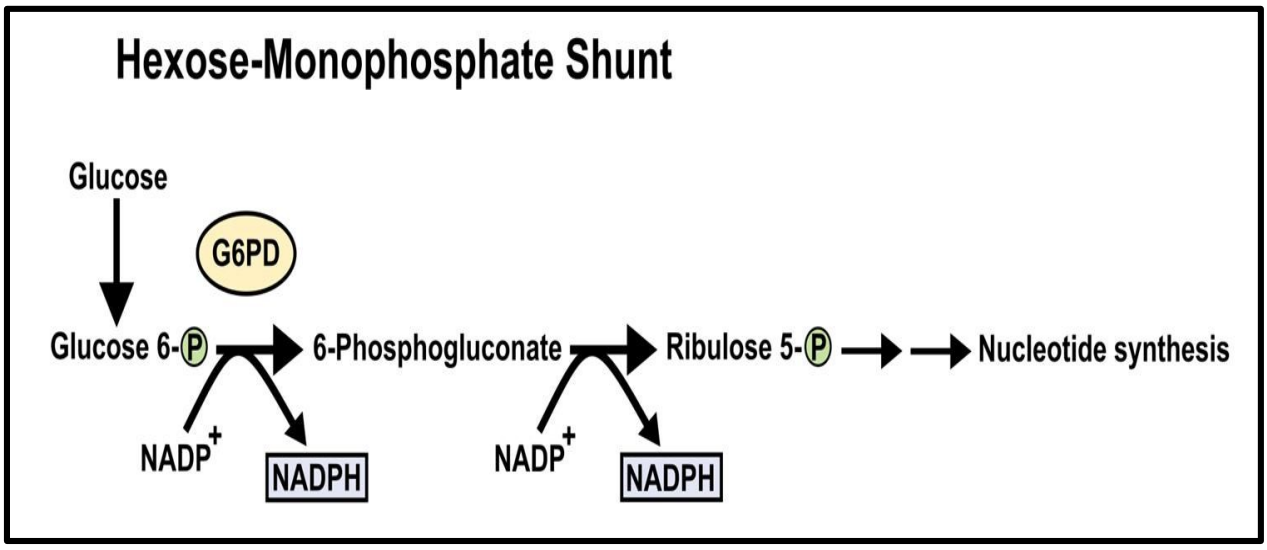
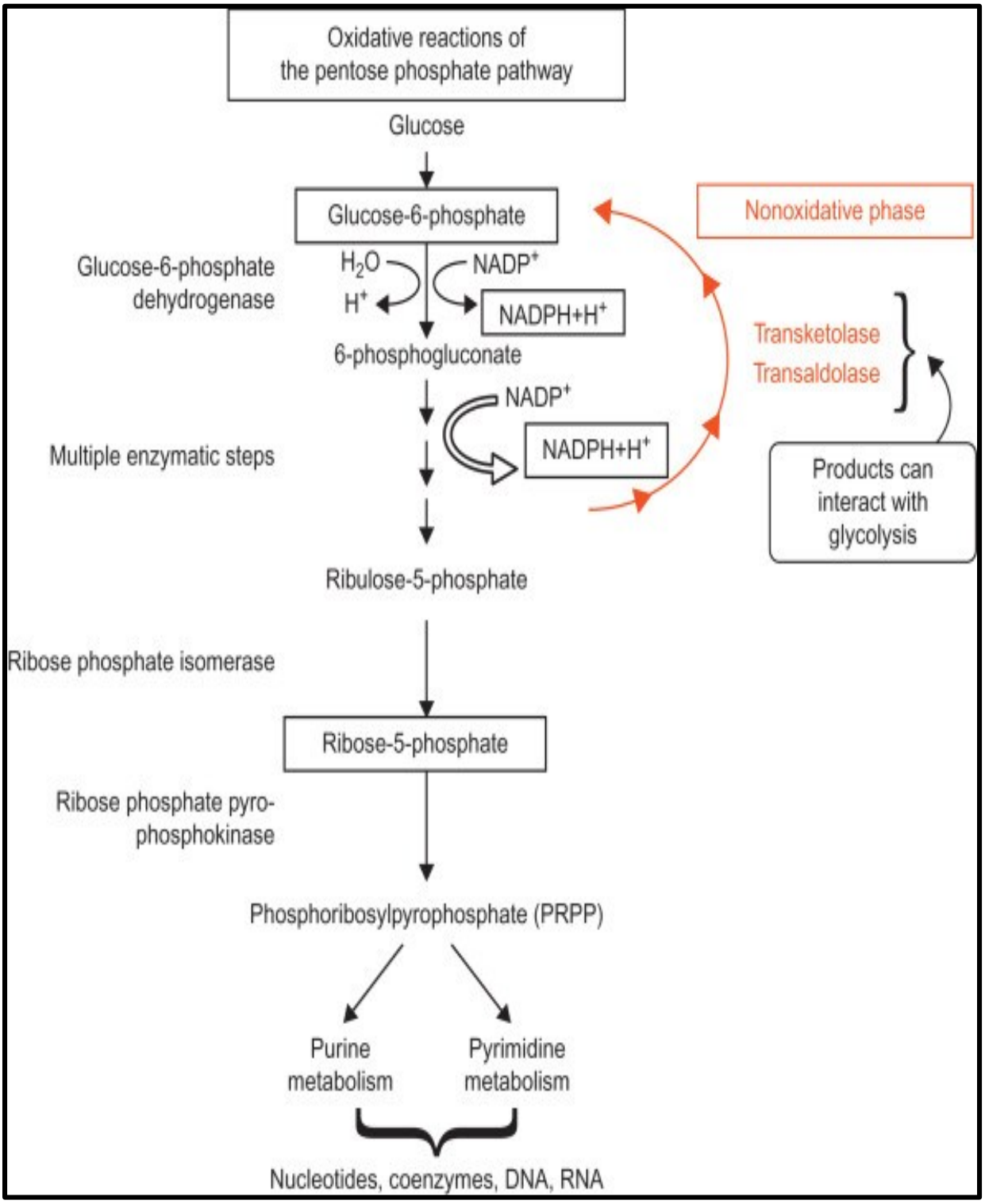
Hexose Monophosphate Shunt

