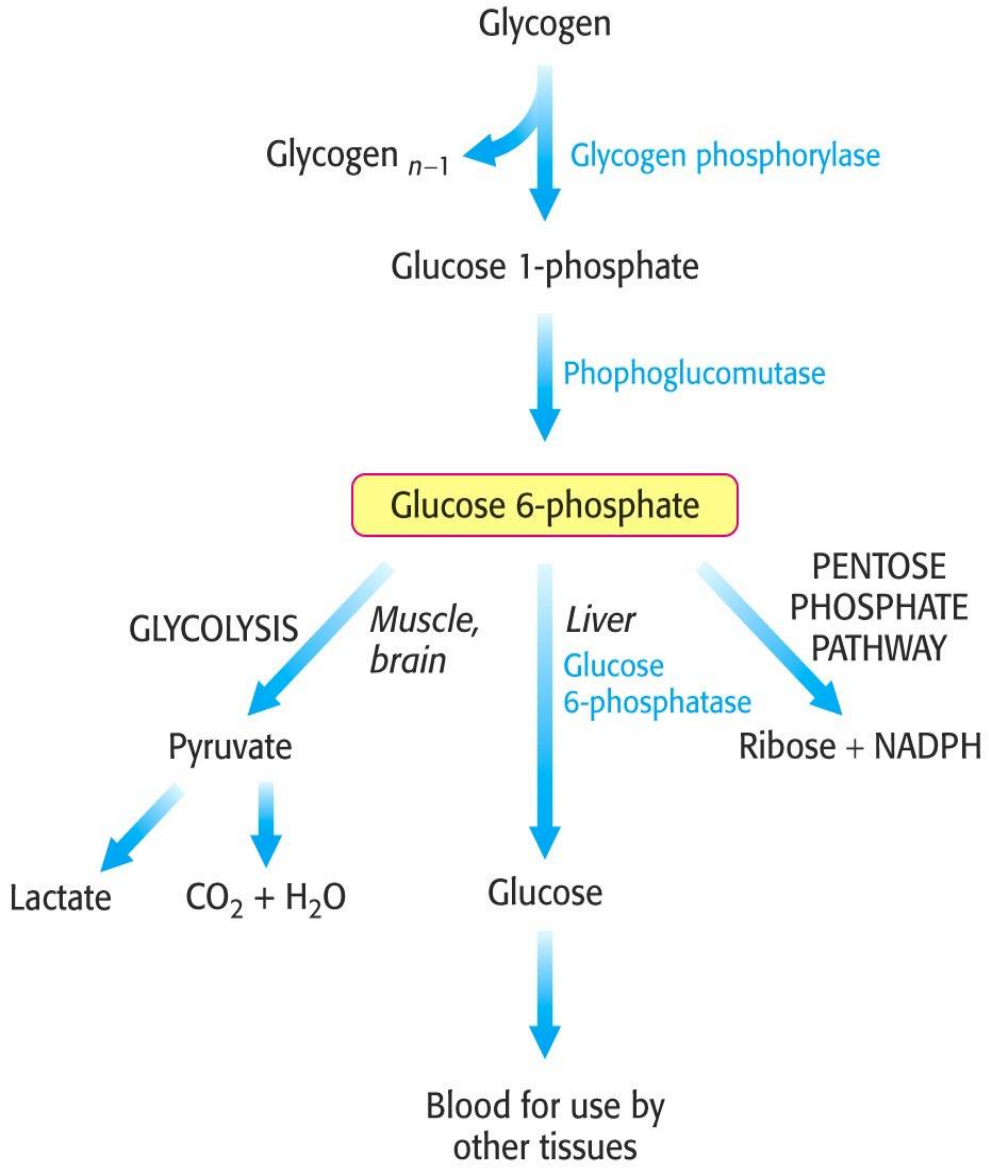
Hexose monophosphate shunt pathway

Dr Gulnaz

Pentose phosphate pathway

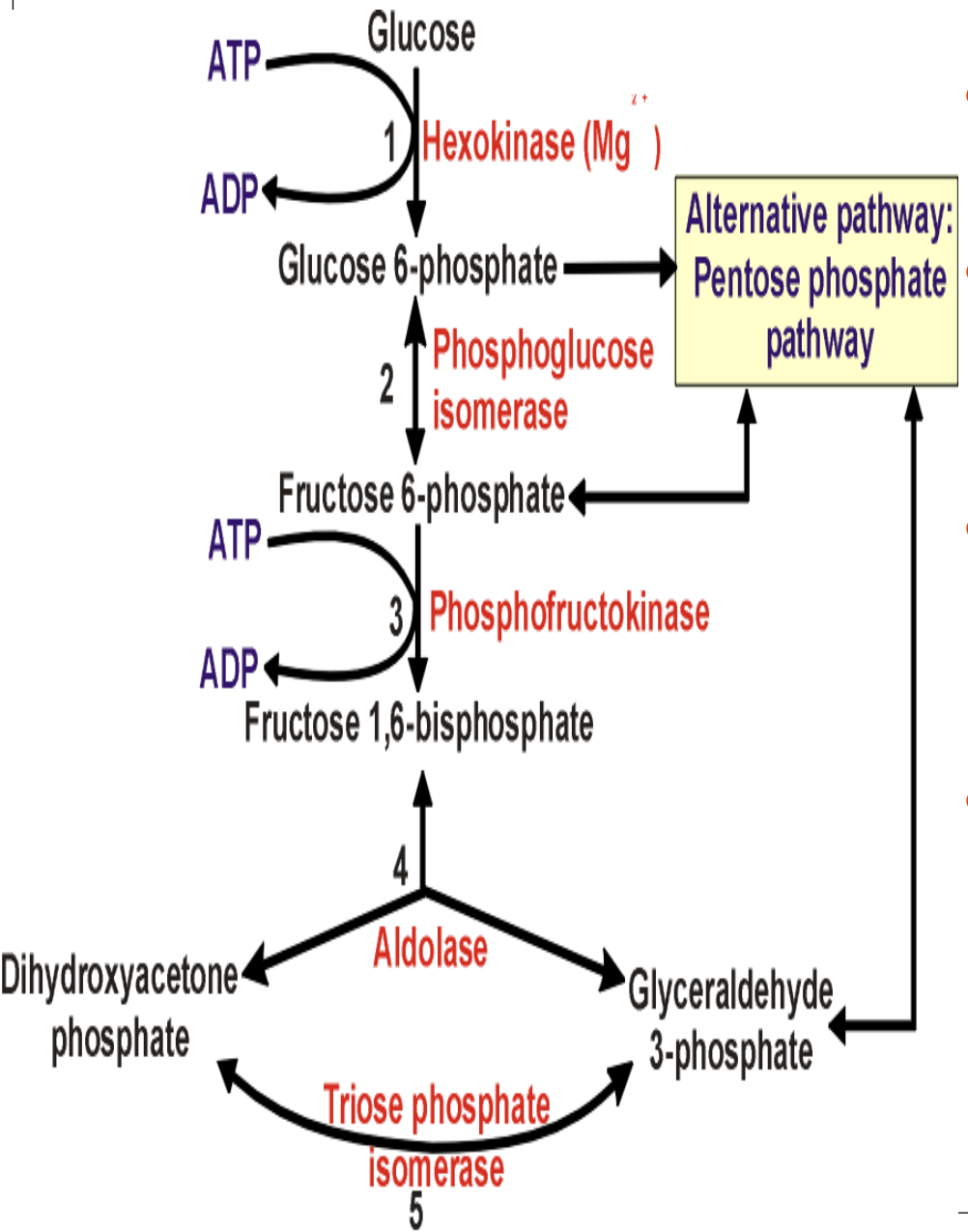


Also known as:

- Pentose shunt
- Hexose monophosphate shunt
- Phosphogluconate pathway

- It occurs in the cytosol.
- Tissue distribution:
- Liver ,adrenal gland,lactating mammary gland,gonads, adipose tissues, cornea and erythrocytes.

BIOMEDICAL IMPORTANCE



- It is an alternative route for glucose metabolism
- Does not lead to formation of ATP, but has two major functions
- 1) Formation of NADPH for synth of F.A & steroids
- 2) Synth of ribose for nucleotide and nucleic acid formation.

