Biochemistry

Title =Lipid metabolism-L(3)
Lec no =16
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وقل رب زدني علما

Lipid metabolism lecture 3 of 3

Cholesterol and eicosanoid synthesis

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Lipids metabolism	1. Fatty acids metabolism a. Fatty acid synthesis b. Fatty acid catabolism 2. Cholesterol synthesis 3. Eicosanoids synthesis from fatty acids

Steroids

- **Definition:** Substances which are derived from C_{17} cyclopentanoperhydrophenantherene ring **(steroid nucleus)**
- Steroids include **sterols**, **bile acids** and **steroid hormones**

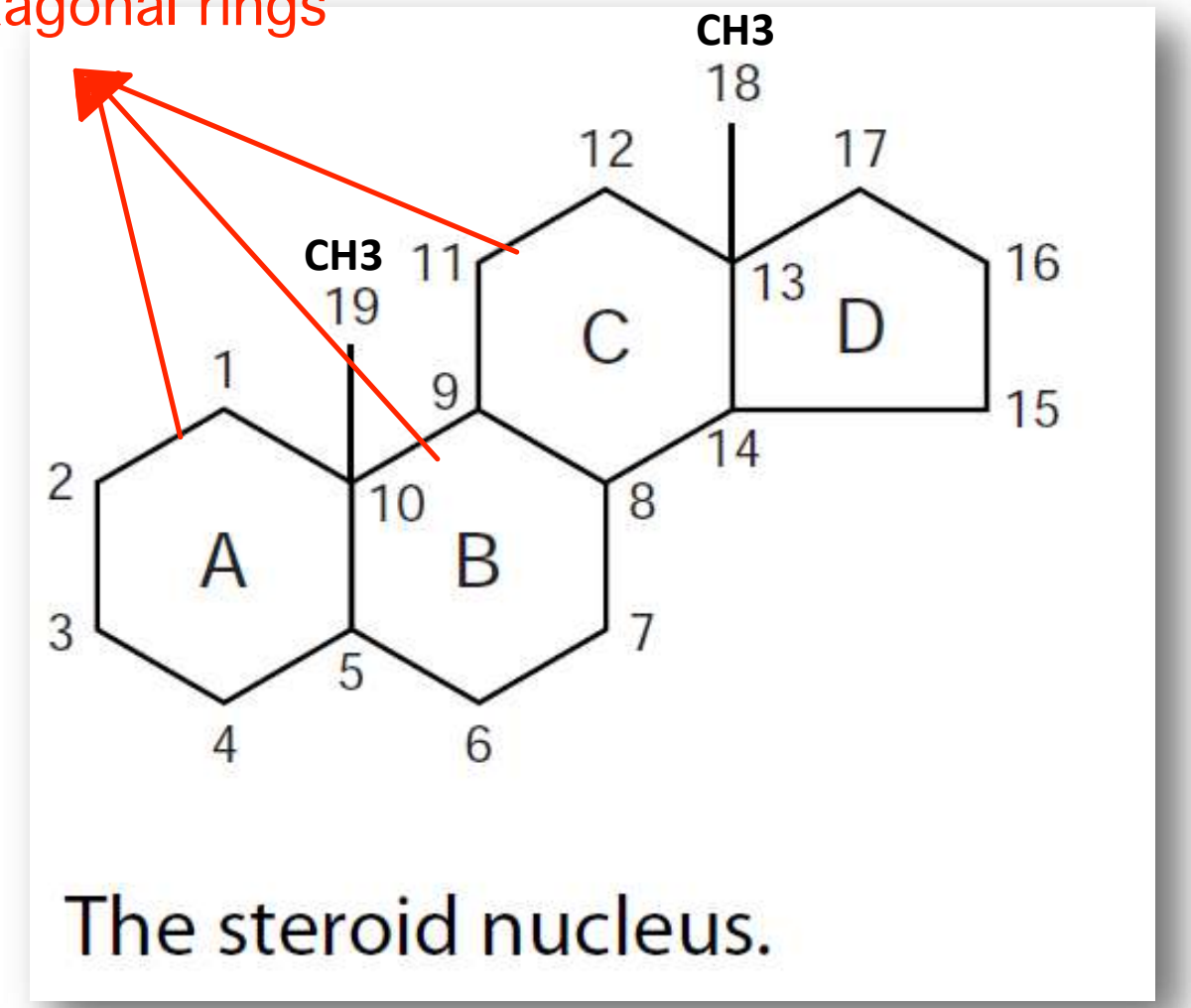
Comments on the terminology used for steroids:

Cyclopentanoperhydrophenantherene ring is due to:

- Cyclo → cyclic
- Pentano → 5 carbon ring (ring D)
- Phenanthrene ring → 3 hexagonal rings (A, B & C)
- Perhydro: saturated with hydrogen (unless noted otherwise)

* انتبه للترقيم

3 hexagonal rings



Cyclopentanoperhydrophenantherene ring (Steroid nucleus)

Sterols

- These are steroid alcohols containing **OH at C_3**

- There are 3 types of sterols which are phytosterol, mycosterols and zoosterols

No audio in this slide

Types of steroids and sterols

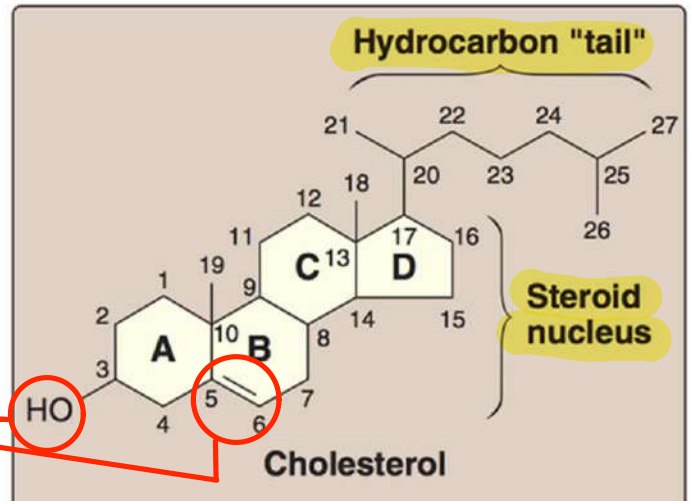
- Cholesterol (animal origin)
- Ergosterol (plant origin)
- Vitamin D group (D2 and D3)
- Bile acids and salts
- Steroid hormones
    - Male sex hormones
    - Female sex hormones
    - Adrenocortical hormones