(HMP)

The hexose monophosphate shunt, also known as the pentose phosphate pathway, is a unique pathway used to create products essential in the body for many reasons. The HMP shunt is **an alternative pathway to glycolysis and is used to produce ribose-5-phosphate and nicotinamide adenine dinucleotide phosphate (NADPH)**




Oxidative reactions of the pentose phosphate pathway
Glucose
Glucose-6-phosphate
Nonoxidative phase
Glucose-6-phosphate dehydrogenase
H_2O
H^+
$NADP^+$
$NADPH+H^+$
6-phosphogluconate
Transketolase
Transaldolase
$NADP^+$
Multiple enzymatic steps
$NADPH+H^+$
Products can interact with glycolysis
Ribulose-5-phosphate
Ribose phosphate isomerase
Ribose-5-phosphate
Ribose phosphate pyro-phosphokinase
Phosphoribosylpyrophosphate (PRPP)
Purine metabolism
Pyrimidine metabolism
Nucleotides, coenzymes, DNA, RNA

Properties of HMP shunt

♣ It is occurs in cytosol

♣It is oxidation of glucose, but it is not meant for energy.

♣ Provides NADPH which is required for various reductive synthesis in metabolic pathways.

♣ Provides pentoses required for nucleic acid synthesis.

Major differences with EM pathway

1- This pathway occurs in certain specialized tissues only to serve specific functions. e.g. liver, adipose tissue, RB cells, tests and ovary, adrenal cortex. It is unimportant for skeletal muscle.

2- It is a multicyclic process, 3 molecules of G-6-P enter the cycle, producing 3 mols of CO_2 and 3 mols of 5-C residues, which rearrange to give 2 mols of G-6-P and one mol of glyceraldehyde-3-P.

$$3 \text{ glucose -6-P} + 6NADP^+ \longrightarrow 3CO_2\uparrow + 2 \text{ fructose-6-p} + \text{glyceraldehyde- 3-p} + 6 NADPH + 6H^+$$

3- Oxidation is achieved by dehydrogenation, but $NADP^+$ is used as hydrogen acceptor and not NAD^+.

