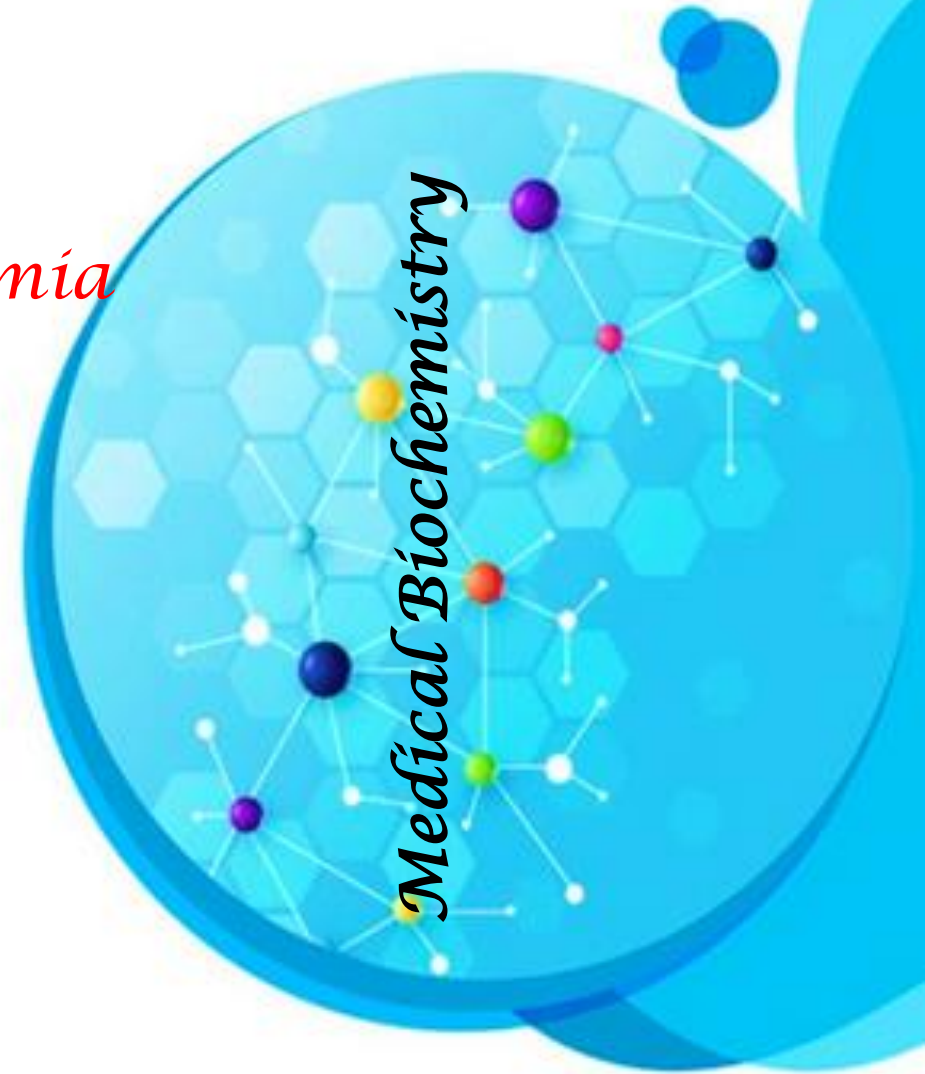


CVS module

*Cholesterol metabolism; Hypercholesterolemia
Hypocholesterolemia*

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Structure and sources of cholesterol:

derived lipid

cholesterol $\Rightarrow$ sterol ($C_3 \rightarrow OH$)

- Cholesterol is classified as an animal sterol (having -OH group at C3).

له معنى انه يتقوى على steroid باضافة
nucleus
الى OH على carbon-3

وقبل هذا حكيانه ال nucleus عباره عن cyclopentoperhydroanphirin

- Endogenous: Cholesterol is formed in the body almost in all nucleated cells from Acetyl-CoA (about 700 mg/day).

يقم تصنيع تقريباً من الكوليسترول يومياً

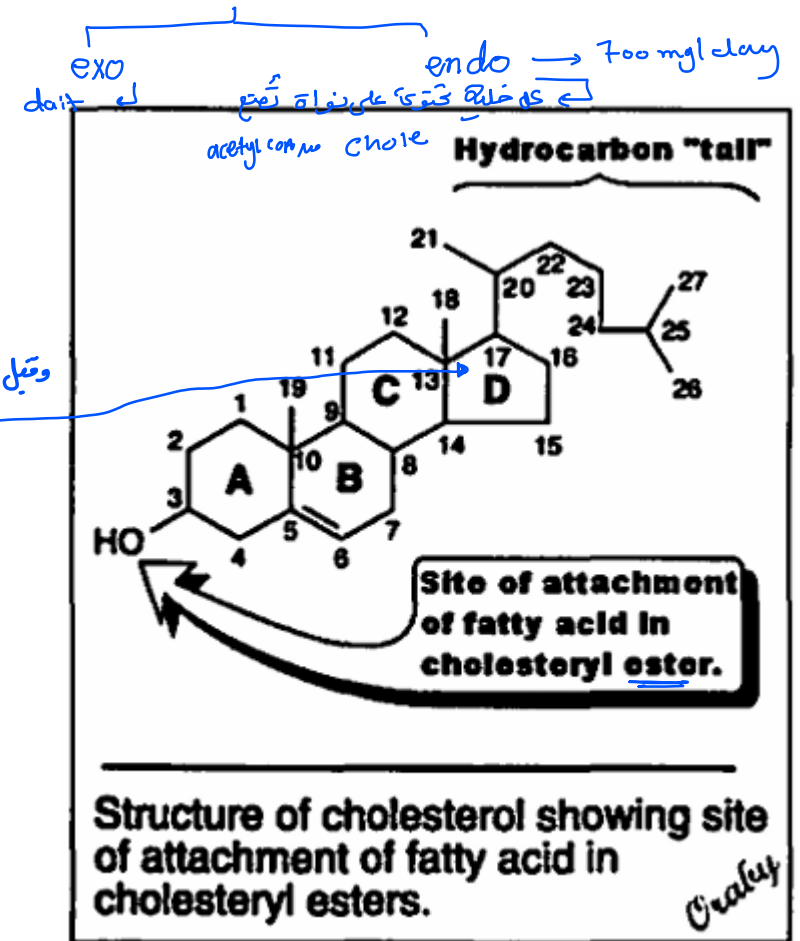
يتصنع في كل خلايا الجسم

التي تقوى على nucleuses من ال [acetyl-coA] ولكن mainly في ال liver

- Exogenous: Cholesterol occurs only in food of animal origin such as egg yolk, meat, liver and brain. Diet supplies about 400 mg/day.

منه source

مفاد



Synthesis of cholesterol:

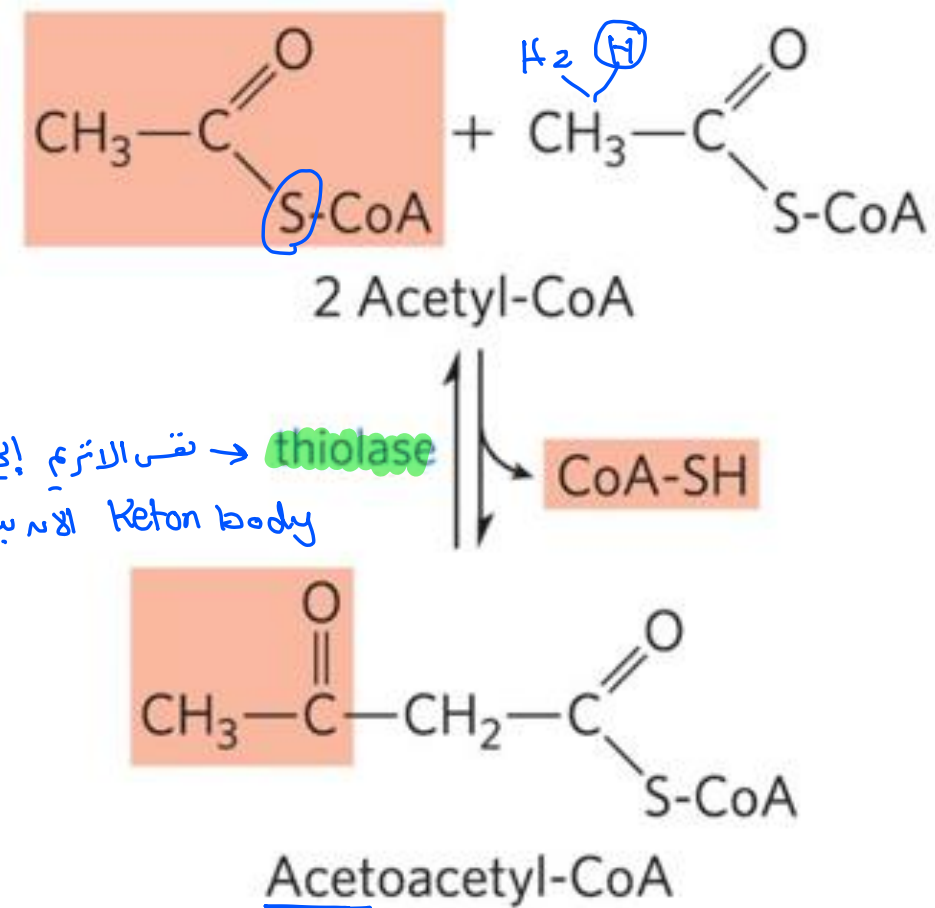
1. Location:

