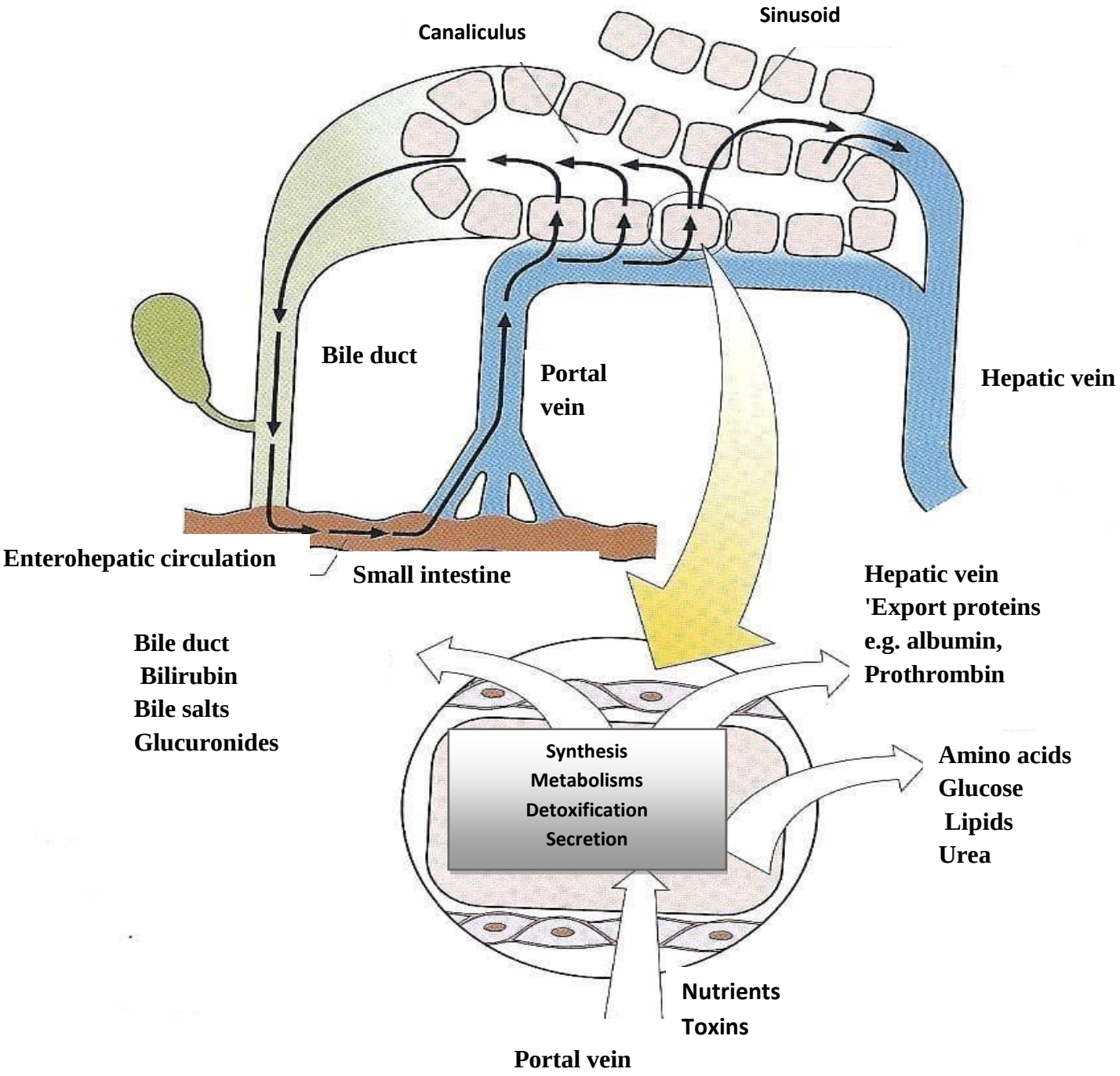
Liver Function Tests

The liver

- Liver is the largest organ in the human body (~1.5 kg in adults).
- It is located in the right upper quadrant of the abdomen and is attached by ligaments to the diaphragm.
- The liver can lose three-quarters of its cells before it stops functioning. It is the only organ in the body that can regenerate and return to normal function.
- It has an abundant blood supply from two major 2 ways:
    1. Portal vein; which carries blood rich in nutrients from GIT.
    2. Hepatic artery; which carries oxygenated blood to the liver.
    3. Hepatic veins; which carries non-oxygenated blood from liver to the inferior vena cava near the right atrium.



