SHEET NO.
11

METABOLISM

DOCTOR 2019 | MEDICINE | JU

DONE BY : **Hani Shihadeh**

SCIENTIFIC CORRECTION :

GRAMMATICAL CORRECTION :

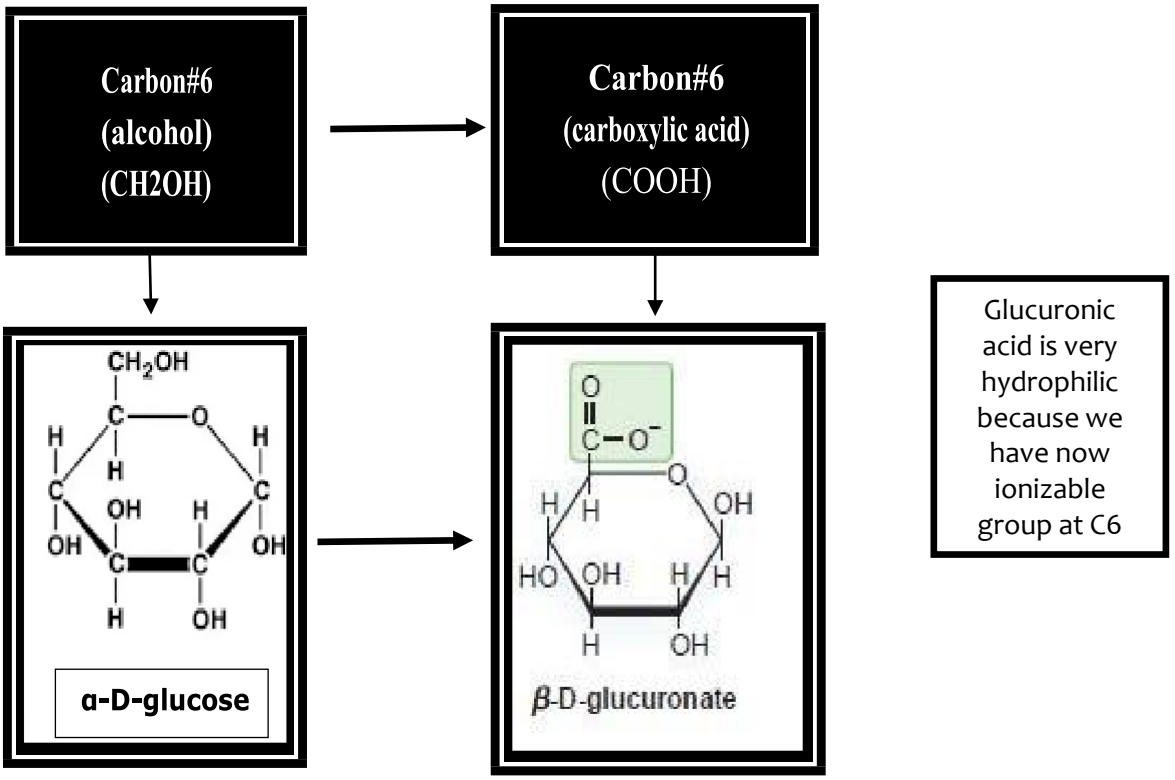
DOCTOR : **Faisal Al-Khatib**

Pentose Phosphate Pathway

- Glucose as we know has two types of functional groups: Aldehyde group (CHO) on C1 and many hydroxyl groups (OH) at several carbons. If these groups get oxidized that will result in the formation of carboxyl group (COOH)
- So if glucose get oxidized at different carbons it will give different acids for example: Glucuronic acid and Gluconic acid.

Glucuronic acid $C_6H_{10}O_7$

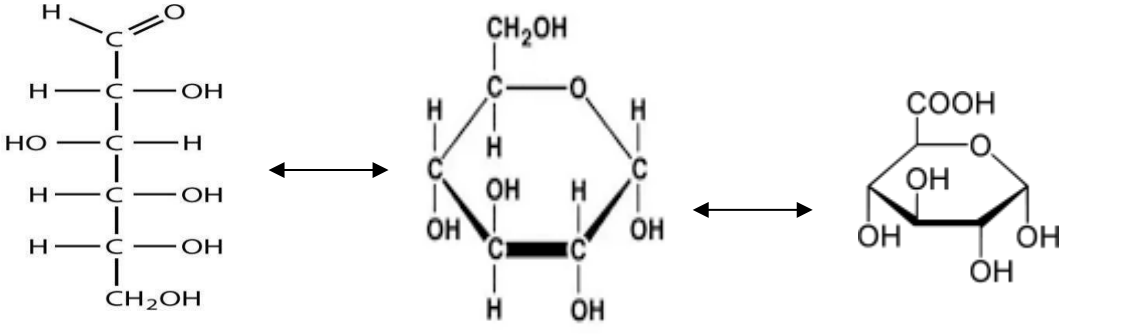
- is a sugar acid derived from glucose, with its sixth carbon atom oxidized to a carboxyl group.



Glucuronic acid is very hydrophilic because we have now ionizable group at C6

Note:

✓ **Glucuronate** is the ionized form of glucuronic acid (unprotonated).



D-glucose | α-D-glucose | α-D-glucuronic acid

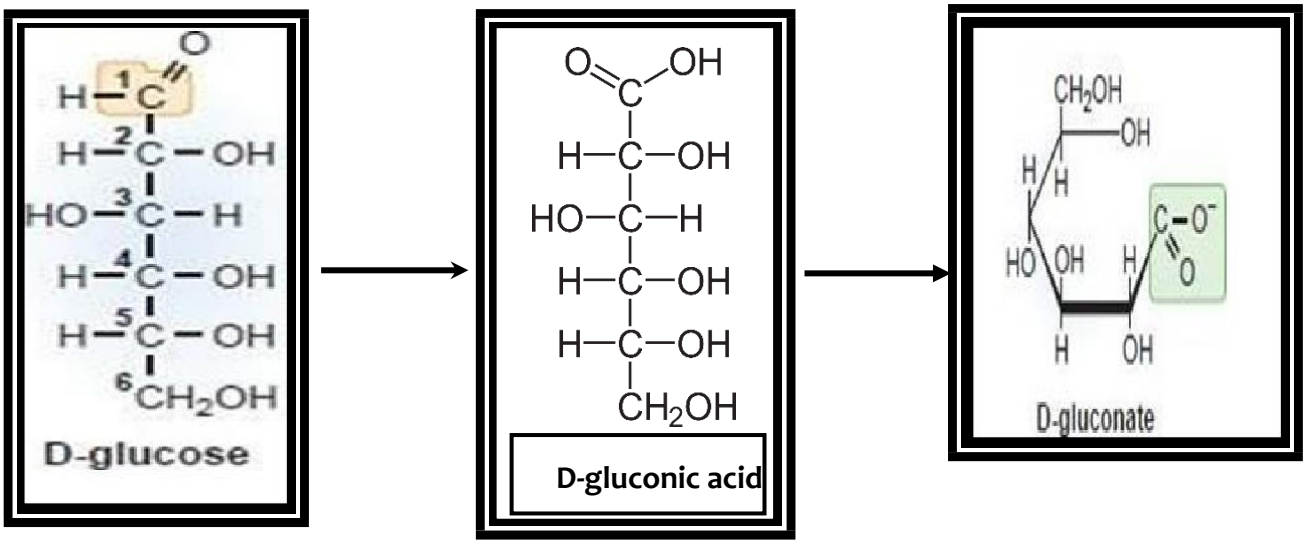
❖ **Remember**

✓ The conversion of glucose from its open chain form into its cyclic form results from the reaction of carbon 1 (aldehyde group) with the hydroxyl group on carbon number five which form hemiacetal

✓ This reaction is a spontaneous reaction that doesn't require a catalyst and is reversible.

Gluconic Acid

➢ Is the carboxylic acid formed by the oxidation of the first carbon of glucose.



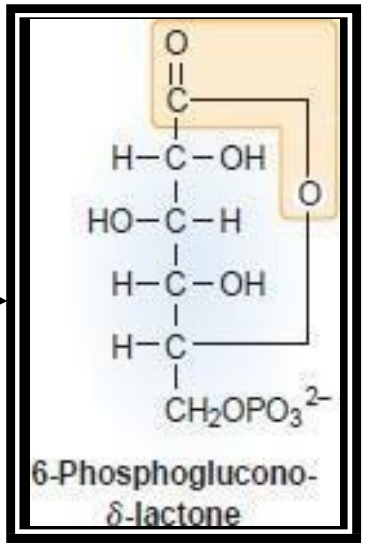
❖ **Note:**

➢ **Gluconate** is the ionized form of gluconic acid (unprotonated). When it's protonated it becomes Gluconic acid.

Gluconic acid cannot exist in a hemiacetal ring form but can form a cyclic structure by forming an intramolecular ester linkage between the carboxyl group of carbon 1 and hydroxyl group of carbon 5 within the same molecule. This type of cyclic ester is known as gluconolactone.

Some notes about the figure (6-phosphoglucono- δ-lactone):

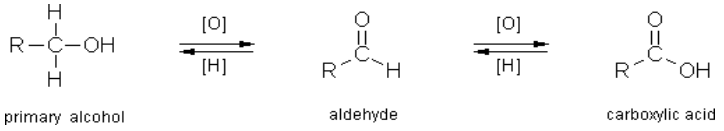
- ✓ Each carbon in the molecule has a name according to its location in regard to the alpha carbon.
- ✓ The first carbon atom that attaches to a functional group is the alpha carbon, the carbon atom next to the α carbon is the beta carbon and so on.
- ✓ In this case the carboxyl group on carbon #1 reacts with the hydroxyl group on carbon #5(delta) forming an ester bond.
- ✓ This forms a delta lactone.
- ✓ In the structure on the left, a phosphate group is present on carbon #6, hence the name 6-Phosphoglucono-δ-lactone.



Formation and functions of Glucuronic acid

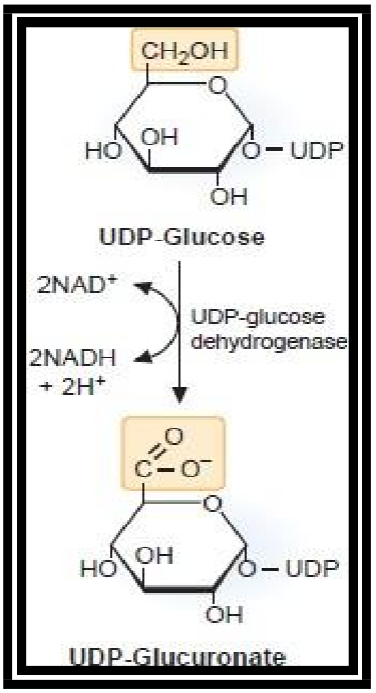
Formation

- Glucose is converted into glucuronate when it's part of UDP- Glucose.
- Glucose Is converted into glucuronate by the oxidation of the alcohol group on carbon #6 in to a carboxyl group.
- Two oxidation steps are involved (since the alcohol group on carbon #6 is a primary alcohol group).