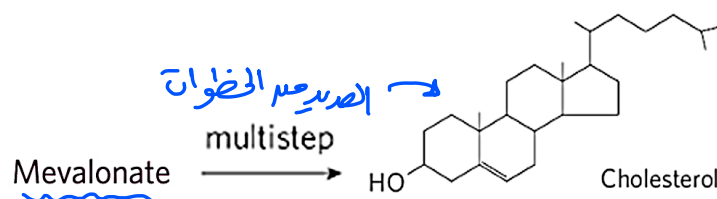
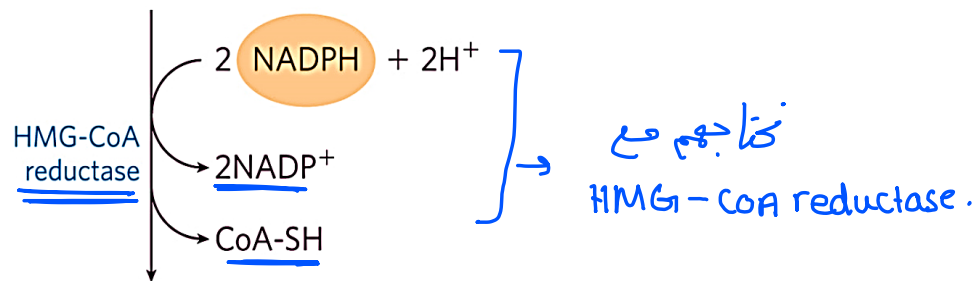
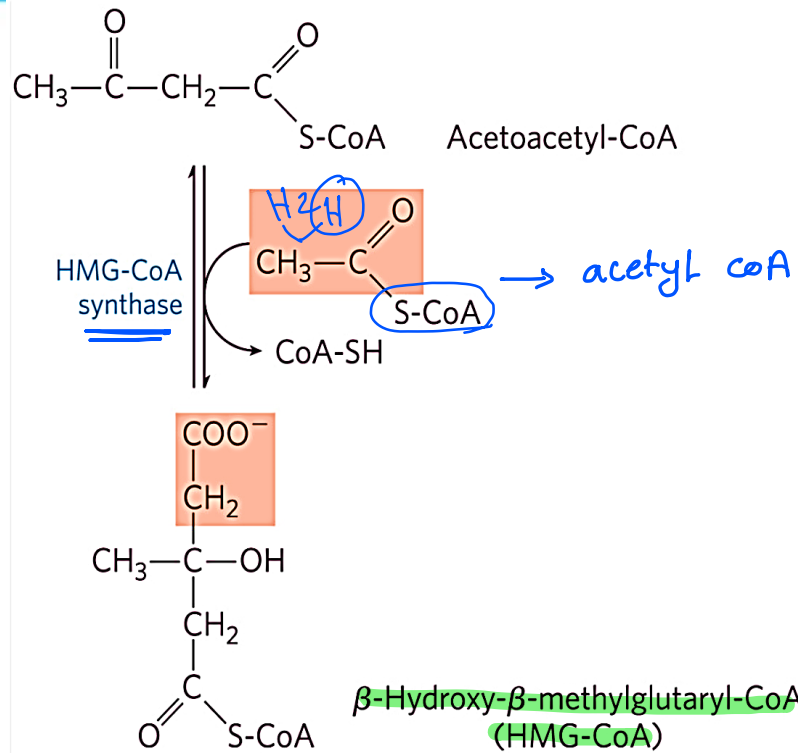
- Intracellular location: Cytosol. تأخذ الخلية الـ endoplasmic reticulum في تصنيع الـ Cholesterol
- Organ location:
 - Liver is the major site of cholesterol synthesis.
 - Other tissues e.g. intestine, adrenal cortex, gonads and skin. لأنه الكوليسترول له دور كبير في تصنيع الـ Progesterone & testosterone & estrogen
← من في تصنيع الـ Vit D

2. Precursor: Acetyl-CoA.

Steps of synthesis of cholesterol

- The first step of cholesterol synthesis is the ¹condensation of two molecules of **acetyl-CoA** to form **acetoacetyl-CoA**.
- This reaction is catalyzed by the enzyme **thiolase**.





acetyl-CoA - acetyl CoA

↓ thiolase

acetoacetyl CoA + acetyl CoA

↓ HMG-Synthase

β-Hydroxy-β-methylglutaryl CoA

↓ HMG-reductase.

mevalonate

↓ الاصدع من الفضول
cholesterol.

Conversion of acetoacetyl CoA to cholesterol

تتم عملية التحكم والتنظيم في Cholesterol metabolism

Regulation of Cholesterol Metabolism. HMG CoA reductase is the key enzyme for cholesterol synthesis

له لوائح ضيقة هناك، major regulation هناك، minor regulation

زيادة

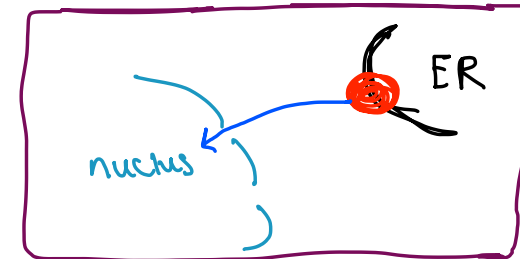
لوائح عملية
regulation

Major regulation is by gene expression

Minor regulatory mechanisms phosphorylation & dephosphorylation التي تتم بواسطة الـ

Major regulation is by gene expression: Three levels

لهذه المستويات مرة واحدة اختتم في HMG reductase.



1. Sterol regulatory element-binding proteins (SREBPs) [transcription factor].

- When sterol levels are high, SREBPs remain bound to the ER membrane.
 (Cholesterol is high, SREBPs are bound to the ER membrane.)
- When sterol levels fall, the complex is cleaved and moves to the nucleus.
 (When cholesterol is low, the complex is cleaved and moves to the nucleus.)
- It activates transcription of HMG-CoA reductase.
 (SREBPs activate the transcription of HMG-CoA reductase.)

2. Translational control on mRNA stability

- Increased mevalonate destabilize the HMG-CoA reductase mRNA.
 (High levels of mevalonate lead to the degradation of HMG-CoA reductase mRNA.)

3. Post-translational control

- High cholesterol produces oxysterol, which allosterically binds HMG-CoA reductase, inducing a conformational change that promotes its ubiquitination.
 (High cholesterol leads to the production of oxysterol, which binds to HMG-CoA reductase, causing it to be ubiquitinated.)
- Proteolytic degradation of HMG-CoA reductase → ↓ cholesterol.
 (The degradation of HMG-CoA reductase leads to a decrease in cholesterol levels.)

(*) نتحكم في عملية تصنيع الكوليسترول عن طريق الأدوية
 خصوصاً في عمليات treatment

Inhibition by drugs:

↓ HMG-reductase
 lova
 mevca

- **Lovastatin** and **mevastatin** are part of a class of drugs known as **statins** that specifically target **HMG-CoA reductase**, the enzyme responsible for the rate-limiting step in cholesterol biosynthesis. They're effective in **treating hypercholesterolemia** (high cholesterol levels).

