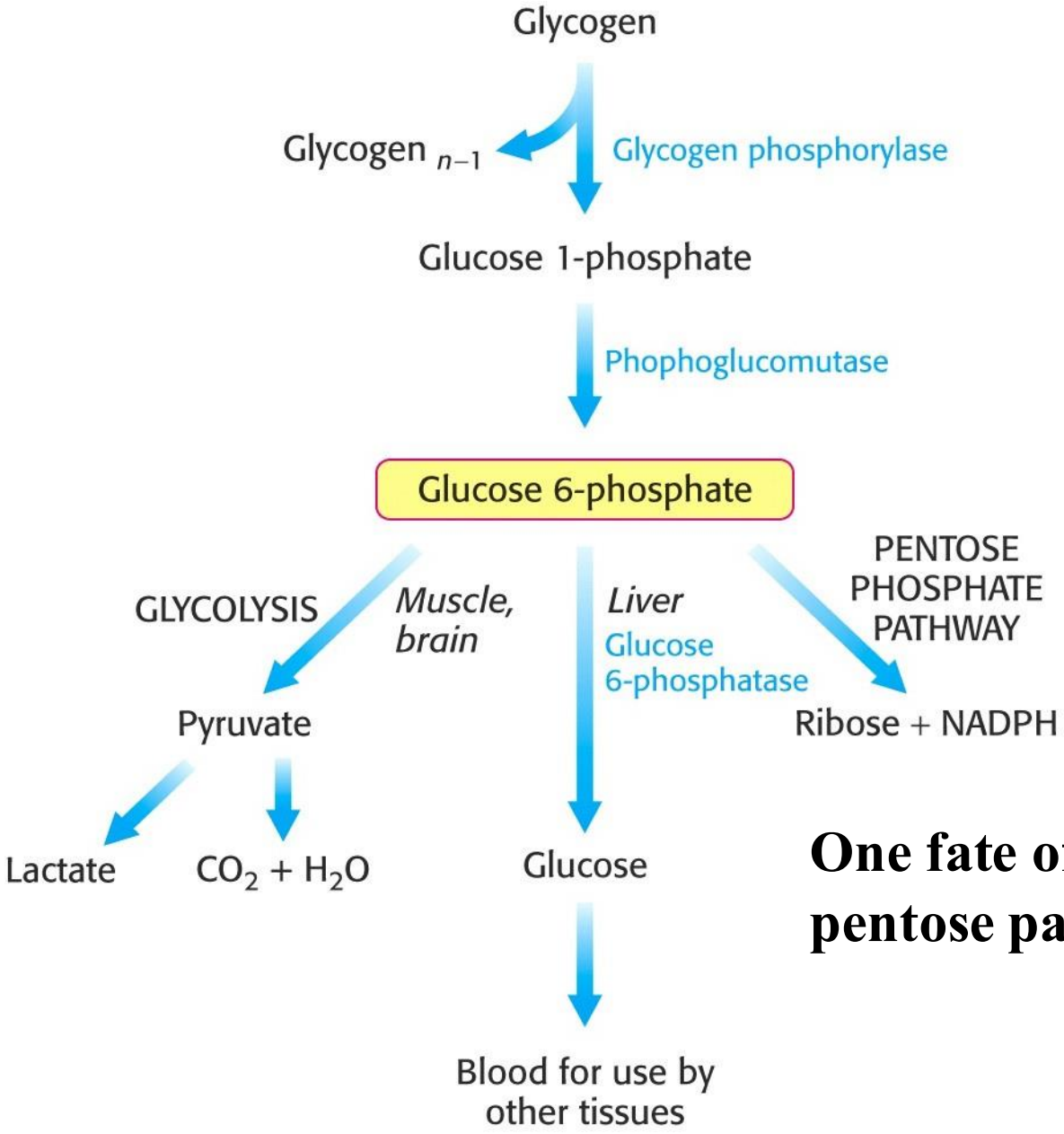
Pentose Phosphate Pathway



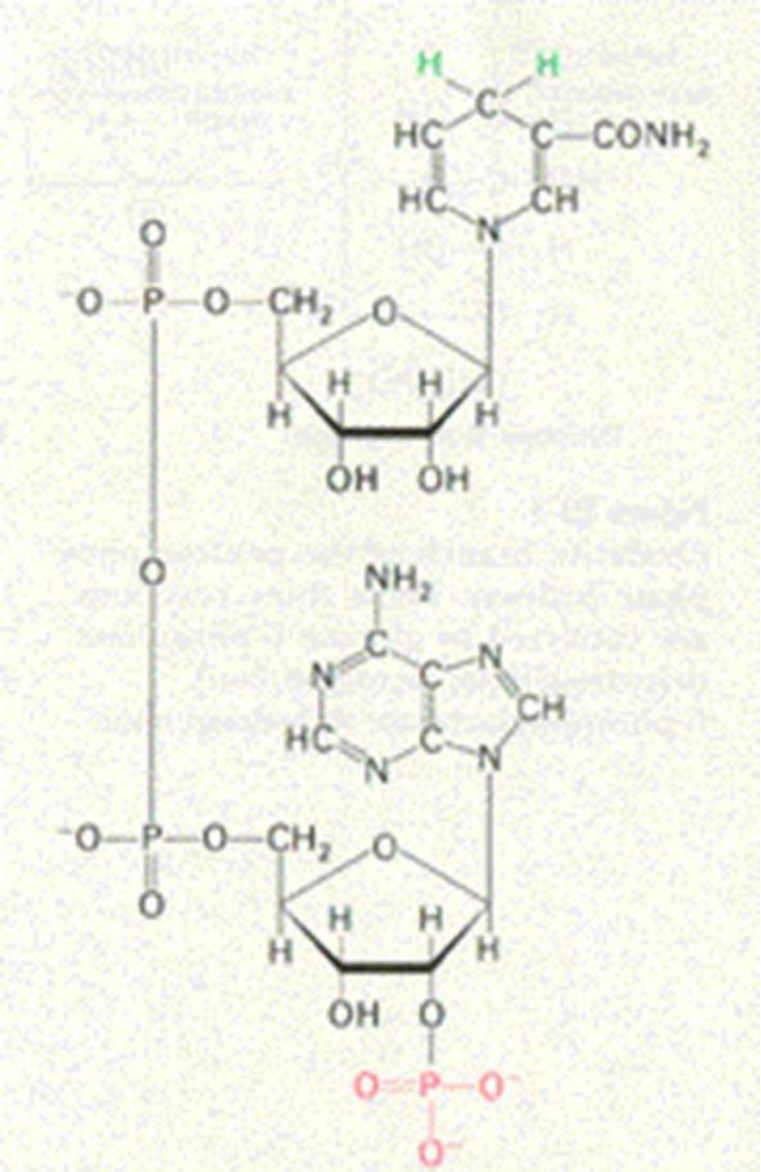
One fate of G6P is the pentose pathway.

The pentose pathway is a shunt.