Rxns occur in CYTOSOL

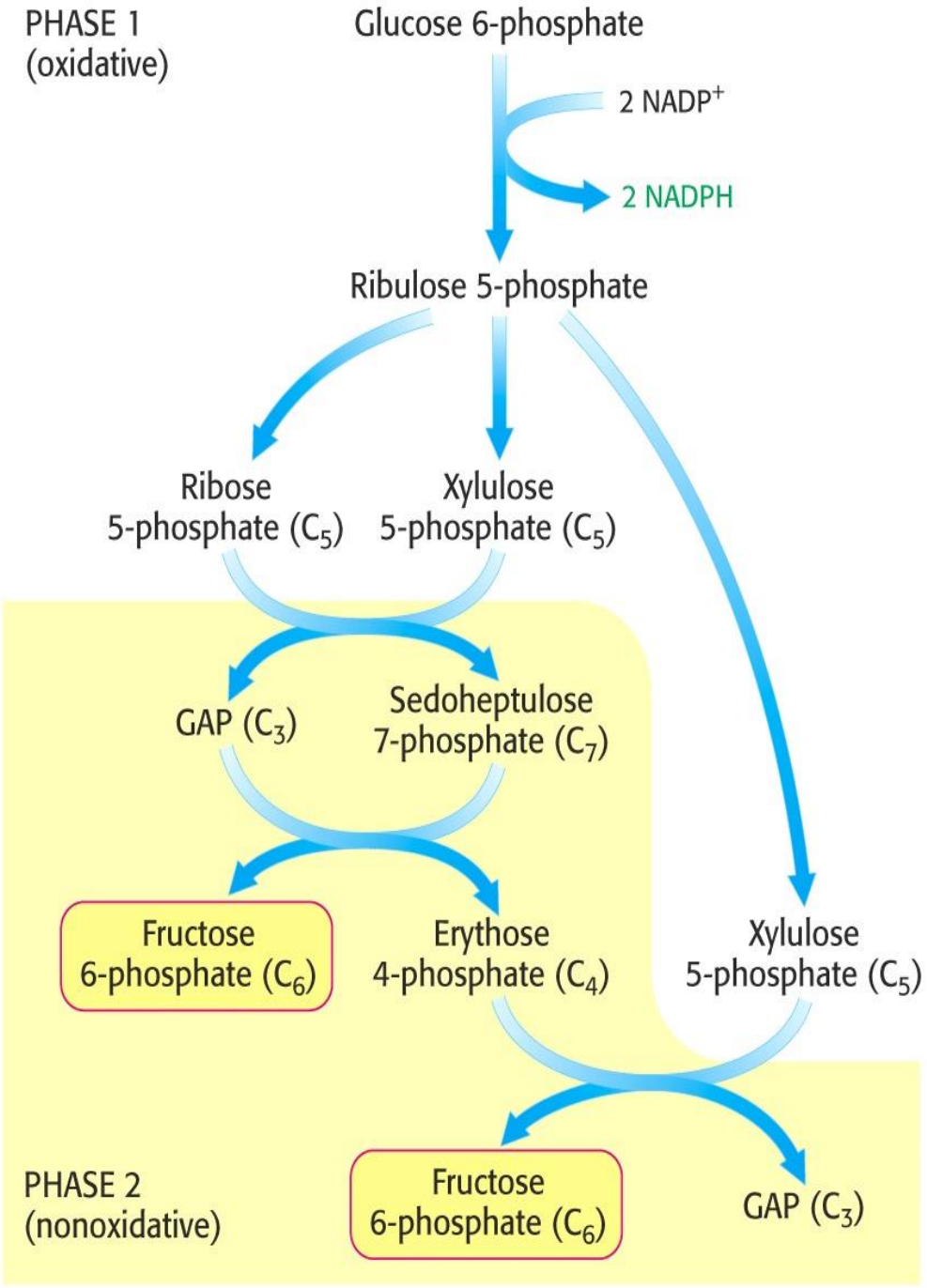
- The enzymes of the PPP are cytosolic.
- Oxidation is achieved by dehydrogenation using NADP, not NAD , as the hydrogen acceptor.

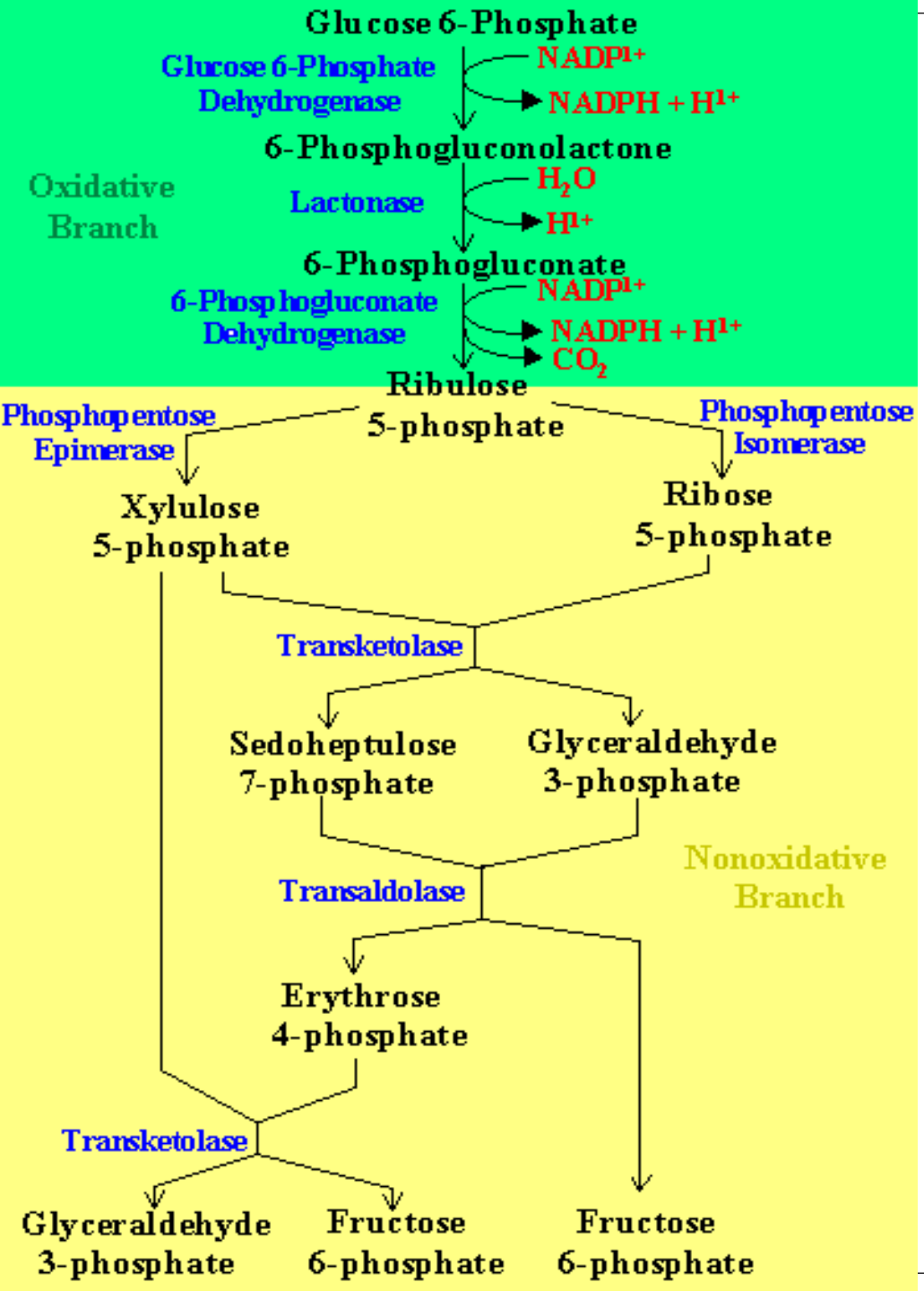
- Pathway is divided into 2 phases

1) ***Oxidative non-reversible phase***

2) ***Non-oxidative reversible phase***

- The pathway begins with the glycolytic intermediate glucose 6-P.
- It reconnects with glycolysis because two of the end products of the pentose pathway are glyceraldehyde 3-P and fructose 6-P
- two intermediates further down in the glycolytic pathway.
- It is for this reason that the pentose pathway is often referred to as a shunt.





- The pentose pathway can be divided into two phases.

- Oxidative phase
- Oxidation of glucose & formation of pentose phosphates.

- Non-oxidative phase
- Conversion of pentose phosphate to hexose phosphate.

OXIDATIVE REACTIONS:

- This portion of the pathway is particularly important

I. In liver, lactating mammary gland and the adipose tissue which are active in the NADPH dependent biosynthesis of fatty acids.

II. In the testes , ovaries, placenta and adrenal cortex, which are active in NADPH dependent biosynthesis of steroid hormones.