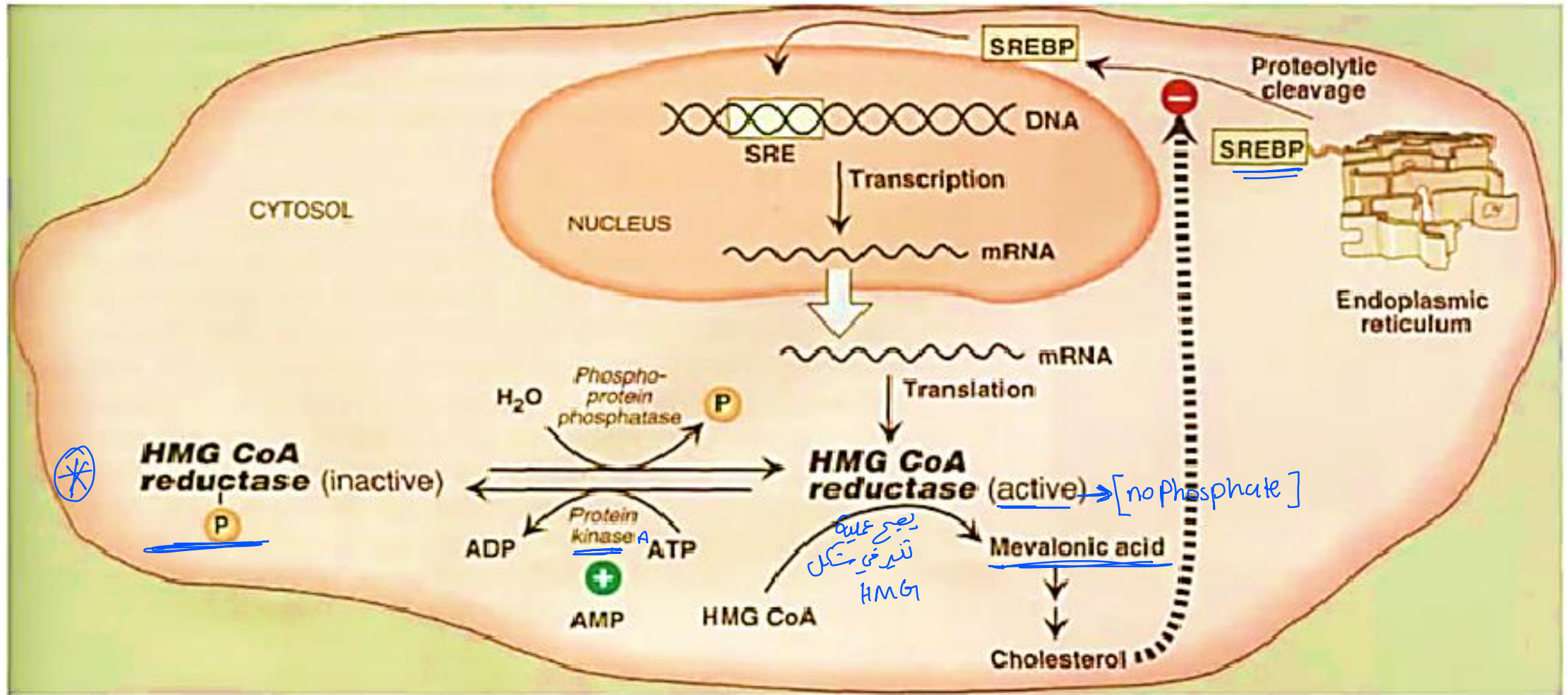
تستخدم في علاج hypercholesterolemia

ميكانيكية العمل
 mechanism
 reversible

- **Competitive Inhibition of HMG-CoA Reductase:** Lovastatin and mevastatin are structural analogs of **HMG-CoA**. Due to this structural similarity, they can bind to the active site of HMG-CoA reductase, effectively competing with HMG-CoA for binding.

تشابه في الـ structure لها

لأنه يشبه في شكله تنافس بغير ربيط مع HMG-CoA reductase
 lovastatin
 mevastatin



Excretion of cholesterol

- About one **gram** of cholesterol is excreted dally. It is secreted as cholesterol, bile acids and coprostanol:

① يتم التخلص منه بهذه الطريقة
② excretion 1g تقريباً يومياً بغير
- A. $\frac{1}{2}$ Gram cholesterol is excreted as such with bile, which transports it to the intestine for elimination.

direct by العصارة الصفراء
Cholesterol هو المركب الذي يتم التخلص منه كـ $\frac{1}{2}$ g
- B. $\frac{1}{2}$ Gram cholesterol is converted to bile acids, which is excreted in the feces.

Cholesterol ($\frac{1}{2}$ g) يتحول إلى bile acid في الكبد
[excretion] بهذا الشكل
- Some cholesterol is synthesized by intestinal cells and modified by bacteria before excretion. Bacterial enzymes reduce cholesterol into coprostanol, which is excreted into feces.

③ هناك بكتيريا في الأمعاء تقوم بتقليل cholesterol reduction إلى coprostanol
أو تغييره في الأمعاء modification بواسطة البكتيريا الموجودة خاصة في الأمعاء large intestine
من أجل التخلص منه بواسطة البراز excretion في براز feces وهو absorption

Plasma cholesterol and conditions associated

- ⊗ Hypercholesterolemia
- ⊗ Hypocholesterolemia

Plasma cholesterol

Free-chole $\Rightarrow$ 26 - 126 mg/dL plasma
 ester + Free $\rightarrow$ 140 $\rightarrow$ 220 mg/dL

cholesterol موجود في الدم بشكلين: free و esterified
 free: cholesterol غير مرتبط بـ fatty acid
 esterified: cholesterol مرتبط بـ fatty acid

- In plasma, cholesterol exists in two primary forms: **free cholesterol**

and **esterified cholesterol** (known as cholesteryl ester).

esterified: cholesterol مرتبط بـ fatty acid
 other fatty acids: ester bond

- **Normal Range:** Free cholesterol typically ranges from 26 to 126

mg/dL in plasma

- **Normal Range:** The optimal total plasma cholesterol level typically falls between 140 and 220 mg/dL.

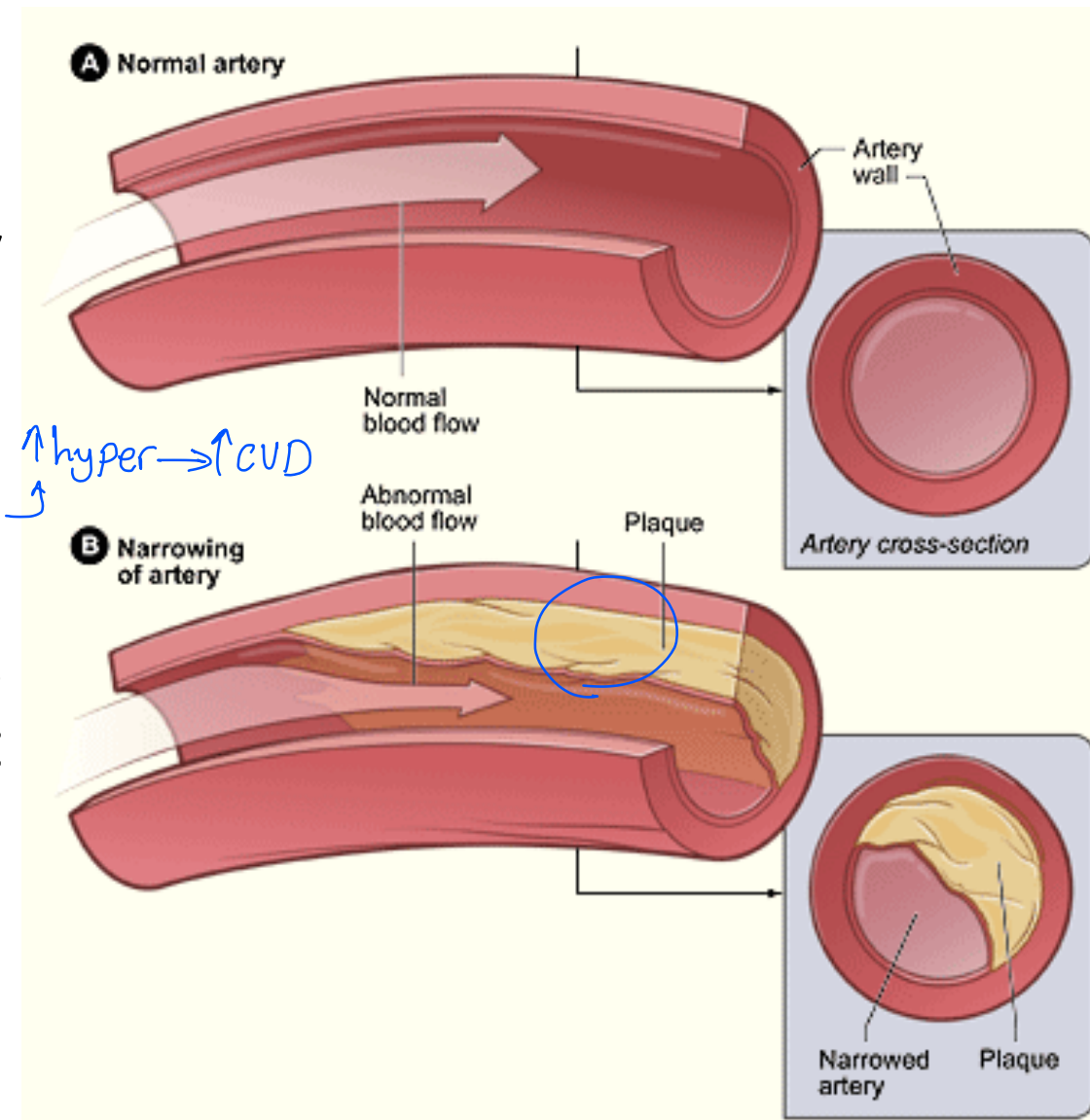
Free cholesterol: cholesterol غير مرتبط بـ fatty acid
 esterified cholesterol: cholesterol مرتبط بـ fatty acid

Hypercholesterolemia

- Hypercholesterolemia is typically defined as a total plasma cholesterol concentration **above 220 mg/dL**.