- 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**; further down in the glycolytic pathway.
- It is for this reason that the pentose pathway is often referred to as a **shunt**.
- The pathway yields **reducing potential** in the form of **NADPH** to be used in **anabolic reactions requiring electrons**, also, it yields **ribose 5-phosphate** for nucleic acids (DNA, RNA), and various cofactors including **(CoA, FAD, SAM, NAD+/NADP+.**

- NADPH is a phosphorylated form of NADH.

- In general, with some exceptions, NADH is used to drive the phosphorylation of ADP to ATP. NADPH is used where reducing potential is required for synthetic reactions.



Reduced nicotinamide adenine dinucleotide phosphate (NADPH)

It's a shunt

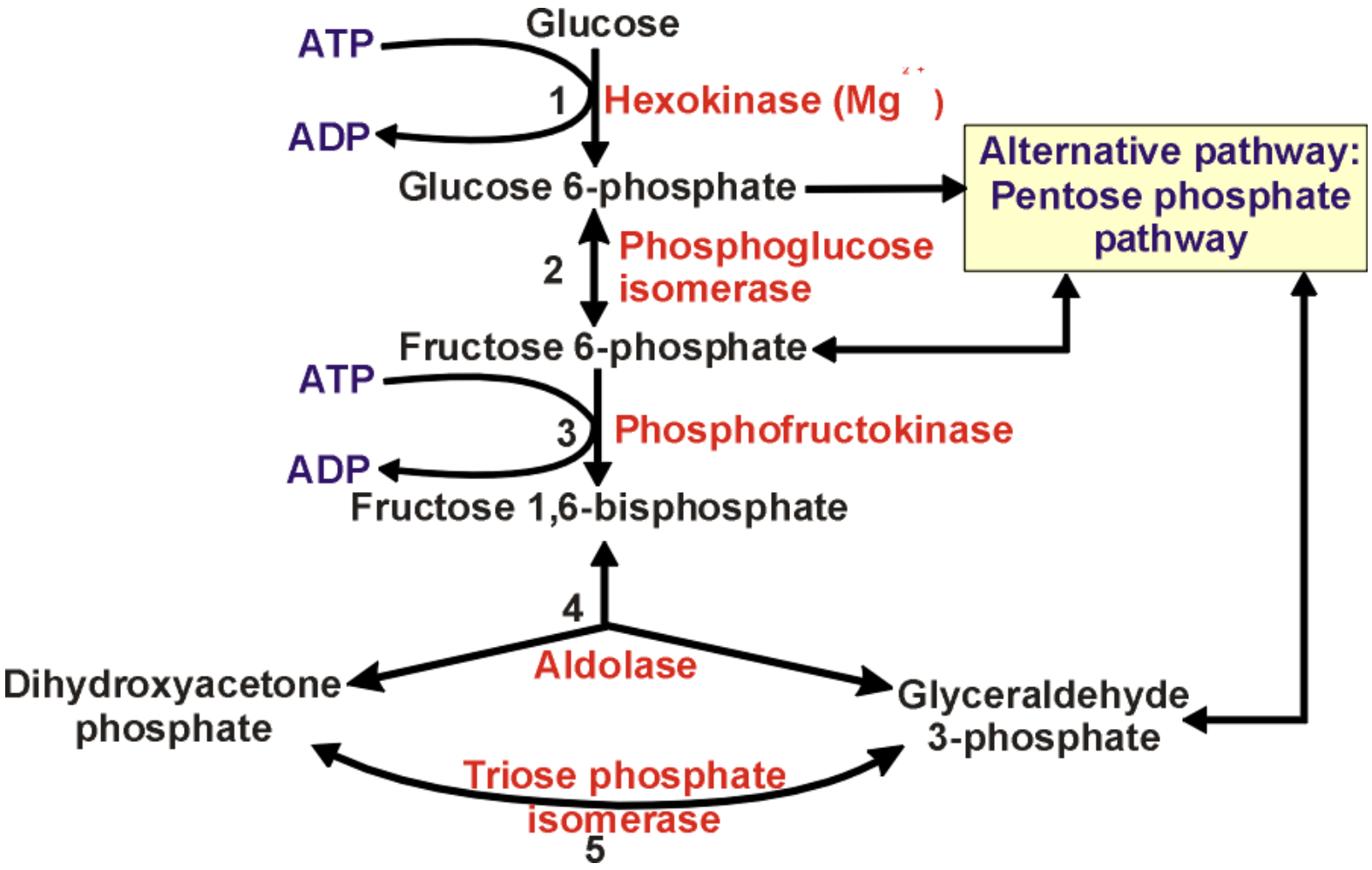

Glucose
ATP
ADP
1
Hexokinase (Mg++)
Glucose 6-phosphate
Alternative pathway:
Pentose phosphate
pathway
2
Phosphoglucose
isomerase
Fructose 6-phosphate
ATP
ADP
3
Phosphofructokinase
Fructose 1,6-bisphosphate
4
Aldolase
Dihydroxyacetone
phosphate
Glyceraldehyde
3-phosphate
Triose phosphate
isomerase
5

TABLE 20.4 Tissues with active pentose phosphate pathways

Tissue	Function
Adrenal gland	Steroid synthesis
Liver	Fatty acid and cholesterol synthesis
Testes	Steroid synthesis
Adipose tissue	Fatty acid synthesis
Ovary	Steroid synthesis
Mammary gland	Fatty acid synthesis
Red blood cells	Maintenance of reduced glutathione

TABLE 20.2 Pathways requiring NADPH

Synthesis

Fatty acid biosynthesis
Cholesterol biosynthesis
Neurotransmitter biosynthesis
Nucleotide biosynthesis

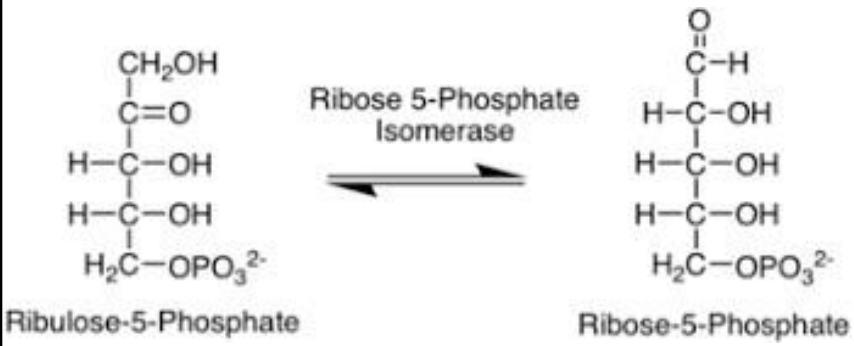
Detoxification

Reduction of oxidized glutathione
Cytochrome P450 monooxygenases

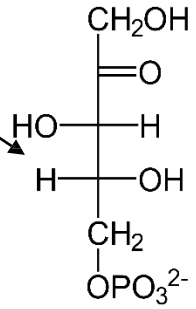
The pentose pathway can be divided into two phases.