Functions of Liver

1) **Metabolic Functions**

   a) Carbohydrates (Glycogenesis, Glycogenolysis, Gluconeogenesis).

   b) Lipids (β-Oxidation, Ketogenesis, synthesis of TAG, VLDL, HDL and apolipoproteins)

   c) Proteins (Deamination of AA, Urea cycle, synthesis of nonessential AA)

2) **Storage Functions: (Vit-A, Vit-D, Vit-B12, Glycogen and iron)**

3) Synthetic Functions: (Albumin, clotting factors and all plasma proteins except Immunoglobulins)
4) Excretory Functions: (Bilirubin, Cholesterol, Bile acids & salts)
5) Detoxification: (Drugs, Ammonia, Steroids, xenobiotics .... etc)
6) Hematological functions: (Blood formation, Blood coagulation)

Liver Functions Test overview

- LFTS are a group of blood tests used to assess liver injury rather than liver function.
- They do not assess quantitatively the capacity of liver to do its functions.
- They are measurements of blood components that provide a lead to the existence, the extent and the type of liver damage.
- The biochemical investigations can assist in differentiating the following:
  1. Acute hepatocellular damage
  2. Chronic liver disease
  3. Obstruction of the biliary tract

Liver Functions Test overview

Blood Tests	Clinical implication of abnormality
Bilirubin Alkaline phosphatase (ALP)	(Excretory Function) Cholestasis or biliary obstruction
Y-glutamyl transferase (GGT)	
5' Nucleotidase (5'NT)	
Alanine Transaminase (ALT)	Hepatocellular damage
Aspartate Transaminase (AST)	
Albumin	Synthetic function
Prothrombin time (PT)	

1) Bilirubin

- Bilirubin is derived from Haem, mainly found in Haemoglobin of RBCS. The body usually produces about 300 mg of bilirubin per day.
- The average life span of red blood cells is 120 days. At the end of this time, they are removed from circulation by reticulo-endothelial cells in liver, spleen and bone marrow where they are haemolysed and haemoglobin released. Globin molecule is hydrolysed into free amino acids.

- **Haem gives iron and bilirubin as follows:**

1. Haem is cleaved by haem-oxygenase to form Biliverdin (green pigment) and iron is removed for reuse.

2. Biliverdin is then reduced by biliverdin reductase into Bilirubin.

3. Transport of bilirubin in the plasma. Bilirubin is non-polar, insoluble in plasma; therefore it binds by non-covalent bonds to albumin to form unconjugated indirect bilirubin.

4. Uptake of bilirubin by the liver: Bilirubin dissociates from the albumin molecule and enters hepatocytes. Bilirubin is conjugated with one or two molecules of glucuronic acid to form conjugated bilirubin (Direct bilirubin) by UDP-glucuronyl transferase (25% bilirubin mono-glucuronoid and 75% bilirubin di-glucuronoid).

