

# Liver

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- The liver is the largest, most versatile organ in the body
  - It consists of two main lobes that, together, weigh from 1400-1600 g in the normal adult
  - It has an abundant blood supply receiving about 15 ml/minute from two major vessels: the hepatic artery and the portal vein ②
  - The hepatic artery a branch of the aorta, contributes 20% of the blood supply and provides most of the oxygen requirement
  - The portal vein, which drains the gastrointestinal tract, transports the most recently absorbed material from the intestine to the liver

# Liver function

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- **The excretion of bile:** Total bile production averages about 3 L per day, although only 1 L is excreted.
- The primary bile acids, cholic acid and chenodeoxycholic acid, are formed in the liver from cholesterol. The bile acids are conjugated with the amino acids glycine or taurine, forming bile salts.
- During fasting and between meals, bile acid pool is concentrated up to 10-fold in the gallbladder.
- When the conjugated bile acids (salts) come into contact with bacteria in the terminal ileum and colon, dehydration to secondary bile acids occurs, and these secondary bile acids are subsequently absorbed.
- The absorbed bile acids enter the portal circulation and return to the liver, where they are reconstituted and reexcreted. The enterohepatic circulation of bile occurs 2-5 times daily.

# Bilirubin

- The principal pigment in bile is derived from the breakdown of hemoglobin when aged red blood cells are phagocytized by the reticuloendothelial system, primarily in the spleen, liver, and bone marrow
- When hemoglobin is destroyed, the protein portion- globin-is reused by the body, The iron enters the body's iron stores and is also reused. The porphyrin is broken down as a waste product and excreted
- Bilirubin is transported to the liver in the bloodstream bound to albumin where it is conjugated with diglucuronide on its two carboxylic acids and excreted to the intestine.
- The normal flora in the colon oxidize it further where it is reabsorbed, excreted to the stool (urobilin, reddish brown) or excreted in kidney (urobilinogen, colourless)

bilirubin bound to albumin  $\Rightarrow$  conjugated

bilirubin is free in bloodstream  $\Rightarrow$  unconjugated

Bilirubin  $\xrightarrow[\text{(oxidation)}]{\text{intestine normal flora}}$  urobilin (reddish brown)

bilirubin  $\xrightarrow{\text{kidney}}$  urobilinogen (no color)



## Bilirubin

المادة التي تسبب صفير الجفون  
والجلد

- > When the bilirubin concentration in the blood rises, the pigment begins to be deposited in the sclera of the eyes and in the skin. This yellowish pigmentation in the skin or sclera is known as jaundice, or icterus
- > The cause can be:

hemolytic anemia: هيموليتية

التي يرتفع في الدم:

unconjugated bilirubin

ما يبين بال ur.in

ما يرتفع كثير بالدم لذلك

قدرة liver على التخلص من كميات كبيرة من unconjugated bilirubin طبيعية وما عنى مشكلة بال liver.

hyperbilirubinemia

Prehepatic: results when an excessive amount of bilirubin is presented to the liver for metabolism, such as in hemolytic anemia. This type of jaundice is characterized by unconjugated (direct) hyperbilirubinemia

The serum bilirubin levels rarely exceed 5 mg/dL because the normal liver is capable of handling most of the overload. bilirubin will not appear in the urine in this type of jaundice.

↑ urobilin

↑ urobilinogen

= عند الأطفال حديثي الولادة تكون Liver غير مكتملة عنم فبصير معهم hyperbilirubinemia

# Bilirubin

بكون في مشكلة بال liver  
نتيجة hepatitis أو تشمع الكبد.

**Hepatic:** Impaired cellular uptake, defective conjugation, or abnormal secretion of bilirubin by the liver cell are the main causes of this kind of jaundice  
↳ secretory problem.

→ ↑ un conjugated  
↑ conjugated -  
secretory problem ←

> **Posthepatic:** results from the impaired excretion of bilirubin caused by mechanical obstruction of the flow of bile into the intestine. This may be due to gallstones or a tumor

بجمل قارر يعجل امراض الكبد  
gall bladder  
bilirubin

↳ When bile ceases to flow into the intestine, there is a rise in the serum level of conjugated bilirubin and the stool loses its source of normal pigmentation and becomes clay-colored  
له لون بياض

↑ conjugated (Liver function is normal)

→ ↓ urobilinogen  
↓ urobilin

> Conjugated bilirubin appears in the urine, and urine urobilinogen levels decrease

له لونه مش قارر يوصل لا intestine.

ارتفاع bilirubin مش كثير مشكلة بالنسبة للكبار، هو مشكلة خطيرة بالنسبة لك طفل لانه ما يكون ممكن عندهم BBB و ممكن يدخل bilirubin للدماغ و يسبب مشاكل كبيرة عند الطفل.