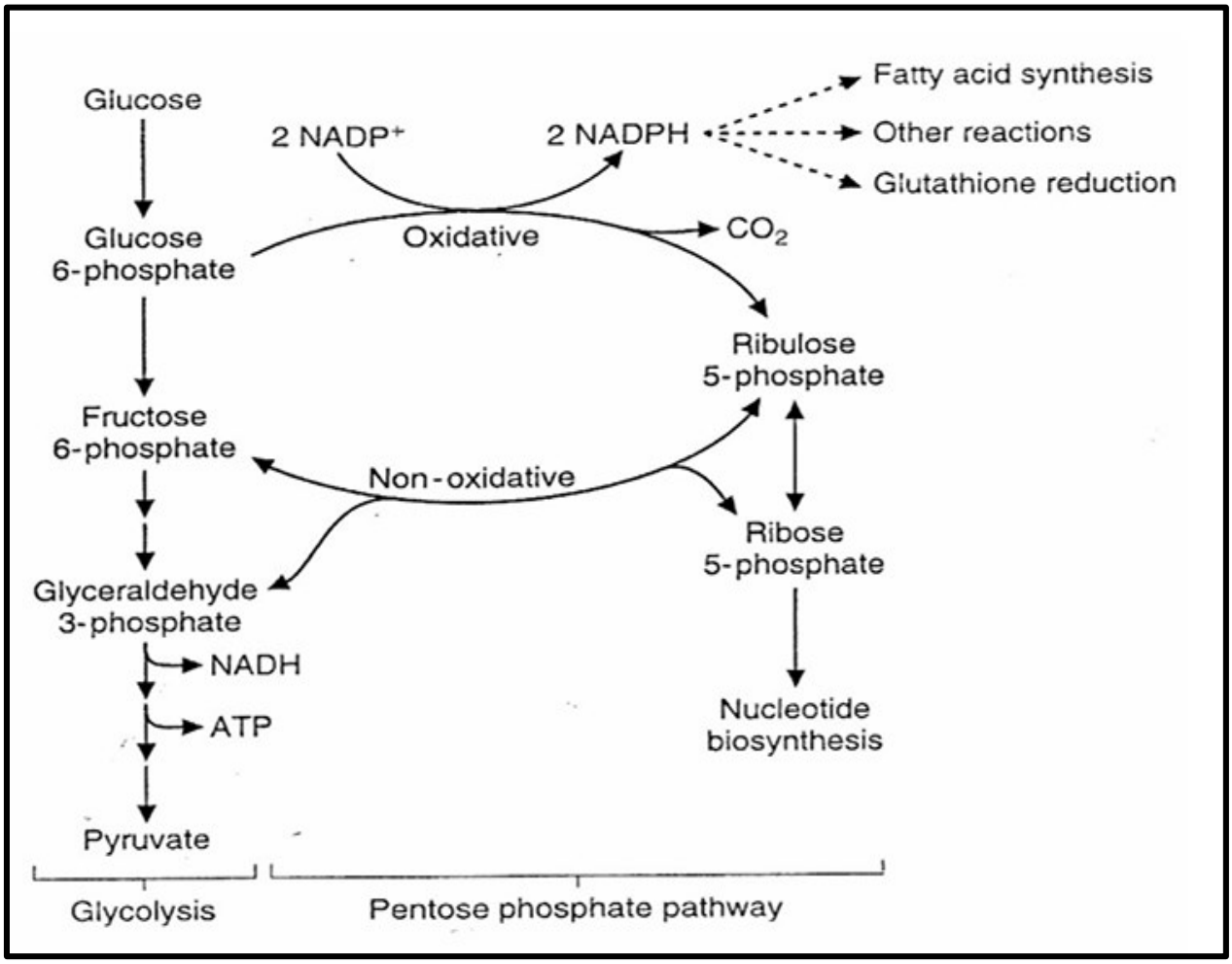
4- CO_2 is produced in this pathway which is never produced in glycolysis pathway.