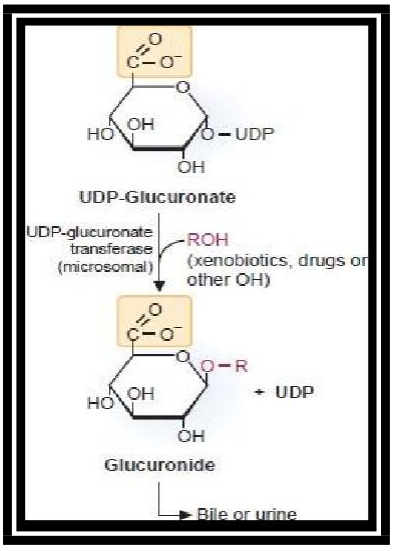
primary alcohol — aldehyde — carboxylic acid

- The enzyme that catalyzes this reaction is called **UDP-glucose dehydrogenase.**
- Since two oxidation steps are involved, two NADH molecules are produced.
- Glucuronate is very soluble in water since it has multiple hydroxyl groups in addition to a negative charge.



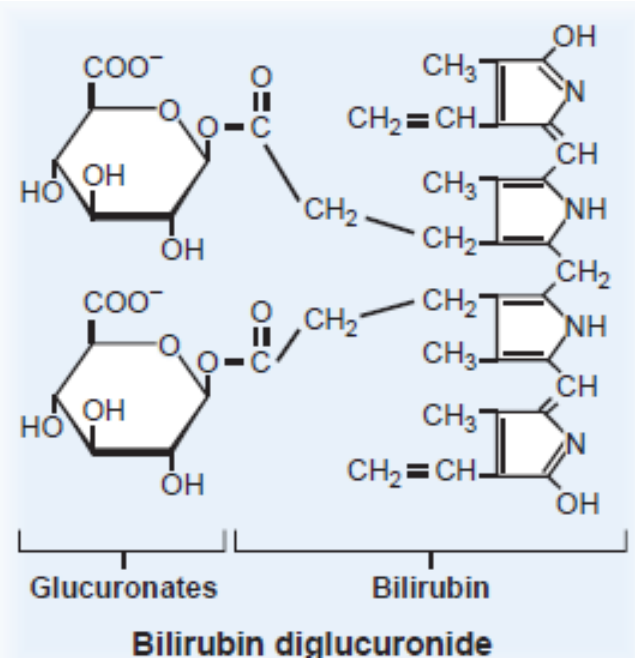
Functions (uses)

- Glucuronate can be transferred to many insoluble substances making them soluble in water.
- This is important in the metabolism of water- insoluble drugs by the liver.
- **UDP-Glucuronate transferase** catalyzes the transfer of glucuronate from UDP-glucuronate to hydrophobic molecules.
- The substance produced by linking glucuronate to the hydrophobic molecule is called Glucuronide, which can be excreted by urine or bile.



✓ **An important example** of the function of Glucuronate is the formation of bilirubin diglucuronide.

- **Bilirubin** is a compound obtained from the degradation of Heme.
- Bilirubin consists of an open chain tetrapyrrole formed by the cleavage of the cyclic structure of heme.
- It's mostly insoluble (since it contains
  - An insoluble tetrapyrrole chain) although it has two polar propionic acid side- chains (they aren't sufficient to make it soluble).
- Once bilirubin is produced in the blood, it gets carried to the liver in order to be excreted.



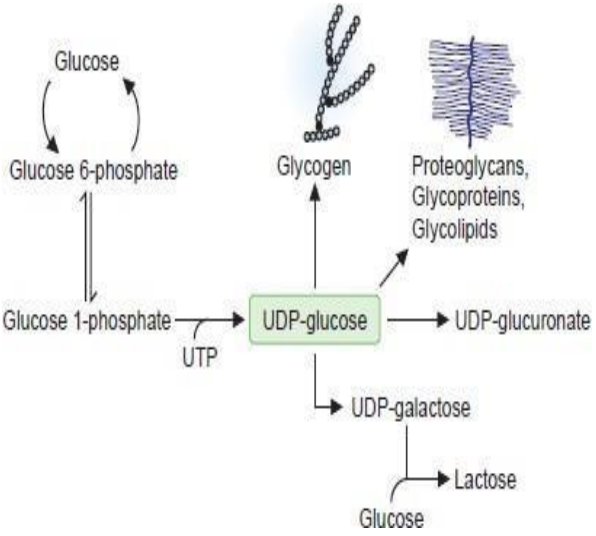
- In the liver, bilirubin (insoluble) binds to two Glucuronic acid molecules forming bilirubin diglucuronide (soluble) which can be excreted through bile.
- The binding occurs between carbon#1 in glucuronic acid and the two propionic acid side-chains of bilirubin as shown in the figure above.
- High level of bilirubin can be very harmful.

❖ **Nice example mentioned in 018 sheet:**

The majority of newborn infants in their first postnatal week have a yellowish colored skin (**J** The majority of newborn infants in their first postnatal week have a yellowish colored skin (**Jaundice**) due to the increased level of bilirubin in their body, that is mainly because their liver isn't mature enough to remove bilirubin by conjugating it with glucuronic acid.

UDP-Glucose has many function

1. Glycogen synthesis
2. Formation of Lactose by exchanging glucose with galactose
3. Formation of UDP-glucuronate
4. Formation of large molecules that require carbohydrates
   e.g. Proteoglycans, Glycoproteins, Glycolipids



Pentose Phosphate Pathway ⟷ Hexose-Monophosphate Shunt

- There are two main functions of the pentose phosphate pathway:
  1. The production of **NADPH**.
  2. Metabolism of five-carbon sugars (Pentoses).
     - Ribose 5-phosphate (nucleotide biosynthesis)
     - Metabolism of pentoses

➢ So far, we have learnt a lot about NADH, from the reactions that produce NADH to the oxidation of NADH by the oxidative phosphoryl at ion process to produce energy.

➢ Well, what about NADPH? How does it differ from NADH?

✓ Obviously, they differ by the presence of an additional phosphate group on one of the ribose units in NADPH.

✓ Though, they both have the same reduction potential.

✓ Since they both have the same reduction potential what is the function of the phosphate group? Why we add it?

It acts just as a tag to make enzymes to distinguish between NADH and NADPH

✓ NADPH has many important distinct functions:

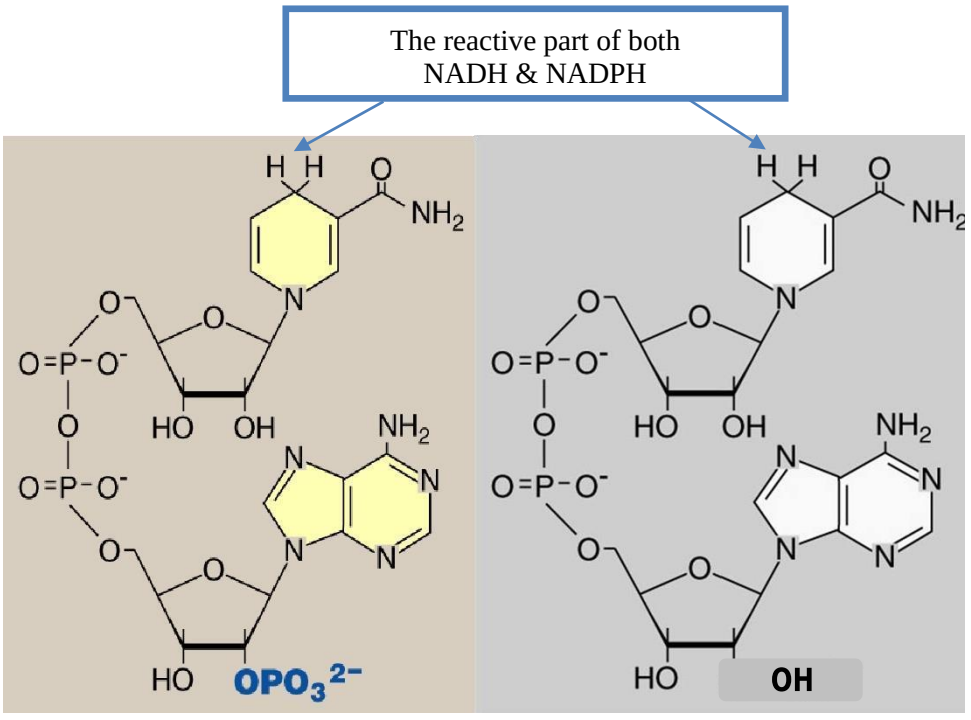
1. NADPH dependent biosynthesis of fatty acids

