Pentose Phosphate Pathway chapter 13 page 145

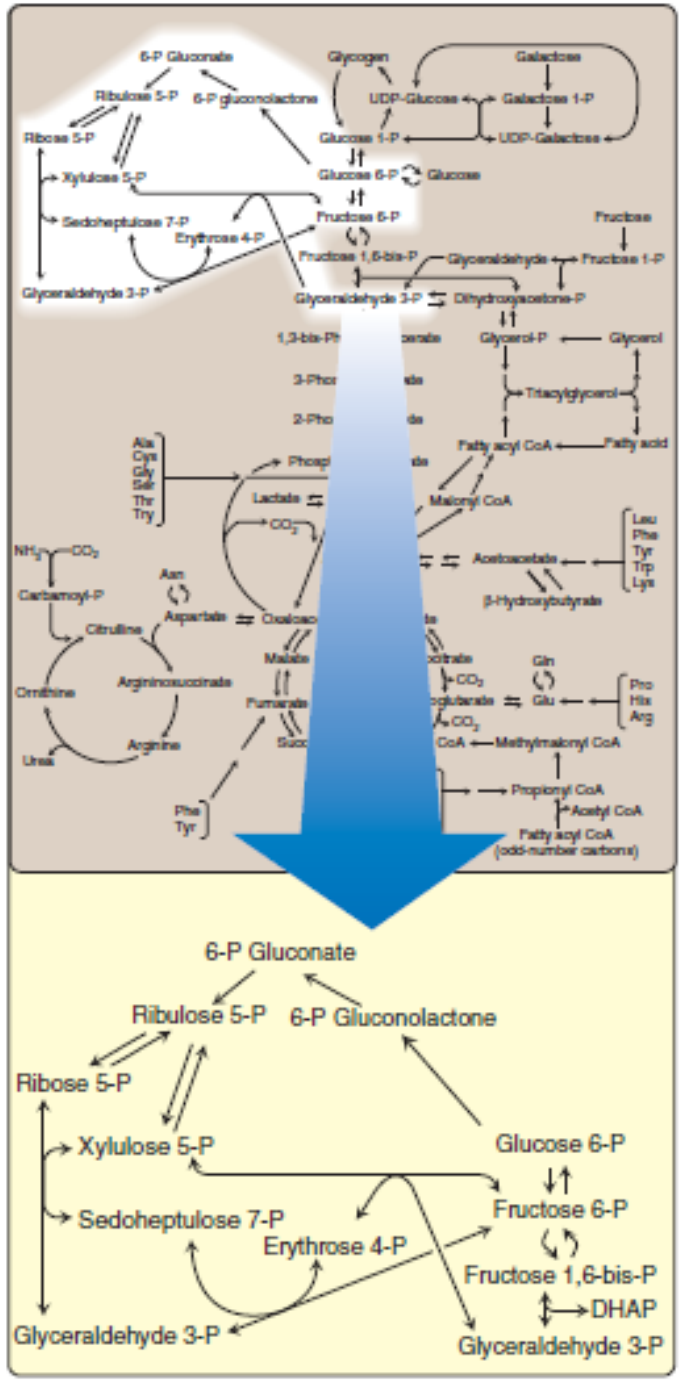
BCH 340 lecture 7

- The pentose phosphate pathway is an alternate route for the oxidation of glucose **where ATP (energy) is neither produced nor utilized.**
- The pentose phosphate pathway **takes place within the cytoplasm** (because $NADP^+$ is used as a hydrogen acceptor) and is also known as the hexose monophosphate shunt or phosphogluconate pathway
- Is used for the **synthesis of NADPH and D-ribose**.

The PPP can be divided into two phases

The irreversible oxidative phase: generates NADPH which is required for many biosynthetic pathways and for detoxification of reactive oxygen species.

The nonoxidative phase: interconverts C_3, C_4, C_5, C_6 and C_7 monosaccharides to produce **ribose-5P for nucleotide synthesis**, and also to **regenerate glucose-6P to maintain NADPH production by the oxidative phase.**



