Internal Medicine -- Hepatology lecture for
4Th-year medical students' . University of Anbar College of Medicine
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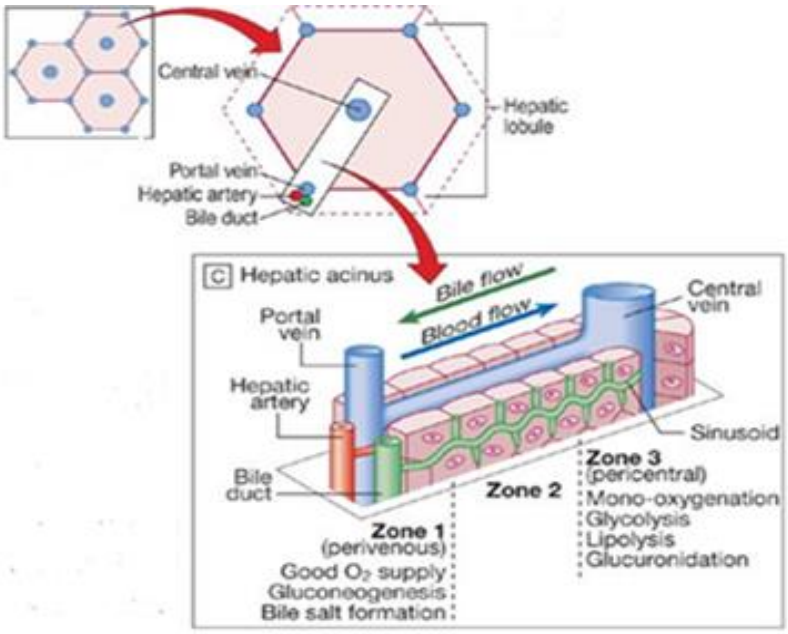
Lecture 1[2hrs]

Hepatology

*Hepatology is Diseases of the largest and the most metabolically complex organ in humans.
*Weight of the liver about 1.2-1.5 kg.
*Liver receives blood from both hepatic artery [coming from coeliac axis] and portal vein [brings blood from the [gastrointestinal tract, spleen, pancreas, and gallbladder].
*Approximately 20% of blood flow is O2 rich coming from the hepatic artery and 80% is nutrient-rich blood coming from the Portal vein.
*The Falciform Ligament divided the liver into right and left lobes, each lobe has its blood supply and duct drainage.
*The Riedle lobe is a caudal prolongation of right lobe which may give a false impression of hepatomegaly.
*The liver is divided into 8 segments based on the vascular or bile duct distribution.
*The caudate lobe [segment 1] receives blood from both rights and left branches of the portal vein and drains directly into the inferior vena cava.
*Each segment is formed by multiple lobules each lobule has a central terminal hepatic vein and bounded by 4-6 portal triads.
*The lobule consists of hepatocytes which are arranged in plates.
*The space between the plates forms the sinusoid.
*Bile canaliculi are situated On the opposite side of the hepatocyte plates.
*Space of Disse [which is a narrow space formed between the endothelial cells and the hepatic cells].
*in the sinusoids blood from the portal vein mixed with blood from the hepatic artery, From the sinusoids blood enters the central vein and then to the hepatic vein.
*Hepatic vein carries blood to the inferior vena cava.
*Bile forms In the bile canaliculi and then flows into bile ducts and then into hepatic ducts.
*Outside the porta hepatic the common hepatic duct joins the cystic duct from the gallbladder to form the common bile duct which drains in the duodenum.
*The functional units of the liver is the hepatic acinus. The acinus divided into three zones:
1-The periportal zone =The circular zone around the portal triad.
2-Midzonal area=The zone between the periportal and pericentral zone.
3-The Central zone =The circular area around the central vein
Blood flows through sinusoids from zone 1 toward zone 3 while bile flows from zone 3 toward zone 1.



Liver structure and microstructure

Sinusoidal Lining Cells includes

1-Kupffer cells [Spindle –Shaped cells]:-

Tissue macrophages form an important part of the reticuloendothelial system.

