Lecture 8

Lipids (pt.1)

اللهم نستودعك أهالي غزّة وفلسطين فانصرهم واحفظهم
بعينك التي لا تنام، واربط على قلوبهم وأمدهم بجُندك وأنزل
عليهم سكينتك وسخر لهم الأرض ومن عليها

Written by:
Mas Nafoukh & Hala Swiedan

Edited
by: Sumayya HajYasin & Mas Nafoukh

Notes Regarding the last 2 slides In the previous lecture

Bacterial Cell wall is made of two specific GAGs
(Consist of at least one Amino sugar that carries a carboxyl - sulfate groups = negatively charged | repeated disaccharides)
Electrostatic interactions between them make the overall structure Rigid \ Tough
Providing support to the tissue (cell wall)

Sialic Acid = negatively charged | the last modified sugar molecule at the end of the chain of sugars at the surface of cells (plasma membrane)
Part of glycoproteins + glycolipids

Lipids

We have four Macromolecules:
1. **Protein (amino acids)**
2. **Carbohydrates (starch = glucose)**
3. **Nucleic acid (nucleotides)**

} **made of monomers (same subunits /repeated residues) = polymers**

4. **Lipids = are not polymers (aren't made of same subunits) but they are large molecule.**

- Lipids are a heterogeneous class of naturally occurring organic compounds that share some properties based on structural similarities, mainly a dominance of nonpolar groups.

even-if lipids are heterogeneous (types of lipids are different from each other) the common is that they are lipophilic + hydrophobic
that's why there are grouped together in one class .

- They are Amphipathic.

It has **2** natures (sides)
one part can be much larger than the other part.
(**hydrophobic** can be larger than **hydrophilic**)
they don't have to be equal.

- They are insoluble in water, but soluble in fat or organic solvents(ether, chloroform, benzene, acetone).

Hydrophobic solvents

- They are widely distributed in plants & animals.

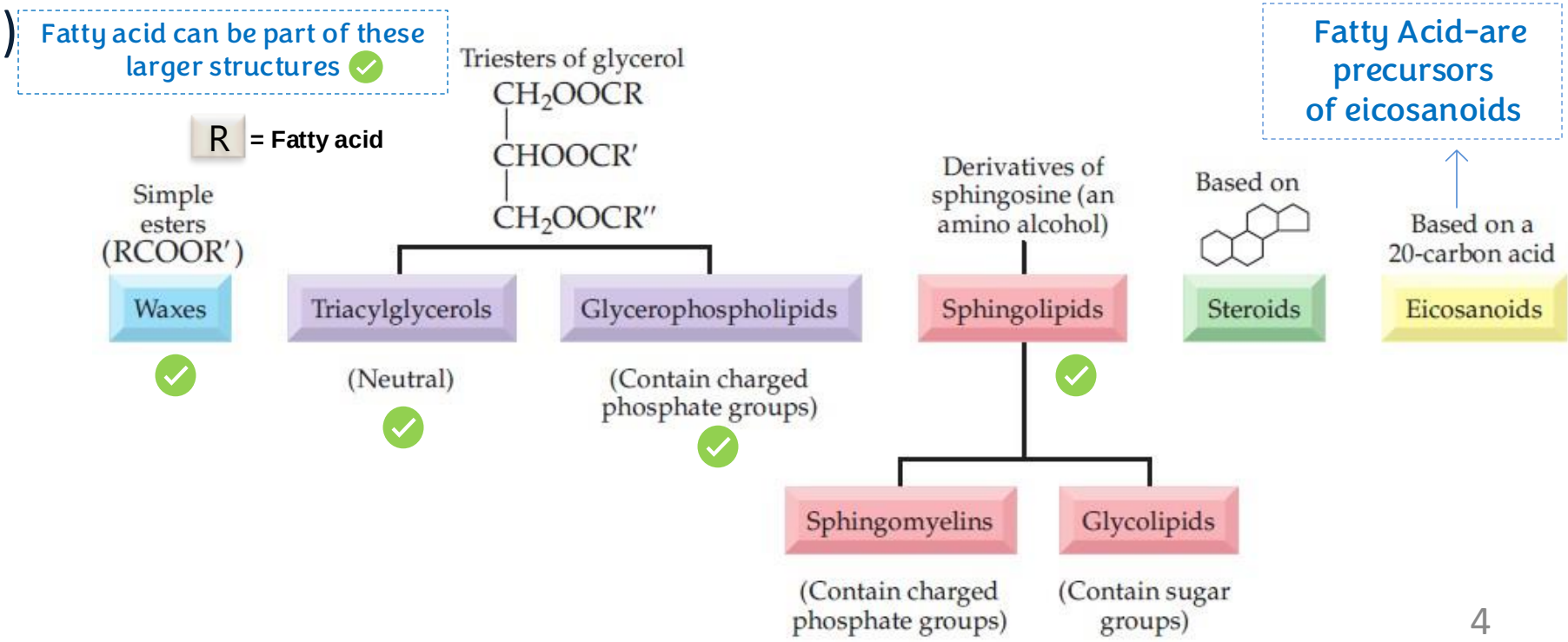
Note :
* Micro = very small.
*Macro = large .

نصائح من دكتور
مأمون
(وَلا تَنْسَ نَصِيبَكَ مِنَ الدُّنْيَا)
Enjoy biochemistry :)

Classes

- Simple lipids (fats, oils, and waxes)
- Complex lipids (glycerides , glycerophospholipids, sphingolipids, glycolipids, lipoproteins)
- Derived lipids (fatty acids, alcohols,
- eicosanoids)

Cyclic lipids (steroids)



Lipid Functions

- Lipids include:
  - Storage lipids for energy purpose

whenever we have excess of lipids (fatty acids mostly)
we store them in fat tissue (adipocyte).
when we need energy
a signal is sent to fat tissue releasing fatty acids
that enter the cells and it is utilized to generate energy (ATP)
-Same as glucose that's stored in starch \ glycogen form-

    - They are storable to unlimited amounts (vs. carbohydrates)
    - They provide a considerable amount of energy to the body (25% of body needs) & provide a high-energy value (more energy per gram vs. carbohydrates & proteins)

? The use of lipids as source of energy is more advantageous than carbohydrates, why ?

Because they carry a lot more electrons (it is saturated C-H = reduced)
The presence of oxygen = we have less electrons
Lipids provide double the amount of energy compared to carbohydrates
*less electrons =less energy *

  - Structural lipids in membranes

plasma membranes surrounding cell organelles such as :
(lysosome, nucleus, endoplasmic reticulum , Golgi , peroxisome)

- Signaling molecules, hormone precursors, cofactors, & pigments
- Shock absorbers and thermal insulators

Cushioning = Lipids covers internal organs to protect them

cell → releases lipid → enters another cell → interacts with plasma membrane →signal becomes inside the cell.
Or inside the cell : lipid molecule interact with another molecule so it sends a signal and so on .
Fatty acids= signaling molecules +have receptors on cell surface and they send signals inside the cell

Fatty acids

=Chain One carboxyl group

- Aliphatic mono-carboxylic acids
- Formula: R-(CH_2)n-COOH When its fully saturated
- Lengths
  - Physiological (12-24) Including carboxyl group
  - Abundant (16 and 18) Most abundant in plasma membrane
- Degree of unsaturation They differ-in degree of-saturation according to the number of double bond
- Amphipathic molecules