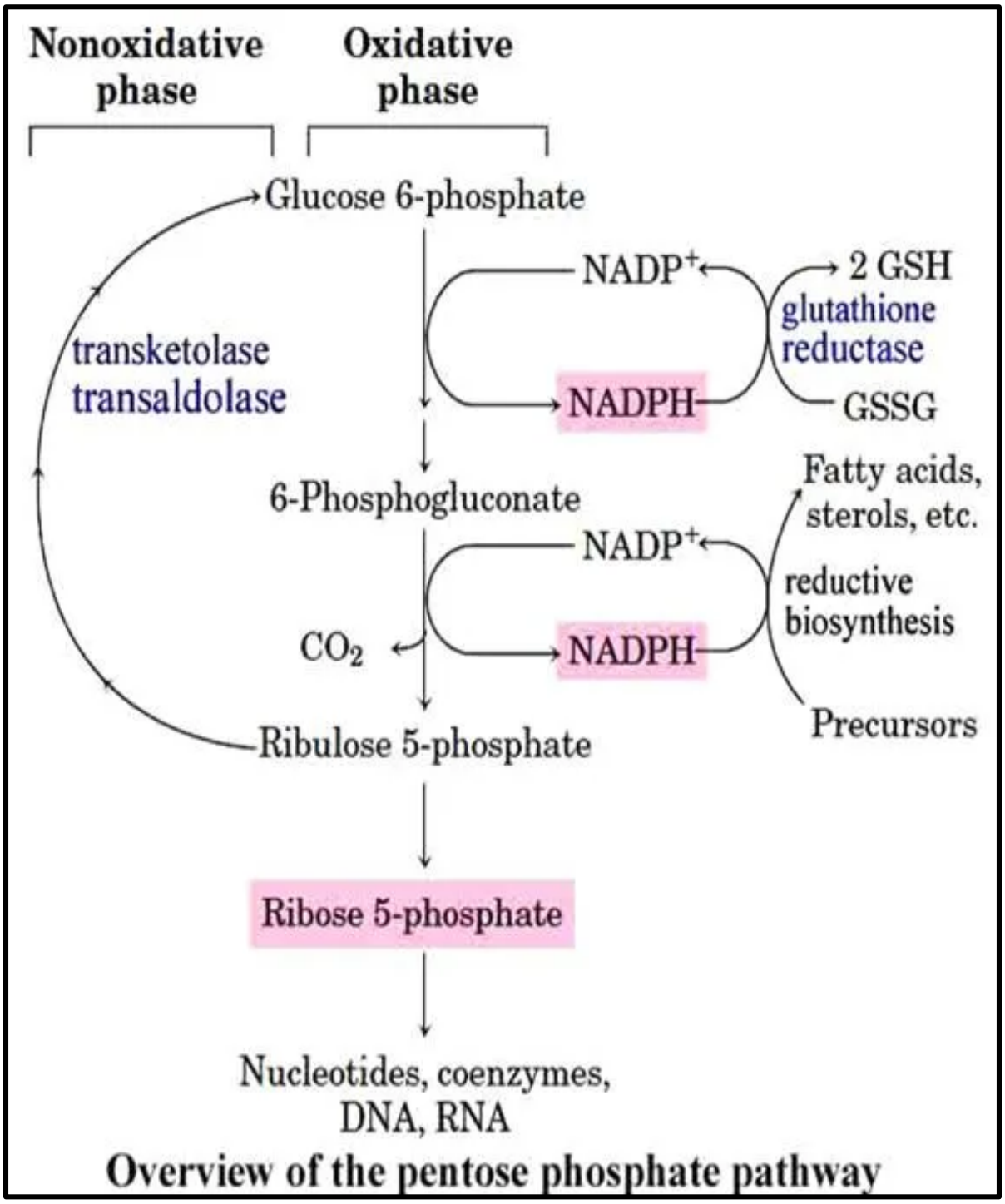
Similarity: The only similarity is that enzymes are extra mitochondrial (Cytosolic) and it operates in cytosol.

