# Liver Function Tests (LFTs)

# Objectives

**Objective**

**Upon completion of this lecture, the students should be able to:**

- Understand the major metabolic functions of the liver and causes of liver dysfunction.
- Discuss markers of liver function tests such as liver enzymes, bilirubin, albumin and prothrombin time that can diagnose hepatic injury and assess hepatic function.

# Liver anatomy

**The liver is the largest organ in the body**

**• It is located below the diaphragm in the right upper quadrant of the abdominal cavity and extended approximately from the right 5th rib to the lower border of the rib cage.**

**The liver is separated into a right and left lobe, separated by the falciform ligament. The right is much larger than the left .**

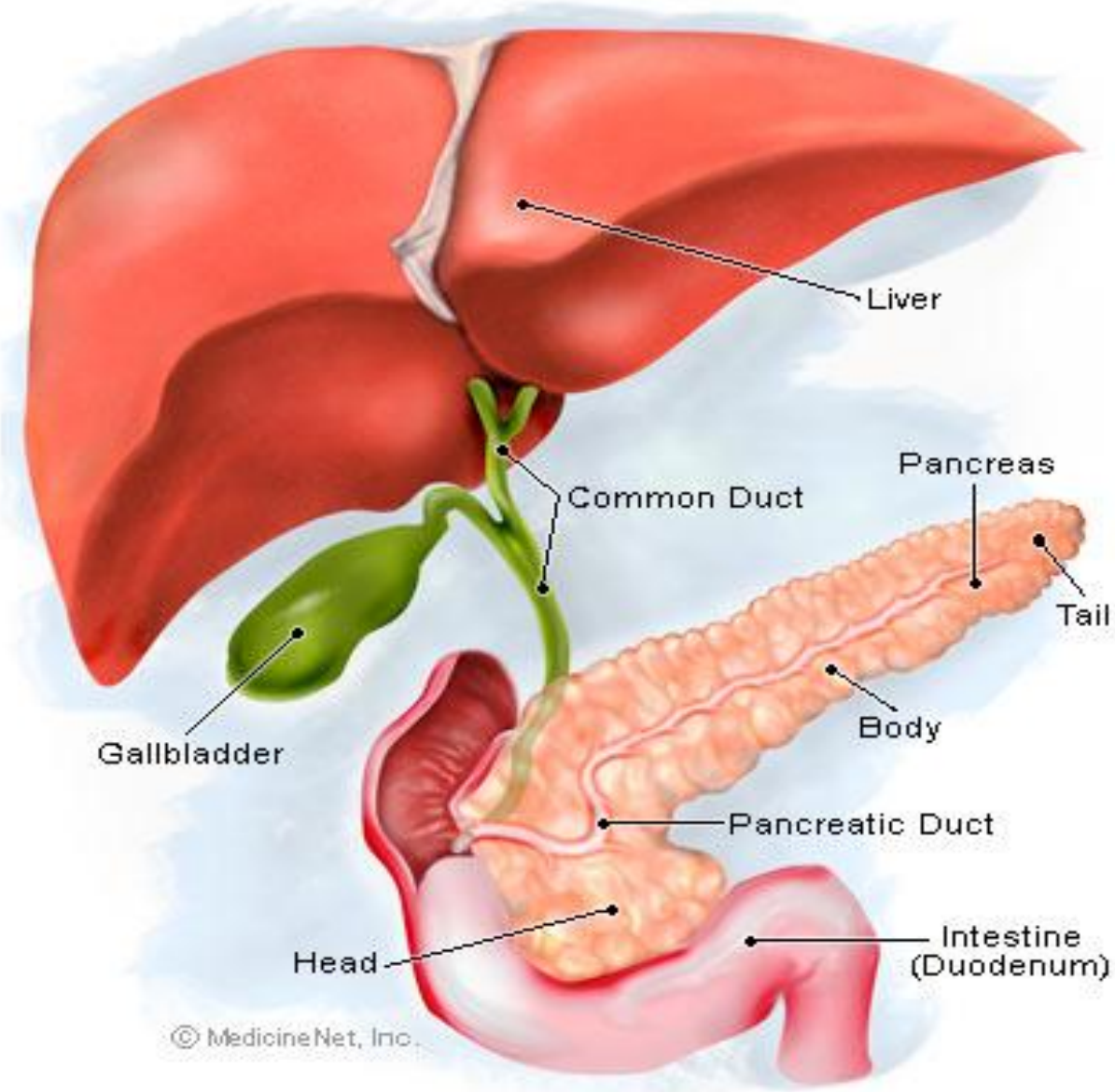
**-Liver have two channels that can supply and oxygen nutriment : hepatic artery and hepatic portal vein .**