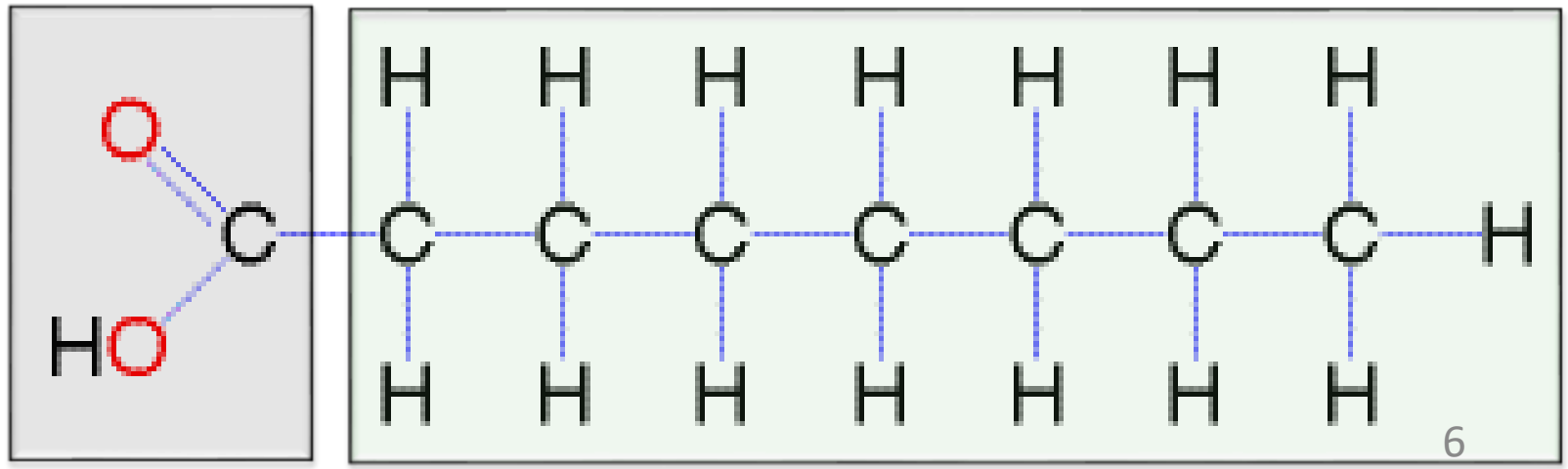
Functions:

- **Building blocks of other lipids** → Part of diff types of lipids
- **Modification of many proteins (lipoproteins)**
- **Important fuel molecules**
- **Derivatives of important cellular molecules .** (ex :eicosanoid)

,

At physiological PH carboxyl group is ionized (unprotonated).

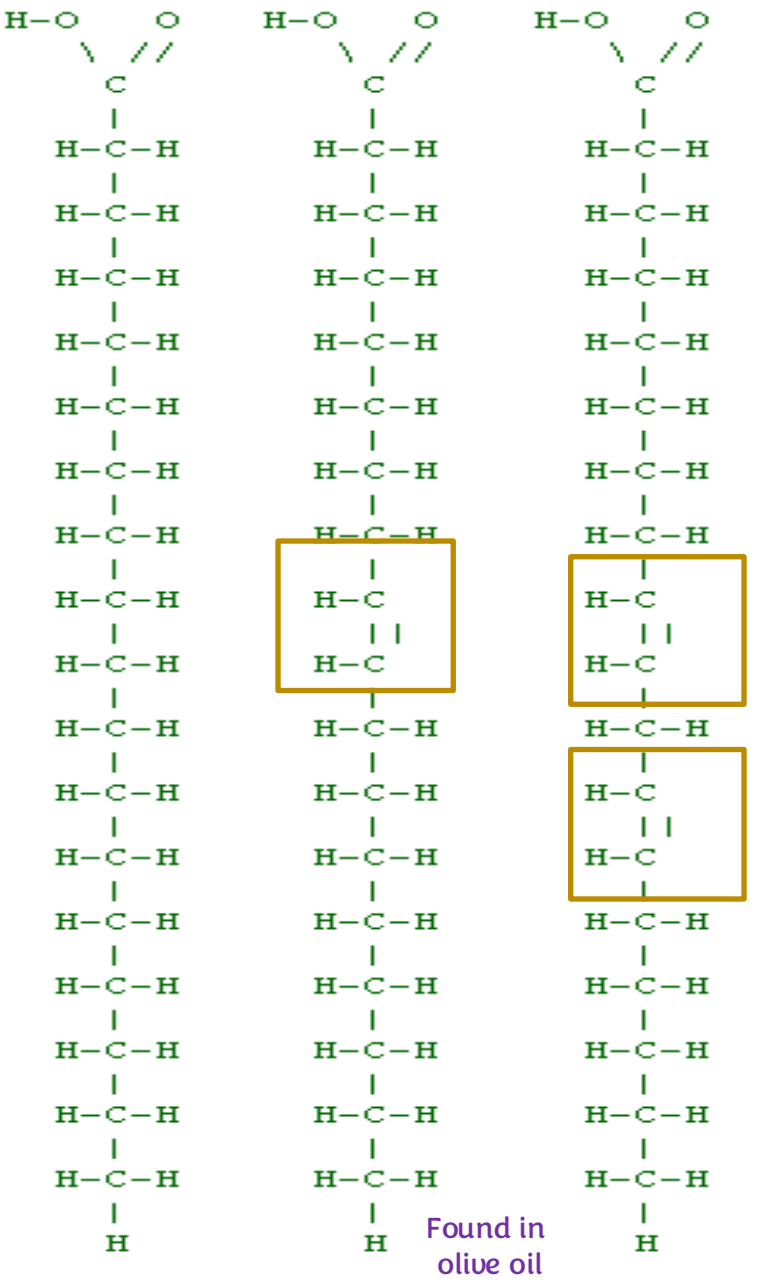
Polar (Hydrophilic) ***Non-polar*** (Hydrophobic) Hydrocarbon chain



Types of fatty acids

Classified according
1.Number of carbons.
2.Number of Double bond

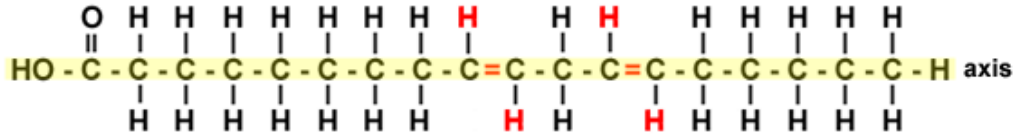
- Saturated fatty acids are those with all of the C-C bonds being single.
- Unsaturated fatty acids are those with one or more double bonds between carbons:
  - Monounsaturated fatty acid: a fatty acid containing one double bond.
  - Polyunsaturated fatty acids contain two or more double bonds.



Memorize the names

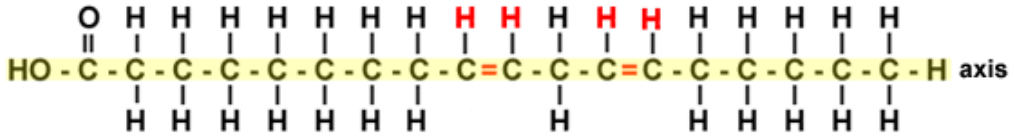
Cis vs. trans bonds

What is the importance of cis orientation ?
In 3D, the structure will have a kink
Molecule is not straight anymore.