- Liver, lactating mammary glands, adipose tissue

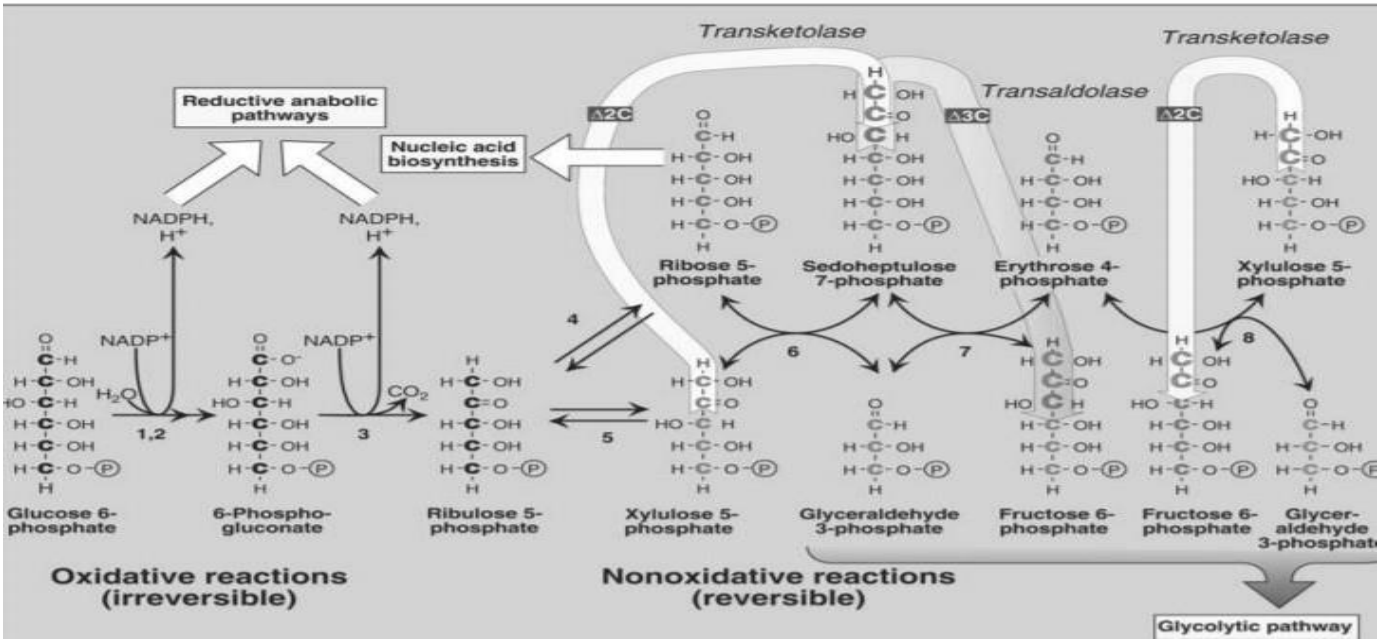
2. NADPH dependent biosynthesis of steroid hormones from cholesterol

- Testes, ovaries, placenta, and adrenal cortex

3. Maintenance of Glutathione(GSH) in the reduced form in the RBCs

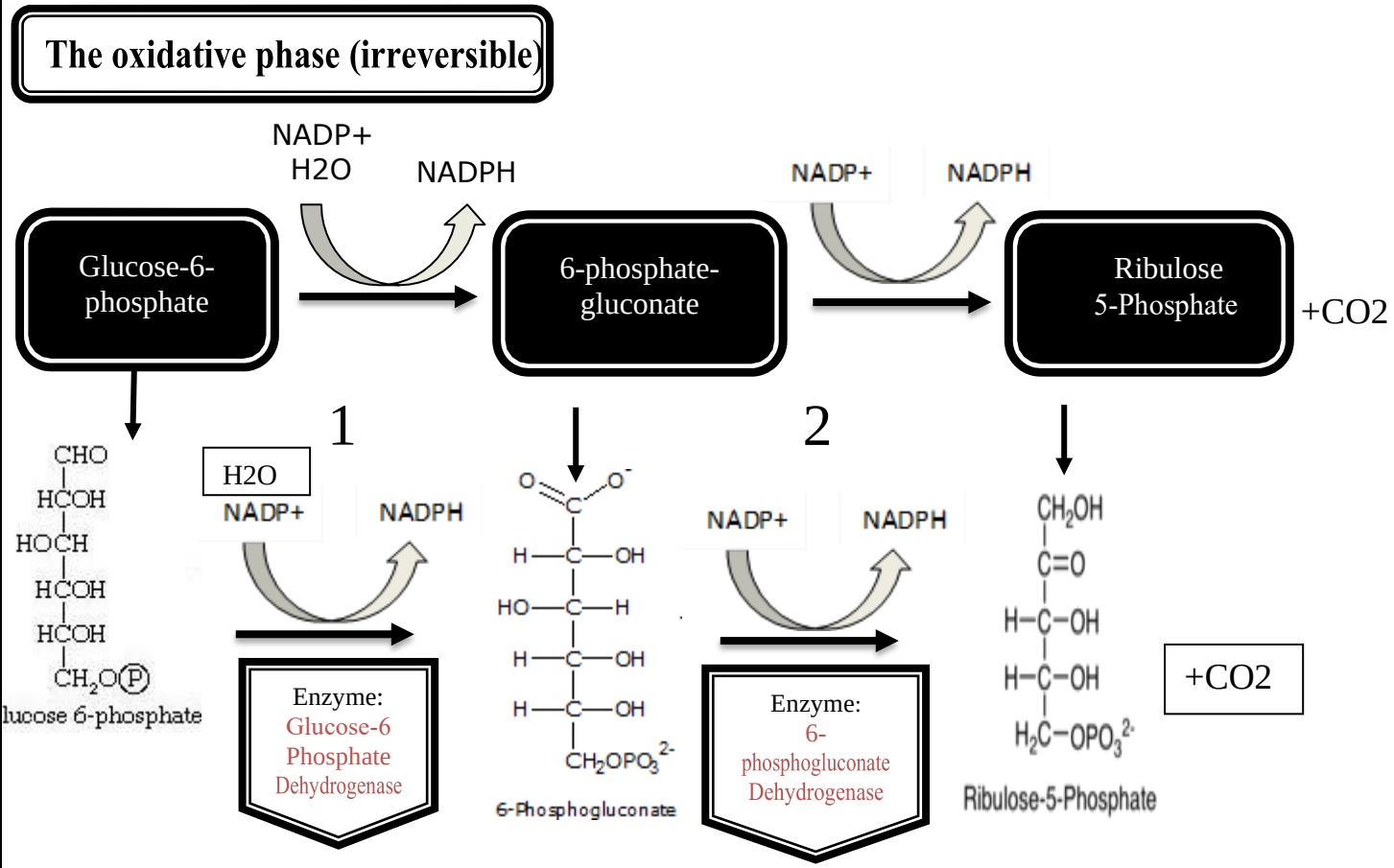


Pentose phosphate pathway (PPP):



The pentose phosphate pathway includes two phases:

1) The Oxidative Phase (irreversible): two irreversible oxidative reactions (oxidation- reduction reactions) and this phase is irreversible because it's decarboxylation reaction with is irreversible
2) The Non-Oxidative Phase(reversible)



Firstreaction (1): the oxidation of **glucose–6–phosphate** into **6–Phospho–gluconate (gluconic acid)** with the production of **1NADPH** molecule.

هذه الخطوة تضم تفاعلين لكن للتسهيل الدكتور طلب نعتبرهم تفاعل واحد وفي الأسفل (في المعلومة الإضافية) موضح التفاعل غير الموضح

- This reaction is the rate-limiting reaction and it is regulated.
- **Catalyzed by G6PD: Glucose-6-Phosphate Dehydrogenase**

Second reaction (2):oxidation of 6–Phospho–gluconate with decarboxylation to produce Ribulose-5–phosphate (ketose and sometimes the presence of U & L in the name that indicate that it's a ketose),1NADPH and a CO_2 molecule.

Oxidative decarboxylation reaction:

- Oxidation of carbon #3 into a ketone group.
- Decarboxylation of carbon #1 as a CO_2 molecule.
- **Catalyzed by 6-PGD: 6-phosphogluconate Dehydrogenase**

Net Reaction:

$$Glc.6Phosphate + 2NADP + \longrightarrow Ribulose\ 5\text{-}Phosphate + CO2 + 2\,NADPH$$

Extra note:

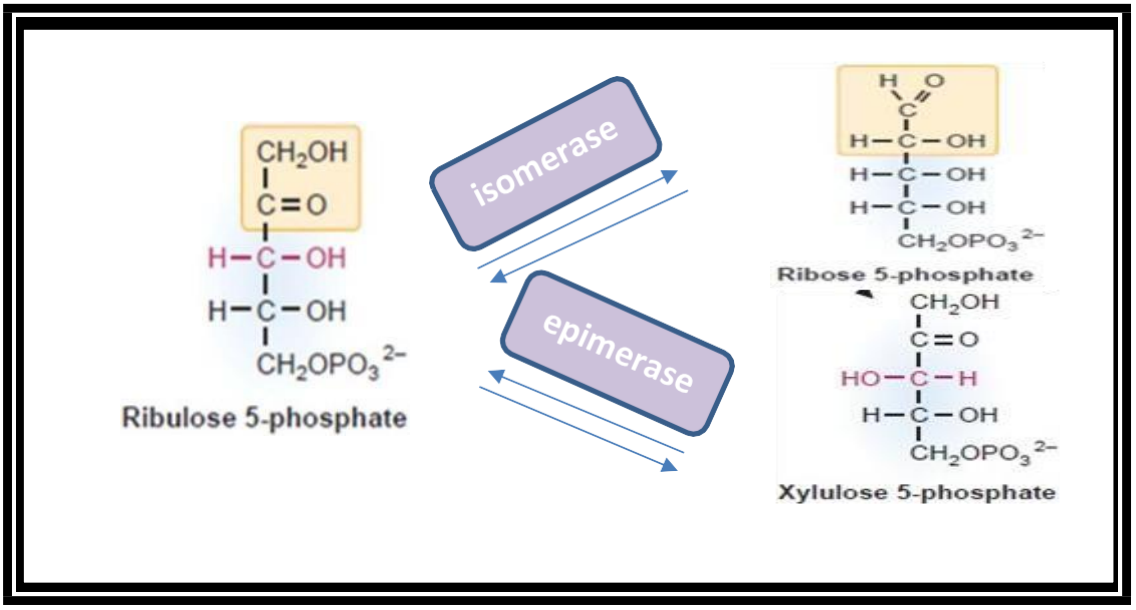
Glucose 6-phosphatedehydrogenase (G6PD) catalyzes an irreversible oxidation of glucose 6-phosphate to 6-phosphogluconolactone which is then hydrolyzed by 6-phosphogluconolactone hydrolase into 6- phosphogluconate. (The oxidative portion of the pentose phosphate pathway consists of three reactions two of which are irreversible oxidative reactions)

The non-oxidative phase (Reversible)

Summary of the non-oxidative reactions:

- All of the reactions in this phase are reversible.
- All of the reactions include transfer of a 2 or 3 carbon fragment from ketose (donor) to aldose (acceptor) (with an emphasis on the point that the transfer occur from ketose to aldose).
- Ketose + aldose $\rightleftharpoons$ ketose + aldose
- The reactions that involve a transfer of a 2-carbon fragment are catalyzed by **Transketolase** (2C).
- The reactions that involve a transfer of a 3-carbon fragment are catalyzed by **Transaldolase** (3C).