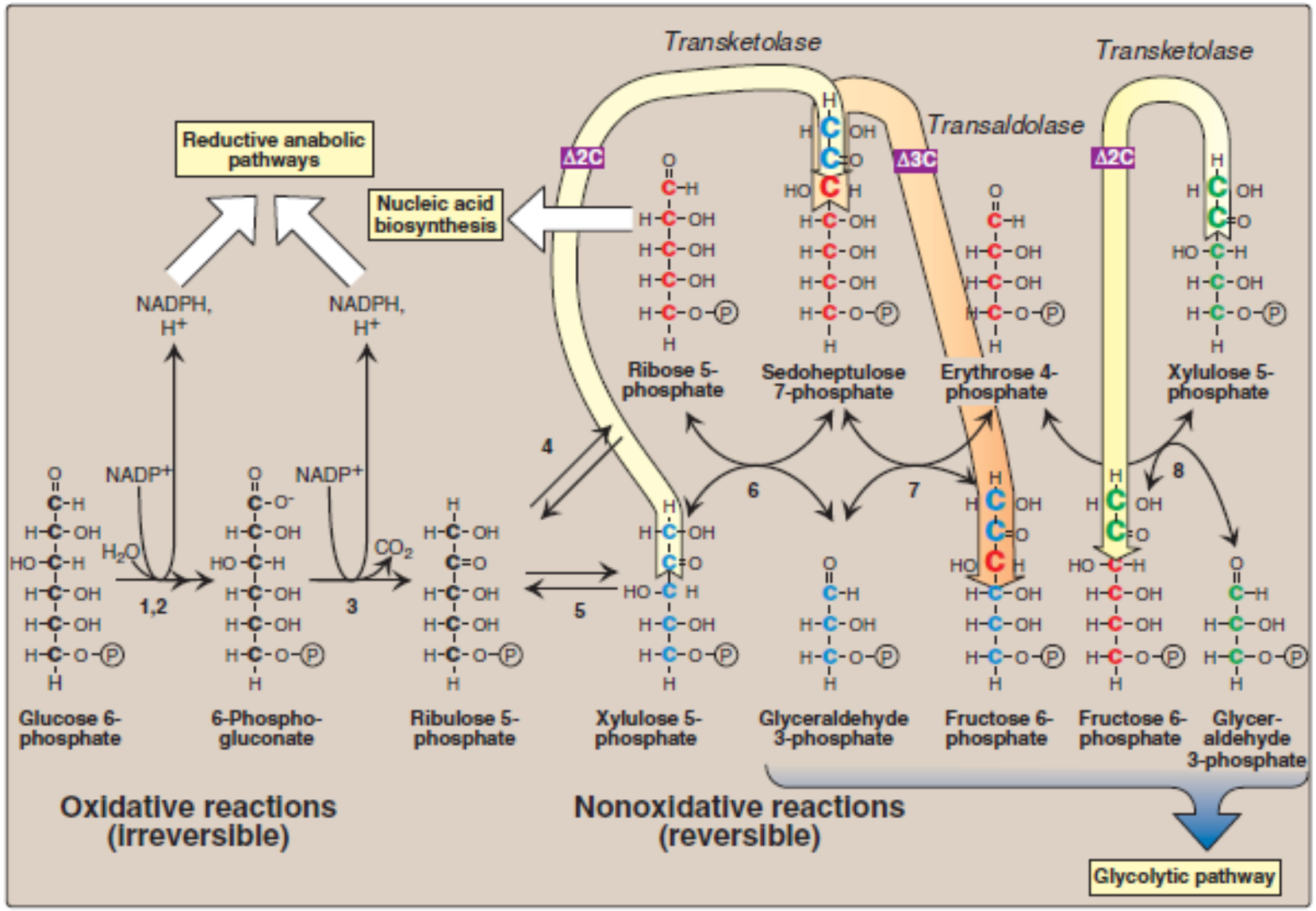
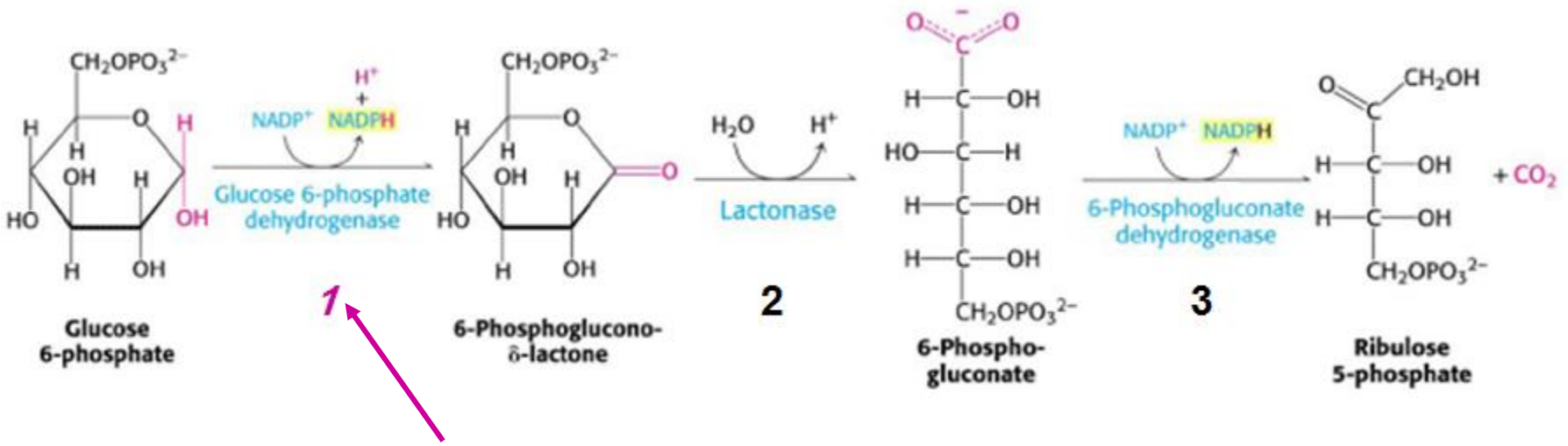


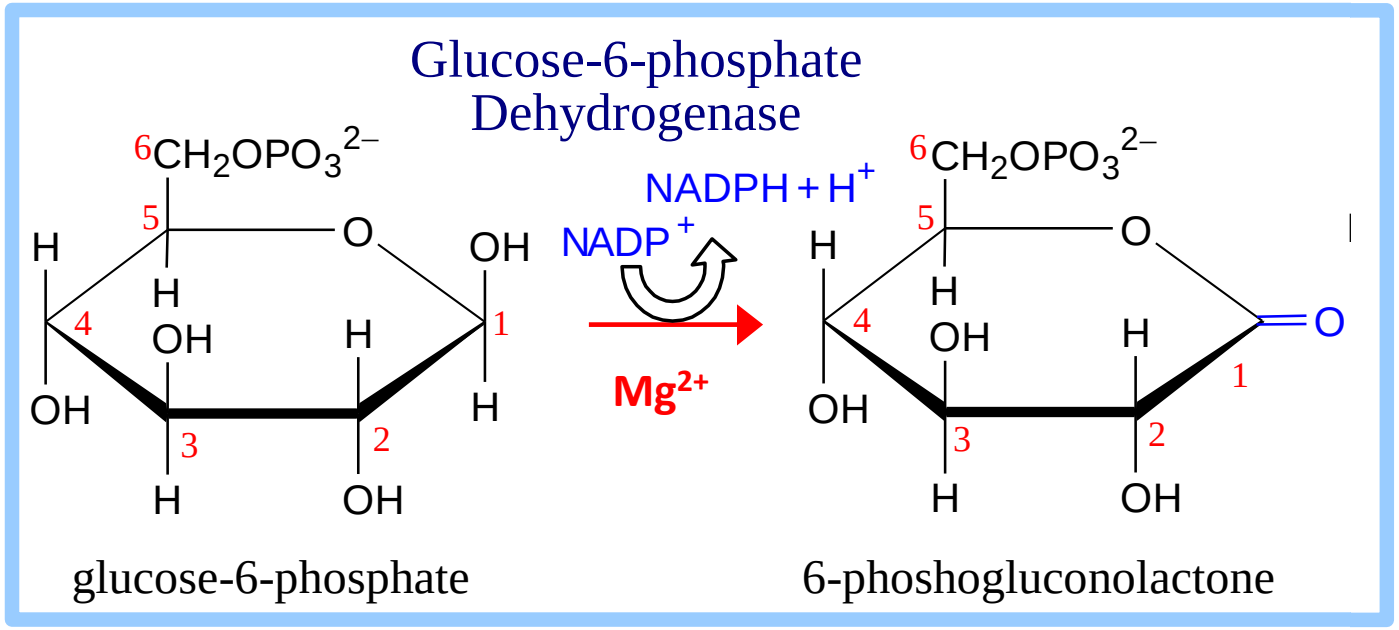
Figure 13.2
Reactions of the hexose monophosphate pathway. Enzymes numbered above are: 1,2) *glucose 6-phosphate dehydrogenase* and *6-phosphogluconolactone hydrolase*, 3) *6-phosphogluconate dehydrogenase*, 4) *ribose 5-phosphate isomerase*, 5) *phosphopentose epimerase*, 6) and 8) *transketolase* (coenzyme: thiamine pyrophosphate), and 7) *transaldolase*. Δ2C = two carbons are transferred in *transketolase* reactions; Δ3C = three carbons are transferred in the *transaldolase* reaction.