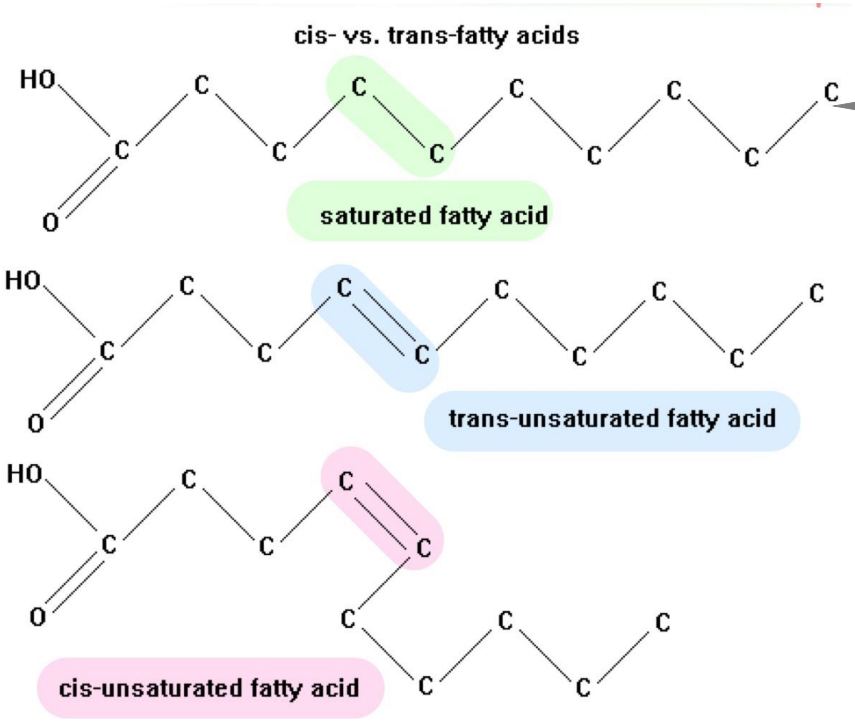


linoleic acid: *trans* configuration (*trans* isomer)

Same orientation

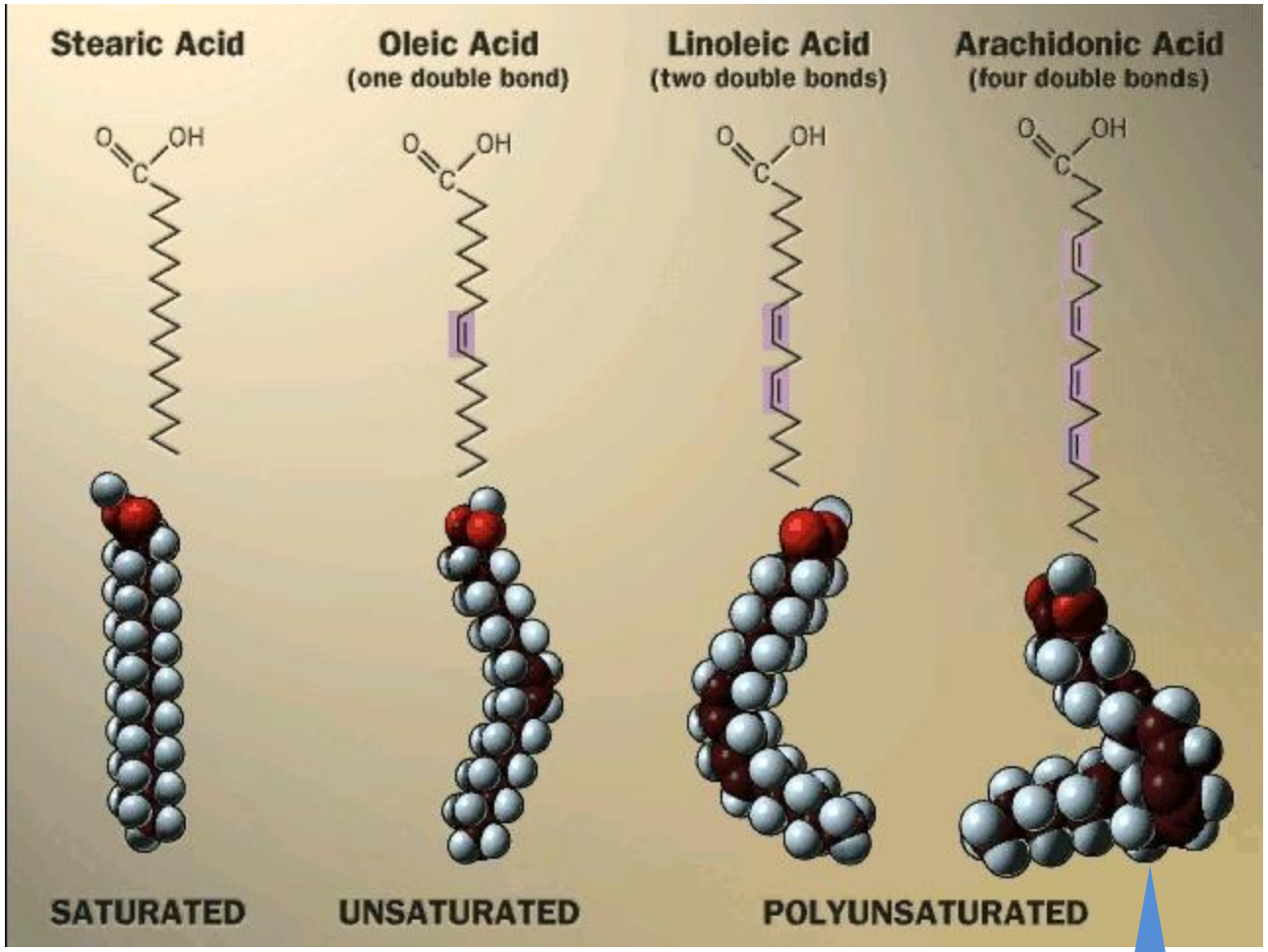


linoleic acid: *cis* configuration (*cis* isomer)



Trans double bond doesn't differ from saturated

Kink (cis) = means it needs more space due to the van der walls interactions. (Repulsion) This makes huge difference in plasma membrane.



Physiologically:

- **cis isomer predominates**
- **trans is rare**

The kink is larger + clear (more double bonds)