Reactions of the HMP shunt

1- The oxidative reactions (or oxidative phase) Oxidation of glucose and formation of pentose phosphate. **The oxidative phase has irreversible reactions.**

2-The non-oxidative reactions (non-oxidative phase) .**These reactions are reversible.**





Overview of the pentose phosphate pathway

Regulation of HMP shunt:

1) G-6-P D, the first reaction enzyme is the "rate-limiting" step. It is primarily regulated by cytoplasmic levels of $NADP^+$ and NADPH, thus the ratio of the two [$NADP^+$] / [NADPH]. If the cytoplasmic ratio is high (rise in $NADP^+$), enhances the "rate-limiting" reaction as well as the shunt pathway. A decrease in the ratio (rise in NADPH level), inhibits both G-6-PD and 6 phosphogluconate dehydrogenase by making less $NADP^+$ available for their catalytic reactions.

2) The activities of both dehydrogenases and the rate of the pathway are enhanced on feeding high Carbohydrate diets and are reduced in starvation and diabetes mellitus.

3) Increase in F.A. synthesis and steroid synthesis, enhances the shunt pathway.

4) Hormones:

• Insulin: induces the synthesis of both the dehydrogenases and thus enhances the activity of the pathway.

• Thyroid hormones: enhance the activity of G-6-PD and thus the shunt pathway.

Metabolic Significance of HMP shunt

1- Formation of NADPH: This is used as electron donor in many reductive synthesis in the body, like:

• Extra mitochondrial F.A. synthesis.

• In synthesis of cholesterol.

• In synthesis of steroids.

• **In conversion of oxidized glutathione G-S-S-G to reduced glutathione G-SH.**

• In synthesis of sphingolipids.

• Cytoplasmic synthesis of L-glutamate by L-glutamate dehydrogenase.

• Conversion of phenylalanine to tyrosine.

2- Provision of pentose's: for nucleotide and nucleic acid synthesis.

3- Supply of arabinose -5-P: used in glycoprotein.

4- Role in R.B. Cells Fragility: HMP shunt in erythrocytes provides NADPH for:

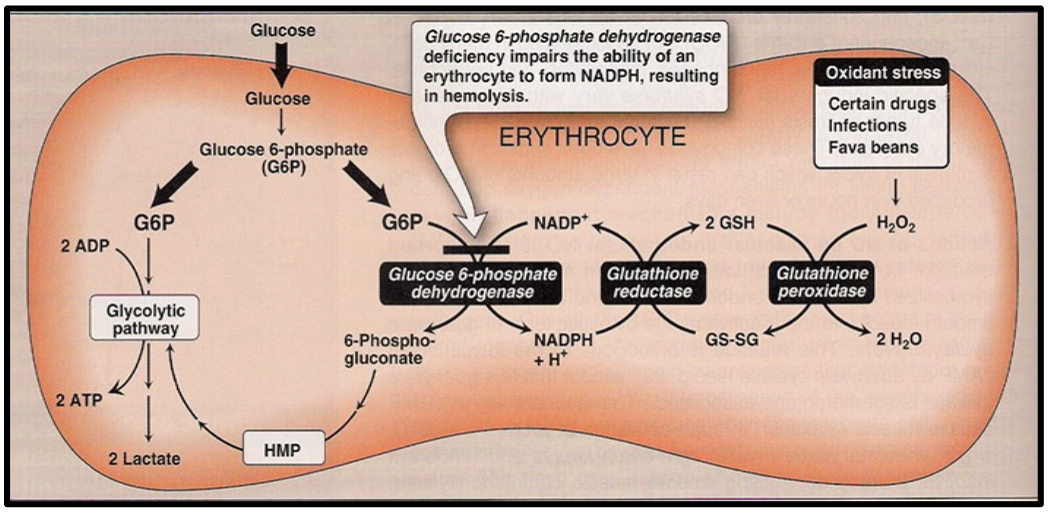
• Reduction of oxidized glutathione (G-S-S-G) to reduced glutathione (2G-SH) catalyzed by the enzyme glutathione reductase.