**• The corresponding channels is hepatic vein and bile ducts.**

**The working cells of the liver are known as hepatocytes, which have a unique capacity to reproduce in response to liver injury.**

**• Liver regeneration can occur after surgical removal of a portion of the liver or after injuries that destroy parts of the liver.**

**• Although the liver's ability to react to damage and repair itself is remarkable, repetitive insults can produce liver failure and death.**


Liver
Pancreas
Common Duct
Tail
Gallbladder
Body
Pancreatic Duct
Intestine
(Duodenum)
Head
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# Major Metabolic Functions of the Liver

- **Synthetic Function**

  **Plasma proteins (albumin, globulins, prothrombine), cholesterol, triglycerides and lipoproteins**

  - **Detoxification and excretion**
  - **Ammonia to urea (urea cycle), bilirubin, cholesterol, drug metabolites**
- **Storage Function**
  - **Vitamins A, D, E, K and B12, glycogen**
- **Production of bile salts**
  - **Helps in digestion**

# Some example of liver dysfunction

- **Hepatocellular disease**
- **Cholestasis (obstruction of bile flow)**
- **Cirrhosis**
- **Hepatitis**
- **Jaundice**
- **Liver cancer**
- **Steatosis (fatty liver)**

- ***Genetic Disorders***
  - **Hemochromatosis (iron storage)**

# Liver Function Tests (LFTs)

**Liver function tests are a group of tests done to assess the functional capacity of the liver as well as any cellular damage to the hepatic cells.**

**-To assess all functional capabilities of the liver such as:**

**(a) Its Synthetic ability: By measuring the various plasma proteins such as albumin and prothrombin that are synthesized by the liver. Also lipids which are also synthesized in the liver.**

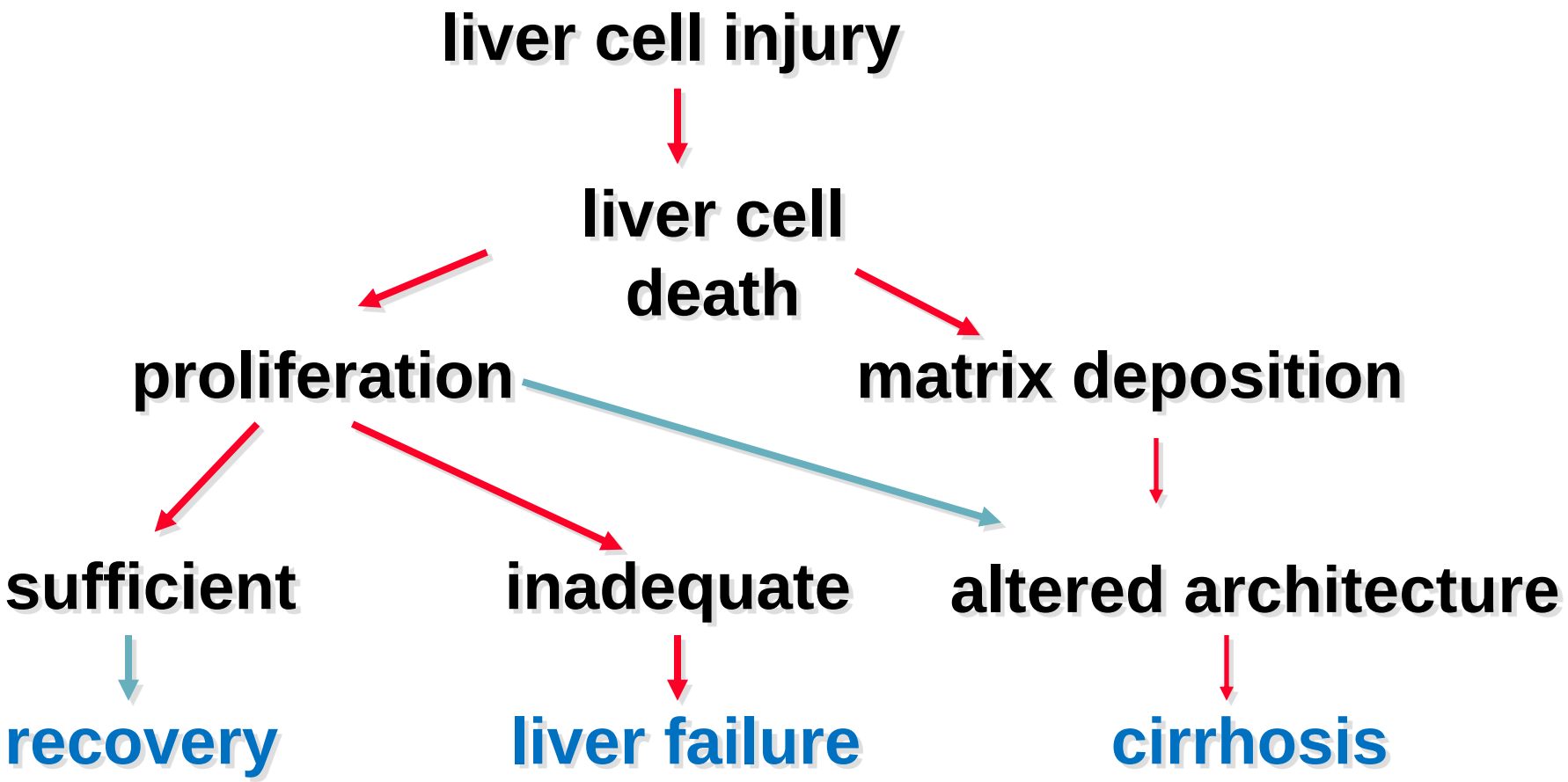
**(b) Its secretory/excretory abilities: By measuring the serum bilirubin level**