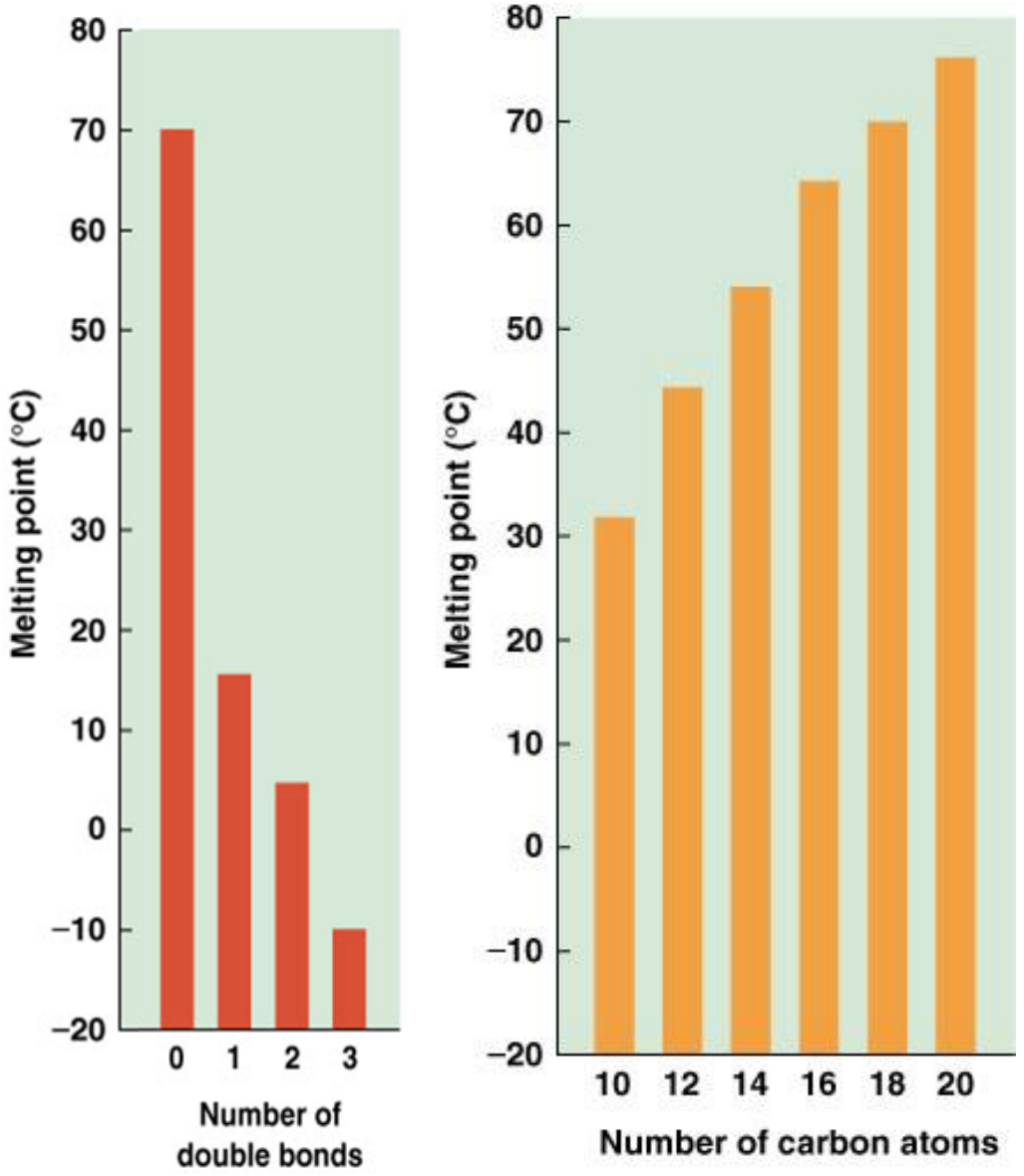
Properties of fatty acids

- The properties of fatty acids (melting point) are dependent on chain length and degree of saturation.

length of hydrocarbon chain **increases** = the melting point **increases.**
Ghee = has saturated fatty acids so it's solid
Oil = has unsaturated fatty acids so it's liquid .

More double bonds (less saturation) = **decreases** the melting point
double bonds have **larger** effect on BP than the length of the chain

The presence of a double bond is very important for fluidity of plasma membrane. Ex: plasma membrane of eye cells (very fluidic like olive oil) =signaling molecules can move rapidly = rapid signals = smooth vision.



Properties of saturated fatty acids

According to the length of the hydrocarbon chain

What about 5c and 11c ?
Usually we use even numbers..

Short chain F.A. (2-4)	Medium-chain F.A. (6-10)	Long chain F.A. (12-20)
They are liquid in nature (fluidic)	Solids at room temperature	Solids at room temperature
Water-soluble	Water-soluble Bcz of COOH	Water-insoluble
Volatile at RT	Non-volatile at RT	Non-volatile
Acetic, butyric, caproic acids	Caprylic & capric acids	Palmitic and stearic acids

20-24 C = very long chain

because hydrophilic group (COOH) dominates the CH3. 4C is also soluble

CH3COOH
In vinegar

In butter
But butter isn't fluidic; since it is composed of other fatty acids besides butyric

In butter
Capri = goat's milk has lots of medium chained fatty acids

Found in The oil of Nutmeg

سبحان الله
الحمدلله
لا اله الا الله
والله اكبر

Greek number prefix

Number	prefix	Number	prefix	Number	prefix
1	Mono-	5	Penta-	9	Nona-
2	Di-	6	Hexa-	10	Deca-
3	Tri-	7	Hepta-	20	Eico-
4	Tetra-	8	Octa-		

Naming of a fatty acid

- Alkane to oic (because of carboxyl group)
  - Octadecane (octa and deca) is octadecanoic acid
    - One double bond = octadecenoic acid
    - Two double bonds = octadecadienoic acid
    - Three double bonds = octadecatrienoic acid
- Designation of carbons and bonds

Number of
Carbons : Double bonds

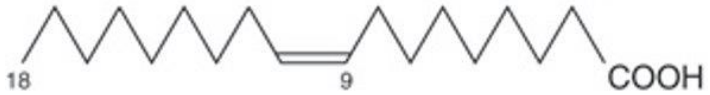
  - 18:0 = a C18 fatty acid with no double bonds
    - stearic acid (18:0); palmitic acid (16:0)
  - 18:2 = two double bonds (linoleic acid)
- Designation of the location of bonds (orientation)
  - Δn: The position of a double bond
    - cis-Δ9: a cis double bond between C 9 and 10
    - trans-Δ2: a trans double bond between C 2 and 3

Between one double bond and another double bond = 3 carbon atoms
(related to the enzyme that forms the bond and how it works + how the molecule fit in the enzyme)

Start numbering from COOH

Palmitoleic acid (ω7, 16:1, Δ^{9})

Between c 9+10

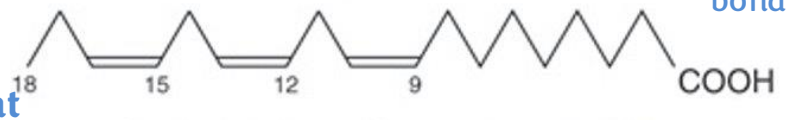


Oleic acid (ω9, 18:1, Δ^{9})

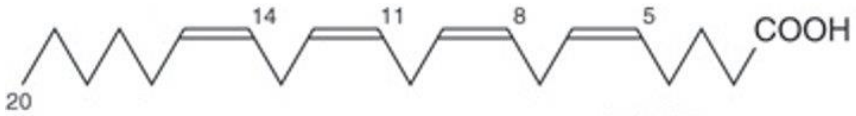
*Linoleic acid (ω6, 18:2, $\Delta^{9,12}$)

Linolenic contain extra "n" –>extra bond .

Very important



*α-Linolenic acid (ω3, 18:3, $\Delta^{9,12,15}$)



*Arachidonic acid (ω6, 20:4, $\Delta^{5,8,11,14}$)

Eicosapentaenoic acid (ω3, 20:5, $\Delta^{5,8,11,14,17}$)

Why myristate not myristic acid (protonated) ?

- Because naturally – physiologically it is ionized (conjugate base form).