*Functions of kupffer cells include *Lipoprotein uptake and metabolism

*lgG complex removal *Clearance of bacteria, viruses, and erythrocytes.

*Binding and removal of lipopolysaccharides *Cytokines production.

2-Stellate cells [fat storing cells, lipocytes,ito cells]:

Stellated cells lie within the space of Disse.

*Stellates cells regulate blood flow and play role in the development of portal hypertension because it contains actin and myosin and contract in response to endothelin-1 and substance P. Their functions include

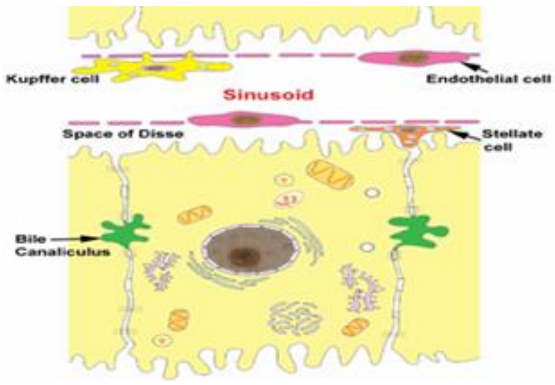
*Uptake and storage of vit A. *Synthesis of extracellular matrix

*Metalloproteinase inhibitor. *Cytokines synthesis and release.

3-Endothelial cells.

*Fenestrated barrier between hepatocytes and sinusoidal blood. that permit hepatocytes to have access to nutrients and macromolecules in plasma. these cells have a high capacity for endocytosis and in clearing macromolecules from circulation.

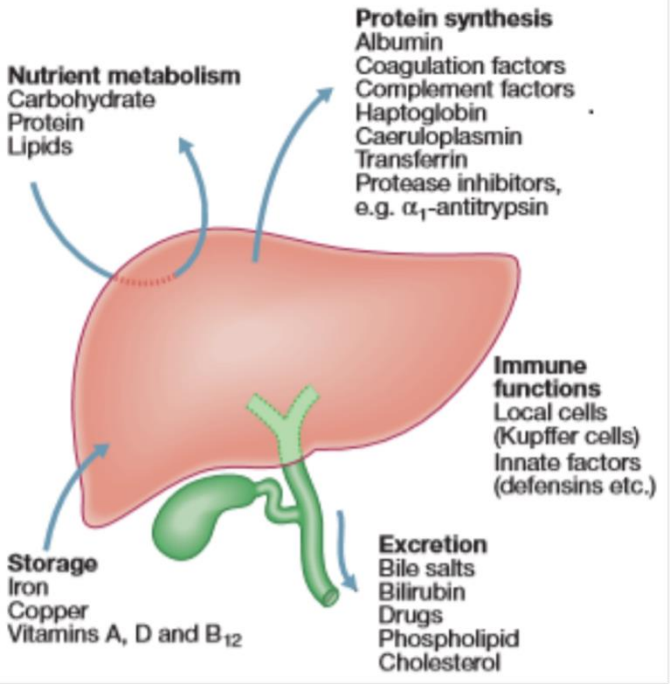
4-Pit cells.Lymphocytes in the portal tract and sinusoids. functions include -[killing tumor cells and virus-infected cells].



Non-parenchymal liver cells

Major Hepatic Functions include

1-Synthesis of essential proteins: -Albumin, Coagulation factors, Complement factors, hepatoglobulin, Caeruloplasmin, Transferrin, and Protease inhibitors.
2-Nutrient metabolism:- Carbohydrate, Protein, and Lipid
3-Storage:- iron, Copper and Vitamins A, D, B12
4-Detoxification or Excretion of Drugs, Hormones, alcohol, bilirubin, and bile salts.