5. Secretion bilirubin into bile: Conjugated bilirubin is transported into bile canaliculi then into the bile.

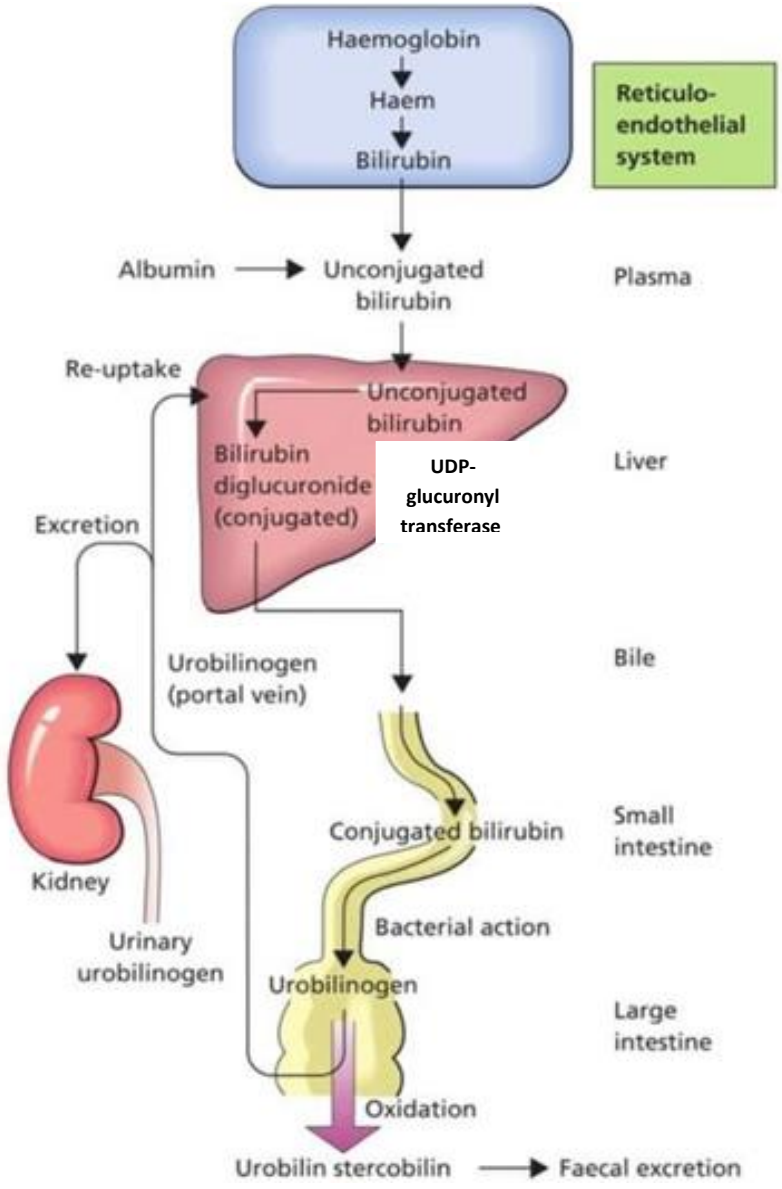
6) Formation of urobilin in the intestine: Intestinal bacteria act on conjugated bilirubin leading to:

a) Removal of glucuronides.

b) Reduction of bilirubin to colourless compounds called urobilinogens.

7. **Excretion of urobilinogens in stool and urine:**

- **Most of urobilinogens are oxidized to coloured stercobilin which excreted in stool giving its characteristic brown colour.**
- **Part of urobilinogens are reabsorbed to the liver then to blood to be excreted by the kidney in urine and converted to urobilin.**
- **Urobilin gives the characteristic yellow colour of urine.**



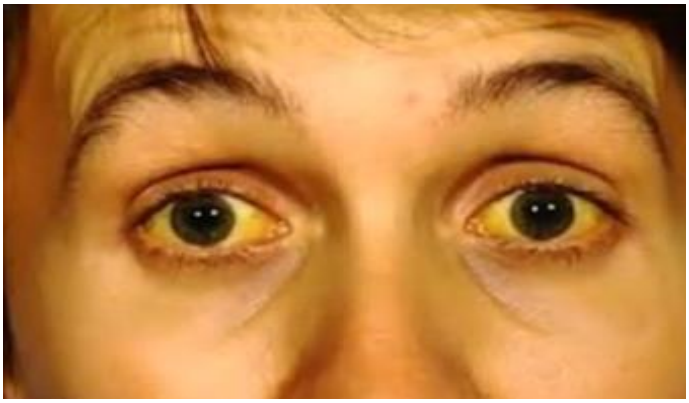
- **Bilirubin is end product of haem catabolism and present in 2 forms unconjugated and conjugated.**