Number of carbons	Number of double bonds	Common name	Systematic name	Formula
14	0	Myristate	n-Tetradecanoate	$CH_3(CH_2)_{12}COO^-$
16	0	Palmitate	n-Hexadecanoate	$CH_3(CH_2)_{14}COO^-$
18	0	Stearate	n-Octadecanoate	$CH_3(CH2)_{16}COO^-$
18	1	Oleate	cis-Δ^9-Octadecenoate	$CH_3(CH_2)_7CH=CH(CH_2)_7COO^-$
18	2	Linoleate	cis,cis-Δ^9,Δ^{12}-Octadecadienoate	$CH_3(CH_2)_4CH=CHCH_2CH(CH_2)_7COO^-$
18	3 extra letter = extra double bond	Linolenate	all-cis-$\Delta^9,\Delta^{12},\Delta^{15}$-Octadecatrienoate	$CH_3CH_2(CH=CHCH_2)_3(CH_2)_6COO^-$
20	4	Arachidonate	all-cis-$\Delta^5,\Delta^8,\Delta^{11},\Delta^{14}$-Eicosatetraenoate	$CH_3(CH_2)_4(CH=CHCH_2)_4(CH_2)_2COO^-$

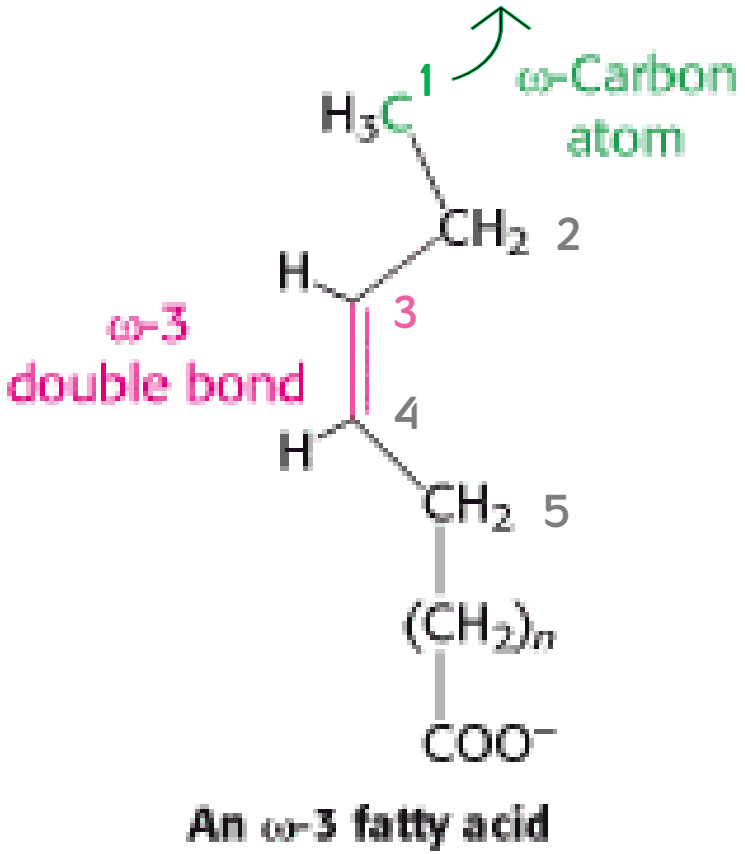
You should know them

Remember !
3 carbon space between every 2 double bonds

Another way of naming

Depends on the position of the first double bond
starting the counting from the methyl group (not the carboxyl group)
even if we have more than one double bond

- (ω)-C: distal methyl C as #1

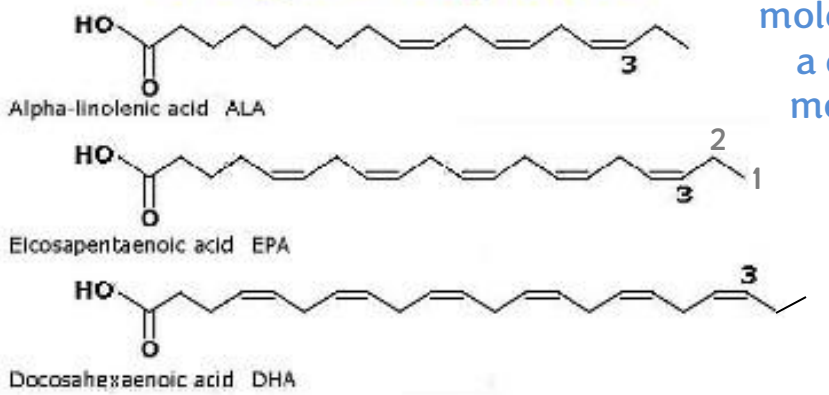


An ω-3 fatty acid

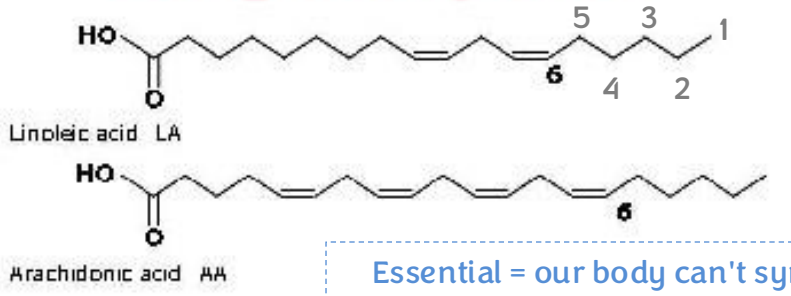
Per softgel		
Organic Flaxseed Oil (Linseed Oil)		400mg
Pure Fish Oil		400mg
Starflower Oil (Borage Oil)		400mg
typically providing:		
Alpha Linolenic Acid (ALA)	Omega-3	200mg
Docosahexaenoic Acid (DHA)	Omega-3	48mg
Eicosapentaenoic Acid (EPA)	Omega-3	72mg
Gamma Linolenic Acid (GLA)	Omega-6	88mg
Linoleic Acid (LA)	Omega-6	204mg
Oleic Acid	Omega-9	168mg

- Contains a number of omega 3 – 6 – 9 fatty acids
- **EPA / DHA** are the most abundant omega 3 fatty acids in it

Omega-3 fatty acids → It is not a single molecule, It is a class of molecules



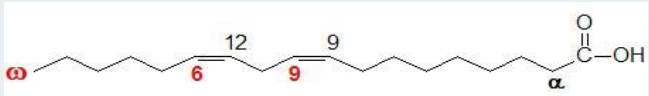
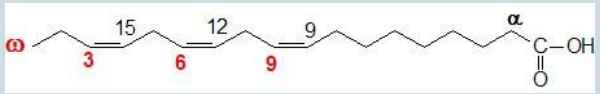
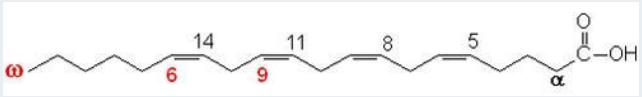
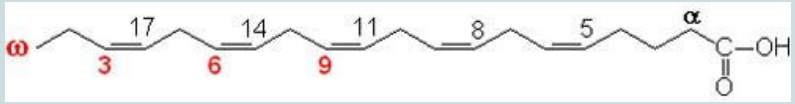
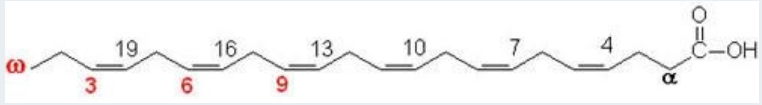
Omega-6 fatty acids



Essential = our body can't synthesize them = we get them from diet

- **Essential FAs:**
  - **Linoleic acid: precursor of arachidonates**
  - **Linolenic acid: precursor of EPA and DHA**

Why do we call it OMEGA system ?
omega is the last letter in Greek alphabet
So In the hydrocarbon chain numbering starts from the last carbon = omega carbon