Cholesterol

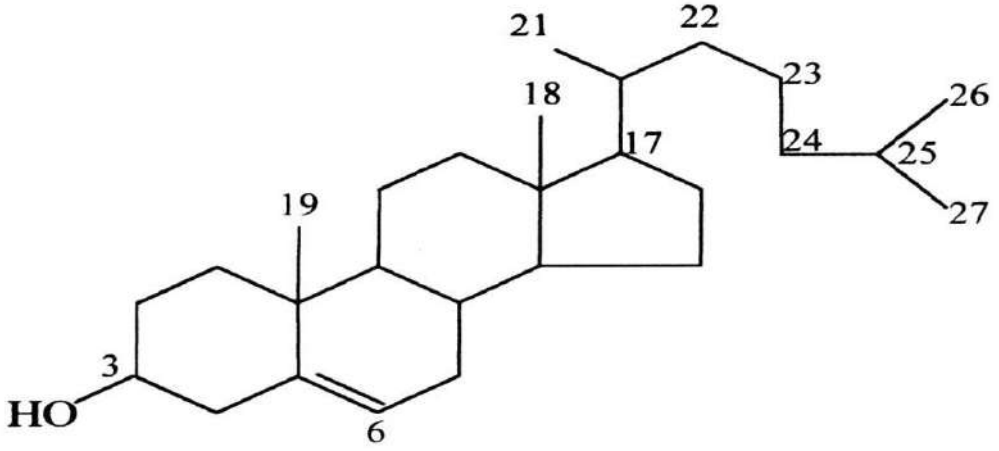
عاد حاي الجملة (3-4 مرات)

It is the main steroid in humans (present in **all** cells especially nervous system & plasma)

- It is a precursor form **all** other steroids
- Egg yolk, red meat, liver, kidney, butter and brain are rich in cholesterol



(أحد الأشياء التي تصنيه)



- Cholesterol contains unsaturated double bond between C5 and C6
  - → It can accept two hydrogen atoms

- Esterification: Cholesterol has – OH at C3, so it can form esters with any fatty acid (hydroxy group)
  - Blood cholesterol is either present in:
    - Free form (33%) → contains 27 carbons
    - Esterified form (67%) (Esterified of unsaturated FA (oleate and linolate) بالأغلب الأعم يكونه)

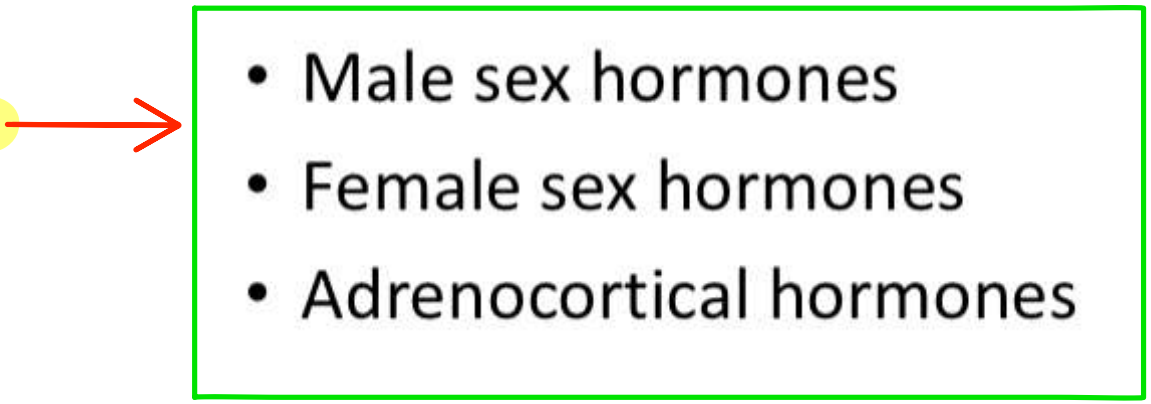
- Normal level of cholesterol in blood is less than 200 or 220 mg/ dL → if increased it is called **hypercholesterolemia**

- It is oxidized in liver, intestine & skin to give 7-dehydrocholesterol which is the precursor of vitamin D3 by exposure to UVR under the skin

Function of cholesterol

- Enters in structure of every body cell especially nervous system + cell membranes

- **Synthesis of:**
  - steroid hormones
  - Bile acids, salts
  - vit D3



Important facts about cholesterol metabolism

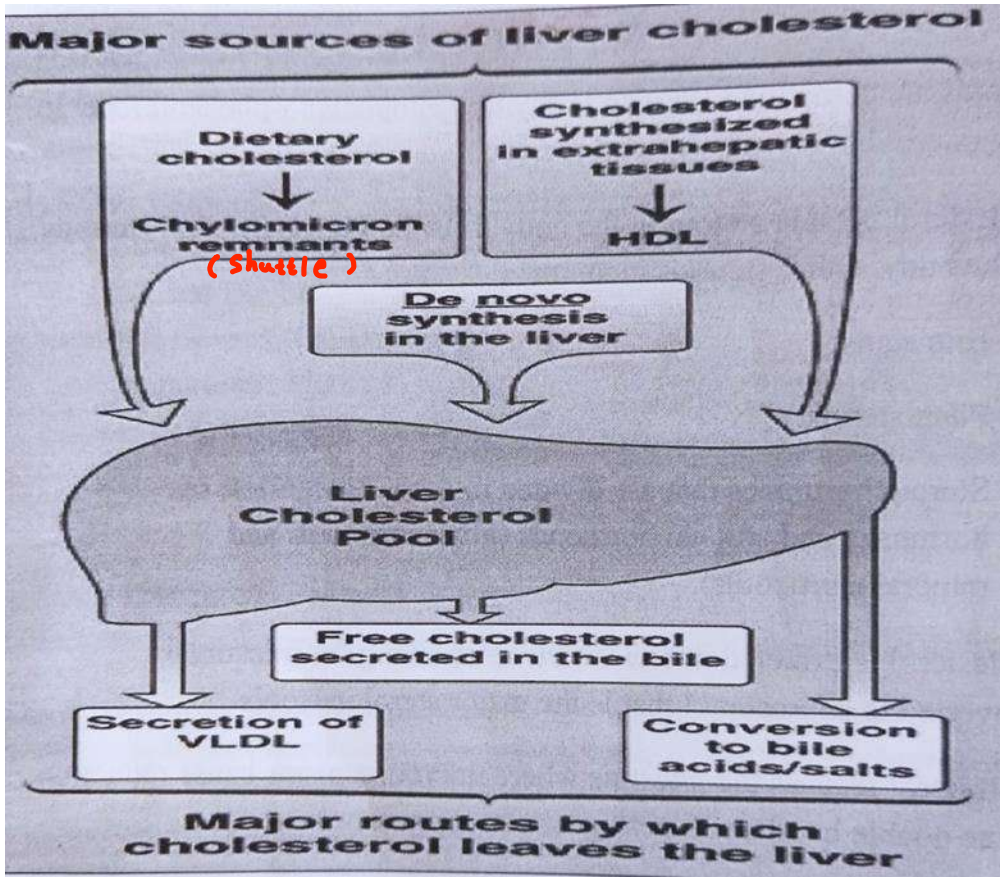
- Liver plays a central role in regulation of body's cholesterol
  - Liver & intestines main site of synthesis
  - Enzymes involved in synthesis are in cytosol & ER
  - Liver is principle organ that removes cholesterol from blood

