limitations of Liver function tests

1. Extra hepatitis factors
2. Enormous reverse capacity of hepatocytes
3. Regeneration of parenchymal cells
4. Tests not affected simultaneously
5. Tests lack sensitivity

❖Therefore diagnosis of liver diseases should be based on history, histology and biochemistry findings .


SYNTHESIS AND STORAGE OF AMINO ACIDS, PROTEINS, VITAMINS AND FATS
DETOXIFICATION
BLOOD GLUCOSE REGULATION
BILE DRAINAGE
BLOOD CIRCULATION AND FILTRATION
LIVER FUNCTIONS

Commonly used LFT in laboratory

1. Biochemical test for bile salts & bile pigments
2. Serum bilirubin (total /conjugated /unconjugated -) Van Der Bergh Test
3. Estimation of serum total protein & A : G ratio
4. Estimation of serum alkaline phosphatase
5. Estimation of SGPT
6. Estimation of Total & Free cholesterol
7. Prothrombin time

Thank you
Google images