The irreversible oxidative phase

- Three enzymatic reactions in the oxidative phase
- Glucose-6-P is converted to ribulose-5-P with production of 2 molecules of NADPH and CO_2

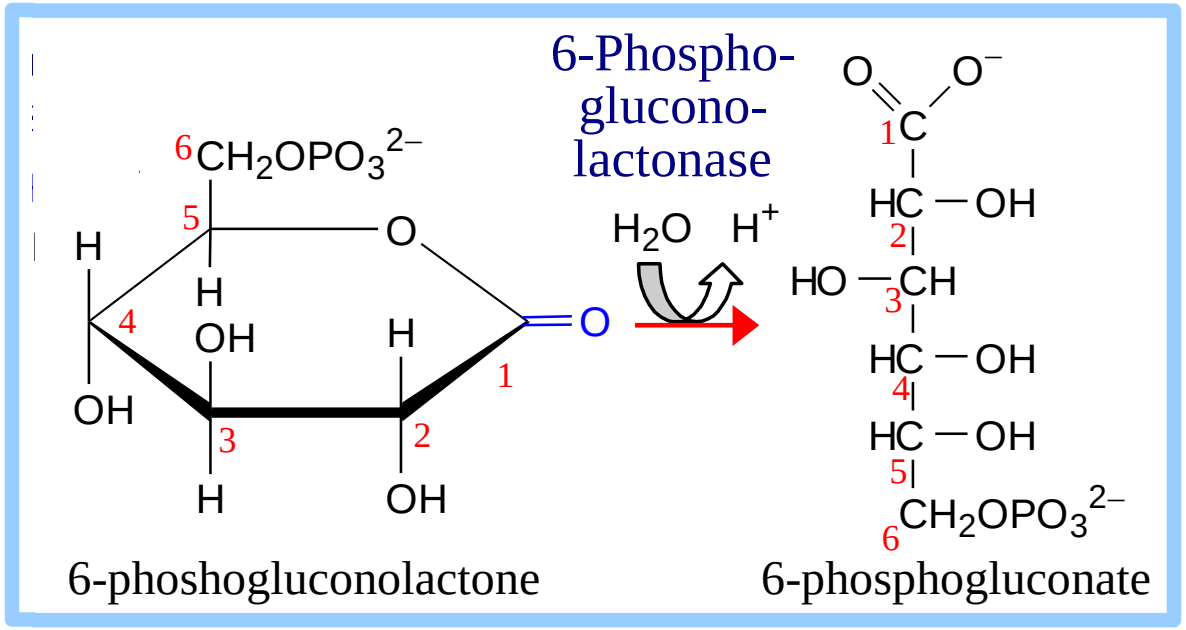


G6PD is the committed step in the Pentose Phosphate Pathway because 6-Phosphoglucono-lactone has no other metabolic fate except to be converted to 6-phosphogluconate.

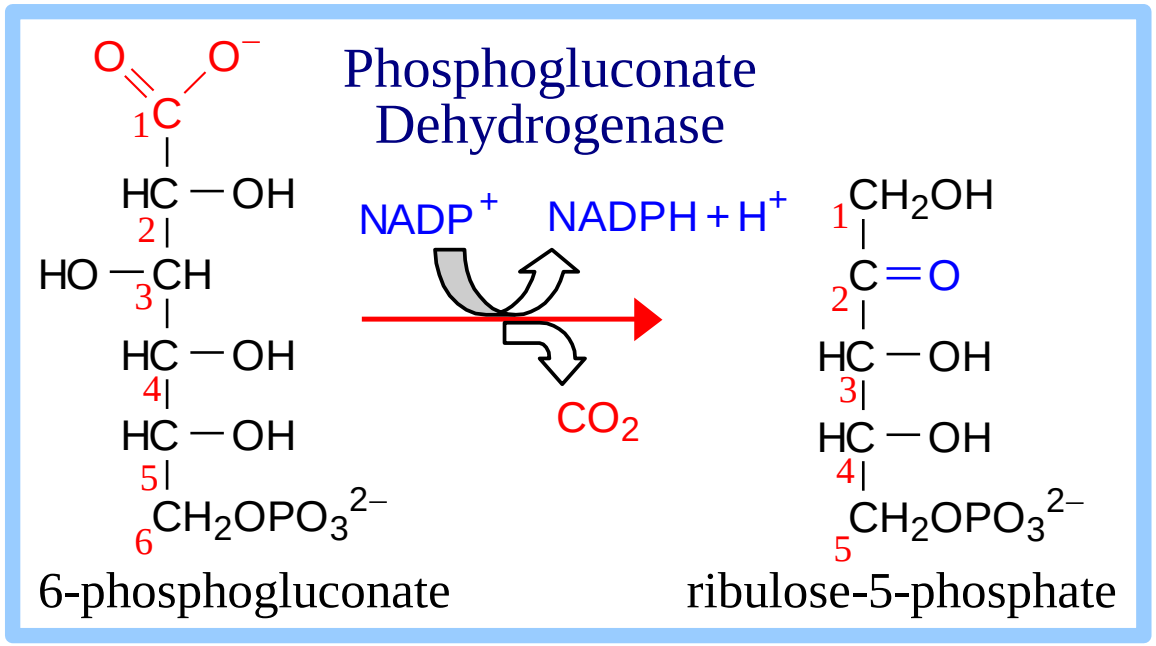


- **Glucose-6-phosphate Dehydrogenase** catalyzes **oxidation** of the aldehyde at **C1** of glucose-6-phosphate, to a **carboxylic acid**
- This enzyme requires **Mg^{2+}** and **$NADP^{+}$** (serves as electron acceptor) as coenzymes
- NADPH is a potent competitive inhibitor of this enzyme

  NADPH/$NADP^{+}$ increases it inhibits the reaction



- **6-Phosphogluconolactonase** catalyzes hydrolysis of 6-phosphogluconolactone
- The product is **6-phosphogluconate**
- It is irreversible but not rate-limiting



- **Phosphogluconate Dehydrogenase** catalyzes **oxidative decarboxylation** of 6-phosphogluconate, to yield the **5-C** ketose **ribulose-5-phosphate**
- The **OH** at C**3** (C**2** of product) is oxidized to a **ketone**
- This promotes loss of the carboxyl at C**1** as CO_2
- **$NADP^+$** serves as oxidant

