Biochemstry Team

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# Oxidative stress

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Objective:
Not be given

Red: Imp

Blue: Explain

Green: addition notes

# Oxidative stress ⟷ Oxidative balance

opposite

**Oxidative stress**

imbalance between

- Oxidants production
- Antioxidants mechanism

**Oxidative balance**

balance between

- Oxidants production
- Antioxidants mechanism

Defense mechanism e.g Inflammation

Normal mechanism

**Oxidative stress**
(happen in the body during)

# Oxidative stress

- **A condition in which cells are subjected to excessive levels of Reactive Species (Oxygen or Nitrative species) & they are unable to counterbalance their deleterious effects with antioxidants.**
- **It has been implicated in the ageing process & in many diseases (e.g., atherosclerosis and coronary heart diseases).**

*Some people does not affected due to natural antioxidant mechanism

## Oxidative damage to:

DNA

Proteins

Lipids (unsaturated fatty acids)

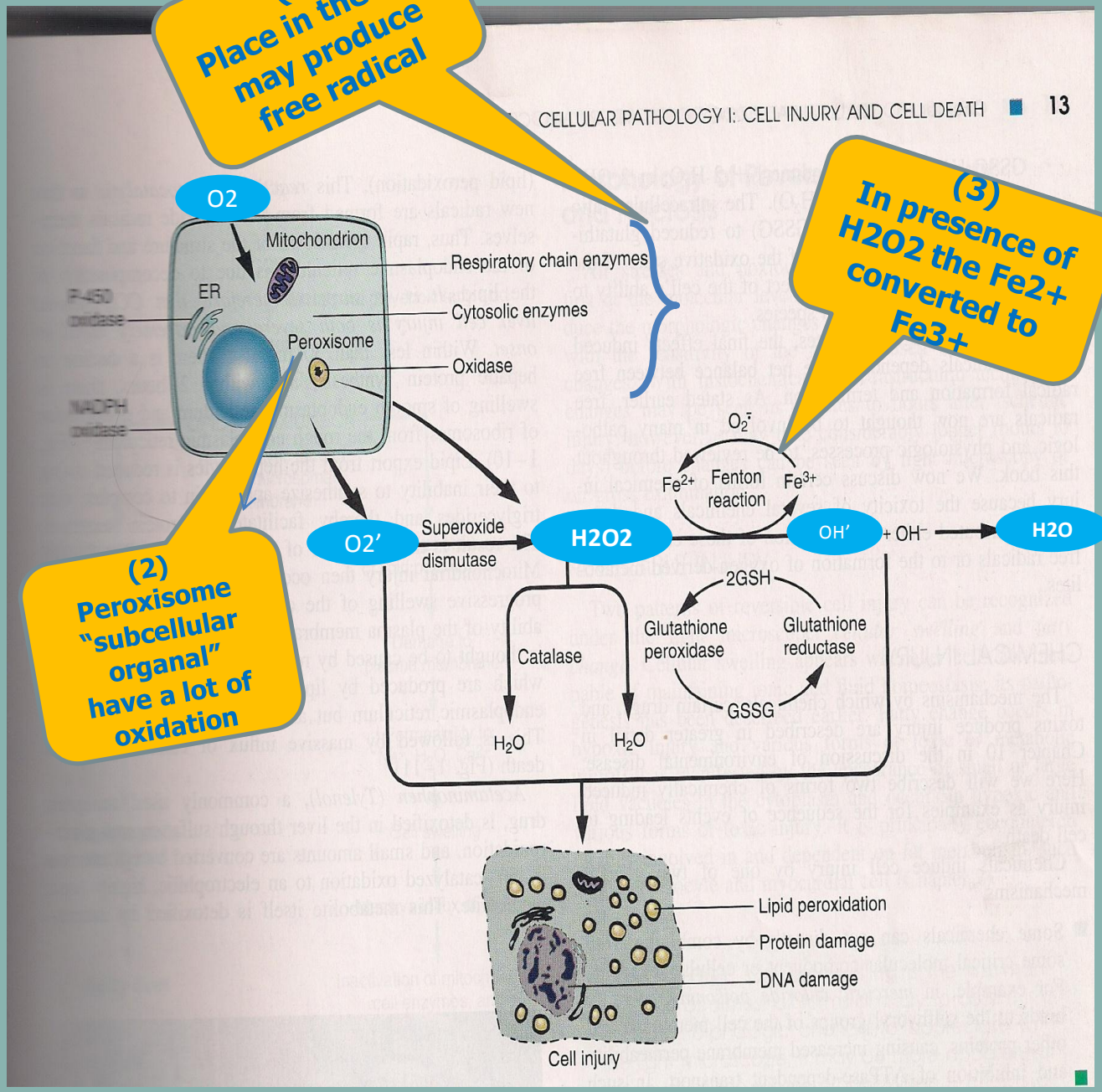
e.g. poly unsaturated fatty acids

*the oxidant will convert unsaturated lipid to free radical to fatty acid

## Oxidative stress and diseases:

- Inflammatory conditions e.g., Rheumatoid arthritis
- Athersclerosis and coronary heart diseases
- Obesity
- Cancers
- G6PD deficiency hemolytic anemia

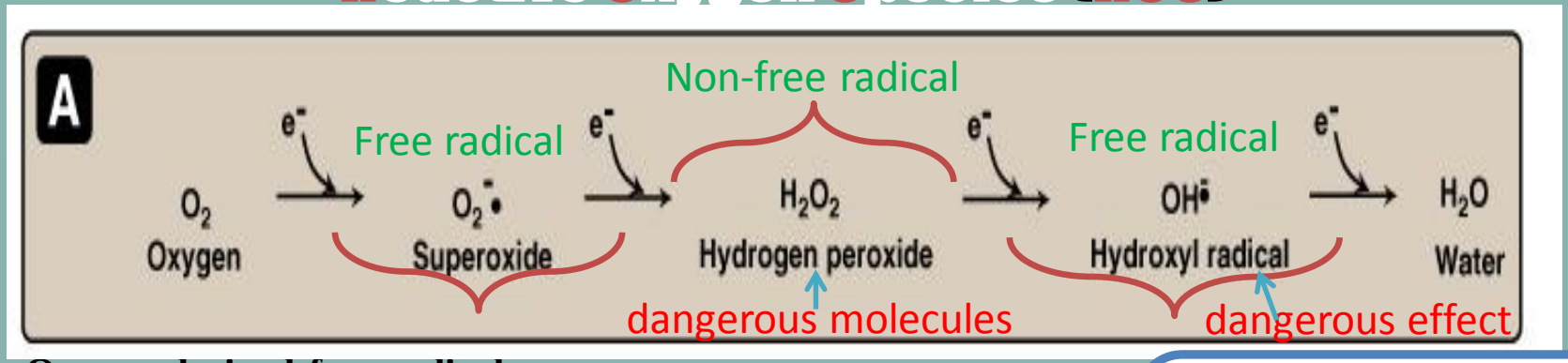
which common in Saudi Arabia.