# Major Synthetic Activity

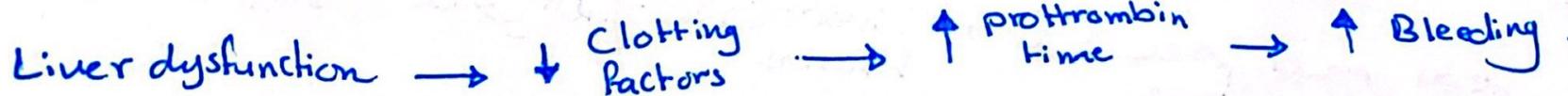
- The liver plays an important role in **plasma protein production**, synthesizing albumin and the majority of the  $\alpha$  and  $\beta$ -globulins. All the **blood-clotting factors (except VIII)** are synthesized in the liver
- The **deamination of glutamate in the liver** is the primary source of ammonia, which is then converted to urea  $\rightarrow$  hyperammonimia.
- **Glycogenesis and gluconeogenesis, lipogenesis, metabolism of cholesterol into bile acids, Very-low-density lipoproteins (transport TG into the tissues), High-density lipoproteins, phospholipids** are all made in the liver
- The **formation of ketone bodies (in malnutrition)**
- The liver is the storage site for all **fat-soluble vitamins (A, D, E, and K)** and several water-soluble vitamins, such as **B12** and is responsible for the conversion of carotene into **vitamin A**

ما ينتج في الكبد

في حالة Chronic Liver dysfunction

دور كبد المتكامل = بالكبد acute عادي يمكن خلال يومين ثلاثة تنحل ويبرح الكبد طبيعي

glucose كعصر للطاقة في حالة نقص glucose



Clotting factor activated by vitamin K (as Co-factor)

ال bile يساعد على امتصاص الدهون والفيتمينات الذائبة فيها (Vitamin K)

Clotting factors كمان

له اذا ما في تصنيع bile  $\leftarrow$  ما في امتصاص Vit(K)  $\leftarrow$  ما في activation لل  
يعني لا تصنيع ولد activation

# Synthesis of liver enzymes

(10)

Many enzymes are synthesized by liver cells, but not all of them have been found useful in the diagnosis of hepatobiliary disorders, this includes:

(not specific) Kidney و liver موجود بال

① Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) which escape into the plasma from damaged liver cells

very specific for liver

differential test.

② Alkaline phosphatase (ALP) and 5'-nucleotidase (5NT): induced or released when the canalicular membrane is damaged and biliary obstruction occurs

وجود بالعظم وبالـ gall bladder

③  $\gamma$ -glutamyltransferase (GGT): increased in both hepatocellular and obstructive disorders

له يكون مرتفع في حالة liver damage بسبب alcohol

انزيم (ALT) موجود بكثرة في خلايا Liver ← liver specific ← من يمكن تمييزه مرتفع لو المتكثرة gall bladder  
 = بقيس (ALT) و AST اذا الئين مرتفعين معناها المشكلة بال Liver.

= انزيم ALP يكون موجود بتركيز مرتفع ب ٣ حالات ← ١. gall bladder disease ٢. pregnant woman ٣. Children  
 \* بين اذا كانت المتكثرة gall bladder عند حريث (5NT) يكون مرتفع بسا اذا كانت المتكثرة gall bladder

## Detoxification and Drug Metabolism

... from potentially injurious substances

# Detoxification and Drug Metabolism

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- The liver protects the body from **potentially injurious substances** absorbed from the intestinal tract and **toxic by-products of metabolism.**
- The most important mechanism in this **detoxification activity** is the **microsomal drug-metabolizing system** of the liver. It is responsible for many detoxification mechanisms, including **oxidation, reduction, hydrolysis, hydroxylation, carboxylation, and demethylation** that convert many **insoluble compounds** into other forms that are **less toxic or more water-soluble** and, so excretable by the kidney.

Phase 1

Phase 2

Conjugation with moieties, such as **glycine, glucuronic acid, sulfuric acid, glutamine, acetate, cysteine, and glutathione**, occurs mainly in the **cytosol or smooth ER**. This mechanism is the mode of **bilirubin and bile acid** excretion.

## Disorders of the liver jaundice

➤ Jaundice, or icterus: is the yellowish discoloration of the skin and sclerae resulting from hyperbilirubinemia

➤ Although the upper limit of normal for total serum bilirubin is 1 mg/dL, jaundice is not clinically apparent until the bilirubin level exceeds 2-3 mg/dL

↔ ما بين الصفر من لون الشرة فيمنهم من لون العين  
➤ In African American or Asian patients, yellowing of the sclerae may be the only clinical evidence of jaundice

➤ Except in infants, hyperbilirubinemia is generally well tolerated. in adults

• ما يكون كامل  
➤ In infants, hyperbilirubinemia (>15-20 mg/dL) may be associated with kernicterus (serious disorder of the CNS resulting from increased bilirubin levels) it only occurs in infants because the immature CNS does not have a well-developed blood-brain barrier

حتى الشخص المريض Jaundice لدرجات يكون bilirubin level بين (2-3 mg/dL)

Jaundice

# Jaundice

- Although all cases of jaundice result from hyperbilirubinemia, not all are caused by hepatic dysfunction.
- hyperbilirubinemia may also result from erythrocyte destruction, or hemolysis in patients with normal liver function
- Hypercarotenemia (excessive ingestion of vitamin A) may produce skin discoloration indistinguishable from that of hyperbilirubinemia. In hypercarotenemia, the sclerae are usually not discolored.