- This level is associated with an increased risk of atherosclerosis and cardiovascular diseases, as excess cholesterol in the blood can deposit on arterial walls, leading to plaque formation.

وذلك لأنه ال Cholesterol لو زاد عن 220mg/dL حصل في اتي
 damage ← vessel حصل بترسيم له Fat في منطقة
 ال damage وبالتالي حصل Plaque وسبب حرقه الدم



أسباب Causes of Hypercholesterolemia

1. Diet rich in carbohydrate, cholesterol and saturated fatty acids. → ↑ total cholesterol in plasma.
2. Hypothyroidism: Thyroxine (T4) regulates cholesterol metabolism by enhancing the conversion of cholesterol to bile acids and increasing the expression of LDL receptors on liver cells. ⇒ LDL receptors في خلايا الكبد لا تظهر
 ↳ hypothyroidism (*) ← نقص نشاط الغدة الدرقية
 ↳ نقص مستقبلات LDL
 ↳ تساعد في تحويل الكوليسترول إلى أحماض صفراوية
 ↳ زيادة التعبير عن مستقبلات LDL
3. Diabetes is often associated with insulin resistance, which impairs lipid metabolism.
 ↳ مقاومة الأنسولين
 ↳ خلل في استقلاب الدهون

4. Kidney Disease (Nephrotic Syndrome)

↳ خروج بروتينات كبدية من الدم
 ↳ انخفاض مستوى البروتينات في الدم
 ↳ انخفاض مستوى الكوليسترول في الدم
 ↳ انخفاض مستوى albumin في الدم
 ↳ انخفاض مستوى cholesterol في الدم
 ↳ انخفاض مستوى liver protein في الدم
 ↳ انخفاض مستوى LDL في الدم
 ↳ انخفاض مستوى VLDL في الدم

M. ELEYAN

- Familial hypercholesterolemia (FH)** is a genetic disorder often caused by mutations in the LDL receptor gene, leading to reduced LDL receptor activity.

- M. ELEYAN**

Hypocholesterolemia:

- Plasma cholesterol levels below 140 mg/dL are considered hypocholesterolemic. Causes:
 - **Prolonged fasting** which causes decreased secretion of Insulin $\uparrow$ glycogen. (decreased activation of HMG-CoA reductase).
 (الانسان صائم : يصدر على HMG-CoA reductase ينزاد وبالتالي cholesterol تنخفض -
 له لعنة تقل عملية استخراج ال cholesterol.
 - **Diet Poor in Saturated Fatty Acids**, Carbohydrates, and Cholesterol.
 - **Liver Diseases** Liver diseases like **cirrhosis** or **hepatitis** impair this synthetic function
 (هو المصير أو الكبد الاصطناعي لتصنيع هو Cholesterol.)
 - **Hyperthyroidism**: excess thyroid hormones (T3 and T4) increase the metabolic rate and enhance **LDL receptor** activity in the liver. This accelerates LDL clearance from the bloodstream.

hyper:-
فائض

TRANSPORT OF CHOLESTEROL:

- Cholesterol is hydrophobic. It is transported in plasma in the more soluble lipoprotein forms: LDL, VLDL and HDL (next lecture).
- Free cholesterol is removed from tissues by HDL and transported to be excreted by the liver.

Storage of Cholesterol (Next lecture)

- Cholesterol ester is the storage form of cholesterol: It is formed in both tissues and plasma.
- In tissues (liver), cholesterol is esterified by ACAT enzyme (acyl CoA cholesterol acyl transferase):



- In plasma, cholesterol is esterified by LCAT enzyme (lecithin cholesterol acyl transferase). LCAT is associated with HDL.



Functions of cholesterol

مادة
مختارة

Functions of cholesterol

1. Cholesterol enters in the structure of every body cell (e.g. cell membrane).

لے پڑھو فی ترکیب Cell membrane لکھو الحاد فی الجسم

2. Cholesterol Is the precursor of:

1. **Vitamin D₃:** (subcutaneous fat) ^{skin} → 7-dehydrocholesterol → Vitamin D₃.
2. **Steroid hormones:**
 - a) Estrogens and progesterone (ovaries).
 - b) Testosterone and androgens (testes).
 - c) Glucocorticoids and mineralocorticoids (Adrenal cortex).
3. **bile acids:** (Liver)

حسباً شرح من آخر الاسم لاوله

Generation the vitamin D₃ (1, 25 dihydroxycholecalciferol)

active form

لنوع على C
رقم 25
هناك مجموعته OH

معناها انه هذا ال
vitamin الذي يتكلم في
Precursor ال
cholesterol قومه هو

لنوع عندي انا vitamin
لنوع هذا ال vitamin بيحل regulation
لد cat level في الجسم

بواسطة
بري
اصنع

- Ultraviolet rays of sun generate the vitamin D₃ from the Provitamin 7-dehydrocholesterol (in human).

7 - dehydro cholesterol
ultra violet بواسطة in skin
cholecalciferol

- 7-dehydrocholesterol is converted into cholecalciferol (Vit D₃)

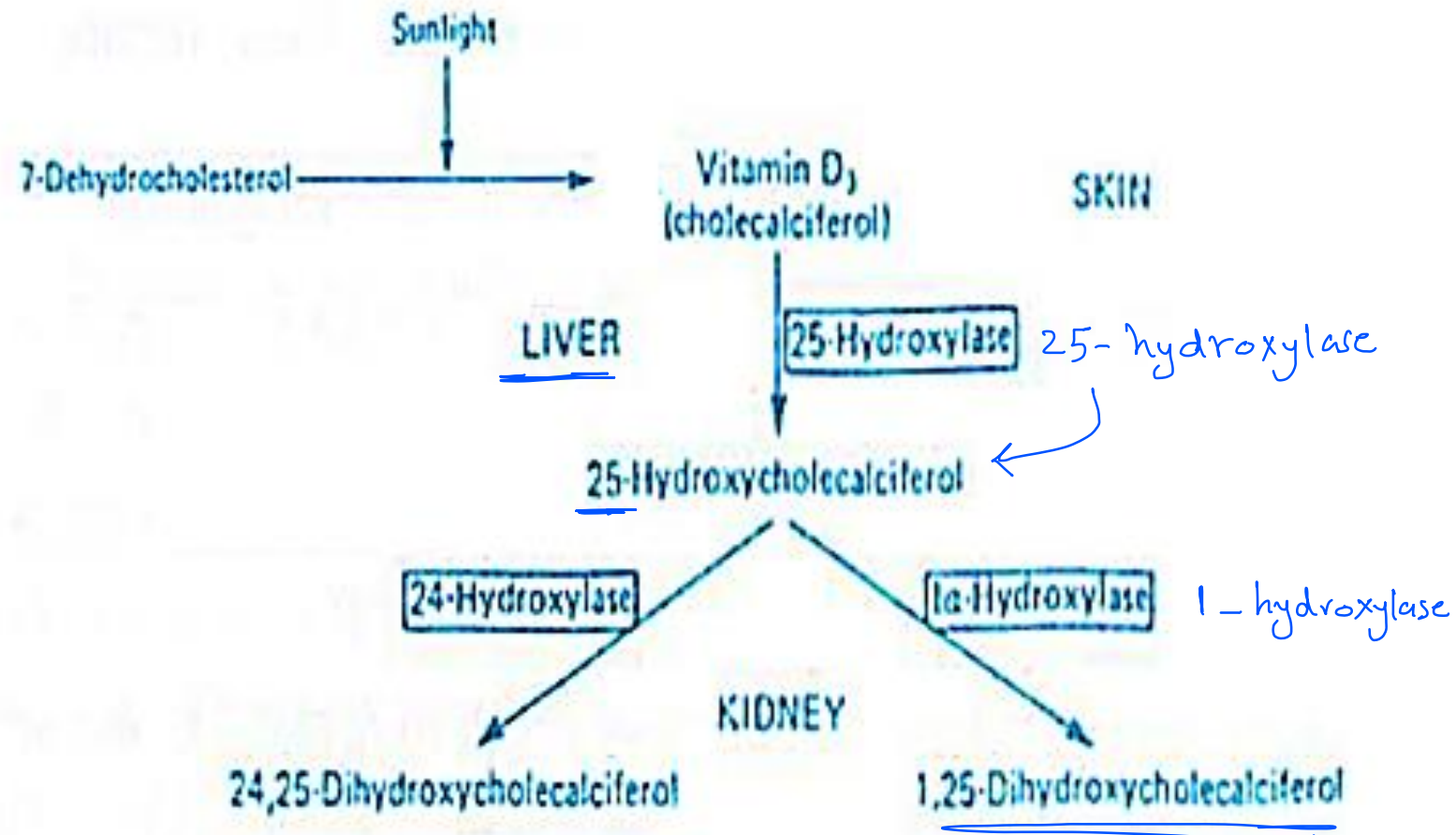
لنوع الى ال liver عنده اضيف عليه اذنه OH وعلى C25

- In the liver, cholecalciferol is converted into 25-hydroxyvitamin D₃.