## Liver Function Tests (LFT) are:

- **Crude Indices of Hepatic Structure, Cellular Integrity, and Function; Based on measurements of substances released from damaged hepatic cells into the blood;**

- **Measurements of blood components that gives idea of the Existence, Extent and Type of Liver damage;**
- **LFT provide useful information about the Presence and Severity of Hepatobiliary Injury or Impairment of Liver Function;**

# Consequences of Liver Injury



# Liver Function Tests (LFTs)

**Broadly classified as:**

1. **Tests to detect hepatic injury:**
   - **Mild or severe; acute or chronic**
   - **Nature of liver injury (hepatocellular or cholestasis)**

2. **Tests to assess hepatic function**

# Classification of LFTs

**LFTs can be classified into Three group**

**Group I: Markers of liver dysfunction**

- **Serum bilirubin: total and conjugated**
- **Urine: bile salts and urobilinogen**
- **Total protein, serum albumin and albumin/globulin ratio**
- **Prothrombin Time**

# Classification of LFTs

## Group II: Markers of hepatocellular injury

- **Alanine aminotransferase (ALT) or glutamic pyruvate transaminase(GPT)**

- **Aspartate aminotransferase (AST)or glutamic oxaloacetic transaminase(GOT)**

# Classification of LFTs

**Group III: Markers of cholestasis**

- **Alkaline phosphatase (ALP)**
- **γ-glutamyltransferase (GGT)**

# Limitations of LFTs

- **Normal LFT values do not always indicate absence of liver disease**
  - **Liver a has very large reserve capacity**
- **Asymptomatic people may have abnormal LFT results**
  - **Diagnosis should be based on clinical examination**

# Common serum liver chemistry tests

| Liver chemistry test | Clinical implication of abnormality |
|---|---|
| Alanine aminotransferase | Hepatocellular damage |
| Aspartate aminotransferase | Hepatocellular damage |
| Bilirubin | Cholestasis, impaired conjugation, or biliary obstruction |
| Alkaline phosphatase | Cholestasis, infiltrative disease, or biliary obstruction |
| Prothrombin time | Synthetic function |
| Albumin | Synthetic function |
| γ-glutamyltransferase | Cholestasis or biliary obstruction |
| Bile acids | Cholestasis or biliary obstruction |

## What are the criteria used to select parameters in LFT?

**Some of these criteria include the following:**

- -***Tests based on substances that are produced or synthesized by Liver,*** Examples:

- **Albumin,**
- **Cholinesterase,**
- **Coagulation factors**

❖ ***Tests based on substances released by damaged Hepatocytes:***

•**These Tests are separated into two groups:**

**-Endogenous compounds released by damaged hepatocytes,**

•**Examples: AST and ALT**

**-Endogenous compounds synthesized at Increased rate or released by Canalicular membrane, Bile duct epithelium and Endothelium of central and periportal veins:**