السلايد اللي بعده راح تكون الصورة اوضح بالنسبة للـ Mechanisms

هذا السلايد واللي بعده التسجيل مهم من الدقيقة ٢٤-٢٩

# Reactive Oxygen Species (ROS)




**Oxygen-derived free radicals :**

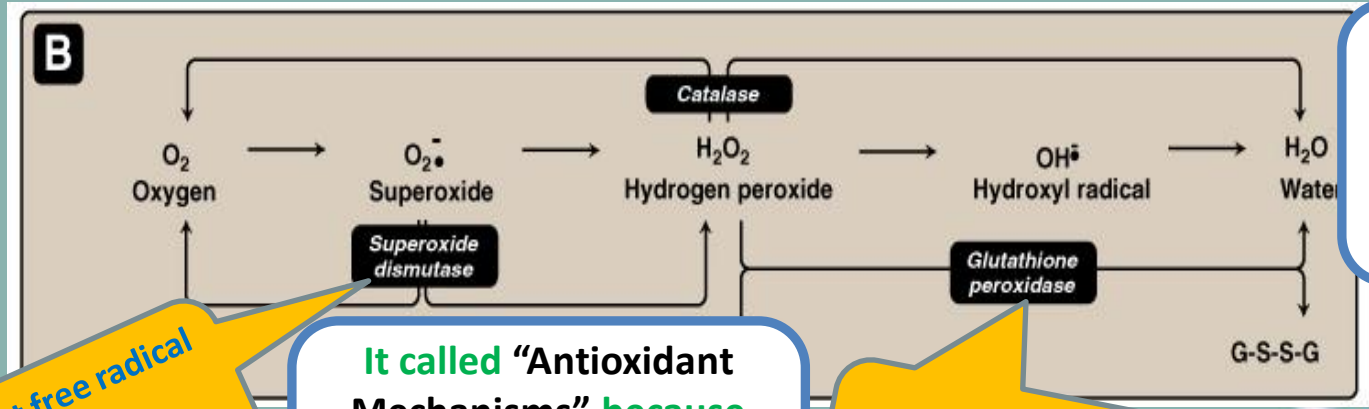
e.g., Superoxide and hydroxyl radicals

**Non-free radical:**

Hydrogen peroxide h2o2 "dangerous molecules"

So we have 2 dangerous molecules: one is non-free radical Other is free radical

## Antioxidant Mechanisms




So we have 3 examples of Antioxidant Mechanisms:
1-superoxide dismutase.
2-catalase.
3- Glutathione peroxidase

Convert free radical into non-free radical but stil reactive.

It called "Antioxidant Mechanisms" because we have good effusion mechanism to disposal H2O2

Glutathione system in presence of Glutathione peroxidase.

## Reactive Oxygen Species (ROS)

**Types:**

**Free radical:**

Superoxide ($O_2^{\cdot}$)

Hydroxyl radical ($OH^{\cdot}$)

Peroxyl radical ($ROO^{\cdot}$) **( is the free radical derivate from fatty acid )**

**Non free radical:**

Hydrogen peroxide ($H_2O_2$)

**Sources:**

**During course of metabolism**

e.g.,

$O_2^{\cdot}$ by auto-oxidation of hemoglobin and xanthine oxidase

$OH^{\cdot}$ by Fenton reaction

$O_2^{\cdot}$ , $H_2O_2$ , $OH^{\cdot}$ By partial reduction of molecular oxygen in electron transport chain in mitochondria

**Ingestion of toxins, chemicals or drugs**

## Antioxidant

**Enzymes:**

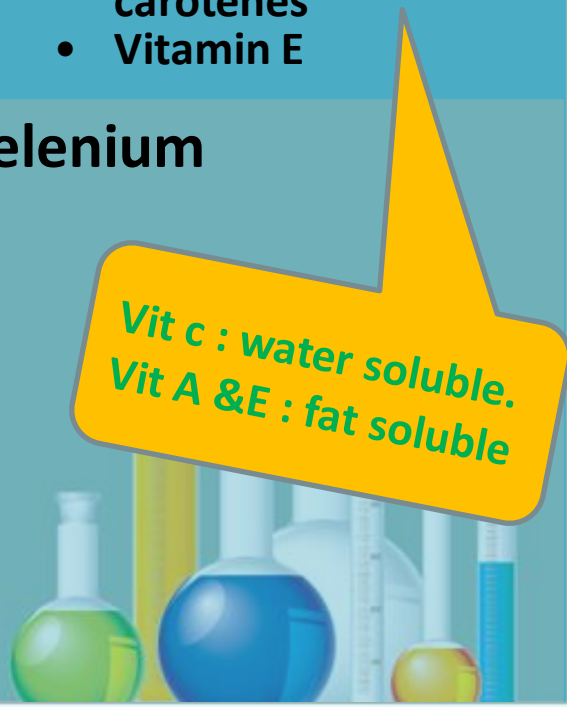
- **Superoxide dismutase**
- **Catalase**
- **Glutathione system** (glutathione, NADPH, reductase, peroxidase & selenium)