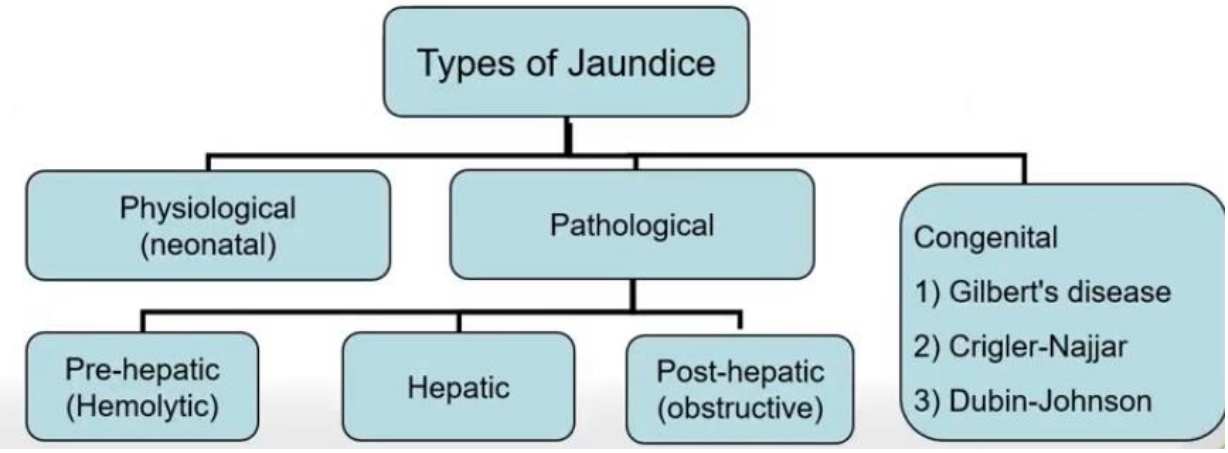
Indirect (Unconjugated)	Direct (Conjugated)
Present normally in plasma	Present normally in bile
Has high M.Wt. cannot be filtered through the kidney	Has small M.Wt. and if present in plasma can be filtered by kidney
Attached non-covalently to albumin	Conjugated to glucuronic acid
Non-polar, insoluble in plasma & can cross blood brain barrier in infants causing brain damage (Kernicterus)	Polar, soluble in plasma & cannot cross blood brain barrier
Give Indirect Van den Bergh reaction	Give Direct Van den Bergh reaction

➢ Jaundice

It is a yellow discoloration of skin and or sclera.

- **It is due to increase plasma bilirubin above 3.0 mg% (50 µmol/L)**
- **Normal is < 1 mg% (17 µmol/L).**





A. Physiological Jaundice

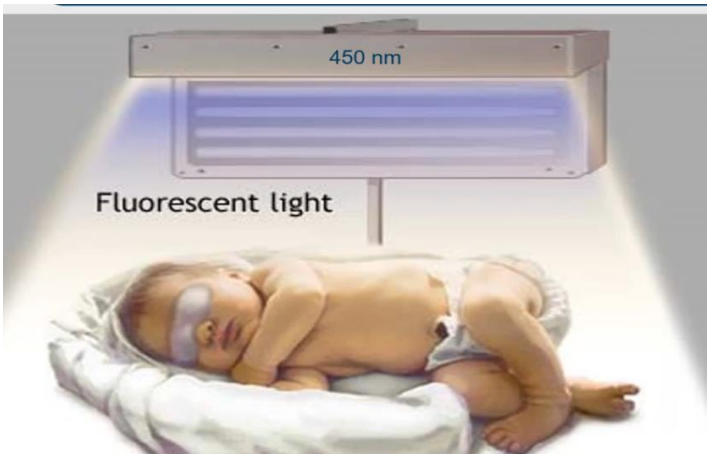
- **It is transient condition occurs in some newborns (neonate) (if they are premature).**
- **Causes:**
  1. **At birth, the liver contains very little UDP-glucuronyl transferase enzyme, which is responsible for conjugation of bilirubin.**

2. Accelerated haemolysis of RBCS.
3. Presence of extra hemoglobin (fetal Hb)

- **Effects:**
- This condition leads to increases in unconjugated (Indirect) bilirubin.
- If unconjugated bilirubin exceeds the concentration which can be tightly bound to plasma albumin (20 - 25 mg/dl), free bilirubin can pass BBB causing Kernicterus (toxic encephalopathy) which can cause mental retardation and death.

Treatment:

- Phenobarbital (liver enzyme inducers) and oral glucose (converted into glucuronic acid) to aid UDP-glucuronyl transferase
- If the concentration > 20 mg%, phototherapy should be used to break down bilirubin. Babies with neonatal jaundice are placed under blue fluorescent (wavelength around 450 nm) light (NOT UV). This result in transformation of bilirubin to more water-soluble isomers can be excreted into bile without need for conjugation.
- If the concentration > 25 mg%, blood transfusion is necessary.



B. Pathological Jaundice

1) *Pre-hepatic jaundice* (Haemolytic jaundice):

- It is characterized by increased unconjugated bilirubin. It occurs in all types of haemolytic anaemia (excessive destruction of RBCS inside blood vessels).
- The increase of unconjugated bilirubin is more than the capacity of the liver that can deal with it.