1- Oxidative irreversible

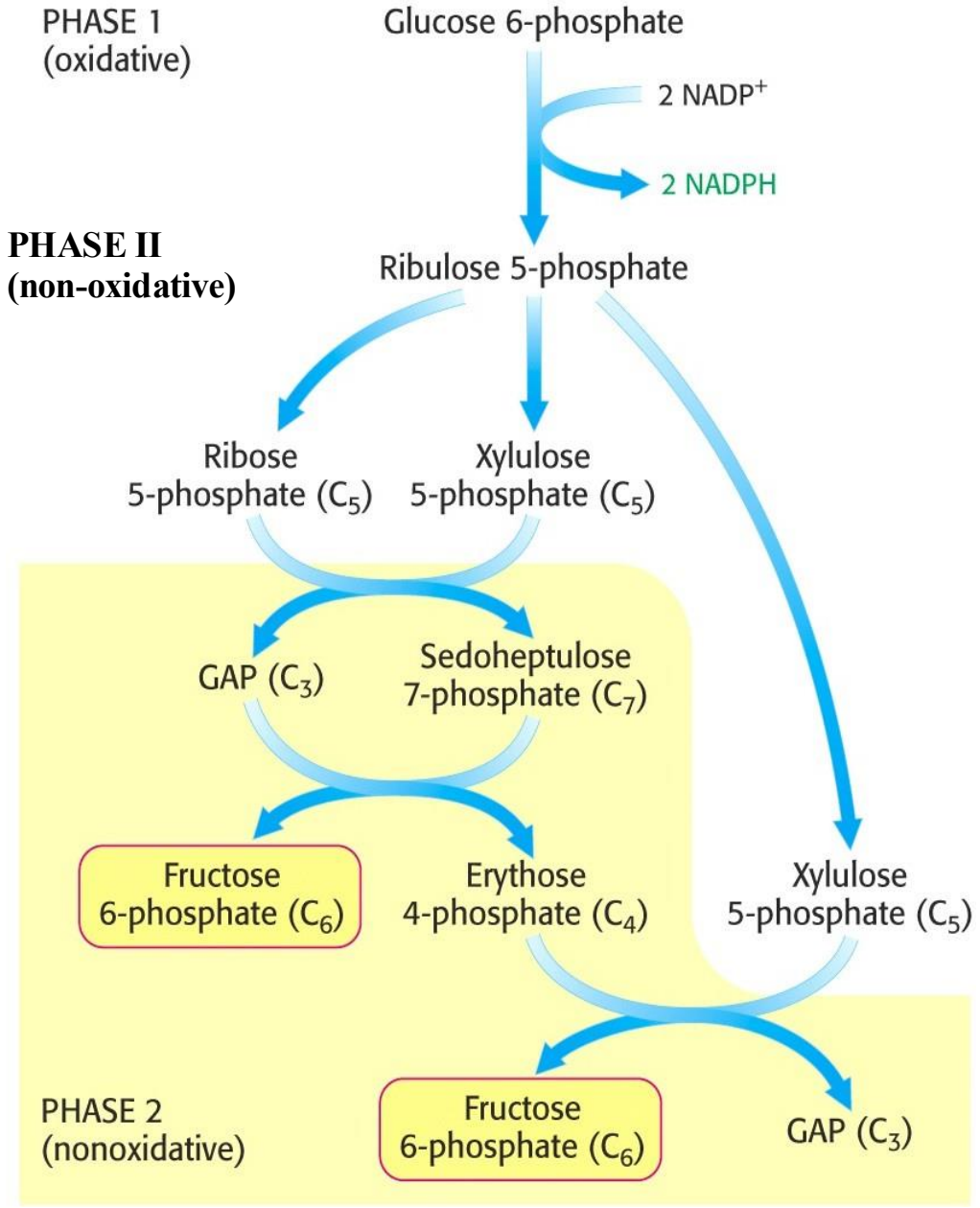
2- Non-oxidative reversible interconversion of sugars