لنوع الى kidney عنده اضيف عليه OH على C1

- Finally, the kidneys convert 25-hydroxyvitamin D into the active form of vitamin D, 1,25-dihydroxyvitamin D₃. (active form for vit D₃).

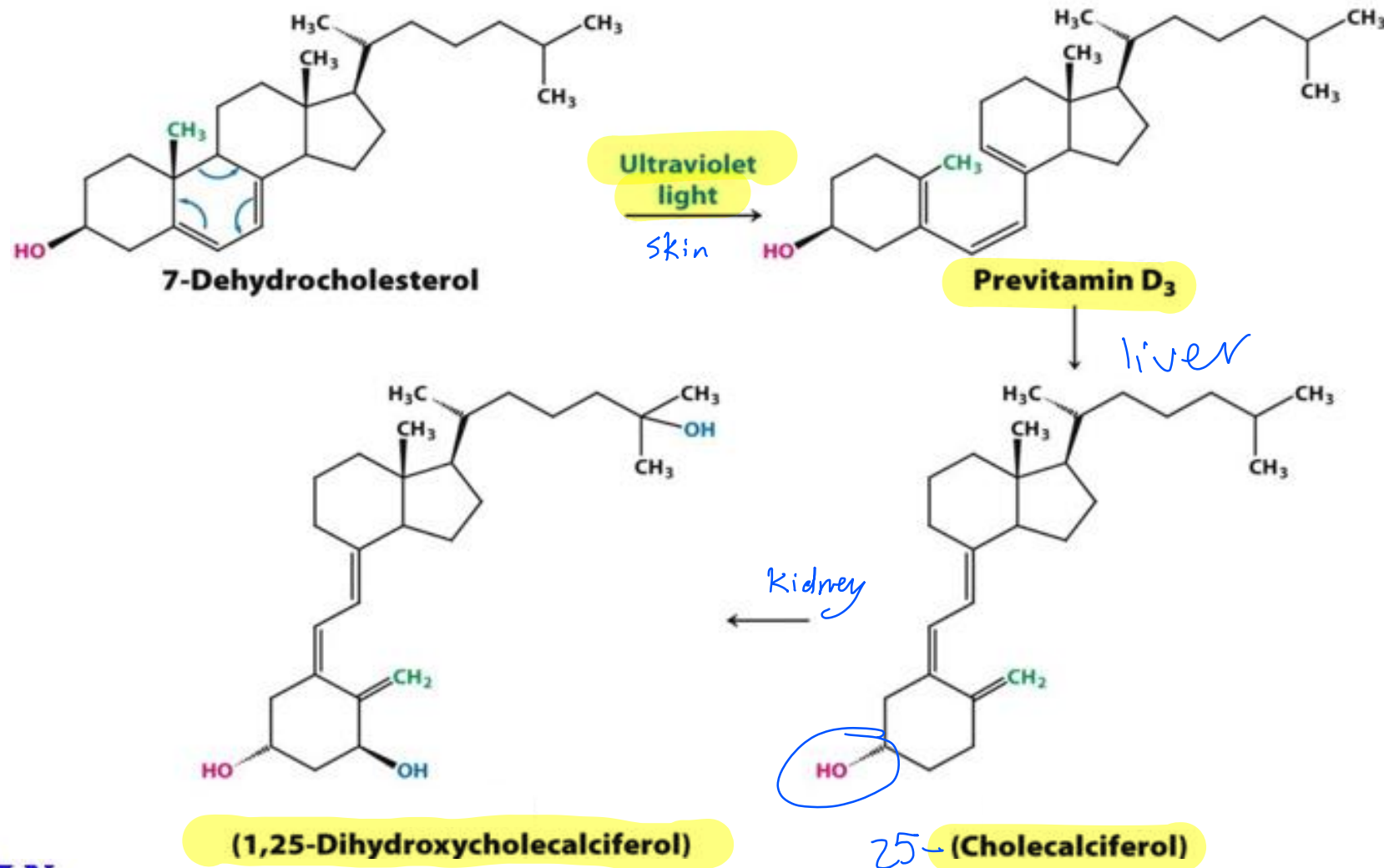
Activation of vitamin D3 to 1,25 dihydroxycholecalciferol



Pro vitamin ~~7~~ dehydrocholesterol



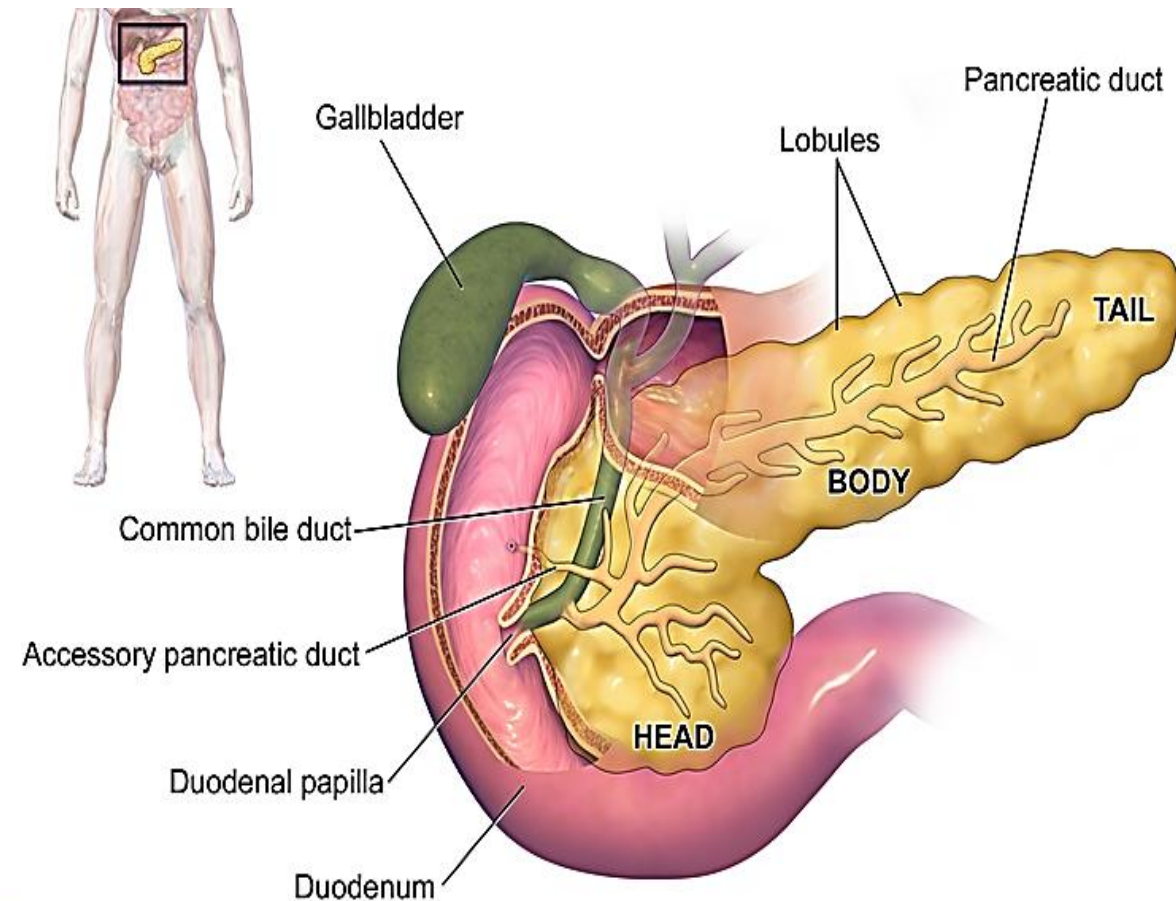
Activation of vitamin D3 to 1,25 dihydroxycholecalciferol