Causes:

a) Haemolytic Disorders: Abnormal haemoglobins (sickle cell anaemia). RBC membrane defects (hereditary spherocytosis). RBC enzyme defects (G6PD deficiency) Malaria infection.

b) Ineffective Erythropoiesis: Megaloblastic anaemias.

c) Blood group incompatibilities: Rh factor or ABO systems commonly responsible

d) Drugs: Salicylates and sulphonamides displace bilirubin from plasma albumin. Novobiocin inhibits UDP-glucuronyl transferase.

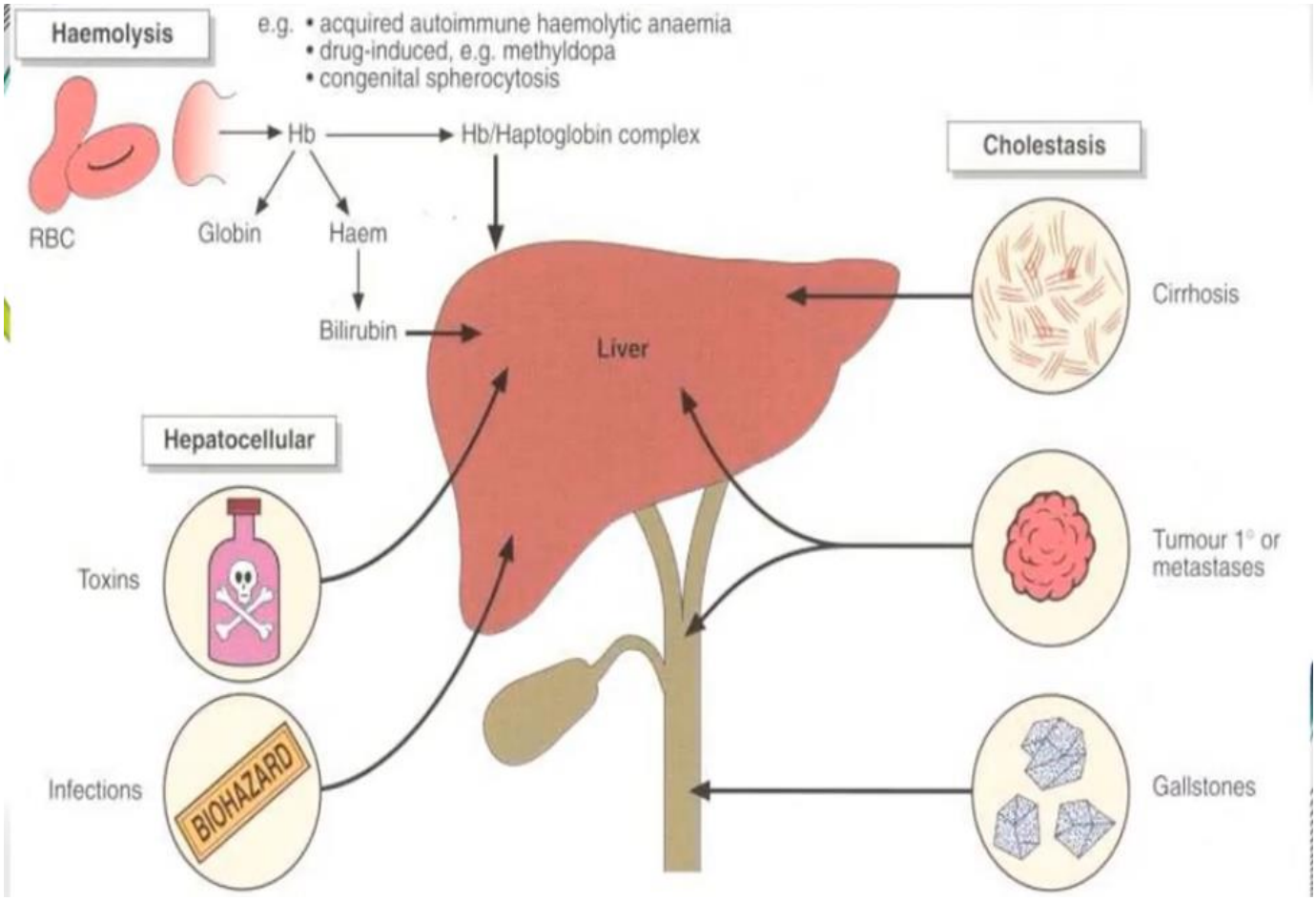
2) Hepatic (Hepatocellular jaundice):