Ribose 5-phosphate epimerase



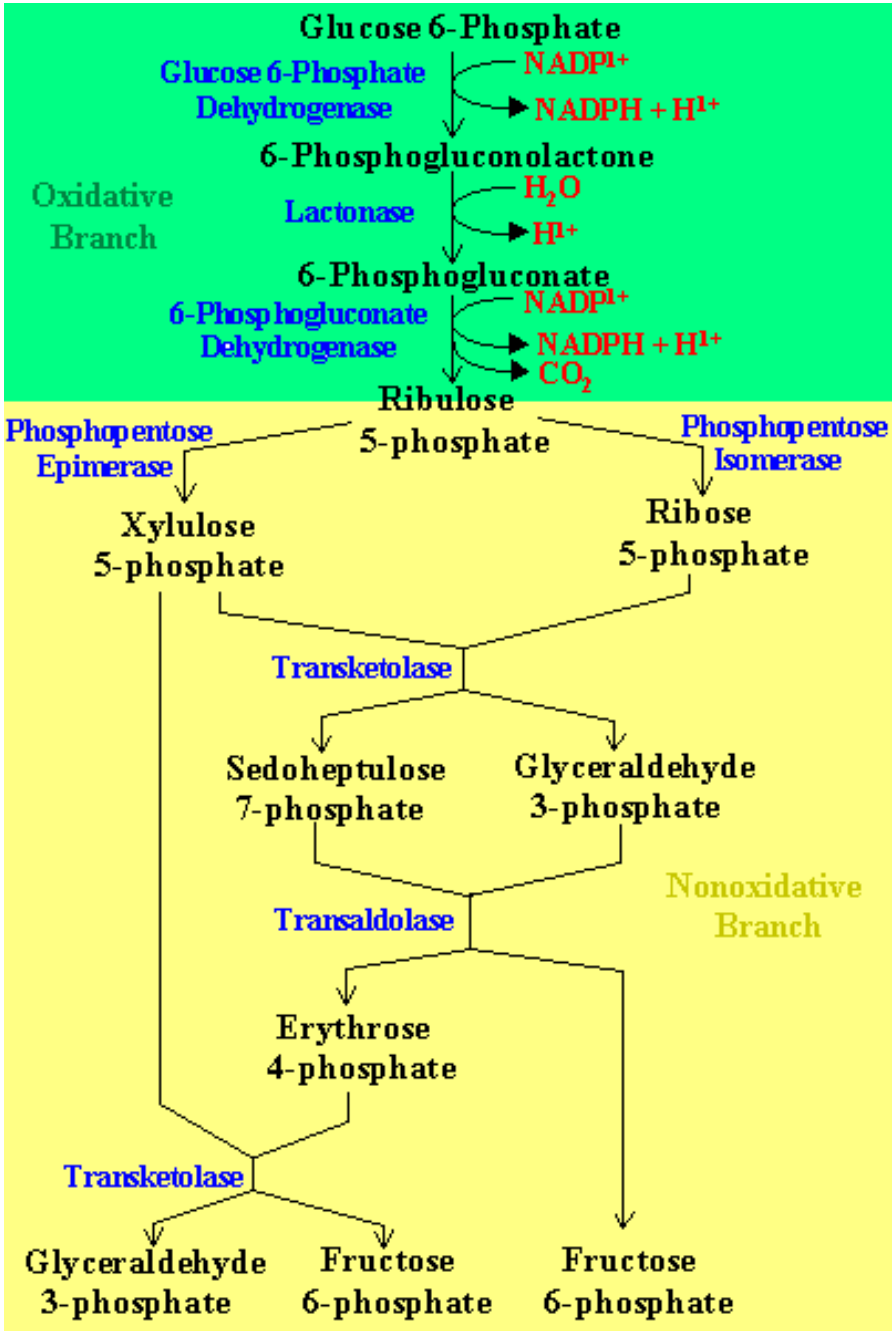
Xylulose 5-phosphate



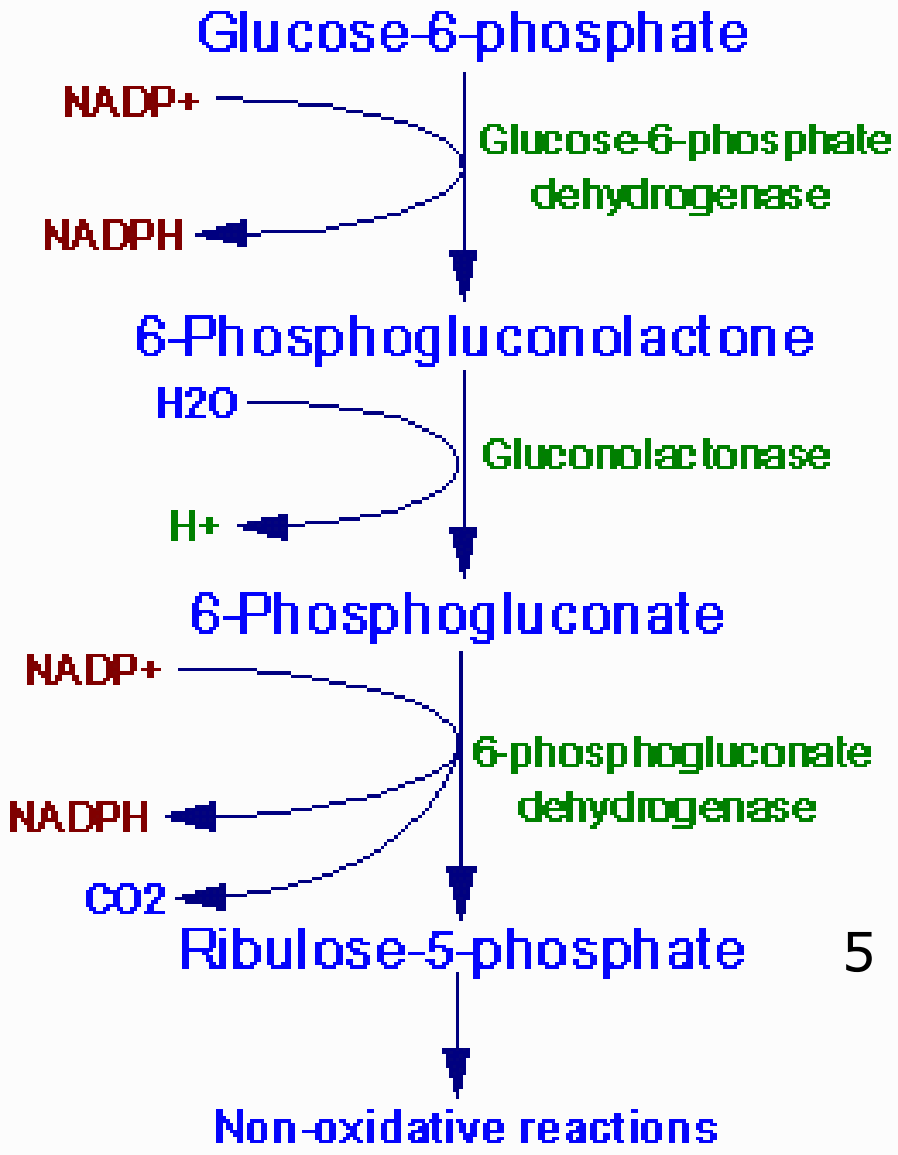
- NADPH + H^+ is formed from two separate reactions, catalyzed by **glucose 6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase**

- The glucose 6-phosphate dehydrogenase reaction is the rate limiting step and is essentially irreversible.

- Cells have a greater need for NADPH than ribose 5-phosphate.

