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# Liver disease

# Liver

- 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  
تقريبًا كيلو جرام
- It has an abundant blood supply receiving about 15 ml/minute from two major vessels: the hepatic artery and the portal vein  
له صافي من الـ O<sub>2</sub> ويأتي فحمل nutrients  
ويعبر عـالـ liver بأغول عشان مع الـ (JS) في  
استواء شيفر الجسم - كيف بيدي عيون أنا اظلم  
مكة انضبط عالج؟ نالكم ما سجد انك عالج او كة هو سجد انك عالج  
له جاي من الـ Aorta التي تزود بالـ أكسجين  
more polar metabolism داخلها
- 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

الخراج لا يلبس و تصفحه يتم بالكبد

- <sup>①</sup> **The excretion of bile:** Total bile production averages about 3 L per day, although only 1 L is excreted.

- The primary bile acids, <sup>①</sup>cholic acid and <sup>②</sup>chenodeoxycholic acid, are formed in the liver from cholesterol. The bile acids are <sup>①</sup>conjugated with the amino acids <sup>②</sup>glycine or <sup>③</sup>taurine, forming bile salts.

from hydroxylase enzyme

- <sup>②</sup> During fasting and between meals, bile acid pool is concentrated up to 10-fold in the gallbladder

بعد ما نأكلنا مع عصير العصارة conjugation يحصلون بال gallbladder و يتركز و اذا منتهي ٢ لتر باليوم مع نستهلك الختر و نطعم ما هو الواحد صاير فحشاها بجل امكن الاحتفاظ تبع الامعاء gall

- <sup>③</sup> 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

بعد ما نأكلنا مع عصير العصارة exc الامعاء  
اشرا الحو عا الامعاء و صاير عنده Normal flora فيترفع تليل الامعاء  
عشان يطلع ال Abs لا تلت  
و ال digestion يطلع

الكمية التي يمكن تطلع بال feces ضئيلة جدا يعني تقريباً ٥%

- 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

له الطية ينشكر حسب كم مرة تناول يفتح تناول مرتين ينشكر مرتين

منه منهم مع عصير العصارة استعملوا و يروحوا عا liver  
مرة ثانية و الخبز الي ضلوا مع سائلها بال الدم و يروحوا  
اشرا الحو عا الامعاء و صاير عنده Normal flora فيترفع تليل الامعاء  
عشان يطلع ال Abs لا تلت  
و ال digestion يطلع

ال cycle  
carries خلاصة يتقارن reabsorb وهناك يرجعوا ال liver و يرحلوا مع cycle و يتعاد ال cycle  
ortho-dexycholate و deoxycholate  
بعض يتحول انده cholate و deoxycholate  
بعض ال reabsorb  
بعض ال reabsorb  
بعض ال reabsorb

# 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

الbilirubin إلا على مدى 120 يوم ويبس تتلفه ال 120 يوم لأنهم تقتت فيتحج كالسpleen - 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

الiron يتركه ويخزنه ويريد مع بروتين  
اسم hemoglobin موجود بالliver يعني  
يخزنه بالliver

- Bilirubin is transported to the liver in the bloodstream bound to albumin where it is conjugated with diglucuronic acid on its two carboxylic acid groups and excreted to the intestine

porphyrin بدوره bilirubin وهذا ما يقتره لعلله مع وحت لدعبلته مع من ال B.M ال spleen لأنهم أكله كال ال Albumin يعني تا يمتص لحاله بالدم واسم ال unconjugated bilirubin  
ويعرف بالliver وهذا يستعمله كغذاء و ال hemoglobin ليس يصل اليه ينتجته الخلايا الجذبة و تحت ال glucuronic acid عليه و سطح عنده انشعابا ال hemoglobin و هذا يروح يترك على gallbladder خلاصه اللي يعني  
اللون الأصفر ال  
هو ال انشعاب ال  
و ينتج مع ال عائل  
ولا ينتج للأسف  
لا تاكل بروج ال normal  
فيككله methemoglobin  
و urobilinogen و urobilin

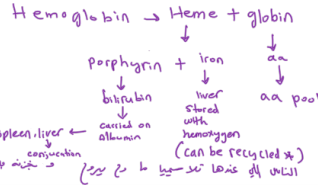
- The normal flora in the colon oxidize it further where it is reabsorbed, excreted to the stool (urobilin, reddish brown) or excreted in kidney (urobilinogen, colourless)

له هاء هي ال بتخلي اللون الغامق ال feces  
حالي عنده obstruction مع يترك لون ال feces  
فاتح

له جزء من ال urobilinogen يتحول ل urobilinogen  
و هذا يعبره renal مرة ثانية للدم و يروح  
بالurine معناه اذا كان تركيز ال urobilinogen بالurine  
قليل معناه ال gallbladder مسكحة و اذا كثر معناه  
في كثر RBC تكسرت معناه مع تدمسها او hemolysis  
او sickle cell anemia و يكون عنده jaundice يعني قليل