•**Examples: ALP, GGT, 5'Nucleotidase;**

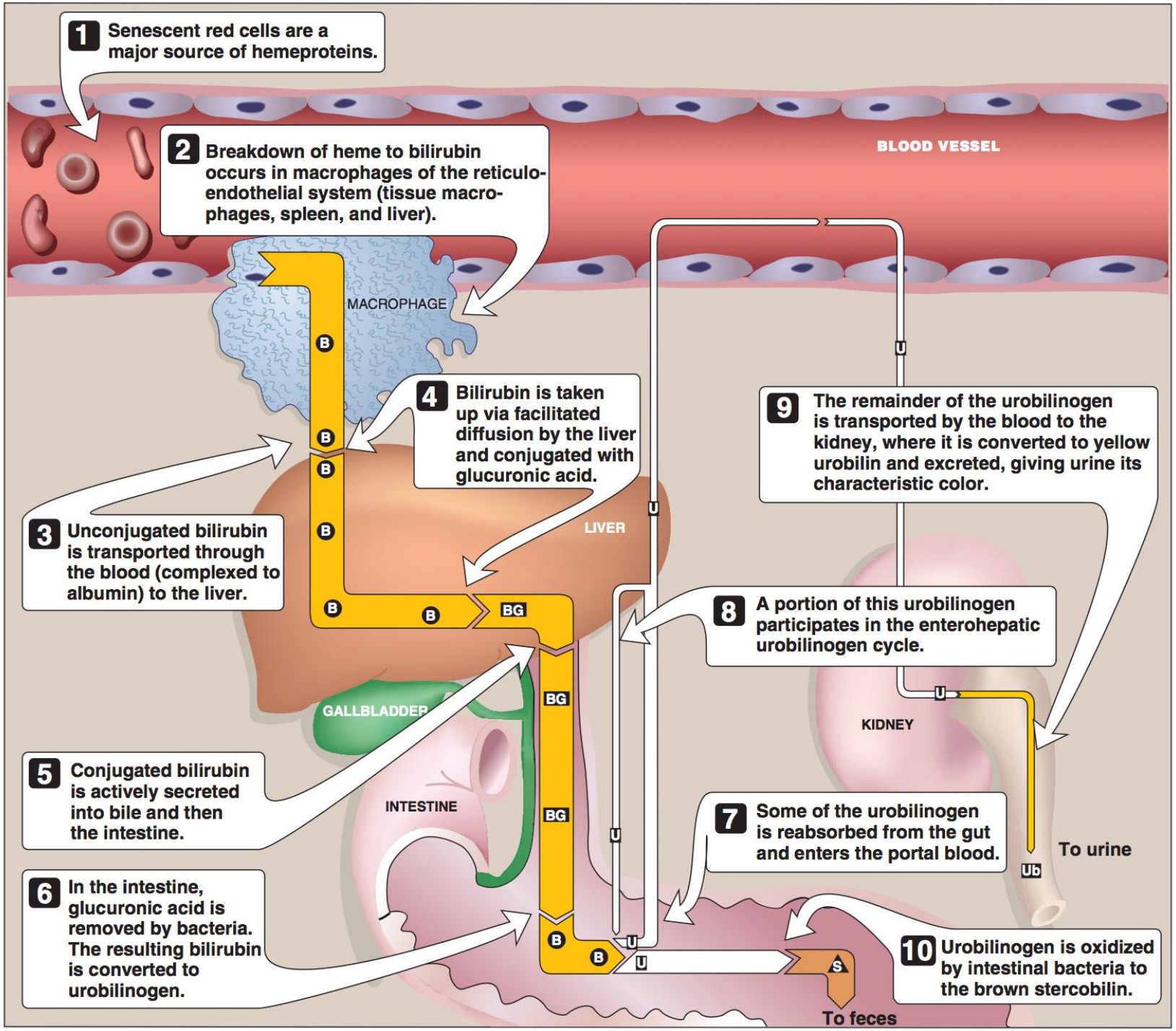
## ❖ ***Test based on substances cleared from plasma by Liver:***