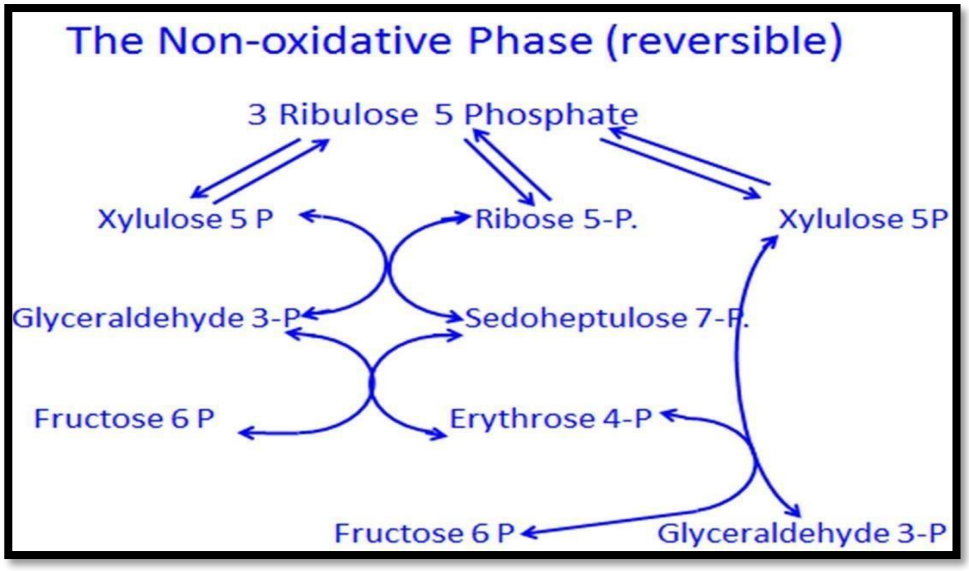
- After production of Ribulose 5-Phosphate, the reversible reactions of the second phase permit **Ribulose 5-phosphate** (produced by the oxidative portion of the pathway) to be **converted either to:**
  - **Ribose 5-phosphate** (needed for nucleotide(DNA,RNA) synthesis)
  - Or to **Xylulose 5-phosphate** to produce intermediates of glycolysis (fructose 6- phosphate and glyceraldehyde 3-phosphate)



- Looking at the structure of Ribose 5-p and Ribulose 5-p we notice that they are isomers thus the enzyme catalyzing the conversion of ribulose 5-p to ribose 5-p is called **isomerase.**

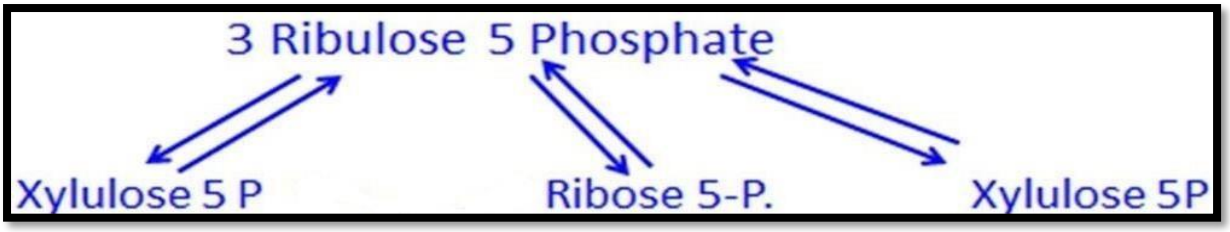
- Looking at the structure of Ribulose 5-p and Xylulose 5-p, we notice that they are epimers at carbon#3 thus the enzyme catalyzing the conversion of ribulose 5-p to Xylulose 5-p is called **epimerase.**

And now let's start discussing the steps of Non-oxidative phase:



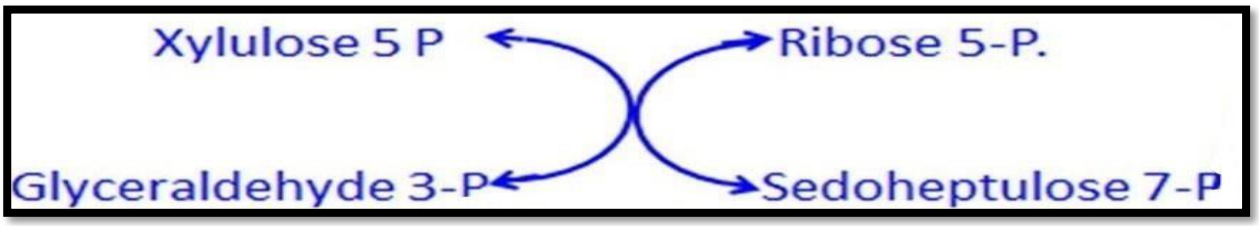
Steps:

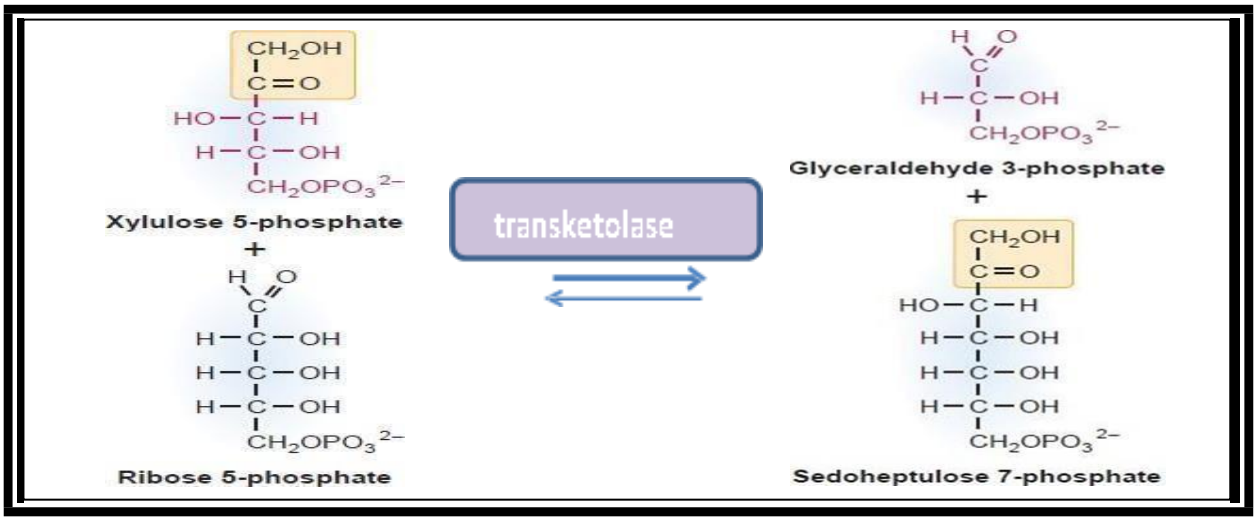
1) The non-oxidative phase stars with **three** ribulose 5-phosphate molecules, **two** are converted into Xylulose 5-P and **one** is converted to Ribose 5-P.



2) One of the two **Xylulose 5-P** (pentose, ketose) molecules donates **two carbons** to **Ribose 5-P** (aldose) which results in the formation of :

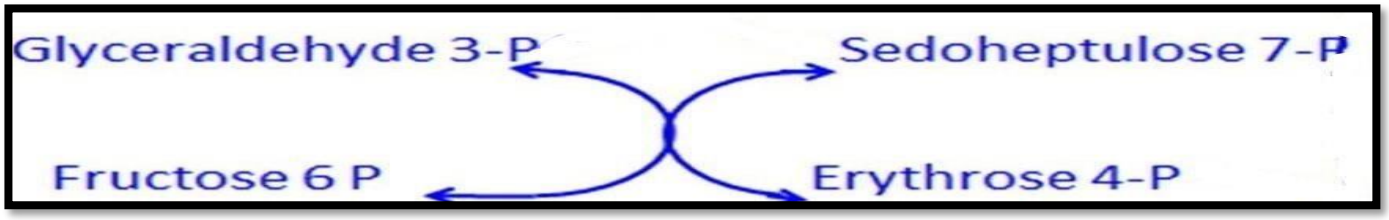
- Glyceraldehyde 3-P(triose)
- Sedoheptulose 7-P(heptose)

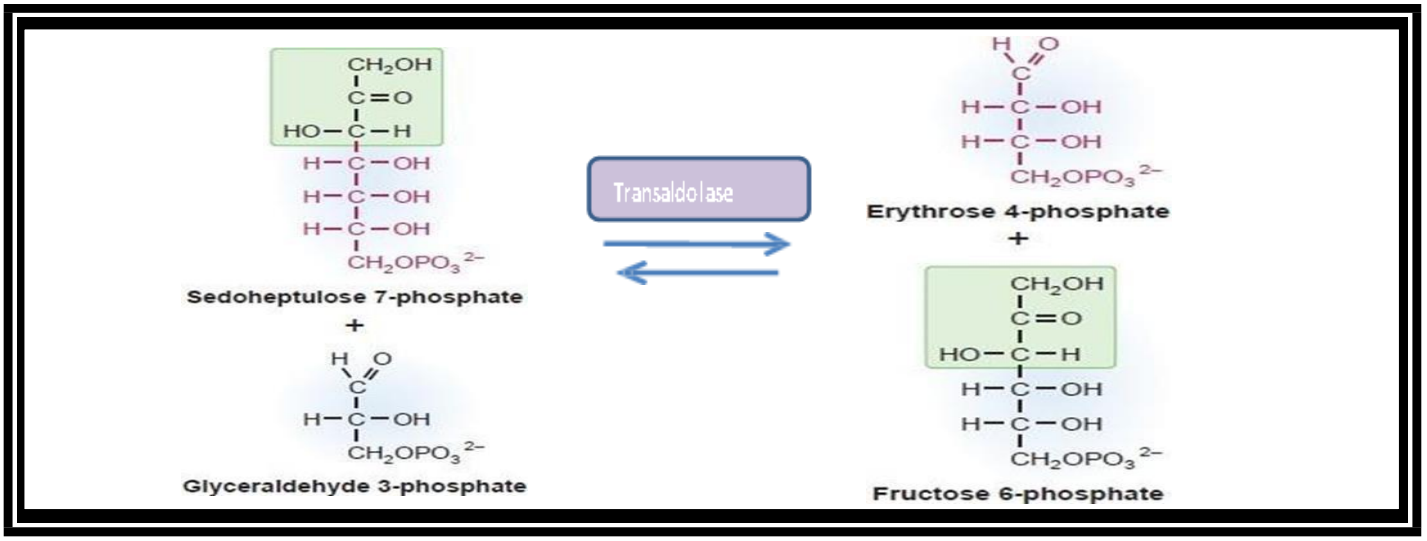




3) **Sedoheptulose 7-P** (ketose) donates **3 carbons** to **Glyceraldehyde 3-P** (aldose) which results in the formation of:

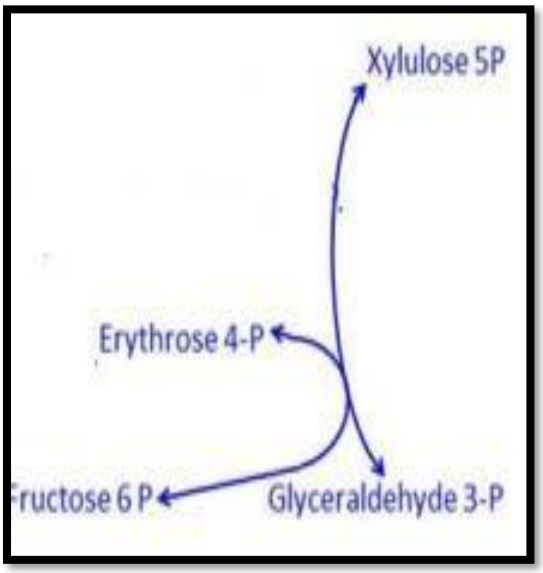
- Fructose 6-P(hexose)
- Erythrose 4-P(tetrose)

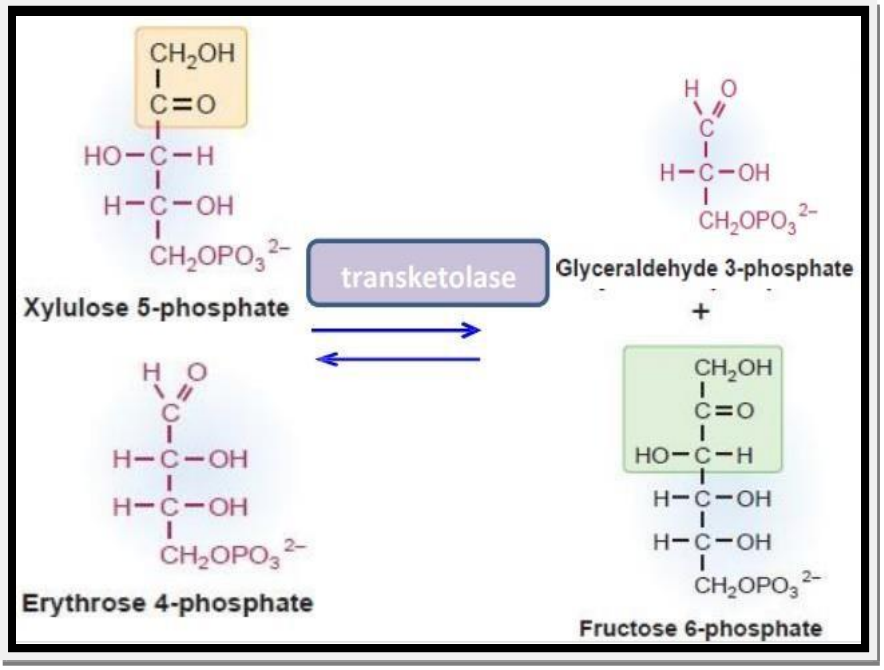




4) The second Xylulose 5-P (ketose) molecule donates two carbons to Erythrose 4-P (aldose) which results in the formation of:

- Fructose 6-P
- Glyceraldehyde 3-P





- After the rearrangement of the sugars the final products are:

3 pentose phosphate ⇌ 2 hexose phosphate + 1 triose phosphate

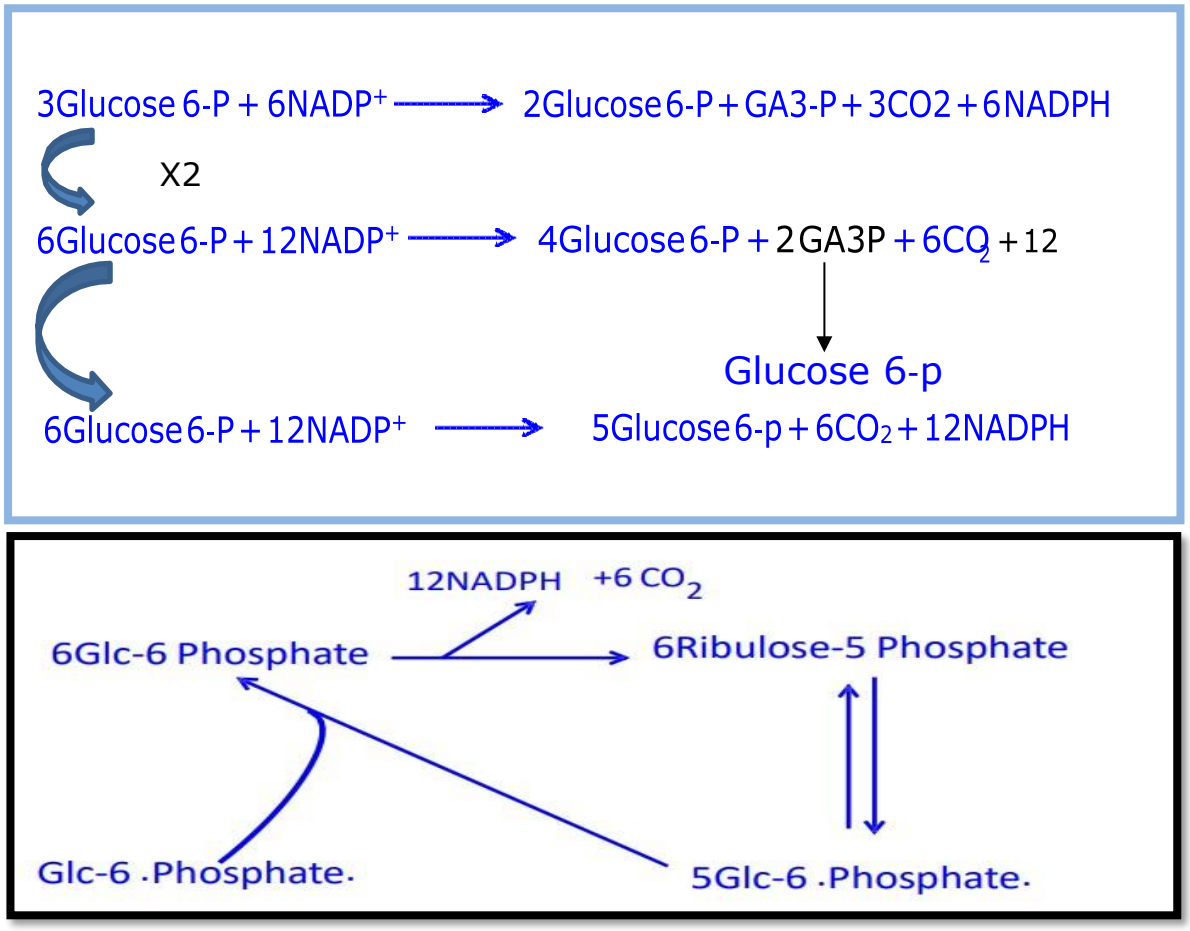
3 Ribulose 5-phosphate ⇌ 2Fructose 6-phoshate+1Glyceraldehyde 3-P

- If we multiply the previous reaction by 2 (as if we started with 6 Ribulose 5-P) 6Ribulose 5-phosphate ⇌ 4 Fructose 6-phospate + 2 Glyceraldehyde3-P

2 Glyceraldehyde 3-P can be converted to Fructose 6-phophate in gluconeogenesis resulting with 5Fructose6-phosphate

- You can notice that the number of carbon atoms between reactants and products don't change, we started with 6 Ribulose -5- phosphate (6*5=30) and end up with the same number (5 Fructose-6-phosphate= 5*6 =30), so pentose phosphate pathway just rearranges carbon atoms
- Fructose-6-phasphate can be easily converted to Glucose-6-phosphate, so we started the whole pathway with **6** Glucose-6-phosphate and by converting the fructose-6-phosphate molecules that result at the end of that pathway to Glucose-6-phosphate by isomerase enzyme activity we end up with **5** Glucose-6-phospate (6 Glucose-6-~~phosphate~~ 5 Glucose-6-phospate)

Adding both phases of the reaction, the final result is:



Some notes about the figure above:

1) In the oxidative phase, **6 Glucose 6-P** molecules are converted to **6 Ribulose 5-P** producing **12NADPH** molecules + **6CO2** molecules **(2NADPH per 1Glucose 6-p).**
2) In the non-oxidative phase, **6 Ribulose 5-P** are converted to **5 Glucose 6-P.**
3) **Addition** of another **Glucose 6-p** to the **5 produced** in the non-oxidative phase results in the formation of **a cycle.**
4) In cells that depend on NADPH (like RBC's), the cycle keeps going on.

5) **12NADPH** molecules are **produced per cycle (per1glucosemolecule)**.

Note :if we simplify the equation below we conclude that 12 NADPH molecules are produced per 1 Glucose molecule.

$$6\text{Glucose}-6-\text{P} + 12\text{NADP}^{+} \longrightarrow 5\text{Glucose}-6-\text{P} + 6\text{CO}_2 + 12\text{NADPH}$$

- If the cell requires only NADPH the whole cycle will be active meaning that we will get NADPH from the oxidative phase and then convert Ribulose-5-phosphate molecules result from this phase into Glucose-6-phosphate again
- If the cell requires pentoses only (Ribose for example for DNA production) the reversable conversion of Glucose-6-phospate to Ribulose-6-phosphate will be active

❖ **NADH vs NADPH**

✓ Enzymes can specifically use one NOT the other.

✓ NADPH and NADH have different roles.

✓ NADPH exists mainly in the reduced form (NADPH). Why? It is needed for biosynthesis not producing energy.

✓ NADH exists mainly in the oxidized form(NAD^+). Why? To keep glycolysis going on.

✓ In the cytosol of hepatocyte

- $NADP^+/NADPH \approx 1/10$
- $NAD^+/NADH \approx 1000/1$

Uses of NADPH

1. Reductive Biosynthesis:

To reduce a substance that is **more oxidized** into another that is **more reduced** during biosynthesis. This reaction requires a high energy reducing substance (e^- donor), and the man for the job here is **NADPH**.

(**NADH** can't be used for this job)

e.g. 8 CH_3COO (Acetate) $\rightarrow C_{15}H_{33}COO$ (the fatty acid palmitate)

Highest percentage of NADPH in the cell is present in the reduced form (NADPH), so it can do the job of reducing other substances by getting oxidized.

$\rightarrow$ notice that the end product is more reduced (it contains less oxygen), so in this kind of synthesis we use a mechanism that reduces the monomers into the required macromolecule, NADPH is needed to accomplish that.