# Bilirubin

Normal Bilirubin: 1.2 mg/dL (0.5-1.2 mg/dL)  
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1

urobilinogen → urobilinogen  
 ↓  
 excretion  
 Reddish brown color

hemosiderosis  
 ↓  
 Hemosiderin  
 ↓  
 Hemosiderin  
 ↓  
 Hemosiderin

## Hemoglobin

Mononuclear phagocytic system  
 (principally spleen)

Bilirubin

Blood

Bilirubin-albumin

Liver

Intracellular bilirubin

Liver

Bilirubin diglucuronide

Intestine

Bilirubin diglucuronide

+ Bilirubin

Intestinal bacteria

Urobilinogen

Urobilin

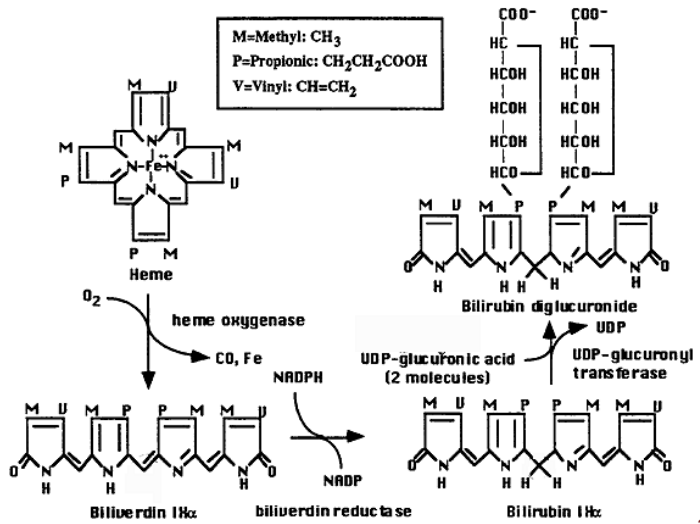
Fecal excretion

Kidney

urinary

urobilinogen

⑤  
 جدا عنده تلامس كثير مع شدة  
 الـ urobilinogen بالبروتين مال bilirubin  
 مع يكثر الـ



← باكثير  
 بزرج الـ

# Bilirubin

- When the bilirubin concentration in the blood rises, the pigment <sup>الصبغ</sup> 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:

- <sup>①</sup> **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 hyperbilirubinemia

بتكون المشكلة طوارىء دخل بال liver و كانت مشغولة عنه *Favism* تفوق د اكل سغلة جيس الدم  
مراح تكسر الدم كله بالتالي كليات صالحة من ال bilirubin مع علاج فدهو بل metabolism ال porphyrin الي طلع من Hb  
الجزء الي واصل للكلى ناع ال uric acid ماله عرق و في ال unconjugated هاد ماد دخل ال liver امد فهدل الاشخاص بتقع عنهم ال uric acid  
ال uric acid و uric acid مع يكون عالي فيه تكسير ال RBC الي فال bilirubin الي دخل و وصل لامعاء كيترا كميته طلع ال feces مع يكون reddish brown و ال urobilinogen الي بوز للبروتين

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.

2-3 mg/dL → jaundice

# Bilirubin

- **Hepatic:** <sup>from blood to liver</sup> Impaired cellular uptake, defective conjugation, or abnormal secretion of bilirubin by the liver cell are the main causes of this kind of jaundice  
١٠ مشاكل: مثل كل كمية ال bilirubin مع تدخل الكبد ١ الجزء إلى وصل للكبد وفي حالة رخ conjugation ٢ إلى كبد له زخم عنده مشكلة بال خلاص  
هذه في خطها ال conj + unconj مرتفعين بالم و ارتفاعات الكبد رخ يكون مرتفعين و قدرة ال liver انما تصنع بروتينات حتى تتفكس ال chronic
- **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  
المسألة تكون بال blockage عن مكان من stones - obstruction منسبب تحسیر ال ملة  
دع يرفع ال bilirubin عاكس الى رخ عمل conj ال bilirubin ديجو به عن ال gallbladder بمرقبة  
مسكن منجوع عالم بالتالي سب ال زخم رخ يضا مرتفع بالم  
head of pancreas له في يكون يسبب  
gallbladder منسبب ال
- 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  
↓ urobilin and urobilinogen  
له فاتح
- Conjugated bilirubin appears in the urine, and urine urobilinogen levels decrease  
لانه طرق ال excretion الثانية منسبب ال polar فان ا  
تغلط بال urine بمرقبة مرة ثانية  
اذا الواح عنده الملاءة يكون في عنده bilirubin باليرتفع في زخم اما لا في hemolytic disease  
رخ يكون unconj و فيقول ال Albin بالتالي ما يقب يصل ال urine