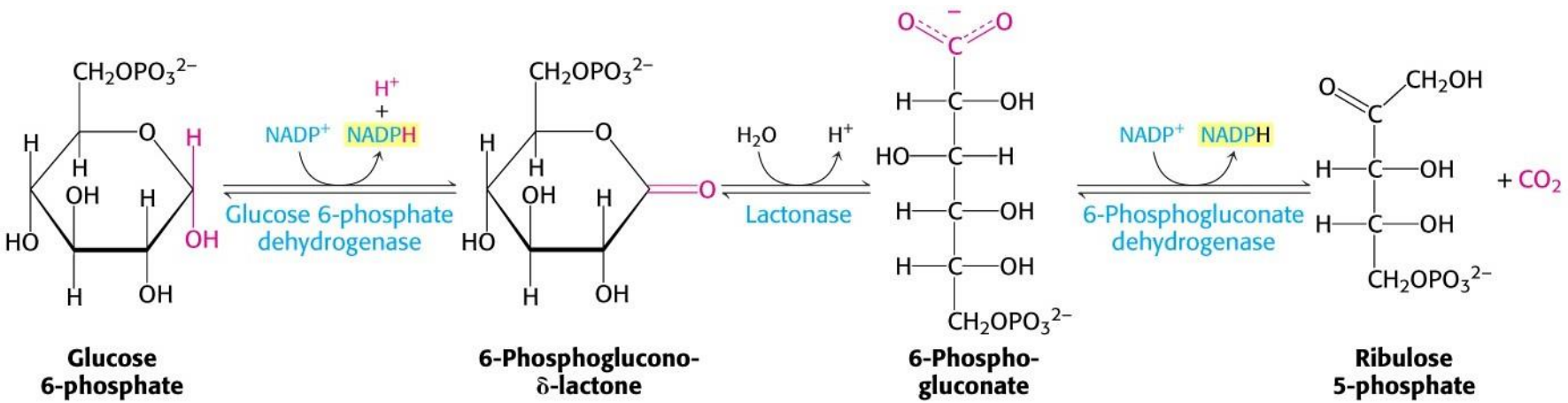


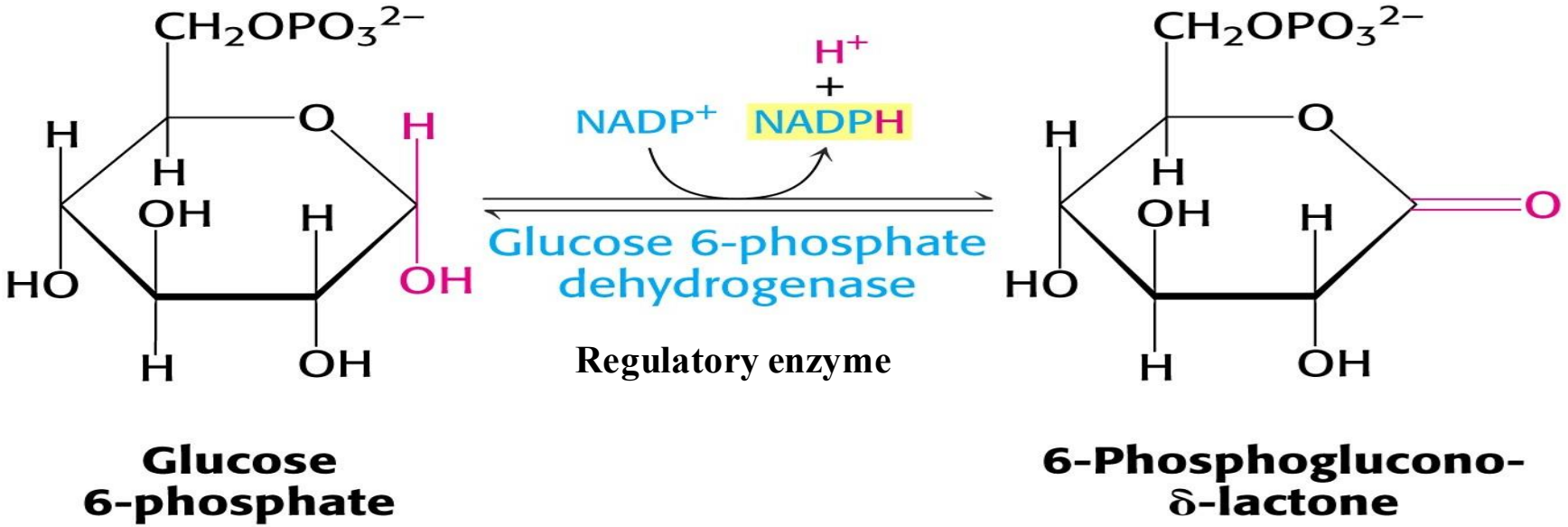
Oxidative Stage of Pentose Phosphate Pathway



Regulatory enzyme

5 carbon atoms





- The enzyme is highly specific for NADP+; the Km for NAD+ is 1000 greater than for NADP+

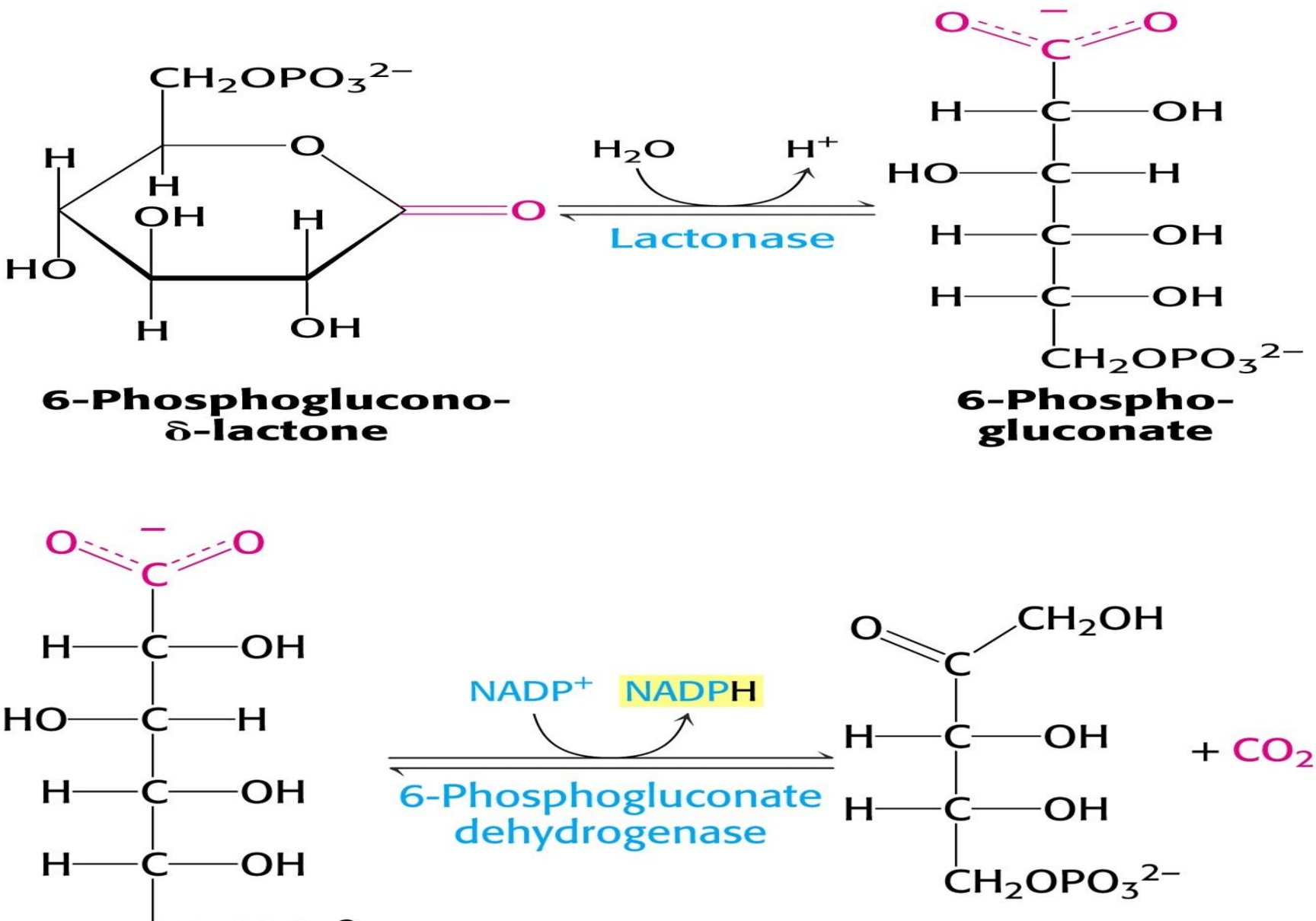
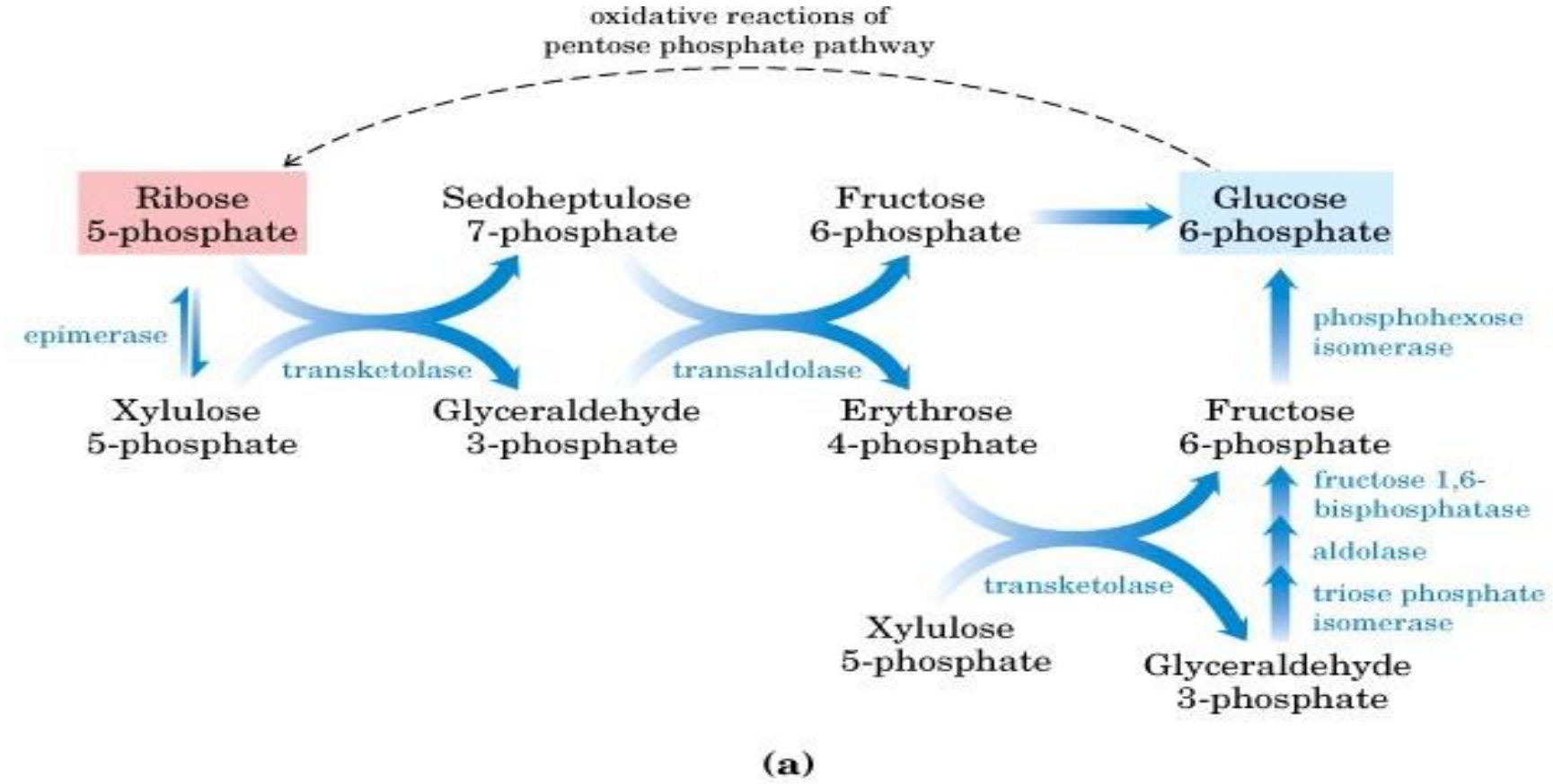