Important liver functions

Investigations of liver disease include.
1-hematological tests include
Complete blood picture:-
*Normochromic normocytic anemia occurs in the acute gastrointestinal tract[G.I.T]. bleeding from Esophageal varices, peptic ulcer disease, and portal hypertensive gastropathy[PHGP].
*Hypochromic microcytic anemia indicates chronic blood loss.
*Mactocytosis occur in- alcohol abuse
*Erythrocytosis occur in–hepatocellular carcinoma[HCC]due to ectopic secretion of Erythropoietin
*Leukocytosis occurs in cholangitis, alcoholic hepatitis, and hepatic abscess.
*Atypical lymphocytes- occurs in infectious mononucleosis.
*Thrombocytosis occurs in acute GIT bleeding and HCC.
*Pancytopenia due to hypersplenism in case of portal hypertension.
2-Liver function tests include
Bilirubin:-
*Normally Serum bilirubin< 1 mg is mainly in an unconjugated form reflecting a balance between production and hepatobiliary excretion.
*Daily production of bilirubin < 500 mg but the normal liver can conjugate up to 1500mg/day.
*Any bilirubin found in urine is conjugated and is an indicator of hepatocellular disease and biliary obstruction.
*in obstructive jaundice urobilinogen disappears from urine.
*Unconjugated Bilirubin production increases in hemolysis, ineffective erythropoiesis, resorption of a hematoma, and rarely in muscle injury.

Blood Ammonia

*Ammonia produced by normal protein metabolism and by intestinal bacteria.
*Liver convert ammonia to urea and excreted by kidneys.
*in Striated muscle ammonia is combines with glutamic acid to form glutamine.

Protein

The liver is the main site for synthesis of most plasma proteins except immunoglobulin's [gamma globulins]

Albumin

*Approximately 10 g of albumin is synthesized and secreted daily by the liver.
*Normal serum albumin level is 4-6 gr%.
*Serum half-life of albumin is 3W. With progressive liver disease, serum albumin levels fall, reflecting decreased synthesis.
*Serum albumin is less useful than PT in assessing hepatic synthetic function in a patient with acute liver disease.

Non-hepatic causes of Hypoalbuminemia are

*Protein-losing Enteropathy
*Nephrotic syndrome*Malnutrition

Globulins [alpha, beta and gamma globulins**]**

*Alpha and beta globulins are synthesized in the liver.
*Gamma globulin is produced by plasma cells,
*in Cirrhosis gamma globulin is increased because the cirrhotic liver is unable to clear bacterial antigens that normally reach the liver so antibodies are formed against such antigens. examples include

Increase IgG occurs in -Autoimmune hepatitis.
increase IgA occurs in Alcoholic liver disease.
Elevated IgM occurs in Primary biliary cirrhosis.

Coagulation Factors

* Except F-VIII all other factors are synthesized in the liver, the half-life of coagulation factors ranges from 6 hrs. for F VII to 5 days for fibrinogen
*Prothrombin time measures the activity of factors involved in the extrinsic pathway.
*in liver disease there is malabsorption of vit K which is required for the synthesis of coagulation factors II, VII, IX, and X
*Prolonged PT not corrected by vit K administration indicates a poor prognostic sign in acute and chronic liver disease. Because of the short ½ life of some coagulation factors measured by PT (6 hrs for F. VII), it is useful in monitoring hepatic function in acute and chronic liver disease. but correlates poorly with bleeding risk in patients with liver disease because of counterbalancing disturbances in the anticoagulant activity of protein S and C which produced by the liver.

Serum Enzyme Tests are grouped in

1-Enzyme that reflect damage to hepatocytes -Aminotransferases
*AST[SGOT] found in liver, cardiac muscle, skeletal muscle, kidneys and brain
*ALT [SGPT] found primarily in the liver when there is damage to hepatocytes causing increase serum concentration.
* In most hepatocellular disorders ALT is higher or equal to AST.
*Normal AST/ALT ratio is 0.7-1.4 * Ratio >3:1 is suggestive of alcoholic liver disease. Ratio < 1 is seen in NASH and viral hepatitis.