2. Reduction of H_2O_2:

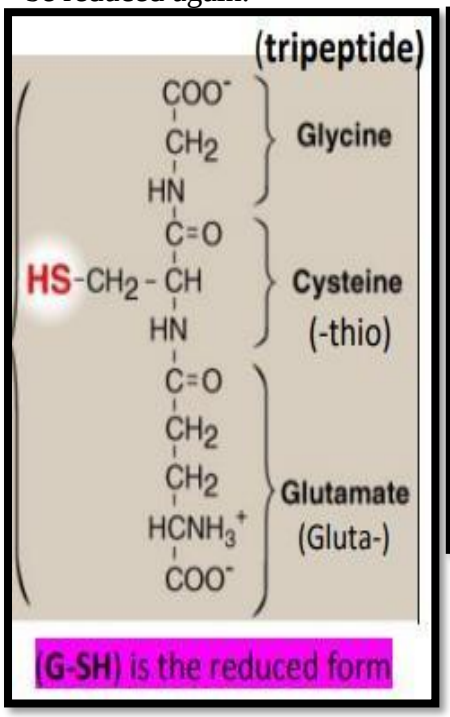
Substances such as H_2O_2 are formed continuously during metabolism, whether **accidentally** as **byproducts**, or **purposefully** to carry out certain functions. (still, they are harmful to the components of the cell, by **oxidizing** them)

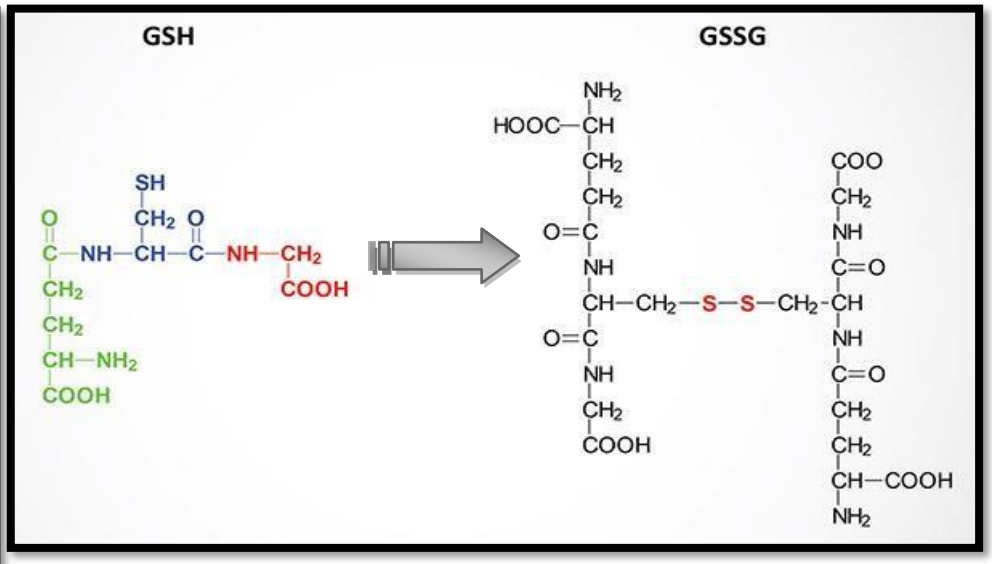
- To fix that we have Enzymes that catalyze antioxidation:
- First, Glutathione peroxidase:
- Glutathione is antioxidant

- H2O2 belongs to a group of substances called Reactive Oxygen Species.
  Other members include:(˙OH, ❖O2●-)
- they can cause chemical damage to proteins, lipids and DNA which may lead to cancer, inflammatory diseases and ultimately cell death
- they Interact with drugs and are environmental toxins.

The antioxidant effect:

It gets **oxidized** by **H2O2** into **GS-SG (** two glutathione molecules are joined by a disulfide bond) which in turn **becomes H_2O**, losing its damaging effect. **Reduced** form of glutathione can reduce **H_2O_2** into **H_2O**, but the oxidized form cannot, that's why we need glutathione to be reduced again.



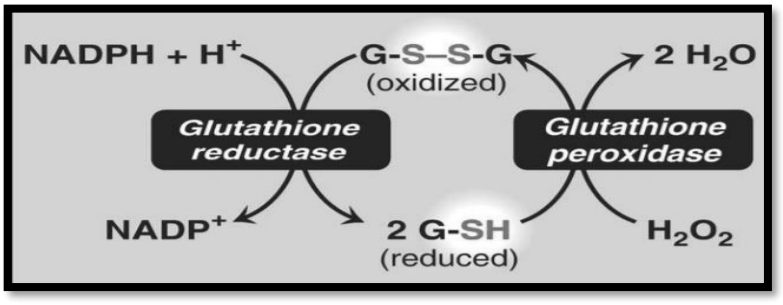


-peptide bond between glu and cys is formed through the side chain, The carboxyl group of glutamate backbone is not involved in the peptide bond as usual

To reduce glutathione again, an enzyme called Glutathione reductase (reductase uses NADPH. We look at it only in the reduction direction, unlike dehydrogenases) reduces it back to it reduces form that can be act as antioxidant.

form that can act as antioxidant.

***Note**: enzymes that utilize NAD are called dehydrogenases*.



- This enzyme **requires selenium** which is an essential trace element required in little amounts to supply this reaction (This is the only reaction in our body that requires selenium) .

Glucose-6-phosphate dehydrogenase deficiency

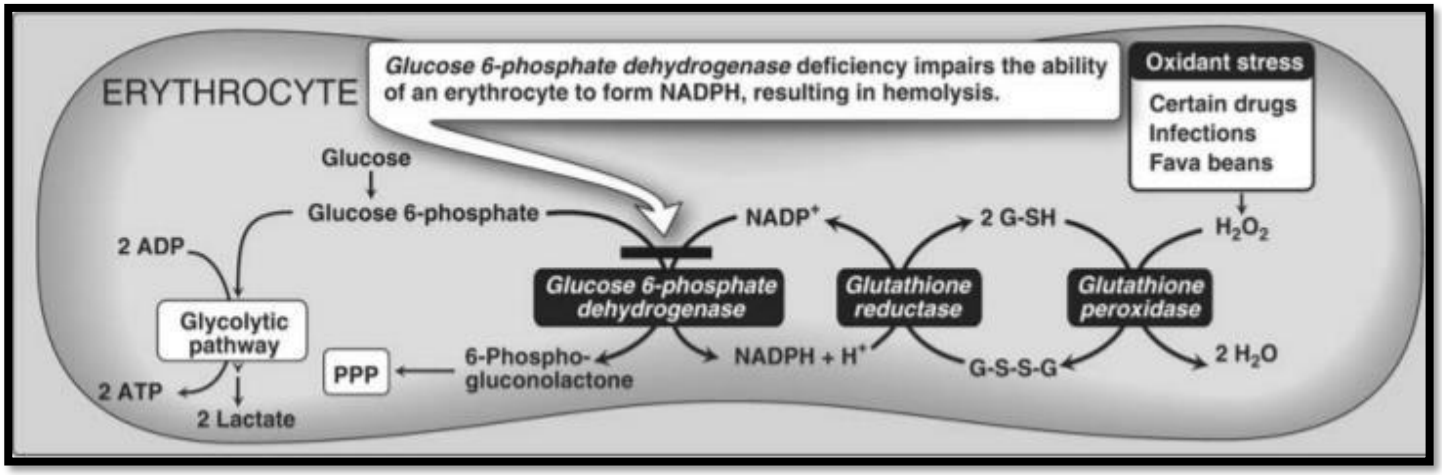
- **Common** disease
- characterized by **hemolytic anemia**
- affects **200 – 400 million individuals** worldwide
- Highest prevalence in **Middle East**, **S.E. Asia**, **Mediterranean**, common in our region.
- **X-linked** inheritance affects **males more** *because they have only one X chromosome*.
- > 400 different mutations, which means it has **many types**.
- advantage: Deficiency provides **resistance to falciparum malaria.**

'Some period of the malaria's parasite's life occurs in RBCs. If red blood cells don't live for a long period of time, malaria can't continue its life cycle, that's why people with G6PD deficiency can survive it better. maybe that's why there's an abundant deficiency in our region, to survive malaria better'

- This disease **can be lived with (compatible with life)**, unless patient faces **oxidative stress** (many free radicals)

- **Elaboration**: RBCs are the most affected, because**:**

1. **the only source of NADPH** in RBCs is **PPP** which utilizes **G6PD**.
2. Since **RBCs are semi-dead** cells (no nucleus, ribosomes, etc.) they **can't compensate** by synthesizing more of the enzyme (There are no requirement of protein synthesis, unlike other cells.



$$H_2O_2 + GSH \longrightarrow G\text{-}S\text{-}S\text{-}G + 2H_2O$$
$$G\text{-}S\text{-}S\text{-}G + NADPH \longrightarrow 2GSH + NADP+$$

We said that deficiency leads to hemolysis, How? Since this deficiency causes inability to synthesize NADPH, reduction of GSSG back is not able

Remember: **glutathione** helps in preventing the -SH groups in proteins from being oxidized into unwanted forms (joined by unwanted disulfide bonds).

• A **decrease in the amount of reduced glutathione** leads to <u>oxidation of these proteins</u> →which leads to their denaturation.