**Vitamins:**

- **Vitamin C (ascorbic acid)**
- **Vitamin A and β-carotenes**
- **Vitamin E**

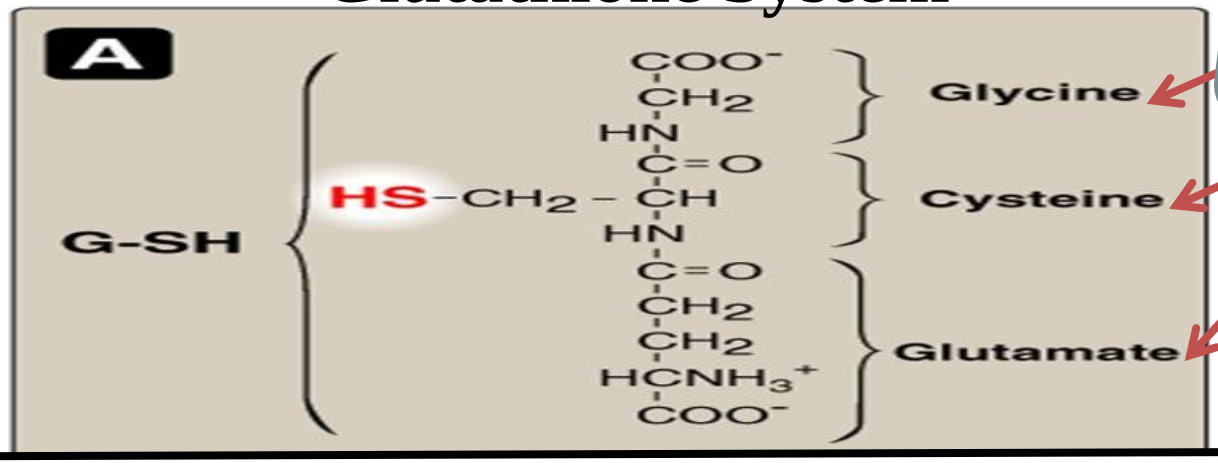
**elements Trace:**

**Selenium**



# Glutathione System

Glutathione is Tripolypeptide which mean 3 amino acid




* Glucose-6-phosphate dehydrogenase (G-6-PD) is the main source for NADPH generation and is, therefore, essential for proper function of glutathione system

This pathway happen in many cells but more imp. In RBC…. Why?