Bile, Bile acids and salts

تعريفه محتوياته Bile definition and content

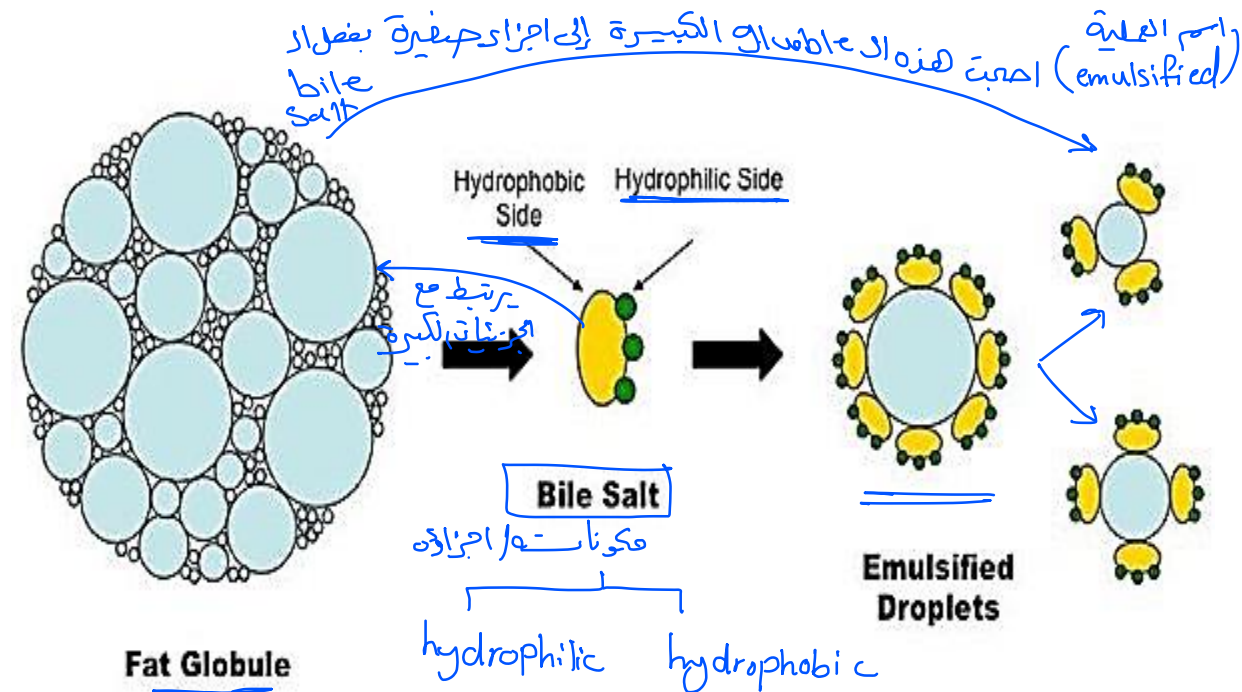
- Bile is a greenish-yellow fluid produced by the liver and stored in the gallbladder.
- It contains ① water, ② electrolytes, ③ bile acids, ④ bile salts, ⑤ cholesterol, ⑥ bilirubin, and ⑦ phospholipid [phosphatidylcholine (lecithin)].



Importance of Bile

- Bile's ^{له دور} role is to **emulsify fats**, which means it breaks down large fat drops into smaller droplets, making them more accessible to the action of enzymes.

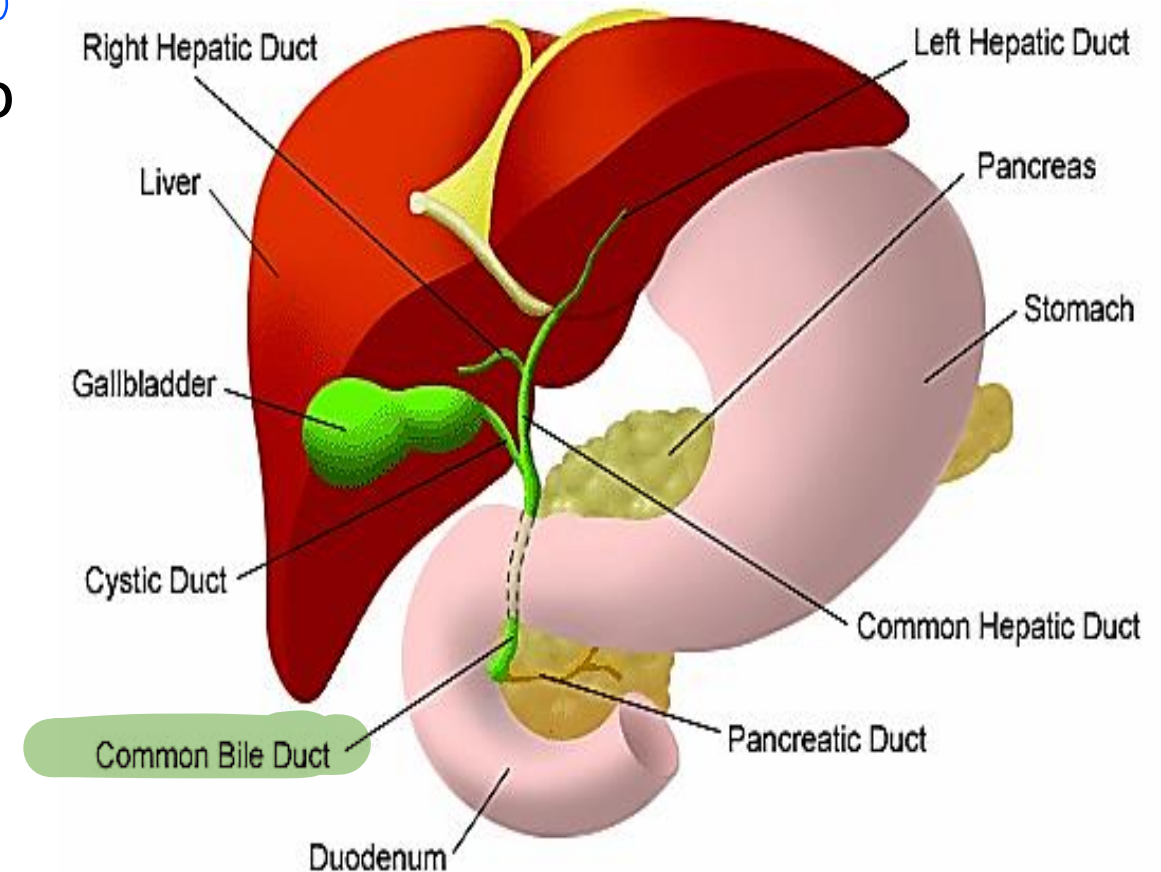
- Bile is essential for the **digestion** and **absorption** of fats and **fat-soluble vitamins** (A, D, E, and K)



Bile has two potential pathways

إذا انه يذهب لـ duodenum ويبدأ العملية
 لو محتاجه منه خلال الـ Common bile duct أو انه يرفع
 لـ gall bladder ويخزنه لاستخدامه في وقت الحاجة
 بعد تصنيع الـ liver
 تكون لها طريقتين

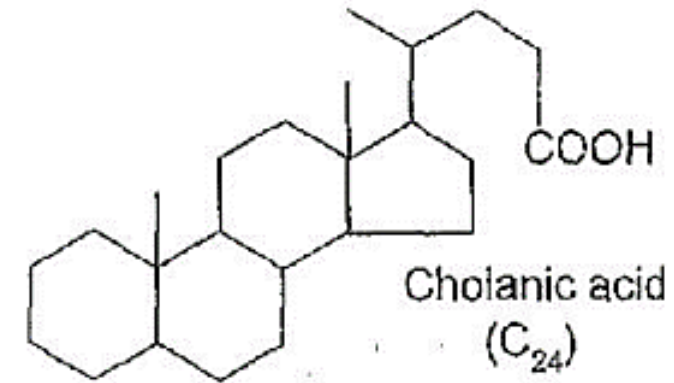
- It can flow directly from the liver into the **duodenum** through the **common bile duct**, or it can be stored in the **gallbladder** for **later use** when immediate digestion is not required.



Bile acids

- **Cholanic acid** is a **carboxylic** steroidal compound (**C₂₄**) that serves as the basis for the structure of various **bile acids** found in bile.