The reversible non-oxidative phase

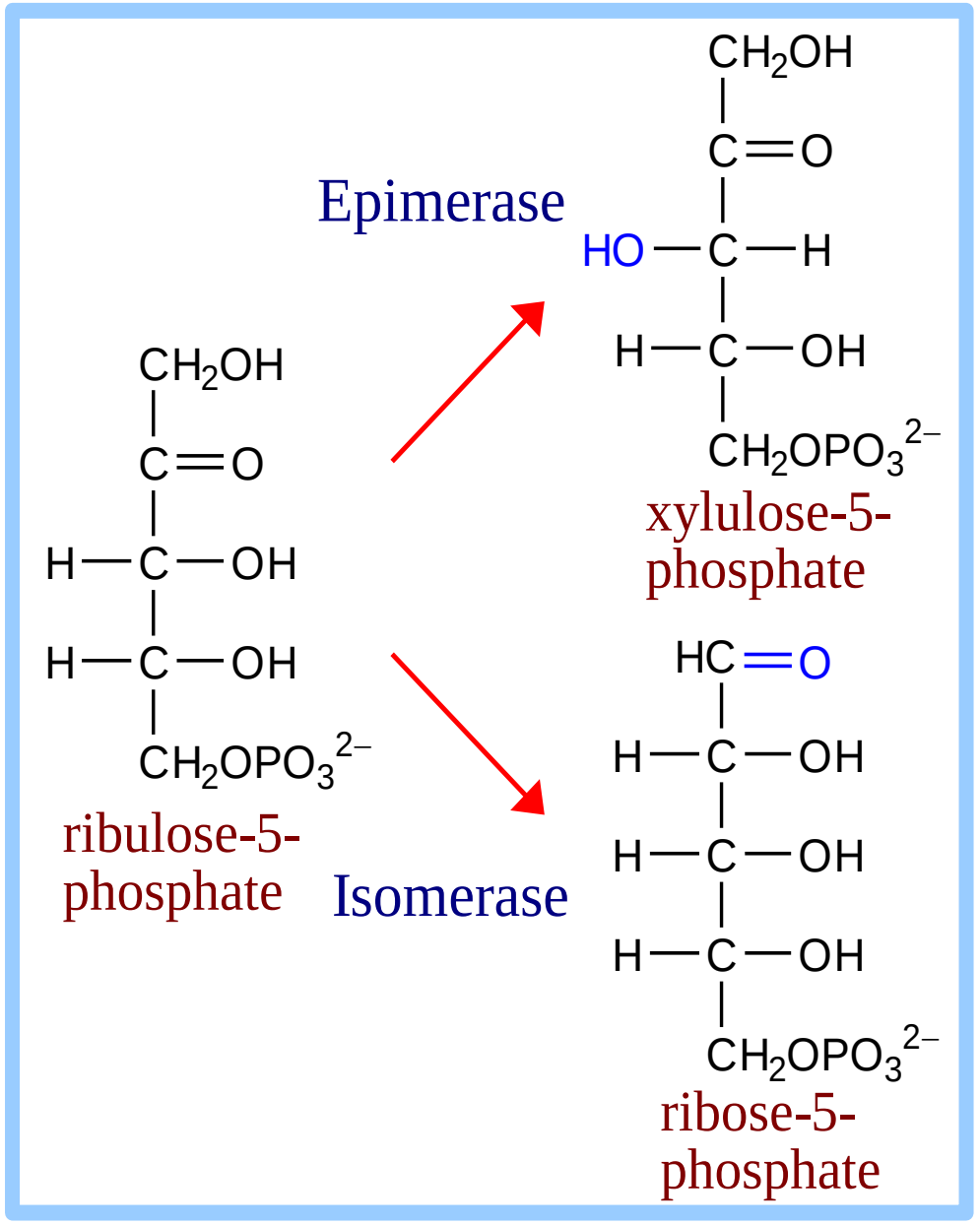
- In nonoxidative phase, **ribulose 5-P is converted back to G-6-P** by a series of reactions involving especially two enzymes

1. Transketolase
2. Transaldolase

- **Epimerase** inter-converts stereoisomers ribulose-5-P and xylulose-5-P

- **Isomerase** converts the ketose ribulose-5-P to ribose-5-P which is used in nucleotide, nucleic acid biosynthesis