سؤال في الإمتحان
(تصنيع الـ(cholesterol يتصرفي الـ(cytoplasm ولسه في الـ(mitochondira)

- Cholesterol is **not** a dietary essential

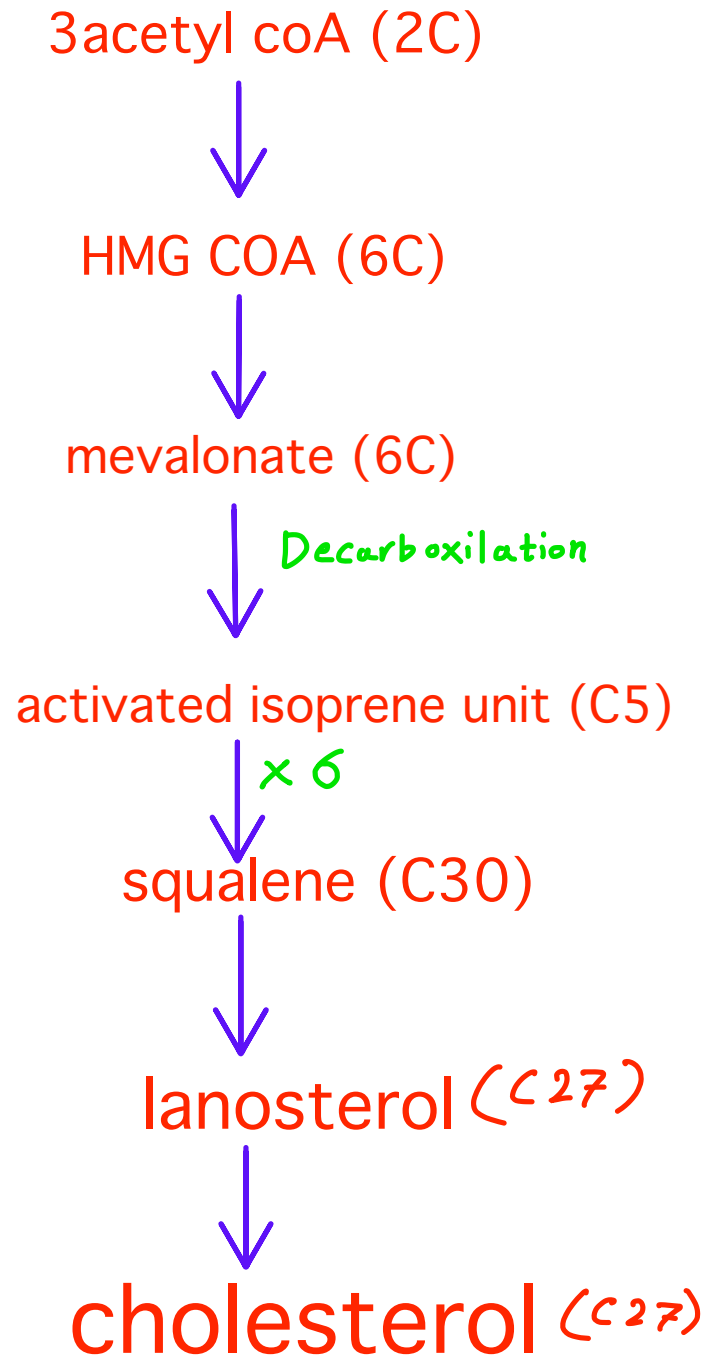
(يمكنه تصنيعه داخل الجسم)

- **All carbons are provided by acetyl coA** + NADPH
- Balance depends on input and output
- Any imbalance leads to gradual deposition of cholesterol in tissues especially lining of vessels → **coronary artery disease**



Stages of cholesterol synthesis

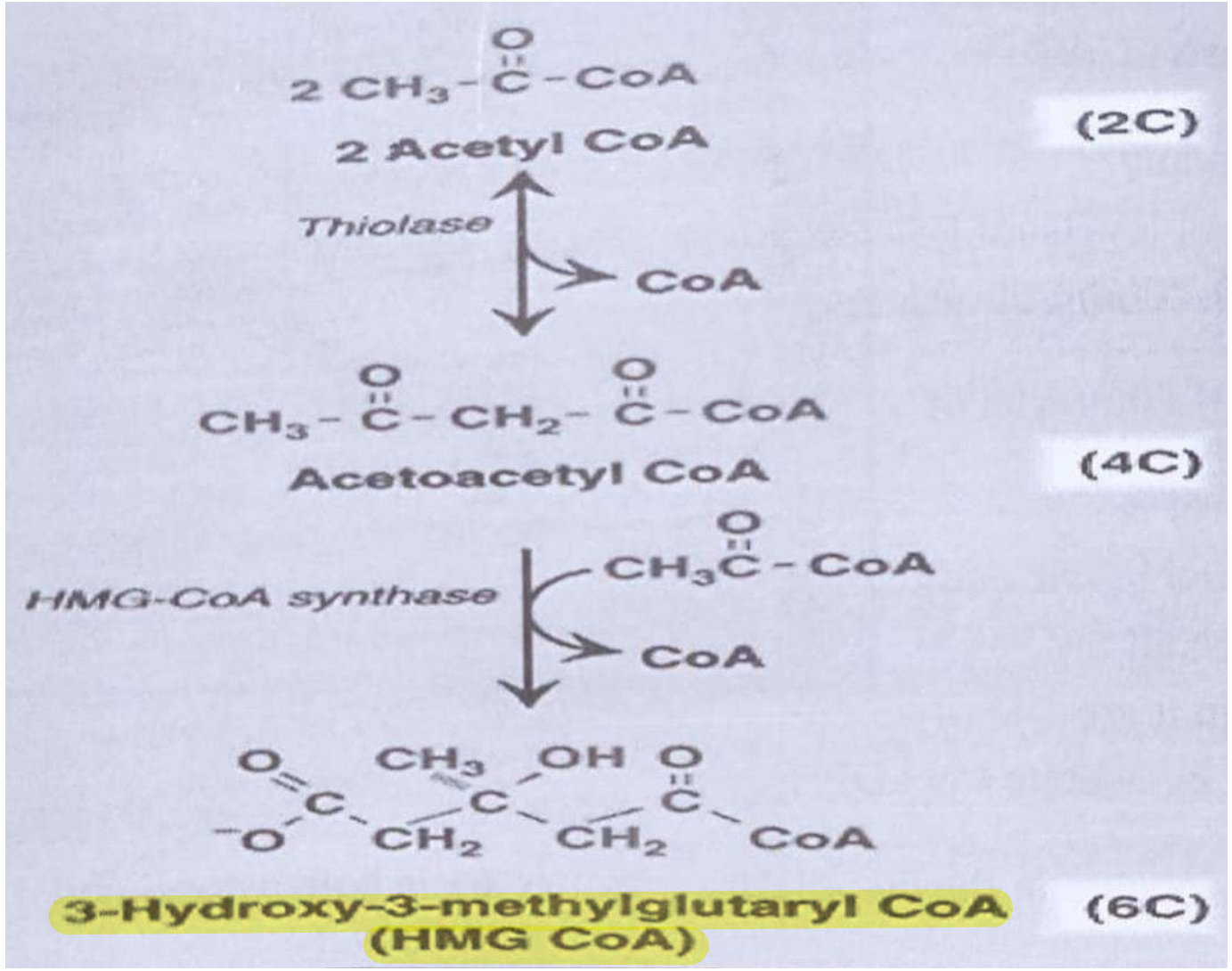
1. Synthesis of HMG coA (6C) from acetyl coA (2C)
2. Conversion of HMG coA to mevalonate (6C)
3. Conversion of mevalonate to activated isoprene unit (C5)
4. Condensation of 6 activated isoprene units → squalene (C30)
5. Conversion of squalene to lanosterol
6. Conversion of lanosterol to cholesterol