• Reduced glutathione (G-SH) removes H_2O_2 from the erythrocytes in a reaction catalyzed by glutathione peroxidase.

5- Oxidation of glucose and production of CO_2 and NADPH.

Glucose 6-P dehydrogenase deficiency diseases

It is an inherited disease characterized by hemolytic anemia, by the inability to detoxify oxidizing agents. This deficiency has the highest prevalence in the Middle East and tropical Africa. A family of deficiencies caused by more than 400 different mutations in the gene coding for G6PD. Only some of these mutations cause clinical symptoms. The life span of many individuals with G6PD deficiency is somewhat shortened as a result of complication arising from chronic hemolysis.



Diminished G6PD activity impairs the ability of the cell to form the NADPH that is essential for the maintenance of the reduced glutathione pool. These results in a decrease in the cellular detoxification of free radicals and peroxides formed within the cell. Although G6PD deficiency occurs in all cells of the affected individual, it is most severe in erythrocytes, where the pentose phosphate pathway provides the only means of generating NADPH. Other tissues have alternative sources for NADPH production.

However, some patients with G6PD deficiency develop hemolytic anemia if they are treated with:

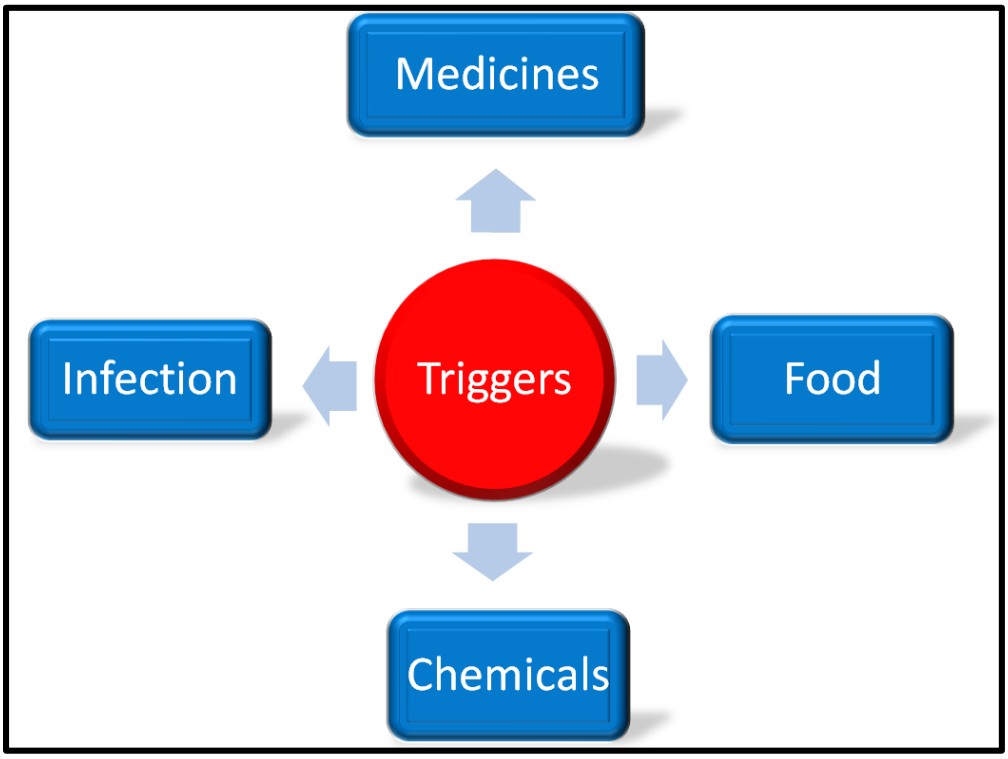
1- An oxidant drugs: Commonly used drugs that produce hemolytic anemia in patients with G6PD deficiency are: Antibiotics, Antimalarials, and Antipyretics