Causes of Elevated Aminotransferase Level

*Common cause include: viral hepatitis, Alcoholic liver disease, Nonalcoholic steatohepatitis, Medications [: non-steroidal anti-inflammatory drugs, antibiotics, HMG Co-A-reductase inhibitors, antiepileptic, antituberculous, herbal], Autoimmune hepatitis,

hemochromatosis, Alfa 1 antitrypsin deficiency, Wilson's disease, Celiac disease, Cytomegalovirus, Epstein–Barr virus infection. Striated muscle disease, endocrine disease: hypothyroidism, Addison's disease, Glycogen storage diseases, Congestive cardiac failure, and ischaemic hepatitis.
Persistence of elevated ALT and AST beyond 6 months in case of hepatitis indicates the development of chronic hepatitis.

Enzymes Whose Elevation Reflects Cholestasis include

Alkaline Phosphatase(ALP).

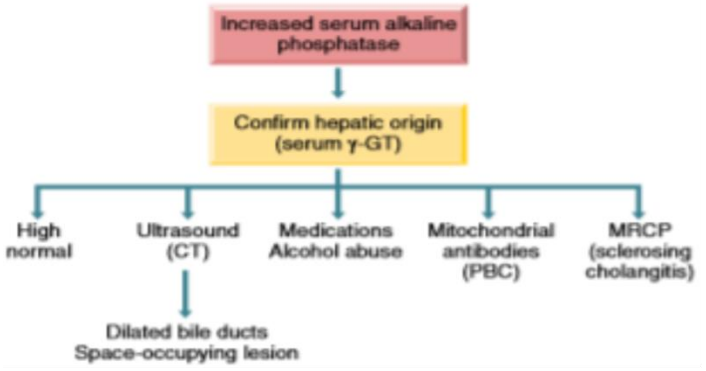
*ALP found in liver, bone, placenta, kidney, leucocytes, and small intestine.
*In cholestatic liver disease, the elevated bile acids stimulate the synthesis of ALP. rather than hepatocytic leakage. the level rises slowly over days or weeks.
*ALP in adolescence up to 3 times more than adult (due to rapid bone growth) and also in pregnancy due to placental growth and metabolism.
*ALP increases after fatty meal therefore ALP should be obtained fasting.
*-½ life of ALP is 1/52 w. [ALP remains elevated for several days to weeks after resolution of biliary obstruction].
*Isolated Elevation of alkaline phosphatase suggests either a physiological cause (pregnancy, growth) or bone disease
High aminotransferase with a small increase of ALP indicates hepatocellular damage.
***Gama-Glutamyle Transferase[GGT]** and **5 nucleotidase**s [**5 NT**]**:-**is used as a diagnostic marker for liver disease. GGT and 5 nucleotidase[5 NT] is especially used to confirm the Hepatic origin of ALP.

Causes of Raised Gamma Glutamyltransferase

isolated increase in GGT may occur during the ingestion of microsomal enzyme-inducing drugs like (a barbiturate, carbamazepine, ethanol, glucocorticoids, Grisofluvin, INH, Meprobamate, phenytoin, Primidone, rifampicin.).
high ALP and GGT with Small increase in aminotransferase indicate biliary obstruction

Causes of Elevated Alkaline phosphatase & Gamma-Glutamyl Transferase include.

*Hepatobiliary disease mainly in Cholestatic conditions (e.g. PBC, PSC, anabolic steroids, partial obstruction of bile ducts). * infiltrating tumors in the liver.



Algorithm for managing a patient with an isolated increase in serum alkaline phosphatase or serum γ-glutamyl transpeptidase (γ-GT).

3-Biochemical Tests include.

*Hyponatremia occurs in severe liver disease due to increase ADH level.
*S.urea increase following gastrointestinal hemorrhage.
*S.urea may be decreased in hepatic failure.

Combination of high or low urea with increase Creatinine and bilirubin and decrease urinary Na excretion indicates Hepatorenal failure which carries a bad prognosis.

4-investigations For Hepatitis an initial diagnostic serological screen include**.**

*Hepatitis A, B, and C serology.

*Autoimmune screen includes antinuclear antibodies (ANA), antimitochondrial antibodies (AMA), smooth muscle antibodies (SMA), and liver/ kidney microsomal antibody.