Synthesis of HMG coA from acetyl coA

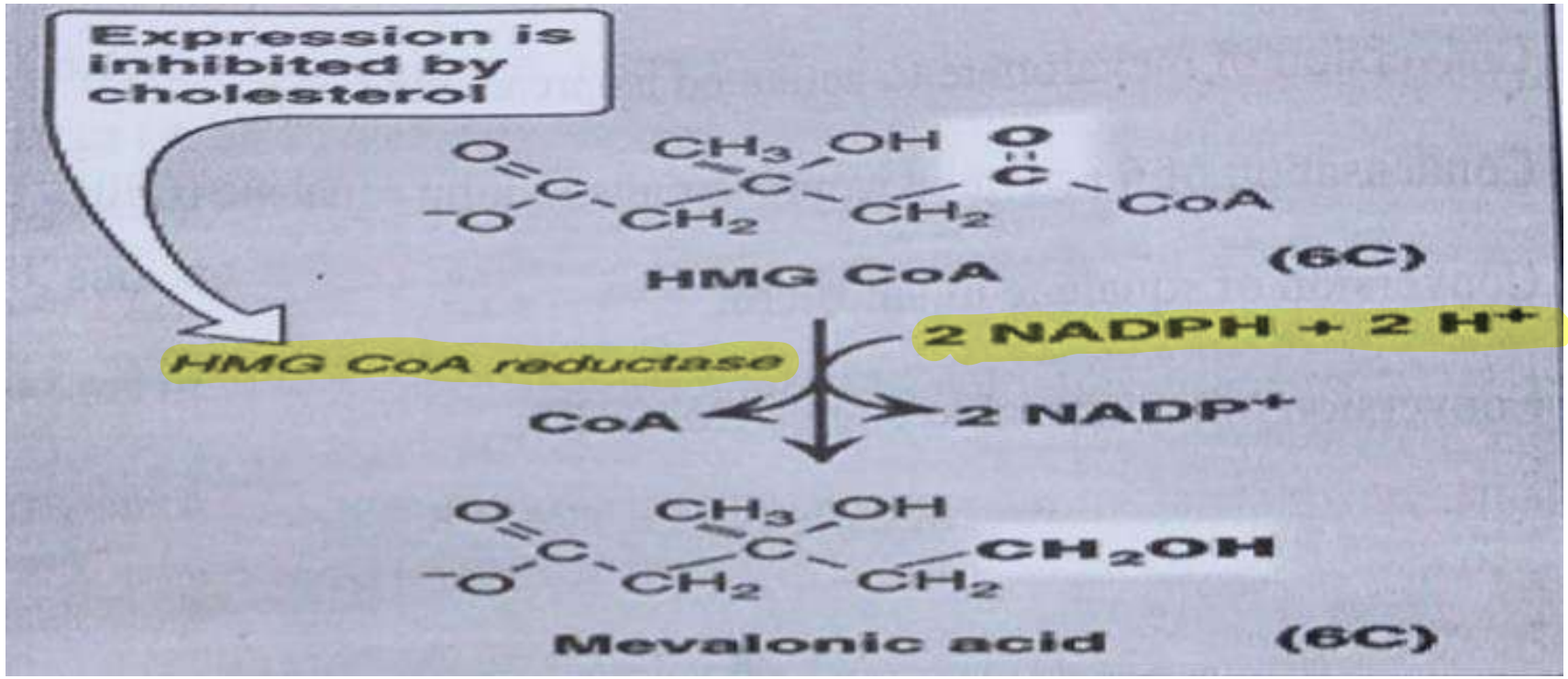
- **Isoenzymes of HMG co synthase**
  - Cytosolic enzyme → cholesterol synthesis
  - Mitochondrial enzyme → ketone body synthesis

سؤال في الإمتحان



Synthesis of mevalonic acid (mevalonate)

- Enzyme: **HMG coA reductase (rate limiting & key regulated step in cholesterol synthesis)** (كرر المعلومة مرتين)
  - **Reaction is irreversible**