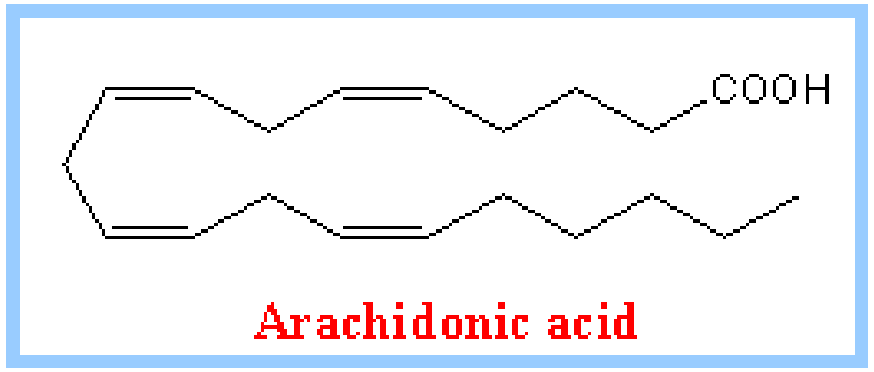
Numerical Symbol	Common Name and Structure	Comments
$18:1^{\Delta 9}$	Oleic acid 	Omega-9 monounsaturated
$18:2^{\Delta 9,12}$	Linoleic acid 	Omega-6 polyunsaturated
$18:3^{\Delta 9,12,15}$	α-Linolenic acid (ALA) 	Omega-3 polyunsaturated
$20:4^{\Delta 5,8,11,14}$	Arachidonic acid 	Omega-6 polyunsaturated
$20:5^{\Delta 5,8,11,14,17}$	Eicosapentaenoic acid (EPA) 	Omega-3 polyunsaturated (fish oils)
$22:6^{\Delta 4,7,10,13,16,19}$	Docosahexaenoic acid (DHA) 	Omega-3 polyunsaturated (fish oils)

Derived fatty acids: Eicosanoids

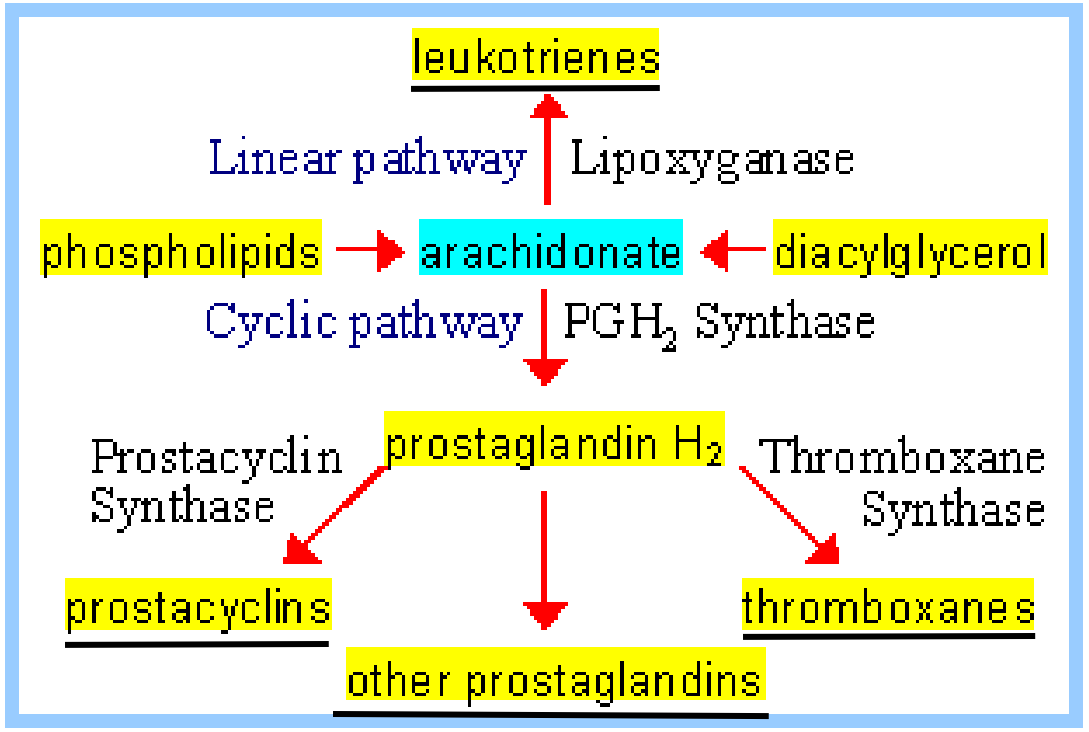
Arachidonate

20 carbon fatty acid with 4 double bonds (20:4 $^{\Delta 5,8,11,14}$) + kinky .

all *cis*-$\Delta^5,\Delta^8,\Delta^{11},\Delta^{14}$-eicosatetraenoate, $CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2COO^-$



Arachidonic acid



•Importance

It is the **precursor of** **Eicosanoids**

that are very imp for **signaling**
specially during **inflammation**
If we have an
infection or injury

it causes redness + swelling
(inflammatory molecules)
REGULATES INFLAMMATORY RESPONSE

Eicosanoids and their functions

They control cellular function in response to injury

Neither memorize the specific functions nor the structures

- Prostaglandins
  - Induction of inflammation
  - Inhibition of platelet aggregation
    - Inhibition of blood clotting
- Leukotrienes
  - Constriction of smooth muscles
    - Asthma
- Thromboxanes
  - Constriction of smooth muscles
  - Induction of platelet aggregation
- Prostacyclins
  - An inhibitor of platelet aggregation
  - Induction of vasodilation

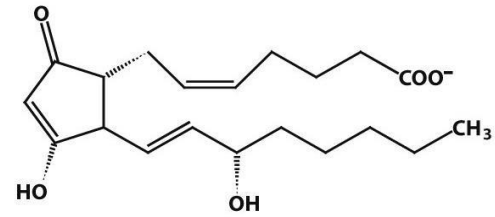
Especially the ones around blood vessels

Some of the functions are contradictory

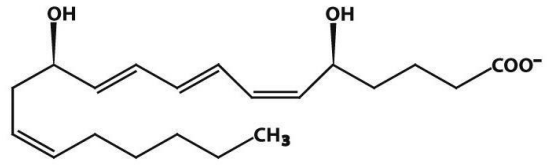
Physiologically, the molecules are not released all at the same time.
There's **Harmoney**
1. Releasing a molecule that induces platelet aggregation (to stop the blood flow to the injury)
2. Then another molecule inhibits the platelet aggregation (cleaning up the area)

Overall, they play a role in the inflammatory response
By either induction - stimulation or inhibition
(balancing inflammation)

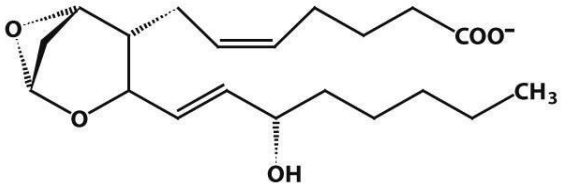
BVs become tight
Blood flow stops -> Allows coagulation
then the formed clot must be removed ...
= harmony in the release of molecules + on which cells they function and so on



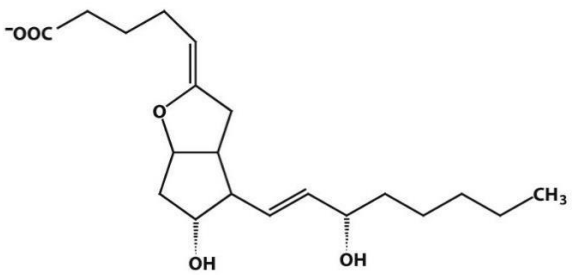
Prostaglandin E_2



Leukotriene B_4



Thromboxane A_2 (TXA_2)