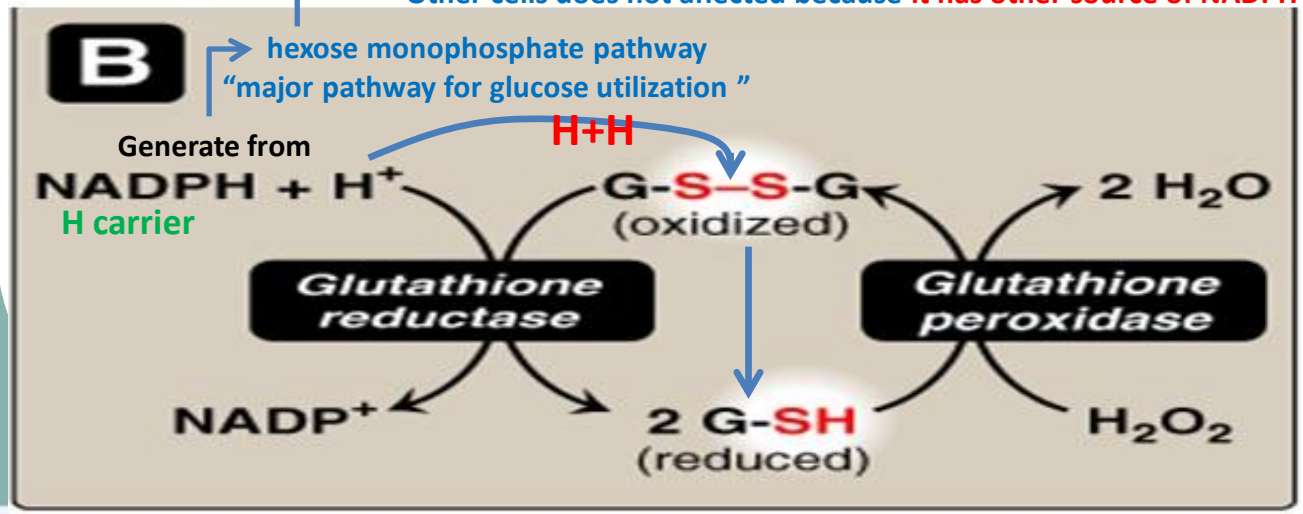
because RBC only is source of NADPH formation by this Pathway

السلايد التالي فيه رسمة توضح هالعملية

This pathway need G-6-PD as enzyme this enzyme deficient in hemolytic anemia.

as aresult of G-6-PD deficiency H2O accumulated in the RBC causing hemolysis.

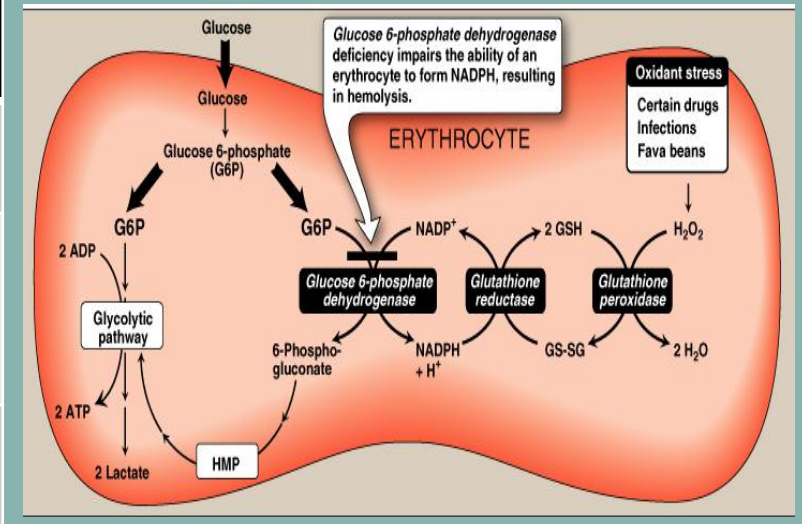
Other cells does not affected because it has other source of NADPH