- **It is due liver cell damage by cirrhosis, infective hepatitis (viral or bacterial), toxins (CCI4, or Paracetamol poisoning).**
- **It is characterized by increased both direct and indirect bilirubin. Also liver enzymes (ALT and AST) are elevated**

3) Post-hepatic (Cholestatic or obstructive jaundice):

- **Cholestasis (stoppage of bile flow) may be due to mechanical obstruction of biliary tree by gall stone in common bile duct or cancer head of pancreas (which exerts pressure on biliary tract). It is mostly of conjugated type,**
- **If the blockage is complete, both bilirubin and ALP are raised**
- **If the blockage is partial, only ALP may by high while bilirubin is normal as the functioning part of the liver is sufficient to process and excrete the bilirubin**
- **In obstructive jaundice bilirubin and bile salts are returns to blood. Increased bile salts in blood lead to { Itching, because bile salts are irritant to sensory nerve }.**

{ Bradycardia, because bile salts are toxic to cardiac muscles }.

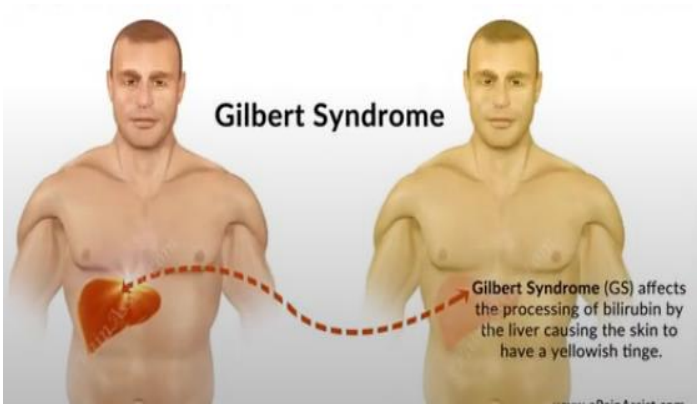


➢ *Differential Diagnosis of Pathological Jaundice*

Type	Hemolytic (Pre-)	Hepatocellular (Hepatic)	Obstructive (Post-)
Total Bilirubin	↑	↑	↑
Conjugated Bilirubin	Normal	↑	↑
Unconjugated Bilirubin	↑	↑	Normal
ALP	Normal	Normal / ↑ later	↑
AST and ALT	Normal	↑	Normal
Urine color	Normal	Dark	Dark
Stool color	Normal	Normal/Pale	Pale

C. Congenital Jaundice

A. Gilbert's Syndrome: It is asymptomatic mild (less than 3 mg% unconjugated byperbilirubinemia; Caused by decreased expression of UDPGT due to a TA insertion in the TATA box. It is harmless and doesn't require treatment however made worse by viral infections and fasting.



B. Crigler-Najar syndrome: unconjugated hyperbilirubinemia

- **Type I: Inherited disorder severe mutation of UDPGT gene leading absent UDPGT activity (unconjugated bilirubin exceeds 20 mg/dL) leading to Kernicterus and often early death.**
- **Type II (Arias syndrome): Inherited disorder milder mutation of UDPGT gene leading to reduced UDPGT activity (unconjugated bilirubin exceeds 3 mg/dL).**

C. Dubin-Johnson syndrome: It is conjugated hyperbilirubinemia without elevation of ALT or AST which occurs during adult life due to defect in hepatic secretion of conjugated bilirubin into bile. Caused by The defect is in carrier protein responsible for excretion of conjugated bilirubin from liver into bile .

2) *Alkaline* phosphatase (ALP)

- **ALP is found in cells lining biliary ducts. .**
- **It is also found in bone, placenta, small intestine and kidneys.**
- **In normal blood, the ALP activity is derived mainly liver and bone**
- **Cholestasis, even for short duration, results in an increased to at least twice the upper limit of the reference interval.**
- **Osteomalacia, rickets, children and pregnancy also show high level of ALP. However, an elevated GGT would suggest that the liver is the source of the increased ALP.**

3) γ-glutamyl transferase (GGT)

- **GGT is found in bile ducts and kidneys.**
- **It is used by the body to synthesize glutathione**
- **GGT level is raised in cholestasis. It's utilized as a supplementary test uses to confirm that elevated ALP comes from bile tract**