# Major Synthetic Activity

- The liver plays an important role in plasma protein production<sup>(1)</sup>, synthesizing albumin and the majority of the  $\alpha$  and  $\beta$ -globulins. All the blood-clotting factors<sup>(2)</sup> (except VIII) are synthesized in the liver  
*إذا صار غير مشكلة بالكلية مع يوقف تصنيع الـ Albumin  
اللي مسؤول عن الـ osmolality بالتالي مع تزييد السوائل بالجسم*  
*لم اذا وقت قصير مع  
عنه زيادة تزيد حالة  
prolonged prothrombin factor*
- The deamination of glutamate in the liver is the primary source of ammonia, which is then converted to urea  
*معناها اذا في مشكلة بالكلية نفس الـ Urea cycle*
- 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
- 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



# Synthesis of liver enzymes

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

- **Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)** which escape into the plasma from **damaged liver cells**  
*هذه الـ 2 يمكن تحليلهم Assessment لا نكتشف انه هنو مشكلة بالكبد  
اذا الـ 2 مرتفعين معناه مشكلة بالكبد liver و اذا بي الـ AST ارتفاع معناه مشكلة تانية غير الـ liver على كبد او kidney او muscles او heart اراضى تاني  
و اذا الـ ALT لحواله على مشكلة بالكبد*
- **Alkaline phosphatase (ALP) and 5'-nucleotidase (5NT):** induced or released when the canalicular membrane is damaged and **biliary obstruction** occurs  
*ALP موجود كميان بالكبد معناه الاطفال عظامهم ح تنكس وتنبت فالـ ALP تتطلع لبر سبي  
ط ح تكون عالية كتير و الـ gallbladder obstruction بيتن اكر من ٢ اضاف و اذا الـ 5NT ضعف يكون cancer معناه  
و عشان اتأكد اذا المشكلة gallbladder من عندها بفحص 5NT اذا كانت الـ 2 عاليين المشكلة بالـ gallbladder سبي اذا الـ ALP لحواله على معناه المشكلة بالـ bone*
- **γ-glutamyltransferase (GGT):** increased in both **hepatocellular and obstructive disorders**  
*الناس الي سببوا كحول على يرتفع عندهم هاد الانزيم*

Obstruction:

↑ GGT  
↑ ALP  
↑ 5NT

# Detoxification and Drug Metabolism

51 toxins او ادوية مناخها بتدخل من خلال ال portal veins للكبد وهناك حد تقبل ال polarity

- 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.
- 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 or *hypercarotenemia*  
إذا مأكّل جزير كثير
- 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
- In African American or Asian patients, yellowing of the sclerae may be the only clinical evidence of jaundice  
هذول املا وهرهم (الفرقا بين) لا نهم غامقين ما بين عوجهم
- Except in infants, hyperbilirubinemia is generally well tolerated.  
it is not toxic in adults
- 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  
دخول ال bilirubin لل brain يمكن ان يخلق مشكلة بالدماع عند الاطفال عشان هيك بدنا نقدر نحرس  
انه الصغار عند الاطفال يكون بين البول ويصفر و دخله و يحطه بالدم لانه ال bilirubin حساس للدمع معناه عنية  
ال bilirubin انه بالغ لازم ابعده عن الدم و منخف ال دمما قدر الامكان انه ما تعطيه حليب لانه (لحاجه) فيه  
سكر و ليبيدات و بروتينات فخطيه مع السكر بين و منخف بالدم الصبح او بالدم لما تقدر الشمس خفيفة عشان الصبح  
كبير ال bilirubin و يخف ال صفار

# Jaundice

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- 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.

# Cirrhosis

تشمع الكبد

من أخضر الكبد إلى بني شحبي

بالكبد قبل الكانسي ومن أكبر مسبباته إيثانول

irreversible change in the architecture of the liver

- Cirrhosis refers to the irreversible scarring process by which normal liver architecture is transformed into abnormal nodular architecture

الكبد البنية الطبيعية إلى خضراء و smooth فالتس إلى غير Cirrhosis يكون في nodules خالكة ويكون حجم الكبد أكبر من الطبيعي

- 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 **micronodular** cirrhosis, although **mixed** forms occur

- In the USA, Canada, and Western Europe, the leading cause of cirrhosis is alcohol abuse, which leads to a micronodular type of cirrhosis

Main Cause

- Other causes of cirrhosis include hemochromatosis, postnecrotic cirrhosis (occurs as a late consequence of hepatitis), and primary biliary cirrhosis (an autoimmune disorder).