$CH_2OPO_3^{2-}$
H
O
H
OH
H
HO
H
OH
O
H_2O
H^+
Lactonase
O
O
C
H
C
OH
HO
C
H
H
C
OH
H
C
OH
$CH_2OPO_3^{2-}$
6-Phosphogluconono-
δ-lactone
6-Phospho-
gluconate
NADP+
NADPH
6-Phosphogluconate
dehydrogenase
CH_2OH
$+ CO_2$
6-Phospho-
gluconate
Ribulose
5-phosphate

TABLE 20.3 Pentose phosphate pathway

Reaction	Enzyme
Oxidative phase	
Glucose 6-phosphate + $NADP^+$ $\longrightarrow$ 6-phosphoglucono-δ-lactone + NADPH + H^+	Glucose 6-phosphate dehydrogenase
6-Phosphoglucono-δ-lactone + H_2O $\longrightarrow$ 6-phosphogluconate + H^+	Lactonase
6-Phosphogluconate + $NADP^+$ $\longrightarrow$ ribulose 5-phosphate + CO_2 + NADPH	6-Phosphogluconate dehydrogenase
Nonoxidative Phase	
Ribulose 5-phosphate $\rightleftharpoons$ ribose 5-phosphate	Phosphopentose isomerase
Ribulose 5-phosphate $\rightleftharpoons$ xylulose 5-phosphate	Phosphopentose epimerase
Xylulose 5-phosphate + ribose 5-phosphate $\rightleftharpoons$ sedoheptulose 7-phosphate + glyceraldehyde 3-phosphate	Transketolase
Sedoheptulose 7-phosphate + glyceraldehyde 3-phosphate $\rightleftharpoons$ fructose 6-phosphate + erythrose 4-phosphate	Transaldolase
Xylulose 5-phosphate + erythrose 4-phosphate $\rightleftharpoons$ fructose 6-phosphate + glyceraldehyde 3-phosphate	Transketolase

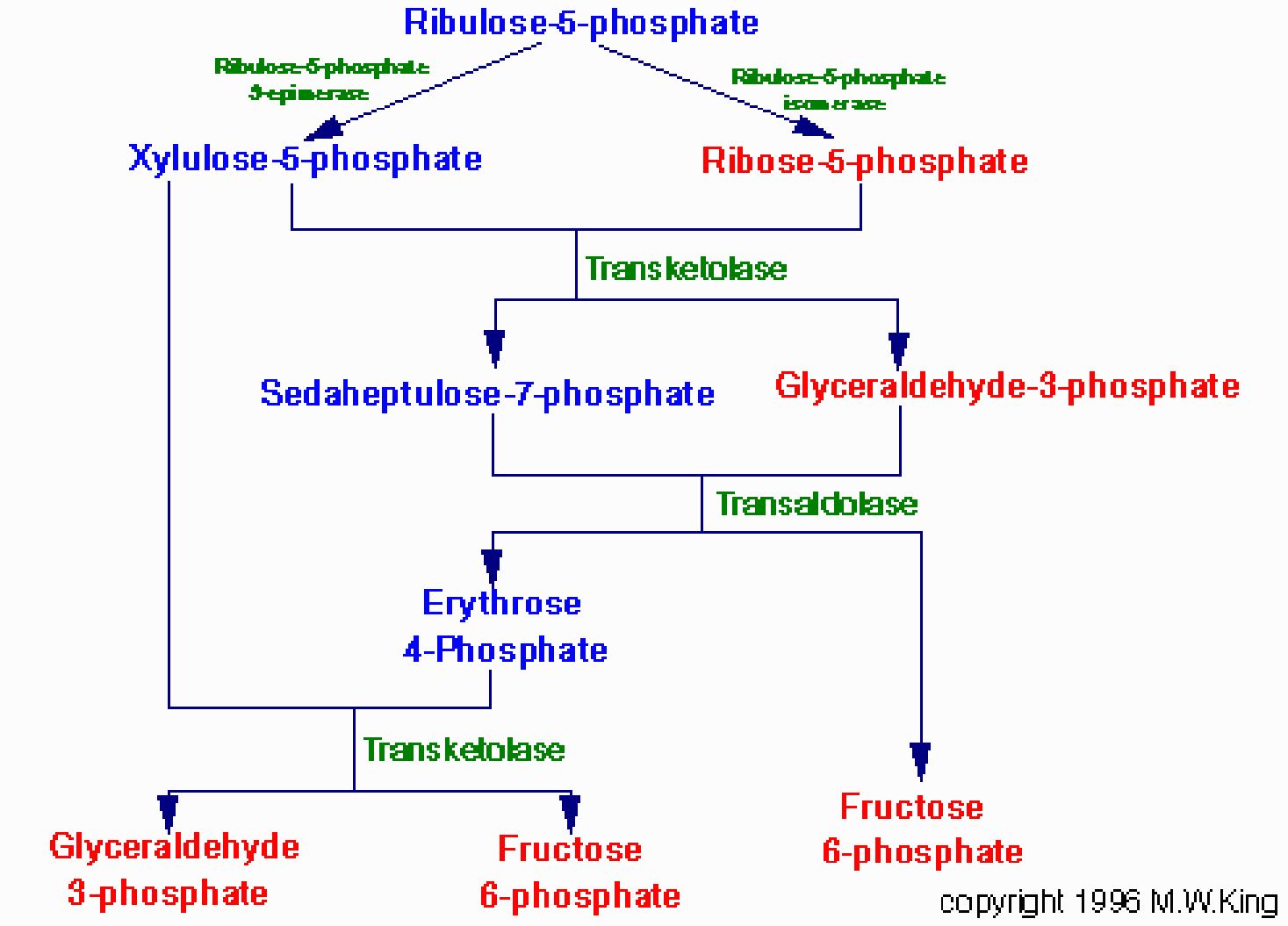
The non-oxidative phase of the pentose pathway