Prostacyclin (PGI_2)

Aspirin is good

COX: Cyclooxygenase

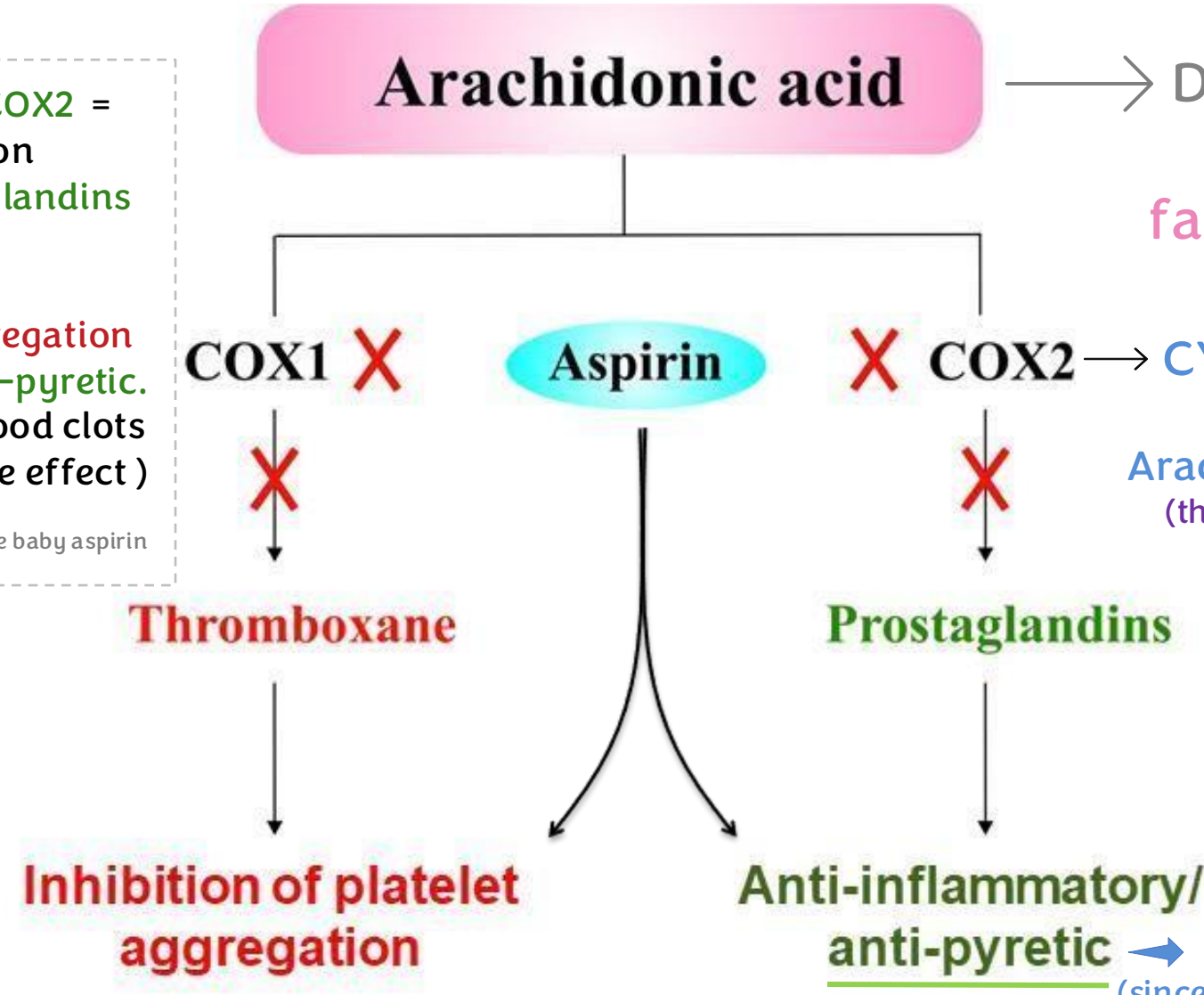
Aspirin inhibits COX1 + COX2 = inhibits the formation of thromboxane + prostaglandins

↓ Inhibiting their functions

- •Inhibition of platelet aggregation
- •Anti-inflammatory + Anti-pyretic.
- • Prevents formation of blood clots + heart attacks (protective effect)

- especially elderly people-

That's why they used to advise them to take baby aspirin



Derived from Linoleic fatty acid (18:2)

COX1 & COX2 → CYCLOOXYGENASES 1 & 2

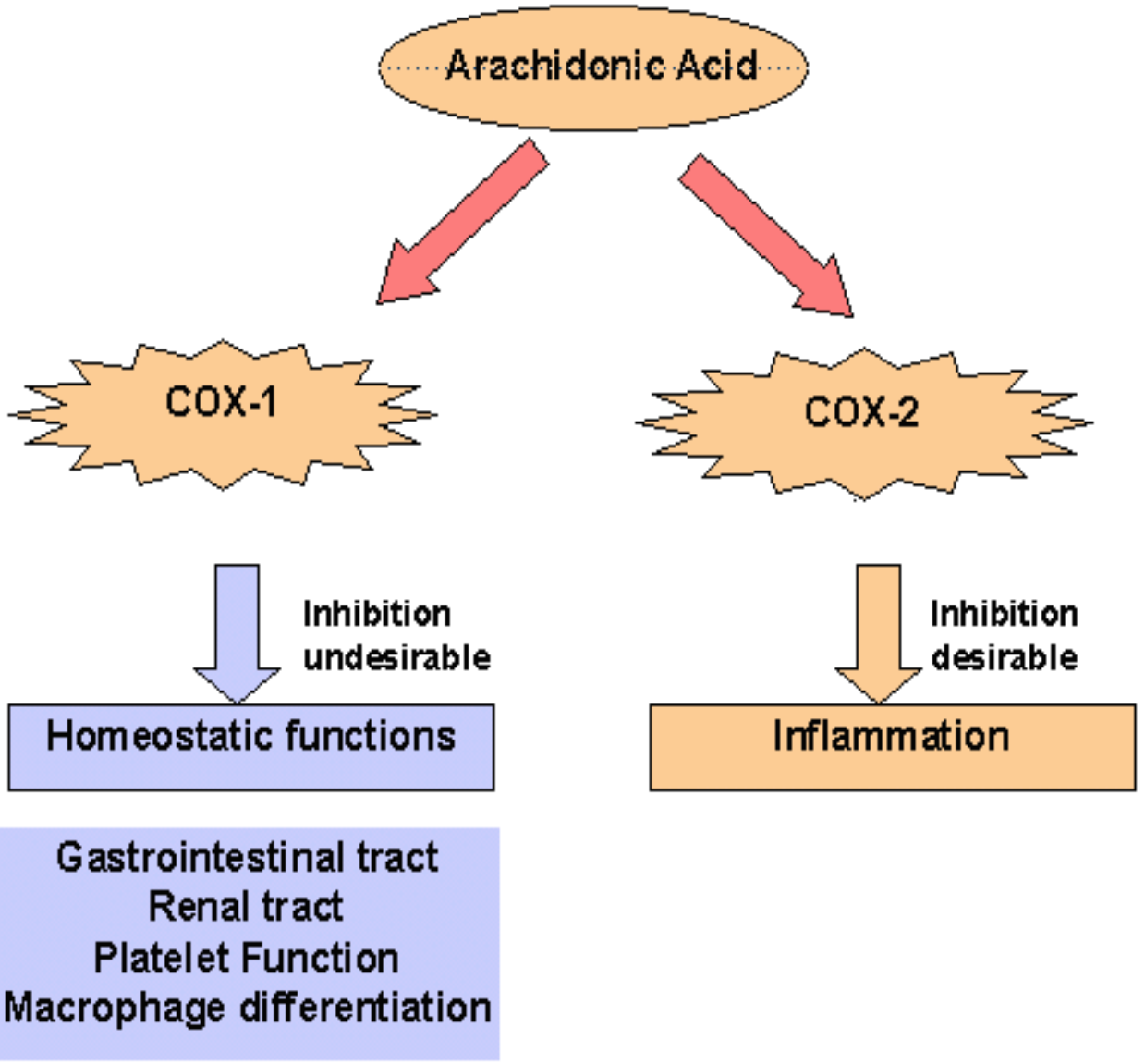
Enzymes that converts Arachidonic acid → Eicosanoids (that causes inflammatory response)