*Testing for anti-Endomysial (EMA) or anti-tissue transglutaminase (tTG) particularly in the patient with GI disturbance, because occult coeliac disease as a cause of LFT abnormalities is increasing.

*Fasting blood sugars and lipids should be tested where fatty liver disease is suspected.

*In the young patient, the genetic causes for LFT abnormalities include, Wilson's disease (serum caeruloplasmin), hereditary hemochromatosis (serum ferritin and transferrin saturation) and alpha-1-antitrypsin deficiency (AAT concentrations) can be screened.

5-Imaging Procedures include

1-Conventional ultrasonography (US):- safe comfortable used in the identification of gallstone, biliary obstruction, and liver lesions> 2 cm, organomegaly, and ascites.

2-Doppler US:- flow inside, PV, HA, HV

3-Computed tomography = the same uses of us but detect smaller lesions especially when used with contrast injection. It is more helpful in assessing the pancreas.

4-Magnetic resonance imaging [MRI] It can detect some lesions poorly seen by US or CT and more helpful for defecting [hemangiomas].

6- Direct Biliary Visualization

*MRCP [Magnetic Resonance Cholangio-Pancreatography]. Can visualize biliary tree but does not permit therapeutic intervention.

*ERCP:- Endoscopic Retrograde CholangioPancreatography.

An upper endoscopy allows direct cannulation of the common bile duct and or pancreatic duct. The injection of the contrast agent yields an excellent definition of ductal anatomy and also allows therapeutic intervention[stone removal, dilatation, biopsy, or stenting].

*PTC:- Percutaneous Transhepatic Cholangiography. Used when it is impossible to access the bile duct by endoscopy. Direct contrast visualization of the biliary tree by percutaneous needle puncture of the liver.

7-Hepatic Aarteriography to localize focal liver lesions and is necessary for planning hepatic surgery

8-Endoscopic US. Provides high-resolution images of the pancreaticobiliary tree, liver. And GIT wall layers.

9-Non-invasive Markers of hepatic fibrosis include

1-APRI **tests**[aspartate, platelet ratio] These results are formulated to determine a fibrosis index

$$\text{APRI} = \frac{\dfrac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count } (10^9/\text{L})} \times 100$$

Ratio >0.7 indicates significant fibrosis

2-FIB-4 Score helps to estimate the amount of scarring in the liver

$$FIB\text{-}4 = \frac{Age\ (years) \times AST\ (U/L)}{Platelet\ Count\ (10^9/L) \times \sqrt{ALT\ (U/L)}}$$

FIB-4 <1.45 indicate non-significant fibrosis, but score >3.25 indicate advance fibrosis

3-Fibroscan' Test- in which ultrasound-based shock waves are sent through the liver allowing hepatic fibrosis to be detected and quantitated**.**

10-Liver Biopsy

A-Percutaneous liver biopsy is performed with a trucut or Menghini needle usually through an intercostal space using local anesthesia.

liver biopsy is a relatively safe procedure in the following conditions:-

1-Cooperative patient

2-Prothrombin time <4 seconds prolonged

3-Platelet count >100x 10^9/L

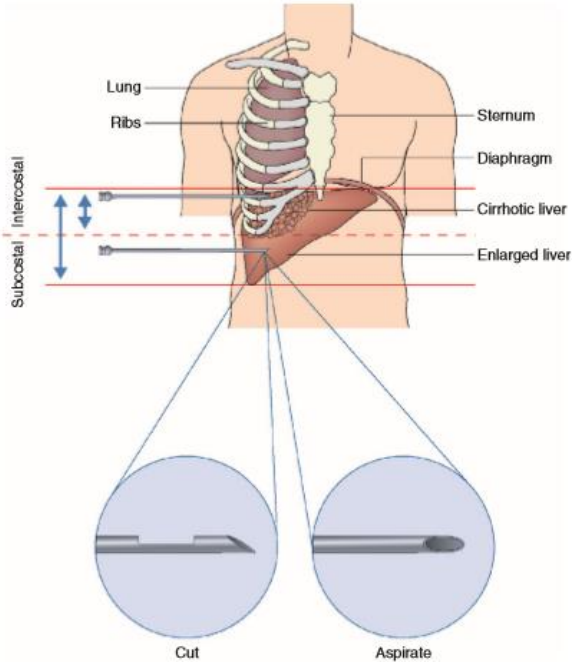
4-Exclusion of; bile duct obstruction, localized skin infection, advanced COPD, marked ascites, and server anemia. defective hemostasis should be corrected with fresh frozen plasma and platelet transfusion before liver biopsy.