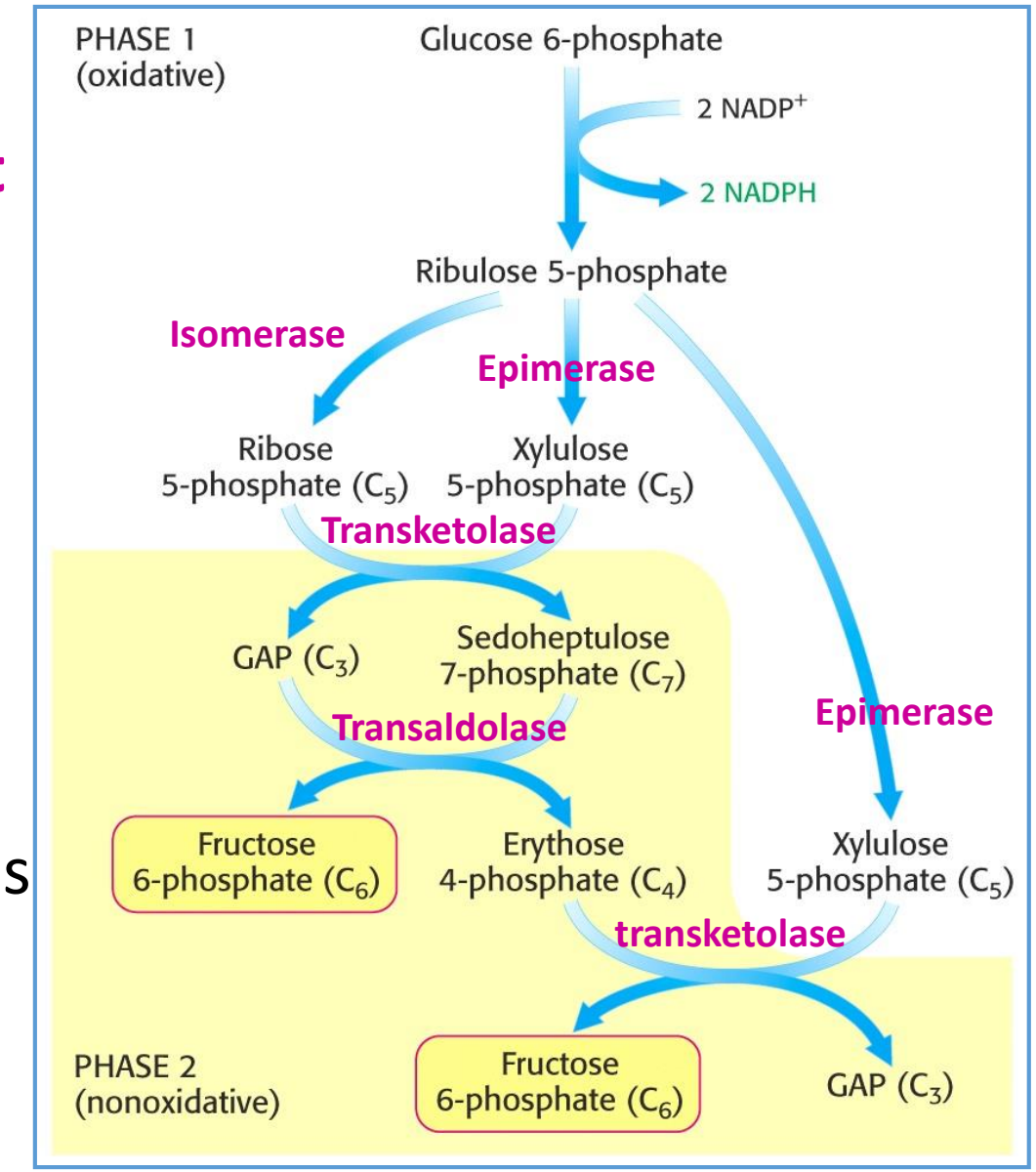
Both reactions are reversible

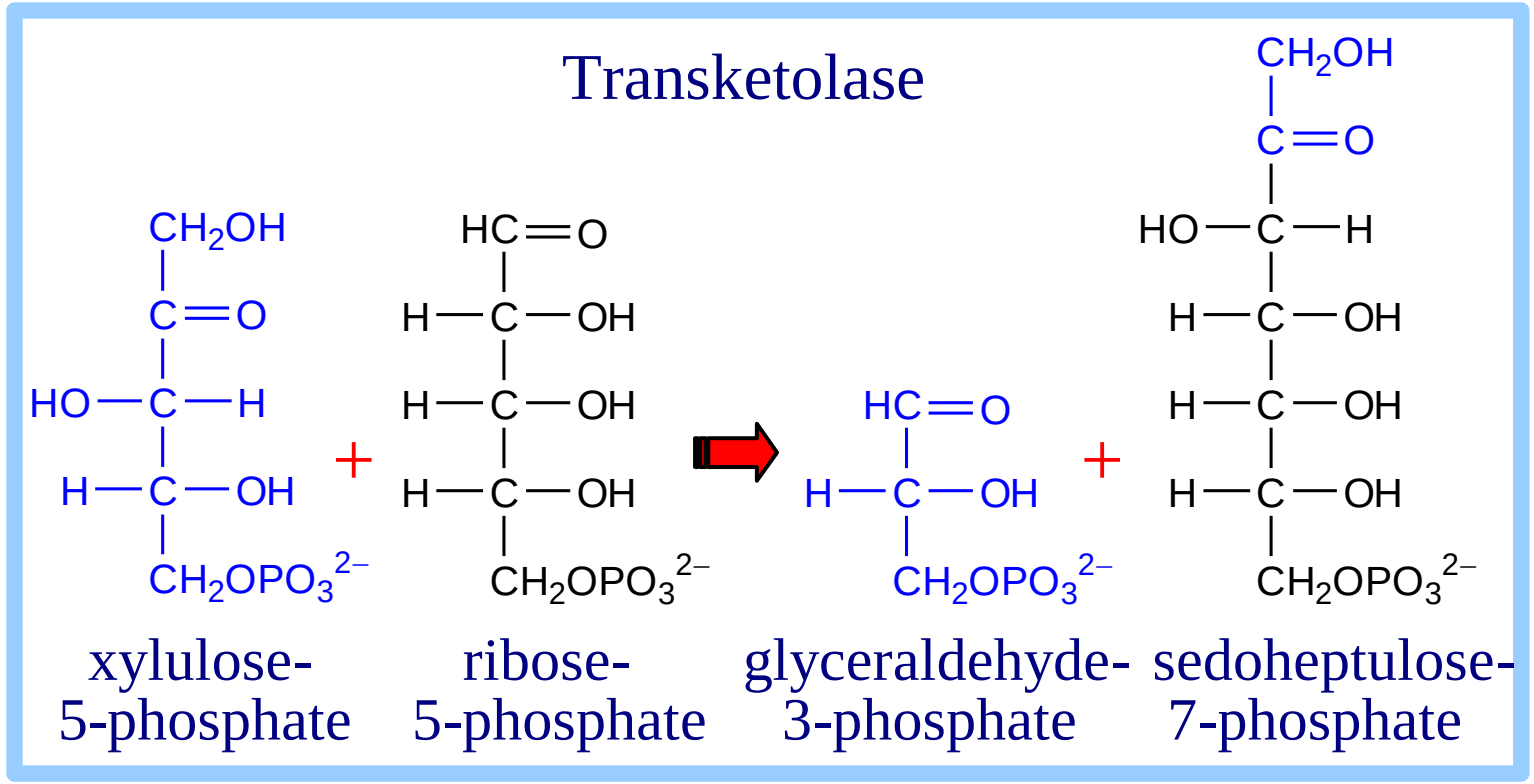


Transketolase

- Transfers a **2-C fragment** from xylulose-5-P to either ribose-5-P or erythrose-4-P.

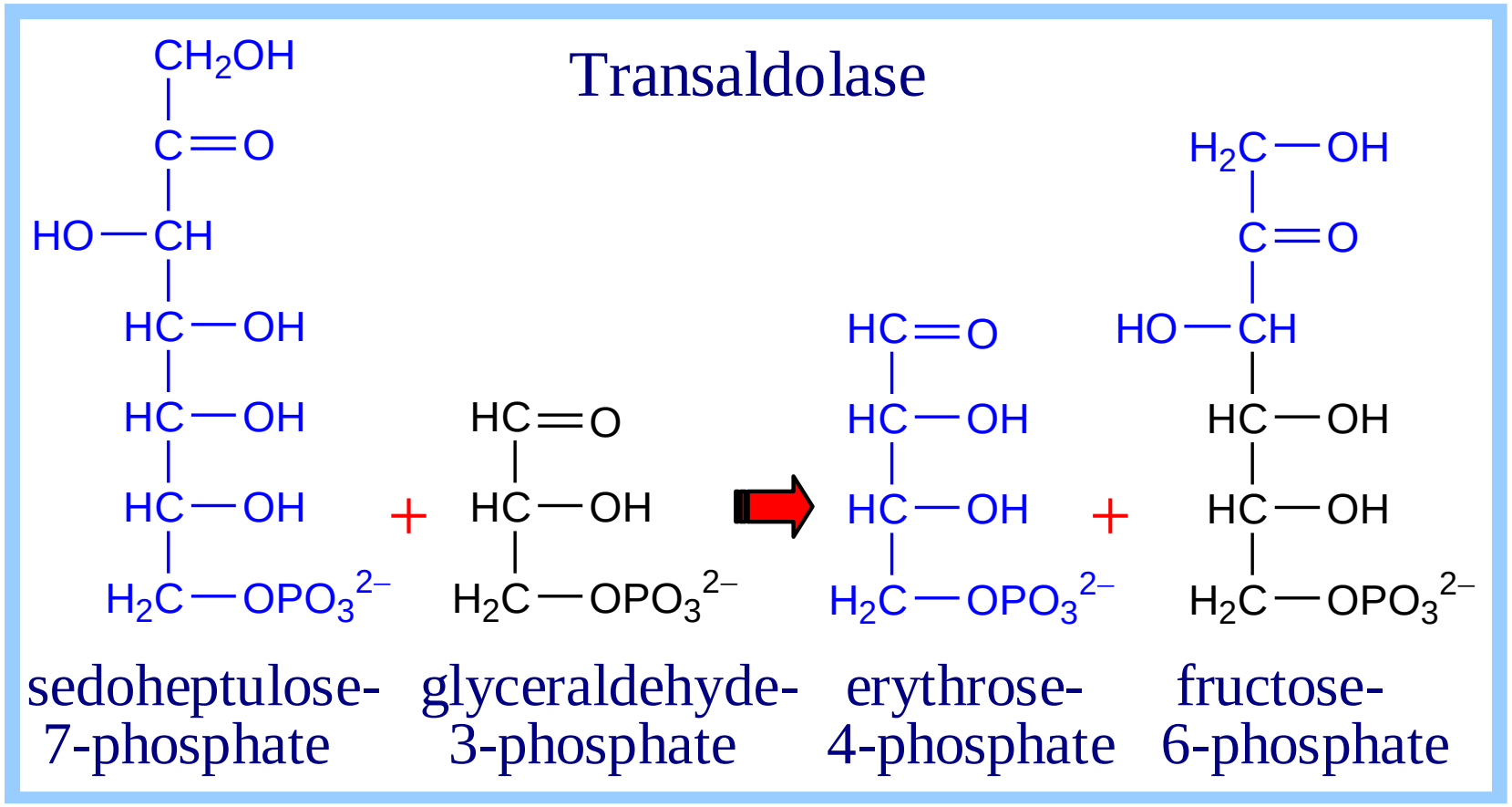
- Requires **thiamine pyrophosphate (TPP)**, a derivative of **vitamin B_1** as coenzyme and **Mg^{2+}** as cofactor