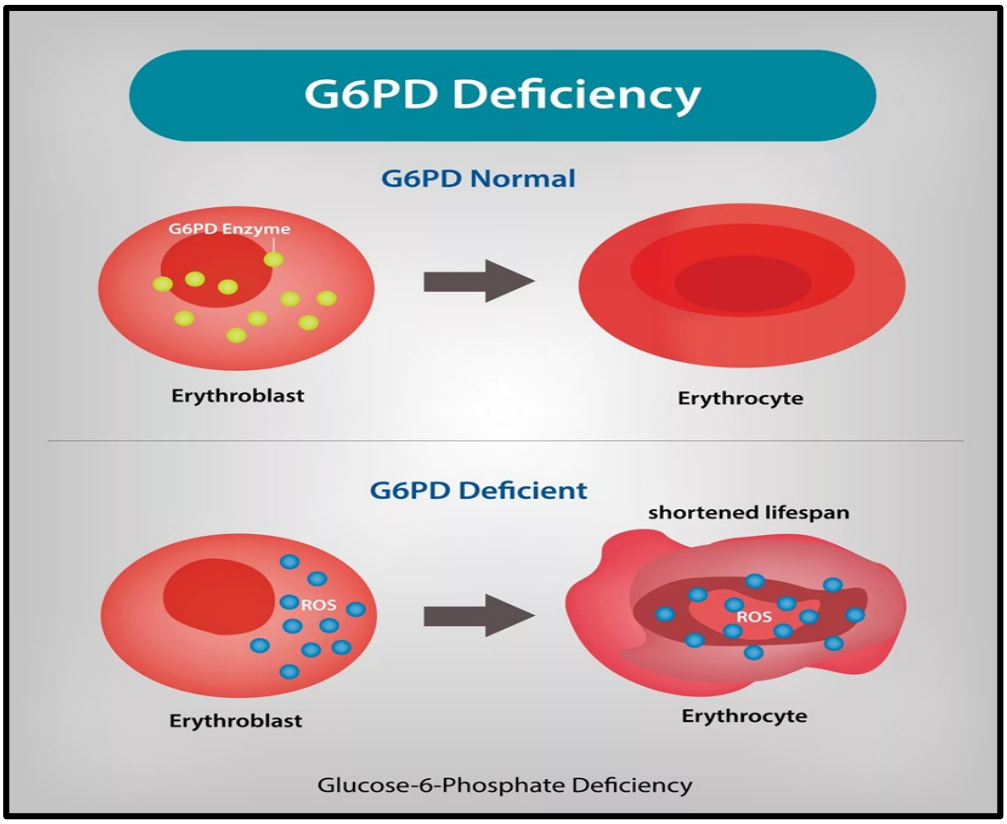
2- Favism: In G6PD deficient subjects, a disorder characterized by an acute hemolytic anemia of sudden onset, often with haemoglubinuria, occurs in persons' sensitive to the "Fava beans" either:

• on ingestion of uncooked or lightly cooked beans, or • In inhalation of pollens from the blossom of the plant. Favism, the hemolytic effect of ingesting fava beans, fava beans produce oxygen radicals which is going to attack RBC. Fauvism is not observed in all individuals with G6PD deficiency, but all patients with Favism have G6PD deficiency.

3- Infection: is the most common precipitating factor of hemolysis in G6PD deficiency. The inflammatory response to infection results in the generation of free radicals in macrophages, which can diffuse into the red blood cells and cause oxidative damage.

4- Neonatal Jaundice: Babies with G6PD deficiency may experience neonatal jaundice appearing one to four days after birth. The jaundice which may be sever, results from impaired hepatic catabolism of heme or increased production of bilirubin.


Medicines
Infection
Triggers
Food
Chemicals


G6PD Deficiency
G6PD Normal
G6PD Enzyme
Erythroblast
Erythrocyte
G6PD Deficient
shortened lifespan
ROS
ROS
Erythroblast
Erythrocyte
Glucose-6-Phosphate Deficiency