- If these **proteins** are **in the membrane**, it affects flexibility of the cell (causes **rigidity in cell membrane**), thus cells **can't go through the capillaries** and they would be removed by *reticuloendothelial systems*. **life span of RBCs will be reduced to less than 120 days.**

- Person with deficiency can be normal until exposed to **precipitating factors** that can cause the hemolysis. So they might not suffer from hemolysis everyday (only upon exposure to some drugs, or eating some types food)

<u>Examples:</u>

Person with deficiency can be normal until exposed to **precipitating factors** that can cause the hemolysis. So they might not suffer from hemolysis everyday (only upon exposure to some drugs, or eating some types food)

- **Oxidant drugs** (can increase the amount of ROS)

– Antibiotics e.g. Sulfamethoxazole
– Antimalaria e.g. Primaquine
– Antipyretics e.g. Acetanilide (not used any longer)

- ***Favism*** فوال: أنيميا تناول الفول *Ingestion of fava beans, can increase oxidative stress → leads to hemolysis*
- **Infection** can lead to ROS production.
- **Neonatal Jaundice**

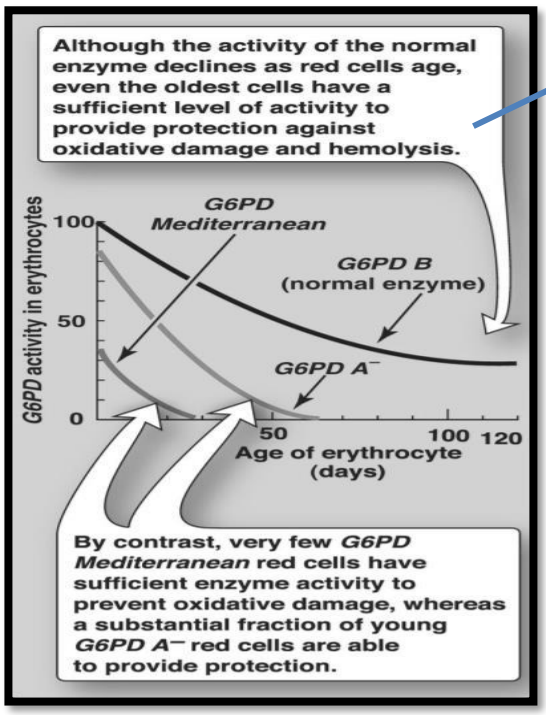
Class	Clinical symptoms	Residual enzyme activity
I	Very severe	<2%
II	Severe	<10%
III	Moderate	10–50%
IV	None	> 60%

Increasing severity ↑

- G6PD Deficiency Variants:

- Wild type B → normal allele, normal enzyme activity.
- Mediterranean Variant B (Class II): 563 C (cytosine)→T (Thymine) - (mutation)
- African Variant A (Class III); two point mutations
- African Variant A; Normal activity 80%
- Very severe deficiency (Class I) {notice red box}
- Majority of mutations are missense point mutations. Like replacement of one N base by another (e.g. C→T in class II)
- Large deletions or frame shift mutations are Not Observed; simply because they're not compatible with life, people can't survive them to be recorded as cases.

NOTE: In all of these cases, the enzyme isn't absent. It's present but it could be less stable, having lower affinity, or achieving lower vMax (less active).



As the **severity** of the case increases, the **life span** of cells decreases. Also, **enzyme's activity is reduced, it declines rapidly with time,** because of decreased stability with time.

If someone is exposed to hemolysis it'll be self-limiting, because **older RBCs will be affected**. However, the **newly synthesized ones** won't be affected by the precipitating factor when their age is still a few days. **So, there's no need for continuous blood replacement.**
Conclusion: It'll be limited with time because it affects only aged RBCs.

Antioxidant reactions' Enzymes

- **superoxide dismutase**: $O2.^-$ is a very strong oxidizing agent. This is fixed by **turning it into H2O2**, which is less vicious. Then **H2O2** is **turned into H2O** by the enzyme **catalase**.

- **chemicals**: such as vitamins, **E (tocopherol)** and **C (ascorbic acid)**, and **Carotenoids** (e.g. alpha carotene, beta carotene). **E is stronger than C** because E's reduced form can't be regenerated once it's oxidized. These were proved to protect against some diseases like cancer, vascular diseases. However, *ingestion of these chemicals in a purified form wasn't proved to fix anything.*

Super oxide dismutase (SOD)

$$2O_2^{\bullet -} + 2H^+ \longrightarrow O_2 + H_2O_2$$

Catalase

$$2H_2O_2 \longrightarrow O_2 + 2H_2O$$

Sources of ROS

- **Oxidases: major producers of H2O2, they're found in compartments of the cell that also contain antioxidant enzymes.**

- **2.oxygenases: monooxygenases (hydroxylases) add a hydroxyl group to their substrate.**

- **dioxygenases in synthesis of prostaglandins, thromboxane, leukotrienes (they get oxidized by it)**

- **CoQ in respiratory chain can accidentally produce reactive oxygen species.**

- **purposefully, during phagocytosis known as respiratory burst. (Res. Burst: rapid production of so many $O2^-$, H2O2 , $OH^{\bullet}$, NO,HOCl)**

- **Ionizing Radiation would form OH•**

Cytochrome p450

- **is an example of monooxygenases: Monooxygenases are known as mixed function enzymes: mono- because they only use one oxygen atom to be added to the substrate. mixed function because the other oxygen would be used to oxidize NADPH.**

$$R\text{-}H + O_2 + NADPH + H^+ \rightarrow R\text{-}OH + H_2O + NADP^+$$

(Notice how the substrate got hydroxylated and NADPH was oxidized)

- **Advantage of adding OH is to make the substrate more soluble (mostly for excretion and stabilization) and detoxicated. (hydroxylation can transform substances from active → inactive or the opposite)**

Sometimes, OH is added to make addition of glucuronic acid possible, which in turn makes the substance more soluble.

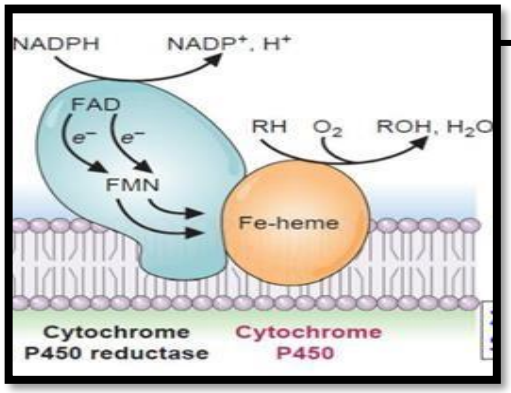
- **There are two systems that contain the monooxygenase:**
- **the mitochondrial system, for Hydroxylation of steroids, bile acids, active form of Vit. D.**
- **the microsomal system for**:

1. **detoxification of substances (First step of detoxification occurs by adding the OH group) e.g. pesticides.**
2. **activation or inactivation of Drugs.**
3. **solubilization**

The action of Cytochrome P450

- (450 → wave length where absorption of light is maximized)

Presenting hydroxyl group to substrate



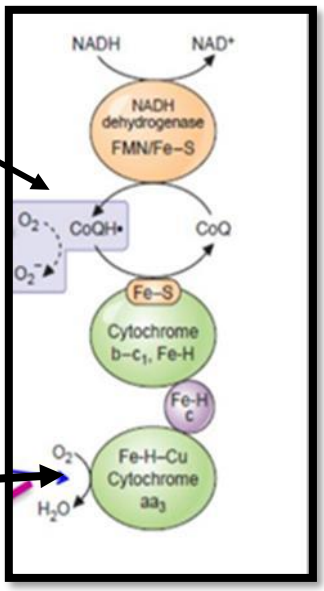
It's complexed with another enzyme called CyCh P450 reductase, to achieve certain things. Cytochrome contains a heme group, and to reduce this heme group we need reductase.

NADPH donates an electron through reductase to FAD, which gives - NADPH donates an e it to FMN which then gives it to the iron of heme (reducing it is then added to oxygen of hydroxyl -). The e 2+ to Fe 3+ from Fe group in the substrate, the other oxygen is reduced producing H2O.

Reaction: $O_2 + S + XH_2 \rightarrow H_2O + SOH + X$

XH2: electron donor ~ **S:** substrate ~ **SOH:** hydroxylated substrate ~ X: oxidized form of reducing substance

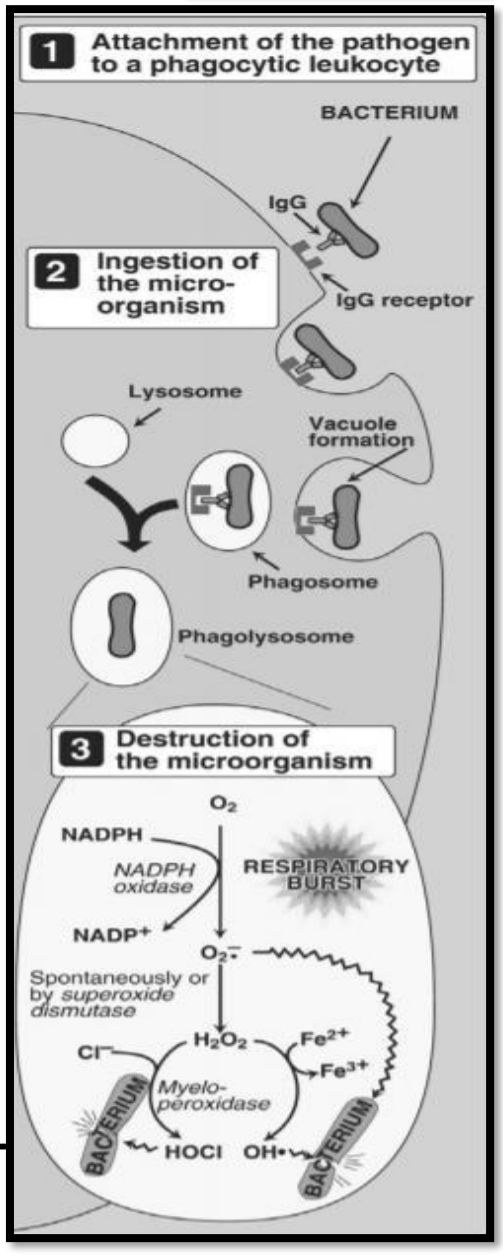
Generation of O2- by the respiratory chain of oxidative phosphorylation



- COQ can hold one or two electrons, if the reduced form of it donates one electron, it'll result in a partially reduced COQ formation. This partially reduced COQ may accidentally reduce oxygen into superoxide.
- 'It's a minor pathway but it occurs all the time, superoxide here is a byproduct'
- If superoxide is produced it has to be taken care of by superoxide dismutase, and catalase.

- However, in **cytochrome oxidase (complex IV)** that reacts with oxygen. superoxide and peroxide won't be formed because oxygen would be bound to copper and iron at the same time (binuclear center).

Phagocytosis



We know the mechanism by which leukocytes fight off Bacteria:

Pathogen recognized by IgG → Binds to a receptor

↓

Endocytosis → Destruction of pathogen

↓

which occur by two ways:

Oxygen independant: Lysomes activity along with many reaction by hydrolases and proteases that deredade it

Oxygen dependant: By super oxide. Oxygen is used to oxidize NADPH purposefully, losing the electron from NADPH to the oxygen will produce superoxide. which spontaneously or by dismutase yields hydrogen peroxide, these both can kill the bacteria. rispiratory burst can occurs here

- There's an enzyme called **myeloperoxidase**, which **adds chloride to H2O2 forming OCl^- (**hypochlorite). It's very active against bacteria and is present in bleach

If Nitrogen is added we have what's called Reactive Nitrogen Oxygen Species, these are also free radicals.