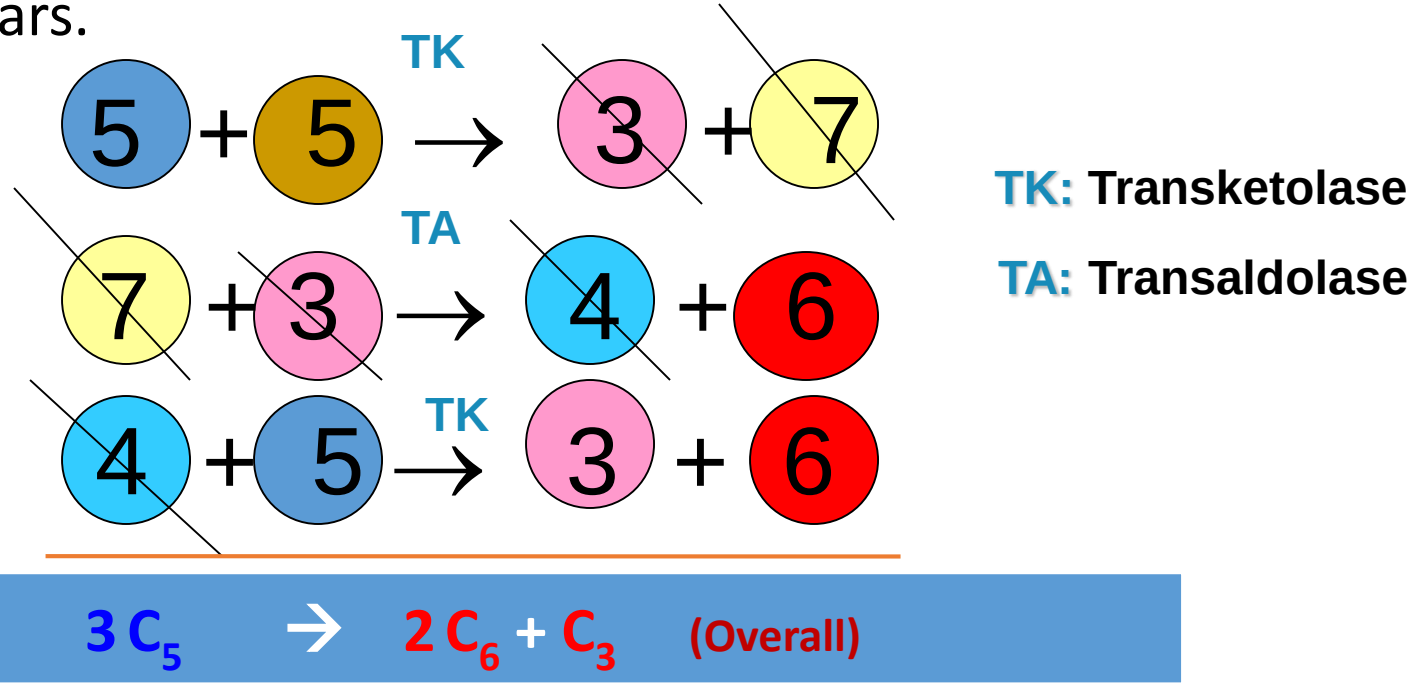
- Transfer of the 2-C fragment to the 5-C ribose-5-phosphate yields **sedoheptulose-7-phosphate**

- Transfer of the 2-C fragment instead to 4-C erythrose-4-phosphate yields **fructose-6-phosphate**



Transaldolase catalyzes transfer of a **3-C** from sedoheptulose-7-phosphate to glyceraldehyde-3-P

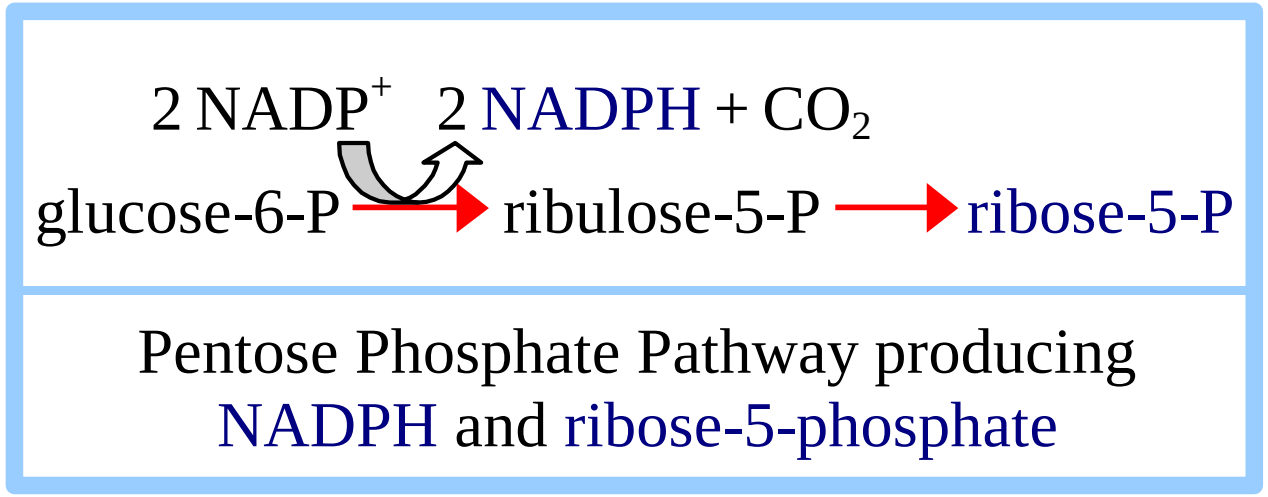
SUMMARY: The **balance sheet** below summarizes flow of 15 **C** atoms Through PPP reactions by which **5-C** sugars are converted to **3-C** and **6-C** sugars.