III. In red blood cells which requires NADPH to keep glutathione in reduced form.

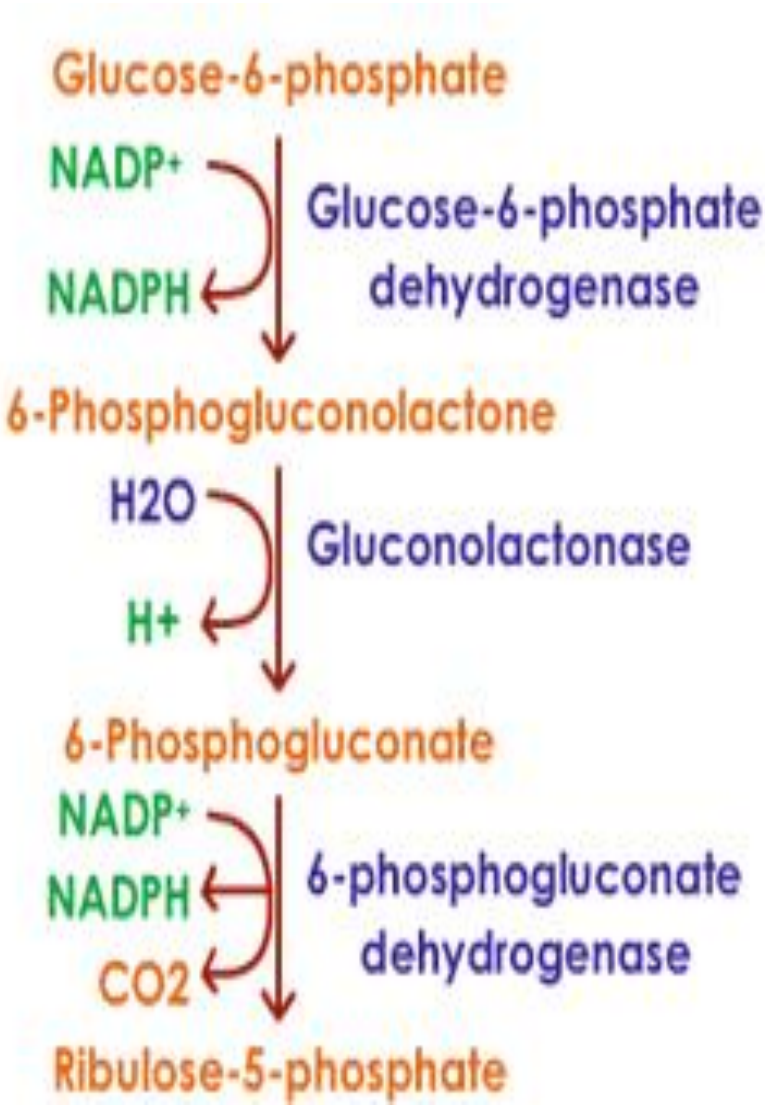
Oxidative phase

In the first phase ***G-6-PO4*** undergoes dehydrogenation & form 6-phosphogluconolactone.

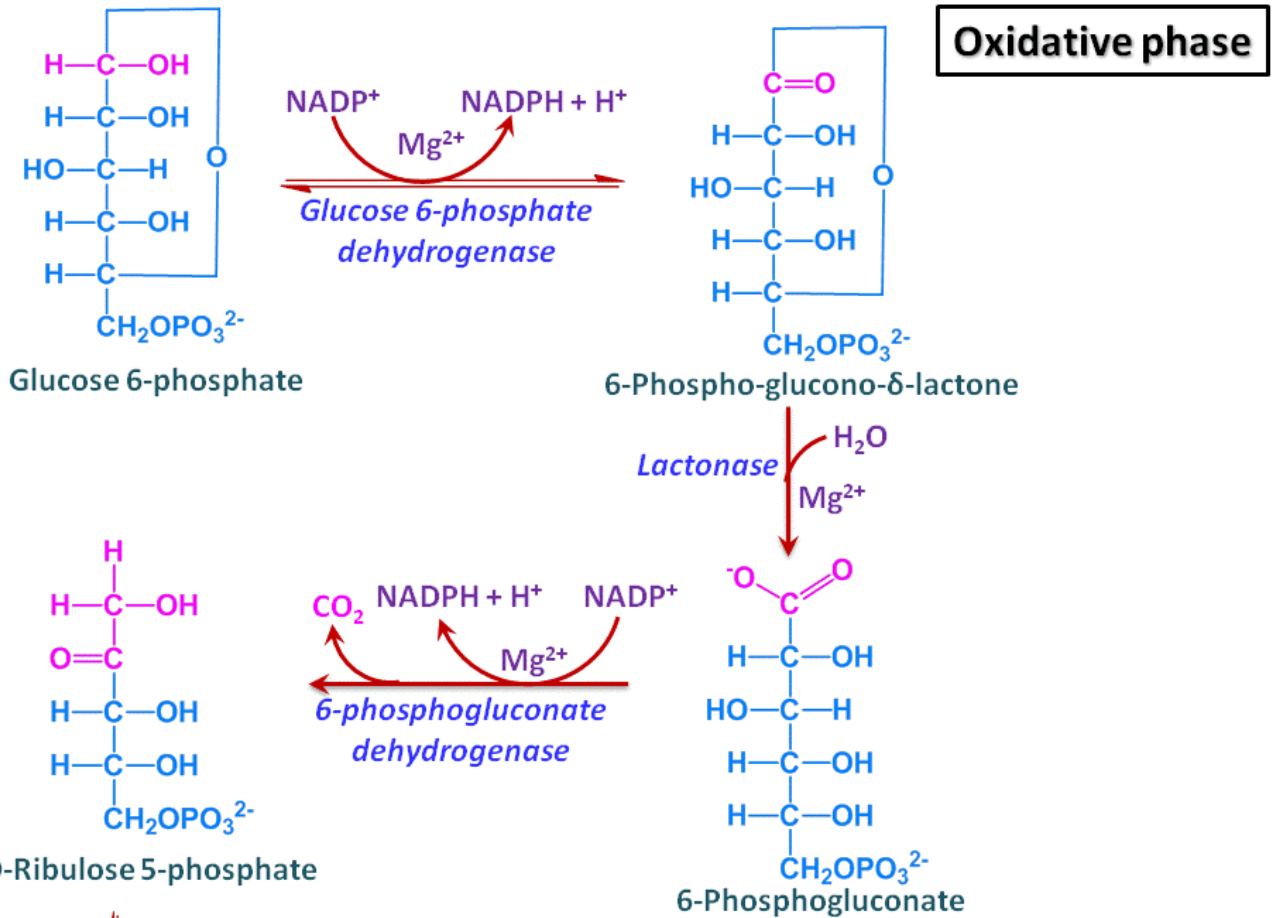
The glucose 6-phosphate DH (G6PD) reaction is the rate limiting step and is essentially irreversible.

$NADPH^{+}$ competitively inhibits G6PD.