Accumulation of iron in liver

في كلا 5 أنواع من الـ ABCDE : viral hepatitis  
B و C خاصة الـ 90% منها يتحول لـ chronic و B ← 5-10% يتحول لـ chronic يعني يظل الـ hepatitis مستمر ويجعل القلب على Cirrhosis ومنها Liver cancer  
B و C خاصة الـ 90% منها يتحول لـ chronic و B ← 5-10% يتحول لـ chronic يعني يظل الـ hepatitis مستمر ويجعل القلب على Cirrhosis ومنها Liver cancer

# Cirrhosis

- Cirrhosis is a serious disorder and one of the ten leading causes of death in the United States. It causes many complications:
  - **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)  
*12 يملك ال portal vein يتلقى nutrients من GI tract و portal HTN و ضغط مرتفع في portal vein و هذا يؤدي إلى تضخم الطحال و زيادة الضغط في ال portal vein و هذا يؤدي إلى تضخم الطحال و زيادة الضغط في ال portal vein و هذا يؤدي إلى تضخم الطحال و زيادة الضغط في ال portal vein*
  - The synthetic ability of the liver is reduced, causing **hypoalbuminemia** and deficiency of the clotting factors, which may lead to hemorrhage → *prolonged prothrombin time*  
*chronic liver disease*
  - **Ascitic fluid** may accumulate in the abdomen
  - Although some patients with cirrhosis are capable of prolonged survival, generally this diagnosis is an ominous one *not sth good to be diagnosed with*

# Tumors *After cirrhosis*

- On a worldwide basis, <sup>① originated from liver: hepatitis → cirrhosis → cancer</sup> primary malignant tumors of the liver, known as hepatocellular carcinoma are an important cause of cancer mortality
- In the United States, these tumors are relatively uncommon. Most cases of hepatocellular carcinoma can be related to previous infection with a hepatitis virus.
- Liver is frequently involved <sup>② originated from other organs</sup> 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
- 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 <sup>3</sup> months   
*الكل عمل عملية جراحية وشلل الكبد ببطء زيادة سنة أو أكثر لأنه لا يمكن قتل  
السرطان سوى ما يتلوا ح ٣ أشهر فقط يوجد*

# Reye's Syndrome

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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)  
*معدل الاستهلاك في مختلف البلدان Metabolism of alcohol*  
*Ethanol → Acetaldehyde → Acetic acid → Krebs cycle*  
*Acetaldehyde is highly reactive and toxic*  
*الاستهلاك بكميات كبيرة يؤدي إلى تلف الكبد*
- Certain **drugs**, including tranquilizers (phenothiazines), certain antibiotics, antineoplastic agents, and anti-inflammatory drugs, may cause liver injury  
*Isotretinoin, Rifampin*  
*Statins, vit A, retinol*
- 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  
*(2 tabs) Paracetamol → radical → bind to glutathione → non toxic*  
*(>15) glutathione not enough → accumulation of radicals*

# Assessment Of Liver Function

## Analysis of Bilirubin (Method Selection)

- Unfortunately, no single method for the determination of bilirubin will meet all the requirements of the clinical laboratory

① في فحصه لا نه تاثيرات  
E واحد مستخدمه للاطفال اقل من شهر  
E واحد مستخدمه للاطفال والكبار اقل من الشهر

For the evaluation of jaundice in newborns (no lipochromes), the direct spectrophotometric method is satisfactory

له (الخصه) كافي فانه غير عيبه من مرض  
centrifugation وقياس Abs على 495  
وهذه الخضره لا تتركب اقل من شهر  
وعليه يتم بوضوحا عاده عند سحب عجله

- The sources of error in this technique are turbidity, hemolysis, and yellow lipochrome pigments

2 centrifugation  
في متخلخل منه عن طريق ال

ويجب ان يمسح عائله جوا

Hemolysis and turbidity can be blanked out by measuring a second wavelength, but the yellow lipochromes cannot be blanked out.

عشان نتخلص من ال hemolysis بقيس على 2: 495 عشان بقيس bilirubin و hemolysis يوم ال 2 على 575 بقيس ال hemolysis ف اذا قرعهم من بقيس بطلت بقي ال Abs ال bilirubin لمان  
bilirubin ما يور عني ال standard بقده لانه sensitive to light ف اذا قرعته للقرع يتغير القيمة فتناخذ ال Absorbance ال بقيس اننا باشر عينة الدم و منى لانم استعن عليها كتر و لانم نضلها بلفه معتقة

In patients older than 1 month, a diazo-colorimetric procedure is necessary

③ ال kit تحت ال bilirubin ال بقيس فيا bilirubin total هو نفس ال بقيس فيا bilirubin direct

➤ ال اذا كان غير شربا اذ  
والا اقل من شهر ما عديت  
lipochromes

Abs = ABC  
path length = 1  
كلم تركه 1 عشان انا  
خرطه اننا اننا حاسبه ل  
دعمه نضلها جوا شرب بطلت  
منى ال قرع كافي غلط  
والا ما يور عني اذا اخذت  
ال الدم من عجله ال الازله  
هناك المخرجه تركه معتقة  
كثيره ال micropipettes  
لانم بيكها مقلوب ال Calibration  
عنه اننا خربله خربله  
الازله كافي غلط