(a)

- Transketolase requires the coenzyme TPP, the transaldolase does not.
- Transketolase (TPP) and transaldolase are the link back to glycolysis.
  Glyceraldehyde 3-phosphate
  Fructose 6-phosphate

Non-Oxidative Stage of Pentose Phosphate Pathway



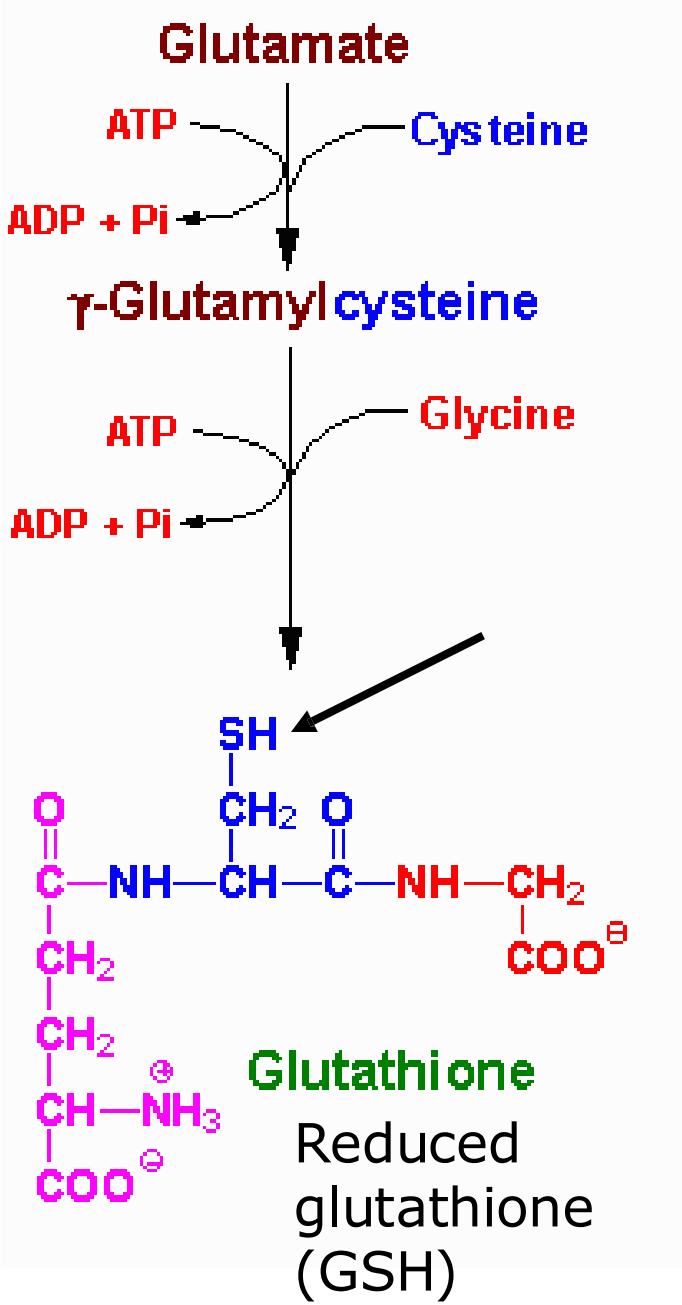
Regulation of the Pentose Pathway

- Glucose 6-phosphate dehydrogenase is the regulatory enzyme.
- NADPH is a potent competitive inhibitor of the enzyme.
- Usually the ratio NADPH/$NADP^+$ is high so the enzyme is inhibited.
- But, with increased demand for NADPH, the ratio decreases and enzyme activity is stimulated.
- 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.

Glutathione and NADPH

Glutathione is a tripeptide composed of glutamate, cysteine, glycine.

Reduced glutathione (GSH) maintains the normal reduced state of the cell.