- Bile acids are **hydroxyl derivatives of cholanic acid** which is derived from cholesterol
- Types of bile acids: Primary & Secondary bile acids



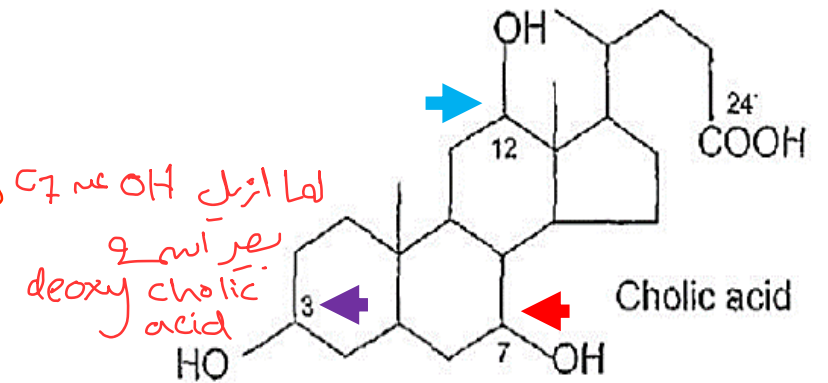
Primary bile acids

- Primary bile acids are synthesized in the liver:

1. Cholic acid (3, 7, 12 trihydroxy cholanic acid)

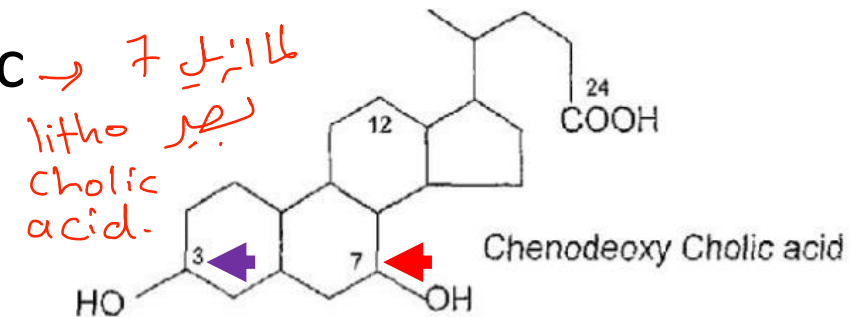
لجيب ال Cholanic acid وسطية عند كربونات 3, 7, 12
OH ← 3, 7, 12

- Cholic acid is one of the most abundant bile acids produced and is a major component of bile.



2. Chenodeoxycholic Acid (3, 7 dihydroxycholanic acid)

Cholanic acid
أقل
C 3, 7 → OH



Secondary bile acids

- **Secondary bile acids** are derived from **primary** bile acids in the intestine.

جائز من

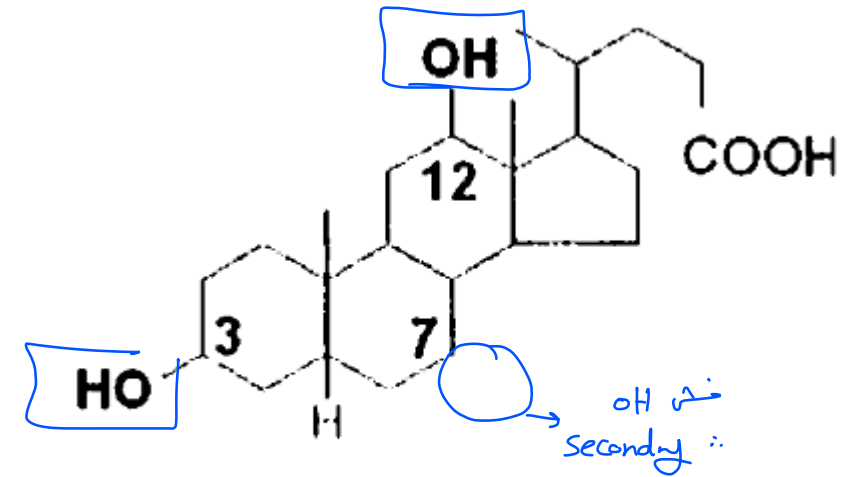
وبذلك يجعل من

- This transformation occurs through the action of **intestinal bacteria**, which remove the hydroxyl group at the 7th carbon position (no **OH** on **C7**; contain **7 α dehydroxylase**).

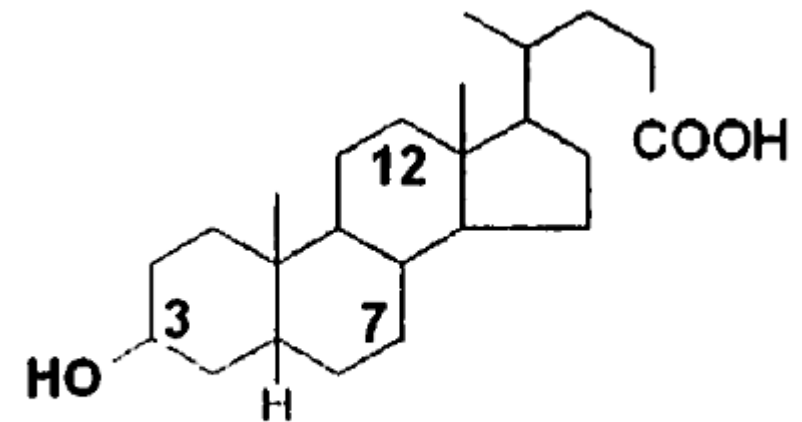
التي تتكون على 7 α dehydroxylase هاداً عنانها انه هذه البكتيريا قادرة على نزع C7 ~ OH في Primary bile acid ← عنانه تنسج secondary

Secondary bile acids

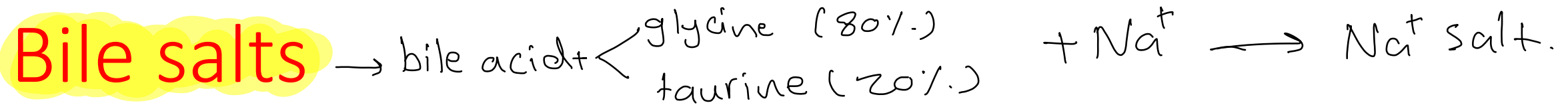
- **Deoxycholic acid** (3, 12 dihydroxy cholanic acid).
 OH ← C_{3,12} على C₇ له OH واحد
 • Formed from the primary bile acid **cholic acid** by bacterial dehydroxylation at the 7th carbon position.
- **Lithocholic acid** (3 ^{single OH on C₃} monohydroxy cholanic acid).
 • It has a single hydroxyl group at the 3rd position.



Deoxycholic acid



Lithocholic acid



- Bile salts are bile acids conjugated with glycine (80%) and taurine (20%), they are excreted by liver in bile as sodium salts.

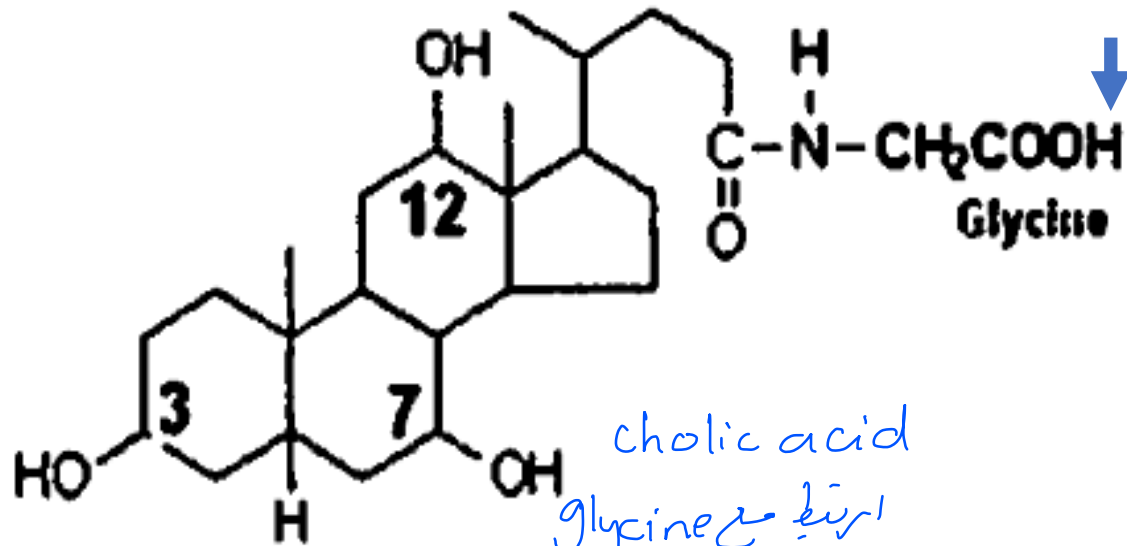
• Bile Acid + Glycine = Glycocholic OR Glychenodeoxycholic acids