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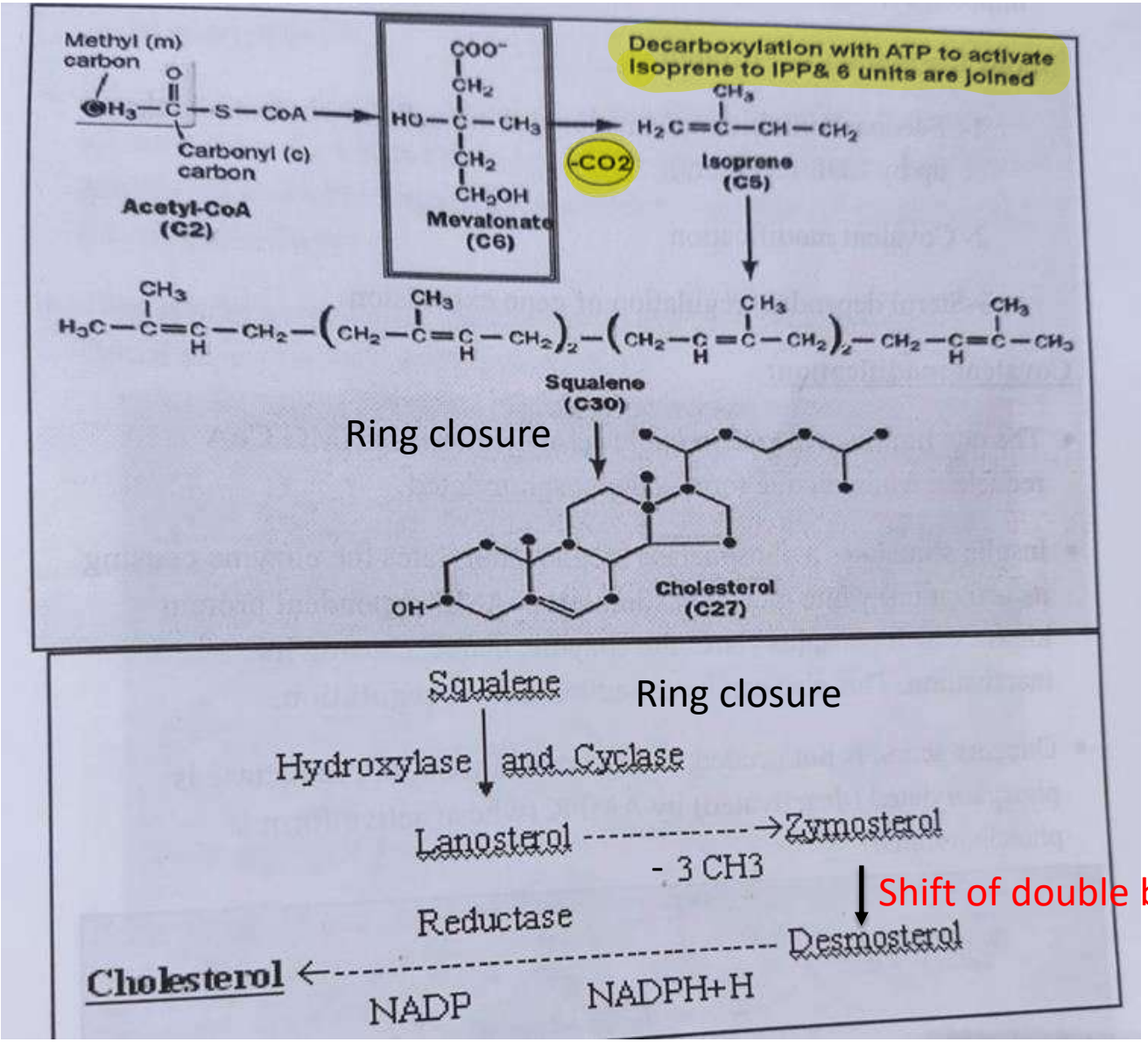
4. **Condensation of 6 activated isoprene units → squalene (C30)**

5. **Conversion of squalene to lanosterol**

6. **Conversion of lanosterol to cholesterol**



it comes from three phosphorylation reactions of mevalonate

Formation of active isoprene unit (5C)

3 phosphomevalonate 5-di-P → isopentenyl di-P (IPP) (isomerisation) يعني
→ 3,3 di-methylallyl di-P (DPP) (Decarboxilation and Dephosphorylation) ال جت

Formation of squalene (C30)

1 IPP + 1 DPP → geranyl di-P (C10)
geranyl di-P + IPP → farnesyl di-P (C15)
farnesyl di-P* + farnesyl di-P* → Squalene (C30) *they loose the 2 phosphates

Formation of lanosterol and cholesterol

A sequence of reactions using molecular oxygen & NADPH:

- squalene is converted to lanosterol
- Shortening of carbon chain from 30 to 27
- Migration of double bond from C8 to C5
- Reduction of double bond btwn C24 & C25

Only3 audio files in this slide (I said 4 by mistake)

Regulation of cholesterol

Regulation of HMGCoA reductase:

1. Sterol-dependent regulation of gene expression:

Low cholesterol level activates a transcription factor leading to increased HMG CO reductase synthesis – increased cholesterol synthesis

2. Enzyme degradation by cholesterol

↑ Cholesterol decreases the stability of HMG CoA reductase resulting in its rapid degradation (لو زاد الـ cholestrol أكيد بده يوقف الإنتاج)

3. Sterol-independent phosphorylation/dephosphorylation

AMP (i.e. decrease ATP availability) causes phosphorylation of HMG CoA reductase causing its inactivation (with decrease cholesterol synthesis)

HMG coA reductase is active in dephosphorylated form; insulin activates it (short term)

(للأنسولين بشتغل عنه طريق dephosphorylation)

4. Hormonal regulation

Insulin causes upregulation of expression of the HMG CoA reductase gene leading to increase cholesterol synthesis (Long term)

5. Inhibition by statin drugs

Lovastatin, rosvastatin & simvastatin are structural analogues of HMG coA reductase
They are used to reduce cholesterol level in hypercholesterolemia

Statin drugs work as competitive inhibitors

Cholesterol excretion

- Ring structure of cholesterol cannot be metabolized to H20 and CO2

- It is excreted
  - In bile (as it is, or as bile acids or salts)
  - Converted to **coprostanol** & **cholestanol** → excreted in stools

Eicosanoids

- Derived from eicosa (20 carbons) polyenoic FAs (arachidonic acid 20:4)
- The dietary precursor is the essential FA linoleic acid (18:2)
- Produced by most mammalian cells
- Have physiological and pharmacological actions
- Hormone-like molecules:
  - Autocrine
  - Paracrine
- Subscript number in an eicosanoid denotes n of double bond (e.g. PGE2)