NO:

•A Free radical that diffuses readily

• Essential for life, but can be toxic easily

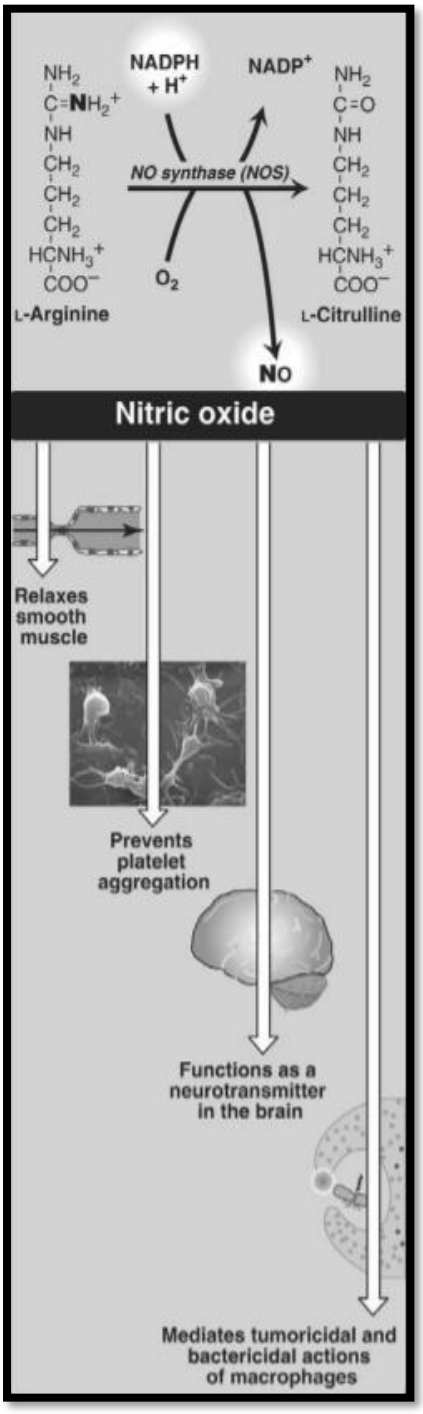
• Works as Neurotransmitter, vasodilator

• NO decreases Platelet aggregation or O2 to form RNOS that can kill

• At high concentration NO combines with O2● or O2 to form RNOS that can kill bacteria

• RNOS are involved in neurodegenerative diseases and inflammatory diseases

NO synthesis



It's derived from arginine with NADPH which causes oxidation of nitrogen to produce NO. The amino acid after losing this NH2 turns into L-citrulline, which is not found in proteins.

Through an enzyme called NO synthase:

has three isoforms:

nNOS neural and eNOS endothelial → both constitutive, meaning their levels remain the same, not increased by signals.

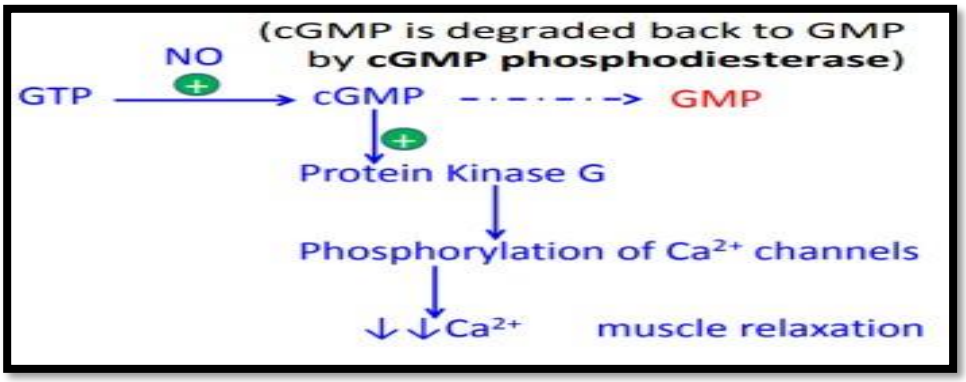
iNOS → this isoform is inducible in immune cells. Its induction leads to production of more RNOS to kill invading bacteria.

Action of NO in vascular endothelium:

NO synthesized in endothelial cells defuses into smooth muscle cells causing relaxation in blood vessels.

How does it act?

NO Converts GTP into cGMP, which stimulates protein kinase G → phosphorylates calcium channels → causes a decrease in calcium level, which leads to muscle relaxation.



- Inhibition of cGMP phosphodiesterase and up regulation (activation) of this mechanism can be done by Viagra, for sexual dysfunction. How does it act? It inhibits the phosphodiesterase leading to cGMP elevation and for muscle relaxation. same drug was used for treating pulmonary hyper tension, it causes relaxation of the pulmonary artery leading to a decrease in the pressure in the pulmonary artery.

دعاء لوالدتنا أم جعفر الزبن
اللهم ارحمها واغفر لها وعافها واعف عنها اللهم اجعلها في عليين واجعلها من ورثة جنة النعيم اللهم احشرها مع الانبياء والصديقين والشهداء اللهم اظلها بظلك يوم لا ظل الا ظلك اللهم امنها يوم الفزع الاكبر اللهم اتها كتابها باليمين واسقها شربة هنيئة لا تظمأ بعدها أبدا من يد سيدنا محمد صل الله عليه وسلم اللهم تجاوز عن سيئاتها وبارك لها في حسناتها اللهم جازها بالاحسان احسانا وبالسيئات عفوا وغفرانا اللهم في القبر آنس وحشتها ونور ظلمتها وفرج كربتها واعف اللهم عن زلتها اللهم ادخلها الجنة بلا مناقشة حساب ولا سابقة عذاب يا رب العالمين
اللهم امين يا رب العالمين

Recommended Videos:

Pentose phosphate pathway-osmosis:
https://mega.nz/folder/R10W2AZY#uFriNGuRrc3Bgl5jhgBRjA/file/pkEzDAiL

pentose phosphate pathway:
https://youtu.be/kBfuDwzSE70

pentose phosphate pathway-Lecturio:

Introduction:
https://mega.nz/folder/R10W2AZY#uFriNGuRrc3Bgl5jhgBRjA/file/Z9tHSYJJ

Part 1:
https://mega.nz/folder/R10W2AZY#uFriNGuRrc3Bgl5jhgBRjA/file/YlkRgSAL

part 2:
https://mega.nz/folder/R10W2AZY#uFriNGuRrc3Bgl5jhgBRjA/file/kstRjIIQ

pentose phosphate pathway-Boards and Beyond:
https://mega.nz/folder/R10W2AZY#uFriNGuRrc3Bgl5jhgBRjA/file/t01WjTJY

Schemes:
https://drive.google.com/drive/folders/1zyygtNYNHI7G5oJtfUTuYWitJ88cH0rM?usp=sharing

summary-Osmosis:
https://drive.google.com/file/d/1sEiuwirj-36kKkKC27PkSouRnOEF4xC4/view?usp=sharing

Questions:

1. NADPH is used by most cells as
   a) A substrate for the electron transport chain
   b) To produce ribose-5-P from glyceraldehyde-3-P and fructose-6-P
   c) A reducing agent in detoxification reactions
   d) An oxidizing agent in reductive biosynthesis
   e) A substrate for transketolase reactions

   Answer: C

2. All of the following enzymes and metabolites are found in the pathway for the reduction of HOOH except
   a) 6-phosphogluconate dehydrogenase
   b) $NADH + H^+$
   c) Glutathione reductase
   d) Reduced glutathione
   e) Glutathione peroxidase

   Answer: B

3. Which of the following statements is correct about oxidative pentose phosphate pathway
   a) It generates NADH
   b) It oxidizes NADPH to $NADP^+$
   c) The pathway supplies ribose 5-phosphate and NADPH in the quantities the cell requires
   d) Glucose 6-phosphatase catalyzes the rate limiting reaction of the pathway

   Answer: C

4. Which one out of the following enzymes acts in the pentose phosphate pathway?
   a) Aldolase
   b) Glycogen phosphorylase
   c) Pyruvate kinase
   d) 6-phosphogluconate dehydrogenase

   Answer: D

5. Oxidation of 3 molecules of glucose by pentose phosphate pathway results in the production of
   a) 3 molecules of pentose, 6 molecules of NADPH and 3 molecules of CO_2
   b) 4 molecules of pentose, 6 molecules of NADPH and 3 molecules of CO_2
   c) 4 molecules of pentose, 3 molecules of NADPH and 3 molecules of CO_2
   d) 3 molecules of pentose, 4 molecules of NADPH and 3 molecules of CO_2

   Answer: A

6. Which of the following statements is correct about the reductive pentose phosphate pathway?
   a) It is not reversible
   b) Transketolase transfers 3 carbon units
   c) Transaldose transfers 2 carbon units
   d) Pentoses can provide glycolytic intermediates

   Answer: D

7. Conversion of xylulose 5-phosphate to ribulose 5-phosphate is catalyzed by
   a) Phospho-pentose epimerase
   b) Transaldolase
   c) Transketolase
   d) Phospho-pentose isomerase

   Answer: A

8. A 19-year-old, African-American male military recruit is about to be sent to Iraq on his assignment. In preparation for his tour of duty. He is given a prophylactic dose of primaquine to prevent malaria. Several days after he develops fatigue and hemolytic anemia which of the following enzymes is likely deficient?

   a) Transketolase
   b) Transaldolase
   c) Glutathione reductase
   d) Glucose-6-phosphate dehydrogenase

   Answer: D

9. Which of the following statement about the nonoxidative phase of pentose phosphate pathway is correct

   a) The nonoxidative reactions of the pentose phosphate pathway not reversible
   b) Transketolase is an enzyme that transfer 3-C units in the pentose phosphate pathway
   c) Transaldolasse is an enzyme that transfer 2-C units in the pentose phosphate pathway
   d) Pentoses can provide glycolytic intermediates in this phase of GMP pathway
   e) Pentoses can be metabolized to provide NADPH in this phase of HMP pathway

   Answer: D

10.all of the following produces ROS except :-

a) CoQ in normal respiratory chain
b) oxidases
c) ionizing radiation
d) respiratory burst
e) lactic acid formation

Answer: E

11.something wrong about pentose phosphate pathway (PPP)

a) necessary for synthesis of steroid hormones in testis and ovaries
b) produce intermediates of glycolysis
c) NADPH inhibits it
d) produces NADPH in the reversal pathway

Answer: D

12.The goal of Pentose Phosphate Pathway is:

a) Generation of NADPH + pentose
b) Generation of ATP
c) Generation of NADH
d) Generation of new glucose

Answer: A