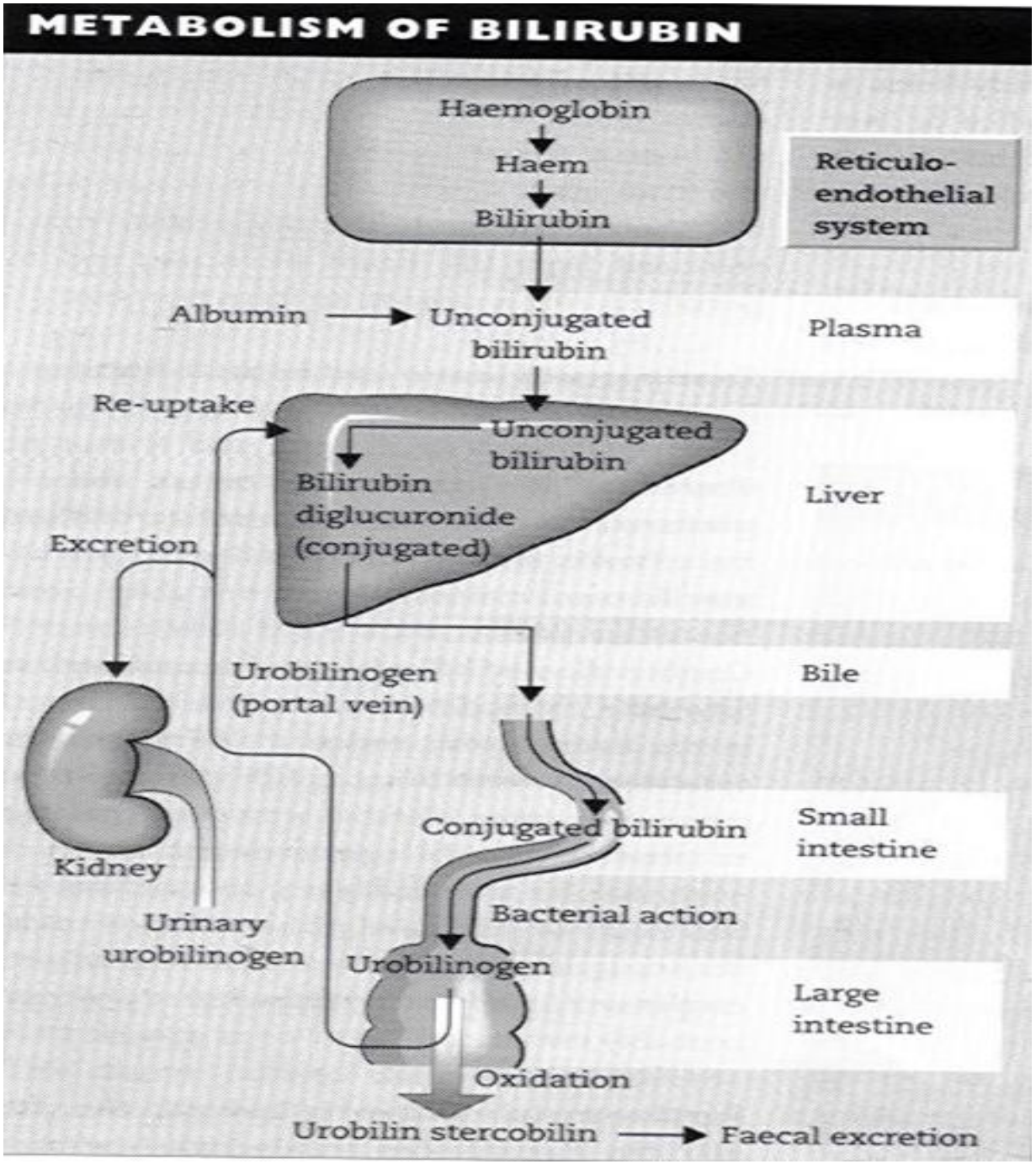
- **Can be separated into two groups:**
- **Endogenous metabolites: Examples:**
  - **Bilirubin, Bile acids, Ammonia;**

- **Exogenous compounds: Examples:**
  - **Aminopyrine, Lidocaine, Indocyanine green, Caffeine**

# Bilirubin

- **A byproduct of red blood cell breakdown**
- **It is the yellowish pigment observed in jaundice**
- **High bilirubin levels are observed in:**
  - **Gallstones, acute and chronic hepatitis**


1 Senescent red cells are a major source of hemeproteins.
2 Breakdown of heme to bilirubin occurs in macrophages of the reticulo-endothelial system (tissue macrophages, spleen, and liver).
BLOOD VESSEL
MACROPHAGE
B
4 Bilirubin is taken up via facilitated diffusion by the liver and conjugated with glucuronic acid.
3 Unconjugated bilirubin is transported through the blood (complexed to albumin) to the liver.
LIVER
BG
9 The remainder of the urobilinogen is transported by the blood to the kidney, where it is converted to yellow urobilin and excreted, giving urine its characteristic color.
U
8 A portion of this urobilinogen participates in the enterohepatic urobilinogen cycle.
GALLBLADDER
KIDNEY
Ub
To urine
5 Conjugated bilirubin is actively secreted into bile and then the intestine.
INTESTINE
7 Some of the urobilinogen is reabsorbed from the gut and enters the portal blood.
6 In the intestine, glucuronic acid is removed by bacteria. The resulting bilirubin is converted to urobilinogen.
S
10 Urobilinogen is oxidized by intestinal bacteria to the brown stercobilin.
To feces


METABOLISM OF BILIRUBIN
Haemoglobin
Haem
Bilirubin
Reticulo-endothelial system
Albumin
Unconjugated bilirubin
Plasma
Re-uptake
Unconjugated bilirubin
Bilirubin diglucuronide (conjugated)
Liver
Excretion
Urobilinogen (portal vein)
Bile
Kidney
Conjugated bilirubin
Small intestine
Urinary urobilinogen
Bacterial action
Urobilinogen
Large intestine
Oxidation
Urobilin stercobilin
Faecal excretion