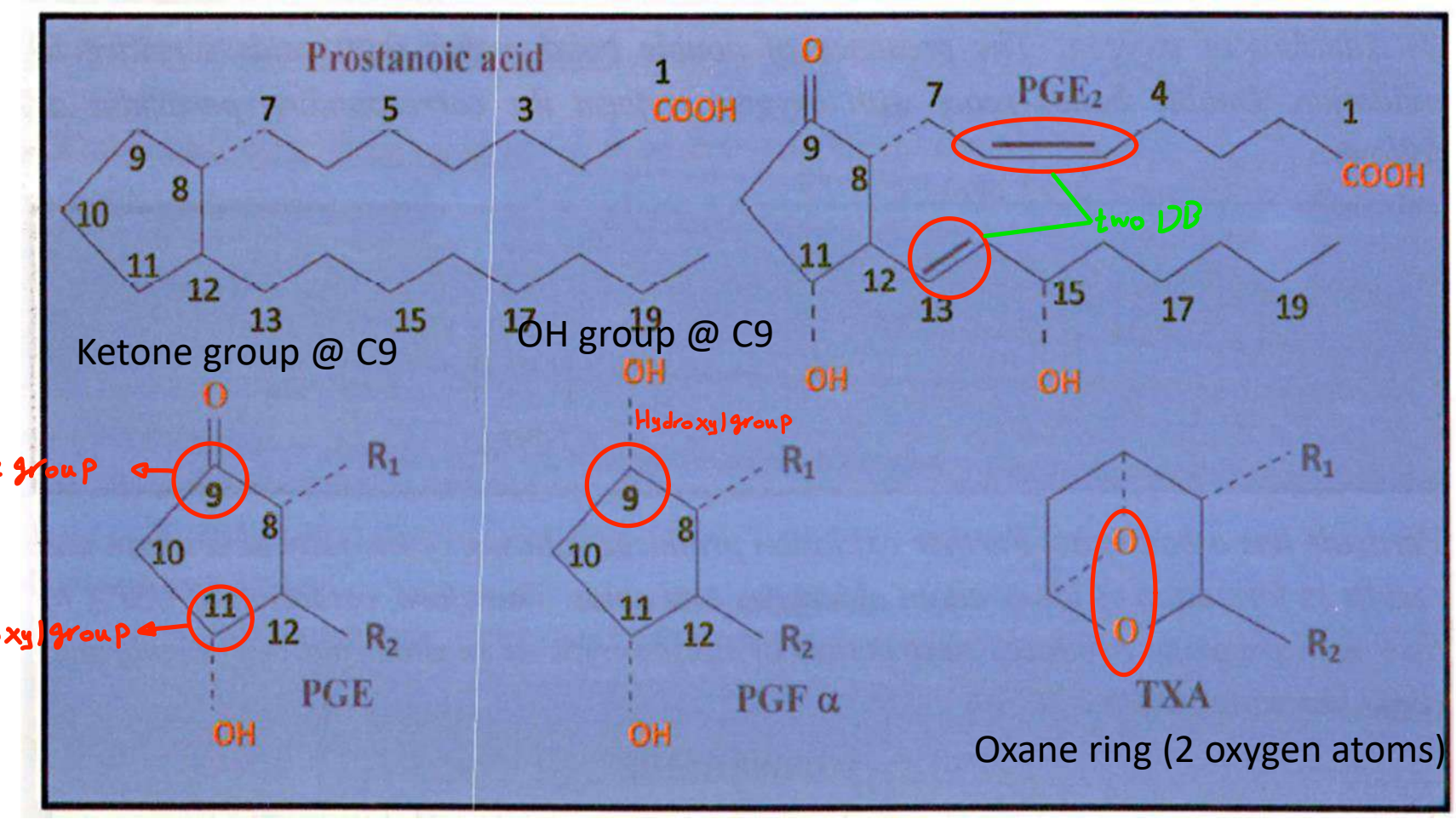
Classification of eicosanoids

- Cyclic compounds (prostanoids)
  - Prostaglandins (PG) → via cyclooxygenase pathway
  - Prostacyclins (PGI) → via cyclooxygenase pathway
  - Thromboxane (TX) → via thromboxane synthase

- Acyclic compounds (via lipoxygenase pathway)
  - Leukotrines (LT)
  - Lipoxins (LX)

Prostaglandins

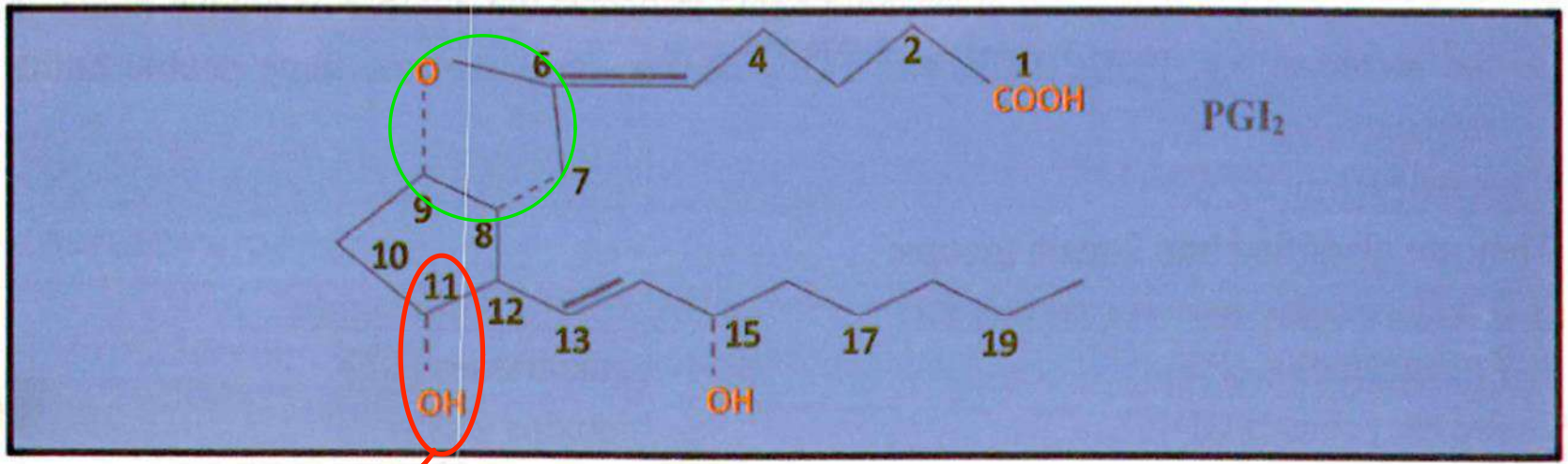
- First discovered in prostate (hence name)
- Present in most human tissues (males & females)
- All have a cyclopentane ring in the middle (C8-12)
- Many types: PGA, PGB, **PGE**, **PGF**, PGG, PGH



two oxygen atoms incorporating between (C11–12)
and they form an oxan ring (hence name)

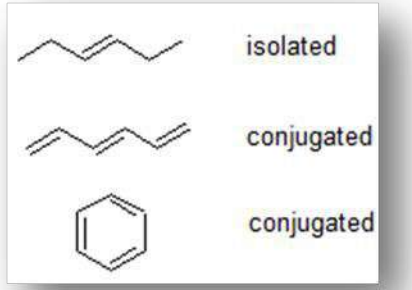
3. Prostacyclins (PGI):

They contain an additional ring in their structure. between (C6-9), and there is an oxygen atom in this ring.