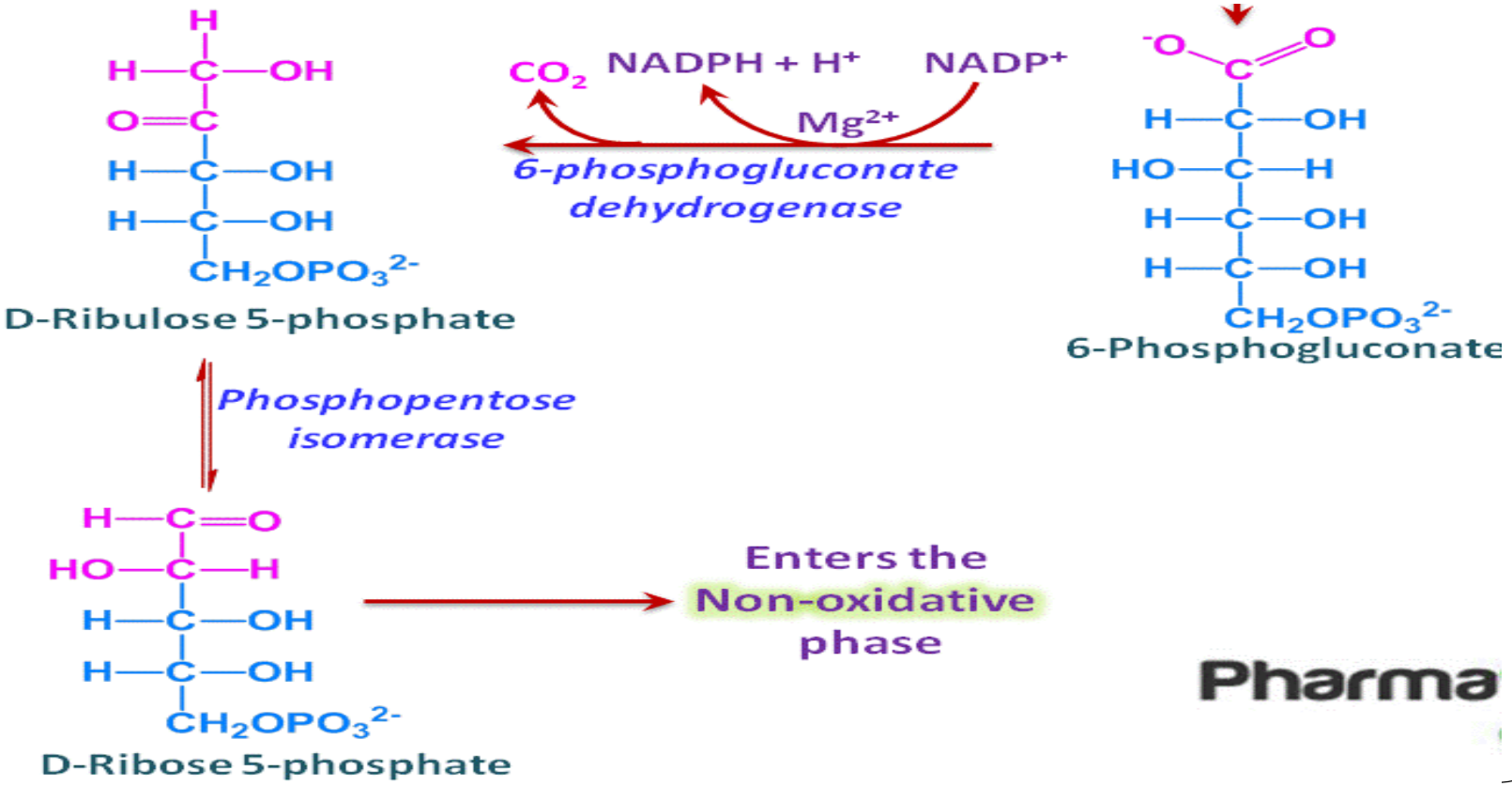
It is the ratio of NADPH/NADP that determines the flux of cycle.



The hydrolysis of ***6-phosphogluconolactone*** is accompanied by the enzyme ***gluconolactone hydrolase.***



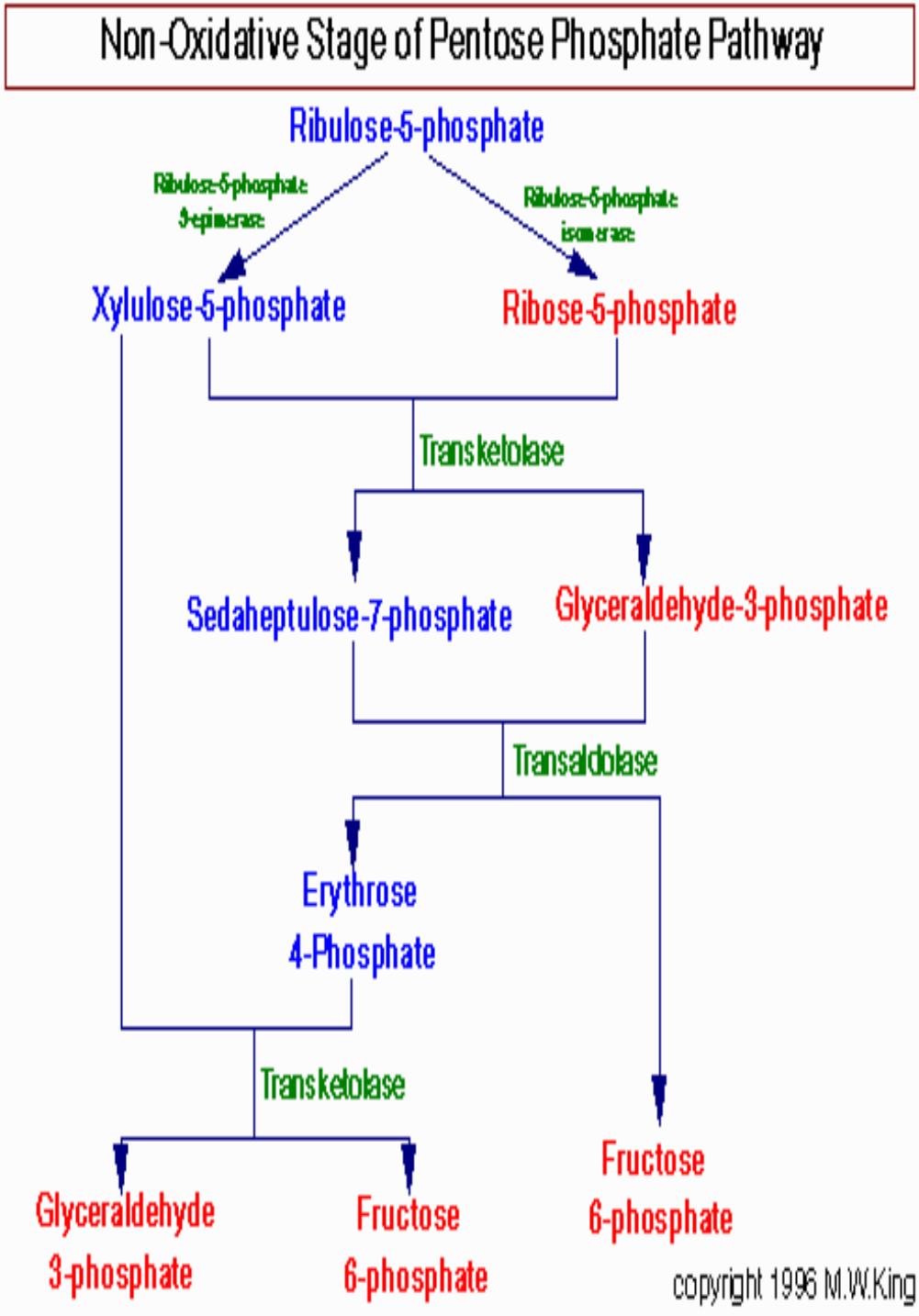
A second oxidative step is catalyzed by ***6-phosphogluconate dehydrogenase,which*** also requires ***NADP*** as hydrogen acceptor. ***Decarboxylation*** follows with the formation of ketopentose ***ribulose-5-phosphate***.



