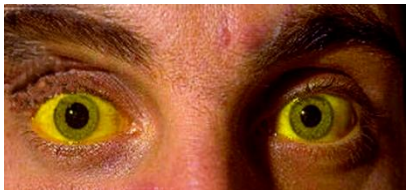
Unit V – Problem 1 – Biochemistry: Liver Function Tests and Jaundice

- **Mention three functions of the liver.**
  - Bilirubin conjugation and secretion.
  - Serum albumin synthesis (plasma proteins).
  - Coagulation factors synthesis (prothrombin, fibrinogen and factor VII).
- **What are the markers of liver injury?**
  - **Abnormality of the above functions.**
  - **Leakage of liver enzymes:**
    - ✓ Aminotranferases.
    - ✓ Alkaline phosphatase.
    - ✓ ± Gamma glutamyl transpeptidase.

    They provide an indication to the existence, extent and type of liver damage.
- **Liver function tests (LFTs):**

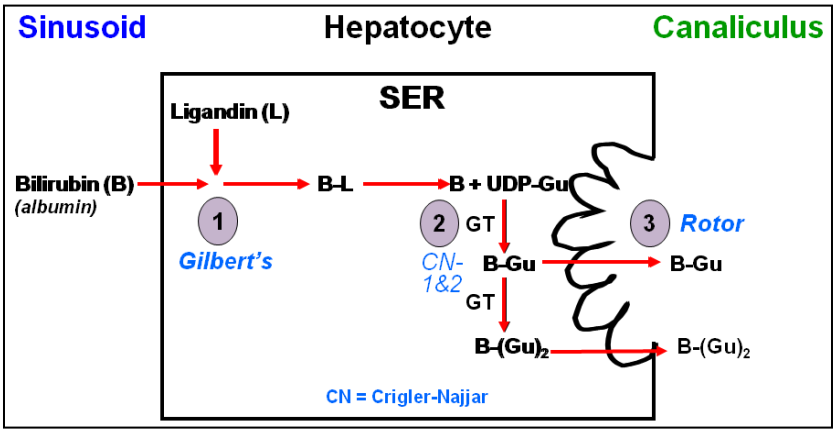
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ALP	Alkaline phosphatase
GGT	Gamma glutamyl transpeptidase

- **Synthesis of bilirubin:**
  - After 120 days, RBCs will be degraded by the reticuloendothelial system (especially macrophages in the spleen).
  - **Hemoglobin will be released and then degraded into:**
    - ✓ Heme: which will be oxidized to biliverdin.
    - ✓ Globin: recycled.
  - Then, biliverdin will be reduced to bilirubin which will be carried in blood bound to albumin.
  - Bilirubin-albumin complex will move into the liver to be conjugated via the enzyme glucouronyl transferase to produce bilirubin diglucouronide.
  - **This conjugated bilirubin will either be:**
    - ✓ Excreted in feces as stercobilin (brown in color).
    - ✓ Excreted in urine as urobilin (yellow in color).
  - **Notes:**
    - ✓ Accumulation of bilirubin in the plasma and tissues results in jaundice (اليرقان). Jaundice is characterized by yellow discoloration of the skin, sclera and mucous membranes.



    - ✓ Patients with large increases in unconjugated bilirubin are susceptible to biliruin encephalopathy (which is known as kernicterus).
- **Jaundice:**
  - It is seen when the serum total bilirubin is > 51 µmol/L (3 mg/dL). Notice that a bilirubin level between 25 and 51 µmol/L is considered as hyperbilirubinemia without the appearance of clinical features characterizing jaundice.
  - **Elevated bilirubin in the absence of other abnormal liver function tests is found in:**
    - ✓ Newborn (neonatal jaundice: due to low levels of glucouronyl transferase which results in increased levels of unconjugated bilirubin).
    - ✓ Inherited disorders of metabolism.

- **Bilirubin metabolism (inherited hyperbilirubinemia):**



  - **Gilbert syndrome:**
    - ✓ Mildly ↓ UDP-glucouronosyl transferase conjugation activity → ↓ bilirubin uptake by hepatocytes.
    - ✓ Characterized by asymptomatic or mild jaundice.
    - ✓ Elevated unconjugated bilirubin without overt hemolysis.
    - ✓ Bilirubin ↑ with fasting and stress.
  - **Crigler-Najjar syndrome, type-I:**
    - ✓ Absent UDP-glucouronosyl transferase.
    - ✓ Presents early in life and patients die within a few years.
    - ✓ Findings: jaundice, kernicterus (bilirubin deposition in brain) and ↑ unconjugated bilirubin.
    - ✓ Treatment: plasmapheresis and phototherapy.
  - **Rotor syndrome:**
    - ✓ Conjugated hyperbilirubinemia due to defective liver excretion but it does not cause black liver (when compared to Dubin-Johnson syndrome).
- **Liver enzymes:**
  - **Alkaline phosphatase (ALP):** there are many isoforms (in liver, bones intestine and placenta).
  - **Gamma glutamyl transferase (GGT):**
    - ✓ Parallels (ALP) level in liver disease.

↑ (GGT) and normal (ALP)	↑ (ALP) and normal (GGT)
• Alcohol • Drugs	• Rapid bone growth • Bone disease • Pregnancy

- **Albumin:**
  - It is synthesized mainly by the liver and considered as the primary plasma protein.
  - It has a long half-life: 14-20 days.
  - When it is decreased, this can be used as a marker for poor nutrition (malnutrition!).
- **Prothrombin time:**
  - Factor VII has a short half-life (4-6 hours).
  - Prothrombin time is an indirect measure of factor VII level.
- **Important diagnosis with liver function tests:**
  - ↑ Total bilirubin and (ALP): cholestasis (biliary obstruction).
  - ↑ Aminotransferases: hepatocellular damage (e.g. hepatitis).
  - ↓ Albumin: chronic liver disease or malnutrition.

	Hemolytic (prehepatic)	Cholestatic (obstructive)	Hepatocellular (hepatic)
Bilirubin (serum)	↑↑ (mostly unconjugated)	↑↑↑ (mostly conjugated)	↑ Later (mixed)
Bilirubin (urine)	– (acholuric)	↑↑	↑
Urobilinogen (urine)	↑↑	–	↗
AST, ALT	–	↗	↑↑
ALP	–	↑↑ > 3 x URL	↑ Later
Other	↓ Hb, Hp ↑ retics	Clay-colored stools	

URL = upper reference range limit; **Hp** = haptoglobin; **retics** = reticulocytes

- **Bile salts synthesis:**
  - **Cholesterol is the precursor which will be converted via the action of the enzyme cholesterol 7α-hydroxylase to bile acids:**
    - ✓ Cholic acid.
    - ✓ Chenodeoxycholic acid.
  - **These bile acids will converted to bile salts by the following:**
    - ✓ Cholic acid + glycine = glycocholic acid.
    - ✓ Chenodeoxycholic acid + taurine = taurochenodeoxycholic acid.
- **Bile salts perform four physiological functions:**
  - Elimination of excess cholesterol.
  - Emusifying agents that render fats accessible to pancreatic lipases.
  - Facilitate intestinal absorption of fat-soluble vitamin.
  - Preventing precipitation of cholesterol in gallbladder.