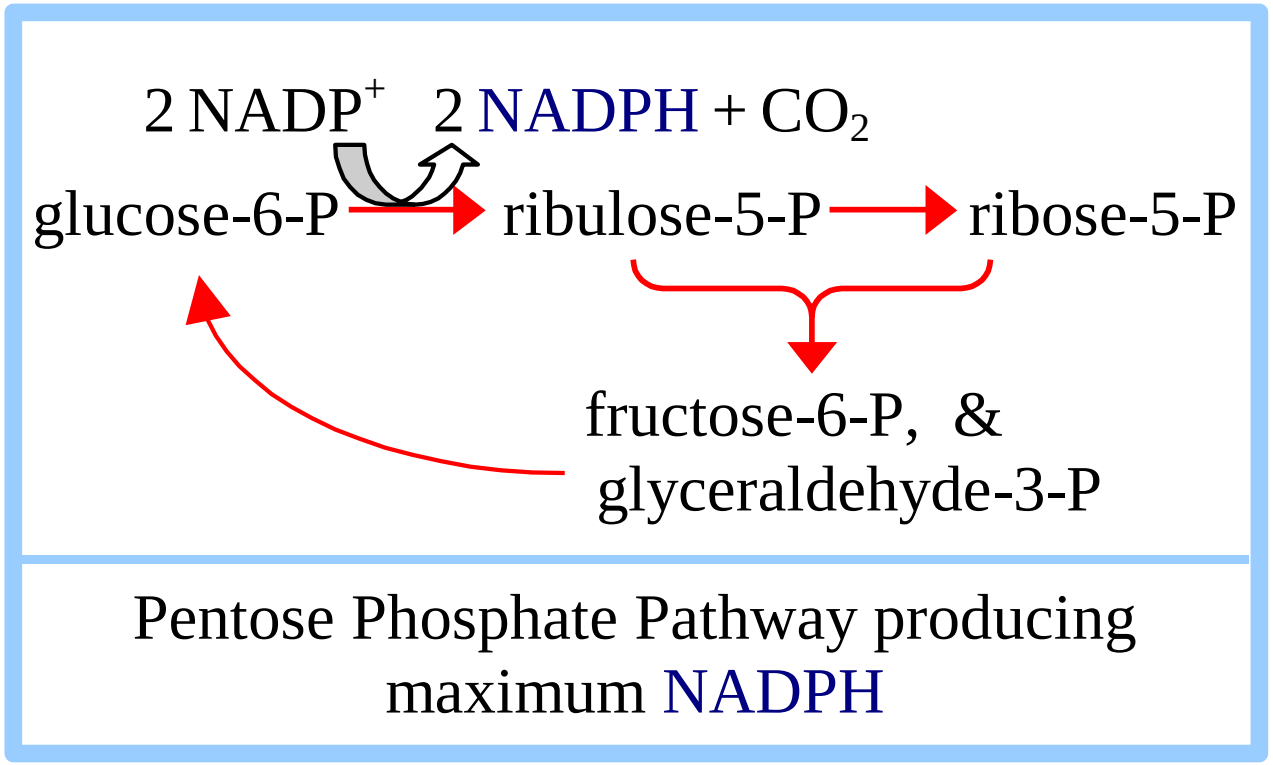
Differences between HMP shunt and glycolysis

	HMP pathway	Glycolysis
Location	In certain cells	In all cells
Oxidation of glucose	Occurs in the first reaction	Phosphorylation occurs first then oxidation
Coenzyme	$NADP^+$	NAD^+
Energy	No energy production	2 or 8 ATP
CO_2	Produced	Not produced
Pentoses	Produced	Not produced

Importance of Pentose Phosphate Pathway



- Ribulose-5-P may be converted to **ribose-5-P**, a substrate for synthesis of **nucleotides**, nucleic acids and coenzymes
- The pathway also produces some **NADPH**



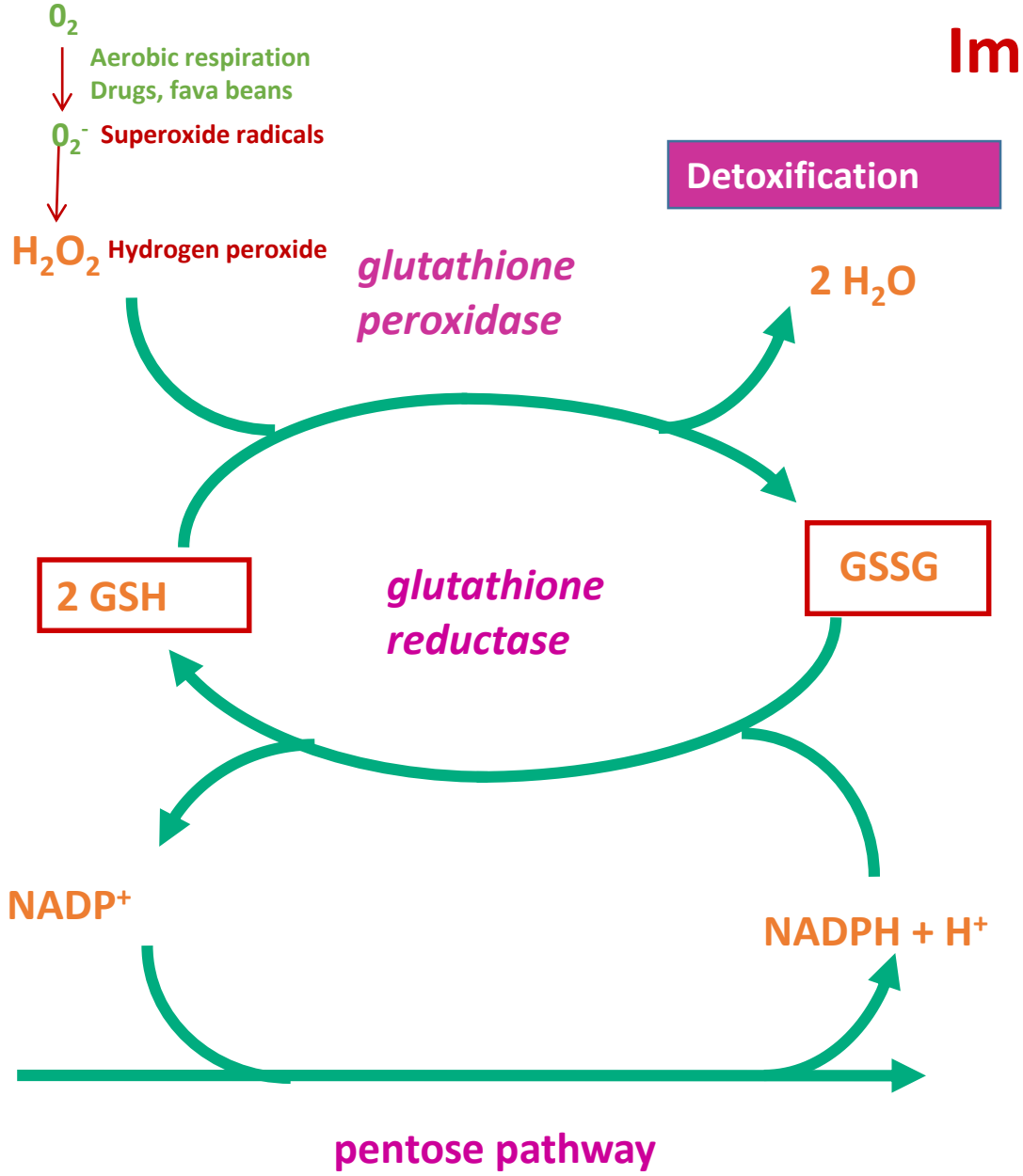
- Glyceraldehyde-3-P and fructose-6-P may be converted to **glucose-6-P**, via enzymes of gluconeogenesis, for reentry to PPP, maximizing formation of **NADPH**, which is need for reductive biosynthesis.