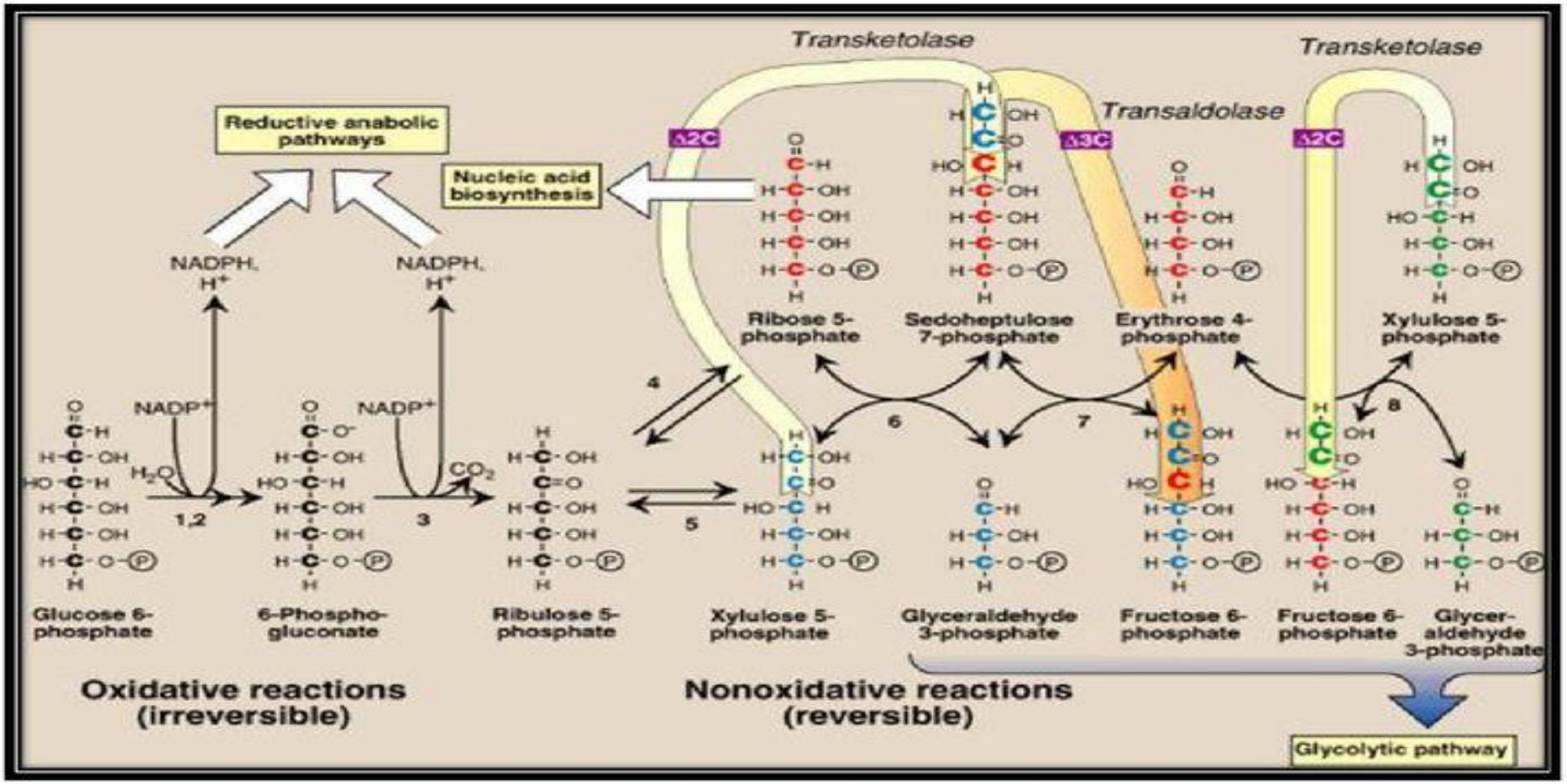
- Non-oxidative phase
- This part of the pathway occur in all cell types synthesizing nucleotides & nucleic acids.
- Ribulose-5-PO4 is substrate for two enzymes

➢ R-5-PO4- epimerase------ xylulose-5-PO4 (ketopentose)

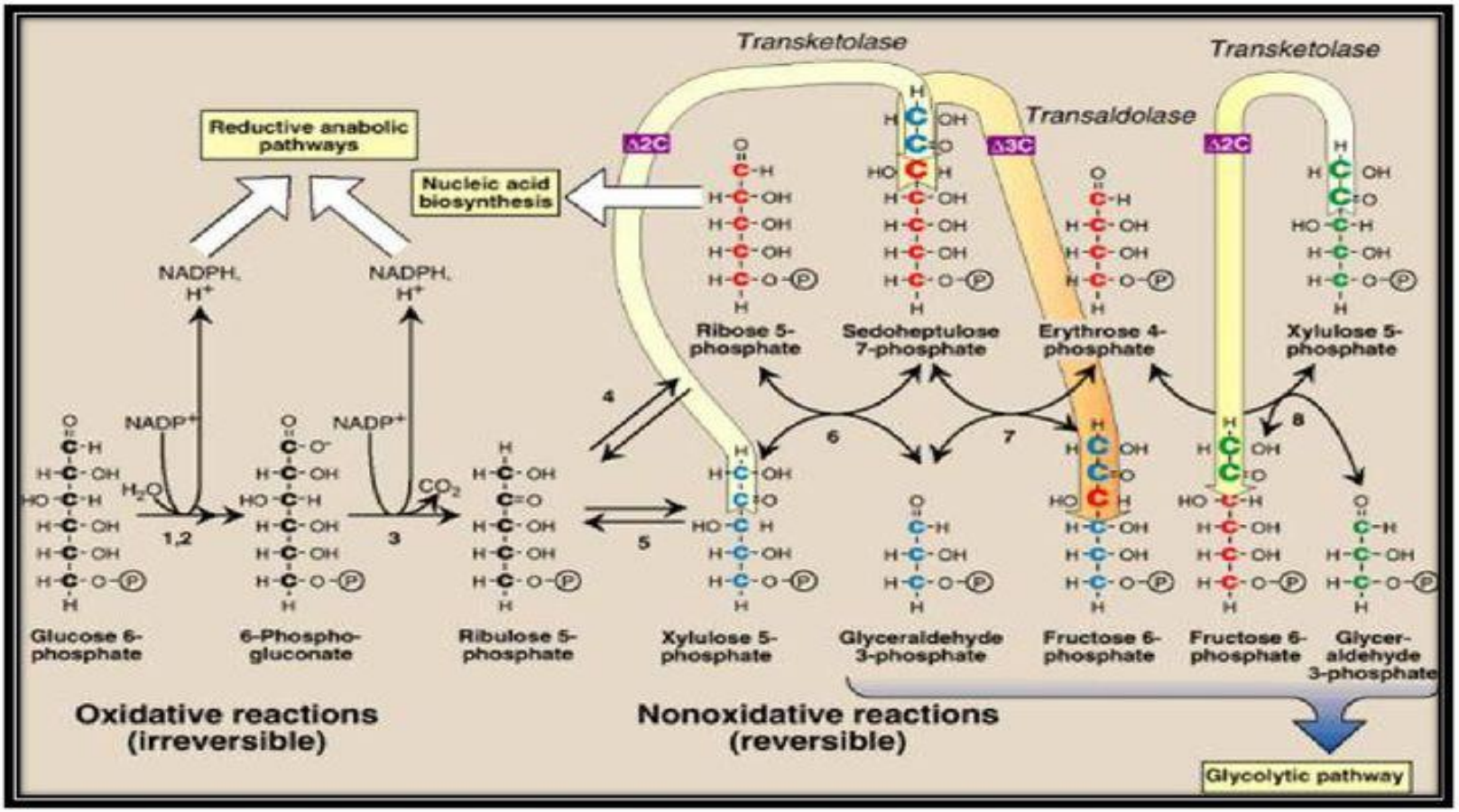
➢ R-5-PO4-ketoisomerase----Ribose-5-PO4 (aldopentose).



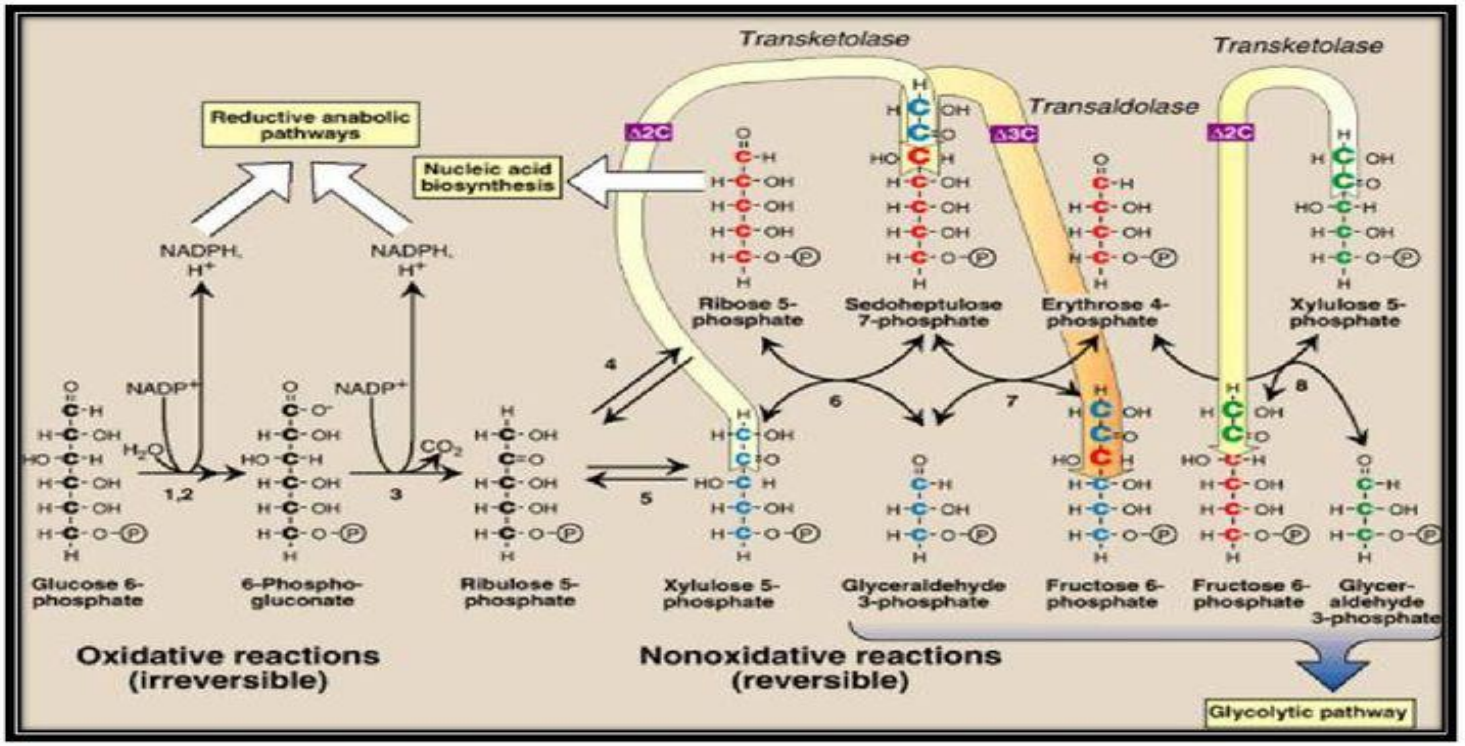
- Transketolase transfers the two carbon unit from xylulose-5-PO4 to ribose-5-PO4------To give
- 7-C ketose-----seduheptulose-7-PO4.
- Aldose------- glyceraldehyde-3-PO4. TPP is co enzyme for transketolase.