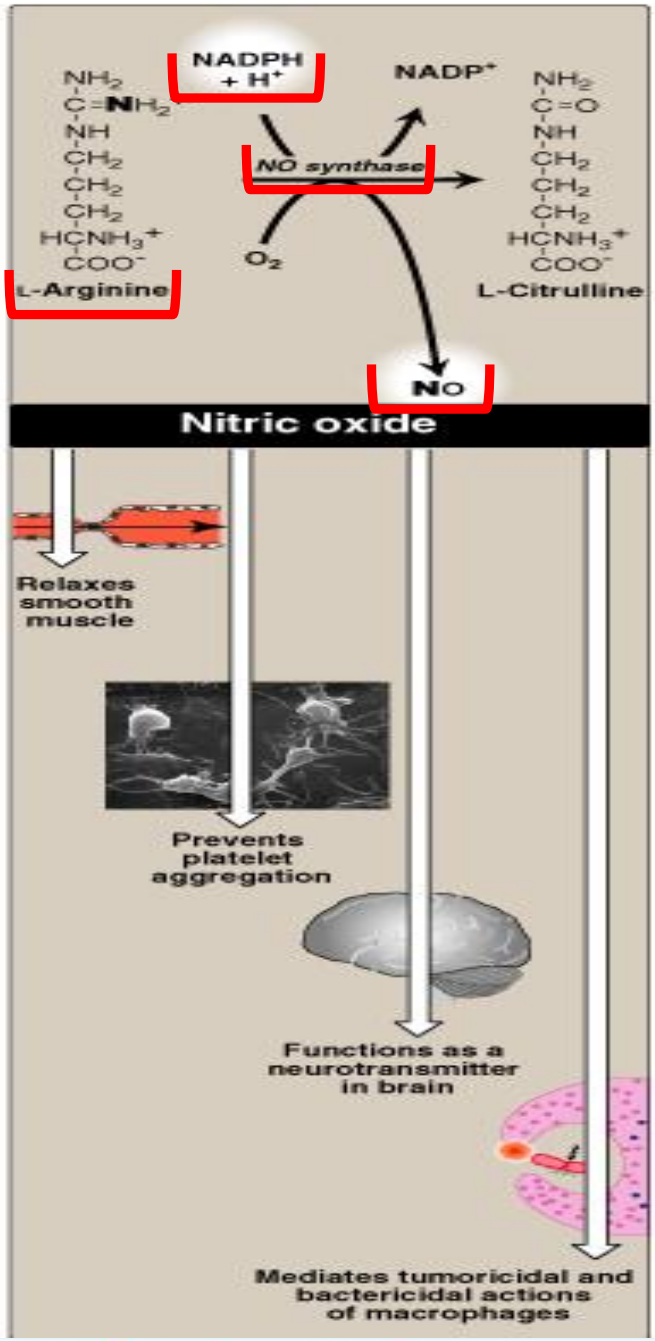

# Molecular & Vascular Effects of ROS

| Molecular effects | Vascular effects |
|---|---|
| Lipid peroxidation (polyunsaturated fatty acids) | Altered vascular tone |
| Protein denaturation | Increased endothelial cell permeability |
| Inactivation of enzymes | |
| DNA damage | |
| Cell signaling effects (e.g., release of $Ca^{2+}$ from intracellular stores) | |
| Cytoskeletal damage | |
| Chemotaxis | |

## Biochemical Basis of G6PD Deficiency Hemolytic Anemia




# Nitric Oxide (NO)




| NO: | Synthesis: | Effects: |
|---|---|---|
| Free radical gas | Enzyme:<br>No synthase | Relaxes vascular smooth muscle |
| Very short half-life (seconds) | Precursor:<br>L-Arginine | Prevents platelet aggregation |
| Metabolized into nitrates & nitrites | | Bactricidal & Tumoricidal effects "as a defensive mechanism against infection" |
| | | Neurotransmitter in brain |

# Oxidative Stress: Role of Nitric Oxide (NO)

- This may be both beneficial and detrimental, depending upon when and where NO is released

- NO produced by endothelial NOS (eNOS) → improving vascular dilation and perfusion (i.e., beneficial).

  Vasodilators such as nitroglycerin is metabolized into NO and causes vasodilatation

- In contrast, NO production by neuronal NOS (nNOS) or by the inducible form of NOS (iNOS) has been reported to have detrimental effects.