Hydroxyl group

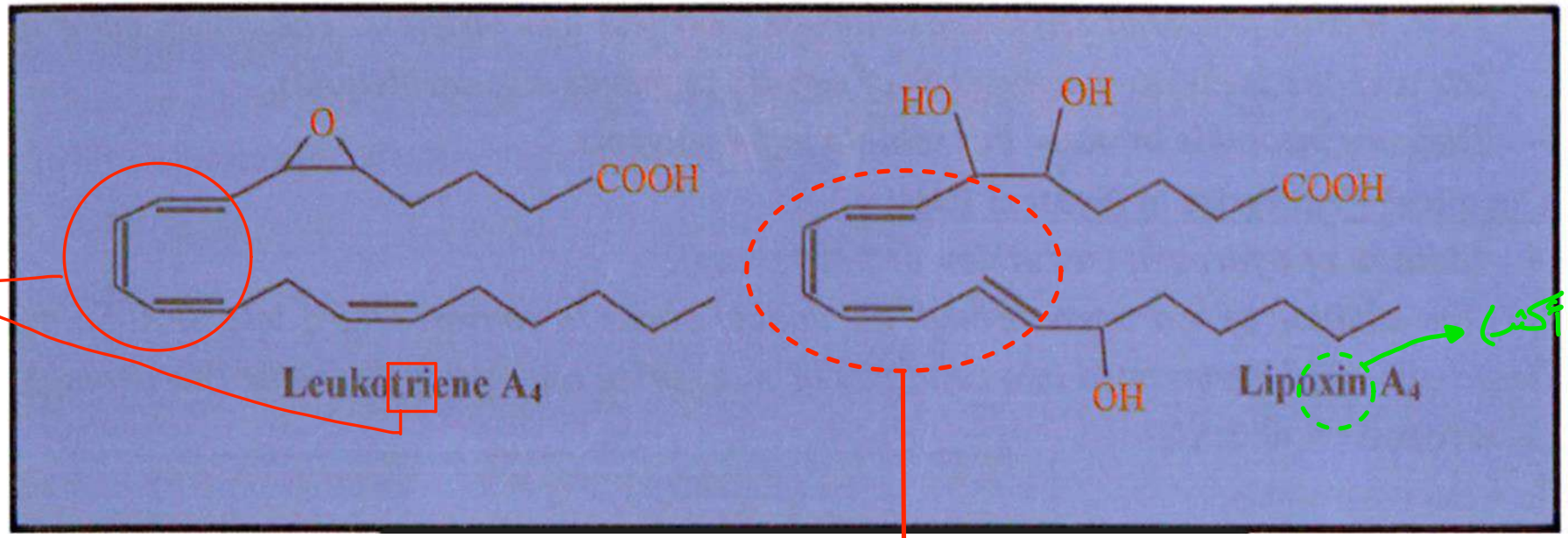
((Location of hydroxyl group) مافي داعي هون نحفظ ال)



LT and LX are both acyclic compounds

LT: 3 conjugated double bonds

LX: 4 conjugated double bonds, contains more oxygen



Effects of eicosanoids

- PGE2 → ***vasodilation***, relaxation of uterus & intestines
- PGF2 → ***vasoconstriction,*** contraction of uterus & intestines
- PGI2 → vasodilation + inhibits platelet aggregation
- TXA2 → vasoconstriction + stimulates platelet aggregation
- Leukotrienes → allergic mediators
- Lipoxins → inflammatory functions

There are two major pathways of arachidonic acid metabolism:

Cyclooxygenase pathway which leads to the formation of the **prostanoids** **(Thromboxane (TX) via thromboxane synthase)**

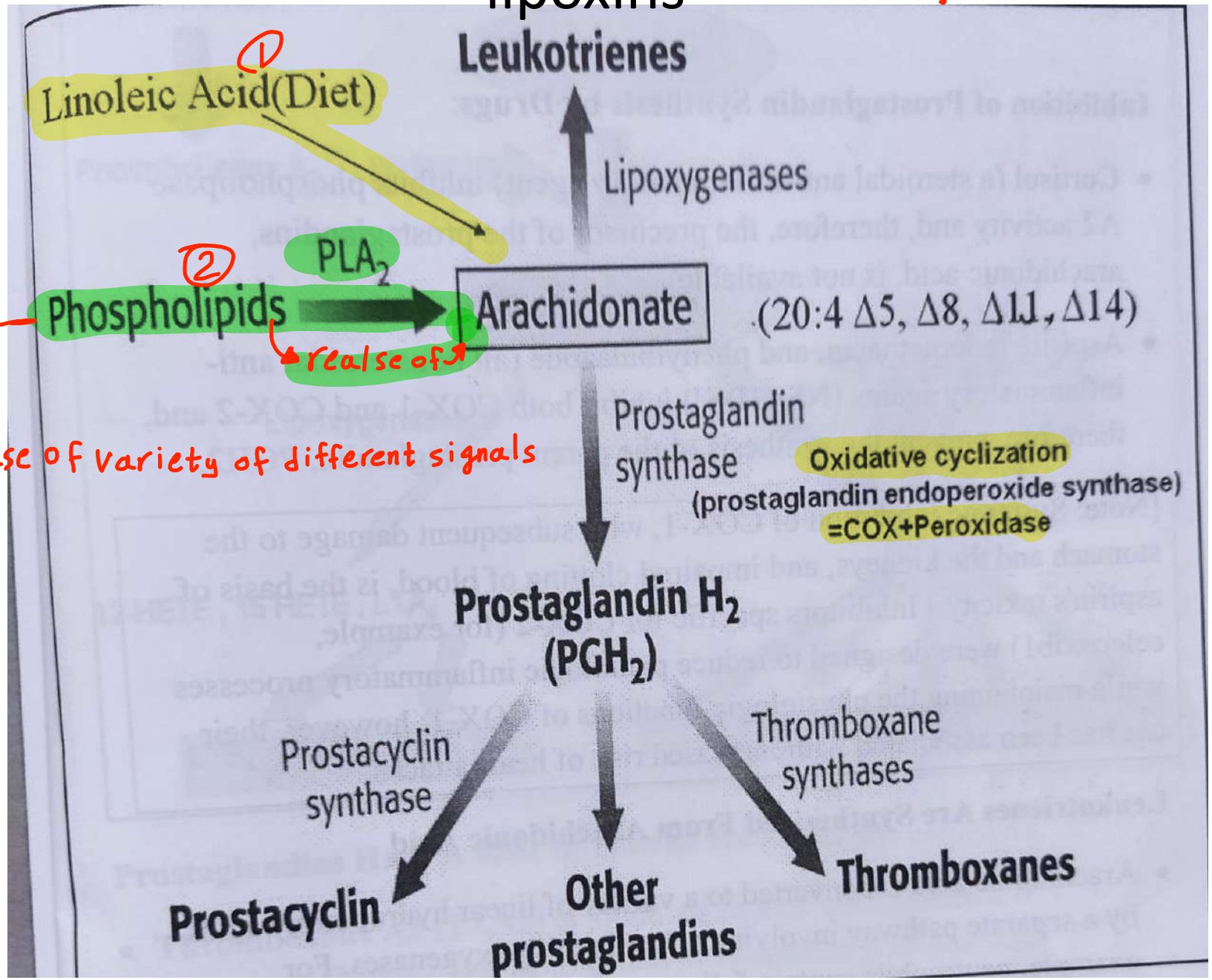
Lipoxygenase pathway which leads to the formation of the **leukotriens** and the **lipoxins**