- These two products will undergo transaldolation.
- Transaldolase catalyses the transfer of 3-C (dihydroxyacetone) from seduheptulose to glyceraldehyde-3-PO4 to form ketose fructose-6-PO4 & erythrose -6 phosphate.



- In further rxn catalyzed by transketolase,xylulose-5-PO4 serves as donor of glyceraldehyde.
- Erythrose -4-PO4 is the acceptor and products are fructose-6-PO4 & glyceraldehyde-3-PO4.
- Fructose-6-PO4 & glyceraldehyde-3-PO4 can be further catalyzed through glycolysis and citric acid cycle.



Regulation of the Pentose Pathway

- Glucose 6-phosphate DH is the regulatory enzyme.
- NADPH is a potent competitive inhibitor of this enzyme.
- When the ratio of NADPH/$NADP^+$ is high so the enzyme is inhibited .
- In diabetes and starvation, the ratio is high and inhibits pathway.
- Insulin also regulate by enhancing pathway by inducing

Glucose 6-phosphate DH & phosphogluconolactone dehydrogenase.

- The reactions of the non-oxidative portion of the pentose pathway are readily reversible.

- The concentrations of the products and reactants can shift depending on the metabolic needs of a particular cell or tissue.

G-6PD DEFICIENCY:

Genetic deficiency of ***glucose 6 phosphate dehydrogenase,*** the first enzyme of the PPP, is major cause of hemolysis of RBCs causing ***hemolytic anemia.***

- It is an inherited x-linked chromosome disorder.
- Hemolytic anemia, is due to inability of RBCs to detoxify oxidizing agents.
- It is the most common disease effecting about more than 200 million people worldwide. Males are more affected.

G-6PD DEFICIENCY:

As HMP shunt is the only source of NADPH+H in RBC , thus the G-6PD deficiency effect is more severe in erythrocytes. (which lack nucleus and ribosomes and cannot renew its enzyme supply).

Precipitating factors

1. Oxidant drugs:

- antibiotics Sulfonamides
  Sulfemathoxazole
  Chloramphenicol
- Antimalarial primaquine
- ASPIRIN

- 2) favism
- 3) Infection

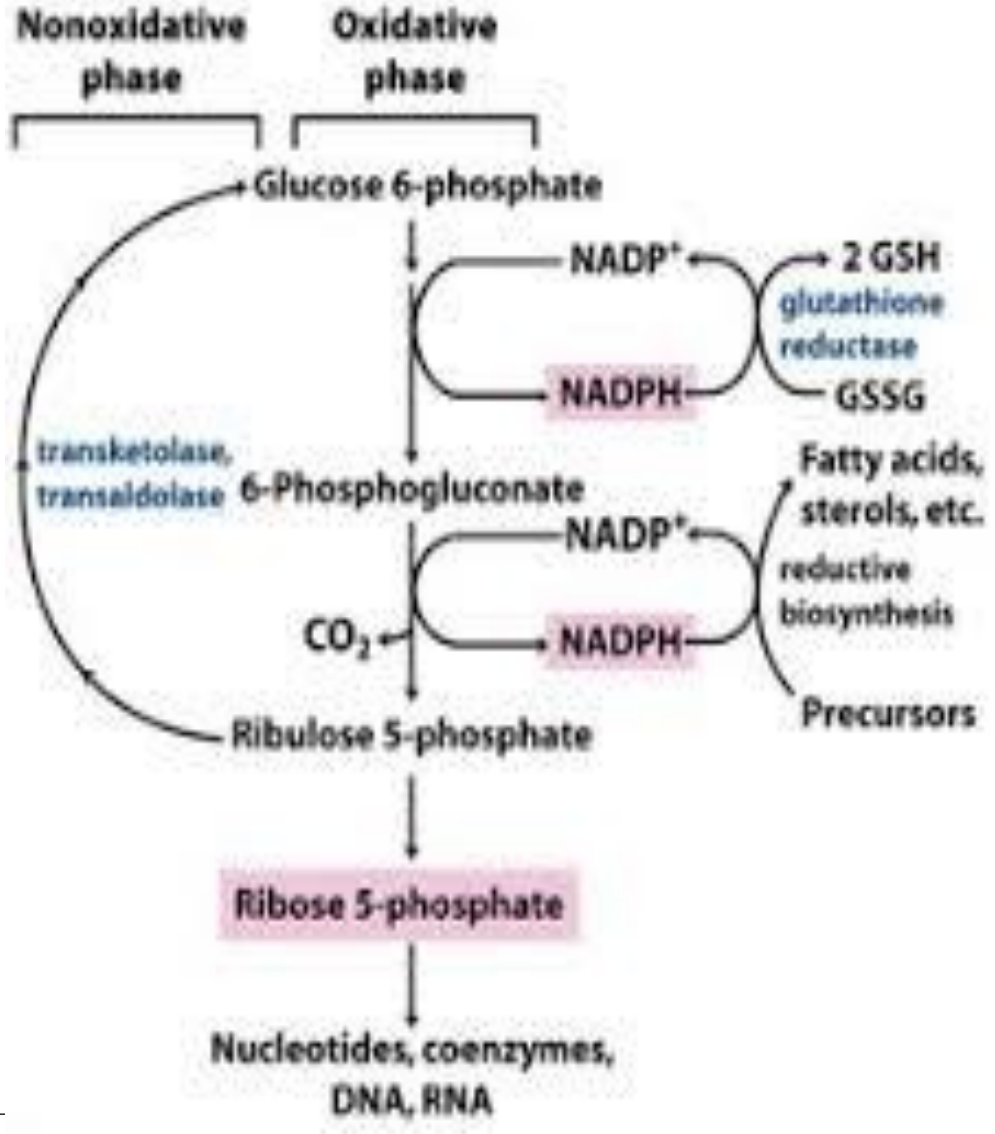
  Generation of free radicals in macrophages which can diffuse into RBC and cause damage.

Interesting feature:

The growth of Plasmodium falciparum (malaria parasite) fails in G6PD deficient individuals.

Significance of HMP shunt

- Formation of NADPH
- Provision of pentoses
- Role in RBCs fragility.
- Role in lens metabolism
- Role in phagocytosis



USES OF NADPH

A.. Reductive biosynthesis.

B.. Reduction of hydrogen peroxide.

C.. Cytochrome p450 monooxygenase system.

1. Mitochondrial.
2. Microsomal.

D. Phagocytosis by WBC.

1. oxygen dependent 2. oxygen independent.