# Serum bilirubin levels

- **Normal**
- **Total bilirubine**
  - **0.2 – 1.2 mg/dL**
- **Unconjugated (indirect):**
  - **0.2 – 0.8 mg/dL**
- **Conjugated (direct):**
  - **0.1 – 0.4 mg/dL**
- **Latent jaundice (existing but not yet developed )**
  - **Above 1 mg/dL**
- **Jaundice:**
  - **Above 2 mg/dL**

# Different between Unconjugated & Conjugated Bilirubin

| | UNCONJUGATED | CONJUGATED |
|---|---|---|
| In water | Insoluble | Soluble |
| In alcohol | Soluble | Soluble |
| Normal | <1.3 | <0.4 |
| In bile | Absent | Present |
| In Urine | Always absent | Normally absent |
| Absorption gut | Absorbed | Not absorbed |
| Diffusion into tissues | Diffuses-yellow colour | Doesn't diffuse |
| Van den bergh | Indirect + | Direct + |

# Bilirubin levels and jaundice

| Class of Jaundice | Causes |
|---|---|
| **Pre-hepatic or hemolytic** | **Abnormal red cells destructur; antibodies; drugs and toxins; thalessemia Hemoglobinopathies, Gilbert's, Crigler-Najjar syndrome** |
| **Hepatic or Hepatocellular** | **Viral hepatitis, toxic hepatitis, intrahepatic cholestasis** |

- **Post Hepatic Jaundice**
  - ✓ Gall Bladder - Common Bile Duct - Pancreatic duct Stone
  - ✓ Gall Bladder - Hepatic – Pancreatic – Duodenal Carcinoma

# Type & Cause of Jaundice

## ➢ Pre-hepatic Jaundice

- ✓ **Neonatal (Physiological) Jaundice**
- ✓ **Malaria**
- ✓ **G 6 PD deficiency**
- ✓ **Thalassaemia**
- ✓ **Sickle cell disease**
- ✓ **Mis-match Blood Transfusion**
- ✓ **Auto-immune**
- ✓ **Hemoglobinopathies, Gilbert's, Crigler-Najjar syndrome**

## ➢ Intra-Hepatic Jaundice

- ✓ **Acute Viral hepatitis**
- ✓ **Alcohol Cirrhosis**
- ✓ **Cirrhosis of Liver**
- ✓ **Primray Biliary Cirrhosis,**
- ✓ **Haemochromatosis**
- ✓ **Wilson Disease**
- ✓ **Alpha-1 antitrypsin deficiency**
- ✓ **Drug induce – Quinine Group, NSAID, Chemotherapeutic drugs**

## ➢ Post Hepatic Jaundice

- ✓ Gall Bladder - Common Bile Duct - Pancreatic duct Stone
- ✓ Gall Bladder - Hepatic – Pancreatic – Duodenal Carcinoma

# Urobilinogen (UBG) and bile salts

- **Most UBG is metabolized in the large intestine but a fraction is excreted in urine (less than 4 mg/day)**
- **Normally bile salts are NOT present in urine**
- **Obstruction in the biliary passages causes:**
  - **Leakage of bile salts into circulation**
  - **Excretion in urine**

- **Major causes for increase bilirubin levels in blood:**
- **Hemolysis**

**Damage to RBC may cause increased breakdown of Hb producing Unconjugated Bilirubin, which may overload liver Conjugating system, causing Hyperbilirubinemia;**

- **Failure of Conjugating system in the liver,**
- **Obstruction in the Biliary System,**

# ToTAL PROTEIN (Albumin and Globulins)

- Albumin and Globulins constitute most of the proteins in blood and are measured as Total Protein;
- Albumin is synthesize in the Liver,
- Albumin transports important blood constituents, such as drugs, hormones, and enzymes,
- Globulins: key components of Antibodies, Glycoproteins, Lipoproteins, Clotting Factors, Complement Proteins, Acute-Phase Reactant,
- Some Globulins are synthesize in Liver, but most are made in Reticuloendothelial System,
- Albumin and Globulins can be measured separately

# Serum Albumin

- **The most abundant protein synthesized by the liver**
- **Normal serum levels: 3.5 – 5 g/dL**
- **Synthesis depends on the extent of functioning liver cell mass**
- **Longer half-life: 20 days**
- **Its levels decrease in all chronic liver diseases**

## *What is the diagnostic significance of Albumin in blood?*

- **Albumin is the major protein synthesized in liver, thus can be use to assess hepatic function,**
- **Estimation of Pre-albumin is a better assessment of liver function,**
- **In some diseases of the liver, hepatocytes are unable to synthesize albumin, thus plasma albumin level drops,**
- **Half-life of albumin is 12 to 18 days, thus, severe impairment of hepatic albumin synthesis may not be recognized for several weeks or even months,**
- **Hypo-albuminaemia is a feature of advanced chronic liver disease and severe acute liver damage**