# jendrassik-Grof Method for Total and Conjugated Billirubin Determination

لبي يرمح اكثر من شهر

↳ or direct bilirubin

إذا سعي الزنك وحسب  
الامتصاص يقرأ الجليج  
الزنك من طريق ابي  
بجرم من بيلي

- Serum or plasma is added to a solution of sodium acetate and caffeine-sodium benzoate, which is then added to diazotized sulfanilic acid to form **purple azobilirubin**  
↳ the reagent used in the test  
يتفاعل مع ال bilirubin ويحطها التركيز بدرجة
- The **sodium acetate** buffers the pH of the diazotization reaction, whereas the **caffeine-sodium benzoate** accelerates the coupling of bilirubin with diazotized sulfanilic acid  
في امتصاص ناتجة موجودة مع ال reagent كسنان تحافظ على ال pH و تسرع علق ال diazotization
- This reaction is terminated by the addition of **ascorbic acid**, which destroys the excess diazo reagent
- A **strongly alkaline tartrate** solution is then added to convert the purple azobilirubin to blue azo-bilirubin, and the intensity of the color is read at 600 nm  
↳ diazotide bilirubin  
لما يصير سبلا بقيه
- A fasting serum specimen, which is neither hemolyzed nor lipemic, is preferred.  
هذا ال دةست بس يقيس ال bilirubin زنك يعني الداي باله و اذا المشكله طبيعي ما عنده اي مشكل ← ال bilirubin يولي bilirubin اقل على ال Albumin وراح للكم و ال كم على الزنك وراح عايزة ستره عصبه عاليه الا اذا كان سكر زاده و الموزون ما عنده بالقي مع تفتت كسبة ال زنك مشكله جزا و السوي الصفر الي موجود يكون لأنه في شد من ال uncomy ال bilirubin  
عنى تفتت عن ال Albumin او ال حطت ال reagent  
يتكون في سبي  
زوت عن ال Albumin و ال قاسم
- The specimen should be **kept in dark** after collection, analyzed within 3hrs, kept for 1 week in the refrigerator or 3 months in -20  
in freezer  
عسان اقيس ال uncomy لازم افكه عن ال Albumin فقيته الهم نهضين على ال organic solvent فينقل denaturation للبروتينات عسان ال Albumin تفل عن ال bilirubin و تتره و استغل ال organic عسان ال bilirubin ما يودي الي عسان هيمو جيلين مع ال Albumin (هذا فلا اضر ال reagent مع يقيس ال الاله  
هذا ال المختص عندي يكون لدموزا hemolysis بس المختص الي فوت  
مسموح لأنه يقدر المرح ال اسلا و تطلع بعد القراءه المصح

# Reference range

direct → measures conj

indirect → both (total)

- Normal blood contains no conjugated bilirubin.
- Some conjugated bilirubin is reported as normal because current available methodology picks up some of the total bilirubin as a false positive
- For **adults**
  - Conjugated: 0-0.2 mg/dL (0-3  $\mu$ mol/L)
  - Unconjugated: 0.2-0.8 mg/dL (3-14  $\mu$ mol/L)
  - Total: 0.2-1.0 mg/dL (3-17  $\mu$ mol/L)

➤ For <b>infants</b>	INFANTS	PREMATURE, TOTAL	FULL TERM, TOTAL
	24 hours	1–6 mg/dL	2–6 mg/dL
	48 hours	6–8 mg/dL	6–7 mg/dL
	3–5 days	10–12 mg/dL	4–6 mg/dL

# Direct Spectrophotometric Method for Determination of Total Bilirubin in Serum

- The absorbance of bilirubin in serum at 455 nm is proportional to its concentration
- The serum of newborns does not contain lipochromes, such as carotene, that would increase the absorbance at **455 nm**. The absorbance of hemoglobin at 455 nm is corrected by subtracting the absorbance at **575 nm**.  
هناك زيادة في الهيموجلوبين
- Error will be introduced if the buffer is turbid. Because the method depends on the extinction coefficient of bilirubin, **all volumes must be accurate** and **cuvettes must be flat-surfaced**, with a path length of exactly 1 cm
- This method is relatively insensitive to hemolysis, which is often present in specimens obtained from infants, due to difficulty in skin puncture technique
- it is significantly affected by the presence of lipochromes and so cannot be used in infants older than a few months of age

إذا طغل قسّمه هذا ليعطى دلالته عند  
القراءة عالية لأنهم أحاطوا بالخداع

# Urobilinogen in Urine and Feces

- Urobilinogen is a colorless end product of bilirubin metabolism that is oxidized by intestinal bacteria to the brown pigment urobilin
- In the normal individual, part of the urobilinogen is excreted in the **feces**, and the remainder is reabsorbed into the portal blood and returned to the **liver**. A small portion that is not taken up by the hepatocytes is excreted by the **kidney** as urobilinogen
- Increased levels of urinary urobilinogen are found in hemolytic disease and in defective liver-cell function, such as hepatitis
- **Absence of urobilinogen** from the urine and stool is most often seen with complete **biliary obstruction**. Fecal urobilinogen is also decreased in biliary obstruction and in hepatocellular disease

↑ urobilinogen : hemolysis  
↓ urobilinogen : obstruction  
X urobilinogen : obstruction