E. Synthesis of NO from amino acid arginine

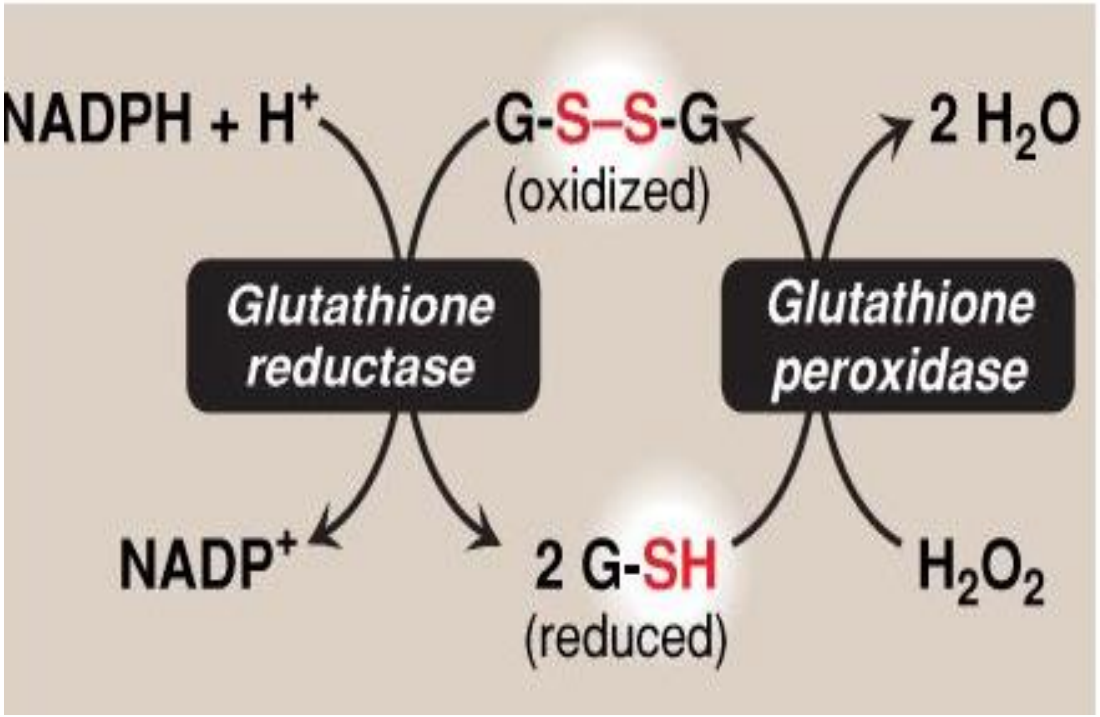
A) REDUCTION BIOSYNTHESIS:

- Reductive biosynthesis of fatty acids & steroids.

- NADPH is used in the synthesis of certain amino acids involving the enzyme glutamate dehydrogenase.

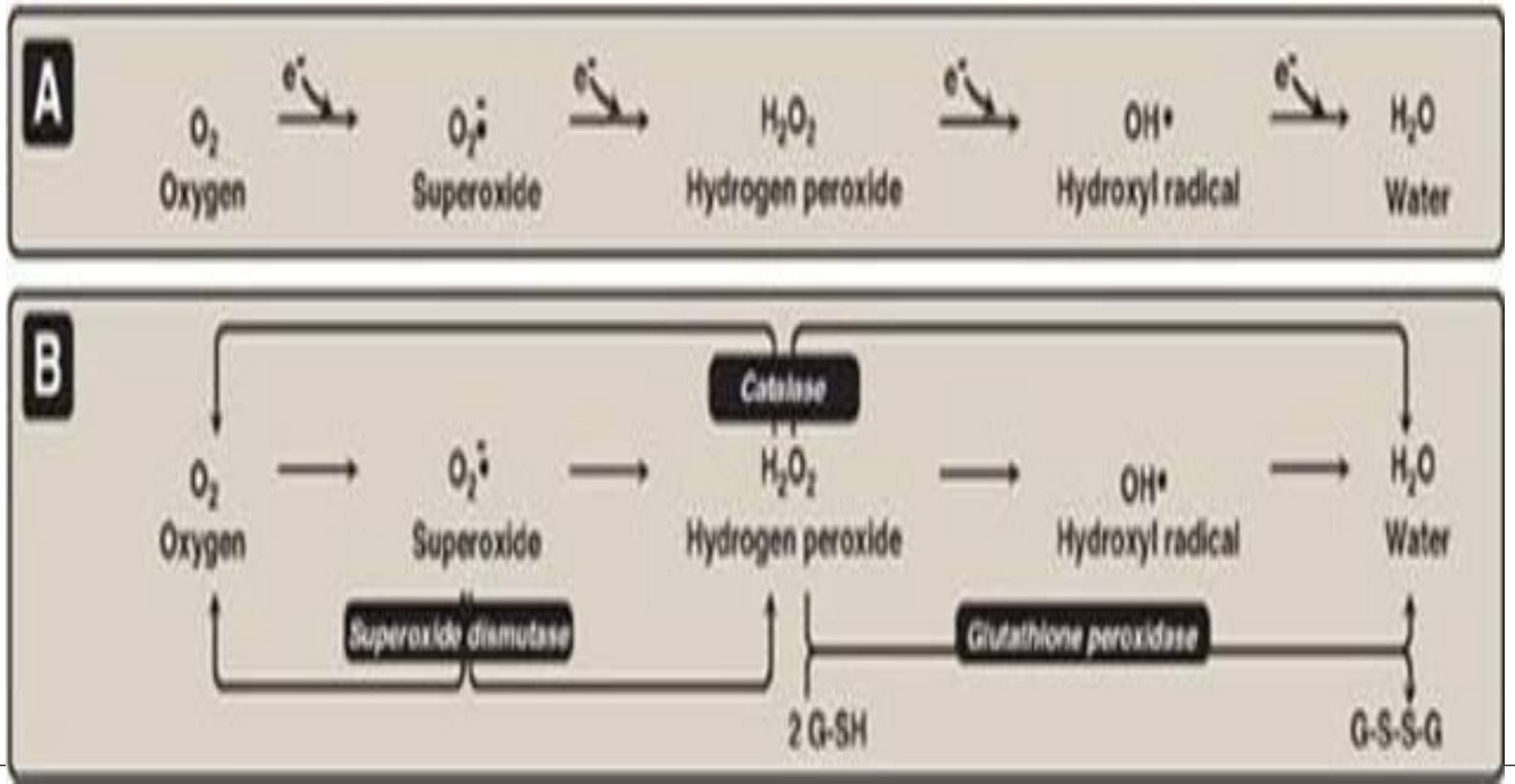
B) REDUCTION OF HYDROGEN PEROXIDE:

- Hydrogen peroxide is one of a family of reactive oxygen species , that are formed from partial reduction of molecular oxygen



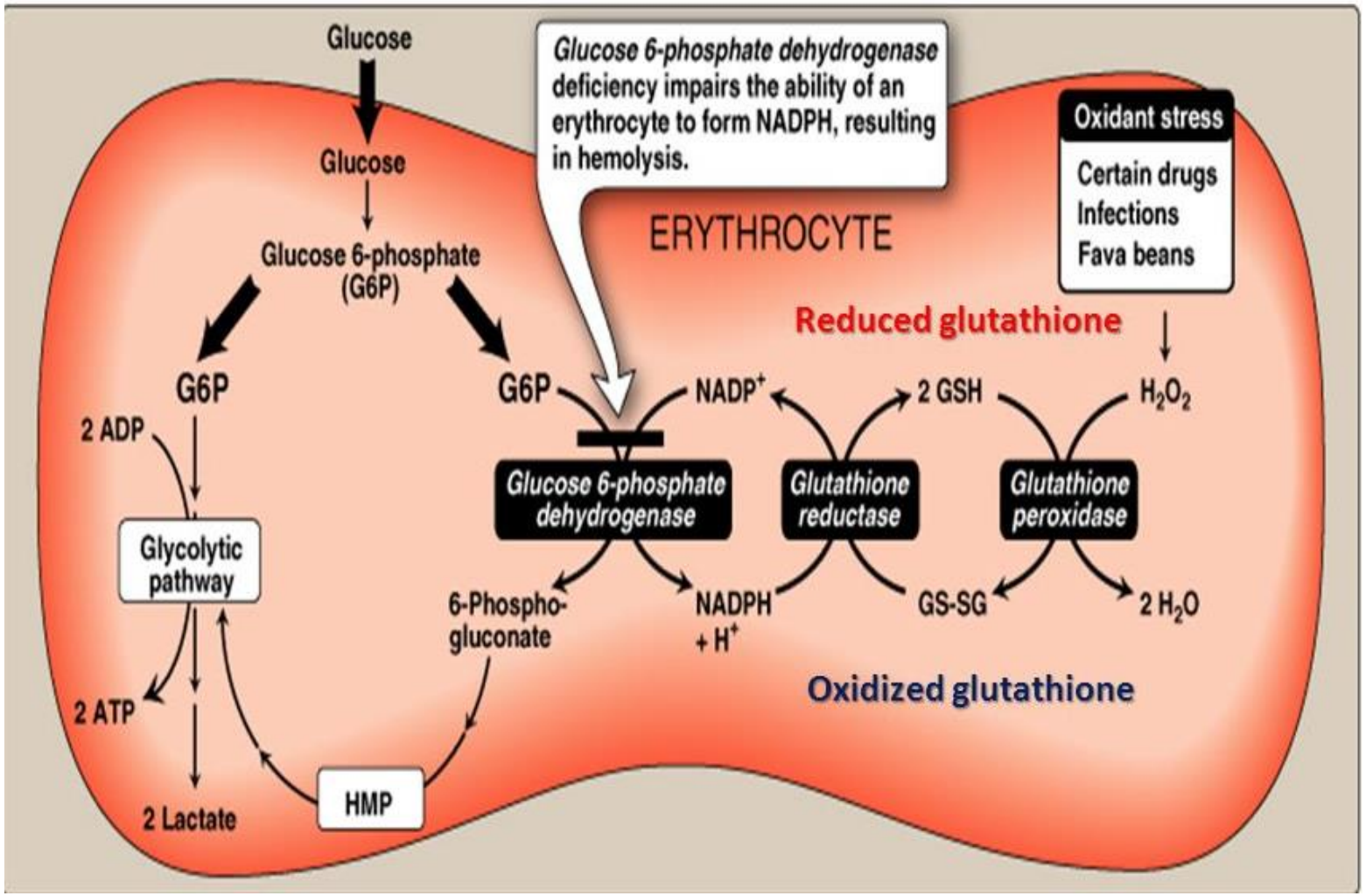
B) REDUTION OF HYDROGEN PEROXIDE:

- The high reactive oxygen intermediates can cause serious damge to DNA , proteins and unsaturated lipids , leading to cell death.



Function in RBCs

- Maintains integrity of RBCs membrane. NADPH keeps ferrous iron of Hb in the reduced state.



C) CYTOCHROME P450 MONOXYGENASE MULTIENZYME SYSTEM

- A) MITOCHONDRIAL: Required in:

i. various hydroxylation reactions.
ii. Steroid hormone synthesis in adrenal cortex, testes, ovaries and placenta.
iii. Formation of bile acids in liver and 1,25 ,D3 in kidney.

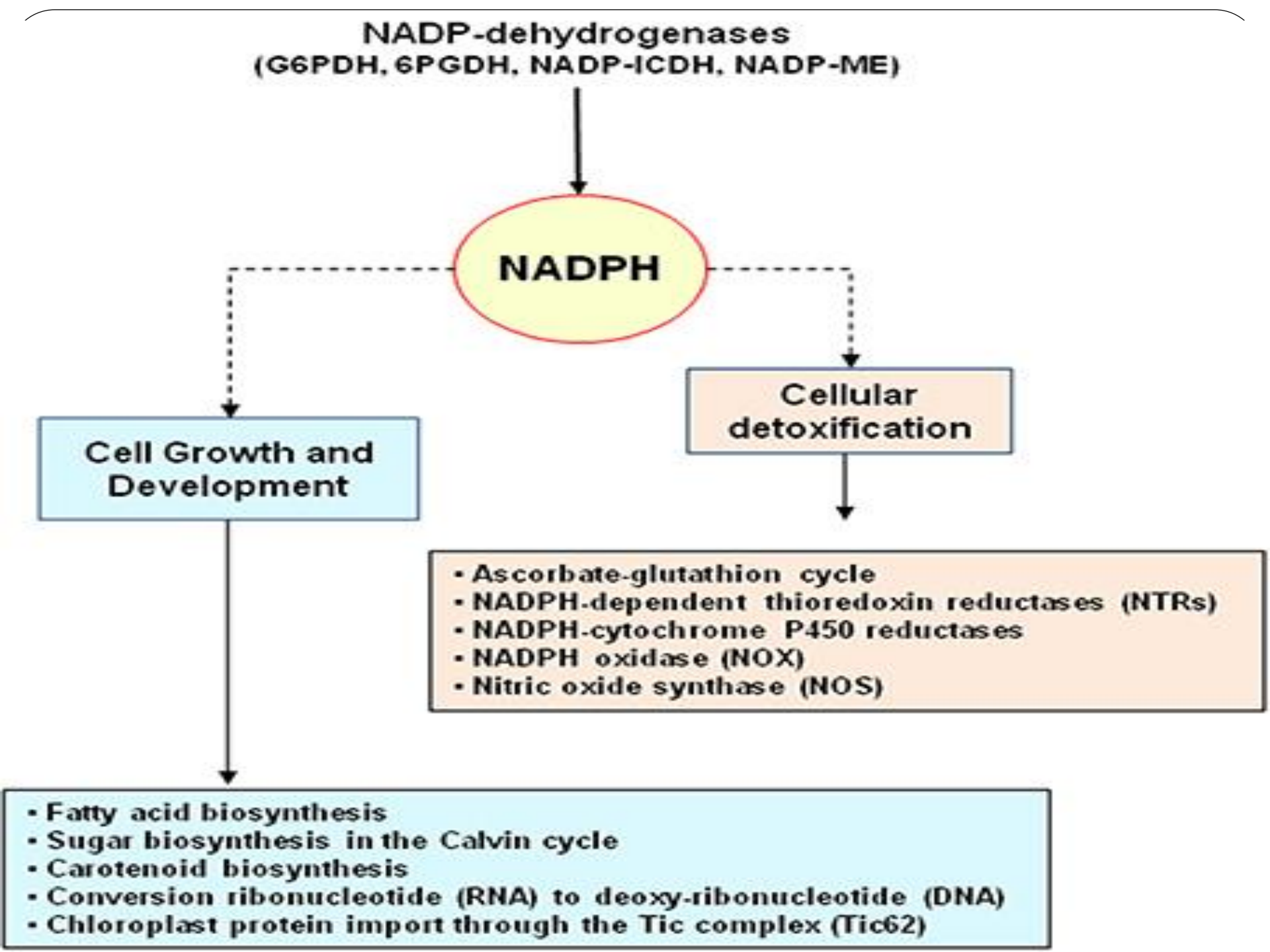
C) CYTOCHROME P450 MONOXYGENASE MULTIENZYME SYSTEM

- B) MICROSOMAL:
- required for the process of detoxification of various drugs , chemicals and toxins.

D) PHAGOCYTOSIS BY WBC:

- Phagocytosis is the ingestion of microorganism , foreign particles and cellular debris by receptor mediated endocytosis of macrophages.

  (monocytes and neutrophils).
- Both type of cells contain oxygen dependent and oxygen independent mechanisms for killing various bacteria.


NADP-dehydrogenases
(G6PDH, 6PGDH, NADP-ICDH, NADP-ME)
NADPH
Cell Growth and Development
Cellular detoxification
• Ascorbate-glutathion cycle
• NADPH-dependent thioredoxin reductases (NTRs)
• NADPH-cytochrome P450 reductases
• NADPH oxidase (NOX)
• Nitric oxide synthase (NOS)
• Fatty acid biosynthesis
• Sugar biosynthesis in the Calvin cycle
• Carotenoid biosynthesis
• Conversion ribonucleotide (RNA) to deoxy-ribonucleotide (DNA)
• Chloroplast protein import through the Tic complex (Tic62)

E) NITRIC OXIDE:

- NO is an important mediator control of vascular smooth muscle tone.
- It is synthesized in the endothelial cells and diffuses into vascular smooth muscle cells , where it activates guanylate cyclase , resulting in a rise in C-GMP , which causes muscle relaxation by activating protein kinase G.

E) NITRIC OXIDE:

- PKG which phosphorylates myosin light chain kinase and makes it inactive , and thus inhibits muscle contraction , resulting in vasodilatation.
- THIS PROPERTY IS USED IN CLINICAL PRATICE:
- vasodilator drugs (nitrates) such as nitroglycine and sodium nitroprusside are metabolized to NO, which causes smooth muscle relaxation and lowering of BP.
- Also used in treating acute anginal attacks.

3) ROLE OF NO IN MEDIATING MACROPHAGE BACTERICIDAL ACTIVITY

- In macrophages, nitric oxide synthase activity is usually low , but the enzyme synthesis is greatly activated by bacterial lipopolysaccharides and gamma interferone released in response to infection.
- Activated macrophages form superoxide radicals that combine with NO to form intermediates that decompose and form highly bactericidal OH redicals.
- NO production is also effective against viral , fungal , helminthic and protozoal infections.
- Potent inhibitor of platelet aggregation.
- Act as neurotransmitter in brain.

THANK YOU FOR LISTENING