- Increased iNOS activity is generally associated with inflammatory processes

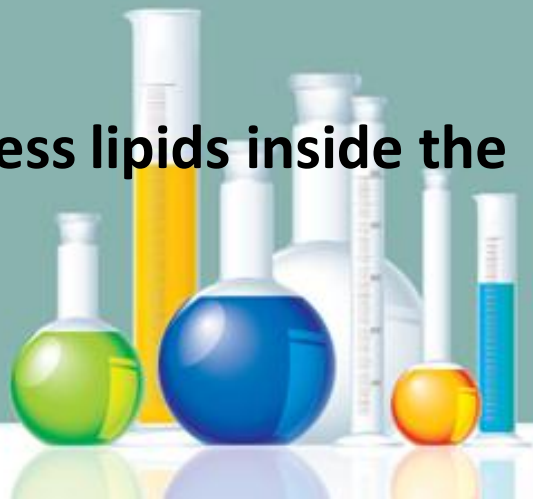
So, NO produced by
1- Endothelial NOS. → Beneficial
2-Neuronal NOS. → Detrimental
3-Inducible NOS.

Inducible:
In normal condition it's very low level but when ever there is trigger e.g, inflammation the level increase

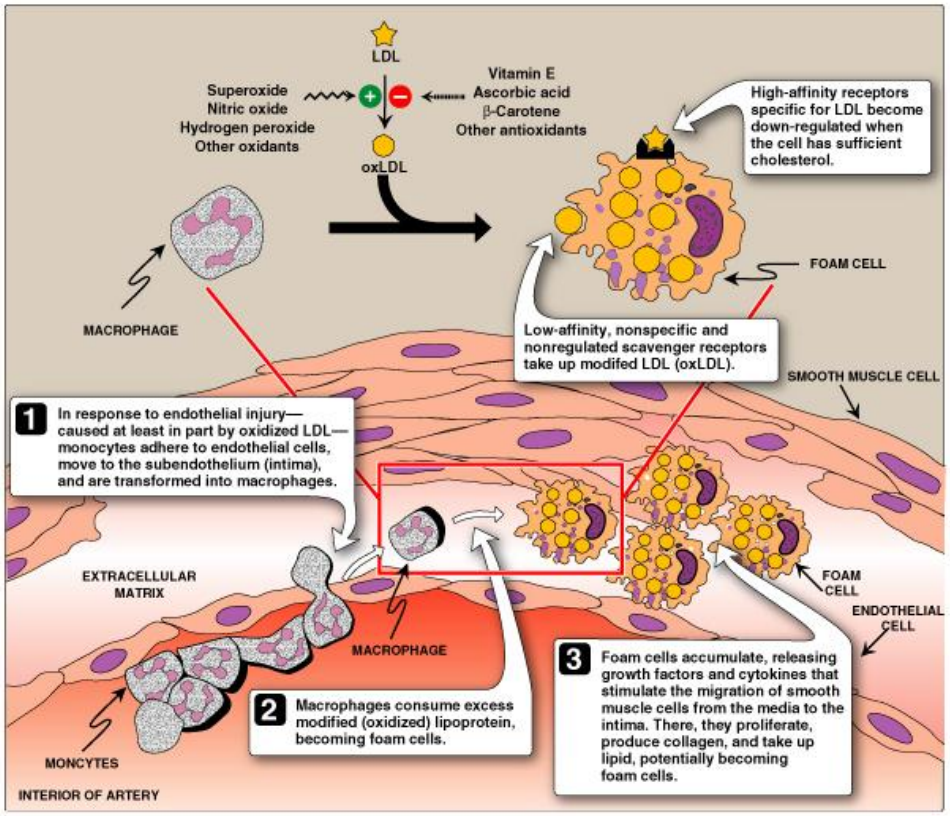
# Pathogenesis of Atherosclerosis

هذا السلايد مشروح في المحاضرة السابقة

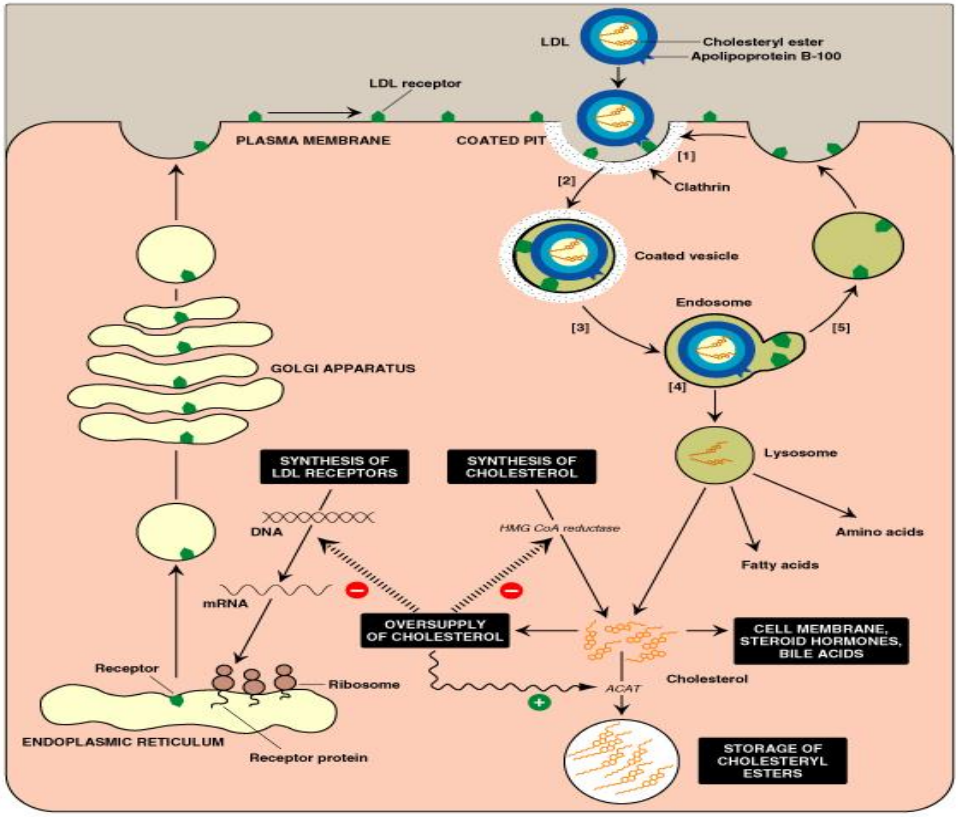
- Modified (oxidized) LDL … Oxidative stress
  (imbalance between oxidants and antioxidants)
  ( the oxidase part could be the Abo-protein or fatty acid in LDL )
- Endothelial injury of arterial wall
- Adherence of monocytes to endothelial cells and their movement into intima where it becomes macrophages
- Uptake of oxLDL by macrophage scavenger receptor:
  Scavenger receptor class A (SR-A)
  Low-affinity, non-specific receptor
  Un-regulated receptor
- Foam cell transformation: Accumulation of excess lipids inside the cells (unregulated receptor)
- Atherosclerotic plaque formation



# Atherosclerotic plaque Formation




# LDL: Receptor Mediated Endocytosis




هذا السلايد مشروح في المحاضرة السابقة

**Compare to physiological uptake of LDL (unmodified) by high-affinity, specific & tightly regulated LDL-Receptor**

# Review MCQs :)

Q1) Which of these Nitric Oxide Synthase (NOS) forms is Beneficial to the Body:

A- Endothelial NOS. B- Neuronal NO.S. C- Inducible NOS.

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Q2) One of the pathogensis of atherosclerosis is:

A- Normal LDL B- modified LDL (oxidized LDL) C- healthy vessel wall

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Q3) Which of these ROS is a result of Fenton Reaction:

A- Superoxide (O2') B- Hydroxyl radical (OH') C- Hydrogen Peroxide (H2O2)

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Q4) Which of these is non- free radical:

A- Superoxide (O2') B- Hydroxyl radical (OH')

C- Hydrogen Peroxide (H2O2)

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Answers

Ql) = A .... Q2) = B .... Q3) = B .... Q4) = C