*The patient usually admitted to the hospital, blood group should be known and facilities for blood transfusion must be available.

*Preliminary US, CT scan is useful to exclude cystic lesion or hemangiomas.

*The liver size should be known by light percussion.

*After adequate local antiseptic measure and anesthesia Because the liver is frequently cirrhotic and therefore small in size, and intercostal approach is necessary. The needle is inserted in the **8 or 9 i**ntercostal spaces in the midaxillary line at the end of expiration, to limit accidental pulmonary injury the direction of the needle is posterior and cranial to avoid the gallbladder. However, in large livers, a subcostal approach is preferred as a safer route of biopsy



*Main complication of liver biopsy are [abdominal or shoulder pain, bleeding, peritonitis, A-V fistula, haemobilia, infection, and intrahepatic hematoma].

B-Transjugular liver biopsy is indicated for patients with bleeding tendencies, marked ascites, and massive intra-abdominal adhesions.
C-Operative or laparoscopic liver biopsy.

Jaundice

*Jaundice is a yellow discoloration of the skin, sclera and mucous membranes, resulting from increased bilirubin in body fluids.

Jaundice is detectable clinically when plasma bilirubin concentration > 2.5 mg %.*

*Bilirubin is the breakdown product of red blood cells.

Unconjugated bilirubin is produced from catabolism of haem after removal of its iron component and circulates in the plasma bound to albumin.

Unconjugated bilirubin passes through the sinusoids into the space of Disse where the bilirubin dissociates from albumin and is taken up by the hepatocytes,

Unconjugated bilirubin is converted to a water-soluble after conjugation with glucuronic acid, which is mediated by the enzyme uridine diphosphate (UDP) glucuronyl transferase.

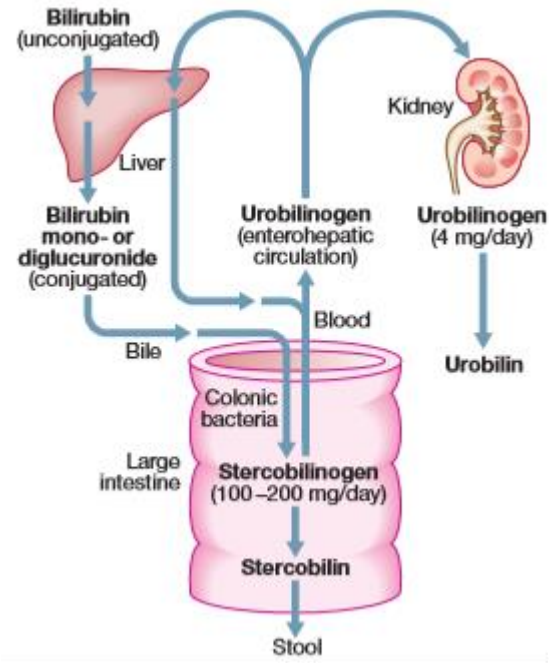
The majority (up to 98%) of conjugated bilirubin is then secreted into the bile.

A small amount of conjugated bilirubin is secreted into the hepatic sinusoids, enters the circulation, and is filtered by renal glomeruli and detected in the urine.

In contrast, unconjugated bilirubin is not filtered by the glomeruli.