↑ or ↓  
حسب الحالة

# Urobilinogen in Urine and Feces

- Most quantitative methods for urobilinogen are based on the reaction of this substance with p-dimethylaminobenzaldehyde to form a red color.  
*↳ reagent used*
- Major improvements were made by using <sup>Reducing agents:  
of Ascorbic acid</sup> **alkaline ferrous hydroxide** to reduce urobilin to urobilinogen and added **sodium acetate** to eliminate interference from such compounds as indole
- The use of **petroleum ether** rather than diethyl ether for the extraction of urobilinogen was introduced to help in the removal of other interfering substances

Ⓢ أكبر مشكلة في Urobilinogen Assay :  
مسألة ال interferences في ال specificity  
الو قليل يقد انه ادوية بحدود المربع في ال  
تداخل مع النتائج

# Determination of Urine Urobilinogen (Semiquantitative)

## ➤ Principle.

- Urobilinogen reacts with p-dimethyl aminobenzaldehyde (Ehrlich's reagent) to form a red color, which is then measured spectrophotometrically.
- Ascorbic acid is added as a reducing agent to maintain urobilinogen in the reduced state.
- The use of saturated sodium acetate stops the reaction and minimizes the combination of other chromogens with the Ehrlich's reagent.

## ➤ Specimen

- A fresh 2-hour urine is collected which should be kept cool and protected from light.

اللون يتركز في  
الأنسجة عند  
الأكسدة  
urobilin

urobilinogen  
عسلان  
لحمي



# Sources of Error

- The results of this test are reported in **Ehrlich units** rather than in milligrams of urobilinogen because of interfering substances
- Compounds, other than urobilinogen, that may be present in the urine and react with Ehrlich's reagent include porphobilinogen, sulfonamides, procaine, and 5-hydroxyindoleacetic acid. Bilirubin will form a green color and, therefore, must be removed, as previously described
- Fresh urine is necessary and the test must be performed without delay to prevent oxidation of urobilinogen to urobilin. Similarly the spectrophotometric readings should be made within 5 minutes after color production because the urobilinogen-aldehyde color slowly decreases in intensity.

**Reference Range:** Urine urobilinogen, 0.1-1.0 Ehrlich units/2 hr or 0.5-4.0 Ehrlich units/day (0.8 - 6.8 mmol/day); 1 Ehrlich unit is equivalent to approximately 1 mg of urobilinogen

# Fecal Urobilinogen

- Visual inspection of the feces usually suffices to detect decreased urobilinogen.  
اللقف بالعين المجردة يمكن ملاحظة اللون الباهت للبراز عند انخفاض urobilinogen مع بقاء اللون فاتح
- The semiquantitative determination of fecal urobilinogen is available It is carried out in an aqueous extract of fresh feces, and any urobilin present is reduced to urobilinogen by treatment with alkaline ferrous hydroxide before Ehrlich's reagent is added  
لا يتم اكون عذقة وزنة عذقة ال faeces التي يتم اخذها و تفل dilution و يقيس reagent
- A range of 75-275 Ehrlich units/100 g of fresh feces or 75-400 Ehrlich units per 24-hour specimen is considered a normal reference range.

# Measurement of Serum Bile Acids

بالكمية بهيبر uptake للكوليسترول و يجل تحويل  
للحمية bile و يجلهم زنت - يبدى على ال gallbladder  
و لا ناكل بهيبرهم secretion و release للاصحاء  
و اذا obstruction بالهم بالكم لكن بال obstruction  
ال ALP يكون ٣ اضعاف ال upper limit و 5NT يكون  
مرتفع و conj bilirubin يكون مرتفع و على ultrasound ال stones  
فيين ف انا شو بدى نحصه ال حمية bile في منى ما ال  
داعى و هو اصغر فحص على فحسان هيك من خلاص  
مختبرات اصغر بتفحص ال حمية

- Unfortunately; complex methods are required for the analysis of bile acids in serum
- they involve extraction with organic solvents, partition chromatography; gas chromatography-mass spectroscopy spectrophotometry ultraviolet light absorption, fluorescence, radioimmunoassay and enzyme immunoassay methods
- Although serum bile acid levels are elevated in liver disease, the total concentration is extremely variable and adds no diagnostic value to other tests of liver function.

ALP  
nucleotidase  
conj bili  
ultrasound

# Enzyme Tests in Liver Disease

- Any injury to the liver that results in cytolysis and necrosis causes the liberation of various enzymes.  
*الانزيمات موجودة في السيتوسول وداخل الخلايا و يلاحظ بالبدن ما يسمى tissue injury و cell damage و يطلق الـ content نتيجا لبر و التلف الطبيعي بعد في كبد صحتك من هذه الانزيمات الالم نتيجة الـ turnover الطبيعية للخلايا  
سواء اذا كانت مرتفعة كثير وقليلة في damage للخلايا و اذا ظلت الانزيمات مرتفعة معناها الـ cell damage فترى و عند chronic disease*
- The most common enzymes assayed in hepatobiliary disease include ALP and the aminotransferases.
- Used less often are  $\gamma$ -glutamyltransferase, lactate dehydrogenase (LD) and its isoenzymes, 5'-nucleotidase, ornithine carbamoyltransferase, and leucine aminopeptidase  
*لـ هاد فلويش داعي  
لان موجود بكثير organs بالتي ازا الانزيمات  
الباقي اللم عاليه من مع احتاج انحصله هاد الانزيم*