Glutathione Functions

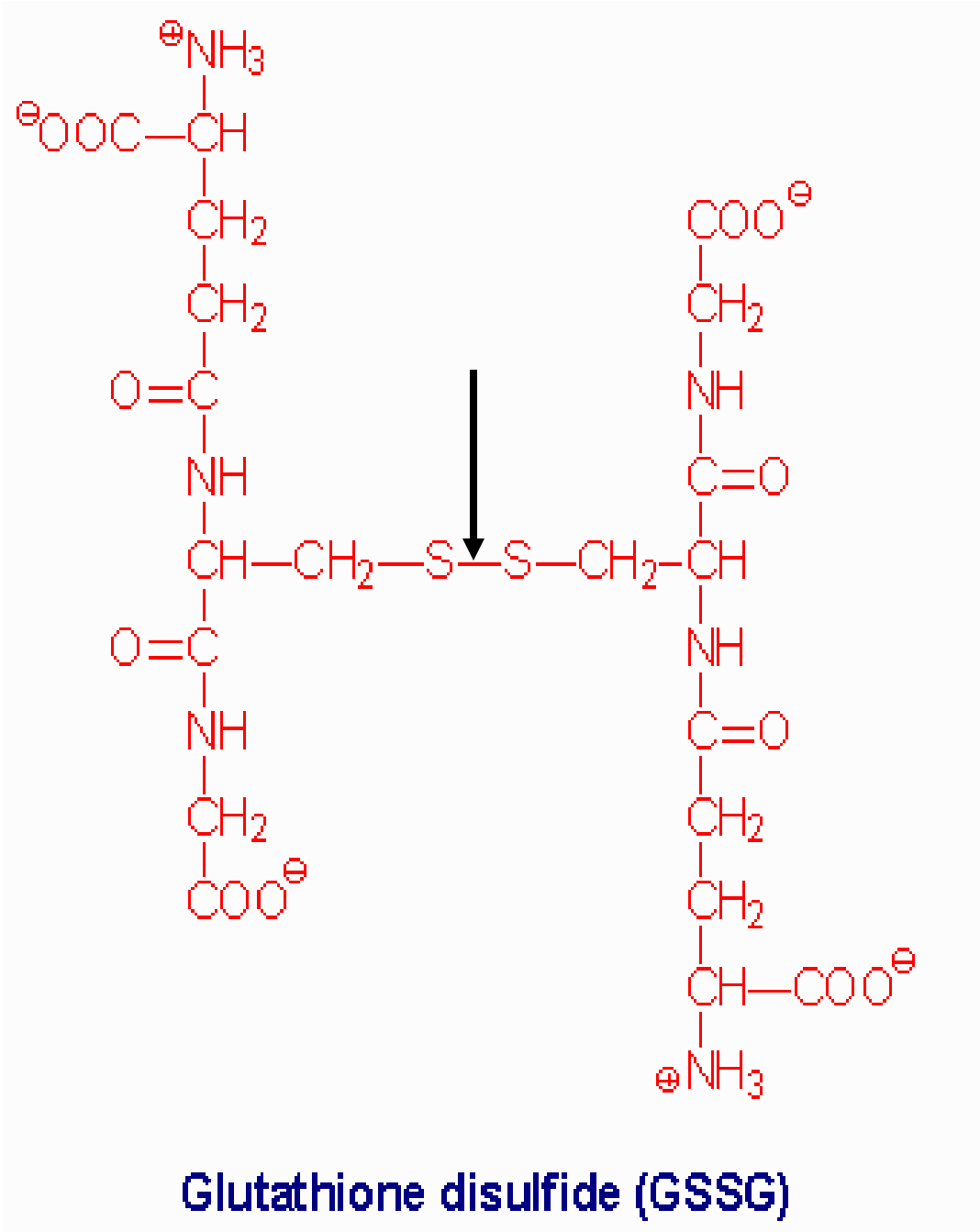
- It serves as a reductant.
- Conjugates to drugs making them water soluble.
- Involved in amino acid transport across cell membranes.
- Cofactor in some enzymatic reactions.

- The sulfhydryl of GSH is used to reduce peroxides (ROS) formed during oxygen transport. ROS can affect DNA, RNA, and proteins leading to cell death.

- The resulting oxidized form of GSH is two molecules linked by a disulfide bridge (GSSG).

-The enzyme glutathione reductase uses NADPH as a cofactor to reduce GSSG back to two moles of GSH.

-Thus, the pentose pathway is linked to the supply of adequate amounts of GSH.



Glutathione and Erythrocytes

- GSH is extremely important particularly in the highly oxidizing environment of the red blood cell.
- Mature RBCs have no mitochondria and are totally dependent on NADPH from the pentose phosphate pathway to regenerate GSH from GSSG via glutathione reductase.
-In fact, as much as 10% of glucose consumption, by erythrocytes, is mediated by the pentose pathway.
- The reduced form of glutathione serves as a sulfhydryl buffer, it maintains cysteine residues in hemoglobin and other proteins in a reduced state.
- GSH is essential for normal RBC structure and keeping hemoglobin in Fe++ state.

- Reduced glutathione also detoxifies peroxides.

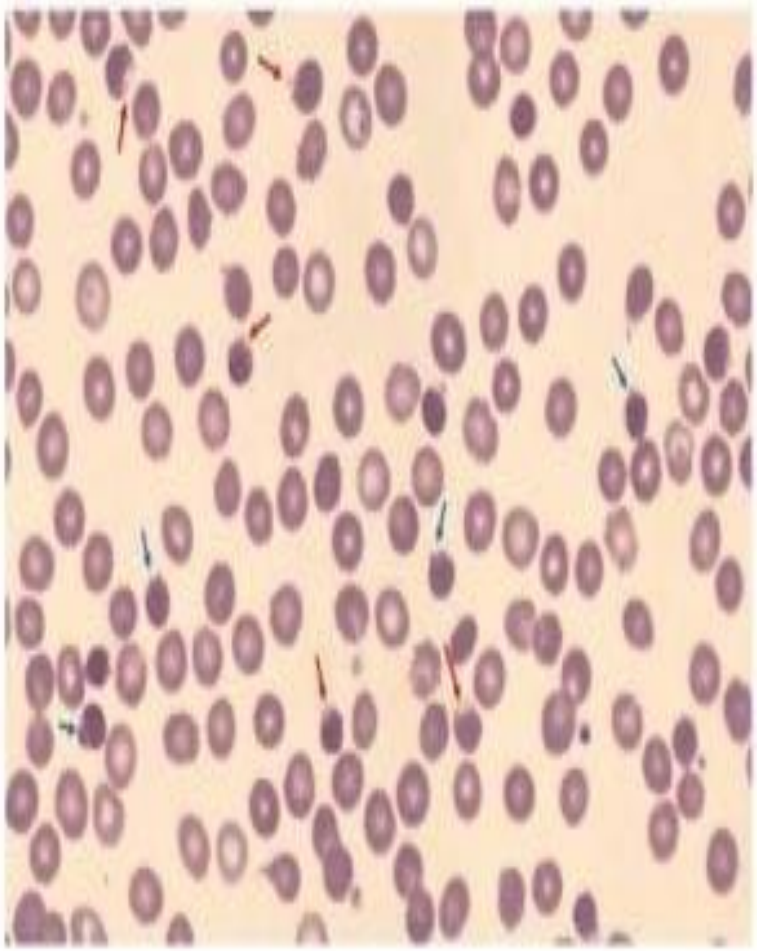
$$2GSH + ROOH \rightarrow GSSG + H_2O + ROH$$

- Cells with low levels of GSH are susceptible hemolysis.
- Individuals with reduced GSH are subject to hemolysis.
- This is often clinically seen as black urine under certain conditions.

<u>Conditions for hemolytic anemia related G6PD deficiency</u>

- The ingestion of oxidative agents that generate peroxides or reactive oxygen species (ROS), such as antimalarial drugs, purine glycoside from fava beans, aspirin and sulfa drugs
- Individuals with G6PD deficiency can not produce sufficient GSH to cope with the ROS.
- Proteins become cross linked leading to Heinz body formation and cell lysis.

- Glucose 6-phosphate dehydrogenase deficiency and non-spherocytic hemolytic anemia.
- Over 300 genetic variants of the G6PD protein are known.
- Thus, there is a remarkable variation in the clinical spectrum. G6PD deficiency is an inheritable X-linked recessive disorder.
- Approximately 10-14% of the male African American population is affected.



- It is also seen in Caucasians from the Mediterranean Basin.

- People with the disorder are not normally anemic and display no evidence of the disease until the red cells are exposed to an oxidant or stress.