Anti-inflammatory/ anti-pyretic → Decreases body's temperature (since inflammation in the region of injury causes swelling + heat \ fever)

Targets of Aspirin

- Cyclooxygenase is present in three forms in cells, COX-1, COX-2, and COX-3.
- Aspirin targets both, but COX-2 should only be the target.

When Aspirin inhibits **COX1**
It causes Stomach Ulcers
⟶ holes + bleeding + pain (it can be fatal)
-That's why people with stomach ulcers + hyperacidity do not take aspirin-



A new drug that only attacks COX2 is needed = celecoxib

Next slide ...

Celebrex

Scientific name = celecoxib
Doesn't affect COX1 so it keeps working = the stomach will not be affected + it can treat inflammation

- A new generation drug, Celebrex, targets COX2, but is prescribed with a strong warning of side effects on the label.

since there was an increase in the cases of cardiovascular diseases / blood clots right after Pfizer has released the drug .

Cardiovascular Risk

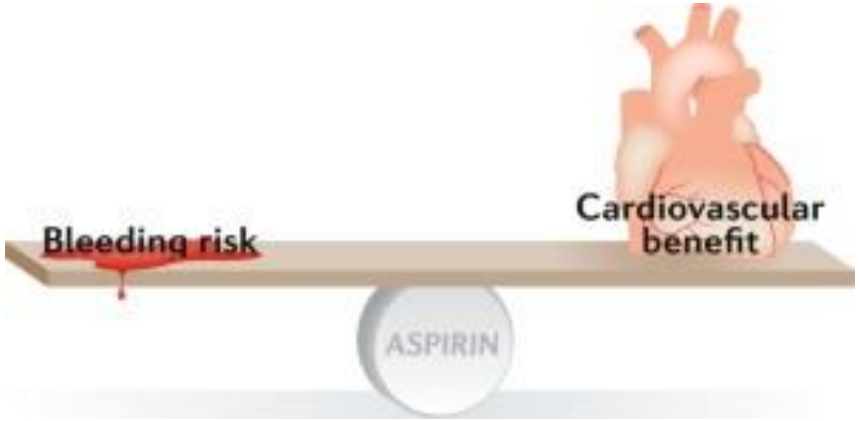
- CELEBREX may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See **WARNINGS** and **CLINICAL TRIALS**).

- CELEBREX is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

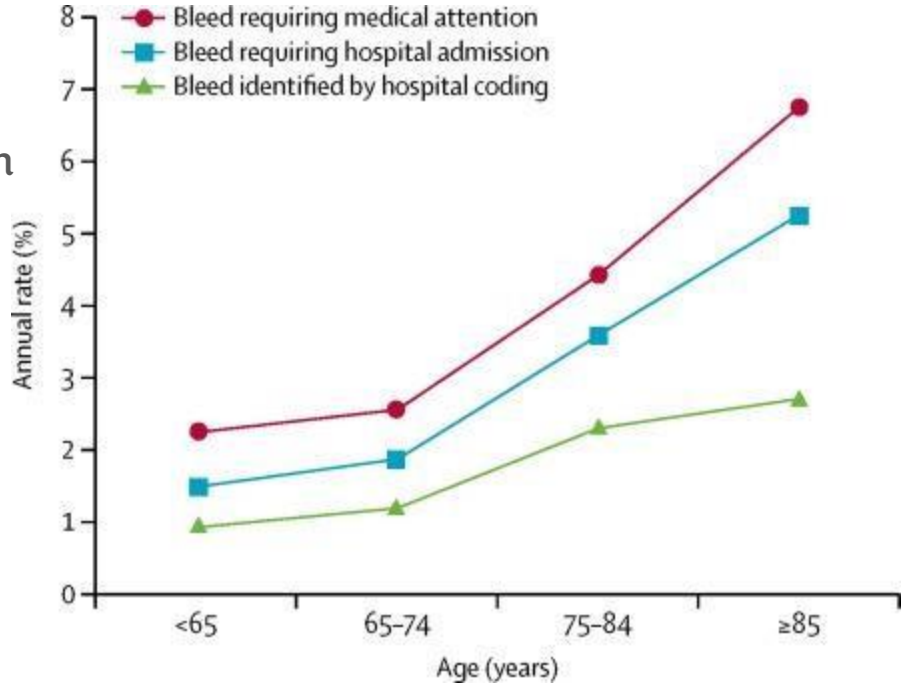
Aspirin can be bad ☹

Cardiovascular disease vs. bleeding

- Aspirin also causes excessive bleeding among the elderly.



Because they are more susceptible to fall down = causes bleeding = it can be fatal if they use aspirin



Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study In 2021

Linxin Li, Olivia C Geraghty*, Ziyah Mehta, Peter M Rothwell, on behalf of the Oxford Vascular Study*

Interpretation In patients receiving aspirin-based antiplatelet treatment without routine PPI use, the long-term risk of major bleeding is higher and more sustained in older patients in practice than in the younger patients in previous trials, with a substantial risk of disabling or fatal upper gastrointestinal bleeding. Given that half of the major bleeds in patients aged 75 years or older were upper gastrointestinal, the estimated NNT for routine PPI use to prevent such bleeds is low, and co-prescription should be encouraged.

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V1 → V2	*Slide 19 , at the top of slide *slide 10. (3 notes have been added.)	* Arachidonic acid is derived from linolenic.	* Arachidonic derived from linoleic acid . * acetic acid found in vinegar. Stearic acid found in nutmeg. 20-24carbon = very long chain .
V2 → V3	* Slide 14 : right bottom corner of the slide a sentence was added regarding the essential FA. It was mentioned by the doctor at the beginning of lec9 *Slide 17 : note is added		* "Essential FA = our body can't synthesize them = we get them from diet" * When its fully saturated
V3 → V4			

Additional Resources:

رسالة من الفريق العلمي:

1. Campbell Textbook: sec 8.1 + 8.2 + 8.8
2. https://youtu.be/F31uPXIrKh8?si=9Wn4qp-KNiAPX12R

Best of Luck(:

تأمَّل حياتك جيّدًا، ضع جانبًا كلّ ما قتل وقتك، وأخذ شيئًا من صحّتك، وهَدَم بُنيانًا طالما حَلُمتَ به، لا مزيد من الفراغ، لا مزيد من العجز، المُمكِن الّذي بينَ يديك، والأُمّة التي تُراهن عليك، أحَقّ أن تُعطيه كُلّك..