# Enzyme Tests in Liver Disease

**Alkaline Phosphatase:** in the clinical diagnosis of **bone** and **liver** disease.

- The most striking elevations occur in extrahepatic biliary obstruction, such as a stone in the common bile duct, or in intrahepatic cholestasis, such as drug cholestasis or primary biliary cirrhosis. This enzyme is almost always increased in metastatic liver disease and may be the only abnormality on routine liver function tests.  
*متلازمة الصفراء، ارتفاع ALP، وارتفاعات الكبدية*
- The enzyme is found in **placenta**, and **pregnant** women also have elevated levels *+growing children*

## Aminotransferases (Transaminases)

- AST and ALT are two enzymes widely used to assess hepatocellular damage. AST is found in all tissue, especially heart, liver, and skeletal muscle.
- ALT is more “liver specific”

# Enzyme Tests in Liver Disease

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**5'-Nucleotidase:** is another phosphatase in the liver and used clinically to determine whether an ALP elevation is caused by liver or bone disease

- This enzyme is much more sensitive to metastatic liver disease than is ALP because, unlike ALP, its level is <sup>جاءت الكانسر</sup> **not** significantly elevated in other conditions, such as **pregnancy** or **childhood**
- Some increase in its activity may occur after **abdominal surgery**

# Enzyme Tests in Liver Disease

↑ GGT → obstruction  
→ Alcohol consumption

- **γ-Glutamyltransferase (GGT):** high in kidney and the liver and is elevated in the serum of almost all patients with hepatobiliary disorders
  - It is not specific for any type of liver disease but is frequently the first abnormal liver function test demonstrated in the serum of persons who consume large amounts of alcohol
  - The highest levels are seen in biliary obstruction
  - Sensitive test for alcoholic liver disease
  - Measurement of this enzyme is also useful if jaundice is absent for the confirmation of hepatic neoplasms and to confirm hepatic disease in patients with elevated ALP
- **Leucine Aminopeptidase:** widely distributed in human tissue, is found in the pancreas, gastric mucosa, liver, spleen, brain, large and small intestine, and kidney. *Everything non specific*
  - The serum activity of leucine aminopeptidase cannot be used to differentiate hepatocellular from obstructive jaundice.
  - The measurement of this enzyme does not provide any useful information

# Enzyme Tests in Liver Disease

- **Lactate Dehydrogenase:** Measurement of total serum LD is usually not helpful diagnostically because LD is present in all organs and released into the serum from various tissue injuries  
افحصه لحال عالفانير في الـ 5 isoenzymes في الدم في اى مكان  
تكون المشكلة فيه
- Fractionation of LD into its five tissue-specific isoenzymes may give useful information about the site of origin of the LD elevation
- LD-5 is mostly present in liver and skeletal muscle. elevated LD-5 is noted in a patient with jaundice  
↑LD5 + jaundice → liver disease  
↑LD5 + no jaundice → skeletal muscle disease
- Moderate elevations of total serum LD levels are common in acute viral hepatitis and in cirrhosis, whereas biliary tract disease may produce only slight elevations  
mild
- High serum levels may be found in metastatic carcinoma of the liver.  
mild → biliary obstruction  
moderate → acute viral hepatitis  
high → metastatic



# Tests Measuring Hepatic Synthetic Ability

هم عشان احدد اذا المشكلة عن هاد النسخه Acute او Chronic

- The measurement of the end products of hepatic synthetic activity can be used to assess liver disease. Although these tests are not sensitive to minimal liver damage, they are useful in quantitating the severity of hepatic dysfunction  

البروتينات الهه  $\pm \frac{1}{2}$  يعني بدنا شو عشان يبين النقص لأنه الكبد غير قادر على انه يصنع  
Hypoalbuminemia → impaired renal function  
→ chronic liver disease
- Most serum proteins are produced by the liver. A decreased serum **albumin** may be a result of decreased liver protein synthesis. The albumin level correlates well with the severity of functional impairment and is found more often in chronic rather than acute liver disease. The serum  **$\alpha$ -globulins** ( $\alpha$ 1-antitrypsin) tend to decrease with chronic liver disease
- Serum  **$\gamma$ -globulin** levels are transiently increased in acute liver disease and remain **elevated in chronic liver disease**. The highest elevations are found in **chronic active hepatitis** and postnecrotic cirrhosis.  

اله دخل بال immune system  
viral hepatitis
- IgG and IgM levels are more consistently elevated in **chronic active hepatitis**, IgM in **primary biliary cirrhosis**, and IgA in **alcoholic cirrhosis**.