Conjugated bilirubin excreted in bile is metabolized by intestinal bacteria and converted to urobilinogen about 10% is reabsorbed in the terminal ileum as part of the enterohepatic circulation before being excreted in the urine. Once in the intestine, conjugated bilirubin is metabolized by colonic bacteria to form stercobilinogen, which may be further oxidized to stercobilin. Both stercobilinogen and stercobilin are then excreted in the stool, contributing to its brown color. A small amount of stercobilinogen (4 mg/day) is absorbed from the bowel, passes through the liver, and is excreted in the urine, where it is known as urobilinogen.

*Obstruction of the biliary system results in pale stools (decreased stercobilin) and dark urine (increased conjugated bilirubin, which is unable to be excreted into bile), but no urobilinogen (because no bilirubin is available for conversion by bacteria in the intestine).



Pathway of bilirubin excretion

jaundice May be Classified as:
(1) –Pre hepatic;
(2) –hepatocellular jaundice.
(3) -Cholestasis.

1-Prehepatic

***Increased bilirubin production**. Causes include:
A-Hemolytic anemia, which can be hereditary (hereditary spherocytosis, sickle cell disease, Thalassemia) or acquired (autoimmune hemolytic anemia).
*Resorption of the hematoma.
*Repeated blood transfusions.
*Ineffective erythropoiesis.
B-Non-hemolytic Hyperbilirubinemia include

1-Isolated unconjugated Hyperbilirubinemia

a-Gilbert's Syndrome

*The most common inherited cause of unconjugated hyperbilirubinemia with partial deficiency of enzyme uridine diphosphate (UDP) glucuronyl transferase.
*Inheritance can be autosomal recessive or dominant disorder.
*Serum bilirubin levels may increase two- to threefold with fasting, dehydration, alcohol ingestion, or acute illness.
*Gilbert's syndrome has a benign course and affected persons are asymptomatic.
*Elevated levels of unconjugated bilirubin between 1.3-3mg% generally are detected as an incidental finding on routine laboratory testing.
*Other liver enzymes and the histologic studies of the liver are normal.

b-Crigler–Najjar syndrome Type I:

*Autosomal recessive disorder.
*UDP glucuronyl transferase activity is absent.
*Very high indirect hyperbilirubinemia and patients often die in the neonatal period due to kernicterus.

c-Crigler–Najjar Syndrome Type II:

*****Autosomal recessive disorder.

*Intermediate UDP glucuronyl transferase activity.

*Patients are usually asymptomatic in the neonatal period but present with jaundice in early childhood.

* Liver histology and liver enzymes are normal.

d-Acquired Deficiency of Glucuronyl Transferase

*Neonatal jaundice

*Hypothyroidism

2- Isolated Conjugated Hyperbilirubinemia

*Dubin–Johnson syndrome and *Rotor's syndrome.

*Inherited in an autosomal recessive pattern.

*These conditions characterized by reduced excretion of bilirubin into the bile canaliculi.

*Patients with Dubin–Johnson syndrome has characteristic black pigmentation of the liver that is not present in Rotor's syndrome.

*Both syndromes have a benign course and do not cause impairment in liver function.

(2) –Hepatocellular jaundice. jaundice occurs in both acute and chronic Liver disease.

Acute Liver Disease –

*These conditions characterized by markedly elevated serum aminotransferase levels out of proportion to the bilirubin and alkaline phosphatase levels.

Examples of acute liver injury include:

*Viral hepatitis (e.g., hepatitis A, B, C, D, E, and Epstein–Barr virus infection).

*Drugs and hepatotoxins (e.g., alcohol, acetaminophen).

*Ischemic hepatitis. *Reye's syndrome.

*Acute fatty liver of pregnancy. *Pre-eclampsia associated with the hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome.

Chronic Liver Disease.

Examples of chronic liver disease include the following:

*Chronic viral hepatitis (hepatitis B, C, and D).

*Chronic exposure to toxins, particularly alcohol.

*Alpha-1 antitrypsin deficiency.

*Autoimmune hepatitis.

*Nonalcoholic fatty liver disease.

*Hereditary hemochromatosis.

*Wilson disease.