- **3-C** Glyceraldehyde-3-P and **6-C** fructose-6-P, formed from 5-C sugar phosphates, may enter **Glycolysis for ATP** synthesis.

- **5-C Ribose-1-P** generated during **catabolism of nucleosides** also enters Glycolysis in this way, after first being converted to ribose-5-P

  - Thus the PPP serves as an **entry into Glycolysis** for both 5-carbon & 6-carbon sugars.

Importance of PPP in RBC



- When erythrocytes are exposed to chemicals that generate high levels of superoxide radicals, **GSH (Reduced Glutathione)** is required to reduce these damaging compounds

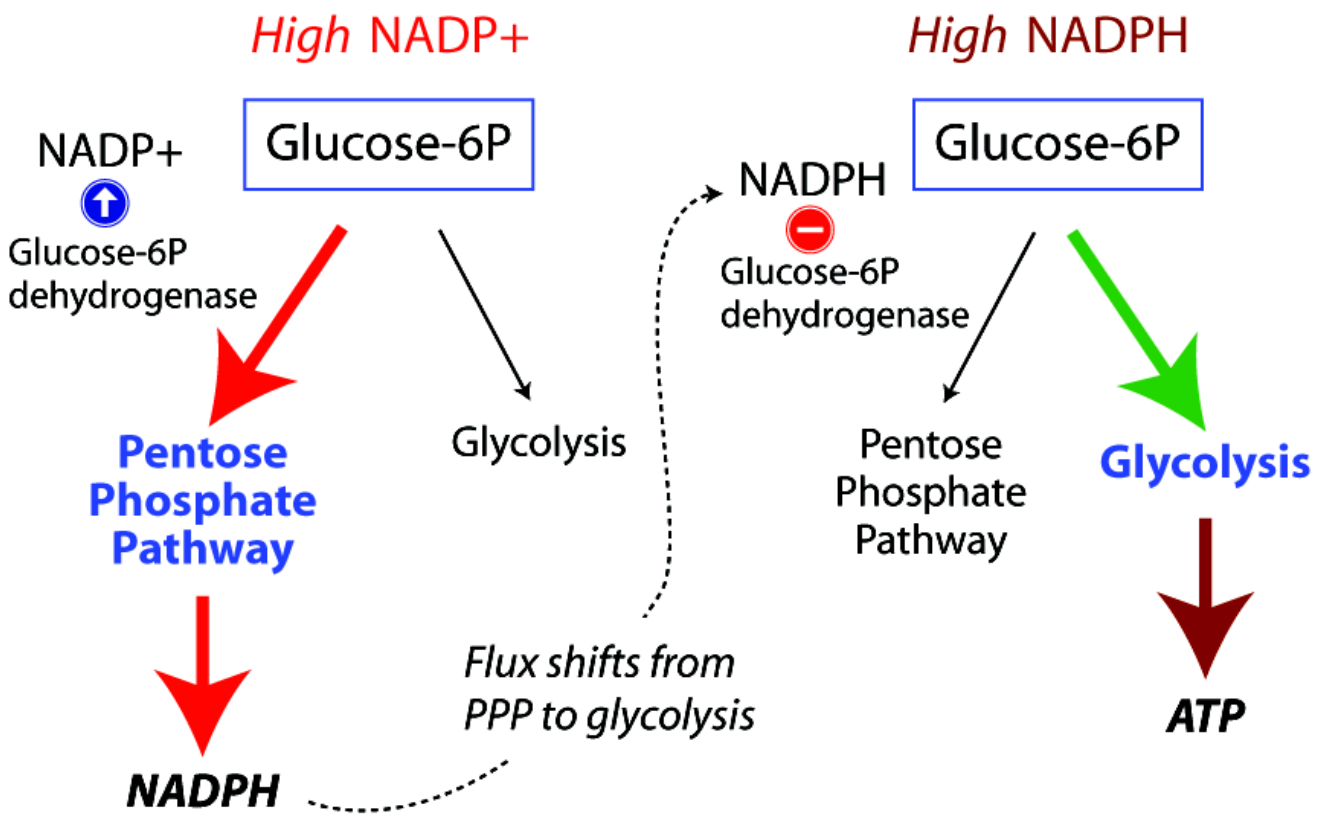
- **Glutathione Peroxidase** catalyzes degradation of organic hydroperoxides by reduction, as two glutathione molecules are oxidized to a disulfide **GSSG**

- The PPP is responsible for maintaining high levels of NADPH in red blood cells for use as a **reductant** in the glutathione reductase reaction.

Regulation of pentose phosphate pathway

- The entry of glucose 6-phosphate into the pentose phosphate pathway is controlled by the cellular concentration of NADPH
- NADPH is a **strong inhibitor** of glucose 6-phosphate dehydrogenase (Rate Limiting Reaction)
- As NADPH is used in various pathways, inhibition is relieved, and the enzyme is accelerated to produce more NADPH

Regulation of the G6PD activity controls flux through the glycolytic pathway and pentose phosphate pathways



Regulation of pentose phosphate pathway

- The synthesis of glucose 6-phosphate dehydrogenase is **induced** by the increased insulin/glucagon ratio after a high carbohydrate meal

- **Insulin**, which secreted in response to hyperglycemia, **induces** the synthesis of G6P dehydrogenase and 6-phosphogluconate dehydrogenase → **increasing the rate of glucose oxidation by PPP**

- The synthesis of glucose 6-phosphate dehydrogenase is **repressed** during fasting