- **Alcoholism results in an increased GGT serum level.**

4) 5-Nucleotidase (5'NT)

- **5-Nucleotidase (5'NT) is a phosphatase that is responsible for catalyzing the hydrolysis of neucleoside-5-phosphate esters.**
- **Although 5'NT is found in a wide variety of cells, serum levels become significantly elevated in hepato-biliary disease (cholestasis or damage of biliary system.**
- **There is no bone source of 5'NT so it is useful in differentiating ALP elevations due to the liver from other conditions.**

5) Aminotransferases

- **These enzymes are located in liver cells and leak out into blood stream when liver cells are damaged.**
- **1. AST: is found normally in liver, heart, RBCS and muscle. AST elevates in diseases of liver, heart as myocardial infarction, and muscle as muscle trauma. It is more sensitive for liver diseases.**
- **2. ALT: is found primarily in hepatocyte thus more specific for liver.**

Serum levels of ALT and AST	Indicates
10 times the upper limit of normal (ALT/AST > 10)	Acute liver diseases
3-5 times the the upper limit of normal	Chronic liver diseases
Normal ALT level with high AST (ALT/AST < 10)	Myocardial infarction

6) Plasma Albumin

- Albumin is synthesized in the liver and its concentration in the plasma is in part a reflection of the functional capacity of the organ.
- Plasma albumin concentration tends to decrease in chronic liver disease, but is usually normal in the early stages of acute hepatitis owing to its long half-life (approximately 20 days).
- A/G Ratio: Normally, there is more albumin than globulins in plasma, giving a normal A/G ratio > 1.

7) Prothrombin time

- Liver is responsible for synthesis of prothrombin and other vitamin-K- dependent clotting factors.
- In liver disease, there is a diminished synthesis, thus PT becomes longer (Normal PT: 10-13 seconds).
- PT may be one of the earliest abnormalities seen in patients with hepatocellular damage, since prothrombin has a short half-life (< 6 h).
- To decrease variability for lab to lab, PT obtained is compared to a normal patient's blood. This ratio is called International Normalized Ratio (INR).
- INR of more than 1.2 is often an early feature of acute liver disease or vitamin- K deficiency (in which case, a single parenteral dose of vitamin K should normalize the prothrombin time within 18 h).

Acute Hepatitis

Acute hepatitis is usually caused by:

1. Viral infection (particularly with hepatitis viruses A, B, C, D and E but also Epstein-Barr virus and cytomegalovirus)
2. Toxins (e.g. alcohol, carbon tetrachloride, various fungal toxins and a host of drugs, of which the most frequently implicated is probably paracetamol)

- **Patients may present with jaundice (icteric) but there is often without jaundice (pre-icteric) stage with relatively nop- specific symptoms such as anorexia and malaise.**
- ***Biochemical changes during acute hepatitis:***

	Pre-icteric	icteric
Serum Bilirubin	Normal	↑
Aminotransferases	↑↑↑	↑
Serum ALP	Normal	↑
Urinary Bilirubin	↑	↑

Chronic Hepatitis

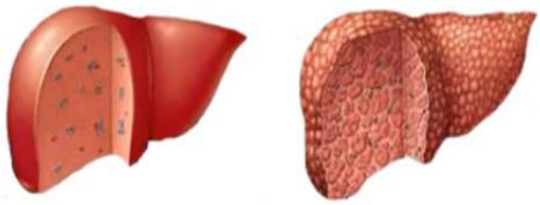
Chronic hepatitis is defined as hepatic inflammation persisting for more than six months.

- **There are many causes:**

1. **Autoimmune hepatitis**
2. **Chronic infection with hepatitis B or C**
3. **Alcoholism Plasma aminotransferase activities are usually elevated hepatitis, but other liver function tests are often normal unless cirrhosis develops.**

Liver Cirrhosis

- **Cirrhosis is the end stage of chronic hepatitis and characterized by extensive liver fibrosis. It is IRREVERSIBLE**
- **Fibrosis is the formation of a scar tissues resulting in the disorganization of liver architecture and its shrinkage.**



- **Ascites: increased portal venous pressure, a low plasma colloid oncotic pressure and Na+ retention due to secondary hyperaldosteronism combine to cause ascites in cirrhotic patients. Th is often develops when serum [albumin] falls below 3 g/dl.**