deoxycholic or cholic acid

• Bile Acid + Taurine = Taurocholic OR Taurochenodeoxycholic acids

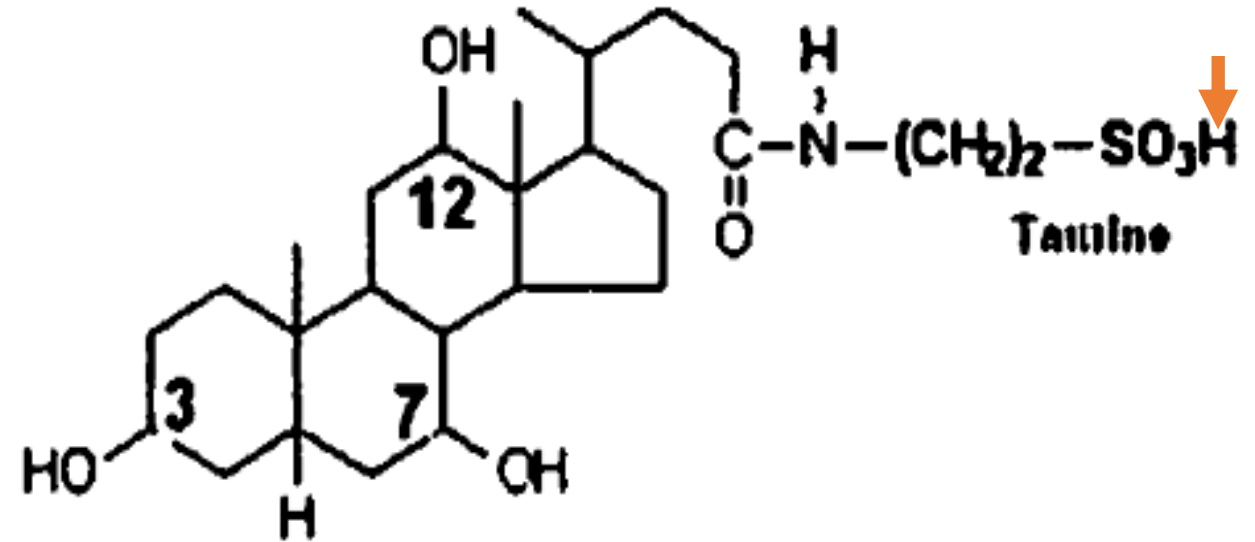
• sodium glycocholate and sodium taurocholate.

sodium glycocholate and sodium taurocholate.



Glycocholic acid

قوة حارة ←
Sodium
glycocholic acid.



Taurocholic acid

Cholic acid + taurine
Na⁺ Taurocholate

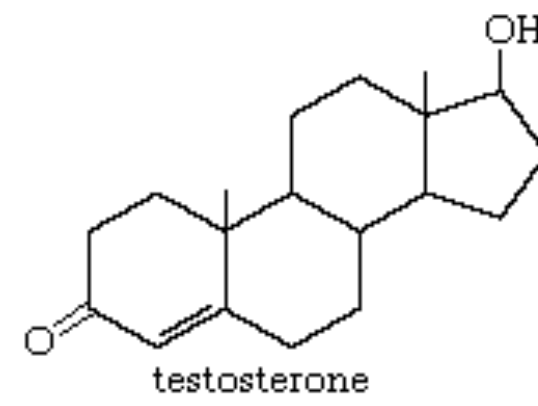
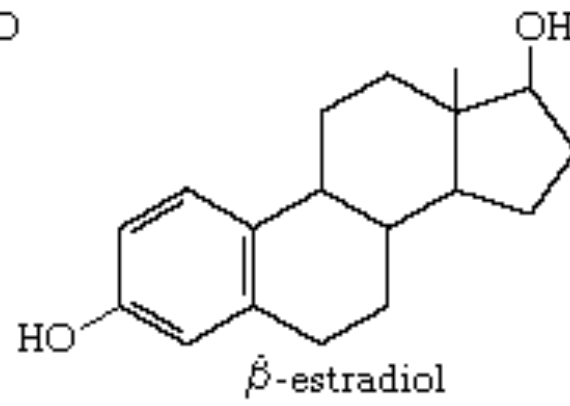
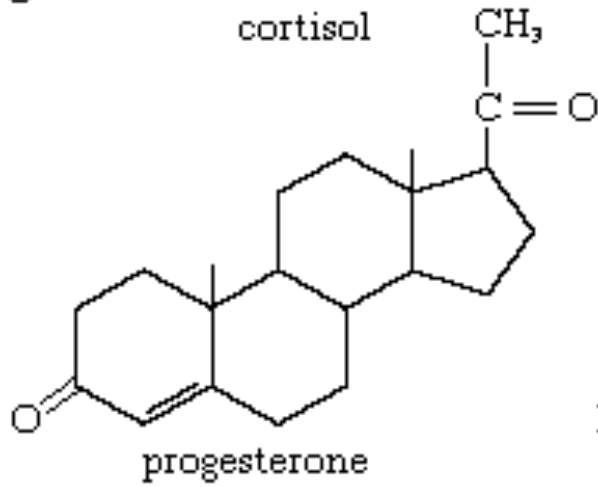
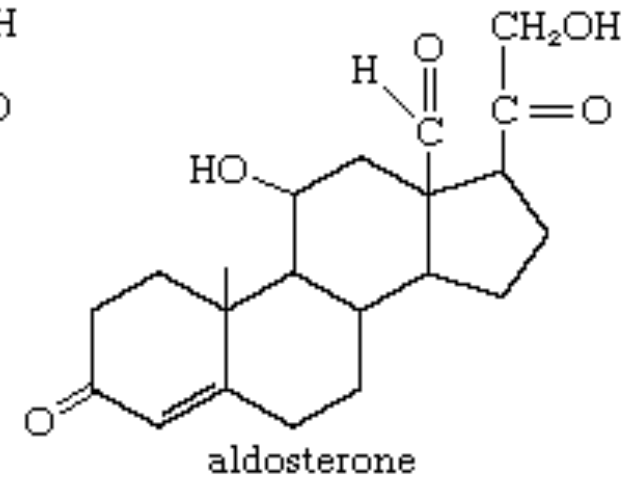
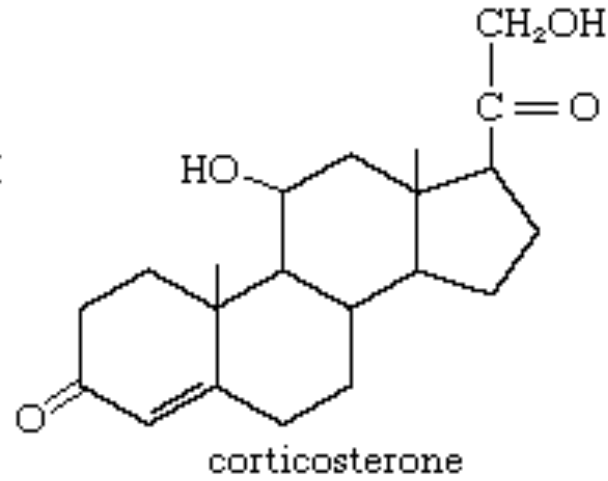
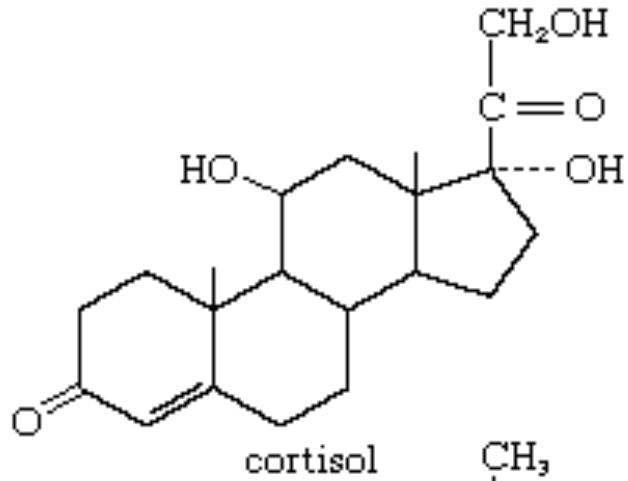
Importance of bile salts

1. Main way for **excretion of cholesterol**. → ^{بطلع على صورة}
_{bile}
 - Prevents precipitation of cholesterol & formation of **cholesterol stones**.
- ^{بعض}
_{الحماض} 2. **Digestion** ^{لحمة} of fat due to **emulsification**.
3. **Absorption** of fat and fat soluble vitamins.

cholestert
 ينتمي اليه
 الهرمونات الجنسية

cyclopentano-perhydro-phenanthrene "CPPP

Steroid hormones



Thanks