**In some Chronic liver diseases, Albumin level is low, but Globulin level is high given normal Total Protein level,**

- **Reason might be that liver cannot produce Albumin, thus the low albumin level, but Globulins are mostly made in Reticuloendothelial system, thus their levels may increase during infection;**
- **These changes can be detected by measuring the Albumin/Globulin (A/G) ratio or performs Protein Electrophoresis,**
- **A/G ratio is not a diagnostic parameter,**
- **Malnutrition can cause decrease Albumin level in blood,**

# Serum Globulin

- **Normal serum levels: 2.5 – 3.5 g/dL**

- **α and β-globulins mainly synthesized by the liver**
- **They constitute immunoglobulins (antibodies)**

- **High serum γ-globulins are observed in chronic hepatitis and cirrhosis:**
  - **IgG in autoimmune hepatitis**
  - **IgA in alcoholic liver disease**

# Albumin to globulin (A/G) ratio

- **Normal A/G ratio: 1.2/1 – 1.5/1**
- **Globulin levels increase in hypoalbuminemia as a compensation**

# Prothrombin Time (PT)

- **Prothrombin: synthesized by the liver, a marker of liver function**
- **Half-life: 6 hrs. (indicates the present function of the liver)**
- **PT is prolonged only when liver loses more than 80% of its reserve capacity**
- **Vitamin K deficiency also causes prolonged PT**
- **Intake of vitamin K does not affect PT in liver disease**

# Aspartate aminotransferase (AST) or glutamicoxaloaceticmtransaminase(GOT)

- **Normal range: 8 – 20 U/L**
- **A marker of hepatocellular damage**
- **High serum levels are observed in:**
  - **Chronic hepatitis, cirrhosis and liver cancer**

## What is the diagnostic significance of AST?

- **AST: {old name is: Serum Glutamate Oxaloacetate Transaminase (SGOT)}**
- **AST is high in Heart muscle, Liver and Skeletal muscle, but low in Kidneys, Pancreas, RBC;**
- **Damage tissues releases AST in blood;**
- **AST level in blood is directly related to extent of cellular damage or injury;**
- **Amount of ASTin plasma depends on length of time that the blood was drawn after injury (Why?)**
- **Because AST is cleared from the blood in a few days;**

**AST level in plasma is elevated 8 hrs after cellular injury, peak at 24 to 36 hrs, and return to normal in 3 to 7 days;**

- **ASTlevel in blood is always high in patients with chronic Hepatocellular disease,**
- **Acute Hepatitis: AST in plasma is about 20 times the normal value;**
- **Acute Extra-hepatic Obstruction (e.g., Gallstone), AST levels quickly rise to 10 times normal and swiftly falls**
- **Cirrhotic patients: level of AST in plasma depends on the amount of active inflammation**

# Alanine aminotransferase (ALT) glutamic pyruvate transaminase(G PT)

- **More liver-specific than AST**
- **Normal range (U/L):**
  - **Male: 13-35**
  - **Female: 10-30**
- **High serum levels in acute hepatitis (300-1000U/L)**
- **Moderate elevation in alcoholic hepatitis (100-300U/L)**
- **Minor elevation in cirrhosis, hepatitis C and non-alcoholic steatohepatitis (NASH) (50-100U/L)**

# Alanine aminotransferase (ALT)

- **Appears in plasma many days before clinical signs appear**
- **A normal value does not always indicate absence of liver damage**
- **Obese but otherwise normal individuals may have elevated ALT levels**

- **ALT found mainly in Liver, lesser quantities are in Kidneys, Heart and Skeletal muscle;**
- **Liver injury causes elevation of ALT level in blood;**
- **ALT: sensitive, specific indicator of liver disease,**
- **ALT level is more Liver-specific than AST;**
- **ALT level is directly related to extent of liver injury,**
- **Elevation of ALT in plasma depends on length of time that the blood was drawn after damage or injury (Why?)**
- **Because ALT is cleared from the blood in a few days**

# Alkaline phosphatase (ALP)

- **A non-specific marker of liver disease**
- **Produced by bone osteoblasts (for bone calcification)**
- **Present on hepatocyte membrane**
- **Normal range: 40 – 125 U/L**
- **Modearte elevation observed in:**
  - **Infective hepatitis, alcoholic hepatitis and hepatocellular carcinoma**

# Alkaline phosphatase (ALP)

- **High levels are observed in:**
  - **Extrahepatic obstruction (obstructive jaundice) and intrahepatic cholestasis**
- **Very high levels are observed in:**
  - **Bone diseases**