لے الجلد بكون افسر بس العيون كذا -

# Cirrhosis

تشمع الكبد

- Cirrhosis refers to the irreversible scarring process by which normal liver architecture is transformed into abnormal nodular architecture.  
↳ nodules may be macro or micro
- One way to classify cirrhosis is by the appearance of the liver (by the size of the nodules). These conditions are referred to as **macronodular** and **miconodular** cirrhosis, although **mixed** forms occur
- In the USA, Canada, and Western Europe, the leading cause of cirrhosis is alcohol abuse, which leads to a **miconodular** type of cirrhosis.  
↳ accumulation of iron in liver (الانسداد الكبدى بنوعه وحصه دم)
- Other causes of cirrhosis include hemochromatosis, postnecrotic cirrhosis (occurs as a late consequence of hepatitis), and primary biliary cirrhosis (an autoimmune disorder).  
↳ after hepatitis.

يمكن الواحد يعيش فترة طويلة وهو بعد تشفع كبد  
 ليس مشكلته بال complications

# Cirrhosis

> Cirrhosis is a serious disorder and one of the ten leading causes of death in the United States. It causes many complications:

- ⑤ > Portal hypertension results when blood flow through the portal vein is obstructed by the cirrhotic liver. This may result in splenomegaly and esophageal varices (may rupture and lead to fatal hemorrhage)
  - ← ما في مسار يدخل فيه الدم جوا الكبد
  - تضخم spleen
  - السترايبات بالمريء بتبلسق تتعبر دما
- > The synthetic ability of the liver is reduced, causing hypoalbuminemia and deficiency of the clotting factors, which may lead to hemorrhage
- > Ascitic fluid may accumulate in the abdomen → hypo electrolytes / hypervolemia
  - ← سبب و osmolality قلت عن ز
  - قل albumin في الدم .
- > Although some patients with cirrhosis are capable of prolonged survival, generally this diagnosis is an ominous one

## Tumors

- On a worldwide basis, primary malignant tumors of the liver, known as hepatocellular carcinoma are an important cause of cancer mortality
- سببه غالباً التهاب كبدى hepatitis -
- In the United States, these tumors are relatively uncommon. Most cases of hepatocellular carcinoma can be related to previous infection with a hepatitis virus.
- كبد الـ Liver Cancer هو مش benign .
- Liver is frequently involved secondarily by tumors arising in other organs. Metastatic tumors to the liver from primary sites, such as the lung, pancreas, gastrointestinal tract, or ovary, are common. Benign tumors of the liver are relatively uncommon
- = صحب كشفه بسريره ولذا علاجه بكون صحب .
- Whether primary or secondary any malignant tumor in the liver is a serious finding with a poor prognosis
- The only hope For cure relies on surgical resection, which is usually impossible. Patients with malignancies of the liver usually have a survival measured in months

## Reye's Syndrome *(viral infection in children and give aspirin)*

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- Reye's syndrome is a disorder of unknown cause, involving the liver and arising primarily in children,
- It is a form of hepatic destruction that usually occurs following recovery from a viral infection, such as varicella (chickenpox) or influenza.
- It has been related to aspirin therapy. Shortly after the infection, the patient develops neurologic abnormalities, which may include seizures or coma
- Liver functions are always abnormal, but the bilirubin level is not usually elevated
- Without treatment, rapid clinical deterioration, leading to death, may occur

## Drug- and Alcohol-Related Disorders

- Many drugs and chemicals are toxic to the liver. This toxicity may take the form of overwhelming hepatic necrosis, leading to coma and death, or it may be subclinical and pass entirely unnoticed
- In small amounts, alcohol may cause mild, inapparent injury. Heavier consumption leads to more serious damage, and prolonged, heavy use may lead to cirrhosis (exact amount is unknown)
- Certain drugs, including tranquilizers (phenothiazines), certain antibiotics, antineoplastic agents, and anti-inflammatory drugs, may cause liver injury
- Usually this is mild and manifested only by elevation of liver function tests, which return to normal when the drug is discontinued. This may lead to massive hepatic failure or cirrhosis
- The most common drug associated with serious hepatic injury is acetaminophen. When taken in massive overdose, it produces fatal hepatic necrosis unless rapid treatment is initiated

(atorvastatin) +

مستوى معروف كمية ما  
السكر

Lethal dose 9-15g