The type of eicosanoids produced in any tissue depends on the enzyme profile of this tissue.

lipoxins

* في طريقتين تجيب الـ (arachidonate) :

② / ①



The cyclooxygenase pathway:

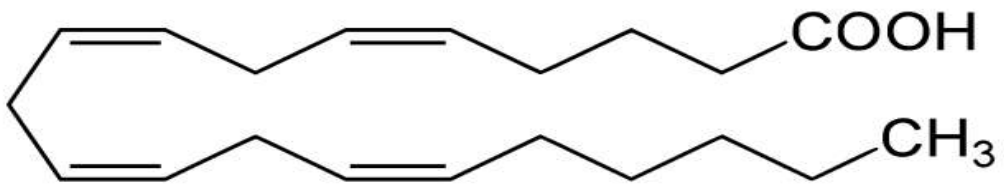
- It is catalyzed by **prostaglandin synthase**, which contain activity of two enzymes; **cyclooxygenase (COX)** and **peroxidase**.

- The cyclooxygenase (COX) component of the prostaglandin synthase complex catalyzes the cyclization of C_8-C_{12} of arachidonic acid to form PGG_2 .

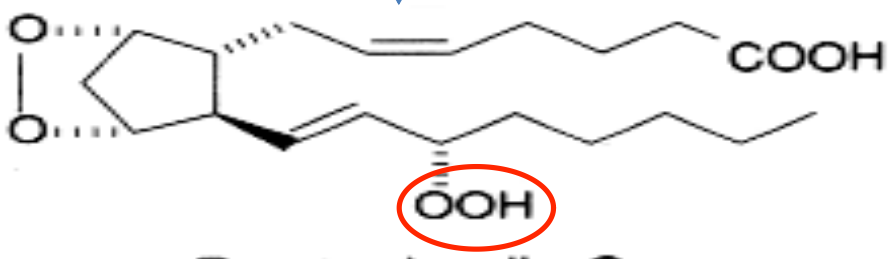
- Then, PGG_2 is converted to prostaglandin H_2 (PGH_2) by the peroxidase (PG hydroperoxidase).

- The finally, additional steps → formation of prostaglandins mainly PGE2 , PGF2α - prostacyclins and thromboxanes

مطالبين فقط
بالأسماء

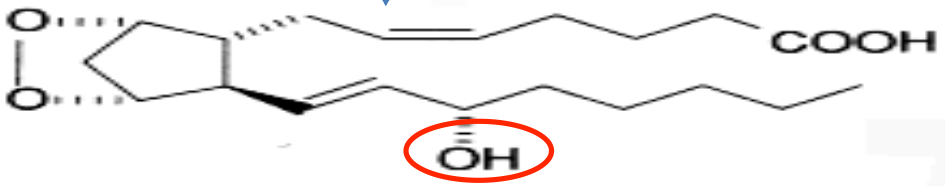


cyclooxygenase

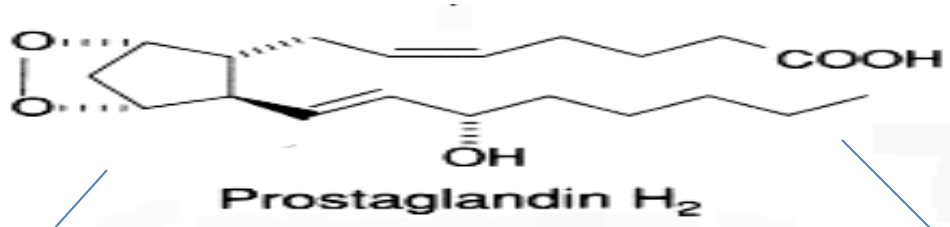


Prostaglandin G_2

peroxidase (PG hydroperoxidase)



Prostaglandin H_2

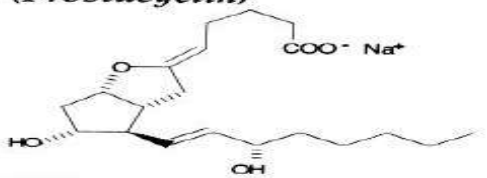


Prostaglandin H_2

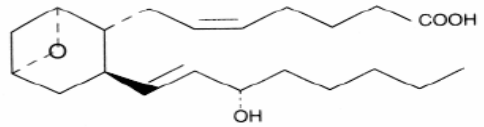
Prostacyclin synthase

Thromboxane synthase

PGI_2 *Prostaglandin I_2*
(Prostacyclin)



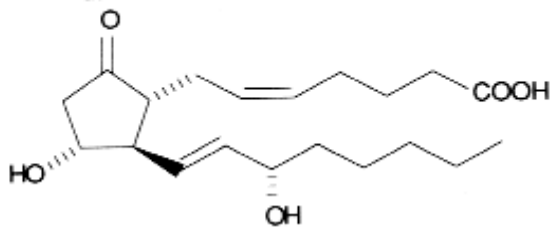
Thromboxane A2



Isomerase

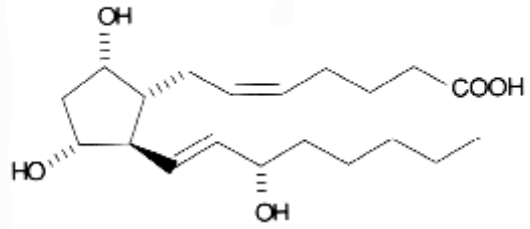
Reductase

PGE_2 *Prostaglandin E_2*



Reductase

$PGF_{2\alpha}$ *Prostaglandin $F_{2\alpha}$*



- **Anti inflammatory drugs: they are used to relief hyperemia, edema, pain and fever.**

A-Steroidal anti-inflammatory drugs: like hydrocortisone and prednisone block the transcription of prostaglandin synthase/ phospholipase A2 activity.

↳ they also block this specific enzyme

B- Non-steroidal anti-inflammatory drugs (NSAID):

1- Aspirin → inhibits the cyclooxygenase by acetylation. Thus, it is **COX inhibitor.**

Aspirin's anti-thromobogenic activity

Aspirin inhibits TXA2 synthesis from arachidonic acid in platelets irreversibly

(بفرق استخدام الـ aspirin)

as treatment in low dose:

to reduce the risk of stroke and heart attack by decrease the formation of thrombocytes

Other NSAID like indomethacin inhibit the cyclooxygenase by competing with arachidonate.