## What are some of the Extra-hepatic sources of ALP?

- **Bone** is the most frequent Extra-hepatic source of ALP;
- New bone growth causes elevated blood levels of ALP;
- Healing fractures,
- Rheumatoid Arthritis,
- Hyperparathyroidism;

- **Placenta,**
- Placental ALP appears in maternal blood usually in the third trimester of pregnancy;

- **Small intestine,**

- **Kidneys,**

## *How are the Isoenzymes of ALP used in diagnosis?*

- **Two major Isoenzymes: ALP-I, ALP-II**
- **ALP-I: produced mainly in Liver is Heat Stable,**
- **ALP-II: produced in Bone (ALP 2) is Inactivated by heat,**
- **They are used to distinguish liver and bone diseases;**
- **By Heat Stability Test and by Electrophoresis,**
- **Detection of Isoenzymes help determine source of pathology condition causing elevated Total ALP in blood;**
- **ALP-I is expected to be higher in Liver disease;**

# γ-glutamyltransferase (GGT)

- **Used for glutathione synthesis**
- **Normal range: 10 – 30U/L**
- **Moderate elevation observed in:**
  - **Infective hepatitis and prostate cancers**
- **GGT is increased in alcoholics despite normal liver function tests**
  - **Highly sensitive to detecting alcohol abuse**

**GGT (γGT):Catalyzes transfer of Amino Acids and Peptides across membrane and involve in Glutathione metabolism;**

- **GGT level is very high in Liver and Biliary Tract, but low in Kidney, Spleen, Heart, Intestine, Brain and Prostate gland,**
- **GGT levels are higher males because of levels in Prostate,**
- **Test for GGT is used to detect Liver cell dysfunction,**
- **GGT test is highly accurate in indicting Cholestasis,**
- **GGT is the most sensitive Liver enzyme for detecting Biliary Obstruction, Cholangitis, or Cholecystitis,**
- **Elevation of GGT parallels that of ALP in Liver disease,**
- **GGT is not increased in Bone disease,**

**Normal plasma level of GGT with elevated ALP level may indicate Skeletal disease,**

**•Elevated plasma level of GGT and elevated ALP may indicate Hepato-biliary disease**

**,**

**•GGT is not elevated in childhood or pregnancy;**

**•GGT can be used to detect Chronic Alcohol Ingestion,**
**•GGT is useful in screening and evaluation of alcoholics,**
**•GGT is elevated in about 75% of patients who chronically drink alcohol,**

**•GGT level is usually elevated about 1 to 2 weeks after myocardial infarction;**

## *What is the significant of Prothrombin Time in LFT?*

- **Prothrombin Timeis a measure of the activities of certain Coagulation Factors made by the Liver,**
- **It is used as indicator of Hepatic Synthetic Function,**
- **Prothrombin has a very short half-life, and**
- **An increased Prothrombin time may be the earliest indicator of hepatocellular damage,**

# $\alpha_2$-macroglobulin

- **Largest non-immunoglobulin protein in plasma**
- **↑ in nephrotic syndrome**

# Haptoglobin

- **Another major $\alpha_2$ protein**
- **Function – to combine with Hb released by RBC lysis to preserve Fe and protein stores**
- **Circulating half-life approx 4 days**
- **↑ in stress, infection, acute inflamm, tissue necrosis**
- **↓ post haemolytic episode**
- **Useful to monitor slow rate of haemolysis i.e. from mechanical valves, exercise associated trauma, haemoglobinopathies**

# Ceruloplasmin

- **Cu containing enzyme (ferroxidase) in serum**
- **↓ in Wilson's disease**
- **Associated with chronic hepatitis and may have neurologic/ psychiatric sequelae**

# α-Fetoprotein

- **One of the major plasma proteins in foetal life**
- **Function not known, similar structure to albumin**
- **Falls thru-out gestation (~10,000 ng/mL at birth) and by age one yr (<10 ng/mL – adult levels)**
- **In acute hepatic injury AFP ↑ 10 – 20X upper ref limits**
- **About 10% ptients with viral hepatitis have ↑ AFP**
- **Fibrosis post chronic liver d/s, AFP ↑**
- **Used to screen and diagnose HCC (Hepatocellular carcinoma) & hepatoblastoma**

# Take Home Messages

- **LFTs help detect liver injury and function.**
- **LFTs do have some limitations.**

# CASE

**52 y/o male transferred for intermittent abdominal pain and progressive jaundice over the past 2 days. Further history reveals symptoms consistent with biliary colic. Exam shows a patient in mild distress with tenderness and jaundice. Labs are significant for: AST 450, ALT 520,, T Bili 4.2**

**What is the most likely diagnosis?**