# Tests Measuring Hepatic Synthetic Ability

- **Prothrombin time** is commonly increased in liver disease because the liver is unable to manufacture adequate amounts of clotting factor or because the disruption of bile flow results in inadequate absorption of vitamin K from the intestine  
*except factor A*  
*obstruction of gallbladder*
- Response of the prothrombin time to the administration of vitamin K is of some value in differentiating intrahepatic disease with decreased synthesizing capacity from extrahepatic obstruction with decreased absorption of fat-soluble vitamins.  
*prolonged prothrombin*  
*activation of clotting factor*  
*chronic liver disease*
- A marked prolongation of the prothrombin time indicates severe diffuse liver disease and a poor prognosis

يمكن ان نرى اذا مشكلة liver و bile فـ bile طبيعي  
منه vit k يفرج بـ carboxylation لا clotting factor  
اذا المشكلة bile فـ DT طبيعي  
مرتفع حتى بعد الـ liver المشكلة و very poor prognosis

# Tests Measuring Nitrogen Metabolism

- The liver plays a major role in removing ammonia from the bloodstream and converting it to urea so in liver failure ammonia will increase leading to coma bc of weak urea cycle
- In brain, glutamate react with ammonia to give glutamine which increases in CSF to cause encephalopathy

Accumulation of glutamate  
↓ urea

وجوده بالانفسي فالصغار اذا  
بشكله كثيره هب عقم

في الدماغ brain او glutamate يتفاعل  
مع الامونيا و يتحول ل glutamine  
كشأن يقلل من ال acidity نتيجة ل glutamate

# Hepatitis

- inflammation of the liver, may be caused by viruses, bacteria, parasites, radiation, drugs, chemicals, or toxins.  
*أشهر أسباب:*  
isoniazid Statin Retinol Rifampicin  
هذه الأدوية تستخدم لعلاج أمراض الكبد و خلال العلاج
- Among the viruses causing hepatitis are hepatitis types A, B, C, D (or delta), and E, **cytomegalovirus**, **Epstein-Barr virus**, and probably several others.  
*الأكثر شيوعاً: A B C D E*
- Hepatitis A is usually transmitted by the **fecal/oral** route and causes a mild or inapparent infection with no tendency to chronic disease.  
*من أكل أو شرب ماء ملوث*
- Hepatitis B and C are primarily transmitted **parenterally**. Hepatitis B causes a serious illness in a minority of patients, however, in many patients, the infection is mild or even inapparent.  
*عن طريق الدم وليس الاتصال الجنسي أو انتقال المرض من الأم إلى الجنين  
بعض المرضى يصابون بمرض مزمن Chronic فيكون Severe  
الناس التي عندهم هذا النوع من الـ Hepatitis يشفى منها ولكن بعضهم يتحول إلى الـ Hepatitis المزمن  
الذي قد يتحول إلى الـ chronic في كثير من الحالات وهذا يعني أنها خطيرة لأنها قد تؤدي إلى الموت  
في حين أن الـ Hepatitis A عادة ما تكون خفيفة ولا تتحول إلى مرض مزمن*

# Hepatitis

- Acute infection with hepatitis C is usually mild to inapparent  
← بين مشكلة انه قد يتحول لـ chronic
- Hepatitis B has a slight tendency to chronic disease, while most patients with hepatitis C infection develop chronic infection.
- Delta hepatitis is a unique satellite virus that causes a superinfection in patients already infected with hepatitis B.
- Hepatitis E is primarily transmitted by the **fecal/oral** route and causes serious disease **only** in **pregnant** women
- Chronic hepatitis is a major cause of morbidity and mortality worldwide  
يمكن تتحول لـ liver cirrhosis و سرطان carcinoma  
very poor prognosis
- Chronic hepatitis is a major risk factor for the development of hepatocellular carcinoma

# Case study

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## CASE STUDY 22-1

The following laboratory test results were obtained in a patient with severe jaundice, right upper quadrant abdominal pain, fever, and chills (Case Study Table 22-1.1).

### Question

1. What is the most likely cause of jaundice in this patient?

### CASE STUDY TABLE 22-1.1. LABORATORY RESULTS

Serum alkaline phosphatase	4 times normal
Serum cholesterol	Increased
AST (SGOT)	Normal or slightly increased
5'-Nucleotidase	Increased
Total serum bilirubin	25 mg/dL
Conjugated bilirubin	19 mg/dL
Prothrombin time	Prolonged but improves with a vitamin K injection



# Case study

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## CASE STUDY 22-2

The following laboratory test results were found in a patient with mild weight loss and nausea and vomiting, who later developed jaundice and an enlarged liver (Case Study Table 22-2.1).

### Question

1. What disease process is most likely in this patient?

### CASE STUDY TABLE 22-2.1. LABORATORY RESULTS

Total serum bilirubin	20 mg/dL
Conjugated bilirubin	10 mg/dL
Alkaline phosphatase	Mildly elevated
AST (SGOT)	Significantly elevated
ALT (SGPT)	Moderately elevated
Albumin	Decreased
$\gamma$ -Globulin	Increased